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Sexual Differentiation of the Brain

edited by
Akira Matsumoto, Ph.D.



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Preface

This monograph is dedicated to Dr. Yasumasa Arai who retired from the professorship in anatomy at the Juntendo University School of Medicine in March 1998. He is an internationally established scientist, contributing to the advance of neuroendocrinology and neuroscience for more than 30 years. He is a member of the Editorial Boards of *Hormones and Behavior* and the *Journal of Neuroendocrinology*. He has conducted important research in the understanding of sexual differentiation of the brain and sex steroid influences on neural and behavioral functions.

Sex steroids exert influences on modulating neural development and neural circuit formation in developing the sex steroid-sensitive neuroendocrine brain. Estrogen or aromatizable androgen can act as a neurotrophic factor on neural tissues, stimulating axonal and dendritic growth and synapse formation. The development of sexual dimorphism in neural structures such as nuclear volume and synaptic organization may reflect sex steroid-modulating neural development and synapse formation during the perinatal period. Recent neurobiological and molecular biological studies in this field have provided new information about mechanisms underlying sexual differentiation of the brain. Moreover, attempts have been made to clarify sex differences in the human brain by using anatomical and noninvasive techniques such as MRI or PET. Psychological studies also have contributed in revealing the difference. All of the contributors, leading scientists in this field, have reviewed the most recent advances in studies on sexual differentiation of the brain. The monograph will provide a valuable insight into the current state of knowledge about this field.

Akira Matsumoto

Editor

Akira Matsumoto, Ph.D., is an associate professor in the Department of Anatomy, Juntendo University School of Medicine, Tokyo (Japan). Dr. Matsumoto received a B.S. degree (biology, 1968) and a Ph.D. degree (biology, 1974) from the University of Tokyo, Tokyo (Japan). He has served on the faculty of the Department of Anatomy, Juntendo University School of Medicine from 1974 to present. He received an International Society of Andrology Award (1993) and a Zoological Science Award (1997). He served as coeditor of the *Atlas of Endocrine Organs* (Springer-Verlag, 1992). He is a member of the Society of Neuroscience, the International Brain Research Organization, the International Society of Neuroendocrinology, the Society of Behavioral Neuroendocrinology, the International Society of Andrology, the Japanese Association of Anatomists, the Japanese Association of Endocrinology, the Japan Neuroscience Society, the Japanese Society for Comparative Endocrinology, and the Zoological Society of Japan. His research interests concern the organizational and activational effects of sex steroids on neural function and structures in the mammalian neuroendocrine brain. He has a number of publications on topics in this field in prominent journals.

Contributors

Laurie A. Abler, B.S., Wisconsin Regional Primate Research Center, University of Wisconsin, Madison, Wisconsin

Paola Agrati, Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Yasumasa Arai, Ph.D., Laboratory of Medical Education, Juntendo University School of Medicine, Tokyo, Japan

Arthur P. Arnold, Ph.D., Departments of Physiological Science and Neurobiology, Laboratory of Neuroendocrinology of the Brain Research Institute, Mental Retardation Research Center, University of California, Los Angeles, California

Laura Bolzoni, Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

S. Marc Breedlove, Ph.D., Department of Psychology, University of California, Berkeley, California

Alessia Brusadelli, Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Gloria Patricia Cardona-Gomez, Instituto Cajal, Consejo Superior de Investigaciones Científicas, Madrid, Spain

Julie Ann Chowen, Ph.D., Instituto Cajal, Consejo Superior de Investigaciones Científicas, Madrid, Spain

Scott E. Christensen, M.A., Department of Psychology, University of California, Berkeley, California

Paolo Ciana, Ph.D., Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

David Crews, Ph.D., Institute of Reproductive Biology, Section of Integrative Biology, University of Texas, Austin, Texas

Maria Carmen Fernandez-Galaz, Ph.D., M.D., Instituto Cajal, Consejo Superior de Investigaciones Cientificas, Madrid, Spain

Luis Miguel Garcia-Segura, Ph.D., Instituto Cajal, Consejo Superior de Investigaciones Cientificas, Madrid, Spain

Roger A. Gorski, Ph.D., Department of Neurobiology, University of California Los Angeles School of Medicine, Los Angeles, California

Elizabeth Hampson, Ph.D., Department of Psychology and Neurosciences Program, University of Western Ontario, London, Ontario, Canada

Melissa Hines, Ph.D., Department of Psychology, City University, London, United Kingdom

John B. Hutchison, Ph.D., St. John's College, University of Cambridge, Cambridge, United Kingdom CB21TP

Cynthia L. Jordan, Ph.D., Department of Psychology, University of California, Berkeley, California

Adriana Maggi, Ph.D., Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Elena Marini, Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Luciano Martini, M.D., Department of Endocrinology, University of Milan, Milan, Italy

Akira Matsumoto, Ph.D., Department of Anatomy, Juntendo University School of Medicine, Tokyo, Japan

Clara Meda, Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Shizuko Murakami, Ph.D. Department of Anatomy, Juntendo University School of Medicine, Tokyo, Japan

Paola Negri-Cesi, Ph.D., Department of Endocrinology, University of Milan, Milan, Italy

Sonoko Ogawa, Ph.D., Laboratory of Neurobiology and Behavior, The Rockefeller University, New York, New York

Cesare Patrone, Ph.D., Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Michael C. Penlington, Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Donald W. Pfaff, Ph.D., Laboratory of Neurobiology and Behavior, The Rockefeller University, New York, New York

Flavio Piva, Ph.D., Department of Endocrinology, University of Milan, Milan, Italy

Angelo Poletti, Ph.D., Department of Endocrinology, University of Milan, Milan, Italy

Giuseppe Pollio, Ph.D., Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Monica Rebecchi, Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Jon Sakata, Institute for Neuroscience, University of Texas, Austin, Texas

Yoshie Sekine, B. Human S., Department of Anatomy, Juntendo University School of Medicine, Tokyo, Japan

Nancy M. Sherwood, Ph.D., Department of Biology, University of Victoria, Victoria, British Columbia, Canada

Rodolfo H. Sialino, Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

Richard B. Simerly, Ph.D., Division of Neuroscience, Oregon Regional Primate Research Center, Beaverton, Oregon and Program in Neuroscience and Department of Cell and Developmental Biology, Oregon Health Sciences University, Portland, Oregon

Ei Terasawa, Ph.D., Wisconsin Regional Primate Research Center and Department of Pediatrics, University of Wisconsin, Madison, Wisconsin

Jose Luis Trejo, Instituto Cajal, Consejo Superior de Investigaciones Cientificas, Madrid, Spain

Elisabetta Vegeto, Ph.D., Center Milano Molecular Pharmacology Laboratory, Institute of Pharmacological Sciences, University of Milan, Milan, Italy

James C. Woodson, M.A., Department of Psychology, University of California Los Angeles, Los Angeles, California

Harold H. Zakon, Ph.D., Section of Neurobiology and Institute for Neuroscience, University of Texas, Austin, Texas

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Section 1

Introduction

- 1 Developmental aspects of the nervous system
- 2 Basic elements of the nervous system

Developmental aspects of the nervous system

During the third week of gestation, the neural ectoderm forms the neural plate, which eventually becomes the neural tube. The neuroectodermal cells that lie dorsolateral to the neural tube constitute the neural crest cells, giving rise to the autonomic and sensory ganglia. Closure of the neuropores and development of the brain vesicles lead to the formation of various compartments of the central nervous system. When the neuropores fail to close, a variety of malformations ranging from anencephaly to spina bifida may ensue. Further differentiation of the primitive neural tube leads to the formation of the ependymal, mantle, and marginal layers. Subdivision of the mantle layer into the alar and basal plates serves as a basis upon which the sensory and motor nuclei are localized within CNS. The neural canal converts into various parts of the ventricular system.

Formation of the neural tube

Genetic and molecular aspects of neural development

Spinal cord (myelencephalon)

Myelencephalon

Metencephalon

Pons

Cerebellum

Mesencephalon

Diencephalon

Telencephalon

Formation of the neural tube

During the third week of gestation (day 16), the notochord (chorda-mesoderm) induces the development of the neural plate, which is located dorsal to the notochord in the rostral part of the embryonic disc (Figures 1.1, 1.2 & 1.3). Proliferation and differential growth of the neural plate cells, changes in the shape of the cells, stretch posed by the rapidly developing embryo, activities of the microtubules and microfilaments, as well as their intrinsic movements eventually lead to the formation of the neural groove (day 18), which acts as a median hinge region around which the neural folds expand (Figures 1.2 & 1.5). Fusion of the neural folds occurs in the future cervical region at certain sites, gradually expanding in both rostral and caudal directions, leading to the formation of the neural tube (Figure 1.5). Failure of the neural folds to fuse, differentiate, and detach from the surface ectoderm may lead to rachischisis, which is, as described later in this chapter, a group of malformations that assumes variety of forms depending upon the involved part of the neural tube. The last portions of the neural tube to close are the rostral and caudal neuropores, which maintain connections with the amniotic cavity.

Detachment of the neural tube from the surface ectoderm (future epidermis) and its assumption of a more ventral position are believed to be enhanced by N-CAM and N-cadherin molecules synthesized by the neural tube itself. As the neural folds fuse, specialized population of cells in the dorsolateral part of the neural tube forms the neural crest cells (Figures 1.4 & 1.5). Neural crest cells lose their epithelial-specific adhesion molecules and express a new group of cell adhesion molecules such as integrin and laminin. With the help of pseudopodia, which develop from the basal aspects, the neural crest cells are pulled through the basal membrane of the neural tube. Thus, via this process both the surface ectoderm and the basal membrane of the neural tube may guide the migration of the neural crest cells. Migration of these cells occurs in a cranio-caudal direction, with the more cephalic cells departing before the closure of the cranial neuropore.

The process that involves formation of the neural plate, floor plate, and neural sulcus, as well as closure of the neuropores with the eventual configuration of the neural tube is known as primary neurulation. Secondary neurulation refers to the development of the caudal neural tube, a process that is initiated by the formation of a solid tube or mass caudal to somite 31 (first or second lumbar somite) and the appearance of ectodermal-lined vacuoles.

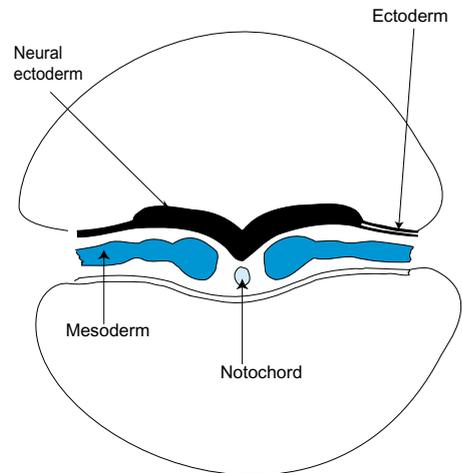


Figure 1.1 Transverse section of the embryo showing the location of the neural ectoderm relative to the notochord and mesoderm

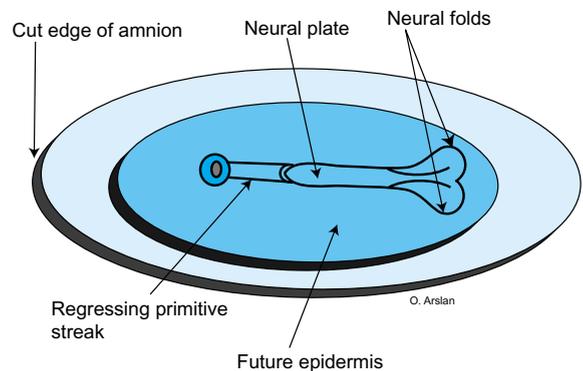


Figure 1.2 Schematic drawing (dorsal view) of the neural plate, neural folds, and their relationships to the future epidermis and primitive streak

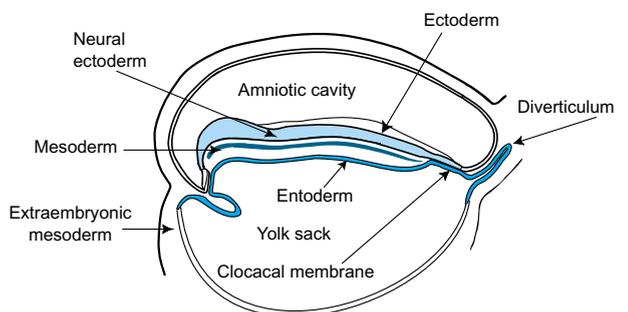


Figure 1.3 Diagram of the neural ectoderm (cephalocaudal) in relationship to the notochord, and intraembryonic coelom. Note the location of the mesodermal tissue

Table 1.1 Derivatives of the neural crest cells

<i>Neuroectodermal cells</i>	<i>Derivatives</i>
Neural crest cells	<ol style="list-style-type: none"> 1. Dorsal root and sensory ganglia of cranial nerves 2. Sympathetic and parasympathetic ganglia 3. Schwann cells 4. Adrenal medulla 5. Melanocytes 6. Neurolemma of the peripheral nerves 7. Cells of the pia and arachnoid mater of the occipital lobe and spinal cord 8. Intraocular muscles 9. Ciliary bodies 10. Carotid bodies

Hirschsprung's disease (congenital megacolon), a congenital anomaly with a male to female ratio of 3:1, and is associated with failure of neural crest cells to migrate. This condition commonly affects the rectum and the sigmoid colon (3/4 of cases), but rarely involves the entire colon. It may also occur in more proximal locations, depending upon the migratory defect of neural crest cells. It is characterized by impaired peristaltic movement at and beyond the affected part of the colon, followed by bowel stasis, chronic constipation, abdominal distention, hypertrophy, constriction of the aganglionic segment, and dilatation of the colon proximal to the affected area. It usually manifests itself in the newborn by inability to pass meconium, followed by intestinal obstruction. The etiology of this disorder may include mutation of RET receptor tyrosine kinase. RET is a tyrosine kinase that undergoes enzymatic activation and initiates intracellular signaling upon binding the glial derived neurotrophic factor and the endothelium B receptor.

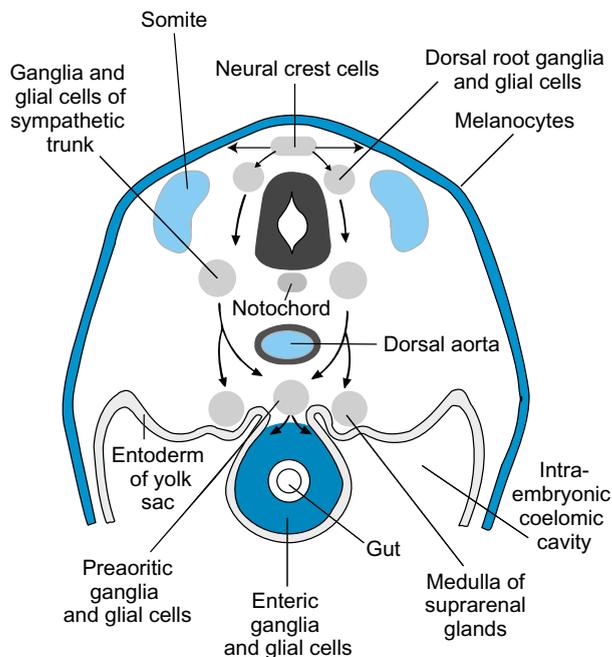


Figure 1.4 Path of migration of the neural crest cells. Note the locations of the somites, notochord, and gut

These vacuoles eventually coalesce and open into the end of the neural tube. Later, canalization and final union of the caudal mass with the rest of the neural tube occurs. In 33-35% percent of embryos the caudal neural tube remains forked.

Neural crest cells contribute to the formation of the sensory ganglia of the dorsal roots, trigeminal, facial, glossopharyngeal, and vagus nerves, autonomic ganglia,

satellite cells of these ganglia. They also give rise to the Schwann cells, adrenal medulla, melanocytes, auditory nerve, neurolemma of the peripheral nerves, cells of the pia and arachnoid mater of the occipital region and spinal cord, intraocular muscles, ciliary body, and the carotid bodies. The target tissue that receives the migrating cells may determine development of these structures.

The target tissue may also influence secretion of catecholamines and acetylcholine by structures of neural crest origin. Eventually, neural crest cells spread segmentally along the entire length of the neural tube, contributing to the formation of the structures associated with the future peripheral nervous system. Failure of neural crest cells to migrate along the wall of the developing intestinal tract produces congenital loss of parasympathetic ganglia in the Meissner's and Auerbach's plexuses and signs of Hirschsprung's disease (congenital aganglionic megacolon).

The posterior neuropore closes at the level of the first or second lumbar somite, which marks the future first or second lumbar spinal segment. Pax-3, sonic hedgehog, and openbrain genes, as well as folic acid (vitamin B12) and cholesterol play important role in the closure of this tube. As mentioned earlier, failure of closure of the neuropores produces various forms of dysphasic defects collectively known as rachischisis. The site of closure of the anterior neuropore is represented in the newborn by the lamina terminalis; a vestigial structure located rostral to the hypothalamus.

The neural tube maintains a connection with the amniotic cavity via the anterior and posterior neuropores,

Failure of closure of the anterior neuropore results in cranioschisis, an anomaly, which is associated with lack of development of the brain (anencephaly), and the skull. Anencephaly may be seen in Meckel (Meckel-Gruber) syndrome, a rare autosomal recessive and fatal condition that is characterized by sloping forehead, posterior meningoencephalocele, polycystic kidney, and polydactyly. It may also be seen in brachydactyly syndrome, an autosomal dominant disorder that exhibits abnormal shortening of the fingers and toes.

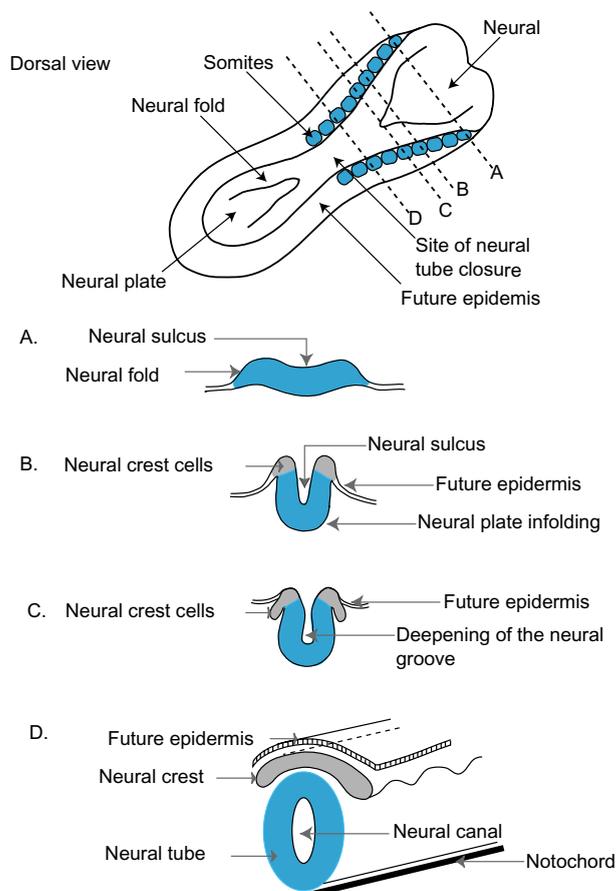


Figure 1.5 Neural crest cells and neural canal. Neural crest cells eventually separate from the newly formed neural tube

which close by the twenty-fifth and twenty-seventh day, respectively.

Neural tube development induces the formation of somites (a paired segmented division of paraxial mesoderm that develops along the length of the early embryo). The underlying paraxial mesoderm also starts segmentation

Anencephaly (exencephaly) is one of the most severe forms of congenital anomalies that occur between days (18-24) of embryonic development. It is relatively common with an incidence of one per one thousand births in the United States. It is most commonly seen in female infants and is usually fatal. The exposed neural tissue undergoes degeneration and becomes converted into a mass of vascular connective tissue, intermixed with masses of degenerated brain and choroid plexus. Due to these defects and the exposure to infectious agents, death usually occurs shortly after delivery. The vault of the skull of the anencephalic fetus fails to form and its base is usually covered with a vascular membrane. Orbits appear shallow and the eyes tend to bulge externally. The fetus exhibits wide shoulders, short trunk, and a neck, which is commonly absent, giving the impression that the head is stemming directly from the body. Anencephaly may also be associated with the absence of vertebral arches, amyelia (absence of the spinal cord) and hydramnios (excess of amniotic fluid) due to the lack of a swallowing reflex. Fifty percent of anencephalic fetuses are aborted spontaneously. Pregnancy with an anencephalic fetus is usually complicated by delayed onset of labor (most delivers after 40 weeks gestational age).

(day 20). Failure of development of the neural tube may impair development of the surrounding somites (e.g. bone, muscles, and skin) and vice versa. Therefore, malformation of the brain and its coverings may also be accompanied by abnormal ossification of the bony skull. Herniation of brain tissue through a gap in the posterior midline of the skull (cranium bifidum) is known as encephalocele.

Incidence of congenital malformations is approximately 3% in neonates, and CNS anomalies make up approximately one third of all congenital malformations. Thus, the incidence of CNS congenital malformation is around 1%. Manifestations of these congenital defects may vary widely from those occurring incidentally without apparent symptoms to those, which are incompatible with life. Malformations may develop as a result of radiation, metabolic disorders, chromosomal abnormalities (e.g. trisomies), chemical exposure (e.g. illicit drugs and alcohol), and infection by viruses (e.g. cytomegalo virus, herpes, rubella), bacteria (e.g. toxoplasma gondii, treponema pallidum), etc.

By the end of the fourth week, and following complete separation from the ectodermal surface, the neural tube is composed of a caudal part which becomes the spinal cord and expanded rostral brain vesicles (Figure 1.8) that forms the brain hemispheres and the brainstem. It is important

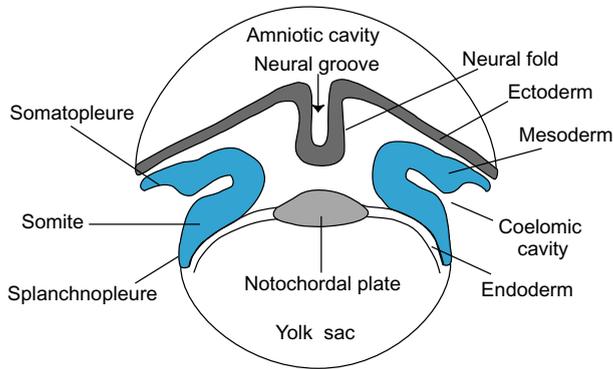


Figure 1.6 Schematic drawing illustrating the neural tube with the dividing sulcus limitans, neural crest cells, and the future epidermis

to note that while the most cephalic portion of the neural tube undergoes drastic differentiation, the caudal portion is still forming. At first, the rostral part of the neural tube consists of three primary brain vesicles; prosencephalon, mesencephalon, and rhombencephalon (Figure 1.9). Rapid growth of the primary brain vesicles during the fifth week results in the formation of telencephalon, diencephalon, mesencephalon, metencephalon, and the myelencephalon as well as associated flexures. The cephalic flexure lies between mesencephalon and rhombencephalon. The pontine flexure, which develops into the transverse rhombencephalic sulcus, separates the metencephalon and the myelencephalon. Furthermore the cervical flexure lies between the rhombencephalon and the spinal cord.

Persistence of the neural canal within the center of the primitive brain vesicles, gives rise to a group of interconnected, fluid-filled cavities that compose the ventricular system. The rhombencephalic vesicle develops into the fourth ventricle; the mesencephalic vesicle becomes the cerebral aqueduct; the diencephalic vesicle converts into the third ventricle, while the telencephalic vesicle develops into the lateral ventricle.

By the middle of the fourth week, the neural tube develops three layers, consisting of the ventricular zone and ependyma (innermost), mantle (intermediate), and marginal (outermost) layers (Figures 1.10 & 1.11). This differentiation commences in the rhombencephalic region and then extends in a cranio-caudal direction. The dendritic processes of the mantle neurons (neuroblasts) form the marginal layer (future white matter). In the spinal cord and the rhombencephalon, the ventral part of the mantle layer represents the sites of the motor neurons that appear earlier than the sensory neurons. The mantle layer

- Meningoencephalocele occurs when the herniated brain tissue is associated with meningeal coverings. Cranial meningocele refers to the protrusion of the meninges into the sac. The bony defect, which results from incomplete closure of the calvaria, may be confined to the occiput or extend to the arch of the atlas.
- Encephalocele is seen in Klippel-Feil deformity, a malformation that is commonly associated with fusion of vertebrae, decrease or sometimes increase in the number of vertebrae, and hydrocephalus (enlargement of the brain and skull subsequent to excess of CSF). The prognosis of this condition depends upon the degree of involvement of the brain tissue and associated meninges. Encephalocele should be corrected surgically unless death is eminent or if it concurrently occurs with dextrocardia, laryngomalacia, renal agenesis, or pulmonary hypoplasia. Encephaloceles, which make up 10-20% of all cranio-spinal malformations, are predominant in female fetuses. The anatomic location of an encephalocele may vary with the geographic regions; in Southeast Asia they are more commonly located in the anterior cranial vault, whereas in Europe and the United States are commonly located in the occiput. The amount of brain tissue within the herniated sac varies and may involve parts of cerebral hemispheres, cerebellum, and even the brainstem. Protrusion of a large amount of brain tissue into the encephalocele may reduce the size of the brain, resulting in microcephaly.
- Microcephaly may also be due to failure of brain growth, producing a smaller brain with less prominent gyri and a considerably smaller skull than usual. Due to the marked difference between the anterior and posterior ends of an encephalocele, blood vessels may be occluded or ruptured leading to infarction and hemorrhage. Sclerosis in the herniated sac, as well as impairment of CSF circulation and resultant hydrocephalus may also occur. The microcephalic brain may be the result of rubella infection or exposure to radiation. At birth the infant with encephalocele is usually neurologically normal or may exhibit increased flexor motor tone. Spells of apnea and bradycardia may occur in severe cases of occipital encephaloceles involving the brainstem. Microcephaly may be associated with holotelencephaly (holoprosencephaly), in which the telencephalon fails to cleave into two cerebral hemispheres and ventricles, but instead forms a single structure with a large single ventricular cavity.

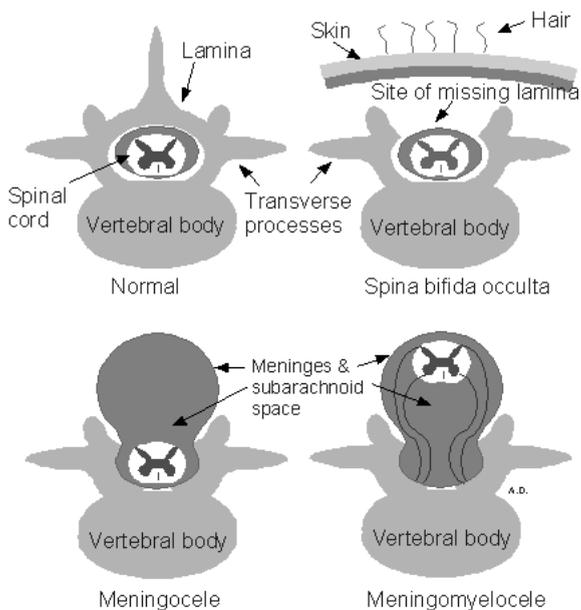


Figure 1.7 Various forms of spina bifida. Note the absence of vertebral lamina and the protrusion of the meninges or meninges and spinal cord tissue

(future gray matter) consists of a narrow dorsal alar plate and a thick basal plate, separated by the sulcus limitans (Figures 1.10 & 1.11). As it forms the lining of the central canal and ventricular system, the ventricular zone (ependyma) separates the cerebrospinal fluid from the blood vessels of the choroid plexus and neurons of the brain and spinal cord. Mitotic division of the neuroepithelial cells in the ependymal layer forms neuroblasts, which migrate laterally to the mantle layer.

Migration of neuroblasts may be guided by the cytoplasmic extensions of the developing neurons, which are anchored, to the pia mater on the outer surface of the central nervous system. Shortening of these processes may also enable some neurons to migrate. This migration is also dependent upon the radial glial cells, which is clearly evident in the development of the cerebral cortex. In the cerebellum, this migration is evident in the course of the developing granule cells parallel to the surface of the neural tube and along the long processes of the Bergmann glial cells. An adhesion protein molecule known as astrotactin may mediate Neuroglial interaction during the migration process. Some investigators propose the possibility of existence of genetically predetermined entities that may guide the migration process.

As the migration from the neuroepithelium, or from one of the secondary proliferative zones continues, the differentiated neuronal and glial cell precursors either are ellipsoidal in shape (apolar) or have a single process (unipolar). Few apolar or unipolar neurons are retained in

the CNS of the vertebrate, but most continue through a bipolar phase. But great majority of neurons develop even more processes and are known as multipolar neurons.

Genetic and molecular aspects of neural development

Expression of certain homeobox genes, at the initial stages of development, may play an important role in the segmentation of the rhombencephalon in which each segment (rhombomeres), a series of eight bilateral protrusions from the rhombencephalic wall may specify the origin of certain cranial nerve. For example neurons of rhombomere-2 (r2) form the trigeminal ganglion, while r4 forms the geniculate ganglion. Domains of gene expression, for example those for the HOX-B genes and the transcription factor Krox20, adjoin rhombomere boundaries. Genes that contain homeoboxes in human are classified into HOX-A, HOX-B, HOX-C, and HOX-D and are identified by numbers 1-13. These genes may regulate the expression of a number of genes that collectively determine the structure of one body region. HOX genes are expressed in the developing rhombomeres and neural crest. Complement of HOX genes is thought to form axial and branchial codes that specifies the locations of somites and neurons along the length of the embryo. An interesting feature of specific homeotic (HOX) genes is their linear order (colinearity) and their transcription in the cephalocaudal and the 3' end to 5' end directions. Since HOX gene expression is affected by teratogenes such as retinoic acid, transformation of rhombomeres may occur. Transformation of trigeminal nerve to facial nerve may occur as a result of induced changes of the rhombomeres 2/3 to a 4/5 disposition. Similar changes may be observed upon the application of retinoic acid to other HOX codes. Ventro-dorsal patterning of the neural tube may be regulated by the Sonic hedgehog (Shh) gene, a product of the notochord and floor plate. Shh gene may act by inhibiting the suppression of the expression of Pax-3 and dorsalin genes. Non-HOX homeobox genes, a separate group of genes are also involved in developmental patterning of the embryo, but lack the cephalocaudal expression seen in the HOX homeobox genes and their role in organogenesis.

PAX genes (Pax-1 to Pax-9), which belong to the segmentation group of genes, regulate the morphology of the developing embryo. They are transcription factors and may be implicated in the specification of different regions of the central nervous system. Pax-3 and Pax-7 are expressed in the alar plate and roof plates as well as the neural crest cells. On the other hand, Pax-5 and Pax-8 are expressed in the intermediate gray columns. Ventricular and basal regions of the neural tube are sites where Pax-6 is expressed. Expression

An abnormally large brain and skull (macrocephaly) is usually a fatal condition associated with syringomyelia, a disease which exhibits cavitation around the central canal of the spinal cord or lower brainstem (syringobulbia), and may occur in one or both cerebral hemispheres, without any detectable change in intracranial pressure. Macrocephaly may also be seen in individuals with Arnold Chiari malformation or trauma.

Spinal dysraphism (defective fusion) refers to a developmental malformation that occurs when the neural tube fails to completely close and the vertebral arches fail to fully form. Non-closure of the posterior neuropore at day 27, a less frequent anomaly, leads to the formation of spina bifida (myeloschisis) or split spine. It may be ascribed to an excess of vitamin A, teratogens such as aminopterin, valproic acid and retinoic acid, high concentration of plasma glucose level, trypan blue, or a deficiency of folate.

This anomaly is classified into spina bifida occulta and spina bifida cystica (Figure 1.7). Amniocentesis (obtaining amniotic fluid sample by surgical trans-abdominal perforation) may be useful in detecting myeloschisis. This procedure is based upon the fact that the levels of alpha-fetoprotein (AFP) at 16-18 weeks of pregnancy in the amniotic fluid are far greater in cases of myeloschisis than in healthy pregnancies.

Spina bifida occulta, the least clinically significant form of spina bifida, is a mesodermal (rather than an ectodermal) abnormality, and is rarely associated with neurological dysfunction. It is a closed neural tube defect which is characterized by defective vertebral laminae at certain levels that expose the meninges through a bony gap, without the actual involvement of the spinal cord or meninges. This malformation is usually asymptomatic, unless a developed lipoma or bony process compresses the spinal cord at the affected area, leading to nocturnal enuresis (neurogenic bladder) and retarded development of the lower limb (asymmetrical or sometimes unilateral shortening of one leg and foot). Compression at L5 motor roots may produce calcaneovalgus, a dorsiflexed, everted, and abducted feet. Equinovarus, a plantar-flexed, inverted, and adducted feet may occur as a result of compression of the S1 motor roots. Back pain, impairment of sensations, and sciatica (pain radiating from the back to the leg) may also accompany this condition. Intrauterine ultrasound had not proven useful in the prenatal diagnosis of this condition. Radiographic plain films of the spine in the neonates are also of no use in detecting spina bifida

occulta since the vertebral laminae at that time are cartilaginous and radiolucent, making it very difficult to reveal defective spinous processes. The most common form of spina bifida occulta is the dermoid sinuses and the lipoma-covered defect in spina bifida.

Dermoid sinuses are deep, epithelial lined tracts, sometimes contain hair, that ascend from an external opening over the spine or scalp. They terminate at the intracranial structures, occasionally communicate with the dura mater, and subarachnoid space, producing meningitis. Dermoid sinuses are most common in the lumbar or sacral region (65%) and less in the occipital region 30%. These sinuses may go unnoticed and is only detected after repeated bouts of meningitis. Occasionally, brain abscesses occur as a consequence of repeated infections and the patient may present with hypertension, seizures and fever. Lipoma-covered defect, another form of spina bifida occulta, occurs in the sacral or lower lumbar regions, and is very rarely associated with neurological abnormalities.

Spina bifida cystica, (spina bifida manifesta, or spina bifida aperta), having an incidence of one per one thousand births, is characterized by a sac-like protrusion of either meninges (meningocele), or a combination of meninges and spinal cord/nerve roots (meningomyelocele).

Meningocele (10% of cases of spina bifida cystica) is not associated with motor or sensory deficits, bowel or bladder dysfunctions. Meningocele is covered by thin easily ruptured meninges and occasionally by skin, and commonly occurs in the lumbosacral portion of the vertebral column. It is frequently associated with myelodysplasia (spinal cord defects), occurring in the majority of cases of spina bifida cystica. A meningomyelocele (90% of cases of spina bifida cystica) is much more common than meningocele and may contain the cauda equina, if it occurs in the lumbosacral region, or the spinal cord when the anomaly involves the thoracic or cervical regions.

A lipomyelomeningocele appears when fatty tissue and skin cover the herniated sac. In this case, neurogenic bladder is almost a universal presentation. Meningomyelocele may be accompanied by hydrocephalus, talipes equinovarus (clubfoot, which is plantar flexed, inverted and adducted), sensory and motor deficits, paraplegia, as well as bowel dysfunction. A high percentage (90%) of infants with the meningomyelocele develops hydrocephalus as a part of Arnold-Chiari Syndrome.

Arnold-Chiari Syndrome is thought to result from fixation of the developing spinal cord in the sac of a meningocele, creating an undue downward strain on the spinal cord, brainstem. This eventually causes displacement of the cerebellum and hindbrain through the foramen magnum into the cervical part of the vertebral canal. Hydrocephalus may be seen in this syndrome as a result of closure of foramen of Magendi and foramina of Luschka of the fourth ventricle. Blockage of absorption of the cerebrospinal fluid into the dural sinuses, and impairment of the circulation of the fluid around the base and lateral surface of the brain may also contribute to hydrocephalus. Herniation of the cerebellar vermis into the cervical part of the vertebral column may occur as a result of early fusion of its hemispheres, followed by fusion of the neural folds higher in the midbrain. The latter may be associated stenosis of the cerebral aqueduct (a canal that runs through the mesencephalon). Additionally, an anomalous small posterior cranial fossa may not be of sufficient size to accommodate the growing cerebellum, leading to displacement and herniation.

Arnold-Chiari syndrome is divided into four types (I through IV). Type I is seen in young adults as a result of downward displacement of the cerebellar tonsils through the foramen magnum into the cervical part of the vertebral column. It manifests hydrocephalus, dysphagia, dysphonia, syringomyelia, and bilateral cerebellar dysfunctions.

Type II has its onset in neonates and is associated with meningocele and more displacement of the fourth ventricle into the vertebral column. Due to the

low level of the spinal cord, the cervical spinal nerve roots assume an ascending course in order to reach their corresponding intervertebral foramina. Patients with this type of anomaly exhibit hydrocephalus, syringomyelia, dysphagia, stridor, and dysphonia. Type III presents a cyst-like fourth ventricle in the posterior cranial fossa, whereas type IV is characterized by shrinkage of the cerebellum due to hypoplasia. This kind of malformation may exhibit hydrocephalus, dysphagia, dysphonia, syringomyelia, and cerebellar dysfunctions. Telencephalic developmental anomaly may lead to the absence of gyri referred to as lissencephaly or abnormally thick and wide gyri known as pachygyria.

Approximately half of the individuals with spina bifida cystica may also exhibit a partial or complete division of the spinal cord into two symmetrical parts (diastematomyelia). A bony projection, cartilage, or fibrous tissue often separates these two parts. Each part may have its own dural, arachnoidal, and pial coverings, and arterial supply. The part of the spinal cord, cranial or caudal to the site of this anomaly, remains united. Although the transverse diameter of the vertebral bodies at the affected site may show perceptible widening, the anteroposterior dimension is often narrowed. This anomaly is compatible with life and may not pose any serious neurological complications. Radiographic imaging techniques, myelography, and visible cutaneous manifestations may make diagnosis of this condition possible. Patients with scoliosis may be examined for this type of malformation via myelography.

of Pax-1 in the ventromedial region of the somite are induced by several factors such as Shh, notochord and floor plate, whereas expression of Pax-3 and Pax-7 within the dorsolateral region of the somites is induced by the dorsal ectoderm. Pax genes may play important roles in certain genetic diseases, such as Waardenburg's syndrome and aniridia. Mutated PAX-3 and PAX-6 may be involved in Waardenburg's syndrome and aniridia, respectively.

Extensions of the developing neuronal processes may be governed by many factors that include the development of growth cones, and presence of nerve cell adhesion molecules (N-CAM), neuroglial adhesion molecules (NgCAM), transiently exposed axonal glycoprotein (TAG-1), actin, extracellular matrix adhesion molecules (E-CAM), and guide-post cells. Growth cones are able to descry the chemical signals (actin and actin-binding proteins) and test the new environment in all directions via filopodia and lamellipodia. Since polymerization of actin

control to an extent the movement of the growth cones, any substances which limit this process such as fungal toxin cytochalasin B may also hinder their further growth. Additionally, calcium, interaction with other intracellular second messenger system, and phosphorylation by protein kinase may indirectly affect the direction of neuritic growth by acting upon the actin-binding proteins. Movements of growth cones may also be shaped by N-CAM, molecule that also enhances neuritic fasciculation, laminin, fibronectin and tenascin (cytotactin) which are members of the extracellular matrix adhesion molecules that act via receptor integrins. NgCAM, integrin, and N-cadherin (calcium-dependent molecule) also share important role in the process of axonal development.

Synaptic connections among developing neurons occur early in development and undergo constant correction and refinement. Non-functional and inappropriate connections may be inhibited by repulsive actions as well

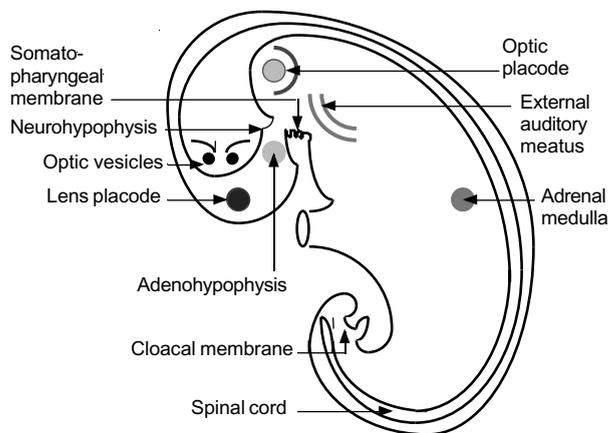


Figure 1.8 Neural tube showing its expanded rostral end with optic vesicles. Observe the location of the adrenal medulla, a derivative of the neural crest cells

as by the mechanical barriers of the surrounding tissue. The time of birth may also determine the ultimate locations and eventually the connections of the neurons.

The initial overproduction of neurons may be controlled by subsequent cell death, which is determined by the available trophic substances in the immediate location. Selectivity of the neurotrophic substances in supporting certain neuronal population may also determine the fate of certain neurons. Extracellular, intracellular, and transmembranous tyrosine kinase domain remain essential in mediating the effects of neurotrophins. Hormones such as testosterone may also govern the extent of development of certain areas of the central nervous system.

Spinal cord (myelencephalon)

The spinal cord develops from the caudal portion of the developing neural tube, extending the entire length of the vertebral column (Figures 1.8 & 1.9). During this stage of development the spinal nerves also appear. After the third fetal month the vertebral column outgrows the spinal cord and as the vertebrae grow caudally, the dorsal and ventral roots, anchored within their appropriate foramina, pursue a longer course within the vertebral canal. This accounts for the formation of the cauda equina and the final position of the dorsal root ganglia and spinal nerves. By birth, the spinal cord terminates at the level of the third lumbar vertebra. Much of the neural canal obliterates, and the remaining part forms the central canal. The alar plate forms the dorsal horn, which represents the sensory area, while the basal plate, representing the motor area, becomes the future ventral horn of the adult spinal cord. Quite early some of the neuroblasts of the basal plates begin to differentiate into the alpha motor neurons that extend to

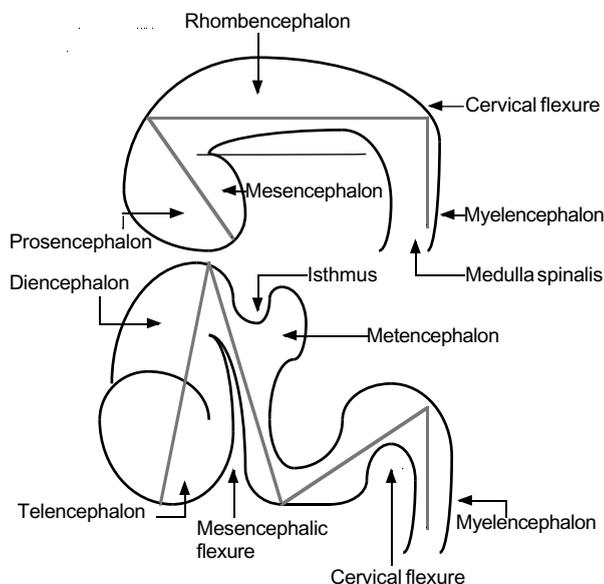


Figure 1.9 Initial differentiation of the rostral neural tube into the primary and secondary brain vesicles. Flexures that separate certain brain vesicles are also illustrated

form the ventral roots of the spinal nerves. As the basal plates enlarge, they protrude ventrolaterally on each side of the floor plate. They do not fuse in the midline, thus producing the midline ventral median fissure. The roof plate obliterates, and the neural canal reduces in size. The lower end of the spinal cord and the intermediate part of the neural (primitive central) canal, between the level of the second coccygeal and third lumbar vertebra, undergoes necrobiosis (selective death), and degenerate and becomes adherent to the covering pia as the filum terminale. The site of degeneration may, occasionally; gives rise to congenital cysts.

Transformation of the dorsal portion of the neural canal, the ependymal cells and their long basal processes gives rise to the dorsomedian septum. Obliteration of the floor plate and extension of axons of some neuroblasts across the midline, result in the formation of the ventral white commissure. Neuroblasts of the neural tube that develop toward the marginal layer of the cord do so primarily by following a ventro-lateral direction. The fasciculus proprius develop from the marginal layer into all three funiculi of the spinal white matter. While the transformation of the neural tube into the spinal cord is progressing, a large mass of axons is added to the cord, which are of neural crest origin.

The cells of the dorsal root ganglia are derived from the neural crest and the neural tube. Their central processes grow into the spinal cord and contribute in great quantity to the white matter of the cord, forming the dorsal

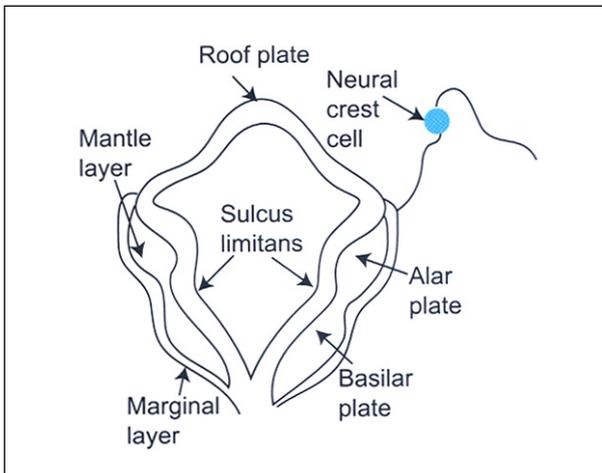


Figure 1.10 A section of the neural tube showing the sulcus limitans, alar and basal plates, the roof and floor plates

columns and the dorsolateral fasciculi. General somatic afferents (generated at or near body surface) and general visceral afferents (generated in or on mucous membranes of visceral structures) lie dorsal to the sulcus limitans and are represented by the dorsal gray and white columns. Conversely, general visceral efferents (autonomic-parasympathetic) and general somatic efferent cell columns (innervate skeletal muscles) lie ventral to sulcus limitans (Figures 1.11 & 1.12).

It is worth to note that the fibers of the corticospinal tract begin to develop in the ninth week of fetal life and by the twenty-ninth week they achieve their final limit. Those fibers that are destined to the cervical and upper first thoracic segment are in advance of the fibers that reach the lumbosacral segments, which, in turn, are in advance of the fibers that project to the face.

Myelencephalon

The embryonic myelencephalon forms the caudal part of the rhombencephalon, consisting of alar and basal plates (Figure 1.13). Due to widening of the roof plate, the alar and basal plates eventually assume a more lateral/medial, rather than dorsal/ventral position. Both the alar and basal plates contribute to the reticular formation, whereas the medullary pyramids remain of telencephalic origin.

The alar plate constitutes the sensory part that contributes to the formation of a variety of nuclei (Figure 1.14) which are listed below:

- Vestibular and auditory nuclei contain neurons that subserve special somatic afferents and transmit senses of balance and hearing).
- Spinal trigeminal, gracilis and cuneatus nuclei receive general somatic afferents generated at or near the body surface.

Waardenburg's syndrome is an autosomal dominant condition associated with Mutated PAX-3. It presents with congenital deafness, wide bridge nose, disorders of pigmentation (white eyelashes, white forelock, and leukoderma), and dystopic canthorum (lateral displacement of the canthi). In aniridia, a rare bilateral hereditary anomaly associated with mutated PAX-6, absence or abnormal development of the retina and iris remains prominent feature.

- Solitary nucleus contains special and general visceral neurons that subserve taste and visceral sensations, respectively.
- Inferior olivary nuclear complex, a cerebellar relay nucleus.

Similarly, the basal plate (Figure 1.14) gives rise to a group of neurons as shown below:

- Hypoglossal nucleus provides general somatic efferents to the lingual muscles.
- Nucleus ambiguus supplies special visceral efferent fibers to certain muscles of branchial arch origin such as laryngeal, pharyngeal, and soft palate muscles.
- The dorsal motor nucleus of vagus and the inferior salivatory nucleus (GVE) (provide general visceral efferents, which carry parasympathetic fibers).
- The roof plate persists to form the ependyma of the tela choroidea, inferior medullary velum, and the caudal part of the roof of the fourth ventricle. Axons of the marginal layer are derived from neuronal extensions of the medial lemniscus and spinothalamic tract. Attachment of the choroid plexus to the roof of the fourth ventricle is secured by the tela choroidea, which is formed by the ependymal layer of the myelencephalon covered by pia mater; they form the tela choroidea. During the fourth or fifth months of development, the paired foramina Luschka, at lateral recesses of the fourth ventricle, and the single median foramen of Magendie make their appearance.

Metencephalon (Figures 1.15 and 1.16)

This differentiates into the pons and cerebellum.

Pons

The basal plate gives rise to primarily efferent nuclei including the abducens, facial, trigeminal, and the superior salivatory nuclei (Figure 1.16).

- Abducens nucleus provides general somatic efferents supplying the lateral rectus,
- Facial and trigeminal nuclei give rise to the special visceral efferents that innervate the facial and masticatory

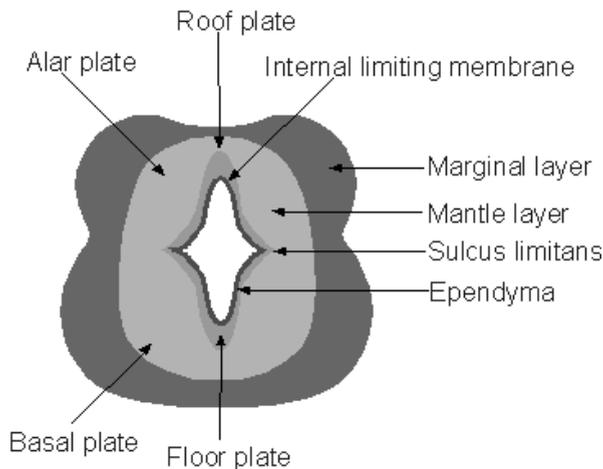


Figure 1.11 Cross section of the caudal neural tube (future spinal cord). The basal plate forms the ventral horn and the associated motor neurons, whereas the alar plate forms the dorsal horn and sensory neurons of the adult spinal cord

muscles, respectively. These skeletal muscles are of branchial origin.

- Superior salivatory nucleus provides general visceral efferents (parasympathetic fibers) to regulate the glandular secretion of the lacrimal, sublingual and submandibular glands.

Derivatives of the alar plate include somatic and visceral sensory nuclei:

- Vestibular and auditory nuclei transmit impulses of balance and hearing (special somatic afferents).
- Principal sensory nucleus conveys cutaneous impulses from the head (general somatic afferents).
- Solitary nucleus receives both general visceral and special visceral afferents.
- Pontine nuclei are cerebellar relay nuclei.

Cerebellum

The cerebellum is derived from the rhombic lip of the alar plate (Figure 1.17). During the fourth month of development, the posterolateral fissure is the first to appear. The cerebellar cortex develops from the migrating neuroblasts of the external granular layer, which is formed by the germinal cells of the rhombic lip that migrate over the surface of the cortical lip. Both the alar and basal plates contribute to the reticular formation. At about the fifth week of embryonic development, the lateral parts of the alar plates on both sides of the roof of metencephalon join to form the rhombic lips, which eventually become the cerebellar vermis and hemispheres. The remaining part of the alar plate forms the superior and inferior medullary veli. Some neuroblasts of the mantle layer migrate outward into the marginal layer (towards the surface) to mature and become cerebellar cortical neurons. This migration is guided by the processes of Bergmann glial cells. The group

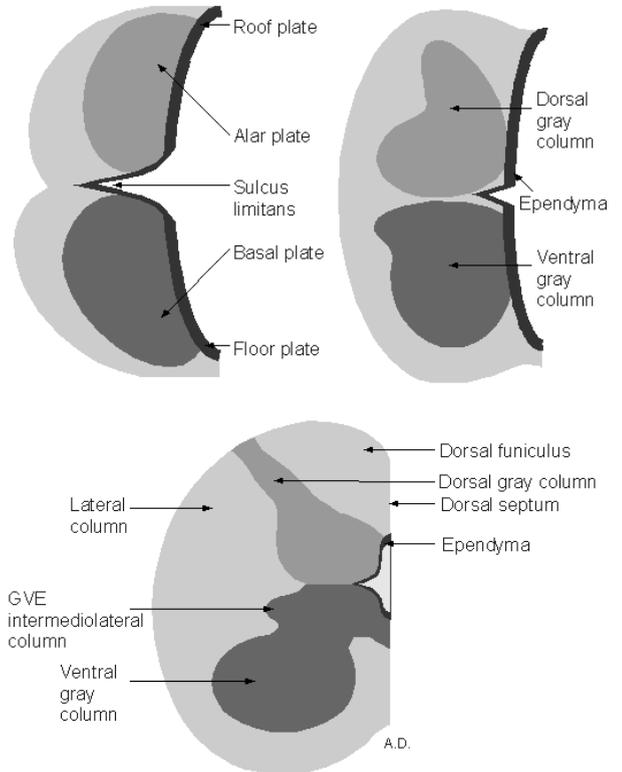


Figure 1.12 Development of the spinal cord. Note the formation of the somatic and autonomic neuronal columns

of undifferentiated neuroepithelial cells that move around the rhombic lip region to form the external granular, a superficial layer beneath the pia mater, eventually differentiate into neuroblasts that move inward and mature into the adult granular layer, stellate and basket cells. The young neurons of the superficial part of the mantle layer form the Purkinje and Golgi type II cells. The periventricular neuroblasts that remain at the site of the original mantle layer become the cells of the cerebellar (fastigial, globose and emboliform, and dentate) nuclei.

Mesencephalon

The mesencephalon, morphologically the most primitive of the brain vesicles, contains both basal and alar plates (Figure 1.18). The basal plate of the mesencephalon differentiates into the trochlear and oculomotor nuclei, providing general somatic efferents (GSE) to most extraocular muscles, and supplying general visceral efferents (GVE) to the constrictor muscle of the pupil and the ciliary muscle via the Edinger-Westphal nucleus.

Differentiation of the alar plate results in the formation of the superior and inferior colliculi, whereas the corticofugal fibers form the crus cerebri. The substantia

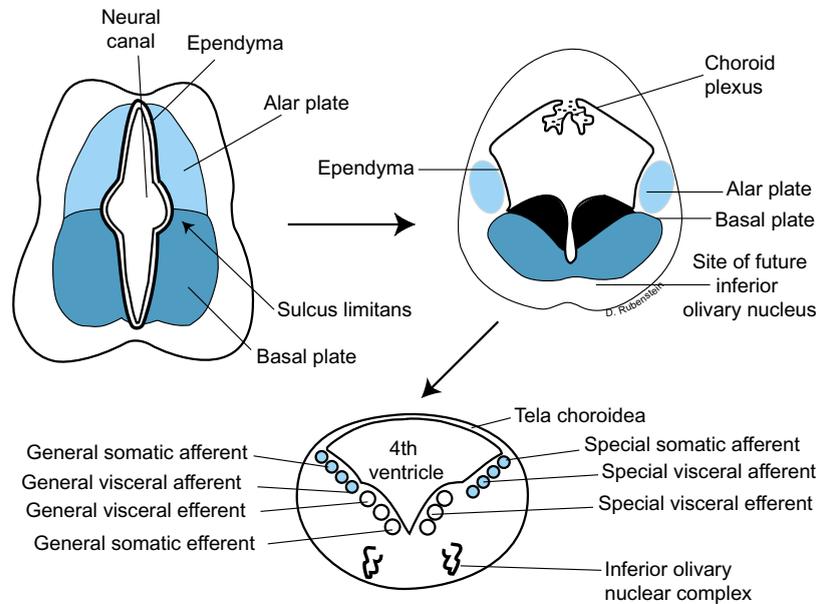


Figure 1.13 Cross section of the developing medulla. The alar and basal plates are arranged in a mediolateral direction, signifying the locations of the motor and sensory neurons

nigra, red nucleus, and the reticular formation are probably of mixed origin from neuroblasts of both basal and alar plates. Neural crest cells of the midbrain gives origin to the mesencephalic nucleus. Development of the isthmus (mesencephalo-metencephalic junction) is controlled by fibroblast growth factor 8.

Diencephalon

The diencephalon consists of roof and alar plates but lacks the basal and floor plates. Differentiation of the alar plate here results in the formation of the thalamus, hypothalamus, neurohypophysis, and the infundibulum. A diverticulum of the stomodeum which is derived from the Rathke's pouch. Derivatives of the roof plate include the epiphysis cerebri, habenular nuclei and the posterior commissure. The ependyma and vascular mesenchyme of the roof plate give origin to the choroid plexus of the third ventricle.

Telencephalon (Figures 1.9 & 1.19)

The two lateral outpocketings, which arise from the cephalic end of the prosencephalon form the telencephalon and its may constituents the cerebral hemispheres. These lateral diverticula evaginate from the most rostral end of the neural tube near the primitive interventricular foramen of Monro, and are connected via the midline region known as the telencephalon impar. These diverticula are rostrally in continuity around the foramen Monro, but caudally remain continuous with the

lateral walls of the diencephalon. Enormous positive pressure exerted by the accumulated fluid within the neural canal results in the rapid expansion of the brain volume in the early embryo (3-5 days of development). This is aided by the constriction of the neural tube at the base of the brain via the surrounding tissues. The foramen Monro forms the rostral part of the third ventricle. At the end of the third month the superolateral surface of the cerebral hemisphere shows a slight depression anterior and superior to the temporal lobe. This occurs due to the more modest expansion of this site relative to the adjoining cortical surface. This depression, the lateral cerebral fossa, gradually overlapped by the expanding cortical area converts into the lateral cerebral sulcus (fissure). The floor of this sulcus becomes the insular cortex. Apart from the lateral cerebral and hippocampal sulci the cerebral hemispheres remain smooth until early in the fourth month when the parieto-occipital and calcarine sulci appear. During later stages of development (5th month of prenatal life) the cingulate sulcus and later (sixth month) the sulci appear on the superolateral and inferior surfaces of the brain. Virtually all sulci become recognizable by the end of the eighth month of development. The ventricular and subventricular parts of the telencephalic lateral diverticula form the ependyma, the cortical neurons, and the glial cells. The intermediate cell layer of the telencephalic diverticula differentiates into the white matter, while the cortical zone differentiates into the various layers of the isocortex.

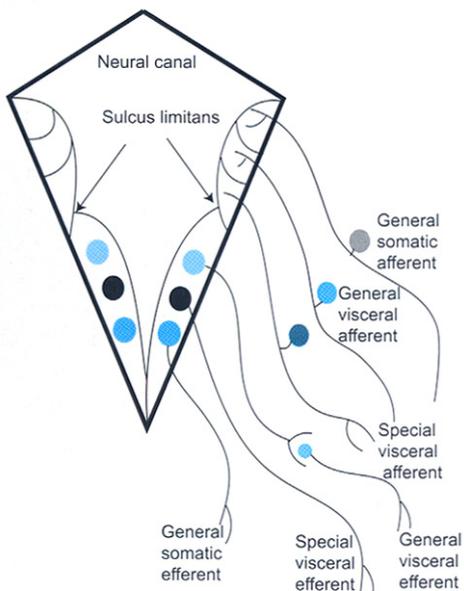


Figure 1.14 Schematic diagram of the somatic and visceral neurons associated with the developing medulla

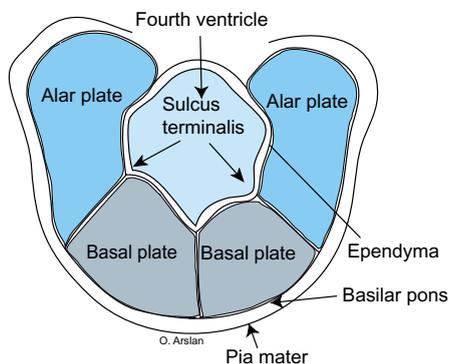


Figure 1.15 Developing pons and associated fourth ventricle

At the beginning, the wall of the cerebral hemisphere consists of three basic layers that include the inner neuroepithelial, mantle, and marginal layers. Each neuroepithelial cell has a single nucleus and double cytoplasmic extensions. The deep extension extends to the internal limiting laminae, whereas the superficial extension stretches to the external limiting membrane which itself is covered by the pia mater. Attachment of the superficial and deep extensions is maintained via end-feet that contribute also to these membranes or laminae. As the nuclei undergo division, the cytoplasmic processes remain solid. One of the nuclei remains near the ventricular surface and the other migrates within the cytoplasmic extensions to the pial surface. As it reaches the pial matter the cytoplasmic process separates from the original cell and begins to surround the newly formed nucleus. Neuroblasts that maintain position near the pia matter are unipolar with one neuronal extension, which eventually divides into finer processes or dendrites. As the thickness of the cortex increases subsequent to increases in the number of

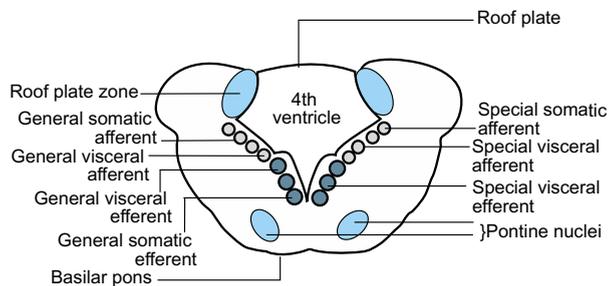


Figure 1.16 A more elaborate diagram of the structures in Figure 1.15. Note the afferent and efferent neurons associated with the basal and alar plates

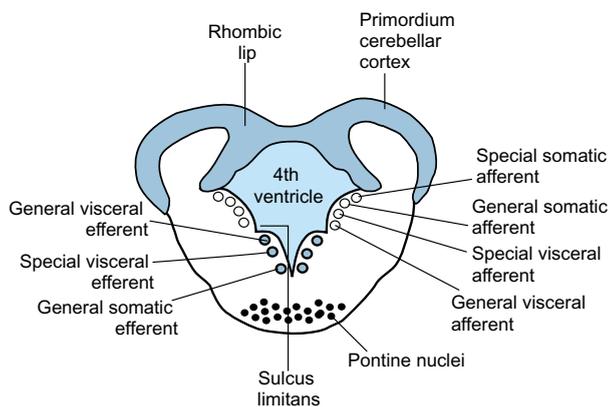


Figure 1.17 Transverse section of the metencephalon. Position of the rhombic lips is also illustrated

neuroblasts, the unipolar neuroblasts become deeply located, at the same time these neuroblasts begin to form axons that stretches to the ventricular surface and dendrites, extending to the subpial layer. Glioblasts, which differentiate into the astrocytes and oligodendrocytes, are derived from the neuroepithelial cells that line the neural canal when the production of the neuroblasts ceases.

Most cortical neurons follow an “inside-out” pattern of migration from the ventricular and subventricular zones to the cortical plate, allowing the neurons that form at a later stage of development to migrate and maintain an outward position to the neurons that develop earlier. Thus, the recently formed neurons occupy the basal layers of the cortex while the older neurons maintain locations in the superficial layers. In the initial stage of migration the neuroblasts are allowed to proceed to a site between the marginal layer and the white matter. The nuclei of the neuroepithelial cells lie near the ventricle while the cytoplasm elongates to form deep and superficial processes. Some neuroblasts traverse the initial group of migratory neuroblasts to assume a position in the middle third of the mature cortex, whereas

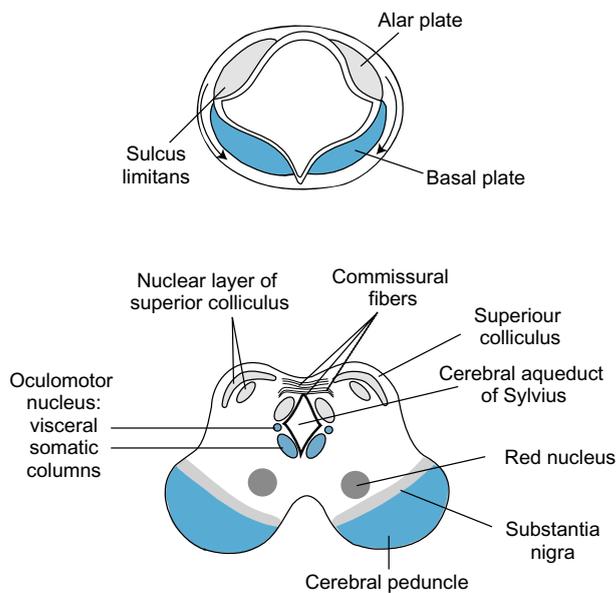


Figure 1.18 The developmental stages of the mesencephalon and derivatives of the alar, basal, roof plates

others may pursue different courses among the previous group of neuroblasts to reach more superficial positions. This pattern of migration is in line with the radial columnar organization of the cerebral cortex.

The invagination formed by the attachment of the cerebral diverticula to the roof of the diencephalon leads to the formation of the choroid fissure. The latter fissure allows a narrow strip of thin ependymal roof plate, with the accompanying pial covering (tela choroidea) to invaginate into the lateral ventricle. As the temporal lobe develops, the choroid fissure, with the invaginating tela choroidea and the choroid plexus, continues to increase in length along the medial wall of the developing temporal lobe. Hence, in the adult, the choroid plexus is a continuous structure found in the third ventricle, interventricular foramen, and in the body, trigone, and inferior horns of the lateral ventricles. In fetal life the choroid plexus occupies most of the lateral ventricle, and then gradually decreases in size.

Formation of the anterior commissure (the first commissure to appear during development) is followed by the development of the hippocampal commissure and the corpus callosum (around the fourth month). These commissures are formed by axons that extend from one hemisphere to the other using the embryonic lamina

Table 1.2 Derivatives of the primary brain vesicles

<i>Primary brain vesicles</i>	<i>Secondary brain vesicles</i>	<i>Neural tube (wall)</i>	<i>Neural canal (ventricular system)</i>
Prosencephalon	Telencephalon	Cerebral hemispheres Rostral part of hypothalamus Rostral part of 3rd ventricle Archicortex, paleocortex, and neocortex	Lateral ventricles
	Diencephalon	Thalamus, metathalamus Subthalamus, epithalamus & part of hypothalamus	Caudal part of the third ventricle
Mesencephalon	Mesencephalon (midbrain)	Colliculi, tegmentum, cerebral peduncles, cerebral aqueduct	Cerebral aqueduct
Rhombencephalon	Isthmus rhombencephali	Superior medullary velum & Superior cerebellar peduncles	Rostral part of fourth ventricle
	Metencephalon	Cerebellum, pons & middle cerebellar peduncles	Middle part of the fourth ventricle
	Myelencephalon	Medulla oblongata	Rostral part of the central canal, caudal part of the fourth ventricle & inferior cerebellar peduncle
Medulla spinalis	Spinal cord	Spinal cord	Central canal

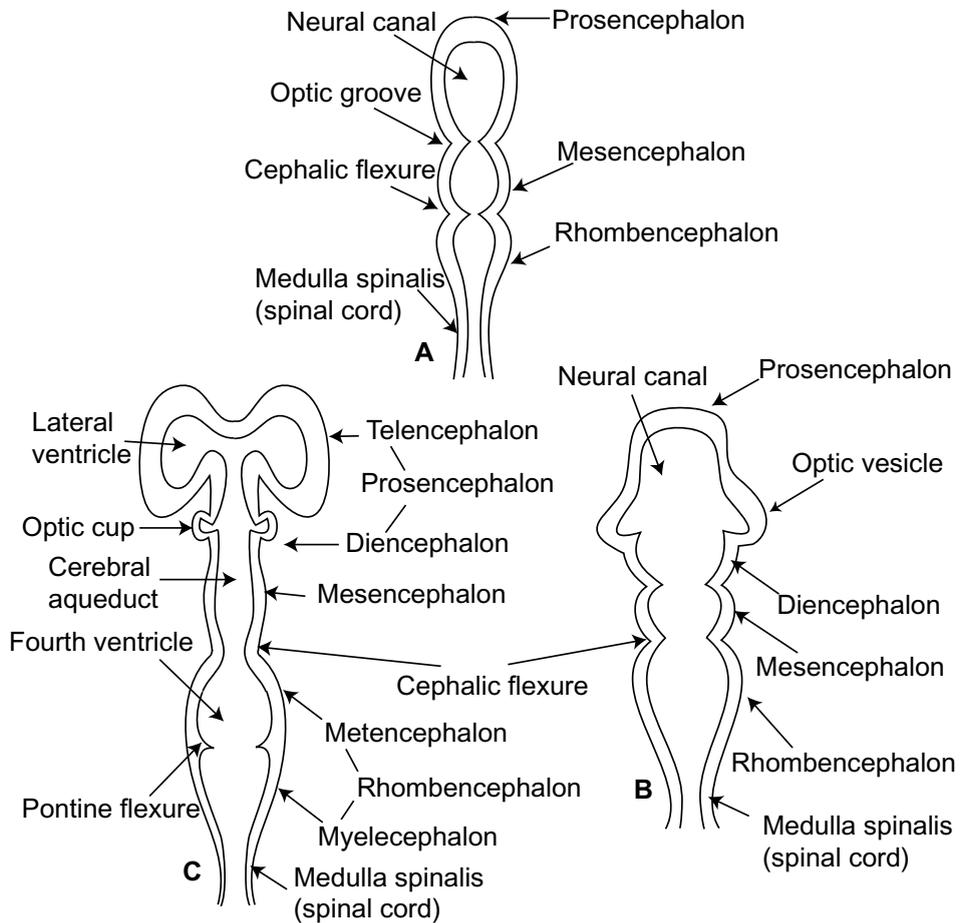


Figure 1.19 Formation of primary and secondary brain vesicles and associated parts of the ventricular system. Letters A, B, and C mark stages of differentiation

terminalis as a bridge. Initially, the hippocampus appears as a ridge derived from the medial cortical wall.

The basal nuclei are derived from the mantle layer of the telencephalon. Specifically, the caudate and putamen derive from the ganglionic eminences in the ventrolateral part of the telencephalic ventricle, while the pallidum originates from lateral and medial hypothalamic analogs. The corpus striatum assumes a striated appearance following the crossing of fibers that connect the telencephalic vesicles to the diencephalon and brainstem.

The nervous system receives, integrates and transmits sensory stimuli. It generates motor activity and coordinate movements. In addition, the nervous system also regulates our emotion and consciousness. In summary, it controls all the activities which preserve the individual and species. These functions are accomplished at cellular levels in the neurons that are enhanced via supportive glial cells. Neurons maintain certain common structural and morphological characteristics that enhance their activities and correlate closely with their functions. Following an injury, these structures may undergo changes or assume different positions in the neurons. Myelin, the covering of certain axons, plays an important role in nerve conduction and exhibits degenerative changes in particular diseases. Glial cells form the skeleton of the nervous system, display several forms and participate in a variety of supportive functions that collectively maintain the optimal environment for neuronal activity.

Neuroglia

Macroglia

Microglia

Neurons

Neuronal processes

Neuroglia

Neuroglia are non-excitable supporting cells; outnumber neurons at a ratio of 2:1, forming the skeleton of the central nervous system. They are of both ectodermal and mesodermal origin and are commonly associated with tumors of the central nervous system. They have only one type of cell process, do not form synapses, and retain the ability to undergo mitosis. Glial cells provide the optimal milieu for neuronal function by balancing ionic concentration within the extracellular space, providing nutrients, discarding metabolites and cellular debris, and sharpening neuronal signals (preventing cross-talk or ephapsis) by forming the protective myelin sheath. The glial cells mediate the extent of impulse flow, activity of neurons, and frequency of excitation. Thus changes in the glial cell-membrane potentials may occur as a result of the fluctuation in the potassium ion concentration which in turn is affected by level of the generated impulses. They also secrete growth-promoting molecules such as the nerve growth factor, glial neurite-promoting factor (GDN) which is a protease inhibitor, and tenascin. Neuronal sprouting may be facilitated by GDN (glial-derived nexin) which prevent the digestion of the extracellular matrix molecules by inhibiting proteases secreted by growth cones. Neuroglia also contribute to the formation of the blood-brain barrier, which selectively permits substances and molecules to enter the central nervous system. They also allow developing neuroblasts to move to their final destinations. Presence of molecules such as fibronectin, laminin, and cellular adhesion molecules may account for the mechanism by which neurons migrate along processes of certain glial cells and not others. Neuroglial cells are classified as macroglial and microglial cells. Macroglial cells are further subclassified into astrocytes, oligodendrocytes of the central nervous system, and Schwann cells of the peripheral nervous system.

Macroglia

Macroglia are classified into astrocytes, oligodendrocytes, and ependymal cells.

Astrocytes (star cells) are the largest, the most numerous, and show the most branching among all the glial cells (Figures 2.1, 2.2 & 2.5). They are present in both gray and white matter and possess processes which branch repeatedly in an irregular fashion and assume star-like configurations. Astrocytes establish contacts with the non-synaptic parts of the neurons and form perivascular end feet that extend to the blood capillaries. They retain the capacity to multiply. Astrocytes retrieve glutamate and g-aminobutyric acid after their release from the nerve endings. They invest most of the synaptic neurons and assume phagocytic function. They also maintain the

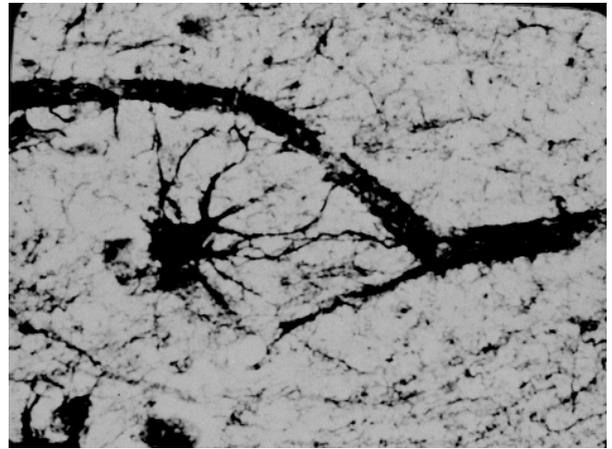


Figure 2.1 Photomicrograph of the astrocytes showing their branches and perivascular end-feet.

normal concentration of potassium, which is essential for neuronal activity by removing it and then facilitating its return to the blood. Astrocytes are also considered as the principal glycogen store site in the central nervous system and glycogen breakdown and release of glucose is accomplished by the action of the norepinephrine upon b receptor molecules in the astrocytes. During embryonic development precursors of astrocytes (radial glial cells) guide the migration of the developing neurons. The superficial processes of astrocytes extend to the surfaces of the brain and spinal cord to form the external glial limiting membrane and expansions that attach to the pia mater (pia-glial layer). They play a major role in providing a form of scaffolding, or structural support, on which the neurons and their processes are assembled. Astrocytic processes ensheath the initial segments of axons and the bare segments at node of Ranvier.

Astrocytes are classified into protoplasmic and fibrous astrocytes. Protoplasmic astrocytes are located primarily in the gray matter and have shorter processes; while fibrous astrocytes have longer processes and are located primarily in the white matter. Fibrous astrocytes are the scar-forming cells that bridge the gap between severed ends of axons in pathological conditions involving the central nervous system. Astrocytes also play a role in the formation of the blood-brain barrier.

Modified astrocytes are classified into Müller cells and Bergmann Glial cells. Müller cells of the retina are

Astrocytoma is the most common form of brain tumor (glioma). This tumor may cause increase in intracranial pressure, headache, nausea, and vomiting. Supratentorial glioma may produce a shift of the pineal gland, third ventricle, and anterior cerebral arteries, whereas infratentorial tumors are most likely to hydrocephalus.

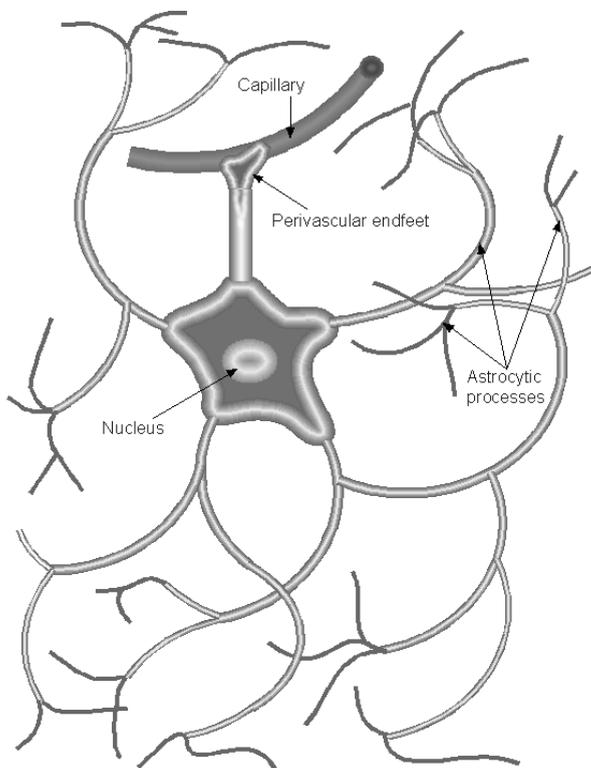


Figure 2.2 Cellular characteristics of the astrocytes and perivascular end-feet

elongated cell column that exhibit an expanded foot processes forming the inner limiting membrane of the retina. Bergmann glial cells of the cerebellum lie at the Purkinje layer, sending several processes with short side branches that ascend and envelop the Purkinje cell dendrites.

Oligodendrocytes, the myelin-forming glial cells in the white and gray matters, are characterized by relatively few branched processes bearing close resemblance to stellate neurons (Figures 2.3, 2.4 & 2.5). Oligodendrocytes lie within the white matter, especially of fetal brain and in myelin sheath bundles, are aligned in rows between nerve fibers, and are known as interfascicular oligodendrocytes (Figure 2.3). They are numerous in the fetus and newborn, but rapidly decrease in number (absolutely or relatively) as myelination progresses. Oligodendrocytes that lie closely opposed to neuronal cell bodies in the gray matter are called perineuronal (satellite) oligodendrocytes (Figure 2.4). A few oligodendrocytes that occupy locations near blood capillaries are known as perivascular oligodendrocytes.

Schwann cells are the supporting cells in the peripheral nervous system which are derived from the neural crest cells, forming the capsular (satellite) cells of the dorsal root and autonomic ganglia.

The ependymal cells are arranged as a single layer of epithelial-like cells with variable heights in different

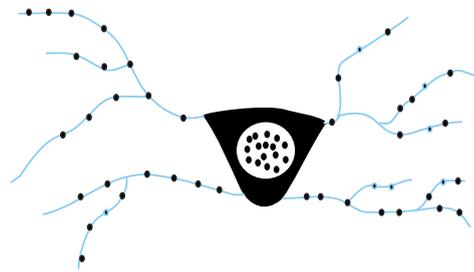


Figure 2.3 This is a simplified diagram of the interfascicular oligodendrocytes with its scanty branches.

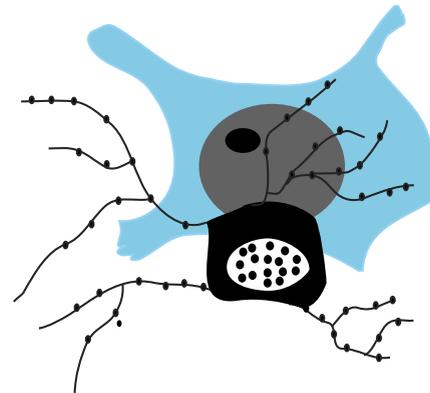


Figure 2.4 This drawing shows perineuronal oligodendrocyte adjacent a neuron.

regions that form the lining of the ventricular system and central canal of the spinal cord. These cells are the remnants of the embryonic neuroepithelium and maintain their original position after the neuroblasts and glioblasts have migrated into the mantle layer. They vary from columnar to cuboidal to squamous, depending upon their location. The variability of their shape often makes their identification difficult. They have processes, which penetrate the brain and extend into the pia mater. Embryonic ependymal cells are ciliated, and some adult cells may retain cilia permanently, producing movements of the cerebrospinal fluid. Modified ependymal cells cover the choroid plexus and play a significant role in the secretion of cerebrospinal fluid. Ependymal cells also have numerous microvilli, exhibiting high oxidative activity. Both cellular structure and chemical reactions reflect the secretory and absorptive functions of these cells. The apices of these ependymal cells are joined by junctional complexes, which are not occluding junctions. Since substances can readily pass between these cells, the brain/CSF interface is not a barrier. The deep basal surface of some adult ependymal cells retains processes that extend for a variable distance from the cell body. Many of the shorter processes are intertwined with a heavy concentration of astrocytic processes forming a subependymal (internal limiting) glial membrane. Specialized ependymal cells may be attenuated and form

the lining of the circumventricular organs (medial eminence, subfornical organ, subcommissural organ, and the organ vasculosum of the lamina terminalis).

Ependymal cells with long basal processes that project into the perivascular space that surrounds the underlying capillaries are known as Tanycytes. Since, these capillaries are fenestrated, they do not form a blood-brain barrier, allowing substances to pass from the blood and nervous tissue to the CSF via these specialized ependymal cells (tanycytes). These cells are found around the floor of the third ventricle, and in the lining of the median eminence of the hypothalamus, which suggest a possible role of these cells in influencing the secretions of the adenohypophysis.

Microglia

The microglia (Figure 2.6) are small cells whose primary function is phagocytosis of cellular debris associated with pathological processes in the central nervous system. They probably possess ion-channel-linked P2 purinoceptors, which may be activated by 5'-adenosine triphosphate in response to injury. Microglia are considered to be a derivative of the angioblastic mesenchyme. Although the consensus dictates that only mature monocytes enter the postnatal brain, the view that monocytes may differentiate into microglial cells has received a large body of support. Microglial cell migration to the nervous tissue occurs through the walls of the parenchymal and meningeal vessels, accounting for the dramatic increase in their numbers at sites of CNS infections. They undergo transformations in and around the site of infection, which include shortening and thickening of cell processes, increase in the volume of the cell body and later retraction of the processes. These changes are followed by complete disappearance of the cellular processes and the conversion of the cell into spherical corpuscular form known as compound granular corpuscles or gutter cells. Promotion of immune response by the microglia and activated T lymphocytes, which enter the brain by crossing the blood-brain barrier, is evidenced in experimentally induced encephalitis. The small microglial cells are more abundant in the gray matter of the CNS and are also found in the retina.

Neurons

Neurons form the trophic, genetic, and excitable components of the nervous system, which receive, conduct and transmit nerve impulses. Neurons can be excitatory, inhibitory, sensory or secretory in function. Constant reduction in the number of neurons after birth and the inability of mature neurons to divide, represent some of the main characteristics of these cellular entities. Collection of neurons that subservise the same over all function and

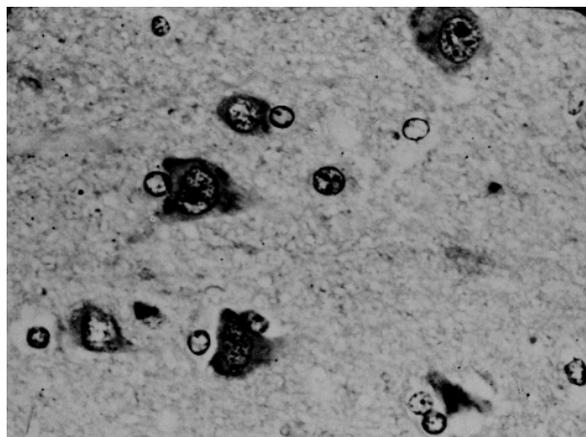


Figure 2.5 Photograph of the various types of astrocytes and oligodendrocytes

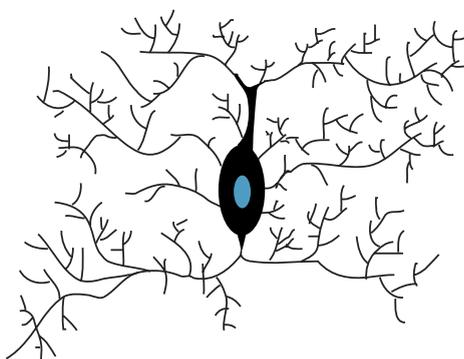


Figure 2.6 Schematic drawing of a microglia

generally share the same efferent and afferent connections is known as a nucleus within the central nervous system (e.g. trochlear nucleus), and as a ganglion in the peripheral nervous system (e.g. dorsal root ganglion). Although many unique features exist that distinguish neurons from each other, there are common characteristics shared by neurons (Figure 2.7).

The soma (perikaryon) represents the expanded receptive zone of the neuron, consisting of a protoplasmic mass, which surrounds the nucleus. It represents the center for protein synthesis. It harbors the organelles needed for the metabolic functions of the neuron. One (rarely more than one) prominent nucleoli are positioned in the centrally located nucleus. The cytoplasm of the soma contains chromatin bodies (Nissl bodies) which are intracytoplasmic basophilic, RNA-rich masses that are more distinct in the alpha motor neuron of the spinal cord and in the large neurons of the dorsal root ganglia. Nissl bodies, which extend along dendrites but not axons, are involved in high cellular activity and protein synthesis. These granules begin to disperse or undergo chromatolysis in response to nerve injury or in degenerative conditions. The anatomic location of the cell body has no functional

significance. The plasma membrane of the soma, although generally smooth, may possess spinous postsynaptic elevations known as gemules. The soma may engage in axo-somatic, dendro-somatic, and soma-somatic synapses. Within the cytoplasm neurotubules, neurofilaments, mitochondria, ribosomes, as well as aging pigment which consists of the lipofuscin granules. Neurotubules are randomly arranged in the perikaryon but assume longitudinal configuration in the axons and dendrites. At the surface of neurons various enzymes exist, such as adenosine triphosphatase (ATPase) which is activated by sodium and potassium.

Neuronal processes

The dendrites are highly branched processes that originate from the soma and represent the afferent or receptive zone of neurons. They show similar pattern of branching in neurons with similar functions. Dendrites have spines that maximize contact with other neurons, mediating excitatory and inhibitory axo-dendritic as well as dendro-dendritic synapses. They contain microfilaments and microtubules, smooth endoplasmic reticulum, ribosomes and Golgi membranes. More peripheral dendrites, free ribosomes and rough endoplasmic reticulum become progressively sparse and may be entirely lacking. Microtubules and microfilaments are much more conspicuous than in the soma and more regularly aligned along the axis of the dendrite, forming the most striking feature of the dendrites. The microtubules are believed to be involved in the dendritic transport of proteins and mitochondria from the perikaryon to the distal portions of the dendrites. The dendritic transport at a rate of 3mm/hour is comparable to some forms of axoplasmic transport. Destruction of the microtubules by drugs, such as colchicine and vinblastine, inhibits this transport. Dendritic transport may also involve viral glycoprotein that is basolaterally targeted. Dendrites contain exclusively the microtubule-associated protein (MAP-2) but do not contain growth-associated protein (GAP-43). For this very reason MAP-2 antibodies are utilized to identify dendrites via immunocytochemical methods.

The axon forms the efferent portion of the neuron, which provides nutrients via the axoplasmic transport. In general, axons are thinner than dendrite, assuming considerable length. Compared to dendrites, axons are more uniform, contain fewer microtubules and more microfilaments, but no ribosomes. Axons are longer than dendrites and may measure up to six feet in length, beginning from the axon hillock and giving rise to collaterals that terminate as the telodendria. They provide an avenue for transport of substances to and from the soma. Axon originates from the soma or, less frequently, from the proximal part of dendrite. It is divisible into axon

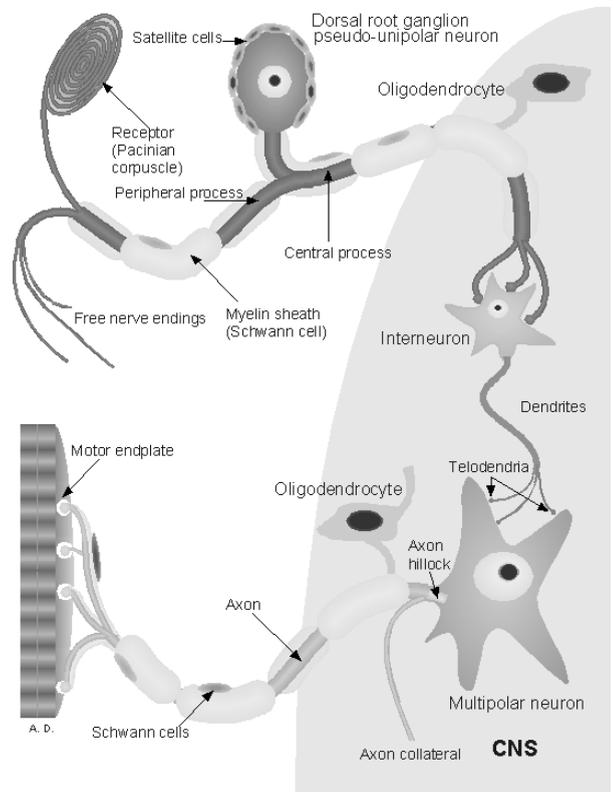


Figure 2.7 Various features of neurons and neuroglia cells. Myelin forming cells within the CNS and PNS, as well as synaptic connections between these neurons are also shown

hillock, initial segment, axon proper and the telodendria (axonal terminal). The axon hillock is a clearly recognizable elevation that continues with the soma. The relative absence of free ribosomes and rough endoplasmic reticulum is the most obvious feature of the axon hillock. In myelinated axons the initial segment is defined from the axon hillock to the beginning of the myelin sheath. This segment is unmyelinated, and maintains an inhibitory axo-axonal synapses. It contains some microtubules, neurofilaments and mitochondria, but lacks free ribosomes and rough endoplasmic reticulum. These neurotubules and neurofilaments are gathered into small parallel bundles, connected by electron-dense cross-bridges. Here at the initial segment, the axolemma (plasma membrane bounding the axon) is undercoated (presence of dense-core beneath the plasma membrane) and spike generating. Additionally, spectrin and F-actin (cytoskeletal molecules) are concentrated allowing voltage sensitive channels to attach to the plasmalemma.

Axonal terminals are initially myelinated, but as they repeatedly branch, myelin sheath will disappear. This will enable these terminals to establish synaptic contacts with neurons in the CNS or with muscle fibers and glands in the PNS. The endings are characterized by tiny swellings known as terminal boutons. Microtubule-associated

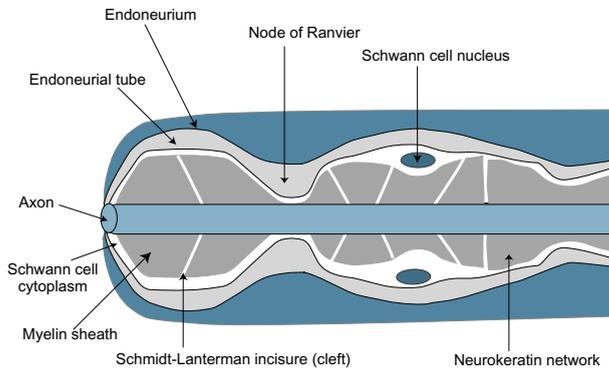


Figure 2.8 Myelin sheath of a peripheral nerve, nodes of Ranvier and associated coverings

proteins (MAP) such as tau interconnect axonal microtubules. Axoplasmic transport within the microtubules may be maintained utilizing protein dynein and kinesin. Neurofilaments are usually found in association with microtubules, as constant components of axons. In the growth cones of the developing axons, filamentous structures finer than neurofilaments exist and are known as microfilaments. These actin filamentous structures facilitate growth and movement and can be inhibited by chemical agents that depolymerize actin. High and low molecular weight proteins of the microfilaments are phosphorylated and antibodies produced for these molecules are used as markers for defining axons and neuronal phenotype. Antibodies raised against the growth associated protein-43 (GAP-43), a protein contained in the growing and regenerating axons, may be useful for identifying regenerating axons following axonal injury.

This axoplasmic transport is a process that enables proteins, neurotransmitters, mitochondria, and other cellular structures synthesized in the soma or proximal portion of the dendrites to be transported to the axon and axon terminals. This transport may be in a distal (anterograde) direction toward the axon terminals, while allowing other substances to be transported in the reverse (retrograde) direction, from the axon toward the cell body. This process may involve fast, intermediate, and slow phases. The fast phase within the axoplasm may include transport of selected proteins (e.g. molecules carried by the hypothalamo-hypophyseal tract), vesicles, membrane lipids, or enzymes which act on transmitters. This phase of the transport occurs at a speed of 100-400 mm/day, both in anterograde and retrograde directions utilizing smooth endoplasmic reticulum and microtubules. The retrograde component of this phase is formed by the degraded structures within the lysosomes.

The fast phase is energy dependent and can be inhibited by hypoxia and inhibitors of oxidative phosphorylation,



Figure 2.9 This is a longitudinal section of a single myelinated nerve fiber

Neurotropic viruses, such as rabies and herpes simplex follow the retrograde direction.

glycolysis, and the citric acid cycle. It has been suggested that proteins that follow the fast axonal transport must either pass through the Golgi complex or join proteins that do, utilizing clathrin-coated vesicular protein. The intermediate phase transmits mitochondrial proteins at a rate ranging between 15-50 mm/day. The slow phase of the transport utilizes microtubules, microfilaments, and neurofilament proteins, mitochondria, lysosomes, and vesicles, proceeding in the anterograde direction only, at a speed of 0.1-3 mm/day. This phase carries eighty percent of the substances carried by axoplasmic transport, providing nutrients to the regenerating and mature neurons. The slowest phase deals with the transportation of triplet proteins of tubulin and neurofilaments.

An axon may be myelinated or unmyelinated and ends in the synaptic terminals. Myelin is an insulating cover of cell membrane that encircles axons and is composed of two-thirds lipid and one-third protein (Figures 2.8 & 2.9). The lipid portion is primarily phospholipid (mostly sphingolipid), and to a lesser extent cholesterol in a free form. Interestingly, the macroscopic difference between gray and white matter is attributed to the lipid content of the myelin. Galactocerebrosides, a form of glycoprotein, represents the main component of the myelin protein. Minor lipid species also exist such as, galactosylglycerides, phosphoinositides, and gangliosides. Gangliosides that contain sialic acid (N-acetylneuraminic acid) form 1% of myelin lipid. PNS myelin is LM1 (sialosyl paragloboside), whereas GM-4 (sialosylgalactocerebroside) is the main ganglioside of CNS myelin. Both PNS and CNS myelin contain, although in low concentration, acidic glycolipids that serve as antigen in myelin. The major ganglioside of

Myelin allows for substances to be transported between the axon and the myelin forming cells (Schwann cell or oligodendrocytes). It maintains high velocity saltatory nerve conduction, a mode of conduction that proceeds from one node of Ranvier to another in a faster and more energy efficient way. Myelin is not a continuous covering,

Multiple sclerosis is the most common demyelinating disease of the central nervous system that leaves the axons relatively preserved. Despite the unknown etiology of this disease, epidemiological, genetic, immunological, and virological evidences exist. Decreased suppressor T lymphocytes and increased frequency of particular kind of HLA are considered some of the immunological abnormalities associated with this disease. Some investigators claim that contraction of measles at an older age and the presence of high measles antibody titer in the CSF may account for the development of this dreadful disease. Europeans and inhabitants of higher altitudes who have lived at least through the age of 15 in cool northern latitudes (above the 37th parallel) may show greater incidence of this disease. It is very rare in Latin America, Japan, and central Africa. Demyelination affects the structures within the CNS (Figure 2.10) with a predilection for the optic nerves, spinal cord, periventricular area, brainstem and cerebellum. Subsequent to demyelination, scar formation and gliosis may lead to the development of plaques. This disease is a more common in the female and shows higher incidence in first-degree relatives and monozygotic twin. The mean age of onset is 33 years with virtually all cases developing between 15 and 50 years. Although rarely advancing from the onset, this disease produces slowly progressive neurological disorders characterized by relapses and remissions. The severity of multiple sclerosis increases with time, although improvement accompanied by remission is common. In general, 2-3 years pass before remission. Initial symptoms and signs of this disease are intensified by fever and emotional stress, following infection, trauma, or childbirth. Demyelination involves the optic nerves and the medial longitudinal fasciculus, producing visual deficits and disorders of ocular movements. It also involves the posterior columns and the motor pathways of the spinal cord, causing ataxia and paralysis. Epileptic seizures may occur in some patients. Subsequent to demyelination, scar formation and gliosis may lead to the development of plaques. Lesions of the dorsal columns and anterolateral systems

are often symmetrical, causing paresthesia sequentially in the digits, limbs, and adjacent parts of the trunk. Locus minoris resistentia, the tendency for relapses in an area of previous activity, may also be seen in this condition.

Selective destruction of the lateral spinothalamic tract may account for the loss of pain and temperature sensations in acute cases. Corticospinal involvement often causes weakness and spasticity along with other signs of upper motor neuron syndromes. Spinal cord lesions can also result, though rarely, in impotence, and bladder dysfunction and incontinence may also occur. Men may experience premature or retrograde ejaculation.

The combination of proprioceptive sensory loss, signs of upper motor neuron palsy and cerebellar dysfunctions, disorders of eye movements (nystagmus), and history of visual deficits are all considered diagnostic for this disease. Some consider dysarthria, nystagmus, and tremor (Charcot's triad) as the cardinal signs of this disease. Depression is common in the initial stage and during remission of this disease. Some exhibit euphoria as a sign of relief when the attack subsides, others may live in psychological denial. Overt intellectual impairment is a late sign of this disease due to the fact that the gray matter of the cortex is spared in this disease and demyelination has to be extensive enough to impede the normal cerebral intellectual process. This fact distinguishes multiple sclerosis from Alzheimer's disease and manifestations of cerebrovascular accidents.

ACTH, prednisone or other steroid medications combined with physical therapy proved to be beneficial. This disease should be differentiated from Guillian-Barre syndrome that produces demyelination in the peripheral nervous system, affecting young and middle-aged individuals. Multiple sclerosis may mimic signs of brainstem astrocytoma, neurologic abnormalities of acquired immune deficiency syndrome (AIDS), systemic lupus (which exhibits seizures, stroke, and psychosis), as well as combined system disease (vitamin B12 deficiency).

but rather a series of segments interrupted by nodes of Ranvier. In the peripheral nervous system, each internodal segment represents the territory of one Schwann cell. These nodes are sites of axonal collaterals and bare areas for ion transfer to and from the extracellular space. Extensions of the myelin on both sides of a node of Ranvier are known as paranodal bulbs. These myelin bulbs may lose contact with the axon and undergo degeneration as a result of crush injury. Interruptions within successive layers of myelin are known as Schmidt-Lanterman incisures. Myelin is formed by the oligodendrocytes or Schwann cells during the fourth month of fetal life, and continues into

postnatal life. Myelination is initiated near the soma of neurons and continues toward the axon terminals. It does not cover the axon hillock, dendrites, or axonal terminals. The first step of this process involves surrounding the axon by cytoplasmic membranes of Schwann cells or oligodendrocytes that are detached initially, but later fuse together. The double layer of Schwann cell plasma membrane forms the meson, which elongates and differentiates, into inner and outer parts. Several layers of cell membranes, separated by cytoplasm, surround a given axon. Since myelin formation occurs at a particular site, elongation of the axon requires successive layers of myelin

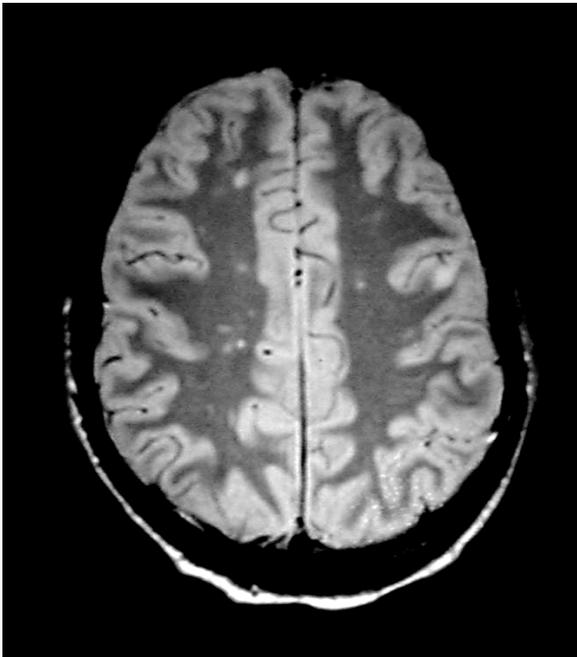


Figure 2.10 This an MR Image of a patient with multiple sclerosis showing multiple foci of demyelination

to stretch, and cover a larger area of the axon. This results in more layers being concentrated near the center of the internode. When the cytoplasmic and external surfaces of cell membranes come into apposition upon recede of the cytoplasm they form continuous major and minor dense lines, respectively. The minor dense line, also known as the intraperiod line, contains a gap that allows extracellular space to continue with the periaxonal space. This intraperiod gap allows metabolic exchange and serves to accommodate the increasing thickness of the axon by allowing lamellae to slip on one another and thus reducing their numbers.

In contrast, oligodendrocyte, the myelin-forming cell in the central nervous system, are associated with more than one axon and with more than one internodal segment (roughly 15-50 internodes). These multiple associations are maintained by extension of the oligodendrocytes around each axon. Myelination in the CNS begins initially with the vestibular and spinocerebellar tracts. Corticospinal tract and dorsal white column pathways may not be completely myelinated at birth. It should also be remembered that axonal growth and elongation to a destination generally occurs before the migration of oligodendrocytes and formation of myelin. Unmyelinated axons in the central nervous system lack any form of ensheathment, whereas, unmyelinated axons of the peripheral nervous system are enveloped by Schwann cell cytoplasm. Peripheral axons are lodged in sulci along the surface of Schwann cell. Some Schwann cells in the PNS

may encase more than 20 axons through the multiple grooves on their surfaces.

Demyelination may be a primary process; associated with intact axons as in multiple sclerosis and myelinopathy that affects the thickly myelinated motor fibers of the lower extremity and spares the small sensory fibers. It may occur secondary to destruction of the axon, as in storage diseases and Wallerian degeneration. Incomplete myelination (hypomyelination) occurs in maple syrup urine disease and in phenylketonuria.

In certain diseases such as Refsum's disease and metachromatic leukodystrophy, impairment of alpha oxidation and accumulation of phytanic acid leads to demyelination and production of easily degradable abnormal myelin. Demyelination also occurs in acquired neurometabolic disease (Korsakoff Wernicke syndrome-thiamine deficiency) and in lipid storage (lysosomal) diseases, which include Gaucher's disease, Globoid-cell leukodystrophy, Fabry's disease, Neimann-Pick Disease, Metachromatic Leukodystrophy, Tay Sachs disease, and Refsum's disease. These genetic disorders are autosomal recessive with the exception of Fabry's disease, a sex-linked abnormality with no ethnic or gender predilection. They are the result of a deficiency of intracellular lysosomal enzymes that regulate the catabolism of sphingolipids. Patients with these disorders carry enzymatic structures in their tissues, which are similar to the normal enzymes, but are not capable of degrading lipids.

The diagnosis of these diseases has been made easier following the recognition that antibodies which bind to the affected enzymes may artificially be prepared, and by the detection of traces of the above mentioned non-functional enzymes in the skin fibroblasts, leukocytes, and amniotic fluid. Fragmentation of myelin sheath, loss of ability to conduct sensory impulses, impairment of motor function, and trophic changes also occurs as the nerve undergoes degeneration (Figure 2.11) following axonal injury. The microscopic alterations (nerve degeneration) in a neuron following damage to its axon which may include changes distal to the site of trauma (anterograde degeneration), proximal to the site of damage (retrograde degeneration), or across the axonal terminal into the adjacent neuron (transneuronal degeneration).

Anterograde (Wallerian) degeneration occurs as early as 12-24 hours and includes disintegration of the mitochondria and neurofilaments followed by retraction and fragmentation of the myelin and axon. Cellular debris is later absorbed by the Schwann cells and macrophages in the peripheral nervous system and by the microglia, macrophages, and astrocytes in the central nervous system. This process is aided by the hydrolytic enzymes of the lysosomes and the axonal protease enzyme. After two weeks the cytoplasm of Schwann cells form tubes or "guidance tunnels" along the course of damaged axons and

- Maple syrup urine disease (branched-chain ketoaciduria) results from anomalies of leucine, valine, and isoleucine metabolism as a consequence of a defect of branched chain keto acid decarboxylase. Patients exhibit convulsions, hypertonicity, characteristic odor of urine and perspiration, hypertonicity, changes in reflexes, coma, and possible death. Prenatal diagnosis may be possible through enzyme assay of the anomalous metabolites. Acute cases of this disease may be treated by peritoneal and/or hemodialysis.

- Phenylketonuria, a hereditary condition caused by a defect in the phenylalanine decarboxylase, is transmitted as an autosomal recessive trait. It is one of the most common aminoacidurias which occurs in one per 20,000 births. This enzymatic defect results in the accumulation of phenylalanine in the blood that may further be metabolized to phenylacetic acid, which is eventually excreted in the urine. Exposure to excessive blood levels of phenylalanine may affect neuronal maturation and myelin formation by desegregation of brain polysomes. It has also been forwarded that high concentrations of phenylalanine may inhibit transport of other neutral amino acids across the blood brain barrier. Others have stated that the inhibitory role of high intracerebral levels of phenylalanine on synaptosomal Na-K-ATPase activity and on the synthesis of neurotransmitters may be responsible for this condition. Newborns with this disease generally do not exhibit clinical manifestations and because of this very reason prenatal screening tests of the amniotic cells and chorionic villi samples are essential for detection of this condition. Affected infants have lighter skin and eye color, and are not retarded at birth. Eventually, however, patients show signs of mental retardation, seizures, psychoses, extreme hyperactivity, "musty" body odor and cutaneous rash (eczema). In rare cases PKU may be caused by defects in the metabolism of tetrahydrobiopterin (BH₄) which is the electron donor

for the phenylalanine hydroxylase that contribute to the formation of tyrosine and dihydrobiopterin (DHP). BH₄ is synthesized from GTP and hydroxylates tyrosine and tryptophan. Thus, in this instance, since patients are unable to hydroxylate tyrosine or tryptophan, which is mediated by BH₄, restriction of phenylalanine may not prevent the neurological complications from occurring. Patients exhibit convulsions and other severe neurological manifestations.

- Gaucher's disease, an autosomal recessive disease, in which the deficiency of the enzyme glucocerebrosidase results from accumulation of abnormal glucocerebrosides in the reticuloendothelial system. It manifests signs of oculomotor nerve palsy, hepatosplenomegaly, hypertonicity, opisthotonos (a prolonged severe muscular spasm that produces acute arched back), hyperextension of the head and neck, hyperflexion of the arm and hand, tetany, spasticity, and seizures. Individuals with Gaucher's disease may also exhibit an expressionless face, which is described as 'wooden figure.'

- Globoid-cell leukodystrophy, a fatal infantile disease caused by deficiency of beta Galactosidase and accumulation of Galactocerebrosides (Krabbe's disease). Accumulation of excess amount of this substance leads to disintegration of the myelin in the cerebrum, cerebellum, brainstem, and possibly the spinal cord. This disease is characterized by progressive mental retardation, blindness, convulsion, deafness, signs of pseudobulbar palsy (loss of cranial nerves motor functions due to disruption of cerebral input), and quadriplegia (complete loss of motor functions in the extremities). Rapid cerebral demyelination and presence of globoid cells in the white matter will be seen. Due to generalized rigidity and tonic spasm, the body stiffens and the hand forms a fist, which would particularly be evident when the affected infant is held.

- Fabry's disease (Angiokeratoma Corporis Diffusum) results from the lack of the alpha-galactosidase (ceramide trihexosidase) and the accumulation of the glycolipid, dihexosidase and trihexosidase in the autonomic and dorsal root ganglia, myelinated fibers of the brainstem and myocardium. Accumulation of glycolipid in the superior cervical ganglia may be associated with anhidrosis (lack of sweating). Glycolipid accumulation may also occur in the renal tubules and glomeruli, which serve as a diagnostic tool, and in the hypophysis, skin, eye, and smooth muscles of blood vessels. This fatal condition is an X-linked anomaly, which exhibits corneal opacity, fever, burning pain in the extremities, and skin lesions in males. Death occurs as a result of renal failure or disorders associated with vascular hypertension. Ataxia, signs of upper motor neuron palsy, and urinary incontinence are also seen. Demyelination and subsequent loss of thinly myelinated fibers, as a result of the deposited glycolipid in the dorsal root ganglia, may account for the burning pain felt by individuals with this disease. Involvement of the blood vessels may explain the frequency with which cerebrovascular accidents occur in patients with this affliction.

- Neimann-Pick disease is a fatal disease of infants, resulting from lack of sphingomyelinase and accumulation of excessive amounts of sphingomyelin in various tissues. However, it is not yet clear whether abnormal breakdown, stereochemical anomaly, or excessive production of sphingomyelin is responsible for the manifestations of this disease. It is thought that presence of this substance is responsible for disintegration of the myelin in the white matter of the brain and brainstem. This disease exhibits pancytopenia (a marked reduction in the number of the erythrocytes, leukocytes, and platelets), xanthoma (a benign, fatty, fibrous and yellowish plaque that develops in the subcutaneous tissue, often around tendons), and feeding problems. It may also manifest growth and mental retardation, seizures, deafness, macular irregularity (cherry red macular spots occur in about one-fourth of patients, leading to blindness). Children are cachectic and commonly die between the age of 6 months and 3 years.

- Metachromatic leukodystrophy is another fatal disease that results from deficiency of cerebroside sulfatase A and

subsequent accumulation of sulfatide in excessive amounts in the myelin. Myelin with its abnormal sulfatide content may stain metachromatically brown upon treatment with acidified cresyl violet. Normally, sulfatide is degraded into cerebroside and inorganic sulfate. Chemically abnormal myelin in the brain, cerebellum, brainstem, spinal cord, and peripheral nerves, does not survive and undergo disintegration. This condition exhibits dementia and progressive paralysis.

- Tay Sachs disease is an autosomal recessive disorder which results from the absence of hexosaminidase A, subsequent to accumulation of GM2 ganglioside in the perikarya of the neurons. Gangliosides are glycolipids normally present in the plasma membrane of neuronal cell bodies. This disease is common in Jewish infants (3-6 months of age) of eastern European origin and French Canadian parents. Patients may exhibit seizures, blindness, laughing spells, abnormal acoustico-motor reaction. The latter reaction is characterized by brisk extension of legs and arms followed by clonic jerks of all limbs, neck extension, and startled facial expression in response to sudden sharp noise. Cherry red spot on the macula and progressive intellectual, physical, and neurologic deterioration are additional features of this serious disease. Infants that live longer than 6 months may develop macrocephaly.

- Refsum's disease (heredopathia atactica polyneuritiformis), an autosomal recessive disease, which results from accumulation of phytanic acid (tetramethylated 16 carbon-chain fatty acid) subsequent to a deficiency in the catabolism of fatty acids. It is characterized by demyelination of the spinal nerves, motor neurons of the ventral horn and the dorsal columns. Signs may include polyneuropathy, polyneuritis, nocturnal blindness, deafness, cardiac manifestations, cerebellar deficits, and locomotor ataxia. It may also include retinitis pigmentosa, which refers to the inflammation of the retina associated with progressive loss of retinal response, clumping of pigment, and shrinkage of visual field). Reduction of phytanic acid and amelioration of certain clinical signs may be achieved by dietary restriction of fruit, vegetables, and butter.

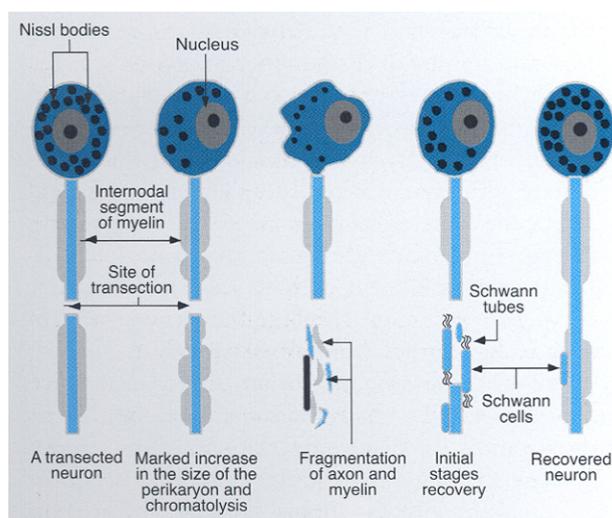


Figure 2.11 Cellular changes and stages of recovery of injured neuron. Note the changes distal and proximal to axonal injury

the macrophages depart. These tubes, known as bands of Bungner, may persist long enough to guide the re-growth of the axon, or may be replaced by the endoneurium. Degenerative changes occur in the terminals earlier if the site of the lesion is adjacent to the synapse.

Retrograde (indirect Wallerian) degeneration is seen in the peripheral and central nervous systems, although it does not occur in all neurons. In this type of degeneration, proximal axonal disintegration and break-up of myelin sheath may occur. These changes are accompanied by sealing off of the severed ends by the axolemma, thus preventing leakage of axoplasm. As the dendrites retract from their synaptic contacts retraction bulbs are formed at the swollen severed ends of the axons. The soma undergoes chromatolysis, where the Nissl bodies break up near the axon hillock, followed by dissolution of the cytoplasm within three days. Swelling of the soma is accompanied by deviation of the nucleolus into a peripheral eccentric position. Dispersion of the Golgi apparatus is accompanied by an increase in number of the lysosomes,

mitochondria, granular endoplasmic reticulum, and free ribosomes. Fully developed neurons may resist the process, allowing slow atrophic changes to occur, whereas poorly developed or immature neurons may die quickly. If regeneration fails, death of the affected neuron may eventually occur which is a most probable outcome in central nervous system injuries.

The transneuronal (transynaptic) degeneration, on the other hand, occurs in neurons, which provide the sole afferents to a neuron that receives axonal injury. It may also be seen in neurons that originally received input from the injured axon. These reactions, which are manifestations of disuse atrophy, extend slowly beyond the synaptic cleft to the adjacent neurons. Thus, the neuronal changes across the synaptic cleft are the result of lack of trophic substances provided to the adjacent neurons by the damaged neurons.

Regeneration refers to the ability of a neuron to restore function following a traumatic injury. In the peripheral nervous system, regeneration does occur, but is influenced by factors such as the site (the degree of regeneration is inversely proportional to the length of the axon) and the type of injury. Since growth cones (growth projections from the severed axon terminal) fail to properly align with the path of the axon that has undergone a transection injury, regeneration is more difficult than that of crushing injuries in the endoneurium when Schwann cells remain intact. It is noteworthy to add that regeneration is more likely if the site of injury is closer to the target site. The rate of growth of the regenerating axon varies, generally ranging between 3-4 mm/day in primates. Signs of regeneration start with the formation of growth cones in the distal end of the proximal segment of the severed axon. These growth extensions, which develop during the first week after the nerve injury, reach the distal segment through guidance tunnels formed by the Schwann cells. These changes are later followed by reconnection with the appropriate target, maturation, which requires recognition, establishment of a functional synapse and myelination as well as increased thickness of the axons. However, neuromas and associated agonizing pain may develop at the ends of the sprouting axons if the distance is long enough not to allow complete approximation of the

Table 2.1 Metabolic diseases, enzymatic deficiencies and associated metabolites

<i>Disease</i>	<i>Deficient enzyme</i>	<i>Accumulated metabolite</i>
Gaucher's disease	Glucocerebrosidase	Glucocerebrosides
Globoid leukodystrophy	Galactocerebrosidase	Glucocerebrosides
Fabry's disease	Galactosidase A	Ceramide trihexoside
Neimann-pick disease	Sphingomyelinase	Sphingomyelin
Metachromatic leukodystrophy	Cerebrosidase sulfatase A	Sulfatide

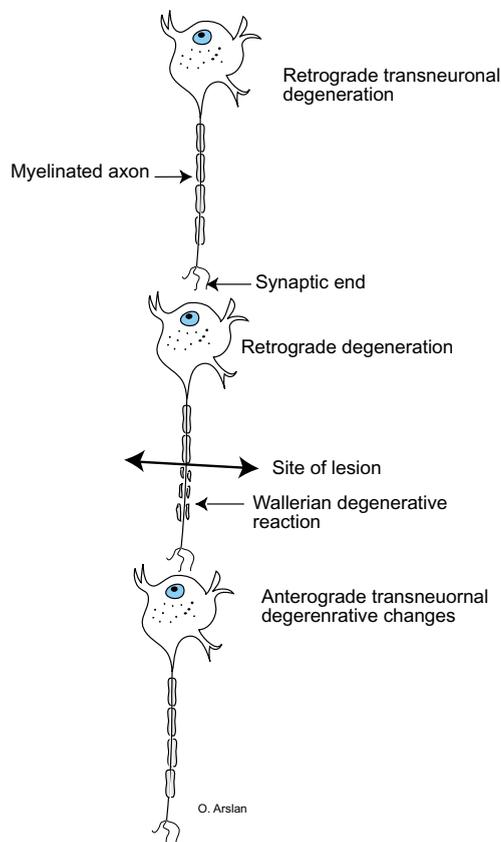


Figure 2.12 Summary of major changes shown in Figure 2.11

distal and proximal segments. Axonal sprouting in peripheral nerves occurs when some fibers within the nerve trunk are damaged while the remaining fibers are intact. These sprouts will extend into areas originally innervated by the injured fibers and will restore their function.

Regeneration seems very limited in the central nervous system, and true growth is almost impossible due to the fact that guidance tunnels are not formed by myelin-forming oligodendrocytes. Additionally, scar and necrotic tissue from trauma or infection may impede the repair process. Growth of axons do not follow a particular pattern to re-establish the connection, thus functional restitution becomes unattainable. The most significant goal of modern rehabilitative medicine is to prevent atrophy of the muscles in individuals with motor neuron diseases. One of the means to achieve this end is to apply electrical stimulation to the affected muscles, preventing denervation hypersensitivity and reducing atrophy.

Neurons are classified according to the chemical nature of the neurotransmitter that they release into cholinergic, adrenergic, noradrenergic, dopaminergic, serotonergic, GABAergic neurons, etc. Cholinergic neurons release acetylcholine and are commonly found at neuromuscular junctions. Noradrenergic neurons are abundant in the sympathetic ganglia and the reticular formation, whereas

Schwannomas and neurofibromas are the most common tumors of the peripheral nervous system, which are represented in von Recklinghausen's neurofibromatosis. This disease exhibits peripheral and central forms. It has an autosomal dominant pattern of inheritance and spontaneous mutations. The gene defect encodes nerve growth factor receptor located on the long arm of chromosome 17. In the peripheral form, patients exhibit cafe-au-lait cutaneous spots in childhood and neurofibromatosis in adults. Mental retardation, epilepsy, spinal deformities, and other tumors such as gliomas and pheochromocytoma may complicate this form of the disease. In the rare central form, multiple meningiomas and Schwannomas occur. It is associated with the loss of specific alleles from chromosomes 22. The possibility of involvement of chromosome 17 does exist.

adrenergic neurons are found in the adrenal medulla and within the synaptic dense cored vesicles. Dopaminergic neurons are present mainly in the substantia nigra, corpus striatum, and cerebral cortex, while serotonergic neurons occur in the raphe nuclei and in the rounded synaptic vesicles. GABAergic neurons are present in the cerebellar cortex and spinal cord. Neurons may also be classified into pseudounipolar, bipolar, and multipolar neurons.

Unipolar neurons is the most simple class of neurons that exhibit a single extension. This process gives rise to branches, some of which are receptive (dendrites); others function as axons. True unipolar neurons, which are relatively rare in vertebrates, form the dorsal root ganglia, the granule cells of the olfactory system, and the mesencephalic trigeminal nucleus (Figures 2.7, 2.13 & 2.14). Pseudo-unipolar neurons give off a single process that divides into a peripheral receptive branch (dendrite) and a central extension serving as an axon. Both of these branches maintain structural resemblance to axons.

Bipolar neurons are also relatively uncommon class of neurons. They are symmetrical cells with ovoid or elongated body and with a single dendritic process and an axon arising from opposite poles. These processes are approximately equal in length. They form the vestibular (Scarpa's) ganglion, spiral (auditory) ganglia, and the retinal bipolar cells (Figure 2.15).

Multipolar neurons (Figures 2.7, 2.16 & 2.17) are the most common types of neurons in the central nervous system; form the autonomic ganglia. They possess a single axon with several symmetrically radiating dendrites. Some neurons have multiple axons or lack axons all together. Multipolar neurons can be classified on the basis of dendritic branching pattern and shape of the soma into

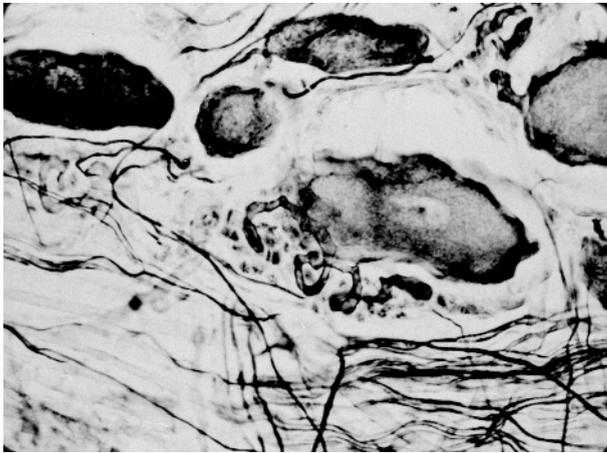


Figure 2.13 Photomicrograph of the pseudounipolar neuron and its initial process

stellate, pyramidal, fusiform, Purkinje, and glomerular cells.

Stellate (star) cells are found in the spinal cord, reticular formation, and cerebral cortex. They have dendrites of equal lengths (isodendritic) that radiate uniformly in all directions.

Pyramidal cells are multipolar, exhibiting pyramidal-shape soma with basal dendrites and a single apical dendrite that ascend toward the surface of the cerebellar cortex. They are most abundant in the cerebral cortex and hippocampal gyrus.

Fusiform cells are distinguished by their spindle-shaped and flattened soma with dendrites at both ends.

Purkinje cells form the intermediate layer of the cerebellar cortex, and have flask-shaped soma with apical tree-like dendritic branches, ascending toward the surface of the cerebellum maximizing synaptic contacts. Purkinje cells are motor neurons that project long axon beyond the area of the soma

Glomerular cells have a few convoluted dendritic branching form the mitral and tufted cells of the olfactory bulb. Mitral cells have an inverted cone-shaped dendritic field and soma that resembles a bishop's miter

Anaxonic cells are abundant in the retina (amacrine cells) and the olfactory bulb, where they are known as granule cells.

On the basis of axonal length, multipolar neurons can also be categorized into Golgi type I, with long axons projecting to distant parts of the central nervous system; and Golgi type II, possessing short axons that establish contacts with local neighboring neurons. The Golgi type II represents the inhibitory interneurons (such as the periglomerular olfactory neurons), which are activated by the ascending sensory pathways and play an important role in lateral inhibition. Neurons without axons, as mentioned earlier, are known as anaxonic, such as the amacrine cells

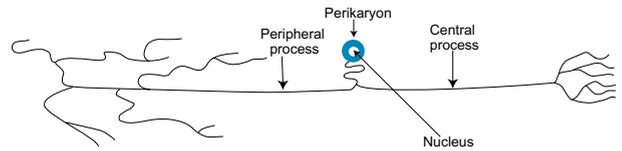


Figure 2.14 Schematic drawing of the pseudounipolar neuron. Cellular elements and associated extensions are also shown

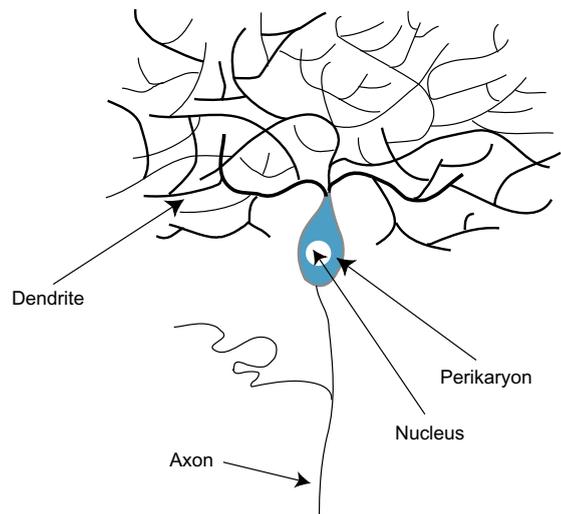


Figure 2.15 Bipolar neuron with branching dendrite and axon

of the retina and granule cells of the olfactory bulb, which establish synapses with parallel neurons.

Neurons can also be classified based on their functional role into somatic motor, somatic sensory, visceral motor, and visceral sensory neurons.

Neuronal communication is maintained through synapses (Figure 2.7), which are specialized junctional complex formed by the axon terminal of one neuron opposing the dendrites, soma or the axon of another neuron. Synapses represent sites of impulse generation (action potentials) and transmission across a population of neurons within the central nervous system. Synapses interfaces between neurons, provide trophic substances, and act as a "gate" for controlling impulses. A single axon may establish a synapse with one neuron (e.g. connections of the olivo-cerebellar fiber with dendrites of the Purkinje neurons). Multisynapses are seen between the parallel fibers of granule cells and the neurons of the molecular layer of the cerebellum. Synaptic glomeruli in the olfactory bulb and the granular layer of the cerebellum consists of an axon that synapses with dendrites of one or more neurons

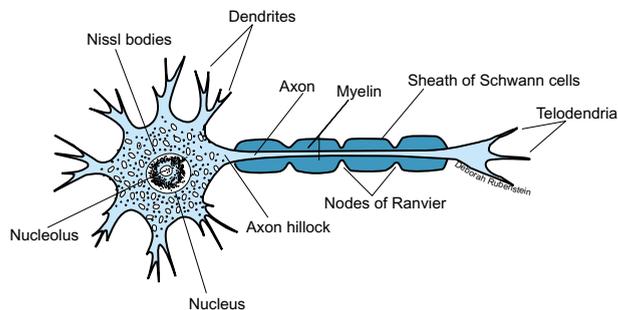


Figure 2.16 Multipolar neuron. Observe the numerous branches of dendrites and a single uniform axon is also shown

encapsulated by neuroglial cells. In general, synapses consist of presynaptic and postsynaptic components separated by synaptic clefts. Presynaptic processes contain round, granular, or flat vesicles filled with a specific neurotransmitter. Typically round vesicles contain acetylcholine, an excitatory neurotransmitter.

Small granular vesicles with electron-dense cores contain noradrenalin, an excitatory neurotransmitter. Flattened vesicles contain GABA, an inhibitory neurotransmitter. The close relationship between the vesicle morphology and functional synaptic type is evident when considering the association of the flattened synaptic vesicles with symmetrical membrane specializations and spherical vesicles with asymmetrical membrane thickenings. The postsynaptic membrane may be part of a muscle cell, or neuron, upon which neurotransmitter molecule bind after crossing the synaptic cleft. The part of the postsynaptic membrane that lies adjacent to the presynaptic membrane is known as the subsynaptic membrane. Synaptotlemma is a term that denotes the combined presynaptic and subsynaptic membranes. An increase in the postsynaptic receptor sites may be responsible for the exaggerated response following denervation (denervation hypersensitivity).

Synapses in the central nervous system morphologically and functionally different from their counterparts in the peripheral nervous system. They are not always cholinergic (as in the peripheral nervous system), utilize several excitatory neurotransmitters such as catecholamines (epinephrine, norepinephrine, and dopamine), aminoacid neurotransmitters (glutamine, aspartate, cysteine, etc.), serotonin, histamine, enkephalin etc. Transmission through the central synapses is governed by factors such as diffusion and reabsorption, and may be excitatory or inhibitory (activation drives the membrane potential of the postsynaptic neuron toward or away from its threshold level for firing nerve impulses). Transmission in the peripheral synapses, as in the neuromuscular junction, is

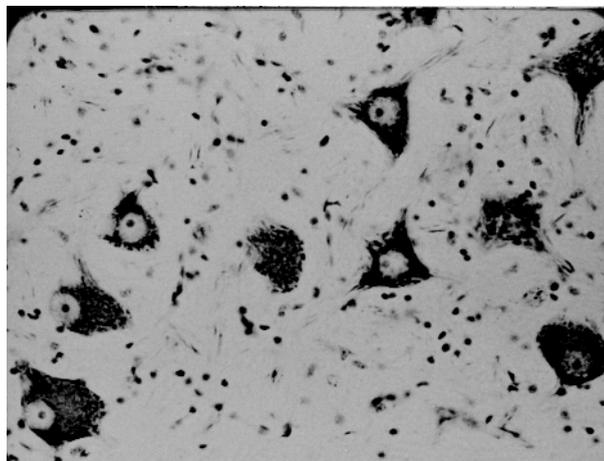


Figure 2.17 These multipolar neurons of the cerebral cortex exhibit an axon with branched apical dendrite

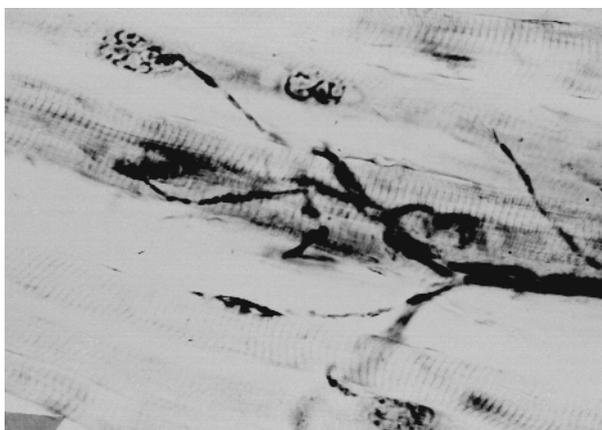


Figure 2.18 Photomicrograph of the motor end plate. The synaptic connection between the terminal axon and skeletal muscle fibers is clearly illustrated

generally excitatory, secured by a single presynaptic activation, and is dependent upon the degradation of the neurotransmitters by cholinesterase. Synapses in the CNS occur between one presynaptic ending and several postsynaptic neurons, contrary to the one to one synapse ratios in peripheral transmission. The variability and efficiency of transmission and neurotransmitter discharge in the central synapses is dependent upon the number of activated presynaptic endings.

Synapses may also be classified as being either chemical or electrical. Chemical synapses are slow which involve the release of a neurotransmitter by synaptic vesicles into the synaptic cleft, producing changes in the permeability of the postsynaptic membrane. The effect of the neurotransmitter is controlled by local enzymes and/or by reabsorption. Chemical synapses are further categorized on the basis of the utilized neurotransmitter. Cholinergic

synapses use acetylcholine, adrenergic synapses utilize epinephrine or norepinephrine, and dopaminergic synapses utilize dopamine. The electrical synapses exhibit close contact between presynaptic and postsynaptic membranes. Gap junctions enable the nerve impulses to cross directly from one cell to another and act on the postsynaptic membrane. These synapses which are common in lower vertebrate motor pathways, are similar to the electrical junctions (intercalated discs) of the cardiac muscle cells. Electrical synapses act much more rapidly than chemical synapses.

Classification of synapses may also be based on the morphological characteristics and the type of action they eventually produce, into Gray's Type I and II synapses. Gray's Type- I Synapse, an excitatory synapse in which the synaptic cleft is wide and the presynaptic and postsynaptic membrane densities are asymmetrical with the subsynaptic zone being thicker than the presynaptic zone. This type of synapse contains a wide variety of neurotransmitters including acetylcholine, glutamate, and hydroxytryptamine. Gray's Type- II Synapse, an inhibitory synapse in which the synaptic cleft is narrower, and the pre-and postsynaptic membrane densities are symmetrical.

Synapses may also be axodendritic; the most common which may be symmetrical or asymmetrical. Symmetrical axodendritic synapses predominate near the soma on the larger dendritic trunks. Axosomatic occur on the perikaryon: exhibiting both symmetrical and asymmetrical synaptic forms. This type of synapses that involve the initial segment of the axon may be inhibitory to cellular discharge. They are commonly symmetrical and may release inhibitory neurotransmitter GABA. Axoaxonic, in general, reduce the amount of neurotransmitter released by the axon and therefore regarded to mediate presynaptic inhibition. Dendro-somatic and somato-somatic synapses are described in the sympathetic ganglia. Dendro-dendritic synapses are for the most part symmetrical type, however, in the olfactory bulb the dendrites of the mitral cells form asymmetrical synapses with on the dendrites of the granule cells.

Neuromuscular junctions (motor endplates, [Figure 2.18](#)) are sites of synaptic contacts between the axons of the peripheral nervous system and the skeletal (striated) muscle fibers. This synaptic junction is the site where depolarization of muscle fiber membrane and muscular contraction is initiated. Structurally, each motor end plate consists of presynaptic and postsynaptic membranes. The presynaptic membrane is formed by the plate-like unmyelinated end of a motor axon, with numerous membrane-bound acetylcholine filled vesicles. The postsynaptic membrane, which is formed by muscle cell invagination that corresponds to the presynaptic vesicles, is separated from the extracellular space by the Schwann cells. The synaptic membranes of the motor endplates are

separated by synaptic clefts that are larger than the synaptic membranes in the central nervous system. The release of acetylcholine is dependent upon the frequency of the action potential and the influx of calcium ions. Once released, the acetylcholine diffuses across the synaptic cleft and increases the permeability of the postsynaptic membrane to the sodium and potassium ions, and thus produces depolarization. The end-plate potential is local, and its amplitude varies with the distance and the amount of the acetylcholine.

Due to development of multiple and highly sensitive ectopic sites, the sensitivity of muscle membrane increases dramatically upon denervation. Denervation hypersensitivity is accompanied by random contraction of individual muscle fibers known as fibrillation. Since these contractions develop individually and are asynchronous, they are not visible through the skin. The postsynaptic membrane contains acetylcholinesterase, an enzyme that limits the duration of action of acetylcholine and curtails the depolarization process by hydrolysis of acetylcholine into choline and acetate.

Antibodies to the (nicotinic) cholinergic receptor may also block transmission at the postsynaptic level of the neuromuscular junction, as in myasthenia gravis (Erb-Goldflam disease). These antibodies bind to the main immunogenic region of the μ -2 subunit receptors and produce cross linkage between cholinergic (nicotinic) receptors and eventually increase the rate of lysosomal degradation and endocytosis. The density of the postsynaptic receptors in this disease may be as low as one third of normal and the synaptic cleft is widened. Some speculate that myocytes, thymic muscle-like cell, may express AChR on their surface, triggering inflammatory response and subsequent production of cross-reacting antibodies from the thymus to the muscular cholinergic receptors.

Disease processes, drugs, and exposure to toxins may disrupt the mechanism of chemical transmission. Local anesthetics such as procaine, tetrodotoxin and saxitoxin block the generation of action potentials. Hemicholinium blocks the synthesis of acetylcholine by preventing the re-uptake of choline into the cell. High concentration of magnesium may block the release of acetylcholine and cause paralysis by competing with calcium receptors.

Transmission at the presynaptic level of the neuromuscular junction may be blocked by exotoxin produced by strains of the bacterium clostridium botulinum. This toxin blocks the release of acetylcholine by either binding calcium receptors or preventing entry of calcium ions during the action potential. Botulinum toxin is synthesized in an inactive form, which must be cleaved into heavy and light chains joined by disulfide bridge to become active. Toxicity is initiated by binding of these chains to specific presynaptic receptors. Ultimately the toxic component is discharged from the lysosomes into the cytoplasm of the presynaptic terminals. Ingestion of clostridial toxin occurs as a result of consuming improperly preserved canned food and vegetables, producing botulism. It may also occur as a result of contamination of a deep penetrating wound with this particular toxin. Symptoms may appear within two days, including nausea, vomiting, diplopia, and blurred vision. Paralysis of the extraocular muscles may be accompanied by dilated and unresponsive pupils, dysphagia (difficulty in swallowing), dysarthria (difficulty in speech), and paresis (weakness and not complete paralysis) of muscles of the neck, trunk, and extremities. Black widow spider venom (α -latrotoxin), a

protein molecule which combines with the presynaptic membrane and allow both sodium and calcium ions to enter the terminal, causing initial massive release of acetylcholine. This is followed by decline and fast depletion of the transmitter that produces initial contraction and painful spasm, rigidity and subsequent paralysis of the associated muscles. Bungarotoxin (venom of *B. multicinctus*) is a protein that inhibits the release of synaptic vesicles from the cholinergic and motor nerve terminals by exhibiting phospholipase A2 activity. Initially, this toxin produces slight reduction in end-plate potential (EPP) amplitude followed by intensification and then progressive decrease and final complete blockage of the transmitter. Tetany, another condition that results from abnormalities at the neuromuscular junction, is associated with deficiency of parathormone (hypocalcemia), vitamin D, or alkalosis due to hyperventilation (high pH increases calcium binding by serum proteins). It is characterized by generalized muscle spasm, tingling sensation in the lips, tongue and digits, and facial muscle spasm. Spasm of the forearm muscles and flexion of the hand at the wrist (Trousseau's sign) may be produced by applying a tourniquet and reducing the blood supply to the forearm. The fingers are pressed together and the thumbs are adducted (obstetrician hand). The lower extremity may be in carpedal spasm, in which the thigh and knee are extended, whereas the feet are plantar flexed and inverted. In latent tetany, contraction or spasm of the facial muscles may be elicited by tapping the facial nerve trunk (Chevostek's sign). It is treated by injection of calcium that restores normal transmitter release.

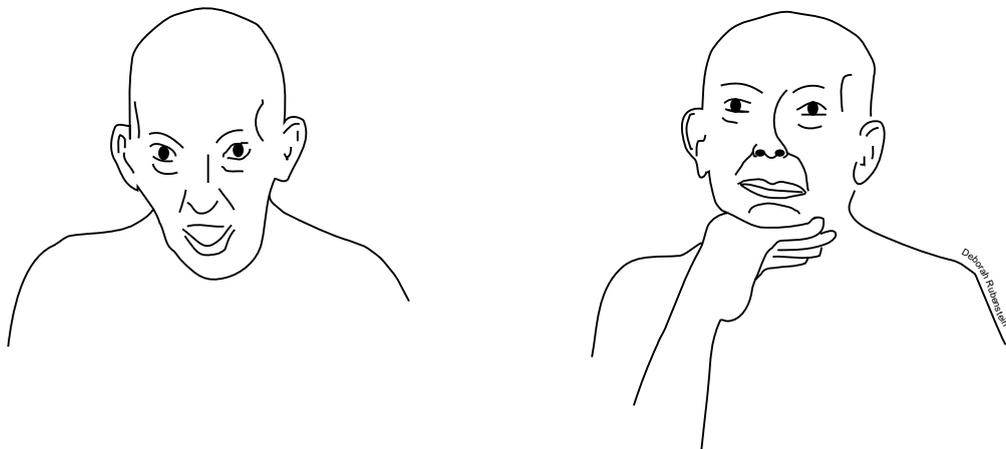


Figure 2.19 These schematic drawing show the manifestations of myasthenia gravis. In (A) observe drooping of the head and jaw. In (B) the patient attempts to hold the head and jaw up with a hand during conversation

Myasthenia gravis (Figure 2.19) is an acquired autoimmune disease of neuromuscular transmission, which is most common in women. It may accompany other systemic autoimmune disorders such as lupus erythematosus and pernicious anemia. This disease usually develops between the 2nd and fourth decades of life. It is characterized by bilateral weakness of the ocular, masticatory, swallowing and muscles of facial expression, as well as muscles of the neck and upper extremity. Clinical signs show varying intensity and occasionally follow an episodic course. Although these signs may be seen occasionally only on one side, weakness of ocular and palpebral muscles remain the first presenting signs. Ptosis (drooping of the upper eyelid) with lid retraction that cannot be masked by contraction of the frontalis, is the most prominent manifestation of this disease. Repeated forceful opening and closure of the eyes may exacerbate ptosis (Simpson's test). Although pupillary light reflex (characterized by constriction of the pupil of both eyes when light is applied to one eye) remains intact; deficits such as diplopia in upward gaze and in convergence (medial deviation of both eyes), and mydriasis (dilatation of the pupil) are also seen.

Nasal speech, dysphagia, and inability to hold the head up may form additional early signs of this condition. Voluntary muscle weakness is heightened by repetitive maneuvers, inducing dramatic fatigue. Increasing fatigue of individual muscles is more pronounced toward evening. Respiratory muscle involvement in some patients may lead to death (myasthenic crisis). Sensory transmission and tendon reflexes are preserved in this disease. Diagnosis of this disease is done by intravenous injection of a short acting anticholinesterase agent known as edrophonium chloride (Tensilon). Edrophonium chloride, a short acting AChE inhibitor can be used to distinguish between myasthenia gravis and cholinergic crisis. Edrophonium causes temporary relief in patients with myasthenia gravis, but not in patients with cholinergic crisis, which is a diffuse over-activation of the muscarinic receptors and depolarization of nicotinic cholinergic receptors of the skeletal muscles. Over-treatment with anticholinesterase or exacerbation of the disorder may lead to respiratory arrest and possible death.

Myasthenia gravis should be distinguished from Eaton-Lambert Syndrome, which is seen in oat cell carcinoma of the lung, and is associated with pernicious anemia. Antibodies that block the calcium channels essential for the release of acetylcholine cause this syndrome. It manifests itself as weakness in the muscles of the upper extremity, sensory loss, ataxia, and deep tendon areflexia. Sparing of the extraocular muscles is one of the pathognomic features of this disease. It should be noted however, that the affected muscles show a maximum increase in strength following voluntary exercise (warm-up) which is a unique characteristic of this neurological disorder.

The "warm-up" phenomenon in Eaton-Lambert Syndrome is the result of concomitant actions of acetylcholine release and then depletion followed by facilitation of transmitter release by repetitive activities. Autonomic deficits such as sexual dysfunction and dry mouth may also be seen.

Curare drugs (d-tubocurarine) attach to the postsynaptic membrane reversibly, thus preventing any reaction to acetylcholine. D-tubocurarine is a short acting drug that may be used with local anesthetics to promote muscle relaxation during anesthesia. Its action is

terminated by the administration of anticholinesterase. Depolarizing blocking agents such as decamethonium bromide and succinylcholine may mimic acetylcholine at the postsynaptic membrane level. Since these agents are not affected by cholinesterase, they induce prolonged depolarization. Anticholinesterase drugs such as physostigmine and neostigmine prolong the action of the acetylcholine by reversibly inactivating the enzyme. Nerve gas (diisopropyl fluorophosphate) and organic phosphates irreversibly bind to acetylcholinesterase producing prolonged depolarization, paralysis, and death due to asphyxiation.

α -neurotoxin, a curaremimetic which is a non-depolarizing blocking agent at the postsynaptic cholinergic receptors. This toxin is produced by snakes of families Elapidae (e.g. cobras, coral snakes, etc) and Hydrophidae (sea snake). α -Neurotoxin consists of two groups; the long toxin with 71-74 amino acids and five internal sulfide bonds, and short group with 60-62 amino acids and four internal disulfide bonds. The toxin with the short amino acids exhibits faster binding to the a subunits of the AChR and a reversible dissociation capacity than the long toxin (irreversible binding).

Section 2

Central nervous system

The central nervous system is derived from the neural tube and is comprised of the spinal cord, brainstem, cerebellum, diencephalon, and telencephalon. It initiates and regulates all motor activities and is responsible for the integration and transmission of sensory impulses. In addition, it also controls and regulates all of the activities that preserve the individual and species.

3 Spinal cord

4 Brainstem

5 Reticular formation

6 Cerebellum

7 Diencephalon

8 Telencephalon

The spinal cord is derived from the caudal part of the neural tube, occupying the upper two thirds of the vertebral column in adults. It stretches between the atlas (upper border of the foramen Magnum) to the intervertebral disc between the first and second lumbar vertebrae. In the newborns, it extends to the level of the third lumbar vertebra. The sites of attachment of the thirty one pairs of spinal nerves mark the individual segments of the spinal cord. Therefore, each spinal segment is associated with one pair of dorsal and ventral roots. There are eight cervical, twelve thoracic, five lumbar, five sacral, and one coccygeal spinal segments. The spinal cord has a cervical enlargement which corresponds to the fifth cervical through the first thoracic spinal segments (roots of the brachial plexus), and a lumbar enlargement, corresponding to the first lumbar through the third sacral spinal segments (roots of the lumbosacralplexus).

Spinal cord

Blood supply

Venous drainage

Internal organization

Gray matter

White matter

Spinal cord segments

Spinal pathways

Ascending tracts

Descending tracts

Spinal cord

The spinal cord is the cylindrical part of the central nervous, occupying the upper two-thirds of the vertebral column. The lower end of the spinal cord (conus medullaris) shows variation relative to the height of the individual, particularly in females. Flexion and extension of the trunk may also produce relative variation of the lower end of spinal cord. In some individuals the spinal cord may terminate as high as the twelfth thoracic vertebra or may extend as far down to the level of the intervertebral disc between the second and third lumbar vertebrae.

Due to the differential growth of the vertebral column relative to the spinal cord, the spinal cord segments do not always correspond to the vertebral levels. In general the rule of 2 applies to the vertebral levels T1-T10. In other words the injured spinal segments are determined by adding 2 to the level of the affected vertebrae. Spinous processes of T11-T12 vertebrae correspond to the lumbar spinal segments. Accordingly, the cervical spinal nerves exit above their corresponding vertebrae, while the remaining spinal nerves emerge from the vertebral column below the corresponding vertebrae. When the dorsal and ventral roots of the lower lumbar and sacral segments assume a longer course around the conus medullaris to reach the corresponding intervertebral foramina, the cauda equina is formed (Figures 3.1 & 3.2).

The spinal cord is invested by the dura, arachnoid, and the pia mater. The dura mater (pachymeninx), a collagenous tissue, is comprised of an inner meningeal and an outer endosteal layer. The outer endosteal layer forms the periosteum of the vertebral canal and the epineurium (the outermost covering) of the spinal nerves at or slightly beyond the intervertebral foramina. Dural continuation around the filum terminale and the lumbar cistern is known as the dural sac. At the level of the second sacral vertebra the spinal dura joins the filum terminale to attach to the coccyx as the coccygeal ligament. The epidural space (Figures 3.3 & 3.4) contains the internal vertebral plexus, a venous network that maintain connection with the systemic veins.

The arachnoid mater is a loose, irregular, and trabecular layer that is continuous with cranial arachnoid mater. It is generally avascular and surrounds the spinal cord without following the sulci. It is pierced by vessels that supply the pia mater.

The pia mater consists of the epi-pia that contains large vessels and the intima-pial layers. It intimately adheres to the spinal cord, giving rise to the dentate ligaments (Figure 3.3). These ligaments are triangular extensions that extend to the dura, coursing between the dorsal and ventral roots. They act as suspensory ligaments for the spinal cord, and extend from the level of the foramen magnum to the level of the first lumbar vertebra. Condensation of the pia mater



Figure 3.1 The caudal end of the spinal cord, filum terminale, and spinal meninges are shown in this picture



Figure 3.2 A more elaborate picture of the caudal spinal cord. Cauda equina and filum terminale are clearly visible

Pain associated with parturition may be alleviated by injection of local anesthetics into the epidural (extradural) space. Epidural anesthesia is a procedure that involves the administration of local anesthetics via a needle that passes between the L3-L4 lumbar vertebrae. In caudal analgesia the epidural space is reached via the sacral hiatus, utilizing a catheter. Diffusion of the anesthetic solution through the dural coverings of the emerging nerve roots ensures a complete pain blockage and inhibition of perineal reflexes that may unduly prolong the labor.

Spinal epidural abscesses may occur as a result of the posterior spread of infection directly from tuberculous vertebral bodies or during epidural anesthesia. They may also occur as a result of systemic disease and hematogenous spread of staphylococcus aureus infection. Low back pain, which may progress gradually to involve motor, sensory, and/or bowel and urinary incontinence may also be seen in this condition. Infection or abscesses associated with epidural space may be diagnosed via blood and CSF culture as well as CT myelography of the spinal cord.

Hematoma in the epidural space may occur as a result of trauma or spinal diathesis which may be partially or completely block the epidural space, producing sudden pain followed by sensory and motor deficits. The dura

mater may also be the site of arteriovenous malformation (AVMA) that commonly seen in the thoracolumbar segments. Dural AVMA may eventually develop into subarachnoid hemorrhage, producing combined upper and lower motor neuron deficits.

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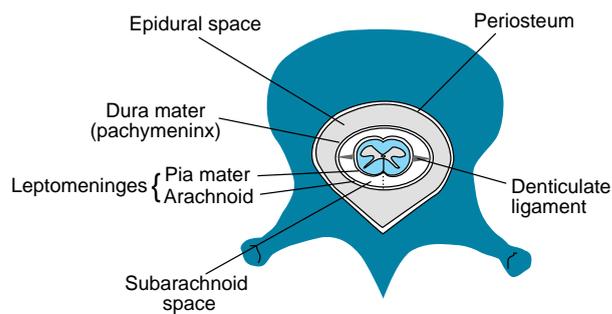


Figure 3.3 Spinal meninges, epidural and subdural spaces. The attachments of the dentate ligaments are also shown

between the conus medullaris and the second sacral vertebra is known as the filum terminale (internum) (Figures 3.1 & 3.2). Both pia and arachnoid mater form the leptomeninges, and they continue around the spinal nerves as perineurium. The subarachnoid space, between the arachnoid and pia mater, contains the cerebrospinal fluid and spinal arteries and veins. This space shows enlargement around the filum terminale and cauda equina and forms the lumbar cistern.

Blood Supply

The vertebral artery (Figure 3.5), the principal arterial source to the cervical segments of the spinal cord, is a branch of the subclavian artery, although occasionally it may arise directly from the aorta, brachiocephalic trunk, or from the thyrocervical trunk. This artery lies anterior to the stellate ganglion, and ascends in the transverse foramina of the upper six cervical vertebrae. In order to gain access to the cranial cavity, it runs through foramen magnum after piercing the posterior atlanto-occipital membrane. It gives rise to the meningeal, anterior and posterior spinal (Figures 3.6, 3.7 & 3.8), and medullary branches. It joins the vertebral artery of the opposite side to form the basilar artery (Figures 3.5 & 3.7). The vertebral arteries establish anastomosis with the multiple radicular arteries through the spinal branches, external carotid artery through the occipital branch, and subclavian artery through branches of the thyrocervical trunk and occipital artery.

The spinal cord is supplied by the anterior and posterior spinal arteries and by the multiple radicular arteries. The anterior spinal artery is a single vessel that supplies the anterior two-thirds, while the posterior spinal arteries supply the posterior one-third of the spinal cord. On the other hand, the radicular arteries that arise from the neighboring segmental arteries include the ascending cervical, deep cervical, posterior intercostal, lumbar, and

Arachnoiditis (inflammation of the arachnoid matter) may be caused by trauma, invasive imaging procedures (e.g. myelography), or it may remain idiopathic. This condition may produce adhesion of the leptomeninges, obliteration of the subarachnoid space, formation of arachnoid cysts, and possible vascular occlusion. Arachnoid cysts, are congenital outgrowth that assume positions outside (extradural) or inside the dura (intradural). Extradural cysts, common in the thoracic region, may remain asymptomatic or produce compression of the spinal cord and/or roots. Intradural cysts may or may not communicate with the subarachnoid space

The subdural space between the arachnoid mater and the dura mater represents a potential interval, which may accidentally be penetrated during induction of epidural anesthesia, producing toxic effects and eventual spinal cord damage.

Subdural abscess may occur as a result of underlying remote or contiguous infections such as dental, retroperitoneal or tuberculous abscesses. It may also be a spontaneous condition, producing fever, and back pain in the thoracic or lumbar region that radiates to areas of the spinal nerve distributions. Compression of the spinal cord as a result of an abscess may produce paraplegia or quadriplegia. Sensory and/or sphincteric deficits may also occur depending on the site and extent of the abscess.

Subdural hematoma may arise as a result of trauma, anticoagulant therapy, or following lumbar puncture. It produces signs and symptoms similar to subdural abscesses. However, paraplegia and quadriplegia usually occur within minutes to hours in individuals with subdural hematoma compared to subdural abscess in which the deterioration may take days.

lateral sacral arteries. They reach the spinal cord via the intervertebral foramina, following the roots of the spinal nerves, and are considered to be the principal blood supply to the thoracic, lumbar, sacral, and coccygeal spinal segments. Frequently the radicular arteries are only present on the left side of the thoracic and lumbar spinal segments, and bilaterally in the cervical segments. In 60-65% of individuals one radicular artery (artery of Adamkiewicz or artery of the lumbar enlargement), generally on the left side, may arise from the lower posterior intercostal arteries or upper lumbar arteries and establish anastomosis with the anterior spinal artery, supplying the lower two thirds of the spinal cord. (Figures 3.6, 3.7 & 3.8).

Lumbar puncture (LP), a procedure which is performed to aspirate CSF from the subarachnoid space for the evaluation of signs of meningitis or subarachnoid hemorrhage. It may also be utilized to administer medications to the lumbar cistern. LP or spinal tap is contraindicated in individuals with increased intracranial pressure. This is based upon the fact that a lumbar puncture may precipitate transtentorial herniation by suddenly reducing the pressure in the vertebral canal. The site of puncture in adults is usually between L3-L4 or L4-L5 vertebral interspace, while in infants a much lower level is indicated (L5-S1). In this procedure the skin and interspinous ligaments are anesthetized while the patient lies on his side. The dura and arachnoid mater must be pierced to gain access to the subarachnoid space.

Spinal anesthesia is performed by the injection of anesthetic solution into the lumbar cistern to block the lower thoracic, lumbar, and sacral spinal nerve roots. This procedure is performed when general anesthesia is not desired as in cesarean section.

Myelography, another procedure that utilizes the lumbar cistern, is used to visualize the vertebral column, spinal cord, and the posterior cranial fossa. A myelographic contrast medium is injected percutaneously via a needle into the lumbar cistern distal to the termination of the spinal cord. The spinal cord and spinal roots become discernible through a series of radiographic images. Since the contrast medium is radiopaque, the spinal cord and the nerve roots may appear radiolucent. For a detailed visualization, CT images may be obtained after contrast injection.

Venous drainage

The spinal veins form anterior and posterior longitudinal channels. The posterior venous channels drain the posterior half while the anterior venous channels drain the anterior half of the spinal cord. Eventually, these two venous channels open into the radicular veins, becoming part of the epidural venous plexus. The epidural venous plexus drains the red bone marrow contained in the vertebral bodies.

Internal organization

Each spinal segment consists of central gray and peripheral white matters that are connected by the corresponding gray and white commissures. The central canal is a tube

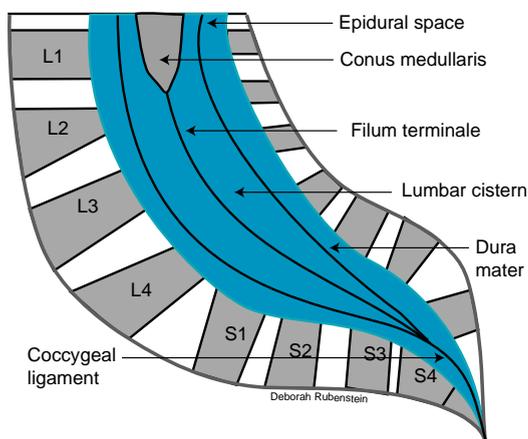


Figure 3.4 Caudal part of the spinal cord showing the meninges, filum terminale, and coccygeal ligament. Corresponding vertebral levels are also shown

that pierces the gray commissure of the spinal cord, ascends into the caudal medulla, and continues with the fourth ventricle. This canal does not stretch the entire length of the spinal cord and is frequently obliterated.

Gray matter

The gray matter is a butterfly-shaped area with an anterior and posterior horns which are present at all spinal levels. An additional lateral horn that lodges the intermediolateral columns (preganglionic sympathetic neurons) exists in the thoracic and upper two or three lumbar spinal segments. Gray commissures surround the central canal and separate it from the white matter. Most of the spinal cord neurons are small and propriospinal (90%), linking the ventral and dorsal horns within one segment or interconnecting several segments (intersegmental). The intermediate zone between the dorsal and ventral horns is generally formed by medium sized neurons, while the largest neurons occupy the ventral horn.

Based upon the cytoarchitecture of the neuronal cell bodies, the gray matter is classified by Rexed into nine laminae and area or lamina X (Figure 3.9). True lamination is evident in the dorsal horn, and considerable overlap exists among certain laminae.

- Lamina I contains the posteromarginal nucleus, consisting of neurons that display horizontal dendrites in order to maximize their contact with the incoming fibers of the dorsal root. The dorsolateral tract of Lissauer separates this lamina from the surface of the spinal cord.
- Lamina II (substantia gelatinosa) consists of Golgi type II neurons, receiving fibers that carry pain and temperature sensations. Axons of these neurons contribute to the formation of the Lissauer zone (dorsolateral fasciculus). This lamina is the main processing center for nociceptive (noxious) stimuli in the spinal cord.



Figure 3.5 Vertebral arteries on the ventral surface of the medulla and the anterior spinal artery

- Laminae III & IV contain the proper sensory nucleus and occupy a large region of the dorsal horn. This nucleus contributes axons to the lateral spinothalamic tract and receives virtually all sensory modalities carried by the dorsal root.
- Lamina V occupies the neck of the posterior horn and establishes synapses with the corticospinal and rubrospinal tracts. The lateral part of this nucleus is known as the reticular nucleus.
- Lamina VI is present in the spinal cord enlargements and particularly absent in the fourth thoracic through the second lumbar segments.
- Lamina VII forms the intermediate zone, receives fibers from the corticospinal & rubrospinal tracts, and contains the Clarke's, intermediolateral and intermediomedial nuclei. Clarke's nucleus extends from the eighth cervical or first thoracic to the second or third lumbar spinal segments, giving rise to the dorsal spinocerebellar tract. The intermediolateral nucleus occupies the lateral horn between the first thoracic and the second or third lumbar spinal segments, providing preganglionic sympathetic axons. At the second, third, and fourth sacral spinal segments, this nucleus provides preganglionic parasympathetic fibers. The intermediomedial nucleus extends the entire length of the spinal cord and receives visceral afferents.
- Lamina VIII occupies the anterior horn in the spinal cord enlargements, and contains commissural neurons which receive axons of the vestibulospinal, pontine reticulospinal and tectospinal tracts.

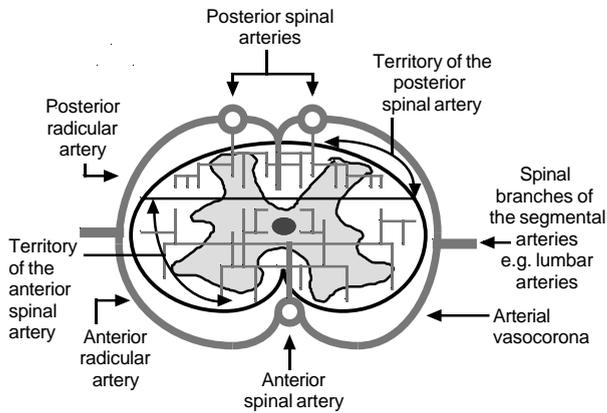


Figure 3.6 Distribution of the anterior and posterior spinal arteries and the formation of the arterial vasocorona

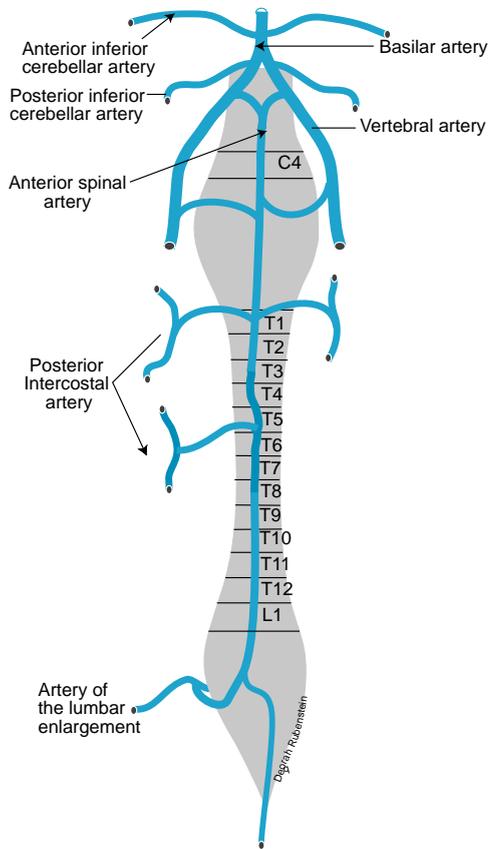


Figure 3.7 Schematic drawing of the anterior spinal artery and its connections to the radicular arteries

- Lamina IX contains a and g motor neurons that innervate the extrafusal and intrafusal muscle fibers, respectively. The a motor neurons excitatory input from the descending pathways and the reflex arcs, and inhibitory input from the propriospinal neurons. Excitatory input far exceeds the inhibitory projections by ration of 2:1. They give inhibitory recurrent branches to the interneurons (Renshaw cells), thus facilitating their

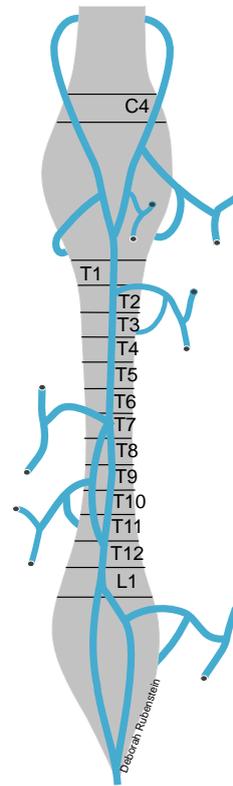


Figure 3.8 Posterior spinal arteries and territory of distribution. Notice their connections to the multiple radicular arteries

Spinal segments T1-T4 and L1 are predisposed to infarctions due to the lack of sufficient arterial anastomotic channels and the great distance between the radicular arteries. These watershed infarctions may be seen as a sequel to cardiac arrest, clamping of the aorta, or acute local ischemia. Occlusion of the artery of lumbar enlargement (artery of Adamkiewicz) may produce paraplegia (paralysis of the lower extremities and lower parts of the body), urinary incontinence, and loss of sensation from the lower extremities. Occlusive diseases of the anterior spinal artery (Beck's syndrome), as a result of aortic dissecting aneurysm or atheroma, produce combined sensory and motor deficits.

action. In general, a motor neurons are arranged somatotopically, in which the abductor neurons are located anteriorly, the flexor neurons are positioned posteriorly, and the extensors as well as the adductor neurons maintain intermediate positions. In the lumbosacral segments the neurons for the trunk are medial, the neurons that innervate the foot occupy a lateral position, while neurons for the leg and thigh have intermediate position. In the thoracic segments, lamina IX

Numerous connections exist at each intervertebral space between the epidural (internal vertebral) venous plexus and systemic veins (superior and inferior vena cava) via the azygos and hemiazygos veins. These connections may serve as a potential route of spread of cancer cells from the thyroid gland and prostate to the vertebral bodies. The internal vertebral (epidural) plexus affect CSF pressure by forming continuous tamponade of the spinal dural sac. Increased intrathoracic or intra-abdominal pressure (coughing, sneezing, and straining during defecation, or abdominal compression) can thereby increase CSF pressure.

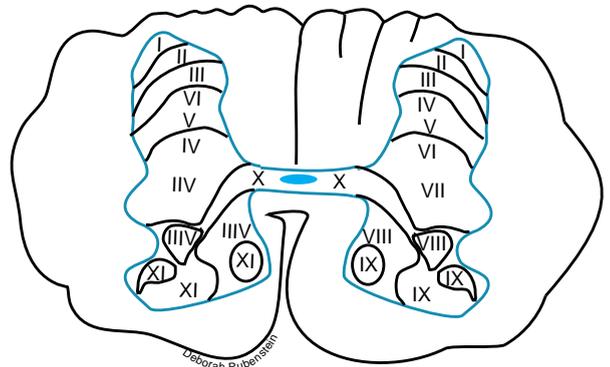


Figure 3.9 Rexed laminae and the cytoarchitecture of the gray columns of the spinal cord

exhibits a similar somatotopic arrangement whereby the neurons associated with innervation of the abdomen lie medial to the intercostal neurons, and the neurons for the innervation of the back muscles and skin assume an intermediate position. In the cervical segments the neurons for the hand are lateral to the neurons that supply the forearm, whereas trunk neurons are the most medial. Neurons for the arm and shoulder occupy position medial to the forearm and lateral to the trunk neurons. These neurons are classified into tonic and phasic neurons. The tonic a motor neurons innervate the slow, oxidative-glycolytic muscle fibers, exhibiting slow conduction and ability to readily depolarize. They are inhibited rapid movement by the Renshaw cells during. Phasic neurons display higher threshold and ability to maintain fast conduction, innervating the fast, oxidative-glycolytic muscles. Phasic neurons also send more recurrent branches to the Renshaw cells than the tonic neurons. The g neurons are located among the a motor neurons, innervating the contractile parts of the muscle spindles. Both a and g neurons are involved in voluntary movement via the a-g co-activation and gamma loop.

- Lamina X (or area X according to some claims) consists of small neurons that form the gray commissures around the central canal. It receives some afferents from the dorsal root fibers and contains neuroglial cells in its ventral part that send cytoplasmic extensions to the adjacent pia mater.

White matter

The white matter occupies the peripheral part of the spinal cord and consists only of neuronal processes. The anterior white commissure connects the white matter on both sides, representing the site of decussation of the lateral and ventral spinothalamic tracts, as well as the ventral spinocerebellar tract, and the anterior corticospinal tracts. The part of the white matter located between the entering fibers of the dorsal roots is known as the dorsal funiculus, containing the dorsal white columns. The part of the white

matter that lies between the dorsal and ventral roots on each side is known as the lateral funiculus, containing the lateral corticospinal, rubrospinal and lateral spinothalamic tracts. The area of the white matter between the emerging ventral roots is referred to as the ventral funiculus and contains the ventral spinothalamic, tectospinal, and the reticulospinal tracts as well as the medial longitudinal fasciculus. A tract refers to a collection of nerve fibers that have the same origin, destination, course, and function. A fasciculus shares common features of the tract with the exception that the constituent fibers maintain diverse origins.

Spinal cord segments

The cervical spinal segments are eight in number, are generally large, and have relatively large amounts of white matter. The posterior funiculus is divided into a medial gracilis and a lateral cuneatus fasciculi (**Figure 3.10**).

The thoracic segments (**Figure 3.11**), which are characterized by a small and distinct lateral horn, containing the intermediolateral cell column which gives rise to the preganglionic sympathetic fibers. The dorsal funiculi of the upper six spinal segments contain the gracilis and cuneatus fasciculi, while the lower six thoracic segments contain only the gracilis fasciculus. Another important feature of the thoracic segments is the presence of Clarke's nuclear column, which is particularly well developed, in the lower two thoracic spinal segments. The axons of this nuclear column form the ipsilateral dorsal spinocerebellar tract that conveys unconscious proprioceptive information from the muscle spindles and Golgi tendons of the lower extremities. Additionally the gray matters of the thoracic segments are tapered in an H-shaped.

The axons of this nuclear column form the ipsilateral dorsal spinocerebellar tract that conveys unconscious

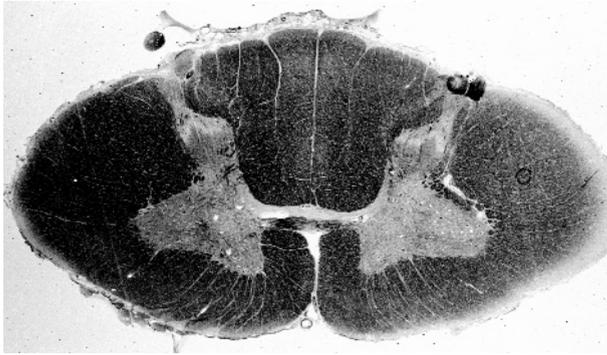


Figure 3.10 Fourth cervical segment. Note the wide transverse diameter and large amount of white and gray matter



Figure 3.11 Transverse section through the fifth thoracic spinal segment, showing Clarke's nucleus and the intermediolateral column, substantia gelatinosa, and the dorsal tract of Lissauer

proprioceptive information from the muscle spindles and Golgi tendons of the lower extremities.

The lumbar segments (Figure 3.12) contain massive amounts of gray matter and relatively less white matter. The upper two lumbar segments contain the continuation of Clarke's Nucleus and the intermediolateral columns.

The sacral segments (Figure 3.13) are small compared to other segments and contain large amounts of gray matter. The intermediolateral cell column in the sacral spinal segments provides preganglionic parasympathetic fibers.

Spinal pathways

Ascending tracts

These ascending pathways (Figure 3.14) convey conscious and unconscious sensory information to the higher levels of the CNS. The first order neurons for all ascending tracts

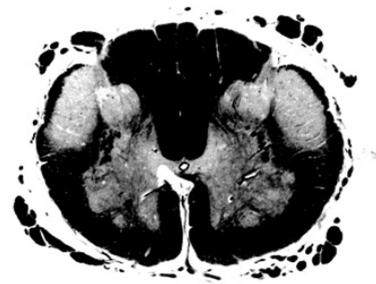


Figure 3.12 Section of the fourth lumbar segment showing the main characteristics of this level

from the body are located in the dorsal root ganglion (DRG) of the spinal nerves. The second order neurons are located either in the gray matter of the spinal cord or in the brainstem. The ventral posterolateral (VPL) nucleus of the thalamus constitutes the third order neurons for these pathways. The signals for the information conveyed by the ascending pathways are concerned with the regulation of muscle tone, joint sensation (position sense), vibration, pain and temperature sensations, discriminative tactile sensations, and intersegmental reflexes. These pathways may establish monosynaptic connections or utilize an extensive network of neurons and are contained in the funiculi of the spinal cord.

Posterior funiculus

The dorsal white columns transmit fine tactile and vibratory sense via the Pacinian corpuscles, position and movement sense (kinesthesia) from the muscle spindle. They also convey two point discrimination of simultaneously applied blunt pressure points from the Ruffini corpuscles; and stereognosis (ability to recognize form, size, texture and weight of objects) via a variety of receptors.

Lateral funiculus

The lateral spinothalamic (neo-spinothalamic or lateral system) tract is a contralateral pathway that conveys thermal and painful sensations from somatic and visceral structures. Pain and temperature, received by the free nerve endings, enter the spinal cord via the lateral bundle of the dorsal root. In the peripheral parts of the lateral funiculus, the dorsal and ventral spinocerebellar tracts are located, carrying unconscious proprioception from the lower extremity to the cerebellum.

Ventral funiculus

The ventral spinothalamic tract (paleospinothalamic or anterior system) runs in the ventral funiculus and transmits signals associated with light touch, and possibly

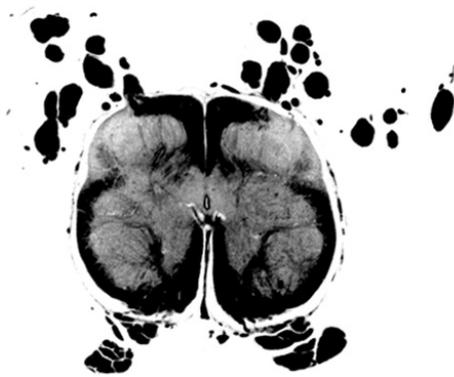


Figure 3.13 Section through the fifth sacral spinal segment

tickling, itching and libidinous sensations. Since fine touch and discriminative tactile sensation are primarily carried in the dorsal columns, the clinical significance of this pathway is not clear.

The spino-olivary tract is a contralateral tract, conveying cutaneous information and afferents from Golgi tendon organs to the dorsal and medial accessory olivary nuclei.

The spino-reticular tract is an integral part of the ascending reticular activating system that plays an important role in changing the electrocortical activity of the cerebrum, regulating the state of consciousness and awareness. It establishes a direct link between the spinal cord and the brainstem reticular formation, extending the entire length of the spinal cord. It also contributes to the formation of the spino-reticulo-thalamic tract.

The spinotectal tract is composed of axons of neurons that are derived from lamina VII of the spinal gray matter. Although the functional significance of this pathway is not clear, its role in modulating the transmission of pain, thermal, and tactile sensation, awaits further study.

Descending tracts

The descending pathways (Figure 3.15) deal with maintenance of posture and balance, control of visceral and somatic reflex activity, muscle tone, motor activity in general, and modification of the sensory signals. The descending pathways include the corticospinal, rubrospinal, tectospinal, and interstitio-spinal tracts. They also include the vestibulospinal and reticulospinal pathways, as well as descending autonomic pathways that are derived from the hypothalamus and the brainstem reticular formation.

Descending tracts in the lateral funiculus

The lateral corticospinal tract is a phylogenetically new pathway and exists in man and other mammals. It

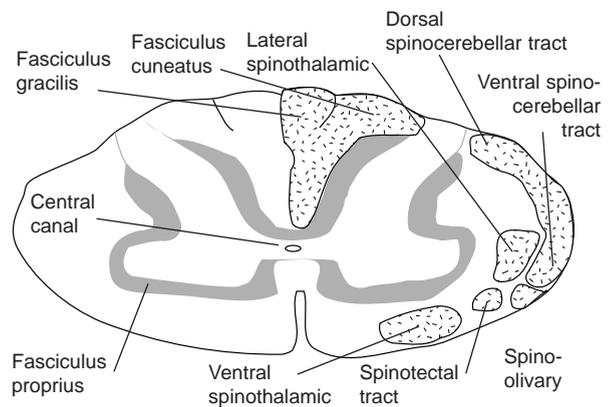


Figure 3.14 Principal ascending pathways within the spinal cord

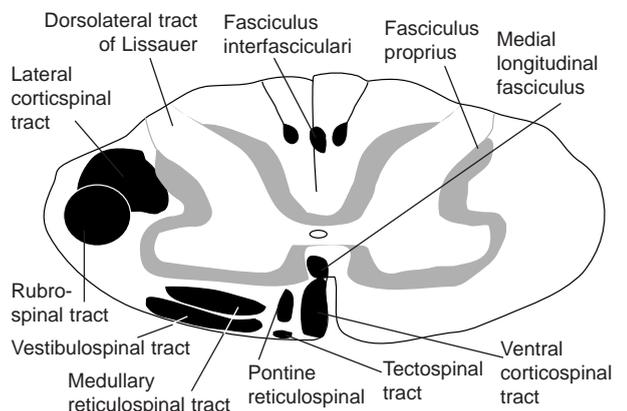


Figure 3.15 Section of the spinal cord showing the descending pathways

continues to develop throughout the first two years of life. This pathway forms the largest crossed component of the corticospinal tract, controlling voluntary motor functions, especially movement associated with the digits.

The rubrospinal tract is a contralateral tract that may be traced from the superior collicular level of the midbrain to the thoracic or lumbosacral segments. This excitatory pathway which regulates the neurons of the flexor muscles, originates from the magnocellular part of the red nucleus.

Descending tracts in the ventral funiculus

The anterior corticospinal tract represents approximately 10-15% of the corticospinal fibers and travels ipsilaterally in the spinal cord near the anterior median fissure. This pathway influences muscles of the upper extremity and the neck via synapses in the corresponding segments.

The vestibulospinal tracts include the lateral and medial vestibulospinal tracts. The lateral vestibulospinal tract is excitatory and runs the entire length of the spinal cord.

Table 3.1 Ascending and descending tracts

<i>Funiculi</i>	<i>Ascending tracts</i>	<i>Descending tracts</i>
Posterior funiculus	Dorsal white columns	Fasciculus interfascicularis and fasciculus septomarginalis
Lateral funiculus	Lateral spinothalamic and dorsal spinocerebellar tracts	Corticospinal and rubrospinal tracts
Ventral funiculus	Ventral spinothalamic, spino-olivary, spino-reticular and spinotectal tracts	Anterior corticospinal, vestibulospinal, reticulospinal and medial longitudinal fasciculus

The medial vestibulospinal tract is monosynaptically inhibitory and extends to the upper cervical segments.

The reticulospinal tracts comprise the ipsilateral pontine reticulospinal and the predominantly ipsilateral medullary reticulospinal tracts. These tracts convey information received by the reticular formation from the cerebral cortex, cerebellum, cranial nerves, and hypothalamus to the spinal cord.

The medial longitudinal fasciculus (MLF) is a composite bundle of ascending and descending fibers that originate from vestibular and reticular nuclei. This tract occupies the dorsal portion of the ventral funiculus.

The spinospinal tract (fasciculus proprius) is an intersegmental tract of ascending and descending fibers (crossed and uncrossed), which mediates the intrinsic reflex mechanisms of the spinal cord. It exists in all spinal funiculi, conveying information to higher segments prior to establishing contact with interneurons.

The brainstem is the infratentorial portion of the CNS, consisting of the mesencephalon (midbrain), pons and medulla. It is connected to the cerebellum via the cerebellar peduncles. The brainstem contains the fourth ventricle, cerebral aqueduct, central canal, and the nuclei of the associated cranial nerves. The reticular formation occupies the central portion of the brainstem, containing the respiratory and cardiovascular centers.

Medulla

Spinomedullary junction

Level of decussation of the internal arcuate fibers

Midolivary level

Rostral medulla

Pontomedullary junction

Pons

Caudal pons

Midpons (level of the trigeminal nerve)

Rostral pons

Midbrain

Inferior colliculus

Superior colliculus

Medulla

The medulla (Figure 4.1) represents the caudal part of the brainstem, continuing caudally with the spinal cord through the foramen magnum. The rostral end of the medulla is demarcated ventrally by the pontobulbar sulcus, giving passage to the abducens, facial, and vestibulocochlear nerves. Dorsally, it is bounded by a line joining the lateral recesses of the fourth ventricle. The dorsal surface of the rostral half of the medulla (open part) forms the lower part of the rhomboid fossa, while the caudal half (closed part) contains the central canal. The junction of the caudal and rostral medulla is demarcated on the dorsal surface by the obex. The ventral median fissure of the medulla is continuous with the corresponding fissure in the spinal cord, bounded on both sides by the pyramids, and it is obliterated at its caudal part by the decussating fibers of the corticospinal tracts. The olivary eminence lies lateral to the pyramid, and is formed by the underlying inferior olivary nuclear complex. The anterolateral (preolivary) sulcus, which contains the filaments of the hypoglossal nerve, separates the pyramids from the olivary eminence. The post-olivary sulcus is the site of attachment for the glossopharyngeal, vagus and accessory nerves.

Caudally, the posterior surface of the medulla contains the posterior median sulcus and is flanked on both sides by the fasciculi gracilis. The medially located fasciculi gracilis are separated from the laterally located fasciculi cuneatus by the cranial extension of the posterior intermediate septum. These fasciculi terminate in the corresponding tubercles that overlie their respective nuclei. The gracilis and cuneate nuclei receive information concerning conscious proprioception, two-point discrimination, vibratory sense, and discriminative tactile sensation from the upper and lower part of the body. Axons of gracilis and cuneate neurons project to the contralateral ventral posterolateral nucleus of the thalamus via the medial lemniscus. The gracilis fasciculus also acts as a conduit for impulses that originate from stretch receptors and Golgi tendon organs in the lower extremity (unconscious proprioception) and terminates in the Clarke's nucleus. The cuneate fasciculus also contains sensory impulses generated from the stretch receptors and Golgi tendon organs of the upper extremity (unconscious proprioception) en route to the accessory (external) cuneate nucleus. The caudal part of the medulla, between the fasciculus cuneatus and the accessory nerve, contains a prominence produced by the underlying spinal trigeminal tract and nucleus. The central canal runs close to the



Figure 4.1 Ventral surface of the brainstem and its connections to the cerebellum. Some of the important features of the medulla, pons, and midbrain are shown in this picture

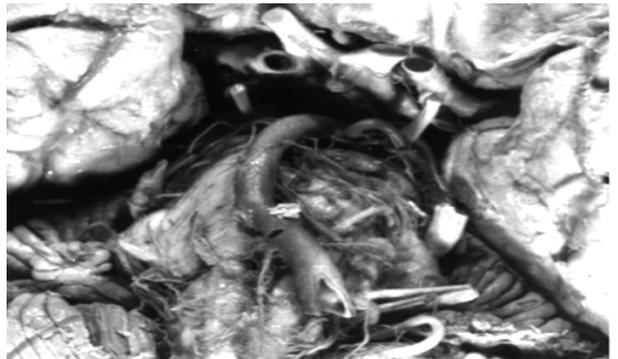


Figure 4.2 Relationship of the ventral surface of the brainstem to the vertebro-basilar arterial system is shown. Most of the associated cranial nerves are also seen

posterior surface and is continuous with the corresponding canal in the spinal cord caudally and the fourth ventricle rostrally.

The rostral (open) part of the medulla is bounded laterally by the inferior cerebellar peduncles that meet at the obex. It contains the fourth ventricle and forms the lower half of the rhomboid fossa. In this region the



Figure 4.3 Level of the decussation of the corticospinal tracts. The spinal trigeminal tract and nucleus and the dorsal column nuclei are clearly demonstrated

A lesion at the site of pyramidal decussation produces cruciate hemiplegia, which is characterized by paralysis of the ipsilateral upper extremity and contralateral lower extremity.

rhomboid fossa contains the hypoglossal trigone medially, and the vagal trigone laterally. These trogons overlie the hypoglossal and dorsal motor nucleus of the vagus, respectively. The stria medullaris emanates from the arcuate nuclei, crossing the inferior cerebellar peduncles and the vestibular area of the rhomboid fossa. The vestibular area corresponds to the site of foramen of Luschka, overlying the medial and inferior vestibular nuclei.

The medial part of the medulla containing the pyramids, medial lemniscus, the hypoglossal nerve and nucleus, and inferior olivary nucleus is supplied by the anterior spinal artery and the bulbar branches of the vertebral artery. While the dorsal and lateral parts of the caudal medulla, which contain the associated cuneate, gracilis, dorsal vagal, and solitary nuclei and fasciculi) receive blood supply from the posterior spinal and posterior inferior cerebellar branches of the vertebral artery (Figure 4.2). The latter arterial branch provides blood

Since the pain and thermal fibers terminate in the most caudal portion of this nucleus and tract, excision of the spinal trigeminal tract (tractectomy) may be performed, although rarely, at the level of the medulla to alleviate the intractable pain associated with trigeminal neuralgia.



Figure 4.4 Section through the caudal medulla at the level of the sensory decussation. At this level the medial lemnisci are formed and the inferior olivary nuclei are seen. The cuneate and gracilis fasciculi maintain similar positions to Figure 4.3

supply to the lateral medulla and inferior cerebellar peduncle.

Venous drainage of the caudal medulla is maintained by the anterior and posterior spinal veins. The rostral medulla drains into the sigmoid, superior or inferior petrosal sinus.

Medullary structures are clearly prominent at three levels and each level may present unique features and contain nuclei or pathways that extend to a more caudal or rostral levels. These levels are comprised of the spinomedullary junction, midolivary level, rostral medulla, and the ponto-medullary junction.

Spino-medullary junction

The spinomedullary junction (Figure 4.3) marks the gradual transition between the spinal cord and the medulla. It contains, for the most part, structures that extend from the spinal cord with some additional unique neurons, specific to this level of the medulla such as the Gracilis and cuneate nuclei. A unique feature of this level is the pyramidal decussation, which marks the site of crossing of the corticospinal fibers.

At a more rostral level, the spinal trigeminal nucleus and tract replace the substantia gelatinosa and the dorsolateral tract of Lissauer, respectively. The spinal trigeminal nucleus extends from the midpons to the upper segments of the spinal cord, representing the rostral extension of the substantia gelatinosa. It receives thermal, painful, and tactile sensations from the head region through branches of the trigeminal, facial, glossopharyngeal, and vagus nerves. The fibers that terminate in this nucleus form the spinal trigeminal tract lateral to the corresponding nucleus. Within the spinal trigeminal nucleus and tract,



Figure 4.5 Caudal medulla rostral the level shown in [Figure 4.4](#). The inferior olivary, hypoglossal, solitary, gracilis and cuneatus are clearly evident

the ophthalmic nerve fibers are caudal to the more rostral mandibular nerve fibers, and the maxillary nerve fibers maintain an intermediate position.

The gracilis and cuneate fasciculi are prominent at this level and occupy the corresponding positions to the spinal cord. The most significant characteristics of this level are the decussation of the corticospinal tracts and the appearance of the dorsal column nuclei. The crossed fibers represent nearly eighty-five percent of the corticospinal tract. The uncrossed fibers form the anterior corticospinal tract, descend in the anterior funiculus, and later cross at the anterior white commissure. Some uncrossed fibers pass into the lateral funiculus, forming the anterolateral corticospinal tract.

The medial longitudinal fasciculus is displaced laterally by the pyramidal fibers. The gray matter around the central canal is markedly expanded into the reticular formation. The spinocerebellar and spinothalamic tracts occupy the same position as in the spinal cord.

Level of the decussation of the internal arcuate fibers

The gracilis nucleus ([Figures 4.4, 4.5 & 4.6](#)) occupies a larger area at this level, stretches rostrally to the level of the obex, and is covered by a thin strip of the gracilis fasciculus. The laterally positioned cuneate nucleus also increases in size and extends more rostrally than the gracilis nucleus, reaching to the mid-olivary level. Also at this level, the fasciculus cuneatus is greatly reduced. The internal arcuate fibers, axons of the dorsal column neurons, run ventromedially through the reticular formation, decussating in the midline and continuing as the medial lemniscus on the opposite side. This sensory

The part of the rhomboid fossa immediately rostral to the obex, the area postrema, a chemoreceptor trigger zone that regulates blood pressure and emesis, responding to apomorphine and certain glycosides. This area occupies the ependyma of the floor of the fourth ventricle. Its activation may account for the emetic action of certain medications. It is rich in dopaminergic receptors, which may account for nausea associated with the administration of high doses of levodopa, and the antiemetic action of the dopamine antagonists. In addition the area postrema, an integral part of the circumventricular organs, lacks the blood brain barrier. Brain barriers are structures that selectively allow certain substances to enter the central nervous system and exclude others.

decussation (decussation of the internal arcuate fibers) is a landmark for this level of the medulla. The accessory (lateral) cuneate nucleus initially appears at this level as a lateral appendage to the cuneate nucleus, receiving information from Golgi tendon organs, muscle spindles, and tactile receptors of the upper extremity. It conveys this information to the ipsilateral cerebellum, via the cuneocerebellar tract, and also to the VPLc (caudal part of the ventral posterolateral) nucleus of the thalamus.

The central gray expands into the reticular formation, containing the lateral, dorsal, and ventral reticular nuclei. The spinal trigeminal tract and nucleus occupy a dorsolateral position. The hypoglossal nucleus, the dorsal motor nucleus of vagus, the solitary nucleus, the ambiguous nucleus, the inferior olivary nuclear complex and the arcuate nuclei are first seen at this level. These nuclei will be discussed at the mid-olivary level.

Midolivary level

The midolivary level ([Figures 4.6 & 4.7](#)). contains important medullary structures such as the medial and inferior vestibular, inferior olivary, hypoglossal, solitary, arcuate, and dorsal motor vagal nuclei. Most of the ascending and descending pathways associated with the spinal cord and lower medulla continue at this level. The central canal is converted into the fourth ventricle at this level of medulla, while the fourth ventricle expands to maintain a close relationship to certain medullary nuclei.

The medial and inferior vestibular nuclei replace the dorsal column nuclei at this level of the medulla. The medial vestibular nucleus (MVN) lies medial to the inferior vestibular nucleus, continuing rostrally with the superior vestibular nucleus. Both the medial and inferior vestibular nuclei receive primary vestibular fibers and convey the information through the juxtarestiform body

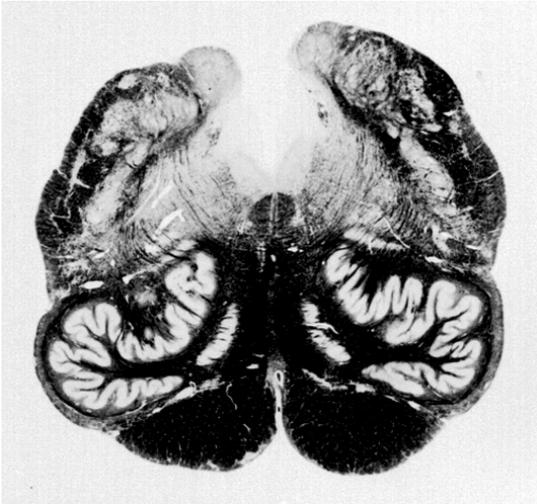


Figure 4.6 The prominent inferior olivary nucleus and expansion of the fourth ventricle are characteristics of this level. The medial longitudinal fasciculus and medial lemniscus maintain similar positions to [Figure 4.5](#)

to the cerebellum. Information received by the medial vestibular nucleus is transmitted to the cervical segments of the spinal cord through the predominantly ipsilateral medial vestibulospinal tract, a component of the medial longitudinal fasciculus (MLF). Ascending fibers from the medial and inferior vestibular nuclei also project to the extraocular motor nuclei via the MLF. The medial longitudinal fasciculus contains axons of the vestibular nuclei that project to the extraocular motor nuclei and to the spinal cord.

The inferior vestibular nucleus, the smallest of the vestibular nuclei, extends from the upper end of the nucleus gracilis to the pontomedullary junction. This nucleus is located between the medial vestibular nucleus and the inferior cerebellar peduncle. It is characteristically speckled due to crossing of longitudinally oriented primary vestibular fibers. Secondary vestibulocerebellar fibers originate almost exclusively from this nucleus and enter the cerebellum through the juxtarestiform body, terminating in the flocculonodular lobe of the cerebellum.

The arcuate nuclei are cerebellar relay nuclei that occupy a position ventral to the pyramids. These nuclei are derived from the rhombic lip and project to the cerebellum via the inferior cerebellar peduncle. Axons of the arcuate nuclei pursue either a midline course, which decussate in the midline and form the stria medullaris of the fourth ventricle, or a more lateral course superficial to the inferior olivary nucleus, forming the posterior external arcuate fibers. The arcuate nuclei, like the pontine nuclei, receive cortical input and convey this information to the opposite cerebellum.



Figure 4.7 Medulla at a more rostral level than in [Figure 4.6](#). Note the great expansion of the inferior olivary and vestibular nuclei, as well as the fourth ventricle

The inferior olivary nuclear complex, the most characteristic feature of this level, occupies the area above the pyramid. It is the largest nucleus in the medulla, which projects to the cerebellum. It consists of the principal and accessory olivary nuclei. The principal olivary nucleus receives the ipsilateral rubro-olivary component of the central tegmental tract. It also receives bilateral cortico-olivary fibers, projections from the periaqueductal gray matter, crossed fibers from the cerebellar cortex and projections from the accessory oculomotor nuclei. These fibers enclose the inferior olivary nuclear complex as *amiculum olivae*. The axons of the principal inferior olivary nucleus form the largest component of the inferior cerebellar peduncle. This crossed olivo-cerebellar tract projects to the lateral parts of the cerebellar cortex. The medial and dorsal accessory olivary nuclei receive impulses from the vestibular, gracilis and cuneate nuclei, and from the spinal cord. They convey this information to the medial portions of the cerebellar cortex.

The hypoglossal nucleus occupies the hypoglossal trigone in the floor of the fourth ventricle. It consists of multipolar neurons that supply general somatic efferents (GSE) to the lingual muscles. This nucleus extends from the level of the inferior olivary nuclear complex to the level of the stria medullaris of the fourth ventricle.

The perihypoglossal nuclei are groups of neurons located adjacent to the hypoglossal nucleus. This group includes the nucleus intercalatus, nucleus of Roller, and the nucleus prepositus hypoglossi. The latter nucleus occupies the same position as the hypoglossal nucleus, but at a more rostral level. Through their connection to the extraocular motor nuclei, cerebellum, and the vestibular nuclei, the perihypoglossal nuclei play an important role in controlling eye movements.



Figure 4.8 Rostral medulla. At this level the inferior olivary nuclei are reduced, the middle cerebellar peduncle is visible, and the cochlear nuclei assume a dorsolateral position to the inferior cerebellar peduncle

The dorsal motor nucleus of the vagus occupies the area dorsolateral to the hypoglossal nucleus, and forms the vagal trigone, a triangular eminence in the fossa rhomboidea. This nuclear column extends from the level of the hypoglossal nucleus both caudally and rostrally, and gives rise to parasympathetic preganglionic (GVE) fibers destined to the thoracic and abdominal viscera.

The nucleus ambiguus lies medial to the lateral reticular nucleus and above the inferior olivary nuclear complex. Neurons of this nucleus give rise to special visceral efferent fibers (SVE), which distribute via the glossopharyngeal and vagus nerves, and general visceral efferents (GVE) via the vagus nerve. The fibers of the ambiguus nucleus join the cranial part of the accessory nerve and travel within branches of the vagus nerve to be distributed to the laryngeal, pharyngeal, and palatal muscles.

The solitary tract is located lateral to the dorsal motor nucleus of the vagus. It is formed by fibers of the vagus, glossopharyngeal, and facial nerves. The solitary nuclear complex surrounds the solitary tract, comprising the medial and lateral nuclear groups. The medial portions of the solitary nucleus unite caudal to the obex, forming the commissural nucleus of the vagus nerve. The medial subdivision and the caudal portion of the lateral subdivision of the solitary nucleus receives general visceral afferents (GVA) which convey information from baroreceptors and chemoreceptors, while the dorsal portion of the lateral nucleus receives taste (special visceral afferent) sensation. The solitary nuclear complex conveys general visceral information to the respiratory, cardiovascular and gastrointestinal centers of the brainstem and also to the autonomic neurons in the spinal cord. The part of the solitary nucleus (gustatory subnucleus) which

deals with taste sensation projects to the ventral posteromedial nucleus of the thalamus via the solitario-thalamic tract.

At this level of the medulla the reticular formation contains neurons for the cardiovascular and respiratory centers. The reticular neurons that remain distinct at this level form the lateral reticular, paramedian reticular, nucleus reticularis gigantocellularis, nucleus reticularis parvocellularis, nucleus raphe obscurus and raphe pallidus. The lateral reticular nucleus lies dorsal to the inferior olivary complex and is primarily a relay nucleus that projects to the cerebellum through the inferior cerebellar peduncle. It receives afferents from the red nucleus, cerebral cortex, and spinal cord. The paramedian nuclei are cerebellar relay nuclei that lie parallel to the median raphe. The nucleus reticularis gigantocellularis occupies the medial zone of the medulla, modulates somatic and visceral motor activity, as well as controls muscle tone through the medullary reticulospinal tract. The nucleus reticularis parvocellularis lies in the lateral (sensory) part of the reticular formation. The nucleus raphe obscurus and raphe pallidus consist of serotonergic neurons. Less visible inferior salivatory nucleus can be seen within the reticular formation of the medulla, which provides parasympathetic fibers to the glossopharyngeal nerve. These fibers synapse in the otic ganglion and later supply the parotid gland. At this level the inferior cerebellar peduncle becomes discernible and continues throughout the upper medulla, occupying the area lateral to the spinal trigeminal tract and nucleus. It is formed primarily by the cerebellar afferents such as the spinocerebellar tracts, cuneocerebellar, etc. Lateral to the raphe nuclei and dorsal to the pyramids, the medial longitudinal fasciculus occupies a vertical position, containing only descending fibers, which project primarily to the spinal cord.

Rostral medulla

In the rostral medullary level (Figure 4.8) enlargement of the inferior cerebellar peduncle and the appearance of the dorsal and ventral cochlear nuclei, dorsolateral to this peduncle will be noticed. Expansion of the medial and inferior vestibular nuclei will be noted at this level. Additionally, the hypoglossal nucleus is replaced at this level by the nucleus prepositus hypoglossi. The reticular formation is expanded and the dorsal motor nucleus of the vagus has disappeared. Similar position to the mid olivary level is maintained by the spinal trigeminal nucleus which is crossed by fibers of the glossopharyngeal nerve.

The nucleus raphe magnus contains the main serotonergic neurons, projecting bilaterally to the spinal cord. This projection courses in the lateral funiculus, inhibiting the spinal neurons that facilitate pain transmission.

Ponto-medullary junction

At the ponto-medullary junction, the cerebellum and the lateral vestibular nucleus appear for the first time, other structures may maintain similar locations and dimensions, or may undergo reduction relative to lower levels. The cerebellum forms the roof of the fourth ventricle, and the flocculus can be observed. The inferior cerebellar peduncle maintains its large size, and is bounded dorsally by the cochlear nuclei. In addition to the medial and inferior vestibular nuclei, the lateral vestibular (Dieter's) nucleus becomes apparent. The medial lemniscus begins to assume a horizontal position and move between the pyramid and the diminishing olivary nuclear complex. You will notice a specific reduction in the size of the inferior olivary nuclear complex, and specifically the accessory olivary nuclei. Furthermore, the nucleus ambiguus, the spinal trigeminal tract and nucleus, and the solitary nucleus maintain their presence at this level. The pyramids begin to disperse, forming fasciculi, as the transition to the basilar pons begins. Additionally, the reticular formation shows expansion. The site of junction of the medulla, cerebellum, and pons form the cerebellopontine angle, a common site for acoustic neuromas.

Pons

The pons (Figures 4.9 & 4.10) forms the mid portion of the brainstem, and the rostral part of the rhombencephalon. It is connected to the cerebellum via the middle cerebellar peduncle. It is bounded rostrally and caudally by the ponto-crural (between the pons and midbrain) and the ponto-bulbar (between the medulla and pons) sulci, respectively. Within the pontocerebellar angle, the pontobulbar sulcus gives passage to the abducens nerve in the midline, and the facial and vestibulo-cochlear nerves more laterally. The dorsal surface of the pons forms the rostral half of the rhomboid fossa, whereas the ventral surface lies adjacent to the basilar part of the occipital bone (clivus) and the dorsum sella of the sphenoid bone. On its ventral surface, the pons is demarcated centrally by the basilar sulcus, which contains the basilar artery. On both sides of the basilar sulcus, the descending cortical motor fibers (cortico-spinal and cortico-bulbar tracts) form the pontine protruberances, which are supplied by the pontine branches of the basilar artery.

Occlusion of the pontine arteries may produce signs and symptoms of locked-in syndrome, a motor disorder that affect the limbs and trunk with the exception of eye movements. For additional information on this condition see [Chapter 20](#) – motor systems.

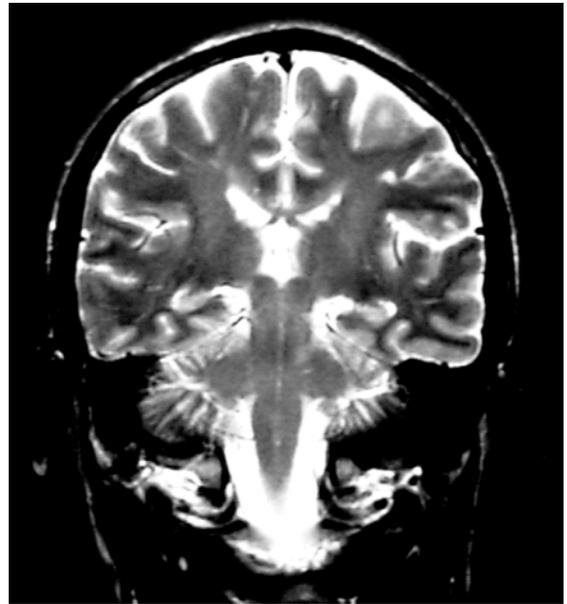


Figure 4.9 MRI Scan illustrating the pons and the prominent middle cerebellar peduncle



Figure 4.10 Ventral surface of the brainstem. The middle cerebellar peduncle is separated from the pons by the trigeminal nerve and the pontomedullary sulcus marks the exit of the abducens, facial and vestibulocochlear nerves



Figure 4.11 Photograph of the basilar artery on the ventral surface of the pons. The anterior inferior cerebellar, the superior cerebellar and the posterior cerebral arteries are shown. Notice the connection of the vertebrobasilar system to the internal carotid artery via the Posterior communicating artery

Ventral to the middle cerebellar peduncle, the trigeminal nerve emerges from the midpons. Transverse section of the pons reveals a dorsal tegmentum and a ventral basilar portion. The tegmentum is the rostral continuation of the medullary reticular formation, while the basilar pons consists of the longitudinal cortico-spinal and corticobulbar fibers, as well as the transverse ponto-cerebellar fibers.

Paramedian branches of the basilar artery supply the medial pons, and the short circumferential branches nourish the pontine nuclei, corticospinal and corticobulbar tracts, and some of the trigeminal nuclei. The long circumferential branches of the basilar artery and some branches from the anterior inferior cerebellar artery supply the caudal pontine tegmentum. The superior cerebellar artery supplies the tegmentum of the rostral pons. At the pontobulbar sulcus, the basilar artery is formed by the union of the vertebral arteries, ending in the rostral pons by dividing into the posterior cerebral arteries (Figures 4.11 & 4.12). It supplies the pons, cerebellum, midbrain, temporal, and occipital lobes of the brain. This vessel gives rise to the anterior inferior cerebellar, labyrinthine, pontine, superior cerebellar, and posterior cerebral arteries. Pontine veins open primarily into the sigmoid sinus, or the petrosal sinuses.

The pons exhibits certain unique structures and features, some of which may continue caudally in the medulla and spinal cord and rostrally with the midbrain. All these

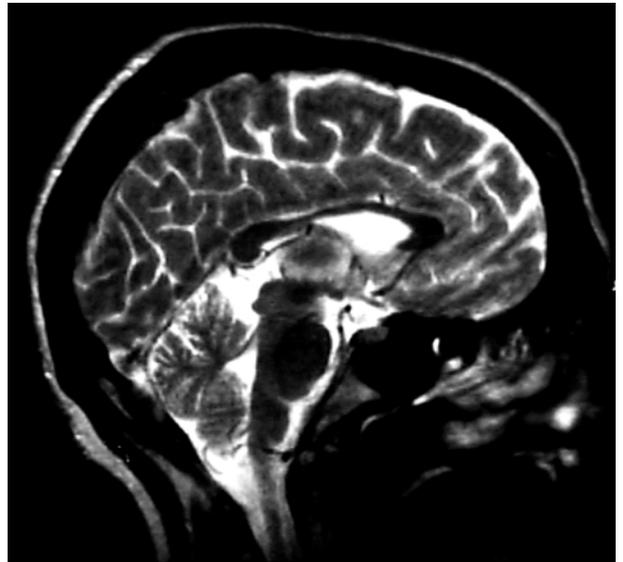


Figure 4.12 MRI scan illustrates the pons ventral to the cerebellum separated by the fourth ventricle. The basilar artery and some of its branches are also identified

neuronal structures are best identified at the caudal pons, midpons, and rostral pons.

Caudal pons

There are characteristic neuronal elements at the caudal pons, which include the abducens, facial motor, superior vestibular and superior olivary nuclei (Figure 4.13). Appearance of the lateral lemniscus and continuation of the basilar pons are additional features of this level.

The abducens nucleus (GSE) lies deep to the ependyma of the rhomboid fossa, and as a component of the facial colliculus. It is surrounded by the motor fibers of the facial nerve. This nucleus is unique among cranial nerve motor nuclei in that it contains two populations of neurons. The larger population is formed by the alpha motor neurons, which constitutes the abducens nerve, whereas the smaller population of internuclear neurones sends axons through the contralateral MLF to the motor neurons of the oculomotor nucleus, innervating the medial rectus muscle during lateral gaze.

The facial motor nucleus (SVE) occupies the lateral tegmentum, adjacent to the superior olivary nucleus, and gives rise to the motor fibers (SVE) that supply the muscles of facial expression, stapedius, stylohyoid, and the posterior belly of the digastric muscle. These fibers encircle the abducens nucleus (internal genu), form the facial colliculus, and later emerge through the ponto-cerebellar angle.

The superior salivatory nucleus (GVE) lies adjacent to the caudal end of the facial motor nucleus. It provides

Presence of these two neuronal populations within the abducens nucleus may account for the distinct difference in the deficits produced by lesions of the abducens nerve versus the abducens nucleus. A lesion that only damages the abducens nerve results in medial strabismus and diplopia, while a damage to the abducens nucleus produces signs of lateral gaze palsy (inability to look to the side of the lesion).

preganglionic parasympathetic fibers to the pterygopalatine and submandibular ganglia via the greater petrosal, and chorda tympani, respectively. Eventually, the generated impulses enhance lacrimation, salivary secretion, and secretion of mucus glands of the palate, nose and pharynx.

The lateral vestibular (Deiter's) nucleus (SSA) consists of multipolar giant neurons, which are the source of the principal vestibulospinal tract. This nucleus is located in the lateral portion of the ventricular floor and extends from the rostral end of the inferior vestibular nucleus to the level of the abducens nucleus. It receives primary vestibular fibers and sends both crossed and uncrossed ascending fibers via the MLF, in a symmetric manner, to the abducens, trochlear, and oculomotor nuclei.

The superior vestibular nucleus (SSA), the most rostral vestibular nucleus, lies inferior to the superior cerebellar peduncle. It receives primary vestibular fibers and sends ipsilateral secondary vestibular fibers through the MLF, predominantly to the trochlear nucleus, and the intermediate and dorsal cell columns of the oculomotor nuclear complex that innervate the inferior oblique and the inferior rectus, respectively.

The ventral and dorsal cochlear nuclei (SSA) are located dorsolateral to the inferior cerebellar peduncle with the ventral cochlear nucleus, the largest, appears to be continuous with the dorsal cochlear nucleus. The dorsal cochlear nucleus forms the acoustic tubercle in the floor of the fourth ventricle. These cochlear nuclei receive auditory impulses via the central processes of the spiral ganglia and convey the processed auditory information through the acoustic striae to the superior olivary nuclei and trapezoid nuclei and eventually to the inferior colliculi via the lateral lemniscus.

The trapezoid body is formed mainly by the decussating ventral acoustic striae from the ventral cochlear, superior olivary, and trapezoid nuclei. This bundle of fibers occupies a midline position ventral to the medial lemniscus.

The superior olivary nucleus is an auditory relay nucleus, which extends from the level of the facial motor nucleus to the level of the trigeminal motor nucleus. It



Figure 4.13 Caudal pons and the level of the abducens and facial nuclei. The medial lemniscus assumes a horizontal position and the middle cerebellar peduncle are enlarged. Trapezoid body and superior vestibular nucleus are illustrated

receives collaterals from the acoustic striae of both sides. This nucleus contributes fibers to the trapezoid body and the lateral lemniscus.

The lateral lemniscus represents the main ascending auditory pathway and is located lateral to the superior olivary nucleus, containing the corresponding nucleus that receives secondary and tertiary auditory fibers.

The spinal trigeminal nucleus lies lateral to the facial motor nucleus and ventral to the lateral vestibular nucleus. It continues rostrally with the chief sensory nucleus of the trigeminal nerve. This nucleus receives pain and temperature sensations (GSA) from the head region through branches of the trigeminal, facial, glossopharyngeal, and vagus nerves. It provides axons to the ventral trigeminal nucleus. Descending fibers from the trigeminal ganglion form the spinal trigeminal tract lateral to the corresponding nucleus.

The inferior cerebellar peduncle reaches its maximum size at this level, connects the medulla to the cerebellum, transmitting most of the cerebellar afferent fibers from the spinal cord. It consists of a medial portion (juxtarestiform body) and a lateral portion (restiform body).

The medial longitudinal fasciculus (MLF) contains ascending vestibulo-ocular fibers and axons of the internuclear neurons of the abducens nucleus en route to the ventral cell column of the oculomotor nuclear complex. It also contains fibers of the interstitio-spinal, medial vestibulospinal and pontine reticulo-spinal tracts.

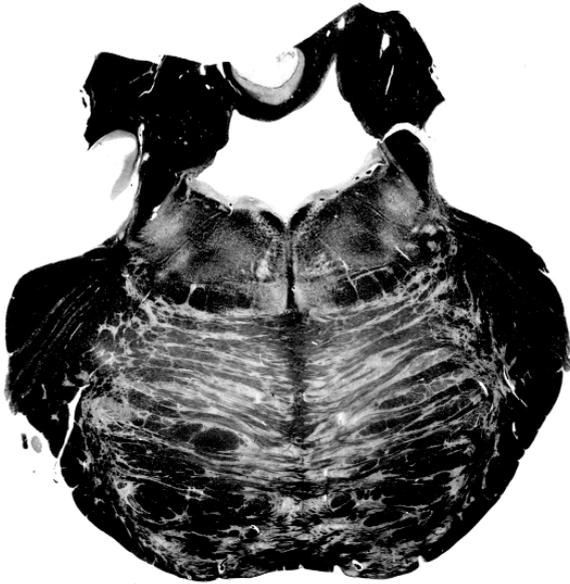


Figure 4.14 Section of the pons at the level of the trigeminal nerve. Corticospinal and corticobulbar tracts and the pontine nuclei occupy the entire basilar pons

The reticular formation at this level of the pons contains the nucleus reticularis pontis caudalis that contributes to the pontine reticulospinal tract. The area of the reticular formation adjacent to the abducens nuclei has been given special consideration due to its involvement in lateral gaze palsy. This region, the para-pontine reticular formation (PPRF), is thought to contain the center for lateral gaze. Ischemic degeneration of the parapontine reticular formation may occur as a result of occlusion of the basilar artery.

In the basilar part of the pons descending corticofugal fibers such as the corticospinal, corticobulbar, and the pontocerebellar fibers lie. Fibers of the pontocerebellar arise from the pontine nuclei, constituting an indirect pathway from the cerebral cortex to the cerebellum through the middle cerebellar peduncle. As it descends through the pons towards the medulla, the central tegmental tract deviates laterally, occupying the center of the pontine tegmentum.

The middle cerebellar peduncle (Figure 4.9), the largest cerebellar peduncle, may remain visible at this level, consisting exclusively of the pontocerebellar fibers.

The medial lemniscus occupies a horizontal position in the ventral part of the tegmentum, dorsal to the trapezoid body.

Mid-pons (level of the trigeminal nerve)

The midpontine level (Figures 4.14 & 4.15) is characterized by the presence of the trigeminal nerve fibers, principal sensory, mesencephalic trigeminal, and

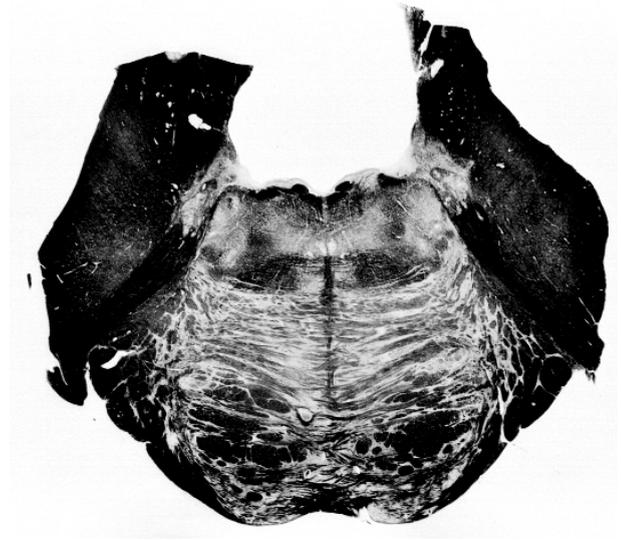


Figure 4.15 Section of the pons at the level of the trigeminal nerve showing the motor and principal sensory nuclei

motor trigeminal nuclei. The distinct appearance of the superior cerebellar peduncle and visibility of the middle cerebellar peduncle are additional features of this pontine level.

The principal (chief) trigeminal sensory (Figures 4.14 & 4.15) nucleus lies lateral to the fibers of the trigeminal nerve and is concerned with pressure and tactile sensations. In this nucleus, the mandibular fibers occupy a dorsal position to the maxillary fibers which assume an intermediate position, whereas the ophthalmic fibers occupy a ventral position in this nucleus. The ascending fibers from the ventral part of this nucleus contribute to the ventral trigeminal lemniscus, while the dorsal part comprises the dorsal trigeminal lemniscus. The most rostral part of the spinal trigeminal nucleus (pars oralis) merges with the principal sensory nucleus.

The motor trigeminal nucleus lies medial to entering fibers of the trigeminal nerve, and provides innervation through its mandibular division (V3) to the muscles of mastication, tensor tympani, tensor palatini, and the anterior belly of the digastric muscle. The motor trigeminal nucleus mediates the jaw jerk reflex and receives bilateral corticobulbar fibers (via interneurons).

The mesencephalic nucleus is the only sensory nucleus, which contains unipolar neurons that are retained within the CNS. This nucleus extends from the level of the trigeminal nerve to the caudal midbrain. It primarily conveys proprioceptive impulses from the muscles of mastication to the motor trigeminal nucleus, mediating the monosynaptic “jaw jerk” reflex. It also receives input from the facial and ocular muscles, temporomandibular

joint, and the peridontium. In that regard it may be considered homologous to some degree to the Clarke's nucleus of the spinal cord. considered homologous to some degree to the Clarke's nucleus of the spinal cord. The mesencephalic tract is formed by processes of the corresponding nucleus and provides collaterals to the motor root of the trigeminal nerve. The mesencephalic tract is formed by processes of the corresponding nucleus, providing collaterals to the motor root of the trigeminal nerve.

- The superior cerebellar peduncle lies dorsolateral to the fourth ventricle and contains cerebellar efferents, which have not yet undergone decussation.
- The middle cerebellar peduncle is pierced by the trigeminal nerve, losing its connection to the cerebellum at this level.
- The nucleus reticularis pontis oralis is part of the medial reticular zone that contributes to the pontine reticulospinal tract.
- The superior central nucleus is also seen at this level of the pons.
- The basilar pons expands at this level containing essentially the same structures seen in the caudal pons.
- The fourth ventricle is narrower and is bounded dorsally by the superior medullary velum.

Rostral pons (isthmus)

At the level of the isthmus (Figure 4.16) the fourth ventricle terminates and the cerebral aqueduct begins. It is the site of decussation of the trochlear nerve fibers and the appearance of the pigmented locus ceruleus. The basilar pons assumes its greatest size and the lemniscal triad occupy a dorsal position in the pontine tegmentum.

At more rostral levels, the central gray matter expands around the fourth ventricle and becomes the periaqueductal gray. At the same time expansion of the basilar part of the pons and narrowing of the tegmental portion occurs. Additionally, the medially directed fibers of the superior cerebellar peduncles begin entering the tegmentum. The locus ceruleus and the trigeminal mesencephalic nucleus occupy basically the same position.

Dorsolateral to the superior cerebellar peduncle the lemniscal trigone occupies the lateral part of the tegmentum. This trigone is formed by the lateral lemniscus dorsally, the medial lemniscus ventrally, and by the spinal lemniscus, assuming an intermediate position. The trigeminal lemniscus appears dorsal to the medial lemniscus and the central tegmental tract becomes very prominent tegmental structure at this level.

The reticular formation at this level of the pons consists of a number of nuclei, which include reticulotegmental, superior central (median), and the dorsal raphe nuclei.

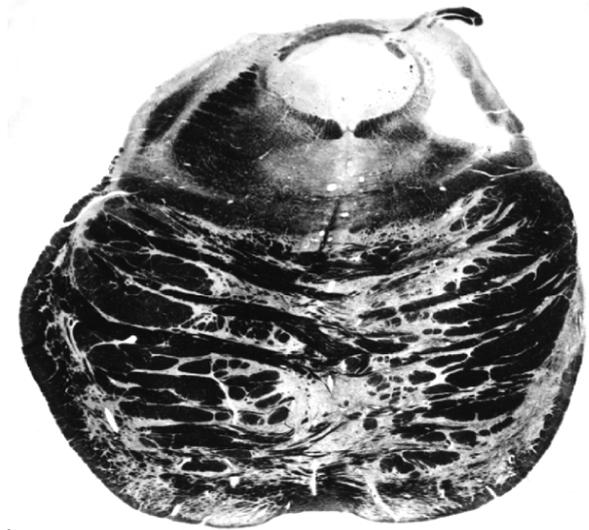


Figure 4.16 Rostral pons (isthmus). Note the decussation of the trochlear nerves in the superior medullary velum and crossing of the superior cerebellar peduncles within the tegmentum

- The reticulotegmental nucleus, one of the pontine paramedian reticular nuclei that receives input from the dentate nuclei of the cerebellum and the cerebral cortex. This nucleus projects back to the contralateral cerebellar cortex and the ipsilateral vermis.
- The superior central (median) nucleus lies dorsal to the reticulotegmental nucleus. It sends impulses to the superior colliculus, pretectum, hippocampal formation, and the mammillary bodies.
- The dorsal raphe nucleus projects to the lateral geniculate nucleus, the neostriatum, the substantia nigra, the pyriform lobe, and the olfactory bulb.

Both the superior central and dorsal raphe nuclei consist of serotonergic neurons which project via the medial forebrain bundle to the hypothalamus which in turn projects to the substantia nigra, intralaminar thalamic nuclei, and the septal area.

Since the medulla and pons contribute to the formation of the fourth ventricle and share important relationships with this cavity, a brief account of this ventricle will serve a useful purpose.

The fourth ventricle lies dorsal to the pons and medulla and is rostrally continuous with the cerebral aqueduct and caudally with the central canal. Lateral extensions of this

Since the superior medullary velum contains the decussating fibers of the trochlear nerves, a lesion of this area may produce bilateral trochlear nerve palsy (superior medullary velum syndrome).

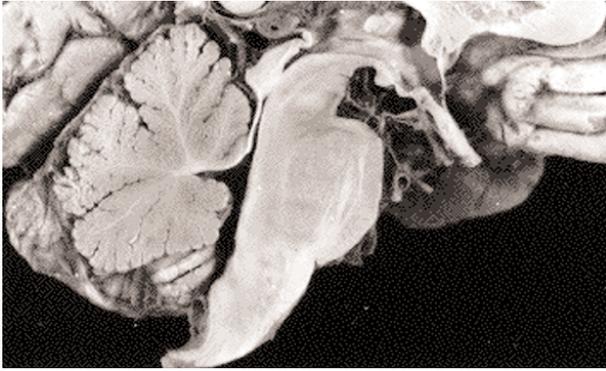


Figure 4.17 Midsagittal section of the brainstem. The midbrain with the associated cerebral aqueduct and tectum are clearly visible

ventricle dorsal to the inferior cerebellar peduncles are known as the lateral recesses, which terminate in the lateral foramina of Luschka. Within the caudal part of the fossa rhomboidea (the floor of the fourth ventricle), the hypoglossal and vagal trigones are seen. These trigones, overlie the hypoglossal and dorsal motor nucleus of vagus, respectively. Pneumotaxic and emetic centers, which lack blood brain barrier, are represented in area postrema, a small site near the vagal trigone and on both sides of the obex. Rostral half of the rhomboid fossa contains the facial colliculus and the pigmented locus ceruleus. The facial colliculus is formed by the facial nerve encircling the abducens nucleus. Noradrenergic neurons are concentrated in the locus ceruleus, a pigmented nucleus, which extends from the rostral pons to the caudal midbrain. Another site in the fossa rhomboidea is the vestibular area overlies the vestibular nuclei, corresponds to the site of the lateral recesses, and is crossed on both sides by fibers of the stria medullaris of the fourth ventricle, emanating from the arcuate nuclei. Examination of the roof of the fourth ventricle reveals a cranial part formed by the superior medullary velum and superior cerebellar peduncles, and a caudal part mainly formed by the inferior medullary velum containing the foramen of Magendie. Circulation of CSF between the subarachnoid space (cerebellomedullary cistern) and the fourth ventricle, is maintained via the foramina Luschka and Magendie.

Mesencephalon (midbrain)

The midbrain (Figures 4.17, 4.18, 4.19 & 4.20) represents the shortest part of the brainstem and is derived from the unmodified third brain vesicle. It is bounded rostrally by an imaginary line that passes behind the posterior commissure and the mammillary bodies, and caudally by another line that connects the ponto-crural sulcus and the posterior borders of the inferior colliculi. The midbrain

consists of the tectum, tegmentum, and the basis pedunculi. Each half of the midbrain, excluding the tectum, is known as the cerebral peduncle. Four rounded eminences connected by commissures constitute the tectum (quadrigeminal plate). The larger and more grayish upper pair of eminences is known as the superior colliculi, while the smaller lower pair is termed the inferior colliculi.

For descriptive purposes the midbrain (Figure 4.18 & 4.19 & 4.20) may be classified into superior and inferior collicular levels. These two levels contain common features and structures that include the cerebral aqueduct, substantia nigra, crus cerebri, and the trigeminal, spinal (anterolateral system), and medial lemnisci.

The cerebral aqueduct interconnects the third and fourth ventricles, separating the tectum from the tegmentum of the midbrain. The periaqueductal gray matter surrounds this duct, containing the accessory oculomotor nuclei and the dorsal tegmental nucleus. This area gives rise to an inhibitory descending pathway for painful stimuli.

The substantia nigra is the largest pigmented nucleus of the midbrain, lying dorsal to the crus cerebri. It consists of pars reticularis and pars compacta. The pars compacta is the main source of the inhibitory neurotransmitter dopamine, forming with the pars lateralis, the group A9 of Dahlstrom and Fuxe. Group A9 together with the retrorubral nucleus (group A8) constitutes the principal dopaminergic neurons of the midbrain. Group A10 (paranigral nucleus) interconnects the pars compacta of the substantia nigra on both sides. Acetylcholine is also contained in these neurons. The substantia nigra receives input from the striatum, globus pallidus, and the subthalamic nucleus. It projects to the striatum, reticular formation, tectum, pedunculopontine nucleus, and the thalamus. Nigral projection to the tectum arises from the pars reticulata, influencing coordination of head and eye movements. In addition to dopamine, the substantia nigra contains a high concentration of substance P, serotonin and glutamic acid decarboxylase (GAD).

The crus cerebri is the most ventral portion of the cerebral peduncles, containing in its medial two thirds the corticospinal and corticobulbar fibers. Within the crus cerebri the frontopontine fibers are medial, while the parietopontine, temporopontine and occipitopontine fibers assume a more lateral position. These peduncles form the boundaries of the interpeduncular fossa that gives passage to the oculomotor nerve. The floor of this fossa forms the posterior perforated substance, allowing passage of the central branches of the posterior cerebral arteries.

The trigeminal lemnisci lie dorsal to the medial lemniscus, carrying pain, temperature, and tactile sensations to the ventral posteromedial nucleus of the thalamus from the face and head region. The ventral trigeminal lemniscus, a crossed pathway derived from the

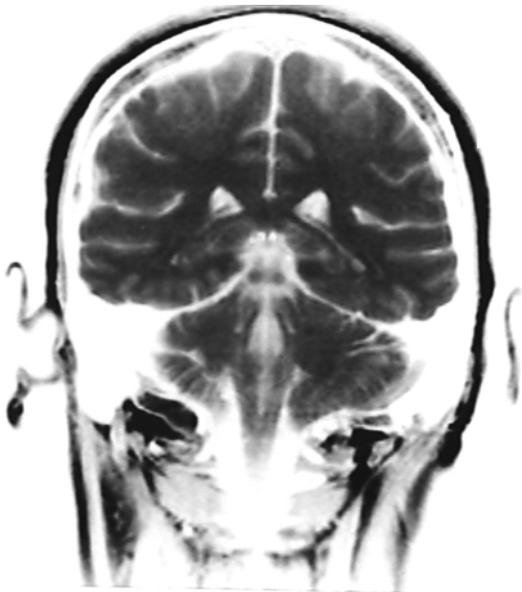


Figure 4.18 MRI scan illustrates the tectum and connection of the midbrain to the cerebellum via the superior cerebellar peduncle

spinal trigeminal nucleus and the ventral portion of the principal sensory nucleus, terminates in the ventral posteromedial (VPM) nucleus of thalamus. The Neuronal axons of the dorsal portion of the principal sensory nucleus form the ipsilateral dorsal trigeminal lemniscus.

The spinal lemniscus (anterolateral system) is located dorsal to the lateral part of the substantia nigra, bounded dorsolaterally by the lateral lemniscus and ventromedially by the medial lemniscus. It consists primarily of fibers of the lateral spinothalamic tract.

The medial lemniscus is the principal pathway that conveys conscious proprioception, fine tactile sensation, and vibratory sense to the thalamus. It assumes a horizontal position ventral to the trigeminal and spinal lemnisci.

The medial longitudinal fasciculus at this level consists of ascending vestibulo-ocular fibers and axons of abducens internuclear neurons, projecting to the trochlear and oculomotor nuclei.

The central tegmental tract, a composite bundle of fibers, lies dorsolateral to the red nucleus and lateral to the MLF. The descending components of this pathway originate from the red nucleus, periaqueductal gray, thalamus, and the tegmentum of the midbrain en route to the inferior olivary nucleus (where it forms the amiculum or the capsule of the inferior olivary complex). This pathway regulates intra-reticular conduction through its

Obstruction of the cerebral aqueduct may occur congenitally, resulting in a non-communicating hydrocephalus.



Figure 4.19 Section of the left half of the midbrain at the level of the superior colliculus. This photograph illustrates the tectum, tegmentum, substantia nigra, and the crus cerebri

A lesion of the substantia nigra is responsible for signs and symptoms of Parkinson's disease.

short ascending fibers. It also conveys cortical motor input to the contralateral cerebellum through the inferior olivary nucleus, and eventually to the red nucleus and basal nuclei (a collection of subcortical nuclei embedded in the white matter of the cerebral hemispheres) via cerebellar projections. The central tegmental tract is also considered to be the main ascending pathway for the reticular formation, conveying impulses to the subthalamus and the intralaminar thalamic nuclei.

The dorsal longitudinal fasciculus, a predominantly ipsilateral tract ventrolateral to the cerebral aqueduct, contains ascending and descending pathways. It connects the hypothalamus to the Edinger-Westphal, solitary, salivatory, facial, hypoglossal and ambiguus nuclei, as well as to the tectum.

The midbrain is supplied by branches of the posterior cerebral, posterior communicating, anterior choroidal, and the superior cerebellar arteries. The paramedian branches of the posterior cerebral and posterior communicating arteries supply midline structures including the oculomotor nuclei, medial longitudinal fasciculi, and medial parts of the substantia nigra. The lateral tegmentum, medial lemnisci, spinal lemnisci, substantia nigra, and crus cerebri are supplied by the circumferential



Figure 4.20 CT scan of the brain showing the tectum of the midbrain in relationship to the third ventricle and thalamus

branches of the posterior cerebral and superior cerebellar arteries. The long circumferential branches of the posterior cerebral artery and small branches from the superior cerebellar artery supply the tectum. Venous blood of the midbrain terminates in the internal cerebral vein or the great cerebral vein of Galen.

Inferior collicular level

The inferior collicular level (Figures 4.21 & 4.22) contains the inferior colliculi, trochlear nucleus, tegmental nuclei, locus ceruleus, lateral lemniscus, and pedunclopontine nucleus.

The inferior colliculus is connected to the medial geniculate body via the inferior brachium, representing the auditory reflex center. It consists of a large central nucleus, responding to binaural impulses, and a pericentral nucleus concerned with the ipsilateral auditory impulses. The principal afferent to the inferior colliculus is the lateral lemniscus that conveys auditory impulses to the medial geniculate body via the brachium of the inferior colliculus.

The trochlear nucleus is a round nucleus embedded within the medial longitudinal fasciculus, lying ventral to the periaqueductal gray matter. Its axons, which constitute the trochlear nerve, travel dorsally and decussate completely in the superior medullary velum. These fibers emerge from the dorsal surface of the pons, immediately below the inferior colliculi, innervating the superior oblique muscle.

The dorsal tegmental (supratrochlear) nucleus is located between the two trochlear nuclei, receiving input from the mammillary bodies and the interpeduncular nucleus through the mammillotegmental tract. Projections from this nucleus ascend within the dorsal longitudinal fasciculus to be distributed to the limbic system nuclei of the diencephalon and telencephalon.

The ventral tegmental nucleus is considered to be a continuation of the superior central nucleus of the pons. Both the dorsal and ventral tegmental nuclei convey impulses to the lateral hypothalamus, the preoptic area, and the mammillary bodies via the dorsal longitudinal fasciculus, mammillary peduncle, and the medial forebrain bundle.

The dorsal raphe nucleus, which lies adjacent to the dorsal tegmental nucleus, synthesizes and transports serotonin.

The interpeduncular nucleus is located dorsal to the interpeduncular fossa receiving the habenulopeduncular tract.

The pedunculo-pontine nucleus, which lies in the lateral tegmentum ventral to the inferior colliculus, modulates the activities of the nigral and pallidal neurons through its connections to the cerebral cortex, globus pallidus, and the substantia nigra. Its compact part is mainly cholinergic that projects to the thalamus, regulating locomotion. This nucleus is crossed by fibers of the superior cerebellar peduncle.

The parabrachial nucleus contains a collection of cholinergic neurons that are located lateral to the lateral lemniscus and ventrolateral to the inferior colliculus. Neurons of these nuclei regulate both moving and stationary visual stimuli via their bilateral connections to the superior colliculus.

The locus ceruleus nucleus appears at the rostral pons medial to the trigeminal mesencephalic nucleus. It is a pigmented bluish nucleus which may readily be identified on a gross brain. This nucleus synthesizes and transports

Lesions involving the trochlear nerve result in extorsion, impairment of downward movement of the affected eye, and vertical diplopia, which increases on, attempted downward gaze. Patients compensate for this deficit and ameliorate diplopia by tilting the head to the contralateral side (Bielschowsky sign). Infants with this deficit may develop torticollis (spasmodic contracture of the sternocleidomastoid muscle) as a result of continuous tilting of the head. This condition is also discussed in detail in [Chapter 21](#).

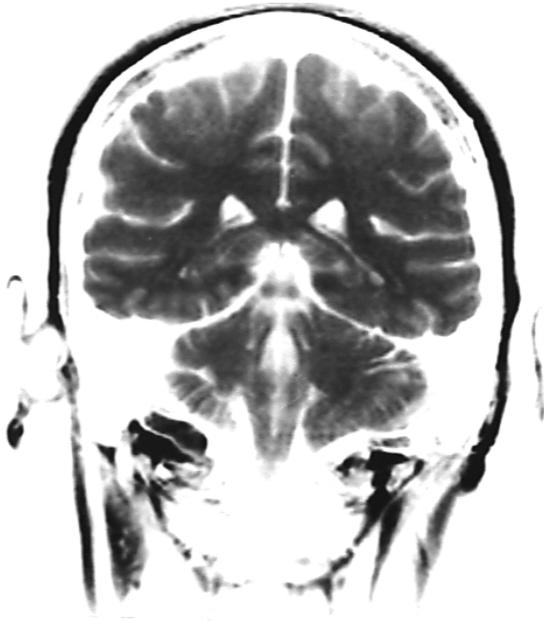


Figure 4.21 Image of the right half of the midbrain. Mesencephalic trigeminal nucleus and lemniscal triad (medial, lateral, and spinal lemnisci)

norepinephrine to the midbrain, cerebellum, medulla, spinal cord, diencephalon, and telencephalon. The spinal projection of the locus ceruleus descends in the lateral funiculus and exerts direct inhibitory influences upon the neurons that form the lateral spinothalamic tract. These projections use a receptors and not the opiate receptors, as is the case with the raphe-spinal tract. Noradrenergic neurons of the locus ceruleus project via the medial forebrain bundle, stria medullaris, and the mammillary peduncle to the cerebral cortex, hypothalamus, midbrain tegmentum, and the telencephalon. Intralaminar thalamic nuclei receive profuse projections from the locus ceruleus. Fibers of the locus ceruleus also terminate on small cerebral vessels and capillaries accounting for the possible role of this nucleus in the regulation of the cerebral blood flow. Locus ceruleus also regulates the functions of the preganglionic sympathetic neurons of the spinal cord and modulates cerebellar activities. Additionally, this nucleus is involved in the reinforcement mechanism essential for learning, and REM sleep (see also the reticular formation, [chapter 5](#)).

The superior cerebellar peduncles complete their decussation within the tegmentum. These peduncles represent the main cerebellar output to the ventral lateral nucleus of the thalamus and the red nucleus.



Figure 4.22 Section of the midbrain at the level of the inferior colliculus illustrating the trochlear nucleus and the site of decussation of the superior cerebellar peduncles

The lateral lemniscus is the principal ascending auditory pathway, which occupies the dorsolateral part of the midbrain, terminating in the inferior colliculus.

Superior collicular level

In addition to the common characteristics discussed earlier the midbrain at this level contains the superior colliculus, red nucleus, and the oculomotor nucleus ([Figures 4.19 & 4.20](#))

The superior colliculus ([Figures 4.19, 4.23 & 4.24](#)) consists of alternate gray and white laminae, constituting the visual reflex and vertical gaze centers. It is connected to the lateral geniculate body and partly to the optic tracts via the brachium of the superior colliculus. The superior colliculus lies ventral to the posterior commissure and the pineal gland, a relationship that bear clinical significance in Parinaud's syndrome in which vertical gaze palsy is associated with a tumor of the pineal gland. Movements of the head and neck toward visual and auditory stimuli are mediated by projections of the superior colliculi to the brainstem and spinal cord via the tectobulbar and tectospinal tracts, respectively. In addition to its role in visual reflexes, the superior colliculus also receives general somatic afferents through the spinotectal tract, a pathway that is incorporated within the spinal lemniscus.

The red nucleus ([Figures 4.19 & 4.20](#)), a highly vascularized nucleus in the center of the midbrain tegmentum, is encircled by fibers of the superior cerebellar peduncle. Medial to the red nucleus the habenulopeduncular tract (fasciculus retroflexus) descends, projecting to the interpeduncular nucleus. It is



Figure 4.23 MRI scan through the midbrain at the level of the inferior colliculus. This image illustrates the relationship of the midbrain to the uncus and posterior cerebral arteries

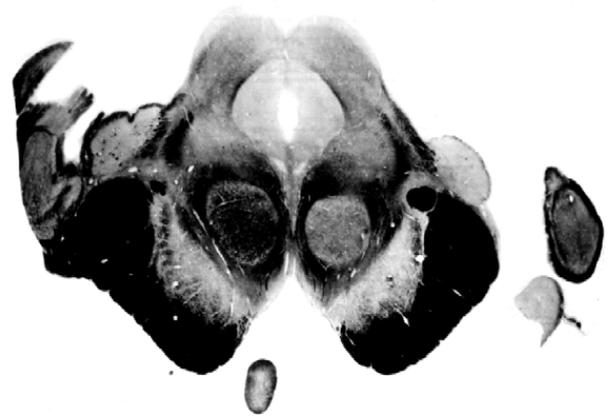


Figure 4.24 Section of the midbrain at its junction with diencephalon. The superior colliculus, oculomotor nucleus and nerve, and the red nucleus are principal features of this level

crossed by fibers of the oculomotor nerve en route to the interpeduncular fossa. It has a caudal magnocellular and a rostral parvocellular part. The magnocellular part gives rise to the contralateral rubrospinal tract, which controls flexor muscle tone; delivering cerebellar input to the upper three cervical spinal cord segments. Fibers of the rubrospinal tract are incorporated within the lateral corticospinal tract, maintaining identical termination sites. Cerebral cortical input to the red nucleus is conveyed via the corticorubral fibers, while cerebellar input emanating from the contralateral dentate, globose and emboliform nuclei are carried via the middle cerebellar peduncle. Information received by the red nucleus is delivered to laminae V through VII of the spinal cord. The parvocellular part of the red nucleus form the rubro-olivary tract that projects to the ipsilateral inferior olivary nucleus within the central tegmental tract. Due to massive connections of the inferior olivary nucleus to the cerebellum, the rubro-olivary tract forms part of a cerebellar feedback loop.

The oculomotor nuclear complex has a “V” shaped configuration and is located medial to the medial longitudinal fasciculus (MLF). It consists of somatic and visceral columns. The somatic columns (GSE) provide innervation to the extraocular muscles (with the exception of the lateral rectus and superior oblique) and levator palpebrae muscles, while the visceral columns (Edinger Westphal nucleus) provide presynaptic parasympathetic fibers (GVE) to the ciliary ganglion which eventually innervate the constrictor pupillae and ciliary muscles.

Embryologically the reticular formation is considered to be one of oldest functional units in the central nervous system. It occupies the central core of the brainstem, extending rostrally to include the midline, intralaminar and reticular thalamic nuclei, and the zona incerta of the subthalamus. Reticular neurons mediate local reflexes, receiving collaterals from the ascending and descending pathways with the exception of the medial lemniscus. The reticular formation is bounded ventromedially by the pyramidal tracts and the medial lemnisci, and dorsolaterally by the secondary sensory pathways. Regulation of both somatic and visceral (autonomic) motor functions and modulation of the electrocortical activities are maintained by massive reticular connections to the autonomic centers in the brain and the spinal cord. Additional functions of the reticular formation include control of emotional expression, pain transmission, and regulation of reflex activities associated with the cranial nerves.

General organization of the reticular formation

General organization of the reticular formation

The reticular formation consists of deeply localized, poorly identified nuclear groups, which are particularly scattered, in the brainstem. It contains centers that generate motor activities (e.g. walking and running), and regulate conjugate eye movements, and respiratory and cardiovascular activities. It also contains centers for expiration, inspiration, vomiting, and deglutition, and is also concerned with the regulation of blood pressure. Reticular neurons are classified into median raphe, paramedian, and medial and lateral nuclear columns.

The raphe nuclei (Figure 5.1) synthesize and transport serotonin to various areas of the central nervous system through ascending and descending projections. Dahlstrom and Fuxe group these serotonergic neurons into nine clusters. Serotonin, the neurotransmitter for raphe nuclei, is involved in the slow (NREM) phase of sleep, behavioral regulation, and inhibition of pain transmission. Raphe neurons also contain substance P. Raphe neurons within the pons project inhibitory impulses to the parabrachial reticular formation (PPRF) producing rapid eye movement (REM) during sleep. They also send inhibitory fibers to the nuclei reticularis pontine oralis and caudalis, which upon release from inhibition, elicit involuntary movements of the trunk and limbs. Inhibitory input to the pontine neurons that project to the lateral geniculate body may be responsible for the pontine-geniculate-occipital spikes and associated visual-natured REM sleep. It has been suggested that the latter phenomenon and dreams may be suppressed by certain medications or upon consumption of dairy product that contain tryptophan. Lesions of the raphe nuclei produce prolonged insomnia. This group of nuclei includes the raphe pallidus and raphe obscurus, raphe magnus, dorsal raphe nucleus, and superior central nucleus

The nucleus raphe pallidus is located in the pons, projecting to laminae I, II and V of the dorsal horns of all spinal segments, as well as to the intermediolateral columns. The spinal projections of the raphe pallidus convey pain-controlling input from the periaqueductal gray matter to the spinal cord.

Nucleus raphe obscurus lies in the pons and forms the inhibitory intermediate raphe spinal projection to the spinal cord, modulating the sympathetic neurons of the intermediolateral column and thus regulating the cardiovascular function.

The nucleus raphe magnus is located in the rostral medulla and caudal pons and contains B3 neurons, maintaining bilateral projections to the spinal cord within the Lissauer tract and to the posterior part of the spinal trigeminal nucleus within the spinal trigeminal tract. These spinal projections descend in the lateral funiculus

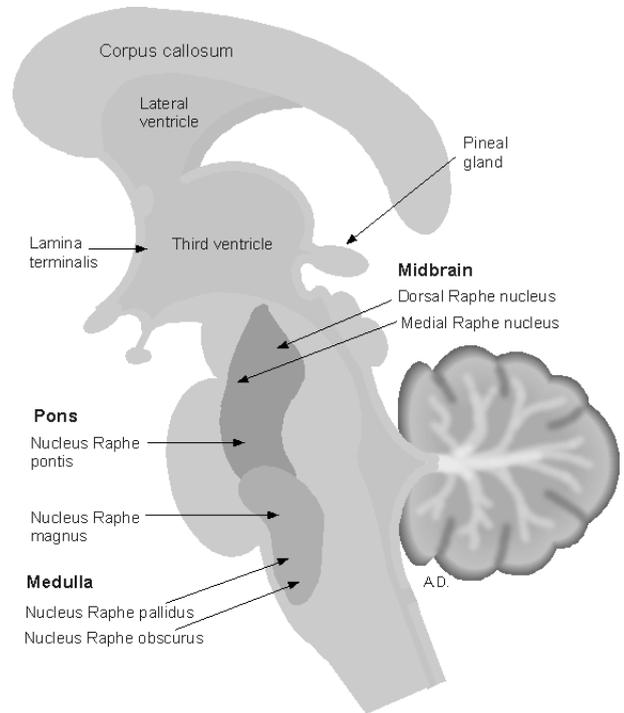


Figure 5.1 Schematic drawing of the brainstem illustrating the midline raphe nuclei of the reticular formation

may inhibit the neurons which transmit painful stimuli, acting as an additional endogenous analgesic pathway. The serotonergic component of the spinal projection, which represents 20% of all these fibers, establish excitatory synaptic contacts with the enkephalinergic neurons and inhibitory contacts with the lateral spinothalamic tract neurons of the substantia gelatinosa. These synaptic contacts at spinal levels produce stimulus-bound profound analgesia, a common phenomenon seen upon stimulation of the periaqueductal and periventricular gray matter. They are also thought to enhance motor response to nociceptive stimuli via fight and flight response.

The dorsal nucleus of the raphe is located in the midbrain, at the ponto-mesencephalic junction. This nucleus corresponds to group B7, conveying impulses to the hypothalamus, putamen, caudate nucleus, amygdala, intralaminar thalamic nuclei, and septal region via the medial forebrain bundle. It also projects to the superior colliculus, mammillary bodies, hippocampal formation, substantia nigra, locus ceruleus, olfactory cortex, and the lateral geniculate body. Reciprocal connections between the dorsal nucleus of raphe and limbic system are documented. Ascending fibers from this nucleus distribute via the dorsal longitudinal fasciculus and the medial forebrain bundle to the mammillary body, ventomedial hypothalamus, habenula, preoptic area, and suprachiasmatic nucleus.

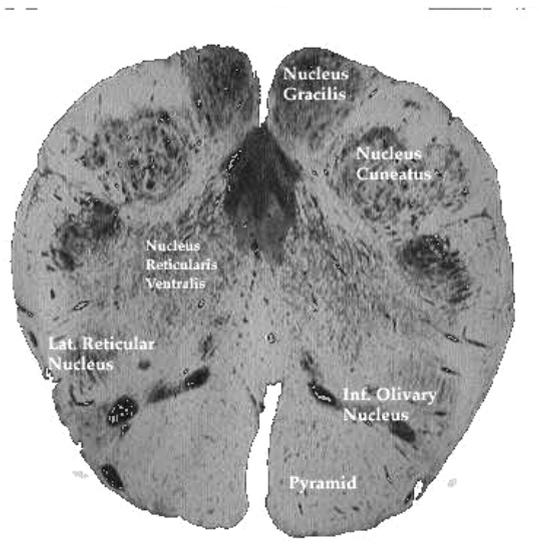


Figure 5.2 Section of the caudal medulla at the level of decussation of the internal arcuate fibers. The lateral reticular nucleus is dorsolateral to the inferior olivary nucleus and the nucleus reticularis ventralis is centrally located

The superior central nucleus (Figure 5.5) is located at the pontomedullary junction, corresponding to groups B6 and B8 of Dahlstrom and Fuxe. It projects diffusely to all areas of the cerebral cortex and specific regions of the cerebellar cortex. It also maintains reciprocal connections with the limbic system, projecting also via the medial forebrain bundle and dorsal longitudinal fasciculus to areas that overlap with the dorsal raphe nuclear projections.

The paramedian nuclei (Figure 5.3) lie parallel to the MLF and the medial lemniscus, and consist of nuclei, which maintain reciprocal connections with the cerebellum. The reticulotegmental, a paramedian nucleus at the rostral pons, which maintains connections with the cerebellum and the globus pallidus.

The medial reticular nuclei form the efferent zone of the reticular formation which receives afferents from the spinal cord and collaterals from the spinothalamic tracts, as well as the cochlear, vestibular and trigeminal nerves. They consist primarily of the nucleus reticularis gigantocellularis (Figure 5.3) in the medulla and the nucleus reticularis pontine caudalis and oralis (Figure 5.4 & 5.5) in the pons. These reticular nuclei convey information received from the cerebral cortex, vestibular nuclei, cerebellum, spinal cord, and the lateral zone of the reticular formation to the spinal cord through the inhibitory medullary reticulospinal tract and excitatory pontine reticulospinal tract. Both reticulospinal tracts control posture (sitting and standing) and automatic movements (walking), and exert powerful influences upon the axial and proximal appendicular muscles. Both tracts function in conjunction with the vestibulospinal tract. The pontine reticulospinal is a massive uncrossed tract that descends through the medial

longitudinal fasciculus and anterior funiculus, terminating in laminae VII, VIII, and IX. It activates extensor motor neurons via the gamma loop. The input of the basal nuclei to the pontine reticular nuclei is evident in the postural disorders exhibited by patients with Parkinson's disease. On the other hand, the medullary reticulospinal tract descends in the lateral funiculi, terminating in laminae VII, VIII, and IX of both sides and laminae IV, V, and VI on the ipsilateral side. This tract synapses upon the flexor motor neurons.

The medial reticular nuclei regulate eye movements through projections via shorter fibers to the extraocular motor nuclei and sensory nuclei of the brainstem. These neurons in the rostral pons and midbrain, which project via ascending fibers of the central tegmental tract to the intralaminar thalamic nuclei and hypothalamus, receive multiple sensory input. This reticular input to the intralaminar thalamic nuclei is utilized to produce alterations in the electrocortical activity and sleep-wake cycle, and affect our consciousness by projecting to diffuse areas of the cerebral cortex via the central tegmental tract. The latter pathway, a component of the ascending reticular activating system (ARAS) is responsible for changing the level of consciousness. The ARAS, a tegmental polysynaptic network is not only associated with consciousness, but also with memory, emotion, drive, and motivation. It has extrinsic and intrinsic elements; the extrinsic element consists of neurons in the medulla and pons that respond to stimulation generated by the cranial and spinal nerves, without being involved in sleep-wake cycle. By contrast, the intrinsic element is represented in the mesencephalic neurons, which exhibit cyclic (e.g. diurnal) activity related to the projection of the anterior hypothalamic (from the suprachiasmatic area) to the midbrain via the medial forebrain bundle.

The lateral reticular zone represents the sensory reticular area that receives input from the ascending sensory pathways as well as the cerebral cortex. In the medulla, this zone contains the nucleus reticularis parvocellularis and nucleus reticularis lateralis. In the rostral pons and caudal midbrain, it contains the reticulotegmental, Kölliker-Fuse, medial parabrachial, and pedunculopontine nuclei. In the caudal medulla it lies medial to the solitary nucleus, nucleus ambiguus and dorsal motor nucleus of vagus,

Damage to the reticular formation at the level of the rostral pons and caudal medulla may lead to coma or akinetic mutism (coma vigil). An EEG similar to the slow phase of the sleep characterizes this condition, with no appreciable change in the autonomic and somatomotor reflexes or eye movements.

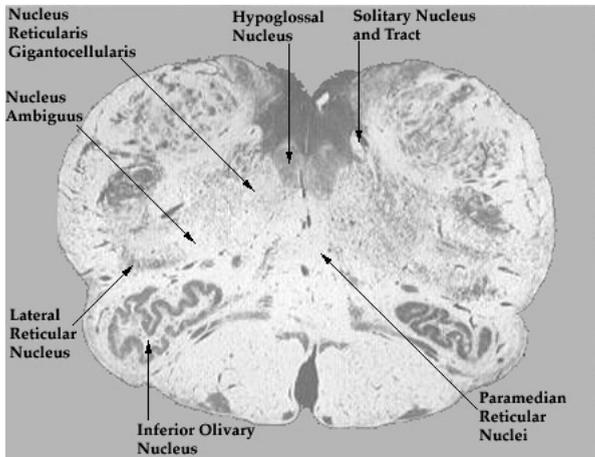


Figure 5.3 Section of the medulla at the mid-olivary level. The paramedian reticular nuclei lie parallel to the midline and lateral to the raphe nuclei. The nucleus reticularis gigantocellularis represents the medial reticular zone and the source of the medullary reticulospinal tract

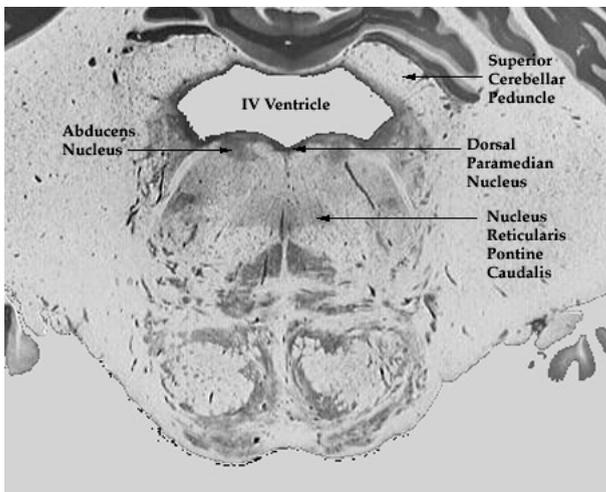


Figure 5.4 In this section of the pons at the level of the abducens nucleus, the nucleus reticularis pontine caudalis is shown superior to the medial lemnisci

containing at this level the adrenergic C2 and noradrenergic A2 groups. In general, these nuclei are precerebellar relay nuclei, which receive input from a variety of sources such as the cerebral cortex, spinal cord and vestibular nuclei and maintain reciprocal connections with the cerebellum. The lateral reticular zone also contains L & M micturition centers, noradrenergic A, adrenergic C, and cholinergic Ch neurons which are scattered in the medulla and upper pons. The noradrenergic neurons are classified into A1, A2, A4, A5, A6 and A7 groups (A3 is absent in humans). Adrenergic neurons are categorized into C1 and C2, while cholinergic neurons are divided into Ch5-Ch6. C2 and A2 groups are

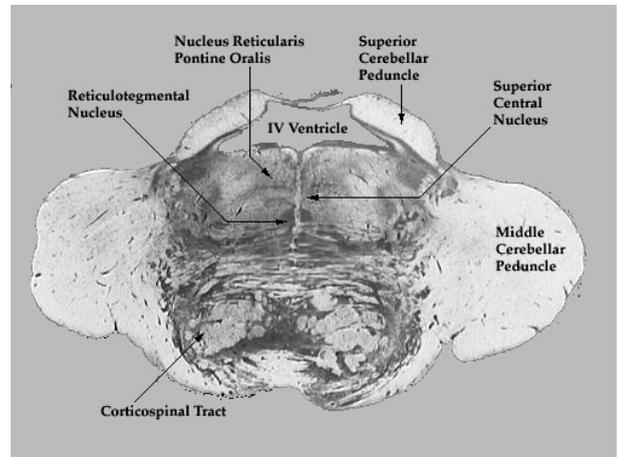


Figure 5.5 Section of the pons at the level of the trigeminal nerve. The locations of the superior central and reticulotegmental nuclei, as well as the nucleus reticularis pontine oralis are illustrated

located in the medulla in close proximity to the nucleus ambiguus. In the lateral tegmental area of the pons noradrenergic cell groups A1, A2, A4, A5, A6 and A7 adrenergic groups C1-C2, and cholinergic groups Ch5-Ch6 are visible. A2, A4, A5 and C1 cellular groups are located ventrolaterally in the pons near the facial motor nucleus. A4 extends along the medial surface of the superior cerebellar peduncle. A5, in conjunction with C1 may act to regulate vasomotor (blood pressure, caliber of the vessels, heart rate etc.) activities. A1 and A7 are located in the lateral pontine tegmentum. A1, A2, A5 and A7 influence the activities of the amygdala, septal nucleus, hypothalamus, bed nucleus of stria terminalis, and diagonal band of Broca via the central tegmental tract (CTT) and the medial forebrain bundle (MFB).

The nucleus reticularis parvocellularis is located between nucleus reticularis gigantocellularis and the spinal trigeminal tract and nucleus. It contains noradrenergic A2 and adrenergic C2 cellular groups. The connections of the hypoglossal to the trigeminal and facial motor nuclei are maintained by the parvocellular reticular nucleus. Afferents to this nucleus arise from the contralateral red nucleus and cerebral cortex.

The lateral reticular nucleus (Figures 5.2 & 5.3) occupies the lateral medulla, projecting to the cerebellum via the inferior cerebellar peduncle.

The reticulotegmental nucleus (Figure 5.5) is located in the center of the ventral pontine tegmentum at the level of the trigeminal nerve and isthmus. It maintains reciprocal connections to the cerebellum, receiving afferents via the superior cerebellar peduncle, and projecting back to the cerebellum through the middle cerebellar peduncle.

The Kölliker-Fuse nucleus is located medial and ventral to the superior cerebellar peduncle. It acts as a

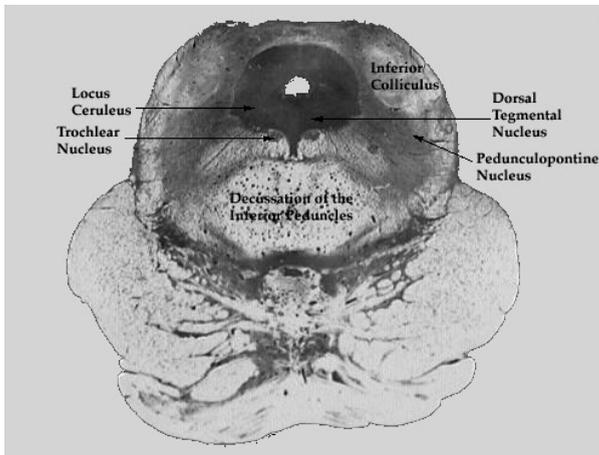


Figure 5.6 Section of the pons at the level of the trochlear nucleus. The pigmented locus ceruleus is located ventrolateral to the cerebral aqueduct within the periaqueductal gray matter. The pedunculopontine nucleus is dorsolateral to the superior cerebellar peduncle

pneumotaxic center by projecting to the inspiratory and expiratory centers in the medullary and pontine reticular formation. These centers convey the input to the preganglionic sympathetic neurons of upper three or four thoracic spinal segments, phrenic nucleus, and the intercostal neurons.

The medial parabrachial nucleus is located medial and ventral to the superior cerebellar peduncle, establishing reciprocal connections with the insular cortex, amygdala, and hypothalamus. This nucleus projects to the pontine micturition M center.

The pedunculopontine nucleus (Figure 5.6), which is classified as group Ch5, is comprised of cholinergic neurons that lie dorsolateral to the superior cerebellar peduncle at the caudal mesencephalon. It continues with the more caudal cholinergic cell group (Ch6) in the pontine central gray matter. This nucleus is crossed by fibers of the superior cerebellar peduncle, and receives input from the globus pallidus, substantia nigra, and primary motor cortex. It projects primarily to substantia nigra.

The locus ceruleus (noradrenergic group A6) and nucleus subceruleus are pigmented noradrenergic neurons (Figure 5.6) contained in the rostral pons which merge caudally with group A4. These nuclei play an important role in the regulation of paradoxical (REM) phase of sleep and control of sensory neurons. The locus ceruleus is known to project monosynaptically to the cerebral cortex, spinal cord (intermediolateral lateral column), hippocampal formation, septal area, and diencephalon. It also projects to structures in the telencephalon and the entorhinal area (secondary olfactory cortex) via the stria medullaris thalami, stria terminalis, fornix and the medial forebrain bundle.

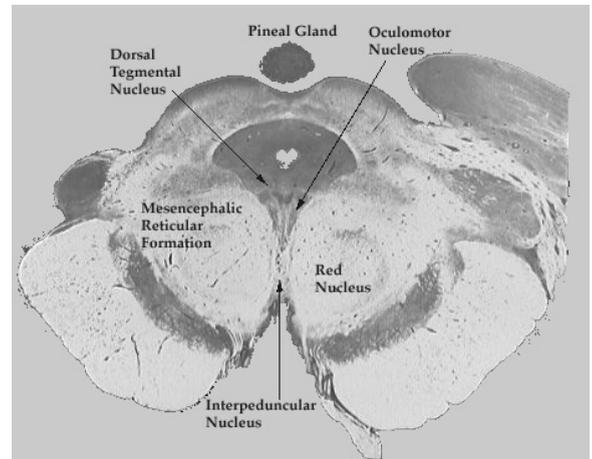


Figure 5.7 Section of the midbrain at the level of the superior colliculus. The mesencephalic reticular formation occupies the center of tegmentum lateral to the red nucleus. The dorsal tegmental nucleus is located dorsal to the oculomotor nucleus, whereas, the interpeduncular nucleus is dorsal to the interpeduncular fossa

The cerebellum is derived from the rhombic lip of the alar plate and constitutes an important part of the rhombencephalon. It is located in the posterior cranial fossa, covered by the tentorium cerebelli, and separated by the fourth ventricle from the dorsal surfaces of the pons and medulla. The tentorium cerebelli is lodged between the cerebellum and the occipital lobes of the brain. The cerebellum coordinates (synchronizes) voluntary motor activity and eye movements, regulates phonation, maintains equilibrium, and processes exteroceptive impulses.

Cerebellar nuclei

Cerebellar afferents

Climbing fibers

Mossy fibers

Cerebellar efferents

Cerebellar circuits

Cerebellovestibular circuit

Reticulocerebellar circuit

Rubrocerebellar circuit

Corticocerebrocerebellar circuit

Intracerebellar circuit

Functional and clinical consideration



Figure 6.1 Mid-sagittal section of the brainstem and cerebellum. The fourth ventricle separates the cerebellum from the pons and medulla. The components of the cerebellar vermis are illustrated

The study of the cerebellum reveals a corpus cerebelli with inputs from the spinal cord, pontine and trigeminal nuclei, and the flocculonodular lobe that maintains primary connections to the vestibular nuclei. The corpus cerebelli may be subdivided into regions that receive spinal and pontine inputs. The cerebellum lies caudal and inferior to the occipital lobes and dorsal to the pons and midbrain (Figures 6.1 & 6.2). It is connected to the midbrain, pons and medulla via the superior, middle and inferior cerebellar peduncles, respectively. It comprises two lateral hemispheres, which are connected by the midline vermis. Vermis and cerebellar hemispheres are separated by the paravermal sulcus. Posteriorly these hemispheres are separated by the falx cerebelli, contained in the posterior cerebellar notch. This deep notch continues inferiorly with the cerebellar valleculla, a median fossa between the two hemispheres. Each cerebellar hemisphere consists of a peripheral cortical gray matter, which is thrown into lamina or cerebellar folia, and a central white medullary substance, containing the cerebellar nuclei. Such an arrangement is also present in the cerebral cortex. In contrast, the spinal gray and white matter assume a reverse arrangement.

The fourth ventricle penetrates the white matter as a transverse gap, the fastigium, marking the junction of the superior and inferior medullary velum (white matter bands that extends rostrally and caudally in the roof of the fourth ventricle). The cerebellar hemispheres are divided into lobes and lobules by the primary, horizontal, pre- and postpyramidal, postlingual and postcentral, and posterolateral fissures (Figures 6.3, 6.4 & 6.5). Developmentally, the posterolateral fissure is the first fissure to appear, marking the caudal boundary of the flocculonodular lobe. The primary fissure serves as a landmark, separating the rostral anterior lobe from the

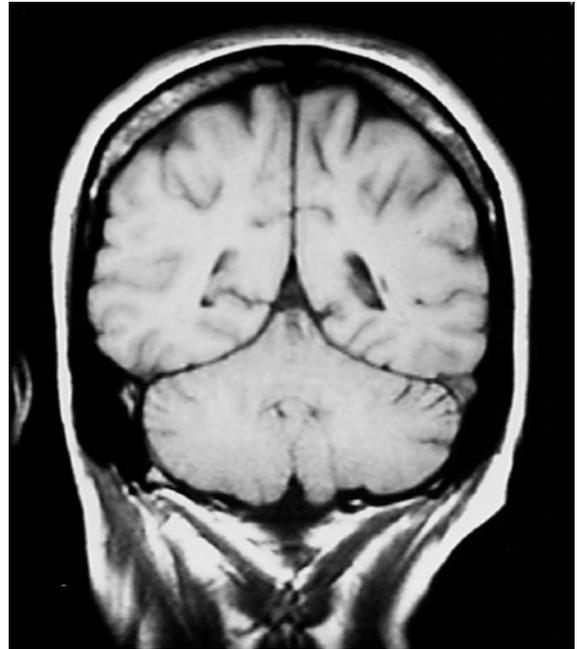


Figure 6.2 MRI Scan of the brain through the occipito-temporal gyri. The cerebellum lies inferior to the occipital lobe and is separated by the tentorium cerebelli.

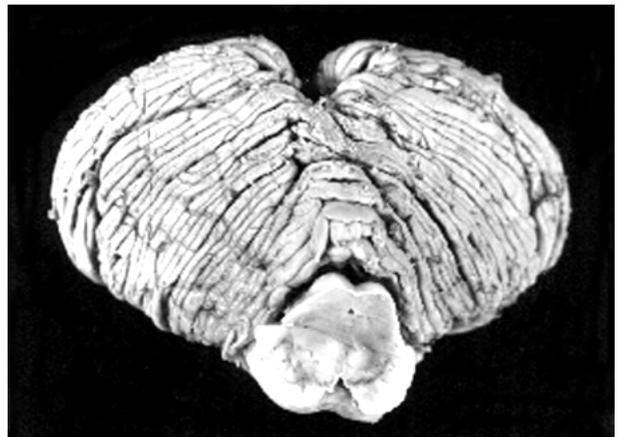


Figure 6.3 Superior surface of the cerebellum. The superior vermis and the corresponding parts of the cortical hemispheric areas are shown

more caudal posterior lobe. The cerebellum further divides into superior and inferior surfaces by the horizontal fissure, which also divides the ansiform lobule (cerebellar cortical areas that correspond to the folium and tuber vermis) into superior and inferior semilunar lobules. The midline vermis, which interconnects the cerebellar hemispheres, is divided into segments. Each vermal segment expands into the cerebellar hemispheres, with the exception of the lingula (Bolk's nomenclature). For example the central lobule of the vermis corresponds to the ala of the cortex, the culmen to quadrangular lobule, declive to the posterior

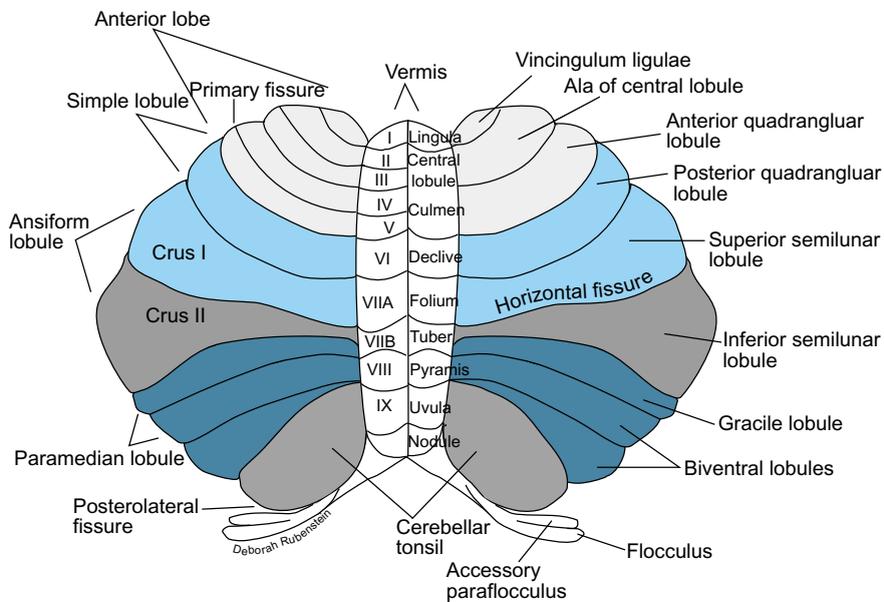


Figure 6.4 Various parts of the vermis and associated cortical parts are shown in this diagram



Figure 6.5 Inferior surface of the cerebellum. Note the branches of the anterior and posterior inferior cerebellar arteries on this surface. Posterior cerebellar notch is occupied by the falx cerebelli

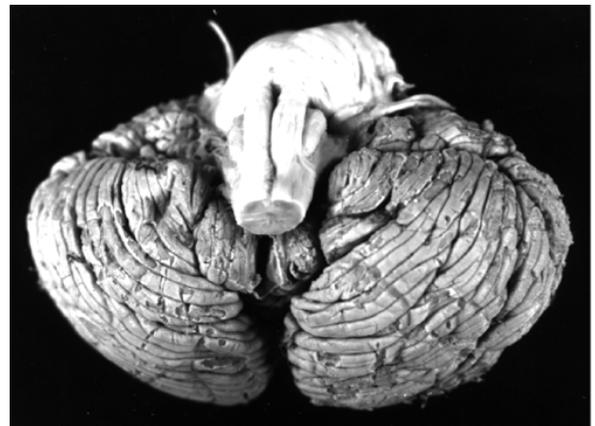


Figure 6.6 Inferior view of the cerebellum. Cerebellar tonsils and flocculus are clearly visible. Biventral, gracile, and inferior semilunar lobules are illustrated

quadrangular (simple) lobule, whereas both the folium and tuber vermis correspond to the ansiform (superior and inferior semilunar) lobules and biventral lobules of the cerebellar cortex.

Similarly, the pyramis corresponds to the biventral lobules, and the uvula is associated with the cerebellar tonsils and medial belly of biventral lobule (Figures 6.4, 6.5 & 6.6). The flocculi, remain attached to the midline nodule, forming the flocculonodular lobe. The prepyramidal fissure bounds the tuber vermis caudally and the postpyramidal fissure separates the uvula from the pyramid.

Larsell classified the vermis in a simplified pattern in which each hemispheric lobule can be related to one of the

vermian parts. Lobules 1-V of Larsell constitute the anterior lobe, lobule VI extends to the cortex as the simple lobule, whereas VII corresponds to the ansiform lobule. In the same manner, lobule VIII has a hemispheric extension represented in the paramedian lobule (a combination of the gracile lobule and lateral belly of the biventral lobule). The paraflocculus is shared by the vermian lobules IX and X. Extension of lobule X is the flocculus.

Voogd divided the cerebellar cortex into longitudinal zones that maintains discrete connections to the cerebellar nuclei. On the basis of this mapping, the efferent fibers from the cerebellar cortex to the cerebellar nuclei appear to arise in cortical zones that belong to the same compartment as the nuclear region to which they project.

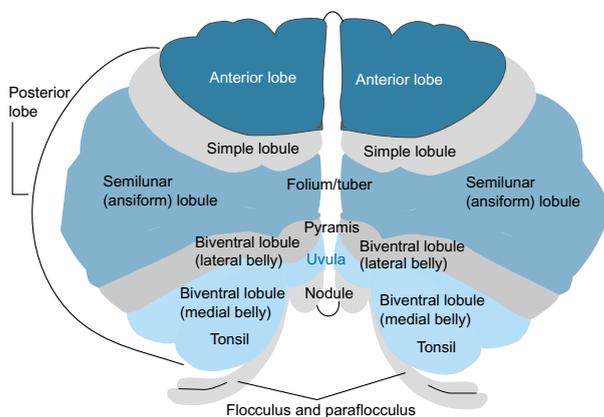


Figure 6.7 Various lobes of the cerebellum and associated fissures. Note that the morphologic divisions may correspond to a great extent to the functional classification

The vermis and its cortical expansions are sites of somatotopic representation of the body. Case in point, the head and face are represented in the simple lobule, the leg in the central lobule, whereas the arm occupies a distinct area in the culmen.

Blood flow to the cerebellum is maintained by the superior cerebellar, anterior and posterior inferior cerebellar arteries.

The superior cerebellar artery supplies the superior portion of the cerebellum, middle and inferior cerebellar peduncles, superior medullary velum, and the choroid plexus of the fourth ventricle. This vessel originates from the basilar artery (an artery formed at the ponto-bulbar sulcus by union of the two vertebral arteries).

The anterior inferior cerebellar artery (AICA) supplies the anterolateral part of the inferior surface of the cerebellum, pyramids, tuber vermis, dentate nucleus, white matter of the cerebellum, and most of the tegmentum of the caudal pons. AICA arises from the lower part of the basilar artery and forms a loop into the internal acoustic meatus, where it frequently gives rise to the labyrinthine artery.

The posterior inferior cerebellar artery (PICA) supplies the cerebellar hemispheres and the inferior vermis, uvula, nodule, cerebellar tonsils, choroid plexus of the fourth ventricle, and dentate nuclei.

Cerebellar veins are classified into superior, inferior, and lateral veins. The superior cerebellar veins drain into the great cerebral vein of Galen, the inferior cerebellar veins open into the straight sinus, while the lateral veins drain into the transverse, superior and inferior petrosal sinuses.

Phylogenetically the cerebellum ranges from the oldest to the most recent, consisting, in that order, of the archicerebellum, paleocerebellum, and the neocerebellum, respectively. The archicerebellum, which corresponds to the flocculonodular lobe, represents the oldest and most

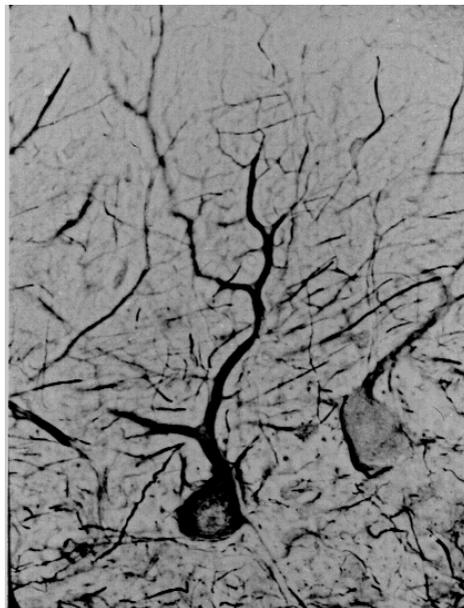


Figure 6.8 Photograph of the Golgi neuron with its prominent apical dendrite

primitive part of the cerebellum. The paleocerebellum, the second oldest cerebellar component, consists of the anterior lobe and part of the anterior vermis. Most of the cerebellar hemispheres (posterior lobe) and part of the posterior vermis are the latest to appear phylogenetically, forming the neocerebellum. Functionally the cerebellum is classified into the vestibulo-cerebellum, spino-cerebellum, and the ponto-cerebellum. The vestibulo-cerebellum is comprised of the flocculonodular lobe and part of the uvula. It has reciprocal connections with the vestibular nuclei, maintaining equilibrium and mediating vestibulo-ocular reflex. The inter-relationship between the vestibular nuclei, oculomotor system, and the cerebellum plays an important role in the coordination of voluntary eye movements. The spinocerebellum includes most of the anterior lobe, pyramis, and corresponding cortical parts (bivalent lobules). It receives input from the spinal cord and mesencephalic trigeminal nucleus and deals with propulsive movements (e.g. walking and swimming).

The flocculonodular lobe deals with activities that govern posture and movement through its connections to the brainstem and spinal cord. The posterior lobe with the exception of the simple lobule, gracile and bivalent lobule and the corresponding vermal parts (declive and pyramis), comprises the pontocerebellum. This lobe receives cerebral cortical input via the pontine nuclei. It coordinates fine movements through its connections to the cerebral cortex.

The cerebellar cortex consists of granular, Purkinje, and molecular layers. These layers contain interneurons (granule, Golgi, basket and stellate cells) which are functionally inhibitory (Figures 6.8, 6.9 & 6.10). The



Figure 6.9 Photograph illustrates the cerebellar cortical layers. Note the single Purkinje layer between the outer molecular and inner granular layer

granular layer (innermost layer) consists of small, densely packed granule cells, Golgi neurons, and mossy fiber rosettes. Granule cells give rise to axons that ascend into the molecular layer through the Purkinje layer, bifurcating into a T-shaped fibers that run parallel to the direction of the cerebellar folia (Parallel fibers). NMDA receptors, which are voltage dependent and produce slow depolarization and opening of the calcium channels in the postsynaptic neurons, are the predominant ionotropic glutamate receptors in the immature granule cells. However, AMP (a-amino-3-hydroxy-5-methyl-4-isoxalone propionic acid) and high affinity Kainate types of Non-NMDA glutamate receptors mediate fast excitatory transmission. It must be realized that receptors mediating cholinergic (nicotinic & muscarinic) receptors also exist in the granule cells. During their course, axons of the granule cells establish extensive contacts with the successive Purkinje cells like telephone poles. This transmission between the parallel fibers of the granule cells and the Purkinje dendrites are mediated by metabotropic receptors (type mGluR2 and ,GluR7) which are coupled to the phosphoinositide hydrolysis second messenger system and by the ionotropic glutamate receptors of the AMP type. Transmission between Purkinje and parallel fibers may be blocked by adenosine that binds to A1-adenosine receptors of the parallel fibers. Desensitization of Purkinje cell AMP and reduction of the synaptic transmission may occur as a result of simultaneous activation of the parallel and climbing fibers, a process known as long-term depression (LTD).

LTD is dependent upon an increase in intracellular calcium and on cyclic guanosine 3', 5'-monophosphate (cGMP)-dependent protein kinase in Purkinje cells. Since synthesis of cyclic AMP is catalyzed by soluble guanylate cyclase (present in all cerebellar cells), which is activated by NO synthetase, inhibition of production of cyclic GMP

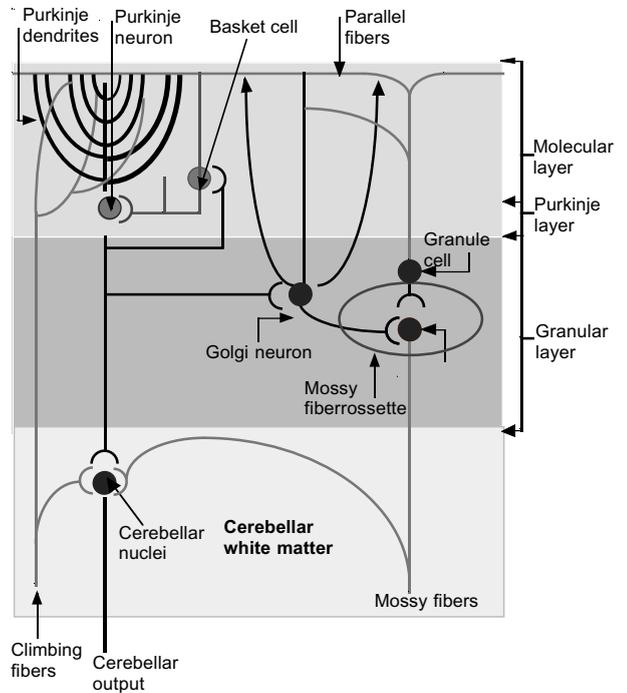


Figure 6.10 Cellular organization of the cerebellar cortex. The mossy fibers, cerebellar glomeruli, and climbing fibers are illustrated

by NO may abolish LTD. Cyclic GMP is located in Bergmann glial cells and astrocytes. Changes in the circuitry of the cerebellum during learning and adaptation processes may be attributed to the LTD. Thus, LTD and adenosine are the two mechanisms by which transmission between granule and Purkinje cells are blocked. Climbing fiber activity determines the extent of release of adenosine. The excitatory input mediated by the parallel fibers and incoming mossy fibers results in repetitive firing of the Purkinje neurons with the conventional type of action potentials.

Golgi neurons (Figure 6.8), which are also located in this layer, have somas that are lodged in the outer portions of the granular layer, and dendrites that extend into the molecular layer. Their dendrites and axonal branches extend in a radially symmetrical pattern, in exact contrast to the pattern of branching of other inhibitory neurons and Purkinje cells. Golgi cells also establish inhibitory axo-somatic contacts with the mossy and parallel fibers of granule cells in the mossy synaptic glomeruli. Golgi cells contain GABA (especially $\alpha 6$ subunit) and glycine, a feature that distinguish these cells from the basket and stellate cells. The predominance of $\alpha 6$ subunit in the Golgi neuron versus the granule cells may account for the scarcity of benzodiazepine-sensitive GABA_A receptors in the granular layer. Some Golgi cells may also contain enkephalin and somatostatin, as well as choline acetyl transferase (CHAT) that catalyze the synthesis of

acetylcholine. However, calcium binding proteins are strikingly lacking in these cells. Since most Golgi cells contain mGluR2 type of metabotropic glutamate receptor that are dependent upon cyclic adenosine monophosphate, inhibition of AMP and subsequently Golgi cells may result from stimulation of the glutamatergic parallel or mossy fibers. Mossy fibers, which constitute the bulk of the cerebellar afferents (non-olivary fibers), terminate in the granular layer as mossy rosettes (Figure 6.10). Sites of linkages between mossy rosettes, axons of the Golgi neurons, and dendrites of the granule cells occur in the synaptic glomeruli.

The Purkinje cell layer (Figures 6.9 & 6.10) consists of a single row of flask-shaped neurons with massive and flattened dendritic trees, establishing contact with the climbing fibers and the axons of the granule cells. Subunits of GABA_A, which are present in the cerebellar neurons, include α1, α3, β2 and γ2. α1, β2, and γ2 subunit combination display high affinity binding for benzodiazepine ligands. Subunit α1 is present in the soma of Purkinje cells, opposite the terminals of the basket cells, whereas α3 subunits occupy the proximal dendritic tree where the stellate cell terminates. Elements of the second messenger system that mobilize calcium from subsurface cisterns (e.g. receptor for InsP₃ or inositol 1,4,5-triphosphate) and protein kinase C are contained in the Purkinje neurons. Calcium binding proteins such as calmodulin, calbindin, and parvalbumin are also located in these cells. In fact, these elements are functionally related to the metabotropic receptors that mediate synaptic transmission between parallel fibers and Purkinje cells. All these factors may play important role in the increase of calcium concentration in Purkinje cells. Purkinje axons project to the cerebellar nuclei in a mediolateral direction (axons of vermal neurons project to the fastigial nucleus, paravermal neurons to the globose and emboliform nuclei, whereas the lateral hemispheric neurons project to the dentate nucleus and the lateral vestibular nuclei). Thus, the cerebellar excitatory input must overcome the tonic inhibitory impulses generated by the Purkinje cells upon the cerebellar nuclei. These projections, which represent the inhibitory corticonucleo-cerebellar tract, are arranged in (a)symmetrical longitudinal bands that reflect the Zebrin-positive cells, a group of proteins that are contained in certain populations of Purkinje neurons.

The molecular layer (Figure 6.10) is largely acellular outer layer, containing the dendrites of the Purkinje neurons, climbing fibers, axons of the granule cells, stellate cells, and the Basket cells. Stellate and basket cells have similar structures and their dendrites extend toward the surface and their axons run transversely to the folia and parallel to the dendrites of the Purkinje cells. They receive excitatory input from the parallel fibers, and their soma receives collaterals from the Purkinje neurons, as well as



Figure 6.11 Section through the medulla at the mid-olivary level. The massive fibers of the olivocerebellar tract represent the main component of the inferior cerebellar peduncle

parallel and mossy fibers. These cells, which contain NMDA receptors, mediate the parallel fiber-Purkinje inhibition. Large epithelial (Bergmann) glial cells and their radiating branches and processes that surround all cerebellar cortical neurons are also present in this layer.

Bergmann cells are associated with signaling processes, and are the primary source of cGMP in the cerebellar cortex. These cells, among all cerebellar neurons, uniquely contain α2 subunit of the GABA_A. The enzyme, which is involved in the hydrolytic cleavage of 5'-nucleotide monophosphates and formation of the adenosine, also resides in these cells. Among other features of Bergmann cells are their possession of Kainate receptors with specific ionic arrangement. The release of homocysteic acid, a putative amino acid neurotransmitter, by these cells is dependent upon the climbing fibers. They are capable of glutamate uptake and its conversion into glutamine, a process that enable the synthesis of glutamate by glutamatergic terminals. These terminals form the external limiting membrane.

Cerebellar nuclei

The cerebellar nuclei are embedded in the white matter, consisting of the fastigial, globose and emboliform, and the dentate nuclei. Neurons of these nuclei contain ionotropic glutamate receptors of the NMDA and Non-NMDA types, as well as GABAergic (GABA_A α1-β2 or γ2-γ2) and glycine receptors.

The fastigial nucleus is the most medial and phylogenetically the oldest deep cerebellar nucleus. It is located near the apex of the fourth ventricle where the superior and inferior medullary velum joins. It receives input from the vermis, and collaterals of cerebellar cortical afferents, and afferents from the medial and inferior vestibular nuclei, locus ceruleus, and the reticulo-

tegmental nucleus. It projects to the vestibular nuclei and the reticular formation.

The globose and emboliform nuclei are intermediate in phylogeny and location, receiving input from the paravermal cortex, reticulo-tegmental nucleus, medial and dorsal accessory olivary nuclei, and collaterals from other cerebellar afferents.

The dentate nucleus is the most lateral nucleus and developmentally is the most recent. Most cerebellar afferents, cortical fibers from the lateral hemispheric zone, afferents from the pontine nuclei, trigeminal sensory nuclei, reticulo-tegmental nucleus, inferior olivary nucleus, locus ceruleus, and the raphe nuclei terminate in this nucleus. It forms the main cerebellar output which projects through the superior cerebellar peduncle to the red nucleus and the ventral lateral nucleus.

Cerebellar afferents

Climbing fibers

The climbing fibers (Figure 6.10), which utilize L-glutamate as a neurotransmitter, primarily represent the olivocerebellar fibers that establish synaptic contacts with the Purkinje dendrite. In addition to the L-glutamate or L-aspartate, peptides are also contained in certain subpopulation of climbing fibers. Corticotrophin releasing factor (CRF) is also contained in these fibers. A single axon of the inferior olivary nucleus establishes excitatory connections with about a dozen Purkinje neurons and each Purkinje neuron in turn receives only one climbing fiber. The dendrites of the Purkinje neurons are entirely entwined by the climbing fiber, making roughly over two hundreds synaptic contacts. A single climbing fiber may evoke excitatory postsynaptic potential which maintains an amplitude greater than 25 mV (complex spikes), and

Secondary trans-synaptic degeneration and atrophy of the inferior olivary nucleus may occur as a result of cerebellar cortical degeneration involving the superior vermis. Olivo-ponto-cerebellar atrophies, as the name indicates, is associated with degeneration of the inferior olivary nucleus, pontine nuclei, and cerebellar cortex. This condition exhibits cerebellar ataxia, signs of upper motor neuron palsy, involuntary movements, autonomic disorders, and mental retardation. A lesion, which disrupts the circuitry between the dentate nucleus and the inferior olivary nucleus, may result in palatal myoclonus, a continuous rhythmic contraction of the posterior pharyngeal muscles that resembles tremor.

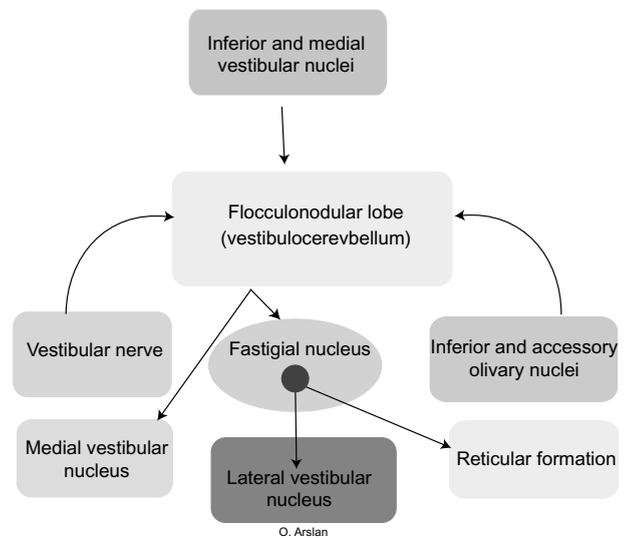


Figure 6.12 Schematic drawing of the projections of the vestibular nerve (primary vestibulo-cerebellar tract) and the vestibular nuclei (secondary vestibulo-cerebellar tract) to the cerebellum

greatly exceeds the Purkinje cell threshold. Due to this very reason a single impulse in the climbing fibers always elicits an action potential in more than ten Purkinje cells. Thus, the action potential of a single climbing fiber is not a graded response, but an all-or-none action. Thus, the Purkinje cells respond to the generated action potential with complex spikes, in contrast to the simple spikes evoked by the T-parallel fibers of the granule cells. According to some investigators the climbing fiber is primarily concerned with fast, ballistic movements. Other scientists claim that climbing fiber-system reflects the summation of the inhibitory and excitatory synaptic activity at any instant time. Some also theorize that the signals in the climbing fibers are meant to ascertain error in executing a motor activity (e.g. during learning stages), which suggest that the frequency of firing of the climbing fibers is not in any way related to the direction or the speed of a motor activity, but rather to the disturbances of that activity. Glutamate receptors at the synaptic connections between the Purkinje neurons and the climbing fibers are non-NMDA type, which are responsible for the influx of calcium ions into the dendritic tree of the Purkinje neurons. The olivo-cerebellar tract (Figures 6.10, 6.11 & 6.14), a contralateral pathway which arises from the inferior and the accessory olivary nuclei, represents the major climbing-fiber system. It crosses the medullary reticular formation to be distributed to the opposite vermal and cerebellar hemispheres via the inferior cerebellar peduncle. The accessory olivary nucleus conveys joint, tactile, visual and vestibular impulses to the cerebellum from certain nuclei of the medulla. The inferior olivary nucleus sends information to the

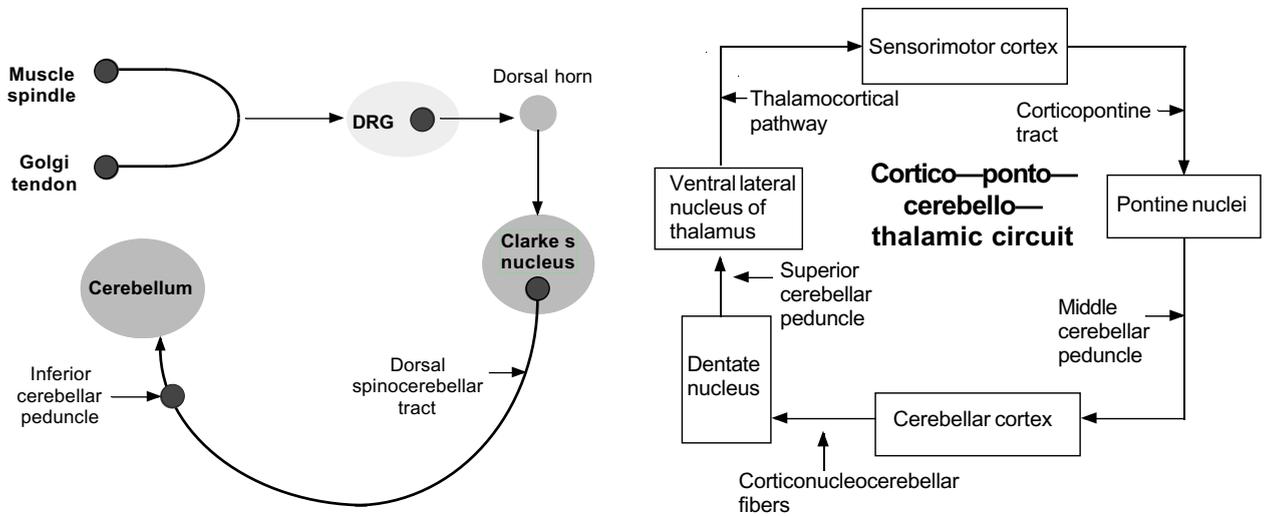


Figure 6.13 Clarke's nucleus and its projection to the cerebellum through the dorsal spinocerebellar tract

Figure 6.15 This circuit is mediated via the connections of the pontine nuclei which project to the cerebellar cortex. Series of neurons are involved, as a closed circuit loop, in the transmission of impulses between the cerebellum, thalamus, and motor cerebral cortex

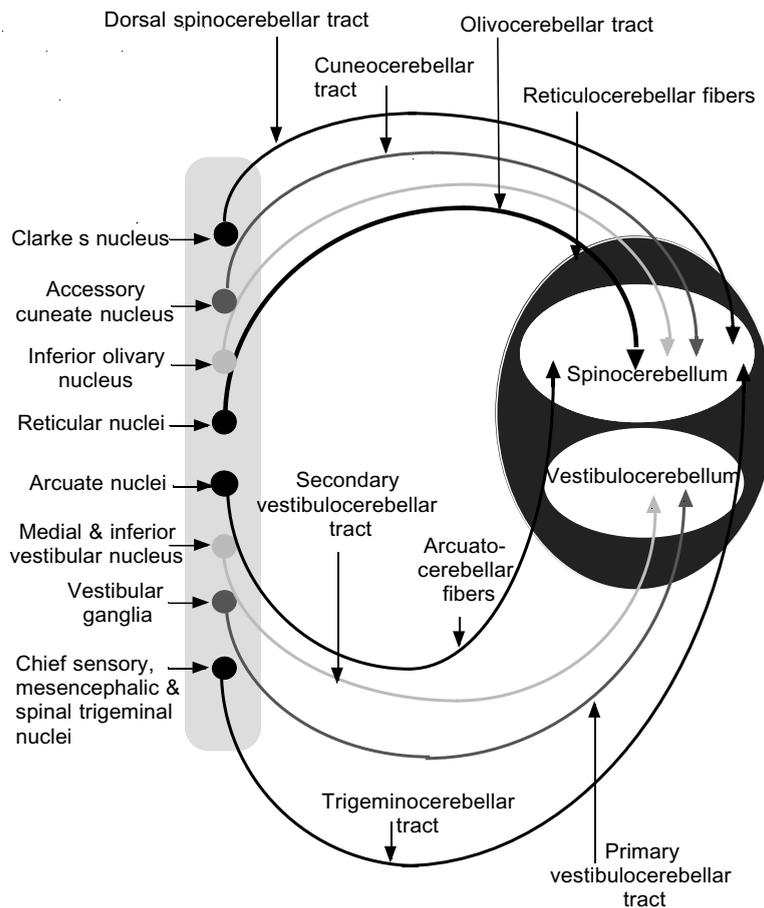


Figure 6.14 The major afferents to the cerebellum via the inferior cerebellar peduncle. Note the bulk of afferents come from the inferior olivary nucleus

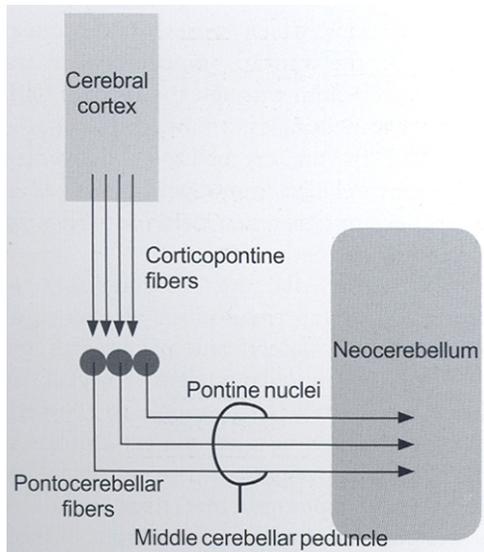


Figure 6.16 Illustrates the neuronal components of the middle cerebellar peduncle. Contralateral axons of the pontine nuclei form this peduncle

cerebellum, which is received from the spinal cord via the spino-olivary pathway, motor cortex, periaqueductal gray, and accessory oculomotor nuclei to the cerebellum.

Mossy fibers

Mossy fibers refer to all afferents of the cerebellar cortex with the exception of the olivocerebellar tract. Some of these fibers may establish excitatory synaptic contacts with the cerebellar nuclei, basket, Golgi, and stellate neurons. These fibers may be concerned with slow and tonic motor activity. L-glutamate is the primary neurotransmitter in mossy fibers with the exception of the secondary vestibulocerebellar fibers that utilize acetylcholine. Mossy fibers include the primary and secondary vestibulocerebellar, spinocerebellar, reticulo-cerebellar, pontocerebellar, tecto-cerebellar, and trigemino-cerebellar tracts.

The primary vestibulo-cerebellar fibers (Figures 6.12 & 6.14) are the central processes of the neurons of the vestibular ganglia. These fibers run within the juxta-restiform part of the inferior cerebellar peduncle and terminate in the vestibulo-cerebellum of the same side.

Secondary vestibulo-cerebellar fibers (Figures 6.12, 6.19 & 6.19) originate from the medial and inferior vestibular nuclei. These fibers run within the juxta-restiform part of the inferior cerebellar peduncle and terminate in the vestibulo-cerebellum on both sides.

The spino-cerebellar tracts (Figures 6.13 & 6.14), which are represented in two principal pathways, carry proprioceptive, stretch, and tactile sensations, terminating in the spinocerebellum (tactile input mainly terminate ipsilaterally in the simple lobule).

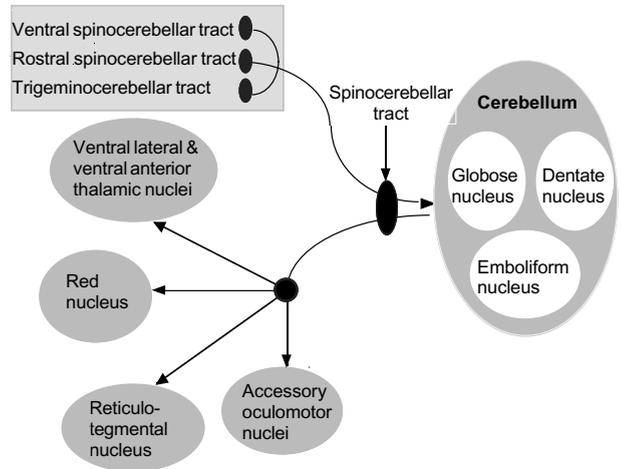


Figure 6.17 Afferents and efferents pathways within the superior cerebellar peduncle. The cerebellar projection to the thalamus constitutes the principal tract within this peduncle. Note that some fibers also terminate in the red nucleus, reticulo-tegmental and accessory oculomotor nuclei

The dorsal spino-cerebellar tract represents the axons of the Clarke's column, which extends in the thoracic and upper lumbar segments of the spinal cord. It is an ipsilateral tract that enters the spinocerebellum through the inferior cerebellar peduncle, carrying proprioceptive, tactile, and pressure impulses from individual muscles and joints of the lower extremity and lower half of the trunk. The upper limb equivalent of this tract is the cuneocerebellar tract that is derived from the accessory cuneate nucleus and terminates ipsilaterally in the pontocerebellum and spinocerebellum via the inferior cerebellar peduncle.

The ventral spino-cerebellar tract (Figure 6.17) is derived from the intermediate gray columns and the border cells of the anterior horn cells of the thoracolumbar and sacral segments. Information conveyed by this crossed tract, originate from the whole lower extremity, reaching the cerebellum through the superior cerebellar peduncle. The fibers of this tract cross again within this peduncle and terminate in the ipsilateral spinocerebellum. Laminae VII of the cervical enlargement gives rise to the rostral spinocerebellar, an ipsilateral tract, which represents the upper limb equivalent of the ventral spinocerebellar tract. It enters the cerebellum through the inferior and superior cerebellar peduncles, to be distributed to the anterior lobe of the cerebellum. The ventral and rostral spinocerebellar tracts act jointly as a relay center reflecting the neuronal activities in the descending motor pathways.

The reticulo-cerebellar tract (Figures 6.14, 6.17 & 6.20) originates from the pontine reticulotegmental, and the medullary lateral and paramedian reticular nuclei. Lateral reticular nucleus projects bilaterally via the inferior

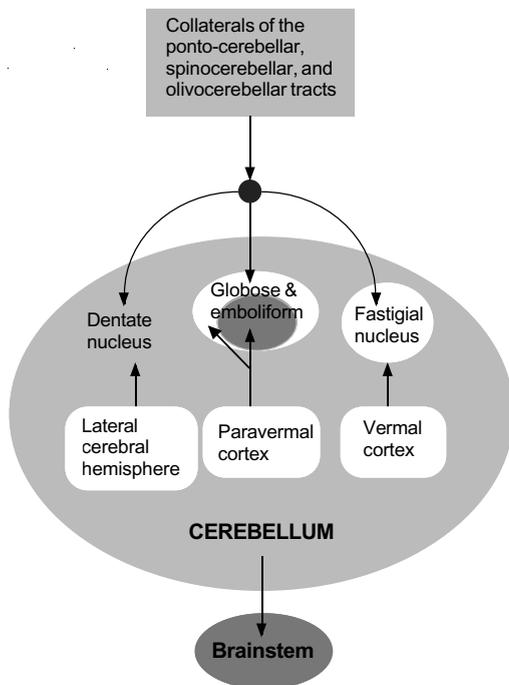


Figure 6.18 Somatotopic projections of the Purkinje cell axons to the cerebellar nuclei. These nuclei also process information received via collaterals of some mossy and climbing fibers. Purkinje axons also convey information to the brainstem

cerebellar peduncle to the vermis of the spinocerebellum, fastigial and emboliform nuclei. This projection conveys information from all levels of the spinal cord (spinoreticular) that initially establishes synaptic contacts with the neurons of the lateral cervical nucleus and later projects to the medullary reticular formation, and eventually to the cerebellum. The paramedian nuclei, which receive fibers from the interstitial nucleus, tectum, spinal cord and cerebral cortex, send efferents to the entire cerebellum with the exception of the paraflocculus. The reticulotegmental nucleus projects to the anterior lobe, simple lobule, the folium and tuber vermis via the middle cerebellar peduncle. Some fibers also terminate in the fastigial, globose, and dentate nuclei.

The ponto-cerebellar tract (Figures 6.16 & 6.22) delivers the cortical inputs from the ipsilateral motor, visual, and auditory cortices to the contralateral pontocerebellum (some to the ipsilateral pontocerebellum) by way of the middle cerebellar peduncle. It comprises, by far, the most massive afferent system which passes through the anterior and posterior limbs of the internal capsule (a massive bundle of fibers, which consists of afferent and efferent fibers, connecting the cerebral cortex to subcortical centers, as well as the spinal cord). It then runs

through the basis pedunculi of the midbrain and enters the basilar pons, establishing synapses with the pontine nuclei.

The arcuato-cerebellar fibers (Figure 6.14) are derived from the arcuate nuclei which are located ventral to the pyramids of the medulla. These fibers pursue two distinct courses, a superficial ventral and a deeper dorsal course. The superficial (ventral external arcuate) fibers run along the lateral and ventral surfaces of the medulla, entering the cerebellum via the inferior cerebellar peduncle. Fibers that follow a dorsal course (posterior external arcuate fibers), run near the midline of the floor of the fourth ventricle and extend laterally as the stria medullaris of the fourth ventricle, entering the cerebellum via the inferior cerebellar peduncle. The sites of termination of the arcuato-cerebellar fibers include the flocculonodular and the pontocerebellum.

The tecto-cerebellar fibers convey auditory and visual information to the pontine nuclei and then to the spinocerebellum, through the superior cerebellar peduncle.

The trigemino-cerebellar tract (Figure 6.14) originates from the mesencephalic nucleus of the trigeminal nerve, conveying proprioceptive impulses from the muscles of mastication and muscles of facial expression to the contralateral simple lobule and rostral vermis (spinocerebellum) via the superior cerebellar peduncle. Some trigeminal fibers also originate from the principal sensory and spinal trigeminal nuclei, which receives tactile sensation, and conveys this sensation to the anterior lobe via the inferior cerebellar peduncle.

Aminergic cerebellar Afferents include fibers from the locus ceruleus and raphe nuclei that project to the cerebellar cortex via the superior and inferior cerebellar peduncles. Axons of the locus ceruleus form a network in the molecular layer where they increase the GABA-mediated inhibition of Purkinje cells which is produced by the cerebellar interneurons (stellate and basket cells). They also enhance the release of glutamate from the parallel fibers onto the Purkinje cells, sharpening the signals and reducing the background activity. Serotonergic fibers emanate mainly from the medullary reticular formation. Noradrenergic projections to the cerebellum inhibits Purkinje cell by β -adrenergic receptor mediated inhibition of adenylate cyclase in the Purkinje cells. Dopaminergic neurons that project to the cerebellum gain origin from the ventral tegmentum and may act upon the D2 and D3 receptors of the molecular layer. Some cholinergic fibers may also be found in the Purkinje cell layer.

Cerebellar efferents

Some cerebellar efferents arise from the cerebellar cortex and project to the vestibular nuclei and the deep cerebellar nuclei as the corticonucleo-cerebellar fibers. Others

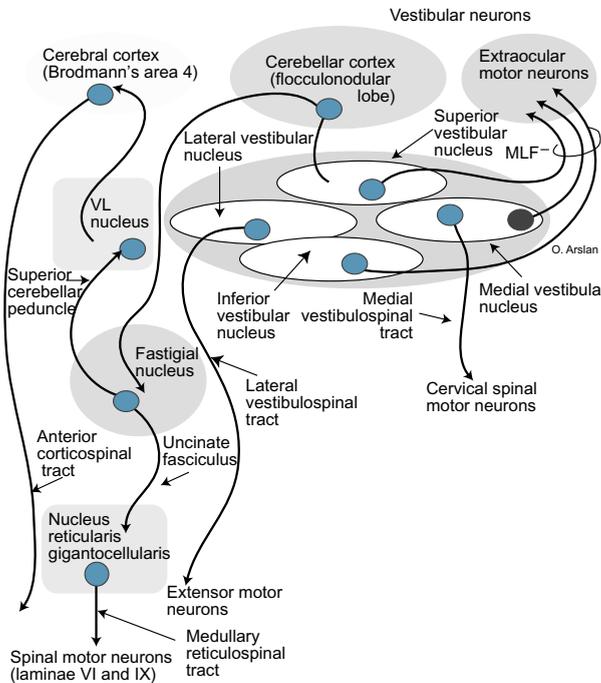


Figure 6.19 Connections of the ascending and descending connections of the vestibular nuclei

originate from the cerebellar nuclei and project to the thalamus and the brainstem reticular formation.

The corticonucleo-cerebellar (Figure 6.18) fibers represent the axons of the Purkinje neurons of the cerebellar cortex that project to the vestibular and cerebellar nuclei. Neuronal axons of the vermal cortex extend to the vestibular and fastigial nuclei with certain degree of specificity. In general, Purkinje neurons of the nodule and uvula project to the cerebellar nuclei and to all of the vestibular nuclei with the exception of the lateral vestibular nucleus, while that of the paleocerebellum projects to the lateral and inferior vestibular nuclei. There are A and B parallel zones of Purkinje cells in the vermis of the anterior lobe and simple lobule that project to the rostral part of the fastigial nucleus and the lateral vestibular nucleus, respectively. Caudal part of the fastigial nucleus receives input from the folium and tuber vermis that in itself receive a visual input. This visual information is used to calibrate saccadic eye movements. Pyramis also projects to the same areas that receive input from the anterior lobe. Uvular projections are more far reaching to the interposed and dentate nuclei. Intermediate (paravermal) zones which include C1, C2, and C3 project to the interposed nucleus. C1 and C3 zones send fibers to the emboliform nucleus, whereas C2 projects primarily to the globose nucleus. Purkinje neurons of the lateral cerebellar cortex form D1 and D2 parallel zones that send axons to the caudolateral and rostromedial parts of the dentate nucleus, respectively.

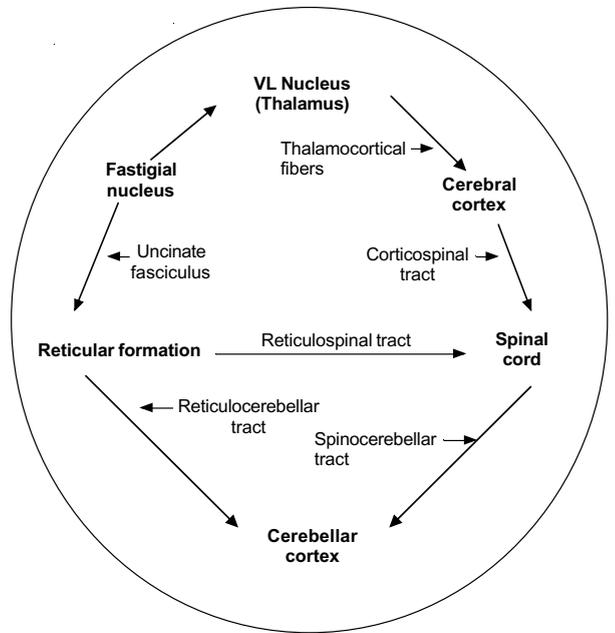


Figure 6.20 Efferent and afferent fibers of the reticular formation within the cerebellar feedback loop

The dentato-rubro-thalamic tract is formed by axons of the dentate nucleus, which runs within the superior cerebellar peduncle, and terminates in the ventral lateral and ventral posterolateral thalamic nuclei. These terminations are specific and do not show overlap with the pallidal termination. The thalamic nuclei that receive cerebellar output project to the motor cortex via the thalamocortical radiation. This connection enables the cerebellum to exert influence over motor activity. Collaterals of this projection are also given to the red nucleus, oculomotor nucleus, and associated accessory oculomotor nuclei (interstitial nucleus of and Cajal and nucleus of Darkschewitch). Efferents from the globose and emboliform nuclei project to the contralateral ventral posterolateral, intralaminar, and ventral lateral thalamic nuclei via the superior cerebellar peduncle. Collaterals of these fibers terminate in the red nucleus.

The fastigio-vestibular pathway (Figure 6.19) is an excitatory pathway derived from the fastigial nucleus that projects to the ipsilateral vestibular nuclei via the juxtarestiform body. It also projects to the lateral and inferior vestibular nuclei, and to the nucleus reticularis gigantocellularis of the contralateral medulla via the uncinate fasciculus (hook bundle of Russel). There are fastigial nuclear projection to the ventral lateral and ventral posterolateral thalamic nuclei. Cerebellar influences upon the motor activity may be mediated via the fastigial projection to the ventral lateral nucleus of thalamus, the primary motor cortex, and the corticospinal tract. The lateral vestibular nucleus conveys this information to the spinal cord, regulating the motor activity of the antigravity

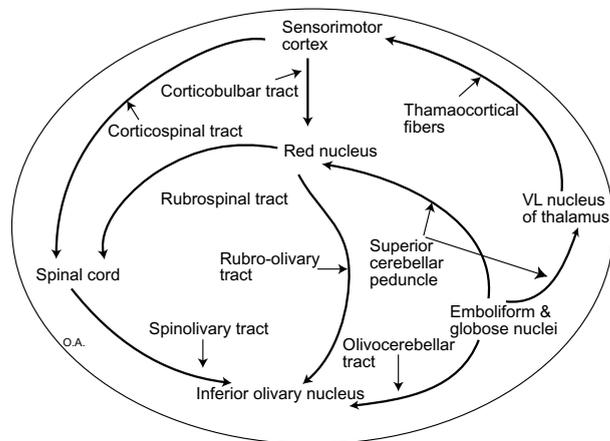


Figure 6.21 Schematic drawing of the connections of the red nucleus within a cerebellar feedback circuit

muscles. Fastigial projection to the nucleus reticularis gigantocellularis allows the fastigial nucleus to influence motor activity via the medullary reticulospinal tract. This connection serves as an additional route by which the fastigial nucleus regulates motor activity.

Cerebellar circuits

The cerebellar functions are performed by series of closed-circuit pathways, which indicate the complexities of cerebellar connections and the role each circuit and associated centers play in the programming, sequencing, grading, and ultimately coordinating motor activities.

Cerebellovestibular circuit (Figure 6.19)

The cerebello-vestibular circuit enables the vestibular nuclei to project to the spinal cord via the excitatory lateral vestibulospinal tract and the inhibitory medial vestibulospinal tract. Through this feedback loop information received from the vestibular receptors is also conveyed to the cerebellum via the primary and secondary vestibulo-cerebellar tracts. Vestibular projections to the flocculonodular lobe eventually influence the activities of the ventral lateral nucleus of thalamus and the motor cerebral cortex via their connections to the fastigial nucleus. Purkinje neurons of the nodule and flocculus project to the medial and inferior vestibular nuclei that receive input from the vestibular nerve. Since these vestibular nuclei project to the motor nuclei that govern eye muscles, the flocculus may play an important role in smooth pursuit movement of the eye by suppressing the vestibulo-ocular reflex.

Part of this circuit is represented by the ascending vestibulocular fibers to extraocular motor nuclei, which

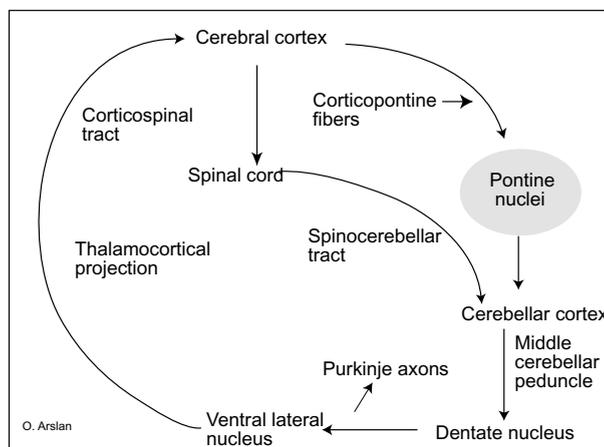


Figure 6.22 The cortico-cerebro-cerebellar circuit and role of the pontine nuclei in mediating coordinated motor activity initiated by the cerebral cortex

run in the medial longitudinal fasciculus, enabling vestibular impulses to coordinate eye movements and fixate gaze.

Reticulocerebellar circuit (Figure 6.20)

Information received by the reticular formation, which originate from diverse sources such as the fastigial nucleus, cerebellar cortex, and spinal cord, is processed and send back to the cerebellum directly via the inferior cerebellar peduncle (as a component of the reticulo-cerebellar tract). It is also sent indirectly via the reticulospinal tract to the spinal cord that projects back to the cerebellum by the spinocerebellar tracts. The spinal cord also conveys impulses to the cerebellum, which are generated in the cerebral cortex and delivered via the corticospinal tract to spinal cord segments.

Rubrocerebellar circuit (Figure 6.21)

The red nucleus receives input from the ipsilateral cerebral cortex and the contralateral cerebellar nuclei. Through its connection to the inferior olivary nucleus (via the rubro-olivary tract), the red nucleus influences activities of the cerebellar cortex through the massive olivocerebellar fibers. Thus, the combination of cortico-rubral fibers, spinal projections of the red nucleus (rubrospinal tract), spino-olivary fibers (conveying multisensory input to the inferior olivary nucleus from the spinal cord), inferior olivary nucleus itself and the olivocerebellar fibers, cerebellar nuclei, and finally the red nucleus serves to complete this feedback circuit.

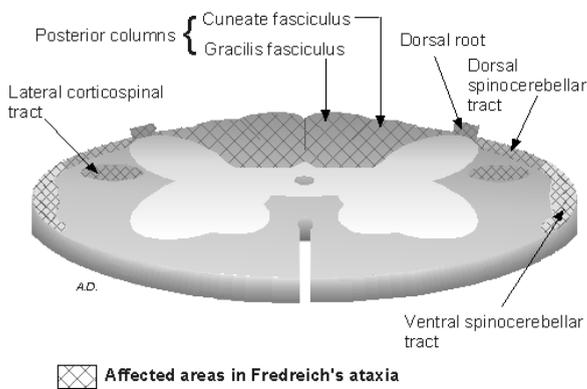


Figure 6.23 Section of the spinal cord showing the lesions associated with Friedreich's Ataxia. The dorsal columns, lateral corticospinal and spinocerebellar tracts are affected

Corticocerebrocerebellar circuit (Figure 6.22)

The cortico-cerebro-cerebellar circuit is mediated by the diffuse projections of the cerebral cortex to the pontine nuclei, which sequentially projects to the cerebellar cortex via the middle cerebellar peduncle, completing the cerebro-cerebellar tract. The cerebellar cortex, via its projection to the dentate nucleus (corticonucleo-cerebellar tract), acts upon neurons that influence the ventral lateral thalamic nucleus (dentato-rubro-thalamic pathway), which eventually affect the cerebral motor cortex. Thus, voluntary movements initiated by the motor cerebral cortex are modulated by this feedback loop.

Intracerebellar circuit (Figure 6.10)

The intracerebellar feedback loop utilizes the inhibitory connections of granule cells with the Golgi neurons and the reciprocal inhibition exerted by the Golgi neurons (negative feedback) which is exemplified by the cerebellar glomeruli. Granule cells also exert feed-forward inhibition upon the Purkinje cells through its connections to other interneurons such as the basket and stellate cells. Within this feedback circuit collaterals of Purkinje neurons project to the inhibitory cerebellar interneurons which sequentially send fibers back to the same Purkinje neurons or other interneurons.

Functional and clinical considerations

The cerebellum maintains balance and posture by gradual modulation of muscle tension and by maintaining the orderly sequence of muscular contractions. It also plays an important role in the timing of movements. These

complex activities are accomplished by integrating information received from certain areas of the cerebral cortex that are involved in the planning and command aspects of movements with the sensory feedback arising in the periphery during the course of movement.

The variations in severity of the signs and symptoms of cerebellar dysfunction depend upon the extent of the lesion and duration of the insult. These manifestations are usually seen ipsilaterally and as a constellation of deficits. They emerge as signs of release from the inhibition exerted on intact structures by the cerebellum. Cerebellar deficits may occur as a result of direct compression or invasion of cerebellar tissue by a developing mass, ischemia, tumors or hemorrhage of the posterior cranial fossa and subsequent obstruction of the cerebrospinal fluid pathway. Developing mass may also produce secondary effects upon other areas of the cerebellum by pressure or compression of the vessels. It should be understood; however, that pure cerebellar deficits produced in experimental animals are rarely encountered in man. Most patients exhibit a combination of gait and postural disturbances (ataxia), asynergy, hypotonia, visual disturbances, vertigo, dementia, headache, nausea and vomiting.

- Posture and gait abnormalities (ataxia) resemble drunken gait, which is broad-based, irregular, and staggering. These deficits include tendency to fall (patients become apprehensive and frightened to stand), limb ataxia (past pointing of the extremities), and difficulty in walking in a straight line. Inability to stand may require the patient to seek support and attempt to alleviate the situation by constant adjustment of the extremities and head (titubation). Patients keep the feet too widely apart or too closely together, with the head and body deviated toward the side of the lesion during walking.

- Asynergy refers to the lack of coordinated action between muscle groups or movements which normally maintain the proper degree of harmony, smooth and accurate sequencing. Asynergistic muscles lack synchronous activity, skill, and speed. Lack of proper sequence and grouping of muscles which are associated with successive components of a motor activity, may produce movement which is decomposed and broken down into puppet-like acts. Asynergy of the muscles of the mouth, pharynx and larynx may lead to disturbance of the mechanism that regulates breathing and phonation (dysarthria). This disturbance produces a peculiar form of speech, scanning (telegraphic) or staccato speech, which is a slow, slurred, explosive, and ataxic speech with prolonged intervals between syllables, and wrong pauses. Asynergy may also be manifested in

the form of dysmetria, adiadochokinesis, hyperkinesia, and rebound phenomenon of Holmes.

- Dysmetria is the inability to gauge the distance, range, rate of speed, or power of movement. Over-shooting (hypermetria) or under-shooting (hypometria) of the intended target may occur as a result of lack of appreciation of distance or range. Individuals may perform the act slowly or very rapidly with minimal or maximal power

- Adiadochokinesis, the inability to perform alternate successive pronation and supination of the forearm, opening and closing of the fists, tapping the finger or properly execute the finger-to-nose or heel-to-shin tests. In the finger-to-nose test, the examiner asks the patient to put his finger on his nose, the finger begins to oscillate gradually and then violently as it approaches the nose). In heel-to-shin test the patient, while in supine position, is asked to touch the knee of one leg with heel of the other extremity and then move the heel downward in front of the shin to the ankle joint.

- Hyperkinesia is seen in the form of a non-rhythmic, jerky, irregular, uncontrollable, coarse, to-and-fro movements of the limbs (kinetic or intentional tremor) during the course of a movement, or upon command as in finger-to-nose and heel-to-shin tests. The amplitude of the tremor increases as the intended target is approached.

- Rebound phenomenon of Holmes refers to the lack of normal checks of agonist and antagonist muscles, and tendency to overshoot the target than stopping smoothly. For example, sudden release of the flexed arm against resistance by the examiner may cause the released arm to strike patient's face due to the delay in contraction of the triceps brachii, a muscle that ordinarily responsible for arrest of overflexion.

- Hypotonia (reduced muscle tone) results in weak, flabby and fatigued muscles (asthenia). The affected muscles may not resist passive movements of the joints into extreme degrees of flexion or extension. The contraction and relaxation phases of movements become slow, delaying the initiation of voluntary movements. When the patient is asked to outstretch his or her forearms, the outstretched forearm on the affected side assumes a pronated position and generally maintains a higher position than the limb on the contralateral side.

- Hyperkinesia manifests as intention tremor, and is characterized by jerky, irregular, coarse, to-and fro movements of the hand. It is commonly seen during

active movement, becoming coarse and attaining high amplitude as the hand reaches the intended point (seen in finger- to-nose test).

Other deficits include nystagmus, vertigo (sense of rotation of self or environment), visual and ocular disorders, hyporeflexia, macrographia, dementia, headache, nausea, and vomiting. Cerebellar disease usually produces anteroposterior or side to side movements of the environment, and sense of instability during walking.

It is important to note that occlusion of the subclavian artery, medial to the origin of the vertebral artery, by arteriosclerotic plaques, may also produce vertigo, a weaker pulse and lower pressure in the upper extremity of the affected side relative to the lower extremity. This results from diversion of blood flow from the vertebral artery on the (intact) opposite side, which maintains a higher blood pressure, to the vertebral artery on the occluded side, with a lower blood pressure, and subsequently to the subclavian artery distal to the site of occlusion. Diversion of blood to the subclavian artery (stealing) from the vertebral artery is generally exacerbated during physical effort (increased metabolic demand), leading to manifestations of cerebellar ischemia which include vertigo and dizziness. On this basis, the described condition is known as subclavian steal syndrome.

Occlusion or stenosis of the proximal part of the vertebral artery, however, may produce, although rarely, transient ischemic attack (TIA), and vertigo at rest (to be distinguished from vertigo associated with exertion, which is seen in subclavian steal syndrome). Other deficits also seen in brainstem and cerebellar ischemia include diplopia (double vision), oscillopsia (sensation of oscillation of the viewed object), numbness and hemiparesis. Occlusion or stenosis of the vertebral artery on one side rarely slows the blood flow to the brainstem or cerebellum if efficient collateral circulation in the neck as well as symmetry of vertebral arteries is maintained. Stenosis of the basilar artery may cause symptoms, which vary from vertigo, nausea, dysarthria (difficulty in speech), hemianesthesia, and paresis of conjugate eye movements, to dysphagia, diplopia, occipital headache, and vertical and horizontal nystagmus.

- Nystagmus is a rhythmic oscillation of one or both eyes at rest or with ocular movements. Patients with cerebellar dysfunction cannot maintain gaze away from the midline (rest) position, and attempts to do so may result in slow

movements of the eyes toward the center (slow component of nystagmus). The rapid corrective movement in the direction of the gaze is considered the fast component of cerebellar nystagmus. The direction as well as amplitude of its fast phase decreases with sustained deviation of the eyes toward the target. Following return of the eyes toward the midline the nystagmus resumes with the fast phase away from the midline.

- Ocular and visual disorders are the result of disruption of the cerebello-vestibulo-ocular reflexes, including nystagmus, ocular dysmetria, disturbances of conjugate gaze, and diplopia. Nystagmus is a rhythmic oscillation of one or both eyes at rest or with ocular movements. Patients with cerebellar dysfunction cannot maintain gaze away from the midline (rest) position, and attempts to do so may result in slow movements of the eyes towards the center (slow component of nystagmus) The rapid corrective movement in direction of the gaze is considered the fast component of cerebellar nystagmus. The direction as well as amplitude of its fast phase decreases with sustained deviation of the eyes towards the target. Following return of the eyes toward the midline of the nystagmus resumes with the fast phase away from the midline. This transient oscillation of the eyes upon gazing towards a target, which is associated with blurred vision, may result from ocular dysmetria. Blurred vision that improves by closing one eye, is a sign of dysconjugate gaze, subsequent to cerebellar dysfunction. Inflammatory and degenerative diseases of the cerebellum may reduce visual acuity or result in transient or permanent blindness. Permanent blindness is seen in certain familial diseases associated with degeneration of the spinocerebellar tracts. Diplopia, the most common ocular manifestation, may be constant or transient deficit. Smooth pursuit movements are also impaired forcing the patient to track moving objects by compensatory saccades.

- Dementia may result from obstructive hydrocephalus, which compresses the enlarged brain against the bony rigid wall of the skull. Obstructive hydrocephalus develops from compression of the fourth ventricle by a cerebellar mass or hemorrhage within the posterior cranial fossa. Impairment of memory and transient confusion is also common features of cerebellar degenerative diseases.

- Headache, the most common manifestation of cerebellar dysfunction, is typically severe, persistent, dull

pain of the occipital or frontal region which shows no lateralization and remains unresponsive to conventional analgesics. Postural changes may exacerbate headache. Frontal headache is a manifestation of deviation of the tentorium cerebelli, which is innervated by the recurrent meningeal branch of the ophthalmic nerve, a branch that also supplies the skin of the forehead.

- Nausea and vomiting are most severe in the morning and may last for months. Postural changes may attenuate or reduce the severity of nausea. Nausea and vomiting may be abrupt dependent upon the extent and degree of progression of cerebellar deficits. With associated weight loss, these deficits may obscure the true etiology and may lead the physician to undertake extensive abdominal evaluation. Nausea and vomiting may result from compression or irritation of the emetic center in the brainstem.

- Neocerebellar lesions involve major parts of the cerebellar hemispheres and the corresponding parts of the posterior vermis. Signs associated with the appendicular muscles include spooning of the hand (hyperextension of the fingers) and intention tremor, which may be unilateral or bilateral, and is noted during movement. The patient may exhibit mild ataxic (broad based and unsteady) gait, hypotonia, tendency to fall toward the affected side, and asynergy (which includes dysmetria, adiadochokinesis, and rebound phenomenon). Rebound phenomenon is characterized by uncontrollable oscillation of the outstretched arm up and down upon sudden release of pressure by the examiner. Scanning (telegraphic) speech, a form of dysarthria, which is characterized by slurred, labored, garbled, hesitating and monotonous speech, with inappropriate pauses may also be observed. Handwriting may be affected in the same manner (macrographia), showing characteristically letters larger than normal. Nystagmus, a late common sign, occurs as a result of destruction of the cerebellar connections to the vestibular nuclei. Horizontal nystagmus, which is seen in neocerebellar lesions, is commonly associated with impairment of tracking movements, and becomes markedly visible upon gazing to the side of the lesion.

- Paleocerebellar lesions are rare and affect the anterior lobe. However, increased extensor muscle tone and postural reflexes accompanied by truncal ataxia (nodding movements of the head and trunk), and signs of

decerebrate rigidity (due to involvement of the brainstem) can also be seen in this type of lesion. Impairment of gait with relative preservation of the upper extremity are some additional signs of this condition.

- Archicerebellar lesions target the flocculonodular lobe, producing deficits identical to midline (vermal) lesions. These lesions may occur as a result of medulloblastoma, a childhood malignant tumor arising in the roof of the fourth ventricle which occurs between five and ten years of age, multiple sclerosis, chronic alcoholism, tumor or vascular disease. Deficit usually include truncal ataxia (staggering gait and unsteady posture while standing) and positional nystagmus without appendicular ataxia (ataxia of limb movement). Truncal ataxia necessitates constant support due the inability of the patient to maintain standing position. Midline lesions of the cerebellum restricted to the lingula, superior medullary velum, and the superior cerebellar peduncle also produce bilateral trochlear nerve palsy, nystagmus, and ipsilateral tremor of the corresponding limb.

Cerebellar lesions may occur in multiple sclerosis, acoustic neuroma, Benedikt's syndrome, cerebellar herniation, Foix's Syndrome, Nothnagel's Syndrome, and cerebellar aplasia, and Friedreich's ataxia.

- Multiple sclerosis (MS), as described earlier, is a multifocal demyelinating disease of the central nervous system. It produces lesions in brain, brainstem, and cerebellum. Patients exhibit an unsteady gait, truncal ataxia, intention tremor and slurred speech. The most severe form of cerebellar ataxia occurs in MS, where the slightest attempt to move the trunk or limbs results in a violent and uncontrollable ataxic tremor. This is usually due to involvement of the dentato-rubro-thalamic tract and the adjacent structures in the tegmentum of the midbrain.

- Cerebellar hemorrhage produces headache, vertigo and ataxia, may also lead to ipsilateral conjugate gaze disturbances.

- Acoustic neuromas, a cerebello-pontine angle tumor, may also produce cerebellar dysfunctions by compressing the flocculus and the middle cerebellar peduncle. This tumor, although commonly benign, is associated with widening of the internal acoustic meatus.

- Benedikt's Syndrome is a condition that results from destruction of the oculomotor nerve, red nucleus, medial

lemniscus, and possibly the spinothalamic tracts. It exhibits signs of ipsilateral oculomotor palsy, contralateral cerebellar dysfunctions, loss of pain, thermal, and position sensations on the opposite side (also described with the motor system and also cranial nerves, chapters XX and XI). Occlusion of the superior cerebellar artery may produce degeneration of the superior cerebellar peduncle, and the spinal and trigeminal lemnisci, producing some of the signs of Benedikt's syndrome. This vascular occlusion results in ipsilateral atonia, ataxia, asthenia, bradyteleokinesis (hesitancy and slowness in completion of a movement), and loss of pain and temperature sensation on the contralateral face and body.

- Herniation of the cerebellum refers to the bilateral or unilateral downward displacement of the cerebellar tonsils that occurs as a result of a tumor of the posterior cranial fossa or frontal lobe, or from the pressure exerted by edematous brain. The paraflocculus and possibly part of the temporal lobe may herniate through the foramen magnum into the cervical part of the vertebral column. Cerebellar herniation is characterized by occipital headache, tonic spasmodic contracture of the neck (nuchal rigidity) and back muscles (cerebellar fits), fixation of the head toward the lesion side, as well as extension and medial rotation of the extremities. These symptoms are followed later by progressive loss of consciousness as a result of destruction of the ascending reticular activating system.

Vasomotor changes such as reduced cardiac contraction and feeble pulse, numbness in the upper extremity, and difficulty of swallowing may all be attributed to compression of the structures and nuclei in the brainstem. Mechanical displacement of the fourth ventricle in this herniation may eventually cause compression of the medullary respiratory center, and death ensues following respiratory arrest. A tumor, which causes upward deviation of the cerebellum, may lead to compression of the fourth ventricle and obstruction of the foramina of Magendie and Luschka, followed by hydrocephalus. These deficits may occur in Dandy-Walker syndrome.

- Dandy-Walker syndrome is caused by failure of development of the cerebellar vermis, thinning of the posterior cranial fossa and the formation of a cyst-like midline structure that replaces the fourth ventricle. In

patients with this condition, the cervical spinal nerve roots assume an ascending course in order to reach their corresponding foramina. This syndrome may also be associated with agenesis (failure of development) of the corpus callosum.

- Foix's syndrome is a manifestation of a lesion involving the red nucleus and the superior cerebellar peduncle, sparing the third cranial nerve. Patients with this condition may exhibit cerebellar ataxia and hemichorea on the contralateral side. However, if the lesion involves the superior cerebellar peduncles at the point of their decussation, cerebellar ataxia will be seen bilaterally.

- Nothnagel's Syndrome results from an expanding lesion of the tectum that impinges upon and exerts downward pressure upon the superior vermis of the cerebellum. Cerebellar symptoms and paralysis of the extraocular muscles ipsilaterally are the distinguishing features of this condition.

- Frontal lobe tumors may produce cerebellar deficits contralateral to the side of the tumor as a result of increased intracranial pressure and possible compression of the corticopontine fibers. Manifestations of mental disorders appear long before any cerebellar signs.

- Cerebellar aplasia, a congenital malformation in which part of the cerebellar hemisphere or most of the cerebellum does not develop, and is usually associated with anomalies of the contralateral inferior olive. Neonates with this condition exhibit intention tremor and other motor dysfunctions associated with standing and walking. Cerebellar aplasia is also seen in individuals with encephalocele and in Klippel-Feil syndrome.

- Friedreich's Ataxia (Figure 6.23) is an autosomal recessive disorder resulting from degeneration of the spinocerebellar tracts, dorsal white columns, Clarke's column, dorsal roots, and dorsal root ganglia. The onset of this disease is usually before the end of puberty, exhibiting gait ataxia of upper and lower extremities, muscular weakness, areflexia, and loss of joint sensation from the lower extremity. Patients may also manifest pes cavus (high arched foot and clawing of the toes), scoliosis (exaggerated lateral curvature of the spine), and cardiomyopathy. Nystagmus, vertigo and hearing loss may also be seen in this disease. Essential tremor, if present, may be a minor manifestation. Refsum's disease and abetalipoproteinemia (Bassen-Kornzweig syndrome) share some features with Friedrich's ataxia.

The diencephalon is bounded by the lamina terminalis rostrally and the posterior border of the mammillary bodies caudally. It is divided by the hypothalamic sulcus, which extends between the interventricular foramen of Monro and the cerebral aqueduct, into dorsal and ventral portions. The dorsal portion consists of the thalamus and epithalamus, while the ventral portion is comprised of the hypothalamus and subthalamus. The third ventricle separates the diencephalon from the corresponding part on the opposite side.

Characteristics of the diencephalon

Thalamus

Ventral nuclear group

Lateral group of thalamic nuclei

Medial group

Intralaminar nuclei

Midline nuclei

Ventral thalamus

Hypothalamus

Hypothalamic afferents

Hypothalamic efferents

Pituitary gland (hypophysis cerebri)

Epithalamus

Subthalamus

Characteristics of the diencephalon

The diencephalon, an important part of the central nervous system rostral to the brainstem, consists of the thalamus, epithalamus, hypothalamus, and subthalamus. The thalamus and epithalamus are separated from the hypothalamus and subthalamus by the hypothalamic sulcus. The latter sulcus extends between the interventricular foramen of Monro and the cerebral aqueduct. The diencephalon lies between the cerebral hemispheres, caudal to the lamina terminalis. It contains the third ventricle (Figure 7.1), which is bounded superiorly by the ependyma and the pia mater that join together to form the tela choroidea. This ventricle stretches from the lamina terminalis rostrally to the cerebral aqueduct caudally. It is connected to the lateral ventricle via the interventricular foramen of Monro and to the fourth ventricle through the cerebral (Sylvian) aqueduct. It extends into the pineal stalk as the pineal recess and to the area superior the optic chiasma as the optic recess. It is frequently crossed by fibers of the interthalamic adhesion (massa intermedia), also extends into the infundibulum as a funnel-shaped infundibular recess. The cerebrospinal fluid within this ventricle is secreted by the choroid plexus, which is attached to the tela choroidea and is supplied by the posterior choroidal artery.

Thalamus

The thalamus is the largest component of the diencephalon, which lies superior to the hypothalamic sulcus. It is separated from the caudate nucleus by the genu of the internal capsule. It forms the floor of the central part of the lateral ventricle, the posterior boundary of the interventricular foramen of Monro, and part of the lateral wall of the third ventricle (Figures 7.1 & 7.2 & 7.3). Both thalami may be interconnected in the midline by an intermediate mass (interthalamic adhesion) which extends behind the interventricular foramen of Monro.

It receives direct sensory impulses of all modalities, with the exception of the olfactory sensation. Olfactory information, combined with some other sensations, is conveyed to the

It receives direct sensory impulses of all modalities, with the exception of the olfactory sensation. Olfactory information, combined with some other sensations, is conveyed to the olfactory cortex, amygdala, and the mammillary body. Impulses that arise from the cerebellum and the basal nuclei are also integrated in the thalamus. These impulses are then projected to the motor and premotor cortices. To the same extent, visceral activities are also influenced by the thalamic connections to the hypothalamus and cingulate gyrus. In general, the thalamus integrates and modifies the sensory and motor

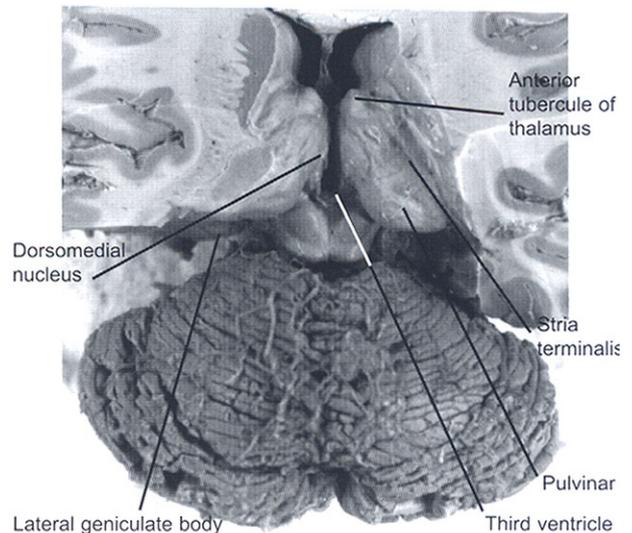


Figure 7.1 Dorsal surface of the diencephalon. Thalami are located on both sides of the third ventricle. The stria medullaris thalami represent a component of the epithalamus

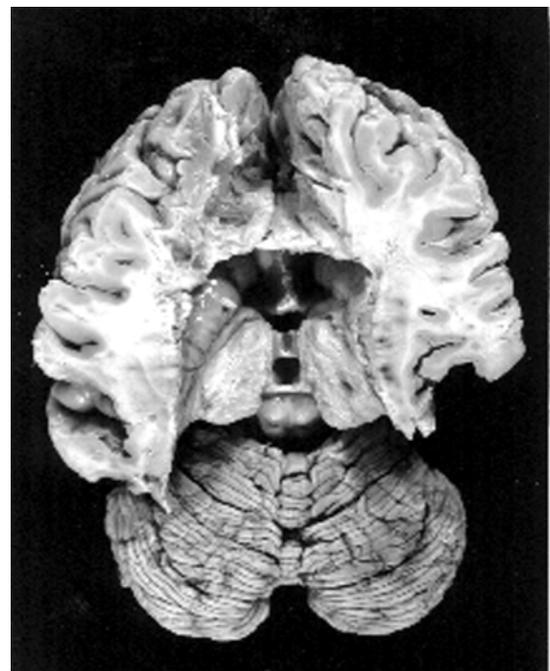


Figure 7.2 Dorsal surface of the diencephalon in relation to the basal nuclei. Note the habenular commissure connecting the habenular nuclei of the epithalamus

inputs and selectively tunes the output signals in a manner most efficient for stimulation of the cerebral cortex. Conscious awareness of pain, crude touch, temperature, and pressure sensations may occur at thalamic level. The thalamus also processes information that influences the Electro-cortical activity in the sleep-wake cycle through the ascending reticular activating system. Additionally, the

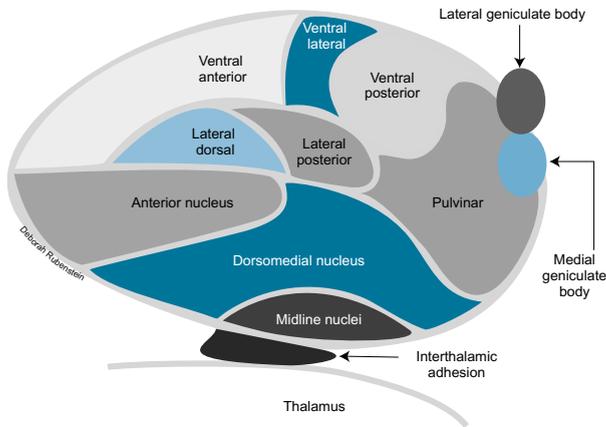


Figure 7.3 Three-dimensional diagram of the thalamus. Major nuclear groups are demarcated by the internal medullary lamina. Midline connection of thalami (interthalamic adhesion) is also illustrated

thalamus is also involved in the modification of the affective component of behavior via its connections to the limbic system.

With respect to the blood supply of the thalamus, the posterior cerebral artery plays an important role (Figures 7.4 & 7.28). As the terminal branch of the basilar artery, it supplies the midbrain and portions of the occipital and temporal lobes, giving rise to the posterior choroidal artery and central branches. These central branches include the posteromedial (thalamoperforating) and the posterolateral (thalamogeniculate) arteries. The latter branch may also arise from the posterior communicating artery, which emanates from the internal carotid artery. Anteromedially, the thalamus is supplied by the thalamoperforating arteries, while the caudal parts of the thalamus, including the pulvinar and geniculate bodies, are supplied by the thalamogeniculate arteries. Numerous branches from the posterior choroidal and posterior communicating arteries supply the superior and inferior parts of the thalamus, respectively. Occlusion of the terminal part of the basilar artery, supplying the diencephalon and midbrain, may result in pupillary dilatation or constriction, loss of light reflex, vertical gaze, and short-term memory, hallucination, agitation and coma or hypersomnolence.

The thalamus has dorsal and medial surfaces that are separated by the stria medullaris thalami. The dorsal thalamus is divided into medial and lateral nuclear groups by the internal medullary lamina (Figure 7.3). The diverging limbs of the internal medullary lamina surround the anterior nucleus of thalamus, forming the anterior tubercle. The ventral portion consists of the caudally located medial and lateral geniculate bodies (metathalamus), ventral anterior, ventral lateral and the

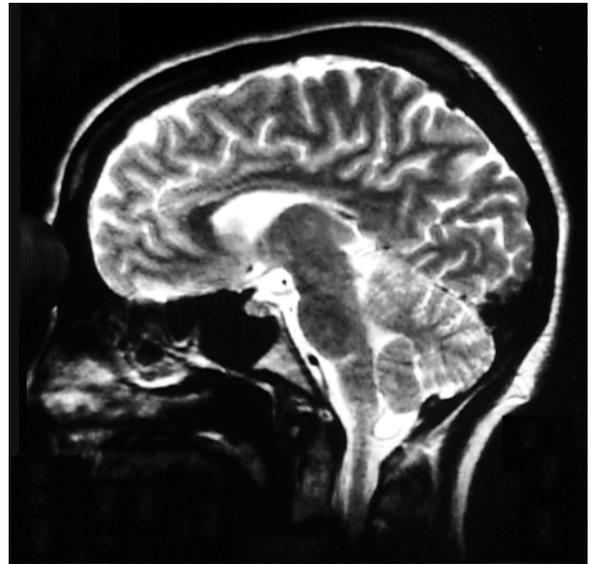


Figure 7.4 MRI scan of the brain showing the thalamus in relation to the caudate nucleus, midbrain, and corpus callosum. The posterior cerebral artery (main source of blood supply to the thalamus) is indicated



Figure 7.5 Mid-sagittal photograph of the brain. Anterior, ventral anterior, and dorsomedial nuclei, as well as the pulvinar are illustrated

ventral posterior nuclear groups. The ventral posterior nuclear complex comprises the ventral posterolateral and ventral posteromedial (arcuate) nuclei. The dorsal portion incorporates the lateral dorsal and the lateral posterior nuclear groups, and the pulvinar. Along the periventricular gray matter of the third ventricle, a group of midline thalamic nuclei exist, which are more prominent in the interthalamic adhesion (massa intermedia). Another group of thalamic nuclei, the intralaminar nuclei, is located in the substance of internal medullary lamina. The reticular nucleus of the thalamus, which is considered to be a continuation of the zona incerta of the subthalamus, is

located in the ventral thalamus, lateral to the external medullary lamina. The latter separates the thalamus from the internal capsule. All thalamic nuclei maintain reciprocal connections with the cerebral cortex. On the basis of their connections to the cerebral cortex and ascending pathways, the thalamic nuclei have customarily been classified as specific and non-specific nuclei. The latter is further subdivided into relay nuclei and association nuclei. However, the assumption upon which this classification rests remains tenable. It is clear that both specific, dense projections exist; all cortical areas receive more than one such type of thalamic input. It is equally clear that diffuse, non-specific projections do not originate from a single, discrete group of thalamic nuclei, and that many 'specific' nuclei may also convey 'non-specific' projections to widespread cortical areas.

The anterior nucleus (Figures 7.1, 7.2, 7.3, & 7.5) is bounded by the bifurcating limbs of the internal medullary lamina, forming a prominent swelling at the anterior pole of the thalamus (anterior tubercle). It also constitutes the posterior boundary of the foramen of Monro. Profuse reciprocal connections between this nucleus and the mammillary body (via the mammillothalamic tract), as well as the hippocampal formation (via the fornix) do exist. This nucleus consists of anteroventral, anteromedial, and anterodorsal subnuclei. The anteroventral and the anteromedial subnuclei receive input from the ipsilateral medial mammillary nucleus, whereas the anterodorsal subnucleus receives bilateral afferents from the lateral mammillary nuclei and the midbrain reticular formation. Projections from the anterodorsal and anteromedial subnuclei are destined to the anterior and middle portions of the cingulate gyrus. The latter gyrus also maintains reciprocal connections to the various divisions of the anterior thalamic nucleus. Additionally, the anterior nucleus interconnects with other thalamic nuclei of the same and opposite sides. It is an integral component of the limbic system, providing a linkage between the thalamus, hippocampus, hypothalamus, and the cingulate gyrus. Constructing a balance between instinctive and volitional behavior is thought to be an important function of this nucleus.

Due to its close association with the limbic system circuitry, the anterior nucleus is considered to be an essential element in the short-term memory. The significance of this fact is illustrated in the anterograde amnesia observed in lesions of the mammillothalamic tract, a pathway that terminates in the anterior nucleus. This type of amnesia is seen in Korsakoff's syndrome, which results from a thiamine deficiency (see the limbic system, Chapter 16).

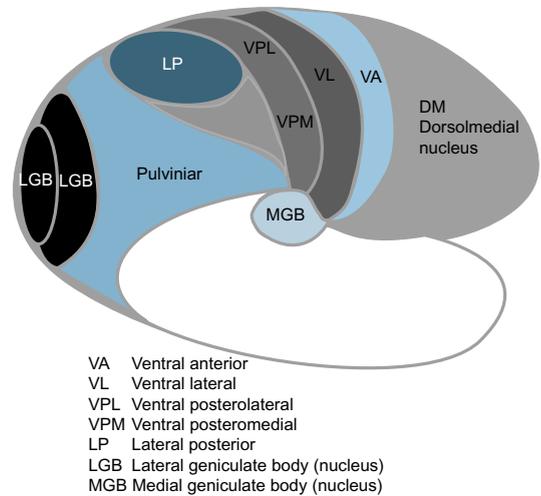


Figure 7.6 Cortical areas of the thalamic projections on the lateral surface of the cerebral hemisphere. These projections are specific sites where certain sensory and/or motor impulses are integrated



Figure 7.7 Section through the thalamomesencephalic junction. Metathalamus (lateral and medial geniculate bodies) are shown. The pulvinar overlies the geniculate bodies, forming the main component of the posterior thalamus

Ventral nuclear group

The ventral nuclear group comprises the metathalamus, ventral posterior nuclear complex, the ventral anterior nucleus, and the ventral lateral nucleus. Metathalamus consists of the lateral and medial geniculate bodies.

The lateral geniculate nucleus (body) is a visual relay nucleus which grossly resembles Napoleon's hat and lies lateral and rostral to the medial geniculate (Figures 7.1,



Figure 7.8 Section through the mid-level of diencephalon. The centromedian (intralamellar) and ventral posteromedial nuclei as well as the pulvinar are clearly shown

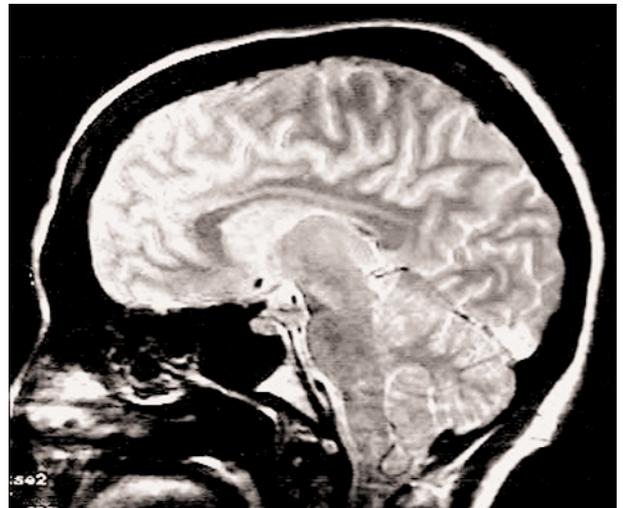


Figure 7.10 MRI scan of the brain showing the ventral lateral, centromedian, ventral posteromedial nuclei

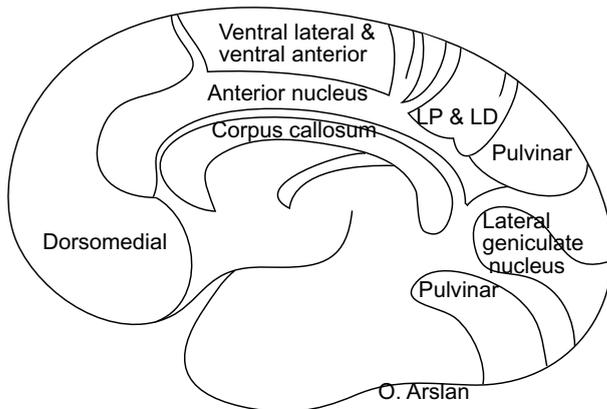


Figure 7.9 Schematic diagram of the medial surface of the brain illustrating cortical projections of thalamic nuclei

7.3, 7.7, 7.9 & 7.21). It consists of six laminae. Laminae 1 & 2 form the magnocellular part, while laminae 3, 4, 5, and 6 comprise the parvocellular part. The neurons of the magnocellular part are only sensitive to the black and white colors, respond quickly, and possess a high-resolution capacity. The parvocellular neurons project primarily to Brodmann's area 17, are responsive to colors, less sensitive to low-contrast stimuli, and remain slow in reacting to visual stimuli. Laminae 1, 4, and 6 receive visual impulses from the crossed fibers of the optic tract

whereas the 2nd, 3rd, and 5th laminae only receive fibers from the ipsilateral optic tract. The inferior visual quadrant is represented in the medial portion, whereas the superior quadrant is represented in the lateral part of the lateral geniculate body. Fibers from the macula project to the caudal part of the lateral geniculate body. The lateral geniculate body has reciprocal connections with the primary visual cortex (Brodmann's area 17).

The efferent fibers from this nucleus run within the retrolenticular part of the internal capsule, forming the geniculocalcarine tract (optic radiation). The lower fibers of the optic radiation course within the temporal lobe and loop backward (Meyer's loop) to join the more dorsal fibers. These fibers terminate primarily within laminae IV of the striate cortex (Brodmann's area 17), parastriate (Brodmann's area 18), and the peristriate (Brodmann's area 19) cortices.

The medial geniculate body (MGB) is an auditory relay nucleus ventrolateral to the thalamus, separated from the pulvinar by the brachium of the superior colliculus (Figures 7.3, 7.6, 7.7, 7.18 and 7.23). It consists of medial, ventral and dorsal nuclei. The medial (magnocellular) nucleus receives fibers from the inferior colliculus and the deep part of the superior colliculus, indicating the possible role of this nucleus in the mediation of modalities other than sound. It projects diffusely to lamina VI of the auditory, insular and opercular cortices. The dorsal (posterior) nucleus overlies the ventral nucleus, receives afferents from the pericentral nucleus of the inferior colliculus and from other auditory relay nuclei. Broad range of frequencies is regulated in the dorsal nucleus, accounting for the lack of tonotopic organization. Projection of the dorsal nucleus is limited to the secondary auditory cortex (Brodmann's area 22). Neurons of the

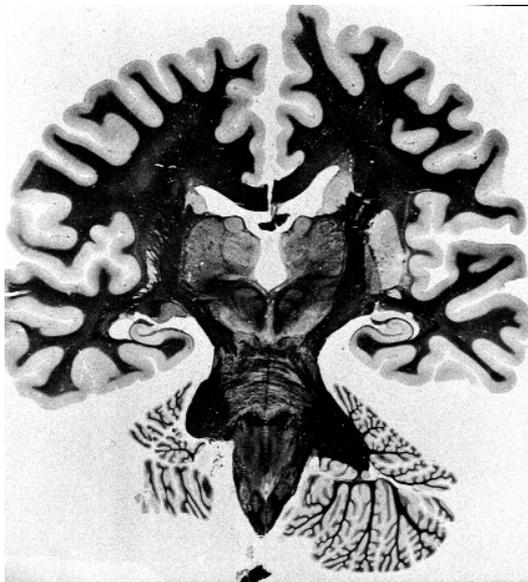


Figure 7.11 Coronal section of thalamus through the ventral posterolateral thalamic nucleus. In this view the anterior, dorsomedial, and ventral lateral nuclei are seen



Figure 7.12 Section of the thalamus through the habenular commissure. Note the distinct ventral posterolateral and ventral posteromedial nuclei as well as the pulvinar

ventral nucleus receive afferents from the inferior colliculus of the same side via the brachium of the inferior brachium. It is interesting to note that the ventral nucleus exhibits tonotopic arrangement in which low frequencies project laterally whereas high-pitched sounds are conveyed medially. The ventral nucleus terminates primarily in layer IV of the primary auditory cortex. Commissural neurones do not exist between the medial geniculate bodies.

The ventral posterior nucleus (VPN) (Figures 7.3, 7.6, 7.11 & 7.12) consists of the ventral posterolateral (VPL), the ventral posteromedial (VPM), and the ventral posterior inferior nucleus (VPI).

The ventral posterolateral nucleus (Figures 7.3, 7.6, 7.11 & 7.12) conveys impulses received via the spinothalamic tract, solitariothalamic tract, spino-cervico-thalamic tract, and the medial lemniscus to the dorsal and the intermediate regions of the postcentral gyrus, and to the secondary somatosensory cortex. Due to the considerable difference in the density of the peripheral innervation of different body regions, many more neurones tend to respond to stimulation of the hand than the trunk. Similarly, the distorted mapping of the body in this nucleus also reflects the difference in innervation density. Within this nucleus, the cervical fibers terminate medially, the thoracic and lumbar fibers terminate dorsally, and the sacral fibers are positioned laterally. Neurones of the VPL are modality specific and are unaffected by anesthesia.

The ventral posteromedial nucleus (VPM) is also known as the arcuate nucleus, because of its crescent shape (Figures 7.3, 7.6, 7.8, 7.10 & 7.12). It lies lateral to the centromedian nucleus and consists of a medial

parvocellular part, which receives gustatory impulses through the ipsilateral solitariothalamic tract, and a lateral principal part, which receives general sensation (tactile, thermal) from the head region. The general sensations from the head region ascend via the crossed ventral trigeminal tract and the uncrossed dorsal trigeminal tract.

The ventral trigeminal tract originates from the spinal trigeminal nucleus and the ventral part of the principal sensory nucleus. The uncrossed dorsal trigeminal tract is derived from the dorsal part of the principal sensory nucleus. Information received by the VPM is conveyed to the lower part of the postcentral gyrus and to the secondary somatosensory cortex via the thalamocortical fibers. VPL and VPM projections to the sensory cortex are contained in the posterior limb of the internal capsule.

The ventral posterior inferior nucleus (VPI) lies in close proximity to the thalamic fasciculus and the reticular nucleus of the thalamus. It receives terminals of the ascending vestibular fibers, which bypass the medial longitudinal fasciculus, delivering this information bilaterally to the vestibular cortical center, which lies adjacent to the facial region in the primary sensory cortex. Neurones of this nucleus respond to deep stimuli, particularly tapping.

The posterior thalamic zone (PTZ) is a nuclear complex, which is located dorsal to the medial geniculate body and medial to the pulvinar. It is comprised of the posterior nucleus, which is continuous with the ventral posterior inferior nucleus, the supragenulate nucleus, and the nucleus limitans (which lies between the pulvinar and the pretectum). This nuclear complex has a broad range of

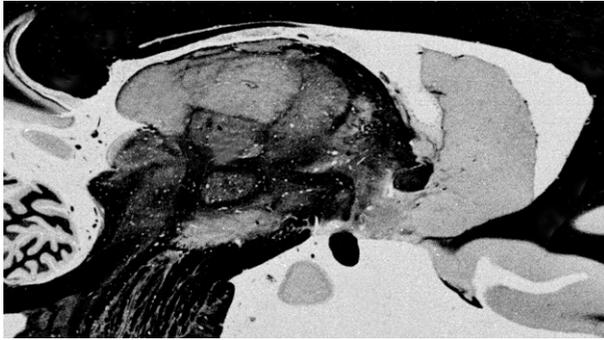


Figure 7.13 Sagittal view of the thalamus showing ventral lateral, dorsomedial, centromedian, and ventral anterior nuclei

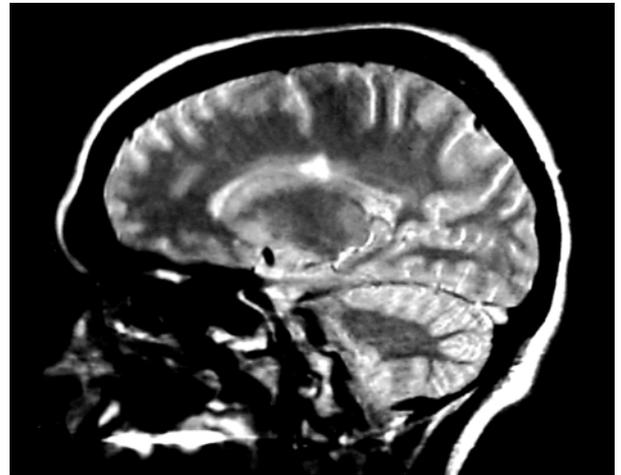


Figure 7.14 MRI scan illustrating the ventral lateral nucleus and pulvinar

connections, and it is neither place nor modality specific. In particular, the posterior nucleus of the PTZ receives pain and nociceptive stimuli via the lateral spinothalamic tract. It also receives tactile, vibratory and auditory impulses. The posterior thalamic nuclei project principally to the secondary somatosensory cortex of both cerebral hemispheres, particularly area IV.

The ventral anterior nucleus (VA) is bounded anteriorly and laterally by the reticular nucleus (Figures 7.3, 7.5, 7.6 & 7.13). It forms the anterior pole of the ventral nuclear group. It has rich connections with midline and intralaminar nuclei as well as the reticular nucleus. It is interesting to note that no fibers have been traced from the VA nucleus to the contralateral thalamus or to the striatum. The mammillothalamic tract crosses the VA nucleus. The magnocellular part of this nucleus receives input from the midbrain reticular formation, midline and intralaminar nuclei, and projecting to the orbitofrontal cortex and Brodmann's area 8. Due to its linkage to the intralaminar nuclei, wide areas of the cerebral cortex can be activated and desynchronization of the electrocortical activity can be achieved by stimulation of this nucleus. The ventral anterior nucleus as well as the orbitofrontal cortex is involved in the physiological phenomenon known as the recruiting response. The substantia nigra also projects to the magnocellular part of the nucleus, running parallel to the mammillothalamic tract. On the other hand, the principal part of this nucleus conveys input generated by the globus pallidus (via the thalamic fasciculus) and contralateral cerebellar nuclei (via the superior cerebellar peduncle) to the premotor cortex (Brodmann's area 6). The connections of the VA nucleus to the premotor cortex, globus pallidus, and substantia nigra (areas thought to be involved in dyskinetic movements) may explain the reduction or abolition of tremor seen in Parkinsonism.

The ventral lateral nucleus (Figures 7.3, 7.6, 7.10, 7.11, 7.13 & 7.14), also known as the ventral intermediate

nucleus, occupies the area posterior to the ventral anterior nucleus. It is divided into a rostral (oral part), a posterior (caudal part), and a medial part. The afferents to the ventral lateral nucleus are derived from the contralateral dentate nucleus (via the superior cerebellar peduncle), ipsilateral red nucleus, contralateral globus pallidus (through the thalamic fasciculus), the pars reticulata of the substantia nigra, and also from the precentral gyrus and premotor cortex. The afferents from the substantia nigra terminate in the medial part, while the remaining afferents terminate in the oral and caudal parts of the VL nucleus. Projections of the VL nucleus to the precentral gyrus are somatotopically arranged and establish monosynaptic connections with the neuron of this gyrus. The VL nucleus is part of the link between the cerebellum and the motor cortex, the basal nuclei and the cerebral cortex. Therefore, the cerebellum and the basal nuclei influence motor activity through their projections to the VL nucleus. Surgical ablation of the VL nucleus may be performed in order to relieve the tremor and rigidity associated with Parkinsonism.

Association nuclei, which project to the cortical association areas, but do not receive direct input from the ascending pathways, include the lateral dorsal, lateral posterior and dorsomedial nuclei, and the pulvinar.

Lateral group of thalamic nuclei

The lateral group of thalamic nuclei includes the lateral dorsal nucleus (LD), lateral posterior nucleus and pulvinar. The lateral dorsal nucleus (Figures 7.3, 7.9, 7.13, 7.16 & 7.18) represents the rostral extension of the dorsal group thalamic nuclei. It lies posterior to the anterior nucleus, and receives input from the superior colliculus and pretectal area. Reciprocal connections exist between this

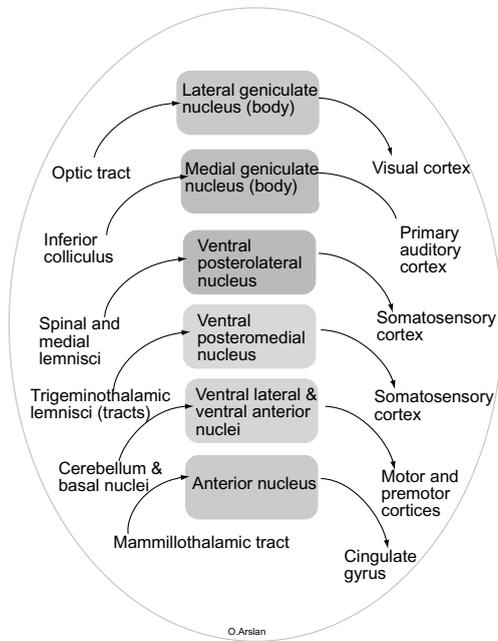


Figure 7.15 Summary of the main afferent and efferent connections of the thalamic relay nuclei

nucleus and the cingulate, and the peruncate gyri. The LD nucleus also projects to the posterior part of the parahippocampal gyrus.

The lateral posterior nucleus (LP) (Figures 7.3, 7.9, 7.17 & 7.18) lies caudal to the lateral dorsal nucleus. The geniculate bodies, as well as neurons of the ventral group thalamic nuclei, convey information to this nucleus. The parietal and occipital lobes (Brodmann's areas 5 & 7) have reciprocal connections with this nucleus. However, no known connections exist between the lateral dorsal nucleus and the primary sensory, visual or auditory cortices.

The pulvinar (Figures 7.1, 7.2, 7.3, 7.7, 7.8, 7.12, 7.13 & 7.19), the largest thalamic nucleus and phylogenetically is the most recent. It overlies the geniculate bodies, separated from them by the brachium of the superior colliculus. It has multisensory functions, receiving input from the intralaminar nuclei, geniculate bodies and the superficial layers of the superior colliculus, as well as reciprocal connections with the temporal, parietal and occipital lobes. Wernicke's sensory speech center (Brodmann's area 22) maintains a rich connection with this nucleus. Visual input from the retina also reaches the pulvinar via the lateral geniculate body and the superior colliculus. Visual impulses from the inferior and lateral parts of the pulvinar, which projects to the supragranular layers of the primary visual cortex, and to layers I, III, and IV of the secondary visual cortex (areas 18 and 19), constitute the extrageniculate visual pathway, linking the retina, tectum and visual cortex. The medial part has primary reciprocal connections with the posterior parietal

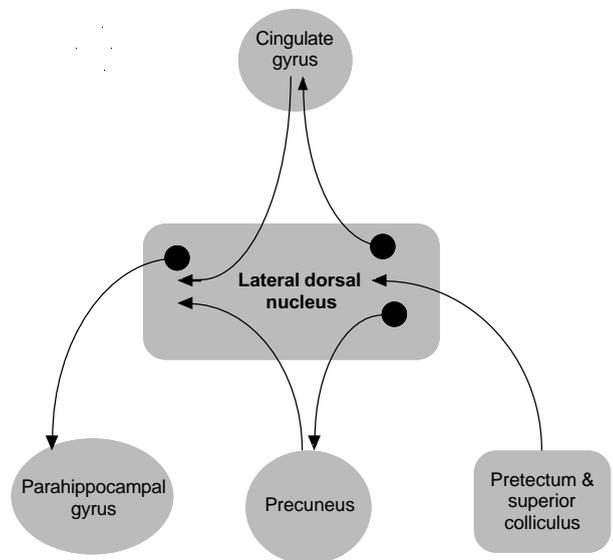


Figure 7.16 Schematic drawing of the afferent and efferent connections of the lateral dorsal nucleus

cortex. Based on these connections, the pulvinar is implicated in visual and oculomotor control, as well as pain and speech modulation.

Medial group

The medial group of thalamic nuclei consists of a single, large dorsomedial nucleus. The dorsomedial nucleus (Figures 7.1, 7.3, 7.5, 7.8, 7.11, 7.13, 7.18, 7.19, 7.23 & 7.24), is located between the internal medullary lamina and the third ventricle. It is considered a relay nucleus for transmission of impulses to the hypothalamus. It has extensive connections with the intralaminar and midline thalamic nuclei. This nucleus consists of a magnocellular, parvocellular, and paralaminar parts. Through its connections, the magnocellular part integrates impulses received through the ansa peduncularis from the amygdala, lateral hypothalamus, diagonal band of Broca, orbitofrontal cortex, and the substantia innominata. Ansa peduncularis is comprised of the inferior thalamic peduncle and the interconnecting fibers between the amygdala and the preoptic area. The parvocellular part establishes reciprocal connections with the prefrontal cortex (Brodmann's areas 9,10, 12 & 13), and receives input from the globus pallidus. The paralaminar part maintains reciprocal connections to the premotor cortex (Brodmann's areas 6 and 8) and also receives input from the pars reticulata of the substantia nigra.

Intralaminar nuclei

The intralaminar thalamic nuclei are embedded in the internal medullary lamina. These include the

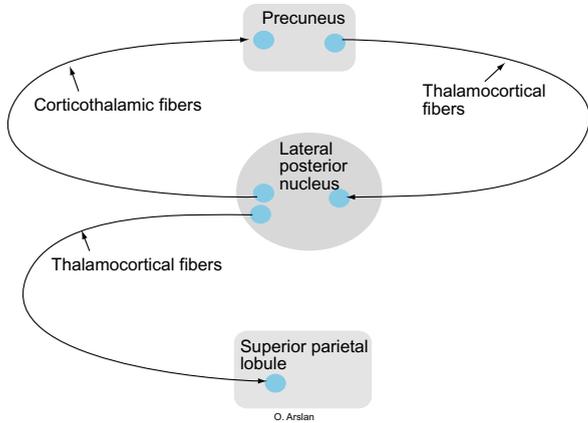


Figure 7.17 Simplified diagram of the main projections and afferents of the lateral posterior thalamic nucleus

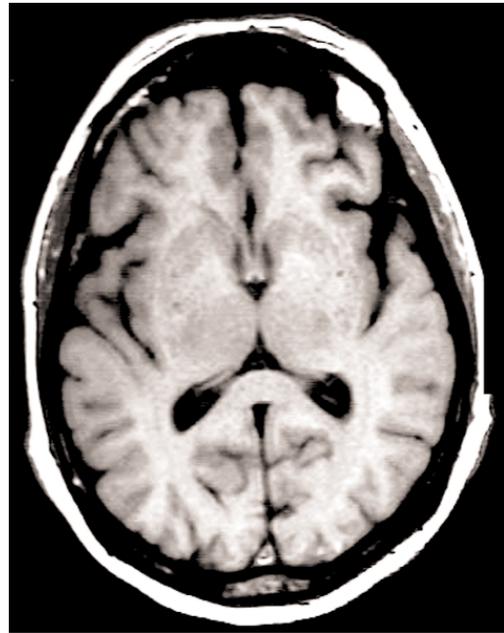


Figure 7.19 An inverted MRI scan of the brain showing the dorsomedial nucleus and the interthalamic adhesion where midline nuclei are located



Figure 7.18 This section through the posterior commissure illustrates the prominent dorsal medial, lateral posterior, and centromedian nuclei and the medial geniculate body

centromedian (Figures 7.3, 7.8, 7.10, 7.13, 7.18 & 7.23), parafascicular, central lateral and central medial nuclei. They receive afferents from the globus pallidus, striatum, and dentate nuclei of the cerebellum, pedunculopontine nucleus and terminals and collaterals from the spinal, medial and trigeminal lemnisci. Ascending reticular fibers, which are derived from the nucleus reticularis gigantocellularis, nucleus reticularis ventralis and dorsalis of the medulla and nucleus reticularis pontis, form the principal afferents to the intralaminar nuclei. They project ipsilaterally to the centromedian-parafascicular nuclear (CM-PF) complex and to the paracentral and central nuclei.

The spino-reticulo-thalamic (paleo-spino-thalamic) tract projects bilaterally to the intralaminar nuclei. Despite

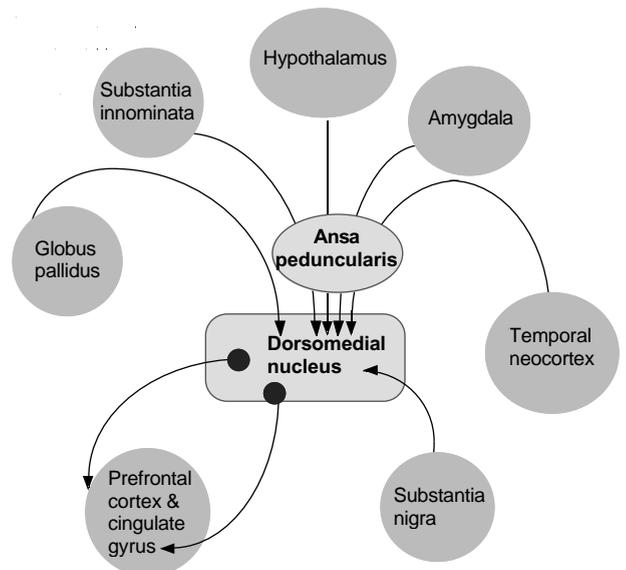


Figure 7.20 Schematic diagram of the afferents of the dorsomedial nucleus of the thalamus which contribute to the formation of ansa peduncularis

the diffuse cortical projections of the intralaminar nuclei, this connection is not reciprocal. The centromedian is the largest nucleus in this group, which together with the medially located parafascicular nucleus, forms the CM-PF nuclear complex. This nuclear complex sends fibers to the putamen and the substantia nigra. Other smaller intralaminar nuclei project to the caudate nucleus. The

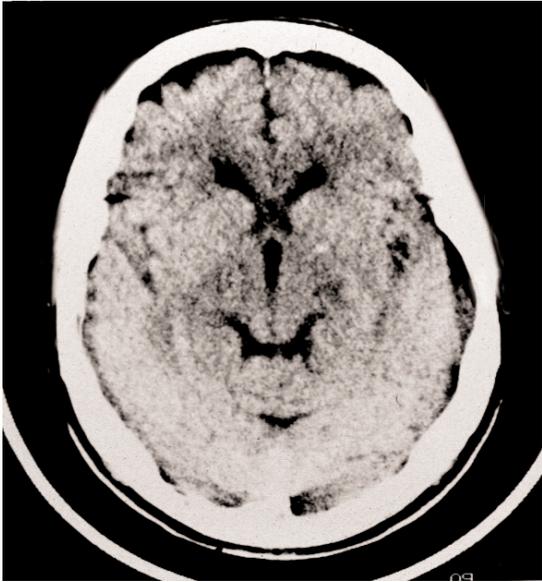


Figure 7.21 This computed tomography scan shows the lateral geniculate body and its location rostral and lateral to the superior colliculus

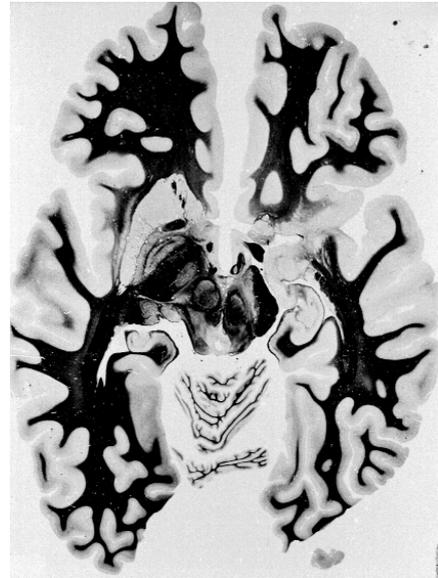


Figure 7.22 Section through diencephalo-mesencephalic junction. The lateral and medial geniculate bodies are prominently illustrated

The DM nucleus is associated with the affective qualities of behavior and somatic sensation through its connections with the hypothalamus and the prefrontal cortex. It has no connection with any particular sensory nucleus. Removal of this nucleus and/or a prefrontal lobotomy may be used to modify or reduce the emotional stress associated with chronic pain. Patients who have undergone this surgical procedure report feeling pain without being distressed. This is identical to the perception of pain that patients report when given narcotics. Reduction in anxiety, aggressive behavior or obsessive thinking may result from destruction of this nucleus. Some degree of amnesia and confusion may develop later.

projection of the precentral gyrus to the centromedian nucleus is predominantly ipsilateral. Some of these fibers run within the internal capsule and crus cerebri. Due to its connection to the striatum (caudate and putamen), motor cortex and indirectly to the globus pallidus, the centromedian nucleus serves as an important element of a feedback circuit between these areas. The habenulopeduncular tract (fasciculus retroflexus) divides the parafascicular nucleus into medial and lateral divisions. The PF nucleus conveys the input received from the premotor cortex (Brodmann's areas 6, 8 and 9) to the putamen. Desynchronization of electrocortical activity is attributed to the diffuse connections of the intralaminar

nuclei to all areas of the cerebral cortex and to their extensive input from the reticular formation. Both the intralaminar thalamic nuclei and the specific thalamic nuclei project to the cerebral cortex, giving off collaterals to the reticular nucleus.

Midline nuclei

The midline nuclei (Figure 7.3) are located, when present, within the interthalamic adhesion (massa intermedia) and in the periventricular area of the third ventricle. These nuclei comprise the paleo-thalamus (relatively new on phylogenetic basis), consisting of anterior and posterior paraventricular nuclei, as well as the rhomboidal, reuniens, central, and paratenial nuclei. These nuclei receive afferents from the reticular formation, corpus striatum, cerebellum, hypothalamus, and spinothalamic tracts. The main projections of these nuclei are to the cingulate gyrus, amygdala, entorhinal cortex, and the prepyriform cortex.

Ventral thalamus

The principal nuclear group of the ventral thalamus is the reticular nucleus. The reticular nucleus structurally resembles and is continuous with the zona incerta. It lies between the external medullary lamina and the posterior limb of the internal capsule. All areas of the cerebral cortex as well as the midbrain reticular formation, and the globus pallidus convey impulses to the reticular nucleus. This nucleus does not project to the cerebral cortex, but it does influence the activity of other thalamic neurons that project to the cerebral cortex.



Figure 7.23 Section of the thalamus through the anterior nucleus. Dorsomedial, centromedian, and ventral posterolateral nuclei are illustrated. The geniculate bodies are also visible

Hypothalamus

The hypothalamus (Figure 7.25, 7.26, 7.27 & 7.28) lies posterior to the optic chiasma, ventral to the thalamus and between the third ventricle and the subthalamus. It is connected ventrally to the pituitary gland, and is divided into lateral and medial parts by the fornix. The hypothalamus is comprised of mammillary bodies, tuber cinereum, medial eminence, and infundibulum.

The hypothalamus may also be classified into the preoptic, supraoptic, tuberal and mammillary areas. The preoptic area is located rostral to the optic chiasma and ventral to the anterior commissure, while the supraoptic area lies above the optic chiasma and includes the supraoptic, paraventricular, and suprachiasmatic nuclei. The preoptic area is the site of termination of many fibers that carry neuromediators such as angiotensin II, delta sleep-inducing peptide, dynorphin, enkephalin, endorphin, galanin, GABA, glycine, substance P, vasoactive intestinal peptide (VIP), serotonin, acetylcholine, adrenaline, dopamine, ACTH, Luteinizing-hormone releasing hormone, etc.

The magnocellular secretory neurons of the supraoptic and paraventricular nuclei of the hypothalamus secrete antidiuretic hormone (ADH) and oxytocin. These hormones are synthesized on the ribosomes of cell body and packaged in Golgi complexes. Both hormones are peptides linked to precursor protein, neurophysin. Exocytosis of the secretory granules into the pericapillary spaces occurs following depolarization of the neuroendocrine cells. Antidiuretic hormone (ADH)

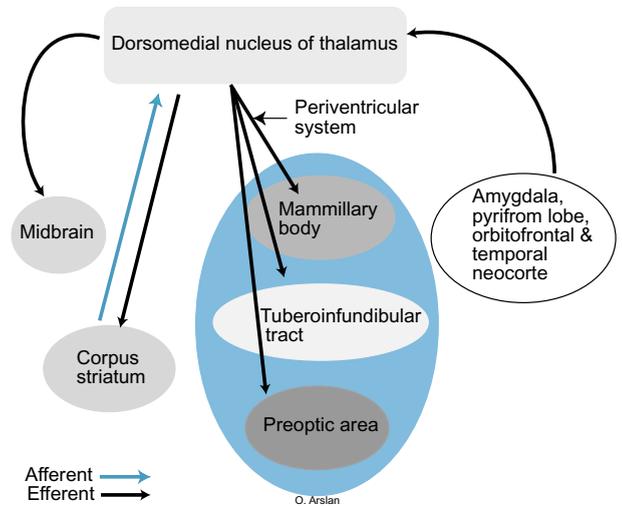


Figure 7.24 Schematic diagram of the afferent and efferent fibers of the dorsal medial nucleus of the thalamus. Note that the connection to the corpus striatum is bilateral. The projections of the dorsomedial nucleus to the mammillary body, tuberoinfundibular region, and preoptic area comprise the periventricular system

changes the permeability of the distal convoluted and collecting tubules, thus increasing the reabsorption of water into the bloodstream and counteracting dehydration. ADH neurons also secrete other peptides such as dynorphin, galanin, and peptide histidine isoleucine. In mammals, ADH neurons receive input from the median preoptic area, and from the noradrenergic neurons of the brainstem that carry cardiovascular input. They are inhibited by GABA and excited by angiotensin II, α_2 adrenergic, glutamate, and acetylcholine. Oxytocin is secreted in conjunction with small amounts of enkephalins, galanin, and dynorphin. Oxytocin secreting neurons receive afferents from the uterine cervix, vagina (Ferguson reflex), and nipple for milk ejection. Thus, oxytocin causes an increase in the contraction of the smooth muscles of the mammary gland and the uterus. Both ADH and oxytocin have overlapping functions and are delivered to the posterior lobe of the pituitary gland through the supraoptico-paraventriculo-hypophysial tract.

The suprachiasmatic nucleus lies postero-superior to the optic chiasma, in close proximity to the third ventricle. It receives bilateral input from the retina, mediating the biological clock. This nucleus which has a ventrolateral and dorsomedial subdivisions, is involved in the regulation of body temperature, hormonal concentrations of plasma, renal secretion, sleep-wake cycle, and day-night cycle in motor activity. The ventrolateral part of the nucleus consists of neurons that remain immunoreactive for vasoactive intestinal peptide (VIP), receiving additional

Thalamic syndrome (Dejerine Roussy Syndrome or thalamic apoplexy) may result from occlusion of the posterior choroidal, the posterior cerebral, and the thalamogeniculate arteries. Hemiparesis on the contralateral side may be seen initially as a result of edema that compresses the corticospinal tracts as they descend through the posterior limb of the internal capsule. Ataxia and clumsiness in the affected limb may occur and is often associated with episodes of severe pain following a transient anesthesia (loss of all sensations) contralaterally. In general, it is attributed to a loss of joint sensation and a loss of the ability to appreciate movement. At the onset of the syndrome, a complete contralateral hemianesthesia and hemianalgesia occurs. Pain, temperature, and crude touch gradually return; however, positional sense and stereognosis are lost permanently. Sensation in the face may or may not be affected, depending upon the involvement of the VPM nucleus of thalamus. Visual deficits, such as homonymous hemianopsia, may also be detected if the lateral geniculate body is damaged. Hypersensitivity to slight superficial stimuli, which results in severe pain, is common in this condition. Thalamic pain is a diffuse, burning and lingering type of sensation that may be elicited by mild stimuli of touch, pressure, and vibration, and aggravated by emotional conditions. A pinprick may cause agonizing and intolerable pain. Pressure from one's clothing or sound from a musical instrument, may produce tremendous discomfort. These sensations occur

afferents from the midbrain raphe and the lateral geniculate body. The glutamatergic retinal afferents, which mediates the rhythm to the light-dark cycle, are received by the neurons of the ventrolateral subdivision of the nucleus. The receiving neurons respond to onset and offset of light and intensity of light, which change their firing rate. One of the striking characteristics of the retinally-related neurons of suprachiasmatic nucleus is their ability to express a specific complement of subunits for the N-methyl D aspartate (NMDA) receptors. It has also been suggested that the expression of c-fos genes within the suprachiasmatic nucleus may be induced by the application of light during the night that reset the biological clock. On the other hand, the dorsomedial subdivision contains parvocellular neurons that are immunoreactive to for arginine vasopressin. Neuronal axons of the suprachiasmatic nucleus project to the paraventricular, tuberal, and ventromedial hypothalamic nuclei. The projections of the suprachiasmatic nucleus to the reticular formation that eventually affect the activities of the sympathetic neurons and secretion of melatonin from the pineal gland may be mediated via the paraventricular nucleus. This nucleus contains vasopressin, VIP, and neurotensin. Vasopressin neurons in the

in response to any stimulus, however, pain threshold is increased and pain sensation is often prolonged and may be elicited by a stronger stimulus.

Occasionally a condition known as thalamic hand may be observed on the contralateral side. It is characterized by flexion of the digits at the metacarpophalangeal joints and extension at the distal phalangeal joints, along with flexion and pronation of the wrist. General hypotonia results in a constant need to re-adjust posture. Thalamic hematomas may cause prominent sensory deficits contralaterally. Due to the caudal location of the corticospinal fibers, relative to the hematoma, muscular weakness is less likely to occur. However, choreiform movements and ataxia may be seen in the contralateral limb. Ocular deviation, in which one eye exhibits a lower position than the opposite eye at rest and maintain an exaggerated convergence (pseudo abducens nerve palsy) and an inability to look upward. These ocular changes, which result of compression of the adjacent tectal and pretectal areas by a thalamic hematoma, gives the appearance of an individual staring at the bridge of his nose. Hematoma of the left thalamus is generally associated with fluent aphasia. A right-sided thalamic hematoma is accompanied by anosognosia and left sided visual neglect. Due to involvement of the intralaminar thalamic nuclei and the central tegmental tract, thalamic hemorrhage may initially be associated with decreased consciousness.

suprachiasmatic nucleus show marked reduction in Alzheimer's disease. One of the most important functions of the suprachiasmatic nucleus is the ability to mediate circadian rhythm, a mechanism that remains active even in the tissue grafts of fetal hypothalamus that contain the suprachiasmatic nuclei.

It is thought that deterioration of the suprachiasmatic nucleus leads to the disruption of the circadian rhythms and disturbances in the sleep-wake cycle. Disturbance during sleep may predispose affected individuals to the development of sundowner syndrome, a condition that is characterized by increased confusion, vocalization, sleep apnea, restlessness, agitation and pacing in the early evening, and dementia.

On each side, the tuberal area extends between the infundibulum and the mammillary bodies, containing the tuberal, dorsomedial, and ventromedial nuclei. The parvocellular neurons of the tuberal nuclei of hypothalamus secrete the hormone regulating factors (HRF), which are delivered to the median eminence (upper portion of the infundibulum) via the tuberoinfundibular tract. The hypophysial portal system then carries these substances from the median eminence to the anterior lobe of the pituitary where they may enhance or

Table 7.1 Summary of connections of thalamic nuclei

<i>Afferents</i>	<i>Thalamic nuclei</i>	<i>Efferents</i>
Medial lemniscus	Ventral posterolateral (VPL)	Somesthetic cortex (postcentral gyrus)
Spinothalamic tract	Ventral posterolateral (VPL)	Somesthetic cortex (postcentral gyrus)
Trigeminal lemnisci	Ventral posteromedial (VPM)	Somesthetic cortex (postcentral gyrus)
Inferior colliculus	Medial geniculate body	Auditory cortex
Optic tract & visual cortex	Lateral geniculate body	Visual cortex (Brodmann's area 17)
Hypothalamus, prefrontal cortex	Dorsomedial nucleus	Prefrontal cortex
Mammillothalamic tract & cingulate gyrus	Anterior	Cingulate cortex
Globus pallidus, motor cortex & cerebellum	Ventral lateral	Primary motor cortex (precentral gyrus)
Substantia nigra, dentate nucleus & premotor cortex	Ventral anterior	Premotor cortex
Hypothalamus	Lateral dorsal	Cingulate and precuneate gyri
Parietal & occipital cortices	Lateral posterior	Parietal and occipital cortices
Intralaminar nuclei & tectum	Pulvinar	Temporal, parietal, and geniculate bodies
Ascending reticular activating system	Intralaminar	Putamen, substantia nigra, globus pallidus, and lateral spinothalamic tracts
Reticular formation, globus pallidus & spinothalamic tracts	Midline	Cingulate gyrus, amygdala, cerebellum, hypothalamus and cortex
Cerebral cortex, globus pallidus & reticular formation	Reticular	Thalamic nuclei projecting to midbrain

inhibit the release of the hormones from the anterior lobe of the pituitary gland. The tuberal nuclei contain histamine, galanin, gamma amino butyric acid, cholinesterase, but not choline acetyl transferase, etc.

The lateral hypothalamic region, which lies lateral to the column of the fornix (and mammillothalamic tract), contains the lateral hypothalamic nucleus. The mammillary bodies (MBs) are located posterior to the tuber cinereum, anterior to the interpeduncular fossa, and rostral to the anterior perforated substance. They consist of the medial and lateral mammillary nuclei. The mammillary area consists of the medial and lateral mammillary nuclei. Histamine and γ -aminobutyric acid (GABA) and galanin are the main content of the medial mammillary nucleus.

The hypothalamus integrates visceral and endocrine functions. It is an important component of the limbic system through which emotions gain expression. It contains sympathetic (postero-lateral) center, parasympathetic (antero-medial) centers, and centers for thermo-regulation (anterior center provides the mechanism for heat dissipation whereas the posterior

center mediates activities that produce and conserve heat). Feeding centers, including the hunger center (lateral hypothalamic nucleus) and the satiety center (ventromedial nucleus), as well as centers for sleep-wake cycle (suprachiasmatic nucleus and anterior hypothalamus), memory and behavioral regulation (ventromedial nucleus) are all contained in the hypothalamus. Behavioral regulation may encompass fear, rage, pleasure, sexual attitude, and reproduction. Stimulation of the anteromedial part of the hypothalamus increases gastrointestinal motility and bladder contractions. It also decreases the heart rate, and produces peripheral vasodilatation. Stimulation of the posteromedial part produces mydriasis (dilation of the pupil) increased heart rate, and peripheral vasoconstriction.

The posteromedial (thalamo-perforating) branches of the posterior cerebral artery primarily supply the hypothalamus, including the mammillary bodies, infundibulum, tuber cinereum, and pituitary gland. The mammillary bodies, tuber cinereum, and optic chiasma are surrounded by the arterial circle of Willis ([Figure 7.29](#)), an

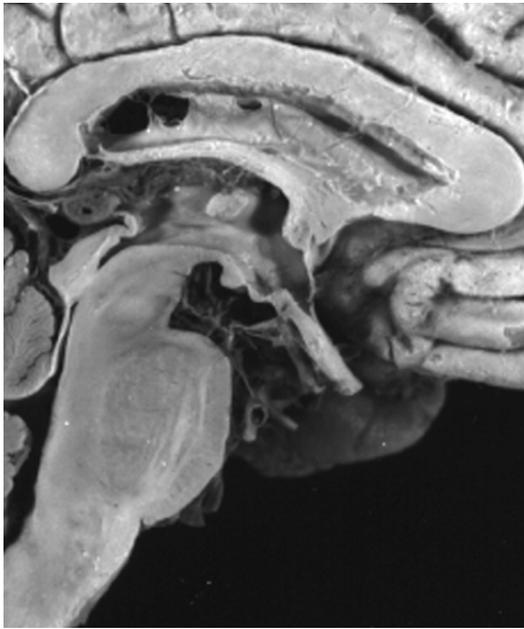


Figure 7.25 Mid-sagittal section of the brain illustrating the components and boundaries of the hypothalamus

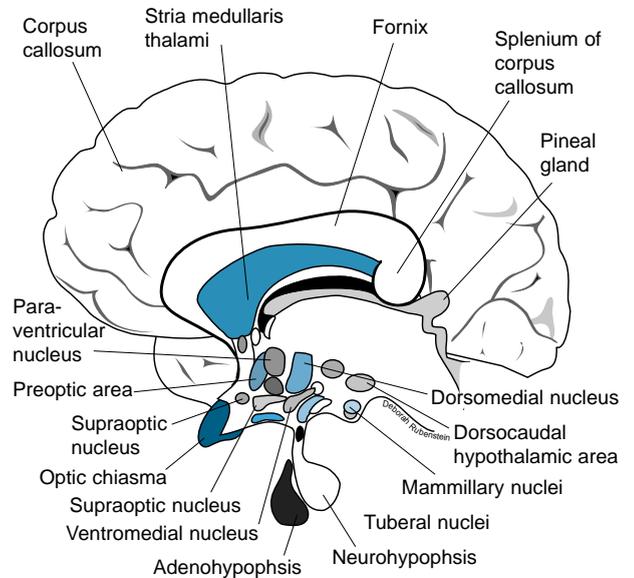


Figure 7.27 Hypothalamic nuclei and associated areas

Hypothalamic afferents

Hypothalamic afferents emerge from various areas of the central nervous system, including the hippocampal formation, septal area, amygdala, zona incerta, subthalamic nucleus, tegmental nuclei, periaqueductal gray matter, and the retina. The hypothalamus also receives noradrenergic input from the locus ceruleus, serotonergic input from raphe nuclei, and the cholinergic afferents from the ventral tegmental nucleus (Figures 7.30 & 7.31). The origin, course, and termination of these afferents are illustrated below, including the hippocampal formation, amygdala, tegmental nuclei, periaqueductal gray matter, nucleus ambiguus, solitary nucleus, superior colliculus, Edinger Westphal and hypoglossal nuclei, retina, locus ceruleus, and the raphe nuclei.

The hippocampal formation projects to the hypothalamus via the fornix, a robust bundle of fibers that emanate from the hippocampal gyrus. As it approaches the anterior commissure, the fornix divides into pre-commissural column, which terminates in the lateral hypothalamic nucleus and post-commissural column, projecting to the medial mammillary nucleus (Figure 9.1).

The septal area and midbrain reticular formation also project to the hypothalamus via the medial forebrain bundle.

The amygdala sends fibers to the hypothalamus via the stria terminalis and the ventral amygdalofugal fibers. The stria terminalis originates from the corticomедial nucleus and terminates in the medial hypothalamic region. Input to the lateral hypothalamic region emanates from the basolateral nucleus and carried by the ventral amygdalofugal fibers.



Figure 7.26 An inverted MRI scan of the brain. The hypothalamus, as indicated, forms the floor of the third ventricle

arterial chamber formed by branches of the internal carotid and vertebral arteries, providing shunting between the vertebro-basilar system and the carotid systems. It does not always show symmetry as one or more branches may undergo hypoplasia. The specific arterial branches involved in this circle are the anterior cerebral, internal carotid, anterior and posterior communicating, and the posterior cerebral arteries.

Locus ceruleus (adrenergic), raphe nuclei (serotonergic), and the mesolimbic dopaminergic neurons also project to the hypothalamus. Adrenergic group A11 projects to the medial hypothalamic nuclei, whereas groups A13 and A14 convey impulses to the dorsal and rostral hypothalamus.

Hypothalamic efferents

The diverse functions of the hypothalamus are maintained through its multiple projections to the anterior nucleus of thalamus, midbrain reticular formation, pituitary gland, and the spinal cord (Figure 7.31).

The principal mammillary fasciculus emanates from the mammillary body and divides into the mammillothalamic, which projects to the anterior nucleus of the thalamus, and mammillo-tegmental tract, terminating in the tegmental nuclei of the midbrain. Mammillary projections of the anterior nucleus of the thalamus to the cingulate gyrus, then via the cingulum to hippocampal gyrus and back to the mammillary body via the fornix, constitute the Papez circuit of emotion, an element thought to be essential in regulating emotion.

The hypothalamo-hypophyseal tracts comprise the supraoptic-hypophysial and the tuberinfundibular tracts. The supraoptic-hypophysial delivers ADH and oxytocin from the magnocellular neurons of the supraoptic and paraventricular nuclei to the neurohypophysis, whereas the tubero-infundibular tract transmits hormone-regulating factors from parvocellular neurons of the tuberal nuclei to the adenohypophysis through the hypophysial portal system. Although the tuberal nuclei are the major source of the dopaminergic hormone regulating factors to the adenohypophysis, the preoptic, periventricular, dorsomedial, and ventromedial hypothalamic nuclei also contribute to this system. Diffuse projections also arise from the tuberal nuclei to areas of cerebral cortex, and to areas that contains cholinesterase that typically undergo neurofibrillary degeneration in Alzheimer's disease.

The dorsal longitudinal fasciculus contains fibers, largely uncrossed, that projects from medial and periventricular areas of the hypothalamus to the central gray of the midbrain, accessory oculomotor, salivatory nuclei, solitary, and facial nuclei transmitting impulses between neurons of the reticular formation and the hypothalamus. Some cholinergic fibers are described as descending from the hypothalamus to the cerebellum via the superior cerebellar peduncle. Serotonergic fibers also ascend from the raphe nuclei of the brainstem within this pathway to the hypothalamus.

Paraventricular and dorsomedial nuclei provide direct hypothalamo-spinal tract, which terminates in the intermediolateral columns of the spinal cord. The ventromedial nucleus projects via the medial forebrain bundle to the midbrain reticular formation, central

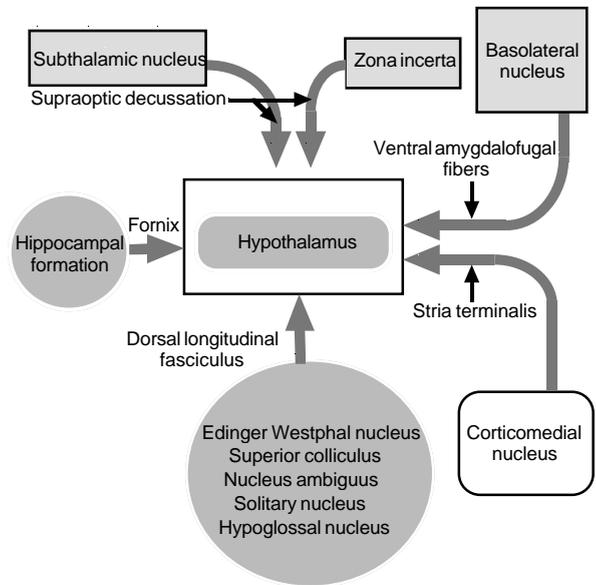


Figure 7.30 Schematic drawing of the afferent and efferent fibers of the hypothalamus. Some of these connections e.g. from the hippocampal formation are bilateral

nucleus of amygdala, bed nucleus of stria terminalis, and the basal nucleus of Meynert. Septal area and amygdala maintain reciprocal connections with the hypothalamus.

The hypothalamus shares embryological, morphological, and functional characteristics with the pituitary gland. The hormonal secretions of the pituitary gland are dependent upon the functional integrity of the hypothalamus. This is accomplished by the hypothalamic input to the medial eminence via the tuberoinfundibular tract which eventually affects the secretion of the adenohypophysis, and by the hypothalamic neurons that secrete the ADH and oxytocin and stored in the neurohypophysis.

Pituitary gland (hypophysis cerebri)

The pituitary gland (Figure 7.32) develops from Rathke's pouch (an ectodermal outpocketing of the stomodeum) and the infundibulum (a downward extension of the diencephalon). Rathke's pouch forms the adenohypophysis, the intermediate lobe, and the pars tuberalis.

The diencephalic (neural ectodermal) part of the pituitary gland contains neuroglia, and receives fibers from the hypothalamus. It consists of the adenohypophysis and the neurohypophysis.

The cavernous sinuses flank this gland, which lies in the hypophysial fossa of the sella turcica. It is covered partly by

Lesions of the hypothalamus produce a multitude of symptoms depending upon the location and the structures involved. To produce hypothalamic dysfunction, a lesion must be bilateral. One of the most common sources of hypothalamic dysfunction is craniopharyngioma, a tumor of Rathke's pouch. Posterior hypothalamic lesions are more likely to injure the major pathways associated with the hypothalamus. Bilateral damage to the medial forebrain bundle may result in deep coma, whereas lesions of the dorsal longitudinal fasciculus may disrupt the heat production and heat-dissipating mechanisms. Destruction of the supraoptic nuclei or supraoptico-hypophysial tract may produce diabetes insipidus, a condition which is characterized by polydipsia (excessive drinking of water) and polyuria (copious urination). Involvement of the tuberal nuclei may lead to cessation of the hormone regulating factors and resultant sexual dystrophy. Destruction of the satiety centre (ventromedial nucleus) produces obesity as a result of hyperphagia (excessive eating), whereas damage to the feeding center results in anorexia. Obesity may be observed in cases where the ventromedial nucleus is damaged. Destruction of the satiety center produces hyperphagia (excessive eating), whereas damage to the feeding center results in anorexia.

Hypothermia and hyperthermia may result from destruction of the anterior and posterior nuclei of the hypothalamus, respectively. Selective destruction of the posterior hypothalamic region causes poikilothermia (a condition in which body temperature varies with the environmental temperature). Bilateral destruction of the medial region of the hypothalamus produces violent behavior in previously docile individuals. Destruction of the posterior hypothalamus may result in hypersomnia (excessive sleeping). Bilateral destruction of the medial region of the hypothalamus produces violent behavior in previously docile individuals.

the diaphragma sella, and is connected to the hypothalamus by the infundibulum.

The pituitary gland is supplied by the superior and inferior hypophysial branches of the internal carotid artery. The superior hypophysial artery supplies the tuberal region, the infundibular stalk, optic chiasma, and the medial eminence. The inferior hypophysial arteries form an arterial ring around the infundibular stem and provide blood supply to the lower infundibulum and the posterior lobe. These arteries establish numerous anastomoses and branch repeatedly, terminating into capillaries and capillary sinusoids in the medial eminence and the infundibular stem. These capillary sinusoids are the

Hypothalamic tumors are often slow growing, achieving a large size prior to the appearance of symptoms. Signs such as hydrocephalus, focal cerebral dysfunction, and hypopituitarism, are often seen. Slow growing tumors produce dementia, disturbances of food intake, and endocrine dysfunctions. Acute destructive processes of the hypothalamus may lead to coma or to autonomic disturbances. Diseases, which affect the hypothalamus and pituitary gland, may have both endocrine and non-endocrine manifestations.

Lesions of the intermediate hypothalamic area that destroy the mammillary bodies, fornix, and the stria terminalis may produce signs of Korsakoff's syndrome. Marked anterograde amnesia (short-term memory loss) and preservation of intermediate and long-term memories characterize this syndrome. Consciousness usually is not altered, but affected individuals have a tendency to fabricate when responding to questions (compensatory confabulation). This syndrome is seen in chronic alcohol abuse associated with thiamine deficiency.

beginning of the hypophysial portal system, which conveys blood to the epithelial tissue of the anterior lobe via primary and secondary capillary venous plexuses. The portal hypophysial system forms two capillary beds, which drain the venous blood of the pituitary gland, carrying the hormone regulating factors (HRF) from the medial eminence of the hypothalamus to the anterior lobe of the pituitary gland.

The adenohypophysis comprises the anterior lobe, intermediate part, and tuberal region. It secretes somatotropin (growth hormone), thyrotropin, prolactin or luteotropin, adrenocorticotropin, luteinizing hormone (interstitial-cell-stimulating hormone), follicle stimulating hormone, and melanocyte stimulating hormone. The hormone regulating factors of the hypothalamic tuberal nuclei regulate the adenohypophysis. The tuberal nuclei project to the medial eminence through the tubero-infundibular tract and regulate the glandular function of the adenohypophysis via the portal hypophysial vessels.

The neurohypophysis is comprised of the posterior lobe and the infundibular stem, and acts as a storage depot for vasopressin and oxytocin. Approximately half the volume of the neurohypophysis consists of axonal swellings; the largest are the Herring bodies, which may be as large as erythrocytes. Herring bodies provide a source of secretory granules and have longer life span (more than two weeks). Vasopressin also known as antidiuretic hormone (ADH) enhances water reabsorption by the distal convoluted tubules of the kidneys, whereas oxytocin causes milk ejection from lactating mammary glands and contraction of the uterine muscles. These hormones are secreted by the

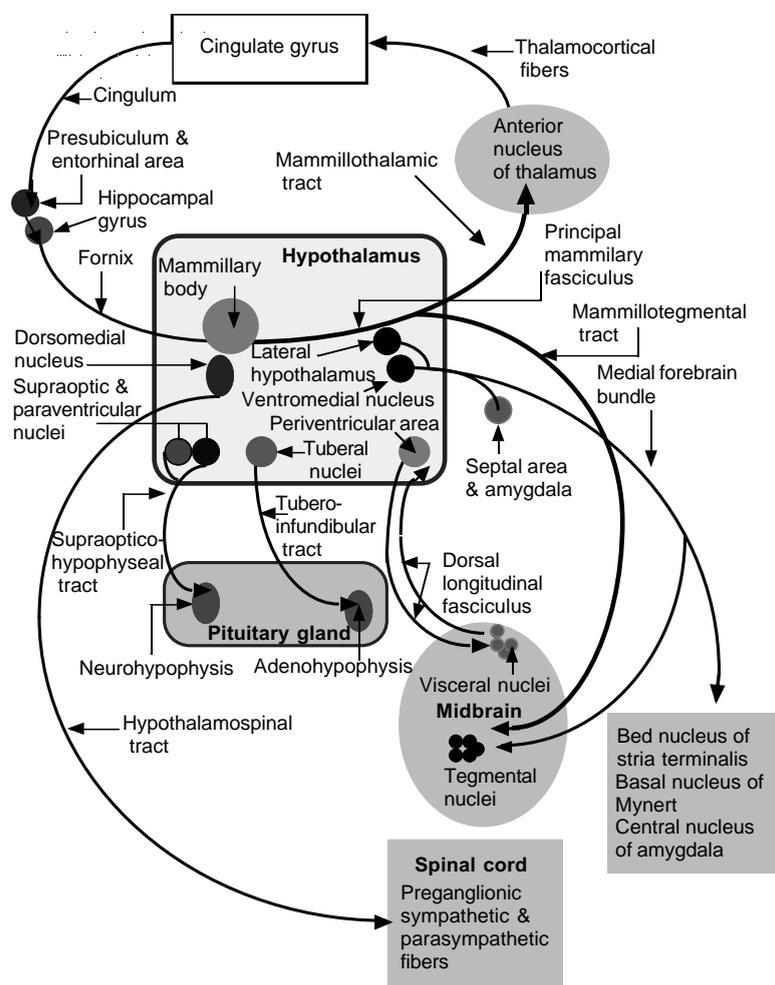


Figure 7.31 The various connections of the hypothalamus. Some of these connections form feedback loops such as Papez circuit of emotion

paraventricular and the supraoptic nuclei of the hypothalamus. During suckling, stimulation of the sensory nerve endings in the female nipple and areola activates the spinoreticular fibers, which subsequently relay the generated impulses to the supraoptic and paraventricular nuclei via the dorsal longitudinal fasciculus. The infundibulum primarily consists of fibers of the hypothalamo-hypophysial tracts that project to the neurohypophysis.

Epithalamus

The epithalamus occupies the dorsolateral part of the diencephalon and consists of the pineal body (epiphysis

cerebri), stria medullaris thalami, habenula and the posterior commissure (Figures 7.33, 7.34 & 7.35).

The pineal gland (Figures 7.33, 7.34 & 7.35) is an endocrine gland, which is located rostral to the superior colliculi and posterior commissure, and inferior to the splenium of the corpus callosum. It is connected to the habenula and the posterior commissure via the laminae of the pineal stalk. The latter contains the pineal recess of the

Remnants of the Rathke's pouch may give rise to craniopharyngioma, a common tumor in children which extends dorsally, and involves the third ventricle, producing dwarfism, visual disturbances, and erosion of sella turcica.

Enlargement of the sella turcica, subsequent to development of a pituitary tumor, may be detected radiographically. The position of the pituitary gland above the sphenoidal sinus may also be utilized in surgical removal of pituitary tumors via trans-sphenoidal approach. Additionally, the location of the adenohypophysis posterior and inferior to the optic chiasma may account for disruption of the nasal retinal fibers as a sequel to an adenoma, and the development of bitemporal heteronymous hemianopsia (tunnel vision).

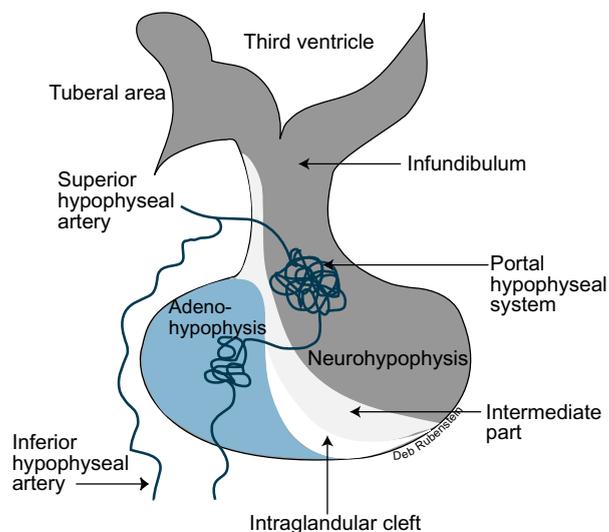


Figure 7.32 The adeno-hypophysis, neurohypophysis, infundibulum, and the intermediate part of the pituitary gland. The formation of the portal-hypophysial system, an important link between the hypothalamus and adeno-hypophysis is illustrated

third ventricle. This gland secretes melanocyte-stimulating hormones (lipotropic hormones), which play an analgesic role due to its endorphin content. It also secretes indolamines such as melatonin and associated enzymes (N-acetyltransferase and hydroxyindole-o-methyltransferase which synthesizes melatonin from serotonin) that shows sensitivity to the variations in diurnal light and circadian rhythms, and is believed to influence the secretion of the gonadotropic hormones, maintaining a regulatory role in reproductive development. Through these secretions the pineal gland may exert a regulatory influence, modifying the activity of the pituitary, adrenal, and parathyroid glands, as well as gonads. Darkness activates the secretion of melatonin, inhibiting sexual development through a series of neuronal chains in the retina, hypothalamus, reticular formation, and the spinal cord. Retinal input to the suprachiasmatic nucleus of the hypothalamus is eventually conveyed to the reticular formation. Activation of the reticular formation produces excitatory effects on the sympathetic neurons of the intermediolateral column of the upper two thoracic spinal segments, via the reticulospinal tracts. Sympathetic neurons convey the secretomotor impulses from the reticular formation to the pineal gland through the nervii Conarii (sympathetic postganglionic fibers), resulting in release of catecholamines from the pinealocytes and subsequent receptor-mediated (β -adrenergic) increase of cyclic adenosine monophosphate (cAMP).

Pituitary gland dysfunctions are associated with a variety of pathological conditions and syndromes. Some of these conditions primarily affect the adeno-hypophysis, while others may be confined to the neurohypophysis.

Sheehan's syndrome, is a condition that exhibits persistent amenorrhea, asthenia (muscle weakness), visual disorders, episodes of hypotension, and altered consciousness. It is associated with hypopituitarism of the anterior lobe, and is observed in individuals with postpartum hemorrhage and spasm of the infundibular arteries.

Adenoma of the anterior pituitary produces a variety of symptoms, depending upon the type of tumor, which may include acromegaly and/or gigantism (enlargement of the face, hand, and feet), impotence, amenorrhea (cessation of menses), galactorrhea, or Cushing's disease. The latter is characterized by moon facies, obesity with prominent fat pad in the neck and shoulder, hypertension, renal calculi, and irregular menses).

Pituitary tumors most often arise from the anterior lobe and are classified, according to the degree of their endocrine activity, into endocrine-active and endocrine-inactive tumors.

Endocrine-active tumors are for the most part microadenomas, and may be detected by radiographic imaging of the sella turcica. They may increase secretion of many hormones such as the growth hormone, producing acromegaly or gigantism. On the other hand, some tumors may result in under-secretion of hormones, producing for example dwarfism (abnormally short body stature) in childhood among other deficits.

Endocrine-inactive tumors, by contrast, become clinically significant only upon enlargement, thus compressing the adjacent nerves or brain tissue. These tumors may produce headache, visual disturbances, and extraocular motor palsies. Surgical removal may be accomplished by trans-sphenoidal approach; however, extensive subfrontal or parasellar expansion of the tumor may require transfrontal approach. Tumors that grow laterally or wedge under the optic nerve may necessitate craniotomy.

Lesions of the posterior lobe may occur in skull fractures, suprasellar and intrasellar tumors, tuberculosis, vascular disease or aneurysms. These lesions produce temporary signs of diabetes insipidus (due to lack of vasopressin), a condition, which is characterized by copious and dilute urination and excessive thirst. The onset is generally sudden and nocturia (excessive urination at night) is a presenting symptom in most patients.

Lesions of the posterior lobe may occur in skull fractures, suprasellar and intrasellar tumors, tuberculosis, vascular disease or aneurysms. These lesions produce temporary signs of diabetes insipidus (due to lack of vasopressin), a condition, which is characterized by copious and dilute urination and excessive thirst. The onset is generally sudden and nocturia (excessive urination at night) is a presenting symptom in most patients.

Pineal gland also secretes norepinephrine and contains significant concentrations of hypothalamic peptides such as luteinizing hormone-releasing factor, thyrotropin releasing factor and somatostatin. Pinealocytes also contains tryptophan hydroxylase and aromatic amino acid decarboxylase, which are involved in the synthesis of serotonin. Increase of cAMP evokes augmentation in serotonin N-acetyltransferase activity that is followed by increased pineal glandular activity and production of melatonin, and eventual inhibition of reproductive development.

The stria medullaris thalami consists of axons that originate from the septal area, runs dorsomedial to the thalamus, and terminates in the habenular nuclei of both sides. It contains afferents to the habenular nuclei from the septal area that receives input from the amygdala, hippocampal formation, and the anterior perforated substance.

The habenulae (Figures 7.33, 7.34, 7.36) are two triangular eminences which are comprised of the medial and lateral habenular nuclei, representing the sites of convergence of major limbic system pathways. The lateral habenular nucleus receives afferents from the globus pallidus, substantia innominata, tectum, lateral hypothalamus, prepyriform cortex, lateral preoptic area, basal nucleus of Meynert, midbrain raphe nuclei, olfactory tubercle, and the pars compacta substantia nigra. Input from the prepyriform cortex, tectum, nucleus basalis of Meynert, septal and the lateral preoptic area travels within the stria medullaris thalami. The stria medullaris thalami contains also fibers that transport neuromediators such as acetylcholine, norepinephrine, serotonin, g-aminobutyric acid, luteinizing hormone releasing factor (LHRF), somatostatin, vasopressin, and oxytocin. The lateral habenular nucleus projects back to the substantia nigra and also to the midbrain reticular formation, and the hypothalamus. The medial habenular nucleus, the smallest component of the habenular nuclear complex receives fibers from the serotonergic neurons of the midbrain reticular formation and from septofimbrial nucleus. The latter nucleus receives input from the amygdala and the hippocampal formation. Some adrenergic fibers also project to the medial habenular nucleus from the superior

Bilateral lesions of the suprachiasmatic nuclei may abolish the rhythmic activities of the N-acetyltransferase and produce low levels of hydroxyindole-o-methyltransferase activity, resulting in disruption of the circadian rhythms associated with the sleep-wakefulness cycle and spontaneous motor activities that pertain to drinking and feeding.

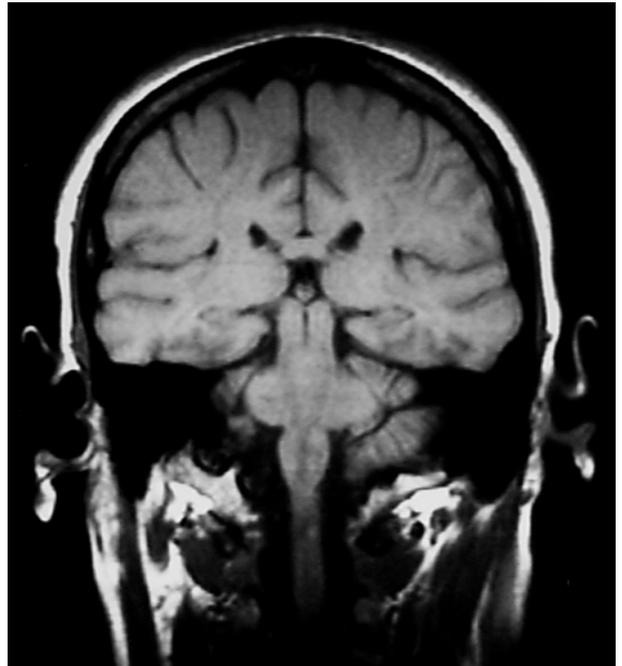


Figure 7.33 An inverted MRI scan showing the epithalamus with its main components the pineal gland and habenula. Observe their relationship to the third ventricle

cervical ganglion of the sympathetic trunk. The output from the habenular nuclear complex primarily emanates from the medial habenular, a cholinergic nucleus that project to the interpeduncular nuclei of the midbrain via the habenulo-peduncular tract (fasciculus retroflexus). This pathway enables the habenula to exert influences upon the gastric and salivatory secretions as well as the preganglionic neurons of the spinal cord via the tectotegmentospinal and the dorsal longitudinal fasciculi. The possible role of the habenula in the regulation of sleep has been suggested by some investigators. Extensive metabolic, thermal, and endocrine disturbances may accompany damages to the habenular nuclei.

The posterior commissure consists of fibers which cross the midline inferior to the pineal gland and dorsal to the superior colliculi and cerebral aqueduct. Accessory oculomotor and pretectal nuclei, project to the

The most common malignant tumor of the pineal gland is germinoma (atypical teratoma), which are frequently seen in young males. Pinealoma (pineal gland tumor) may compress the tectum and the posterior commissure, producing signs of Parinaud's syndrome, which is characterized by bilateral vertical gaze palsy, hydrocephalus, and loss of pupillary light reflex. Cysts or tumors associated with pineal gland may compress the hypothalamus, resulting in obesity and hypogonadism.

Pineal (sand) concretions or corpora arenacea in the astrocytes were considered as an important radiographic site for detection of brain shift associated space-occupying intracranial mass on the contralateral side. Deviation of the gland from a midline position may be considered significant. However, it must also be remembered that due to the relative large size of the right cerebral hemisphere, a normal pineal gland may slightly deviate to the left side.

corresponding structures on the contralateral side through this commissure.

Subthalamus

The subthalamus is a small area of the diencephalon that lies ventral to the hypothalamic sulcus and lateral and caudal to the hypothalamus. It contains the subthalamic nucleus, zona incerta, cranial portions of the red nucleus, and substantia nigra. It also contains the spinal and medial lemnisci, and efferent fibers from the globus pallidus (ansa lenticularis, lenticular, thalamic and subthalamic fasciculi) and cerebellum which are destined to the thalamus. In mammals it also contains the entopeduncular and prerule nuclei. It continues caudally with the tegmentum of the midbrain, separated from the globus pallidus by the internal capsule (Figure 7.36).

The subthalamic nucleus (Figures 7.7, 7.12) is a biconvex nucleus which lies medial to the internal capsule, caudally overlying the substantia nigra. It receives input from the lateral segment of the globus pallidus, reticular formation and the motor and prefrontal cortices. It projects to both segments of the globus pallidus via the subthalamic fasciculus and to the pars reticulata of the substantia nigra. It is also connected to the ipsilateral red nucleus, mesencephalic reticular formation, and zona incerta. The subthalamic nucleus integrates motor activities through its connections with the basal nuclei, substantia nigra, and tegmentum of the midbrain. It is thought to have an inhibitory influence upon the globus pallidus.



Figure 7.34 Dorsal surface of the diencephalon illustrates the epithalamus and its relationship to the third ventricle and tectum

The zona incerta is a thin layer of gray matter ventral to the thalamic fasciculus that extends with the reticular nucleus of the thalamus and the midbrain reticular formation. It contains dopaminergic neurons and receives cholinergic afferents from the midbrain tegmentum.

The prerule and entopeduncular nuclei are located ventral to the zona incerta, and adjacent to the posterior limb of the internal capsule. It receives fibers from the globus pallidus, which are destined to the midbrain reticular formation. These nuclei project through the central tegmental nuclei to the inferior olivary nucleus.

The posterior commissure may be damaged by pineal tumors. However, no known symptoms are associated with lesions of this commissure, though impairment of visual tracking movement has been reported.

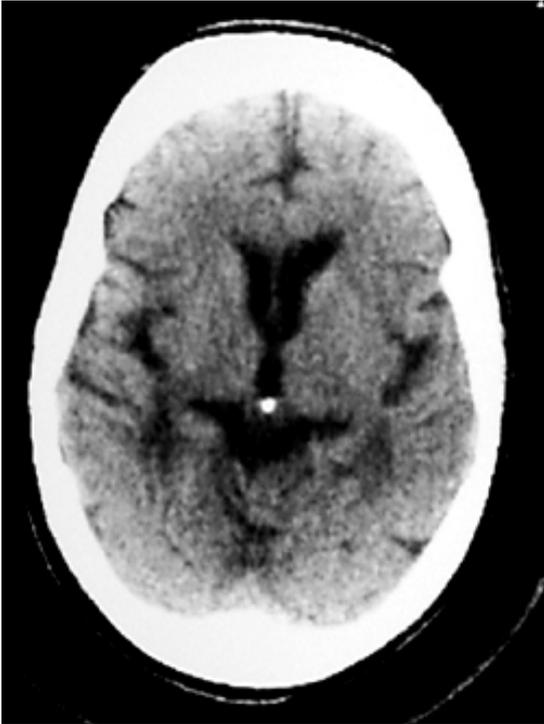


Figure 7.35 This computed tomography scan shows the pineal gland with calcareous concretion (brain sand) and the third ventricle.

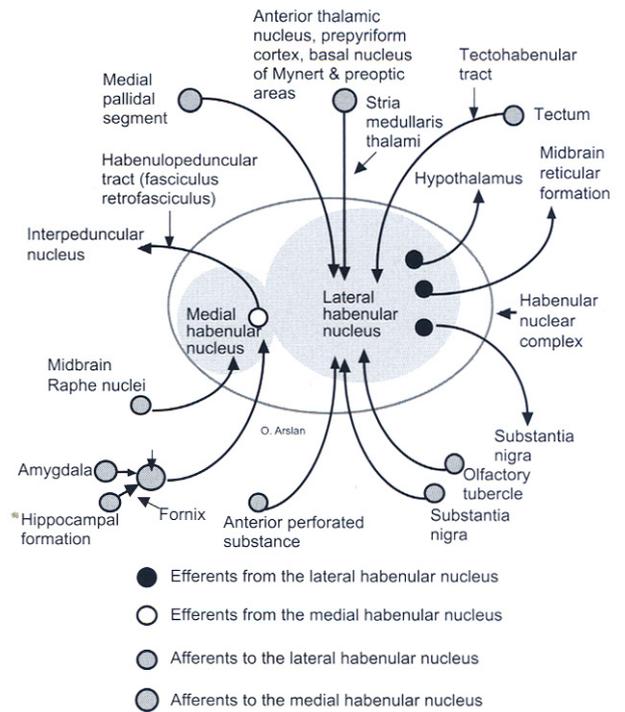


Figure 7.36 Schematic diagram of the principle afferents and efferents of the habenula

Lesions of this nucleus produce violent, uncontrollable movements of the contralateral extremities, a condition known as hemiballismus, which is described with the extrapyramidal motor system.

The telencephalon is comprised of the cerebral hemispheres and the basal nuclei, containing the lateral ventricles. It is a derivative of the lateral diverticula, which are interconnected by the median telencephalic impar. The cerebral hemispheres are comprised of the frontal, parietal, temporal, occipital, limbic, and the central (insular cortex) lobes. Examination of the cerebral cortex reveals an outer gray cortical area and an inner white matter. Fasciculi cross the white matter connecting areas within the same and opposite hemisphere. Blood supply of the cerebral hemisphere is secured by the carotid and vertebral systems.

Central hemisphere

Frontal lobe

Parietal lobe

Temporal lobe

Occipital lobe

Insular cortex (central lobe)

Limbic lobe

Cerebral cortex (gray matter)

Sensory cortex

Primary sensory cortex

Secondary sensory cortex

Motor cortex

Cortical afferents

Cortical efferents

Cerebral white matter

Commissural fibers

Association fibers

Projection fibers

Cerebral dysfunctions

Cerebral dominance

Basal nuclei

Blood supply of the cerebral hemispheres

Venous drainage of the cerebral hemispheres

Meninges

Dural sinuses

Posterosuperior group of dural sinuses

Anteroinferior group of dural sinuses

Cerebral hemispheres

The cerebral hemispheres are mirror image duplicates that occupy the cranial cavity and are interconnected by the corpus callosum. The corpus callosum, which lies ventral and partly caudal to the anterior cerebral vessels and the falx cerebri, consists of the rostrum, genu, trunk, and splenium. The sagittal (interhemispheric) sulcus that partially separates the cerebral hemispheres, contains the falx cerebri. Both cerebral hemispheres are composed of an outer gray matter thrown into folds (gyri) and an inner white matter, containing the basal nuclei. Each cerebral hemisphere is divided into the frontal, parietal, temporal, occipital, central (insular cortex), and limbic lobes via sulci and fissures (Figures 8.1, 8.2, 8.6, 8.7, 8.8 & 8.9). The frontal, parietal, temporal and the occipital lobes are interconnected by the genu, trunk, and the splenium of the corpus callosum, respectively. The central sulcus separates the frontal and parietal lobes and contains the Rolandic branch of the middle cerebral artery. The lateral cerebral (Sylvian) fissure (sulcus) begins in the Sylvian fossa, contains the middle cerebral artery and demarcates the temporal lobe from the frontal and parietal lobes.

The lateral cerebral fissure gives rise to an anterior, ascending, and posterior rami that divide the inferior frontal gyrus into orbital, angular and opercular parts. The angular and opercular parts form the Broca's motor speech center. The insular cortex forms the floor of this fissure.

Each hemisphere contains the lateral ventricle. This ventricle extends in a rostrocaudal direction from the frontal lobe to the occipital lobe, and inferiorly to the temporal lobe. The lateral ventricle on each side consists of an anterior horn that continues with the body (central part) and posterior and inferior horns. The lateral ventricles are separated via the septum pellucidum, communicating with the third ventricle via the interventricular foramen of Monro. Within the frontal, the anterior horn extends inferior and posterior to the corpus callosum and superior and lateral to the caudate nucleus. The anterior horns are separated by the septum pellucidum. The floor of the central part (body) is formed by the thalamus and caudate nucleus, which are separated by the stria terminalis and the thalamostriate vein. The central part contains the choroid plexus and continues with the posterior horn in the occipital lobe and inferior horn in the temporal lobe. The posterior horn stretches in the occipital lobe medial to the calcarine fissure which forms the calcar avis, a visible prominence on its medial wall. The lateral wall and the roof of this horn are formed by the tapetal fibers of the trunk of the corpus callosum. The transition zone between the posterior and inferior horns is termed the collateral trigone (Figures 8.3, 8.4, & 8.5).



Figure 8.1 Photograph of the lateral surface of the brain showing prominent gyri. Lateral cerebral fissure and central sulcus are also shown

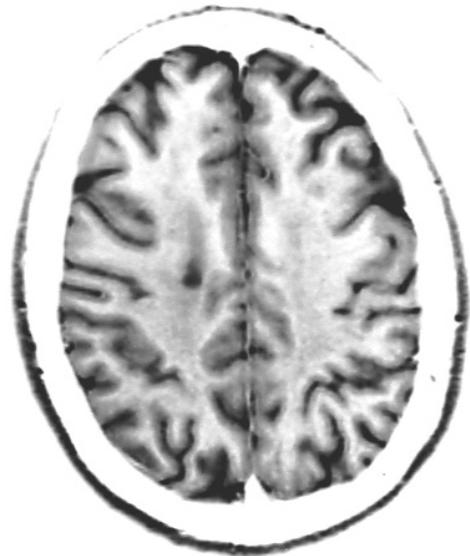


Figure 8.2 In this inverted MRI scan cerebral cortex and central white matter are shown

The caudate nucleus is contained in the floor of the posterior horn and the roof of the inferior horn. The amygdala, which is attached to the tail of the caudate nucleus, lies immediately rostral to the tip of the inferior horn. The inferior horn curves downwards and ends near the temporal pole, containing in its floor the collateral eminence (formed by the collateral sulcus), hippocampal gyrus, fimbria of the fornix, dentate gyrus, and the choroid plexus. The roof and the lateral wall of this horn are formed by the tapetal fibers of the trunk of the corpus callosum. This plexus is supplied by the anterior and



Figure 8.3 Horizontal section of the brain illustrating the boundaries of the anterior and posterior horns of the lateral ventricle and its central part. The connection of the lateral and third ventricles is maintained via the interventricular foramen of Monro

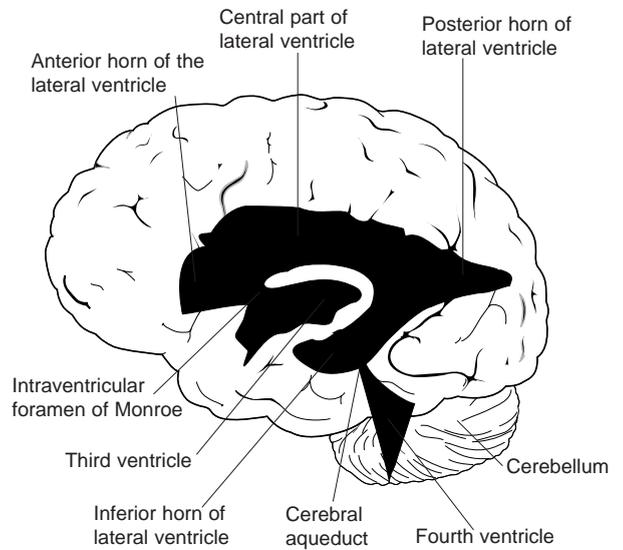


Figure 8.5 Diagram of a lateral view of the ventricular system

posterior choroidal arteries that originate from the internal carotid and posterior cerebral arteries, respectively.

Frontal lobe

The frontal lobe (Figures 8.1, 8.2, 8.7, 8.8 & 8.9) lies rostral to the central sulcus, superior to the lateral cerebral (Sylvian) fissure. It occupies the anterior cranial fossa, superior to the olfactory bulb and tract, as well the cribriform plate of the ethmoid bone. It contains the superior and inferior frontal sulci, which separate the superior, middle and inferior frontal gyri. Medially, the cingulate sulcus separates the medial part of the superior frontal gyrus (medial frontal gyrus) from the cingulate gyrus. The orbital gyri on the inferior surface of the frontal lobe are demarcated from the rectus gyrus by the olfactory sulcus that contains the olfactory tract. This lobe contains the primary motor center (Brodmann's area 4) in the precentral gyrus, and the frontal eye field (Brodmann's area 8) in the middle frontal gyrus which is responsible for conjugate deviation of the both eyes to the opposite side. It also contains Broca's motor speech center (Brodmann's areas 44 and 45) in the inferior frontal gyrus. Within Broca's motor speech center, linguistic rules and grammar (syntax) and the template for phonation are formed, as well as speech melody and rhythm are regulated. The prefrontal cortex occupies the area rostral to premotor cortex.

As discussed earlier, numerous gyri and cortical areas constitute the frontal lobe, which include the precentral, superior, middle, and inferior frontal gyri, premotor, prefrontal, and supplementary cortices.



Figure 8.4 Horizontal section of the brain showing the location of the caudate nucleus and thalamus in relation to the anterior horn and central part of the lateral ventricle. The transition between the atrium and inferior horn of the lateral ventricle is visible

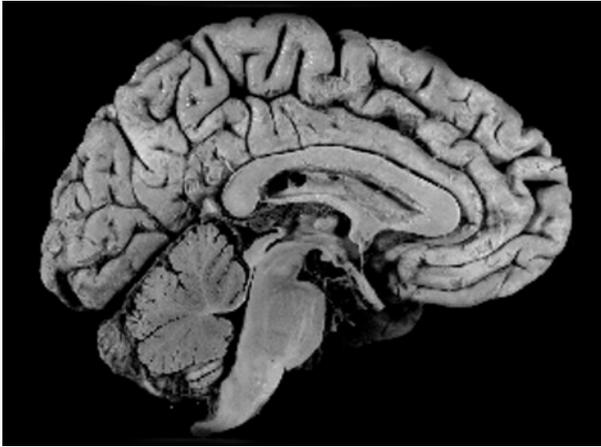


Figure 8.6 Mid-sagittal section of the brain showing the medial surface of the frontal parietal, and occipital lobes

Damage to the motor cortex, as a result of trauma, tumor, hemorrhage or thrombosis of the middle cerebral artery produces signs of upper motor neuron (UMN) palsy which are confined to the upper extremity, trunk, and head region (see the motor neurons, chapter XX).

Frontal lobe seizures may activate the frontal eye field and produces conjugate eye movement to the opposite side. Damage to this area, however, produces tonic deviation of both eyes to the side of the lesion (as if the patient were pointing to the affected side). This is due to the fact that a lesion in one hemisphere leads to the unopposed action of the contralateral frontal eye field. It is interesting to note that this condition gradually attenuates, and in a matter of hours or days, movement of the eyes as far as the midline becomes possible again. However, free gaze movement will be regained much later, with nystagmus being the final diagnostic indicator of the lesion

The precentral gyrus (Brodmann's area 4) lies between the central and the precentral sulci and constitutes the primary motor cortex for the entire body, with the exception of the lower extremity. A distorted somatotopic organization of the body in this gyrus is known as the motor homunculus. Neurons of the precentral gyrus contribute to the formation of the corticospinal and corticobulbar fibers and maintain reciprocal connections with the ventral lateral nucleus of the thalamus.

Damage to the inferior frontal gyrus in the dominant hemisphere results in expressive aphasia or dysarthria (will be discussed later in detail).

Ablation of the motor and premotor cortices leads to flaccid paralysis, for unknown reasons. Isolated lesion of Brodmann's area 6 results in motor apraxia (inability to perform familiar motor activity in the absence of any detectable motor or sensory deficits).

Prefrontal lobotomy is a surgical procedure, although very rarely used, that involves bilateral removal of the prefrontal cortices. It is utilized to modify the behavior of psychotic individuals, and to relieve the intractable chronic pain, which is unresponsive to conventional analgesics. Patients who have undergone this type of operation no longer complain of pain and appear to be oblivious to it. They exhibit emotional lability and superficial affect. Alterations in personality, disposition, drive and outlook are also prominent. Patients become disinhibited, lack initiative, and become less creative. They display irresponsible attitude and seem indifferent, with no changes in recent memory and intelligence. Lobotomized patients show a lack of restraint, an absence of hostility and boast. Reasoning, logical thinking, and problem-solving abilities are all impaired. Considerable loss of drive and ambition is observed.

Recent studies conducted on patients with depressive diseases indicate that transcranial electromagnetic stimulation of the prefrontal cortex, in which bouts of magnetic waves are passed through the brain, may be effective in the treatment of certain depressive illnesses.

Above the superior frontal sulcus lies the superior frontal gyrus that continues medially with the medial frontal gyrus.

The middle frontal gyrus, as mentioned earlier, contains the frontal motor eye field (Brodmann's area 8) which is not regulated by the visual stimuli.

The inferior frontal gyrus is subdivided into orbital, triangular and opercular parts. The orbital part is anterior

Since the prefrontal cortex is supplied by the orbito-frontal branches of the middle cerebral artery, infarction in the territory of the orbitofrontal branch may produce depressive syndromes which may not respond to cyclic antidepressants.

- Unilateral lesion of the Brodmann's area 6 produces contralateral transient pathological grasp reflex, while bilateral lesion causes hypertonia in the muscles of the upper extremity. Paralysis or paresis is not seen in these lesions.
- Frontal lobe hematoma may occur as a result of rupture of the middle cerebral artery or its branches, producing abulia, which is characterized by a lack or impairment of verbal spontaneity and initiative as well as the inability to perform volitional acts or make decisions. Patients appear sedentary and withdrawn. Expansion of the hematoma to involve the frontal eye field may produce tonic conjugate deviation of both eyes toward the side of lesion. It usually resolves after a few days as the intact contralateral frontal gaze center compensates for the deficit. Involvement of the precentral gyrus in this hematoma produces paralysis of the opposite half of the body.
- Occlusion of the middle cerebral artery may produce coma and forced deviation of the eyes toward the occluded side when the frontal eye field is involved. Occlusion of the anterior cerebral artery proximal to the callosomarginal branch may cause a large infarction on the medial surface of the frontal lobe, resulting in intellectual deterioration, apraxia, visible primitive reflexes (such as sucking reflex), incontinence, and possible aphasia. Although rare, bilateral occlusion of the anterior cerebral arteries may occur when both arteries arise from a common stem, producing significant infarctions in both frontal lobes. Patients with this extensive lesion exhibit a variety of symptoms which include paralysis or paresis of both legs, urinary and bowel incontinence, behavioral changes, development of primitive reflexes (e.g. grasp reflex and sucking reflex), and abulia (inability to perform volitional acts or make decisions). Frontal lobe lesions may also induce bowing shift of the anterior cerebral artery, and Brun's ataxia, a broad-based, short-stepped gait, increasing the risk of the affected individuals for falls.

Many pathological reflexes may be observed in individual with frontal lobe lesions such as grasp, snout, suck, and palmomentary reflexes.

- The grasp reflex is an involuntary tonic grasp response, associated with slow flexion of the fingers. Attempts by the examiner to withdraw the grasped fingers will only augment the patient's grasp. It may be elicited by touching or stroking the anterior surface of the wrist, the center of palmar surface of the hand and digits, and between the thumb and index finger.
- The snout reflex is characterized by puckering and protrusion of the lips upon light percussion of the middle upper lip.
- The suck reflex is an involuntary sucking movement of the lips, produced by a blunt object stroked across the lips.
- The palmomentary reflex exhibits contraction of the mentalis and the orbicularis oris muscles upon striking the palm of the infant's hand with a sharp object.

to the anterior ramus; the triangular part lies between the anterior and ascending rami, whereas the opercular part is lodged posterior to the ascending ramus of the lateral cerebral fissure. As mentioned earlier the opercular and triangular parts of this gyrus collectively form Broca's motor speech center.

The premotor cortex is composed of Brodmann's areas 6 and 8. It occupies the area immediately anterior to the motor cortex, which includes part of the middle and frontal gyri. Most of the afferents to this cortical area are derived from the ventral anterior thalamic nucleus. Stimulation of Brodmann's area 6 produces motor activities, which are characterized by attentive or orientative movements such as turning the head and eyes.

The prefrontal cortex is rostral to the premotor cortex, a well-developed area in the human. It includes Brodmann's areas 9 and 10 and the orbital gyri (Brodmann's area 46). This cortical area has reciprocal connections with the dorsomedial nucleus of the thalamus. It is also connected to the temporal cortex via the uncinate fasciculus and to the parietal and occipito-temporal association cortices. The prefrontal cortex is important in the establishment of emotional responses, programming and intellectual functions.

The supplementary motor area (Brodmann's area 6) primarily refers to the medial frontal gyrus, which forms the medial extension of the superior frontal gyrus above the cingulate gyrus. This area exhibits a small motor homunculus that functions independently from the primary motor cortex. Stimulation of this region results in bilateral synergistic movements of a postural nature of both the axial and appendicular musculature, and rapid

uncoordinated movements, as well as complex pattern of motor activities.

Parietal lobe

The parietal lobe is bounded by a line which connects the pre-occipital notch to the upper end of the parieto-occipital sulcus (Figures 8.7 & 8.8). On the lateral surface, this lobe consists of the postcentral gyrus, (Brodmann's area 3, 1, 2) and the superior and inferior parietal lobules. Medially, it contains the precuneus and the posterior part of the paracentral lobule. This lobe is concerned with mimicking (imitation of speech or action), pantomimicking actions (imitation of gestures without words) or copying.

The postcentral gyrus contains neurons which represent the primary sensory cortex (Brodmann's areas 3,1,2). The main input to this area arises from the ventral posterior nuclei of the thalamus (VPL and VPM), a somatotopically arranged projection in the form of a sensory homunculus (lips, tongue, and thumb have a larger representation). The Body's distorted and disproportionate representation in this gyrus is also based upon the relative densities of the neuronal populations (sensory homunculus). Brodmann's area 3 responds to joint sensations, Brodmann's area 1 responds to cutaneous stimuli, and both Brodmann's areas 1 and 2 are excited by stimuli from joints. There are neurons in the in this gyrus that evoke a motor response upon stimulation. Some fibers of the postcentral gyrus

Parietal lobe hematoma may produce loss of general sensations on the opposite side of the body. When the dominant hemisphere is involved, signs of neglect on the contralateral half of the visual field may also occur. Frequently, parietal lobe diseases may mimic certain manifestations of frontal lobe diseases.

The site of termination of the fibers that emanate from the postcentral gyrus may explain the deficit in kinesthetic perception that follows upper motor neuron lesions.

Ablation of the postcentral gyrus may result in the inability to appreciate texture, weight, and slight changes in temperature. The ability to recognize painful, tactile, pressure and proprioceptive sensations may not be significantly impaired. Although, localization of noxious and tactile stimuli may severely be affected.

A lesion of angular gyrus in the dominant hemisphere may produce visual agnosia, in which the ability to read and comprehend written word (alexia) and copy (agraphia) are lost. Bilateral damage to the angular gyri may result in the loss of ability to judge the location of objects and their relationship to each other in space.

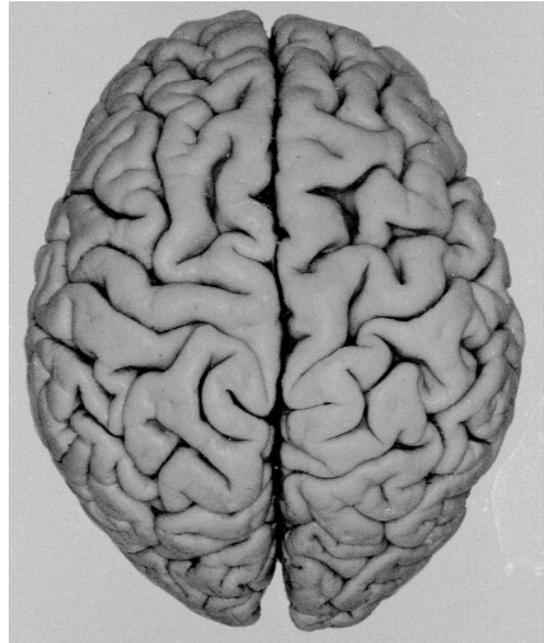


Figure 8.7 Dorsal surface of the brain with the precentral, postcentral, and supramarginal gyri are clearly demarcated

descend in conjunction with the pyramidal tract and terminate in the gracilis and cuneatus nuclei.

The secondary somatosensory area is located at the base of the postcentral gyrus. However, certain parts of the body (e.g. face, mouth and throat) are not represented in this area. Lesions of this area do not result in any recognizable deficit.

The superior parietal lobule is represented by Brodmann's areas 5 and 7. Damage to this lobule in the dominant hemisphere may impair the ability to recognize certain parts of one's body on the contralateral side. Initial hypotonia may also be observed. The inferior parietal lobule, which consists of the supramarginal and angular gyri, is separated from the superior parietal lobule by the interparietal sulcus.

- The supramarginal gyrus (Figure 8.7) encircles the posterior end of the lateral cerebral sulcus, and is designated as Brodmann's area 40.
- The angular gyrus (Figure 8.1) designated as Brodmann's area 39, surrounds the terminal part of the superior temporal sulcus. Due to its massive connections with the association cortices of the

Damage to the paracentral lobule may result from occlusion of the anterior cerebral artery, producing spastic paralysis of the muscles of the contralateral lower extremity, and bowel and urinary incontinence.

Damage to the anterior portion of the parietal lobe results in Dejerine's cortical sensory (Verger-Dejerine) syndrome, which is characterized by contralateral loss of discriminative sensory modalities (joint sensation and stereognosis), including the face. Pain and temperature sensations remain intact, but the ability to localize these sensory impulses may be affected.

auditory, visual, and superior parietal lobe, the angular gyrus acts as a nodal point of integration for these modalities of sensations into symbols. It also signals the premotor cortex in the dominant hemisphere to initiate action via the superior longitudinal (arcuate) fasciculus within the same hemisphere and via the corpus callosum to the non-dominant hemisphere. On the left side, it converts the written word to its auditory equivalent (graphemes to phonemes).

The precuneus is bounded by the marginal branch of the cingulate sulcus rostrally and the parieto-occipital sulcus caudally.

The paracentral lobule is formed by the medial extension of the precentral and postcentral gyri. It contains neurons, which are responsible for the motor and sensory innervation of the lower extremity and the regulation of certain physiological functions such as, defecation and micturition.

Temporal lobe

The temporal lobe (Figures 8.1 & 8.9) lies inferior to the lateral cerebral fissure, rostral to the pre-occipital notch, and inferior and caudal to the frontal lobe. It contains the inferior horn of the lateral ventricle, the hippocampal and dentate gyri, fimbria of the fornix, and the amygdala. The lateral surface of this lobe consists of the superior, middle, and the inferior temporal gyri, which are separated by the temporal sulci. The superior temporal sulcus runs between the superior and middle temporal gyri, and is surrounded caudally by the angular gyrus. Separation of the middle and inferior temporal gyri is maintained by the inferior

Destruction of the supramarginal gyrus in the dominant hemisphere may disrupt its connection to other association cortices, resulting in tactile and proprioceptive agnosia or astereognosis, a condition refers to the inability to recognize the texture, form, and size by palpation, apraxia, left-right disorientation, and disturbances of body image.

Temporal lobe hematoma may produce herniation and brainstem compression, and may lead to stupor and possible death.

Selective destruction of parts of areas 41 and 42 produce sigoma contralaterally, a condition, which is comparable to scotoma associated with lesions of the visual pathway.

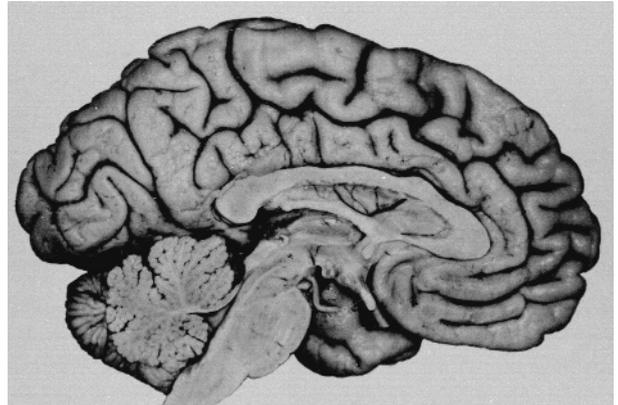


Figure 8.8 In this photograph of the medial surface of the brain and the individual gyri of the frontal, parietal, and occipital lobes are shown. The parieto-occipital and calcarine fissures are prominent

temporal sulcus. Additional gyri exist on the inferior surface of the temporal lobe, which include the occipito-temporal and the parahippocampal gyri. Medial to the superior temporal gyrus the transverse gyri of Heschl (Brodmann's areas 41 and 42) make their appearance, constituting the primary auditory cortex.

In the dominant hemisphere, the posterior part of the superior temporal gyrus contains the secondary auditory cortex (Brodmann's areas 22, 51 and 52) or Wernicke's zone. Wernicke's zone is the site where templates for phonemes (speech sounds such as "f" or "ph" and words) are linked to primitive auditory sensations received from the primary auditory cortex. These templates are also linked to the auditory, visual and olfactory systems, as well as to other sensory modalities in the angular gyrus. Due to these connections, Wernicke's area can regulate auditory perception and store visual imagery and verbal comprehension. Aside from the superior temporal gyrus, other gyri also exist on the lateral surface of the temporal lobe. Between the superior and inferior temporal sulci lies the middle temporal gyrus. The inferior temporal gyrus (Brodmann's area 20) lies lateral the occipito-temporal sulcus, making appearance on both the inferior and lateral surfaces of this lobe. This cortical area is considered a

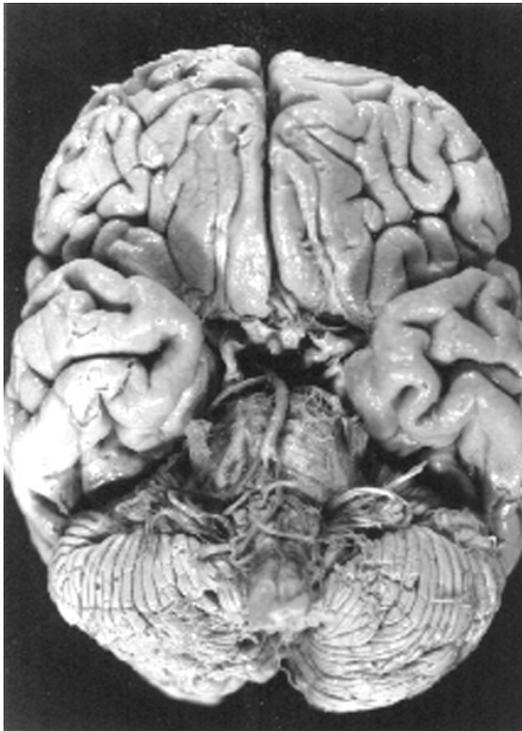


Figure 8.9 Inferior surface of the brain illustrating the gyri associated with the frontal and temporal lobes

higher visual association zone, which receives, in its posterior part major input from the occipitotemporal cortex, representing the contralateral visual field.

Immediately lateral to the parahippocampal (fusiform) gyrus, the occipito-temporal gyrus makes its course. The parahippocampal gyrus (Figure 8.9) represents the inferior portion of the limbic lobe, expanding rostrally and medially into the uncus, a small tongue-like

projection between the collateral and hippocampal sulci. This projection constitutes the primary olfactory center (Brodmann's area 34) which receives and processes olfactory information received from the lateral olfactory stria. Uncus and olfactory pathways are considered integral parts of the limbic system.

Occipital lobe

The occipital lobe (Figures 8.6, 8.8 & 8.10) lies caudal to the imaginary line that connects the pre-occipital notch to the upper end of the parieto-occipital fissure. On its lateral surface the superior and inferior occipital gyri are separated by the lateral occipital sulcus. Caudal to the lateral

A hemotoma that damages the superior frontal gyrus in the dominant (usually the left) hemisphere may produce receptive aphasia (inability to comprehend spoken language).

- Uncal herniation is a condition in which the uncus as well as the medial portion of the temporal lobe are forced to protrude, usually as a result of supratentorial mass (hematoma) into the middle cranial fossa, over the sharp margin of the tentorial notch. The mass often causes a substantial rise in the intracranial pressure and displacement of the uncus into and below the tentorial (Kernohan's) notch. The swollen uncus may compress the midbrain, oculomotor nerve, crus cerebri, and the posterior cerebral artery. Patients with uncal hernia exhibit signs of ipsilateral or bilateral oculomotor palsy, which include mydriasis (pupillary dilatation) and lateral strabismus (lateral deviation of the eye), followed by downward and lateral deviation of the eye, and eventual external ophthalmoplegia.

Irregularities in respiration ranging from Cheyne-Stokes breathing to respiratory arrest also occur. As in subdural hematomas, reduced states of consciousness and coma develop rapidly, as a result of compression of the ascending reticular activating system following oculomotor palsy. Signs of ipsilateral upper motor neuron paralysis, followed by decerebrate rigidity as a result of destruction of the inhibitory corticospinal tract in the crus cerebri and unopposed action of the excitatory pathways, are eventually concluded in total flaccidity.

- Uncinate fits are seizures that produce involuntary movements of the mouth and tongue and the perception of noxious hallucinatory odors which may be accompanied by irrational fears of the surroundings. They may occur as a result of a lesion, infarct or tumor affecting the uncus, amygdala and possibly the gustatory area. Due to involvement of the temporal lobe, cognitive functions, such as memory, orientation and attention, may also be impaired.

- Pick's disease is another condition that selectively produces atrophy of the temporal and frontal lobes, sparing the posterior two thirds of the superior temporal gyrus. It may also involve the occipito-temporal region (the silent cortical area) which is concerned with the storage of memories from the visual and auditory systems. Damage to this wide array of cortical areas may result in epileptic seizures combined with amnesia, auditory hallucinations, and the "deja vu" phenomenon.



Figure 8.10 An inverted MRI Scan of the medial Surface of the brain showing some of the associated gyri

occipital sulcus, the descending occipital gyrus makes its appearance. Medially, this lobe is formed by the cuneus and lingual gyrus. The cuneus, which is bounded rostrally by the parieto-occipital sulcus and caudally by the calcarine fissures, receives visual impulses from the lower quadrant of the opposite visual field. Inferior to the calcarine fissure and medial to the collateral sulcus lies the lingual gyrus that receives input from the upper quadrant of the opposite visual field.

Rostral to the occipital pole, the lunate sulcus runs vertically between the striate and peristriate cortices. The lunate sulcus, which contains the parastriate cortex, is crossed at its upper and lower ends by the superior and inferior polar sulci, respectively. Enclosed between the polar sulci is the macular area of the primary visual (striate) cortex.

Insular cortex (central lobe)

The insular cortex ([Figure 8.11](#)) or central lobe consists of long and short insular gyri, forming the floor of the lateral cerebral fossa. It continues anteriorly with the anterior perforated substance and is surrounded by an incomplete circular sulcus. This sulcus is deficient rostrally and inferiorly where the limen insula is located. Continuation of the insular cortex is marked by the opercular areas of the frontal, parietal and temporal lobes. It receives input from the ventral posterior nucleus, medial geniculate body, dorsomedial thalamic nucleus, pulvinar and intralaminar nuclei, maintaining ipsilateral connections with the primary and secondary somatosensory cortex, inferior parietal lobule, and the orbitofrontal cortex. It has been suggested that the insular cortex plays an important



Figure 8.11 Here, the lateral surface of the brain is dissected to clearly delineate the boundaries of the insular gyri

modulatory role in the perception and recognition of fine touch, auditory impulses, and taste, and is thought to be associated with language function.

Limbic lobe

The limbic lobe consists of the subcallosal, paraterminal (septal area), cingulate, and the fasciolar gyri ([Figures 8.8, 8.9, 8.10 & 8.12](#)). A rostral region of this lobe, which lies between the lamina terminalis and the posterior olfactory sulcus, is termed as the subcallosal (para-olfactory) gyrus. It should also be noted that the paraterminal (precommissural septum) gyrus receives input from the olfactory system via the medial olfactory stria; hippocampal gyrus through the precommissural column of the fornix; and the lateral hypothalamus via the medial forebrain bundle (MFB). It also receives impulses from the tegmental nuclei via the mammillary peduncle. Aside from its projection to the tegmental nuclei of the midbrain through the MFB, the paraterminal gyrus also sends fibers to the habenular nuclei contained in the stria medullaris thalami. It is also connected through the diagonal band of Broca to the periamygdaloid cortex.

The cingulate gyrus ([Figures 8.8, 8.10 & 8.12](#)) is part of the limbic lobe, maintaining reciprocal connections with the anterior nucleus of the thalamus. Through this thalamic nucleus, the hypothalamus influences the activities of the cingulate gyrus. This gyrus projects to the entorhinal cortex, and influences the hypothalamus through fibers of the fornix. Due to these diverse connections somatic and visceral responses may be elicited by stimulation of the anterior part of cingulate gyrus. Stimulation of the posterior cingulate gyrus elicits pleasurable reactions.



Figure 8.12 Inverted mid-sagittal MRI of the brain illustrating some components of the limbic lobe that surrounds the corpus callosum as well as adjacent structures

A unilateral cerebral mass that compresses the cingulate gyrus of the contralateral hemisphere against the falx cerebri may produce cingulate or subfalcial herniation, a serious condition that may end in death.

The fasciolar (retrosplenial) gyrus connects the cingulate and the induseum griseum to the dentate gyrus of the hippocampal formation.

Midline interconnection of the cerebral hemispheres is maintained primarily by the corpus callosum (Figures 8.8, 8.12 & 8.13). This commissural structure, covered by the ventricular ependyma, forms the roof of the lateral ventricle. Superior to the corpus callosum lies the anterior cerebral vessels and the falx cerebri. It consists of the rostrum, genu, trunk and splenium. Fibers of the genu (forceps minor), which lies between the rostrum and trunk, connect the frontal lobes. Apart from its small size, the rostrum extends from the genu to the lamina terminalis; its superior surface is attached to the septum pellucidum. Wide cortical areas of the hemispheres are connected via the trunk, whereas the splenium, the thickest part of this commissure, forms the base of the longitudinal sagittal cerebral fissure, connecting the occipital lobes (forceps major). The splenium protrudes into the posterior horn of the lateral ventricle as the bulb of the posterior horn. Callosal trunk is covered by the induseum griseum (supracallosal gyrus), a thin lamina of gray matter which is continuous with the cingulate, fasciolar, and the paraterminal gyri, containing the medial

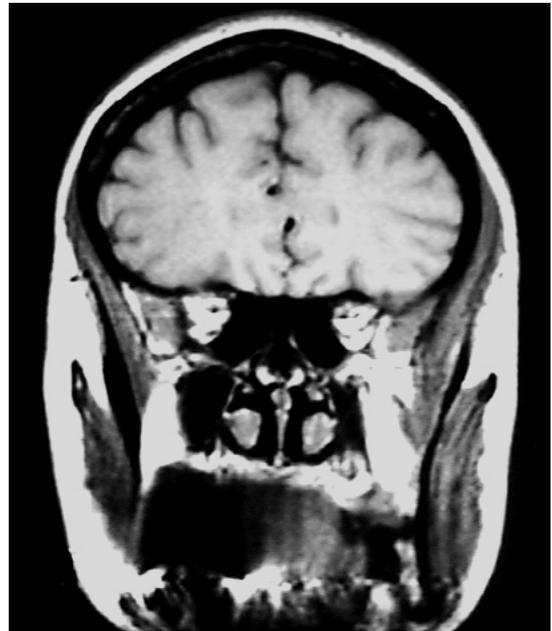


Figure 8.13 MRI scan through the genu of the corpus callosum. The frontal lobes are connected by the forceps minor, an extension of the genu of the corpus callosum

and lateral longitudinal striae of Lancisi. Fibers of the trunk and splenium form the tapetum, which constitutes the roof and the lateral walls of the posterior and inferior horns of the lateral ventricle.

A vertical partition, the septum pellucidum (supracommissural septum) extends between the corpus callosum and the fornix, forming the medial wall of the anterior and central parts of the corpus callosum. This septum (Figures 8.12 & 8.14) consists of two laminae of fibers, sparse gray matter and neuroglia. Note that the fornix (Figures 8.6, 8.8, 8.12 & 8.14), a robust bundle at the inferior border of the septum pellucidum, is formed by the axons of the pyramidal layer of the hippocampal gyrus. This bundle starts as the alveus, converges into the fimbria, which ascends toward the splenium of the corpus callosum, and more rostrally above the thalamus as the crura of the fornix. These crura interconnect by the hippocampal commissure and unite rostrally to form the body of the fornix which attaches to the corpus callosum. Eventually the body of the fornix divides into precommissural and postcommissural columns by the fibers of the anterior commissure. The precommissural column terminates in the lateral hypothalamus, while the postcommissural column projects primarily to the mammillary nuclei.

Cerebral cortex (gray matter)

In human, the cerebral cortex (pallium) is the most highly evolved portion of the central nervous system in general

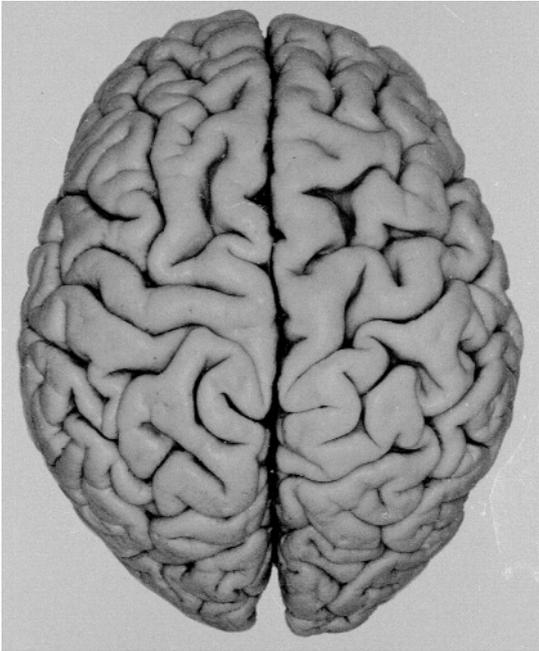


Figure 8.14 In this horizontal section the septum pellucidum and its relation to the fornix is illustrated



Figure 8.15 Typical pyramidal neuron showing the single axon and a distinct apical dendrite

and the cerebral hemisphere. It consists of a thin shell of a large number of neuronal cell bodies, unmyelinated nerve fibers, glial cells, and blood vessels. The presence of the neuronal cell bodies and extensive capillary network is responsible for the gray appearance of the cerebral cortex. It is well documented that the cerebral cortex maintains crucial role in the perception, fine discrimination, integration of various modalities of sensation, and in the regulation of visceral and somatic motor activities. It contains afferent (thalamocortical), efferent (projection), commissural, and association fibers. In order to increase the surface area of the brain, the cortex is thrown into convolutions (gyri) separated by sulci.

On phylogenetic basis, the cerebral cortex is divided into archipallium, paleopallium, and neopallium. The archipallium (oldest cortex) is comprised of the hippocampal, dentate, and fasciolar gyri, and the subiculum. The hippocampal gyrus (cornu ammonis) is superior to the subiculum and the parahippocampal gyrus. It lies in the floor of the temporal horn of the lateral ventricle and forms the pes hippocampi; a rostral swelling which is covered by ependymal layer. As mentioned earlier, the axons of the hippocampal neurons form the alveus, which continues with the fimbria of the fornix. The dentate gyrus, which lies between the hippocampal gyrus (cornu ammonis) superiorly and the subiculum inferiorly, is separated from the subiculum by the hippocampal sulcus. A transitional zone between the six-layered cortex of the parahippocampal gyrus and the three-layered cortex

of the cornu ammonis is termed the subiculum (see also the limbic system).

The paleopallium (old cortex) includes the olfactory cortex and the pyriform lobe, which are integral parts of the limbic system. Both the archipallium and paleopallium comprise the allocortex or heterogenetic cortex, consisting of three layers. Most of the cerebral cortex, approximately 90%, constitutes the neopallium (neocortex, or isocortex), which is formed by six distinct layers (homogenetic cortex). By the seventh month of intrauterine development, the six layers of the homogenetic cortical regions become distinct.

The cerebral cortex consists of pyramidal and non-pyramidal neurons such as the stellate (granule), fusiform, horizontal cells of Cajal, and cells of Martinotti, which are arranged in horizontal and vertical layers. The pyramidal cells (Figures 8.15 & 8.16) have apical dendrites, which run perpendicular to the cortical surface, and basal dendrites and branch locally parallel to the cortical layer. Axons of the pyramidal neurons travel to the subcortical areas as projection fibers or course within the white mater as association fibers. These axons may give rise to recurrent collaterals, and represent the primary output of the cerebral cortex. Betz cells are giant pyramidal cells, occupying the precentral gyrus. There are numerous granule cells, which function as interneurons, with their axons and many dendrites concentrated in lamina IV of the cerebral cortex (Golgi type II). Fusiform cells (Figure 8.16) occupy mainly the deep cortical layers, particularly

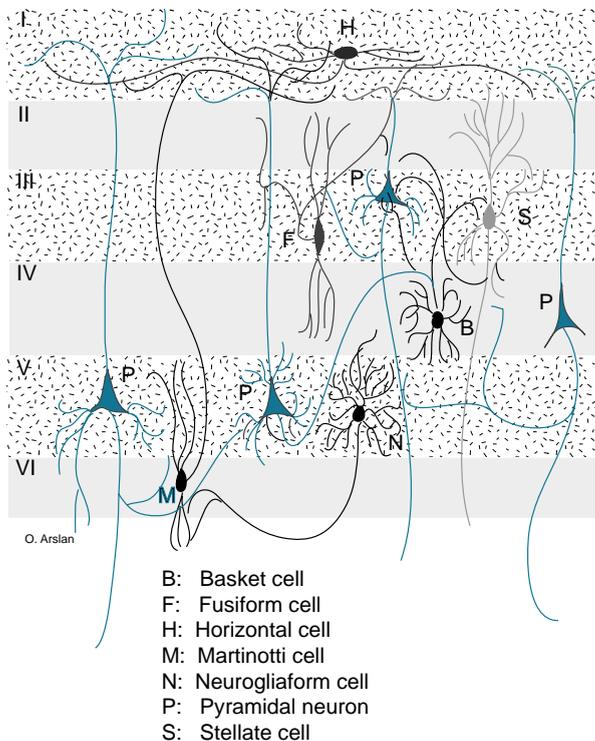


Figure 8.16 Schematic representation of the various neurons associated with the cerebral cortex

layer V, and possess axons that form projection fibers. Horizontal cells of Cajal (Figure 8.16) have axons that are confined to the superficial layers of cerebral cortex, whereas Martinotti cells (Figure 8.16) are scattered diffusely throughout the cortical layers.

Neuronal cytoarchitecture of the homotypical isocortex reveals six layers or laminae (Figures 8.16, 8.17 & 8.18).

I. The molecular layer consists of horizontal cells of Cajal, dendrites of the pyramidal neurons, and axons of Martinotti cells.

II. The external granular layer is a receptive layer, consisting of small pyramidal and granule cells. Neurons of this layer project to the molecular layer and to deeper cortical layers in order to mediate intracortical circuits.

III. The external pyramidal layer primarily contains pyramidal neurons, projecting to the white matter as association fibers and to the opposite hemisphere as commissural fibers. This layer also contains granule and Martinotti cells, as well as the horizontal band of Kaes-Bechterew (distinctive stripes in layers II and III). Laminae I, II, and III are concerned with associative and receptive functions.

IV. The internal granular layer receives all of the sensory projections from the thalamic relay nuclei via the thalamocortical fibers (e.g. optic radiation, auditory radiation, and primary sensory systems). It consists of densely packed stellate cells, containing the external

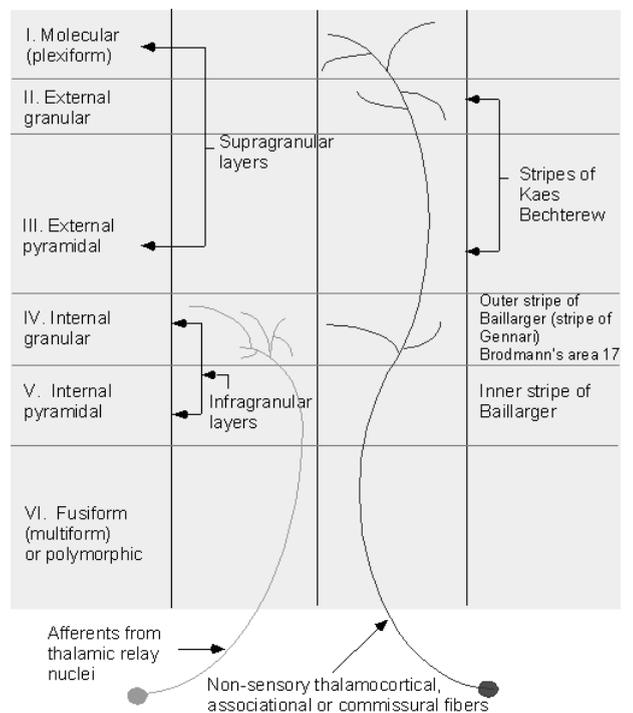


Figure 8.17 The six layered isocortex. Note the supragranular and infragranular layers and the sites of termination of the specific thalamic afferent and non-sensory thalamocortical fibers

myelinated bands of Baillarger. These outer and inner bands are formed by tangential thalamocortical fibers and may be visible to the naked eye. The outer band lies in lamina IV and is produced by afferents from the specific thalamic relay nuclei. The outer band is conspicuous in the striate cortex as the strip of Gennari, while the inner band is formed by the basal dendrites and the myelinated collaterals of the large pyramidal (Betz) cells. In the visual cortex the internal granular layer consists almost exclusively of simple cells which respond to stimuli from only one eye (but not both). The cortical layers that lie superficial and deep to layer IV respond to visual inputs from both sides. The infragranular (V and VI) layers are the first to be formed during embryological development. Subsequent cell migration through the infragranular layers allows the neurons to form more superficial layers.

V. The internal pyramidal (ganglionic) layer contains the largest pyramidal (Betz) neurons, giving rise to the corticospinal and corticobulbar fibers. It is pierced by dendrites and axons from other layers, including association and commissural fibers.

VI. The multiform layer contains small pyramidal and Martinotti cells, giving rise to projection fibers to the thalamus. It is crossed by commissural and association fibers. Cortical neurons of this layer project fibers, which maintain a feedback loop with the thalamic nuclei.

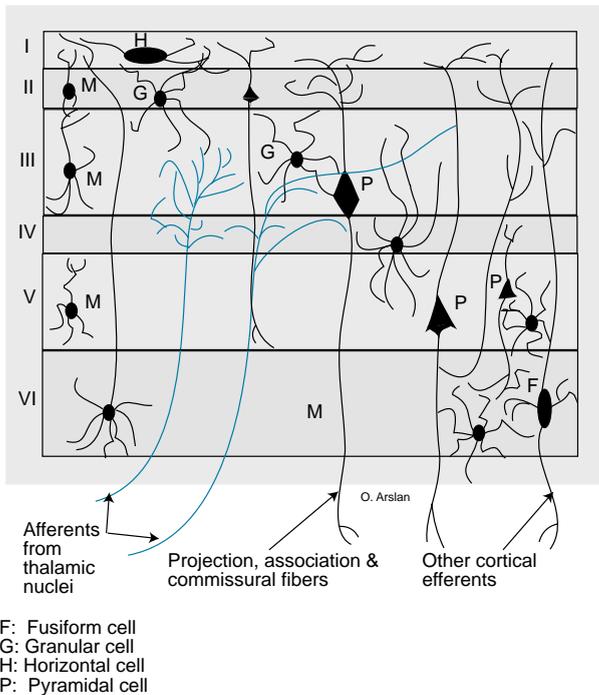


Figure 8.18 Cortical layers with their distinct neuronal population, showing areas of distribution of the afferents derived from the specific thalamic nuclei and areas of distribution of the commissural and association fibers

The relative thickness of the pyramidal and granular layers may be used as a basis to classify the cerebral cortex into five distinct areas. This classification grades the cortex from a purely motor to a purely sensory cortex and from the thickest to the thinnest. These cortical layers also vary from a layer that contains the least number of granule cells to a layer that consists mostly of granule cells. According to this classification the cerebral cortex is divided into agranular, frontal, parietal, polar, and granular cortex.

The agranular (motor) cortex is the thickest type that lacks or contains only a few granule cells in layers II and IV. It is exemplified in the heterotypical motor cortex (Brodmann's area 4), partly in the premotor cortex (Brodmann's areas 6 and 8), paracentral lobule.

The frontal type of cortex is a homotypical cortex with a very thin granular layer, which is represented in the superior frontal, postcentral, and the inferior temporal gyri, superior parietal lobule, precuneus, and in parts of the middle and inferior frontal gyri.

Examination of the parietal type of cortex reveals six distinct layers with particularly thin pyramidal layer, which is evident in the prefrontal cortex, inferior parietal lobule, and the superior temporal, occipito-temporal gyri.

In the polar cortex, which is represented in the frontal and occipital poles, a well-developed granular layer is evident.

The granular (konicortex), the thinnest of all cerebral cortices, contains a granular layer that achieved maximum development, and is symbolized in the homotypical cortices of cuneus, lingual, parahippocampal, and postcentral gyri as well as the transverse gyri of Heschl.

The cerebral cortex also exhibits vertical lamination, which represents the functional units of the cerebral cortex, extending through all cellular elements. This arrangement is absent in the frontal cortex, but distinctly evident in the parietal, occipital, and temporal cortices. The neurons of the vertical columns in the sensory cortex establish contacts with each other via interneurons (Golgi type II cells). Each column receives impulses from the same receptors, is stimulated by the same modality of sensation, and discharges for the same duration, maintaining an identical temporal latency. The isocortex (neopallium) is also divided into a sensory, motor, and association cortices. The sensory cortex is further subdivided into a primary, secondary, and tertiary sensory cortices. The motor cortex is classified into primary motor, premotor, and supplementary motor cortices. On the other hand the association cortices include parts of the parietal, temporal, and occipital cortices.

Sensory cortex

The sensory cortex deals with the perception and recognition of sensory stimuli. It imparts unique characteristics to sensations, enabling their identification on the basis of both comparative and temporal (spatial) relationships. It includes primary and secondary sensory cortices.

Primary sensory cortex

The primary sensory cortices are modality and place specific, receiving information from the specific thalamic nuclei. Depending upon the modality, sensations from body, projections from the visual fields and auditory spectrum are represented topographically in the contralateral primary sensory cortices. They include the somesthetic cortex (Brodmann's areas 3, 1, & 2), visual or striate (Brodmann's area 17), auditory (Brodmann's areas 41 & 42), gustatory, and vestibular cortices.

The primary somesthetic cortex (Brodmann's areas 3, 1, and 2) subserves general somatic afferents (deep and superficial), occupying the postcentral gyrus (Figure 8.19 & 8.32). It consists of three cytoarchitecturally distinct cortical stripes. Area 3 receives tactile sensation and area 1 forms the apex of the postcentral gyrus, receiving deep and superficial sensation. Area 2 lies in the posterior surface of the postcentral gyrus, deals with deep sensation, and receives collaterals from the other two areas. The primary somesthetic cortex receives projections from the ventral posterolateral and the ventral posteromedial thalamic

nuclei. Pain and thermal sensations are only minimally represented. The distorted representation of the body in this cortex is known as the sensory homunculus. This homunculus is formed according to the innervation density of the body part.

The primary visual (striate) cortex, representing Brodmann's area 17, lies on the banks of the calcarine fissure of the occipital lobe (Figure 8.23). It receives information from the third, fourth, fifth and the sixth layers of the lateral geniculate body. There is a visuotopic representation in which the peripheral part of the contralateral visual field is represented rostrally, while the macular visual field is delineated caudally in the occipital pole. No commissural fibers connect the striate cortices of both hemispheres. This cortical area receives blood supply from the internal carotid artery and the vertebro-basilar systems via the middle and posterior cerebral arteries, respectively. This cortex consists of vertical columns that discharge more or less as a unit, maintaining a topographical representation. It contains simple cells in the internal granular layer that respond to edges, rectangles of light, and bars presented in a particular receptive field axis of orientation to one eye. They possess 'on' and 'off' (inhibitory surrounding) centers. Complex cells have no 'on' and 'off' centers, spread in many layers of the striate cortex, and receive input from the simple cells. However, they do respond constantly to moving stimuli from both eyes. The vertical columns of the striate cortex may also be viewed as ocular dominance and orientation columns. Ocular dominance columns receive visual input from one eye only, are divided into alternate, independent, and super-imposed stripes. Each column receives visual information from either the left or right eye. Development of these columns requires visual input. Deprivation of the binocular vision, as may be experienced in individuals with severe strabismus, may lead to unequal development of the ocular dominance columns and potential blindness. Orientation columns are much smaller than the dominance columns are genetically determined, present at birth, and respond to a slit of light at a certain axis of orientation.

The primary auditory cortex (Brodmann's areas 41, 42) lies in the medial surface of the superior temporal gyrus (Figure 8.19). It is represented by the transverse gyri of Heschl, receiving the auditory radiation via the sublenticular part of the posterior limb of the internal capsule. Auditory radiation is formed by the axons of the ventral nucleus of the medial geniculate neurons. It should be noted that impulses reach the primary auditory cortex emanate from the auditory receptors of both sides with contralateral predominance. In this cortex a distinct tonotopic representation is exhibited in which higher frequencies are received medially and caudally, while lower frequencies occupy lateral and rostral areas.

Due to the bilateral representation of the auditory impulses, a unilateral lesion of the auditory cortex produces impairment of hearing on the contralateral side, but not total loss, with some degree of hearing loss on the ipsilateral side.

The gustatory cortex (Brodmann's area 43), confined to the parietal operculum, receives afferents from the ventral posteromedial thalamic nucleus.

The vestibular cortex is not a distinct cortical center, since the vestibular input is intermingled with other sensations. It is thought to occupy the distal part of the primary sensory cortex, a cortical area adjacent to Brodmann's area 2. The thalamic nuclei which receives somatosensory (VPL and VPI) and motor impulses (VL) also receive vestibular input. This overlap may play a role in the regulation of conscious awareness of spatial relationships at the level of the thalamus.

Secondary sensory cortex

The secondary sensory cortices surround the primary sensory cortices, occupy a smaller area than the primary cortices and receive input from the intralaminar and midline thalamic nuclei. Their topographic representation is either a mirror image or an inverted image, relative to the one perceived by the primary cortices.

The secondary somesthetic area is primarily associated with noxious and painful stimuli. It occupies the superior lip of the lateral cerebral (Sylvian) fissure, distal to the postcentral gyrus. Large and diverse receptive areas convey variety of sensory impulses to this cortex. Impulses are conveyed bilaterally, with a unilateral predominance, from the posterior thalamic zone and the ventral posterolateral thalamic nuclei. This cortex exhibits a distorted somatotopic arrangement in which the facial region lies adjacent to the corresponding area in the primary sensory cortex.

The secondary visual cortex (Brodmann's areas 18 and 19) surrounds the striate cortex and receives information from the primary visual cortex (Brodmann's area 17) and the pulvinar. The visual impulses, which reach the superficial layers of the superior colliculus, project to the inferior and lateral part of the pulvinar. These impulses eventually terminate in the secondary visual cortex, constituting the extrageniculate visual pathway. Both secondary visual cortices are connected, subserving visual memory functions and other components of vision. In the

Interestingly, anesthetics have a far greater effect on the secondary sensory area than on the primary sensory cortex.

Table 8.1 Primary sensory cortex

<i>Cortical areas</i>	<i>Major afferents</i>	<i>Major efferents</i>	<i>Function</i>	<i>Deficits</i>
Postcentral gyrus, Brodmann's areas 3, 1 & 2	Ventral posterolateral & ventral postero-medial nuclei, secondary somato-sensory cortex along the upper bank of the lateral cerebral fissure claustrum, basal nucleus of Meynert & locus ceruleus	Superior parietal lobule (Brodmann's areas 5, 7 & 6); ventral postero-medial and ventral posterolateral nuclei & corticopontine fibers	Perception of somesthetic sensations in a somatotopic manner	Loss of discriminative sensations such as position of body parts, weight differences, texture and two-point discrimination Slight reduction in pain & temperature perception
Inferior part of the postcentral gyrus adjacent to insular cortex	Visceral afferents	Not well defined	Integration of visceral sensations	Not well documented
Striate cortex- area 17 (cuneate & lingual gyri)	Lateral geniculate nucleus	Lateral geniculate body & Brodmann's area 18 spatial representation	Primary center for visual perception hemianopsia	Contralateral Brodmann's homonymous (commonly with macular sparing, stimulation produces flash of light & visual hallucination)
Transverse gyri of Heschl (Brodmann's areas 41 & 42)	Medial geniculate body	Wernicke's zone & medial geniculate body	Perception of auditory impulses and tonotopic representation	Due to bilaterality of auditory projections no noticeable auditory deficits will be detected
Olfactory cortex (pyriform lobe)	Olfactory bulb via olfactory tracts & striae.	Dorsomedial nucleus, orbitofrontal and insular cortex, amygdala, entorhinal cortex & hypothalamus	Perception of olfactory impulses	Ablation of the olfactory cortex produces anosmia Irritation, as in uncinata fits, produces olfactory aura that precedes seizures

peristriate cortex (Brodmann's area 18) an inverted visual field receptive topography exists, as compared to the striate cortex. It receives input from Brodmann's area 17, pulvinar, and the lateral geniculate nucleus. It projects to the peristriate cortex of the opposite hemisphere. This cortical area is essential for visual depth perception (stereoscopic vision). The unique bilateral representation of the visual image is achieved by the interhemispheric connections of the peristriate cortices through the corpus callosum. This bilaterality, which is not mediated by the lateral geniculate nucleus, ensures that no gap exists between the single image generated by both eyes. The parastriate cortex (Brodmann's area 19) surrounds Brodmann's area 18, maintaining identical retino-topic representation.

The secondary auditory cortex (Wernicke's zone- Brodmann's area 22) surrounds the primary auditory cortex, and receives afferents from the dorsal and medial subnuclei of the medial geniculate nucleus. This cortical area maintains reciprocal connections with the opposite hemisphere.

Motor cortex

The motor cortex is also known as agranular cortex because of the masking (attenuation) of the granular layers, particularly the inner granular layer. It occupies most of the frontal lobe and exerts control over the axial and appendicular muscles. It has a number of subclassifications, which include the primary and

supplementary motor cortices, as well as premotor area and motor eye field.

The primary motor cortex (Brodmann's area 4), represented by the precentral gyrus and part of the paracentral lobule, contains giant pyramidal cells of Betz that project to the lumbosacral segments of the spinal cord (Figures 8.19 & 8.32). Like the primary sensory cortex, the body is also represented here in a distorted fashion and arranged according to the relative innervation density (motor homunculus). In this homunculus, the foot, leg, and the thigh occupy the medial part of the paracentral lobule, whereas the gluteal region, trunk, upper extremity, followed by the hand, digits, and the head, in a descending, on the precentral gyrus. On the lower end of this homunculus, the tongue, muscles of mastication, and the larynx are designated. A brief glance at the homunculus reveals disproportionately large areas for the hand and especially the thumb, as well as the face. Ablation of the precentral gyrus results in spastic palsy (increased muscle tone in the antigravity muscles) on the contralateral side. Approximately, up to 30% of corticospinal tract fibers arise from the primary motor cortex. The connection of the primary and secondary somatosensory cortices to the primary motor cortex enables the ventral posterolateral nucleus to convey information to the motor cortex. Specific projections to lamina V of the primary motor cortex arise from the ventrolateral (VL) nucleus of thalamus. Other cortical areas such as Brodmann's areas 5 and 6 also project to the motor cortex. Thus the VL nucleus conveys the input received from the cerebellar nuclei to the motor cortex.

The supplementary motor cortex (Brodmann's areas 8 & 9), a duplication of the primary motor cortex which occupies the medial frontal gyrus (medial part of the superior frontal gyrus), may overlap Brodmann's area 4 and 6. It mediates contraction of the postural muscles on both sides. It also plays an important role in the planning and initiation of movements. It becomes active even if the intended movement did not occur.

The premotor cortex (Brodmann's area 6) occupies part of the superior frontal gyrus and maintain functional and topographical representations similar to the primary motor cortex (Figures 8.19 & 8.32). The motor programs in this cortex regulate the activities, which are essential for any motor activity such as the rhythm and strength of contraction of the muscles. The frontal motor eye field (Brodmann's area 8) controls conjugate eye movement to the opposite side (Figure 8.19).

Association cortices includes cortical areas that are located between visual, auditory, and somatosensory cortices which integrate generated auditory, visual, gustatory, and general sensory impulses. This integration serves variety of functions, including recognition of shape, form, texture of objects, awareness of body image,

Contralateral flaccid palsy, followed by a gradual spasticity, Babinski sign, increased deep tendon reflexes, and clonus are the prominent (upper motor) signs of lesions of the primary motor cortex. Recovery from such injury is only moderate.



Figure 8.19 Lateral surface of the cerebral hemisphere. The main gyri of the frontal temporal and parietal lobes are indicated. Speech areas, frontal eye field, and auditory cortex are shown

Ablation of this cortical area produces an increase in flexor muscle tone, leading to spasmodic contracture and a pathologic grasp reflexes on both sides. The face and upper limb is represented anteriorly, lower limb posteriorly, and the trunk occupies a more inferior position in this cortex.

relationships of body parts to each other and their location. These cortical areas also regulate the conscious awareness of body scheme, physical being, and recognition and comprehension of language symbols. They may also be involved in planning of motor functions, and modulation of sensory impulses. Association cortices encompass the superior parietal lobule (Brodmann's areas 5 & 7), inferior parietal lobule which comprise the supramarginal (Brodmann's area 40) and the angular gyri (Brodmann's area 39), the posterior part of superior temporal gyrus (Wernicke's area-Brodmann's area 22), and the secondary visual cortex (Brodmann's areas 18 & 19).

Cortical afferents

Cortical afferents are derived primarily from the spinal cord, cerebellum, and basal nuclei. They project to the cerebral cortex via the thalamocortical radiations

Table 8.2 Motor cortex

<i>Cortical areas</i>	<i>Major afferents</i>	<i>Major efferents</i>	<i>Function</i>	<i>Deficits</i>
Precentral & postcentral gyri, and paracentral lobule	Premotor (Brodmann's area 6), postcentral gyrus (areas 3,1,2), contralateral (Brodmann's area 4, and Brodmann's areas 5&7), ventral lateral &ventral anterior nuclei	Corticospinal, corticopontine, corticotegmental, cortico thalamic to ventral lateral and ventral anterior nuclei	Provide motor control to the alpha motor neurons & regulates reflexes and muscle tone	Contralateral spastic palsy, Babinski sign, hyperreflexia, clonus & loss of superficial abdominal and cremasteric reflexes
Premotor cortex (Brodmann's area 6)	Precentral gyrus, postcentral gyrus, superior parietal lobule (areas 5 &7), ventral anterior and ventral lateral nuclei	Corticostriate, ventral anterior & ventral lateral nuclei	Motor for skeletal muscles	Stimulation of this area produces generalized movements. When area 4 is destroyed it mimics the activities of area 4
Frontal eye field (Brodmann's area 8)	Corticobulbar (e.g. pyramidal)	Other parts of the cortex	Voluntary eye movements conjugately to the opposite side	Both eye conjugately moves to the side of the lesion
Supplementary motor cortex	Postcentral gyrus (area 3,1,2), precentral gyrus (area 4),VL & VL nuclei	Area 4, striatum,; spinal cord via the corticospinal tract	Controls contraction of the postural muscles	Ablation produces spastic contracture of flexor muscles & grasp reflexes

(peduncles). The cortical afferents that originate from the spinal cord include the dorsal column-medial lemniscus and the spinal lemniscus. These afferents convey impulses to the sensory cortex via thalamocortical fibers that emanate from the ventral posterolateral nucleus. Other afferents from the spinal trigeminal and principal sensory nuclei are conveyed through the trigeminal lemnisci to the ventral posteromedial thalamic nucleus. These fibers also project to the sensory cortex via thalamocortical fibers. Afferents, which carry motor information, are conveyed to the motor and premotor cortices from the cerebellum and basal nuclei via neuronal axons of the ventral lateral and ventral anterior thalamic nuclei. Limbic lobe and prefrontal cortex receive afferents, subserving emotion, behavior, memory and mood, from the anterior and dorsomedial nuclei of the thalamus. Visual and auditory cortical afferent derived from the lateral and medial geniculate nuclei, are carried by the optic and auditory radiations, respectively. Sleep-wake cycle is partly regulated

by cortical afferents from the intralaminar thalamic nuclei within the ascending reticular activating system. Noradrenergic afferents that arise from the locus ceruleus project to the all cortical areas and laminae (especially to lamina I) via the central tegmental tract and internal capsule, bypassing the thalamus. These noradrenergic fibers may inhibit the moderately active cortical neurons and enhance the signal-to-background ratio. They do not affect the cortical sensory neurons.

An important and consistent feature of the thalamocortical fibers is their organization into the superior, inferior, anterior, and posterior peduncles. The superior peduncle contains fibers that connect the ventral posterior nucleus to the postcentral gyrus, and the ventral anterior nucleus to the premotor cortex. It also contains fibers that connect the ventral lateral nucleus to the motor cortex, and the lateral dorsal and lateral posterior nuclei to association cortices of the parietal lobe. The inferior peduncle contains the auditory radiations, projecting from

Table 8.3 Association cortex

<i>Cortical areas</i>	<i>Major afferents</i>	<i>Major efferents</i>	<i>Function</i>	<i>Deficits</i>
Superior parietal lobule (Brodmann's areas 5 & 7)	Lateral posterior, lateral dorsal nuclei; Brodmann's area 3,1,2 (postcentral gyrus)	Corticotegmental & corticopontine pathways	Integration of general sensory visual information	Contralateral astereognosis & inability to recognize writing on skin although ability to feel and appreciate general weight & temperature remains unchallenged.
Brodmann's areas 18 & 19	Brodmann's area 17 and pulvinar	Midbrain tegmentum, tectum, pontine nuclei & pulvinar	Interpretation of visual information & regulation of optokinetics & accommodation reflexes	Inability to recognize an object in the opposite field of vision. Deficits in optokinetic & accommodation reflexes. Stimulation of this area produces visual hallucinations
Brodmann's area 22 Wernicke's speech center (Brodmann's area 22)	Primary auditory cortex (Brodmann's areas 41 & 42) & other cortical areas	Other association cortices	Integrates auditory & visual information	Sensory aphasia may result from unilateral lesion, but are most pronounced when the damage is bilateral
Prefrontal cortex	Dorsomedial nucleus & other cortical areas	Pontine nuclei, dorsomedial nucleus & other cortical areas	Personality, drive, emotion, intellect. Affective component of pain	Marked changes in personality, behavior & judgment, most evident when lesions are bilateral. Stimulation produces changes in blood pressure, respiratory rate, gastric motility
Cingulate gyrus	Anterior nucleus of thalamus	Anterior nucleus of thalamus	autonomic manifestations & pain perception	Vascular changes & changes in temperature regulation
Broca's speech center (Brodmann's areas 44 & 45)	Wernicke's zone & other cortical areas	Contralateral Broca's center & motor nuclei of cranial nerves	Phonation	Broca's aphasia
Inferior parietal lobule (Brodmann's areas 39 & 40)	Pulvinar & secondary visual cortex	Prefrontal & premotor and insular cortices	Spatial & three dimensional perception	Inability to draw, place blocks, orient spatially or identify contralateral body parts

the medial geniculate nucleus to the transverse gyri of Heschl via the sublenticular part of the internal capsule. The anterior peduncle contains fibers connecting the dorsomedial and anterior thalamic nuclei to the cingulate and prefrontal cortices. The posterior peduncle runs in the retrolenticular part of the internal capsule, connecting the lateral geniculate nucleus to the primary visual cortex of the occipital lobe.

Cortical efferents

Massive cortical efferents project from to the spinal cord, brainstem, and the thalamus. Some of these fibers are destined to the spinal cord, while others terminate in subcortical area (e.g. thalamus, brainstem, etc.)

A prominent projection of the cortex is represented in the corticospinal tract (described in detail later with the upper motor neurons) which originates from motor, premotor, and somesthetic areas of the cerebral cortex and descends in the ventral part of the brainstem. Most fibers of the corticospinal tract decussate at the level of the caudal medulla, forming the lateral corticospinal tract, while the remaining ipsilateral fibers constitute the anterior and anterolateral corticospinal tracts.

The corticobulbar tract (CBT), also described with upper motor neurons, is a cortical pathway that acts upon the motor nuclei of the cranial nerves.

The cortico-thalamic tracts form part of the reciprocal pathway that connects certain areas of the cerebral cortex to the thalamic nuclei. These corticofugal pathways include projections from the primary motor cortex (Brodmann's area 4) to the ventral lateral and centromedian nuclei, as well as projections from the prefrontal cortex to the dorsomedial nucleus. They also encompass projections from the cingulate gyrus to the anterior nucleus and from the premotor cortex (Brodmann's area 6) to the ventral anterior and ventral lateral nuclei. In addition, cortical projections from premotor and motor cortical fibers to the intralaminar nuclei, and from the primary sensory cortex to the ventral posterolateral and ventral posteromedial nuclei, are also included. Projections from the primary auditory and visual cortices to the medial and lateral geniculate nuclei respectively constitute additional corticothalamic pathways. It is interesting to note that the thalamic reticular nucleus receives afferents from all areas of the cortex with no reciprocal projections to this area.

Fibers of the corticopontine tract that project to the pontine nuclei, maintain diverse origin from the pyramidal neurons in layer V of the primary motor and prefrontal cortices (fronto-pontine), primary sensory cortex (parieto-pontine), temporal lobe (temporo-pontine), and the visual cortex of the occipital lobe (occipito-pontine). These fibers show a somatotopic arrangement in the crus cerebri of the

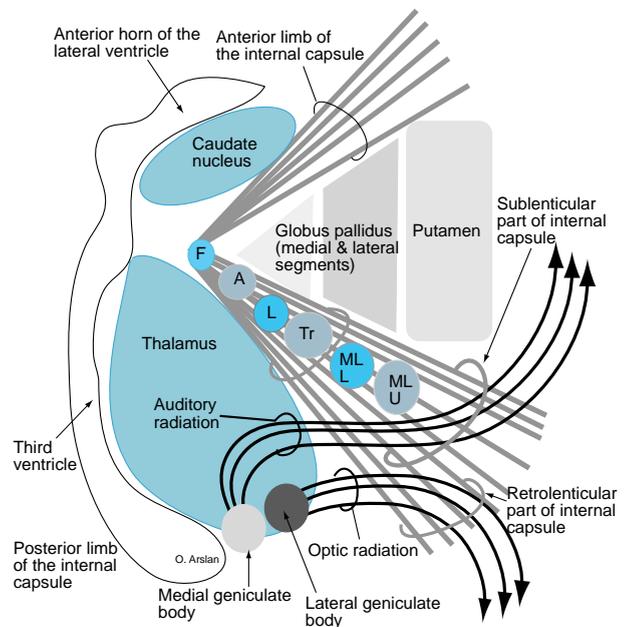


Figure 8.20 Topographic location of the internal capsule and its main constituents. Note the massive number of fibers crossing through the posterior limb of the internal capsule. Letters F, face (corticobulbar fibers); A, arm; L, lower extremity; Tr, trunk (corticospinal fibers); ML U, Medial lemniscus fibers from the upper extremity; MLL, medial lemniscus fibers from the lower extremity

midbrain, in which the fronto-pontine fibers occupy a medial position to the parieto-occipito-temporo-pontine fibers. This tract, the ipsilateral component of a major pathway known as the cortico-ponto-cerebellar, enables the cerebral cortex to influence cerebellar activity.

A third group of fibers form cortico-reticular tract which originates from the motor, premotor, visual, and auditory cortices and terminate in the nucleus reticularis gigantocellularis of the medulla and the nucleus reticularis pontis oralis of the pons. This pathway may be partially responsible for signs of decerebrate rigidity, which is seen upon transection of the brainstem at the intercollicular level.

Another cortical projection, the cortico-tectal tract, consists of fibers from the secondary visual and primary auditory cortices as well as the frontal eye field. Visual tracking movements are regulated by fibers from the secondary visual cortex (Brodmann's areas 18 & 19) that projects to the superficial layers of the ipsilateral superior colliculus. Whereas control of saccadic eye movements is maintained by the projections of frontal eye field

(Brodmann's area 8) to the middle layers of the superior colliculus. In the same manner, movements of the eye and the head toward auditory stimuli is mediated by the projections of the primary auditory cortex to the deep layers of the superior colliculus.

The cortico-rubral tract is a component of the cortico-rubro-spinal tract, which originates from the motor and premotor cortices of both hemispheres and descends to terminate somatotopically in all areas of the red nucleus. Note that the ipsilateral cortico-rubral fibers from the motor cortex mainly terminate in the magnocellular part of the red nucleus, whereas the contralateral fibers from the premotor and motor cortices terminate in the parvocellular part of the red nucleus.

Finally, fibers from all areas of the cerebral cortex form the corticostriate which project bilaterally to all regions of the caudate and putamen. Bilateral corticostriate fibers are primarily derived from the motor, premotor, and sensory cortices, and are somatotopically arranged. In order for the contralateral fibers to reach the striatum, they cross in the corpus callosum and pursue their course in the subcallosal fasciculus. In particular, the caudate nucleus, a component of the striatum, receives input primarily from the prefrontal cortex.

Cortical afferents accompanied by cortical efferents are contained in the internal capsule, a V-shaped bundle which consists of anterior limb, genu, and posterior limb with retro- and sublenticular parts (Figures 8.20, 8.21 & 8.24). The corticothalamic and thalamocortical projections form the bulk of the internal capsule. An important aspect of the internal capsule is the somatotopic arrangement of its fibers. For instance, the anterior limb contains fibers which maintain reciprocal connections with the frontal lobe, the genu consists of corticobulbar and corticospinal, whereas the posterior limb (lenticulothalamic) is much more massive consisting of fibers of the corticospinal and fronto-pontine pathways, and the superior thalamic radiation (spinothalamic tracts and medial lemniscus). It also contains the optic and auditory radiation in the retrolenticular and sublenticular parts, respectively. Due to this extensive concentration of sensory and motor fibers within, occlusion or hemorrhage associated with a small artery that supplies the posterior limb may lead to profound sensory or motor or combined deficits as in lesions of the posterior limb. Visual and auditory deficits may also be observed if the retrolenticular and sublenticular portions are involved. Other deficits, such as spastic paralysis of the muscles of mastication, muscles of facial expression, and palatal muscles may be observed if the corticobulbar fibers are involved.

Diverse arterial sources contribute to the blood supply of the internal capsule. In particular, the posterior communicating artery, which is most commonly hypoplastic, supplies the genu and a portion of the

posterior limb of the internal capsule. Additional blood supply to the genu of the internal capsule may be derived from the internal carotid artery. The medial striate artery (recurrent artery of Heubner), which arises from the anterior cerebral artery, and sometimes from the middle cerebral artery, pierces the anterior perforated substance to supply the rostral part of the anterior limb. The anterior choroidal artery, a branch of the internal carotid artery, runs above the uncus along the optic tract, and enters the inferior horn of the lateral ventricle via the choroidal fissure, to supply the posterior limb, including the retrolenticular part. The lateral striate (lenticulostriate) artery supplies the anterior limb and the dorsal part of the posterior limb of the internal capsule.

Cerebral white matter

The white matter of the cerebral hemispheres lies deep to the gray matter of the cerebral cortex, consisting of nerve fibers and glial cells. It contains the basal nuclei and the central branches of the cerebral arteries. The fibers that course within the white matter are classified into commissural, association, and projection (Figure 8.22).

Commissural fibers

The commissural fibers interconnect identical or non-identical areas of the two cerebral hemispheres, forming the corpus callosum, anterior commissure, and the hippocampal commissure. Interhemispheric communication that mediate learning process is accomplished to a great extent by the corpus callosum, largest of all commissures, which interconnects the cerebral hemispheres (Figures 8.23 & 8.25). However, exceptions exist in regard to this fact, for instance, the striate (primary visual) cortex and the hand area of the cerebral cortex do not project commissural fibers through the corpus callosum.

The anterior commissure (Figures 8.24 & 8.26) is embedded in the upper part of the lamina terminalis, superior to the optic chiasma, resembling the handle of a bicycle. It divides the fornix into pre-commissural and post-commissural columns. This commissure exhibits an anterior smaller portion, which connects the olfactory tracts to the anterior perforated substances of both sides, and a posterior larger portion, interconnecting the parahippocampal and the middle and inferior temporal gyri, as well as the amygdaloid nuclei. In addition, the anterior commissure interconnects the anterior olfactory nuclei, diagonal bands of Broca, olfactory tubercles, prepyriform cortices, entorhinal areas, nucleus accumbens septi, bed nuclei of stria terminalis, and the frontal lobes.

Another smaller, yet important posterior commissure exists which lies caudal to the pineal gland and rostral to

Occlusion of the anterior cerebral artery proximal to the origin of the recurrent artery of Heubner may produce no detectable deficit if the collateral circulation from the corresponding artery of the opposite side is maintained. However, a lack of efficient anastomosis may result in infarction of the anterior limb of the internal capsule and destruction of the cortico-ponto-cerebellar tract, producing frontal dystaxia (partial ataxia in which the patient exhibits difficulty in controlling voluntary movements).

the superior colliculi. It contains fibers, which arise from the habenular and Darkschewitsch nuclei, interstitial nucleus of Cajal, and the nucleus of the posterior commissure. It also contains fibers from the superior colliculi and the pretectal nuclei.

Additional interhemispheric linkage is secured by the hippocampal commissure, which extends between the crura of the fornix and hippocampal gyri, and inferior to the splenium of the corpus callosum.

Association fibers

Association fibers establish linkage between areas within the same cerebral hemispheres, consisting of short and long fasciculi, with the short fasciculi interconnecting adjacent gyri within the same cerebral hemisphere. Long fasciculi, which include the cingulum, uncinata, superior longitudinal, inferior longitudinal, superior and inferior occipito-frontal fasciculi connect distant areas of the cerebral hemispheres.

Structures that comprise the limbic system such as the subcallosal and paraterminal gyri rostrally and the parahippocampal and adjacent temporal gyri caudally are interconnected by the cingulum, a curved bundle of association fibers that lies deep to the cingulate gyrus and follow its course (Figures 8.27 & 8.28). On the other hand, Broca's speech center connects to the rostral parts of the temporal gyri via the uncinata fasciculus, which enable input generated/or integrated in the temporal lobe to affect articulation (Figures 8.29, 8.30 & 8.31).

A group of large association fibers that course lateral to the corona radiata and the internal capsule form the superior longitudinal (arcuate) fasciculus, connecting the rostral parts of the frontal lobe to the secondary visual cortex (Brodmann's area 18, 19) and the parietal and temporal gyri (Figures 8.28, 8.30 & 8.31).

Another group of association fibers forms the inferior longitudinal fasciculus (Figure 8.28) which extends from the secondary visual cortex to the inferotemporal cortex,

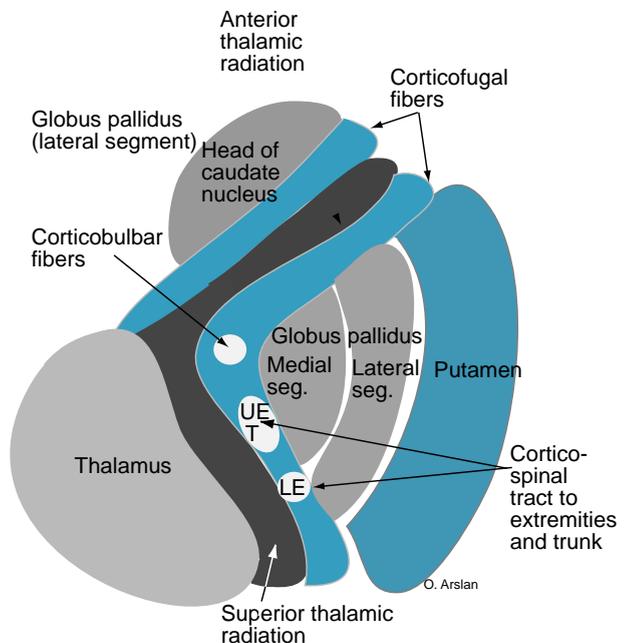


Figure 8.21 The internal capsule. Note its location between the thalamus, caudate nucleus, and the lentiform nucleus



Figure 8.22 Horizontal section of the brain indicates the distinction between the central white matter and the peripheral cortical areas

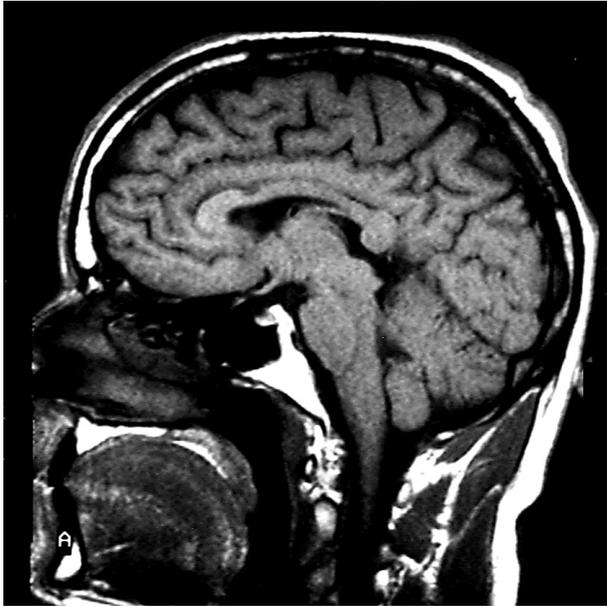


Figure 8.23 Inverted MRI showing components of the corpus callosum and their relationships to individual cerebral lobes, gyri and the septum pellucidum

coursing lateral to the occipital horn of the lateral ventricle, and is separated by the optic radiation and tapetum.

Frontal and occipital lobes are also connected by the superior occipito-frontal (subcallosal) fasciculus that lies inferior and lateral to the corpus callosum. This fasciculus is separated from the superior longitudinal fasciculus by the corona radiata.

Additional bundle, the inferior occipito-frontal fasciculus, connects the frontal to the occipital lobe, and runs within the temporal lobe proximal to the uncinate fasciculus. It has been suggested that the uncinate fasciculus is part of the inferior occipitofrontal fasciculus (Figure 8.31).

Projection fibers

Projection fibers are corticofugal axons which extend from the cerebral cortex to the subcortical nuclei, brainstem, and the spinal cord. They form the corona radiata that runs between the superior longitudinal and the superior occipitofrontal fasciculi. They run within the internal capsule and may descend to terminate in the spinal cord or other subcortical areas. These projection fibers include the corticospinal, corticobulbar, corticostriate, corticopontine, etc.

Disconnection syndrome (split brain) encompasses constellation of symptoms, which results from interruption of the interhemispheric commissures or intrahemispheric connections. This syndrome may be produced by a mid-sagittal section of the corpus callosum, a procedure commonly used in the past as a treatment for intractable epilepsy. Infarction of the pericallosal branch of the anterior cerebral artery may result in similar deficits, producing two hemispheres that function independently. This functional independence involves perception, cognition, mnemonic, learned, and volitional activities. Therefore, information generated in the non-dominant hemisphere is expressed only in a non-verbal manner and could not be expressed in writing or speech, as the dominant hemisphere has a major role in linguistic expression. In individuals with divided corpus callosum, most voluntary daily activities, native intelligence, memory, verbal reasoning, and temperament are not generally affected.

Presence of bilateral sensory representation and the compensatory development of bilateral motor representation may explain the intactness of these functions. Various forms of agnosia may also be associated with lesions of the corpus callosum. Owing to interruption of the callosal fibers and the fact that information is not transferred from the right hemisphere to the speech center in the left hemisphere, patients may exhibit an inability to name objects presented into the left visual field or placed in the left hand. Affected individuals are also unable to carry out verbal commands with the left hand, but are capable of naming objects presented into the right visual field or hand. Thus the inability to match an object in one hand (or seen with one eye) with one placed in the other hand (or seen with the other eye) becomes evident. These observations indicate that information received or generated by the non-dominant hemisphere could not be expressed verbally or in writing, and that visual information is not transferred between the two hemispheres. Comprehension of spoken and written languages is not affected due to bilateral representation.



Figure 8.24 The course of the anterior commissure as a midline structure and its continuation inferior to the lentiform nucleus is illustrated

Occlusion of the posterior cerebral artery may result in disruption of the splenium of the corpus callosum, preventing transfer of information from the right to the left visual cortices, a process, which is essential for the visual recognition of objects. Therefore, patients with this type of lesion are able to read, but unable to write or name colors. In normal individuals, the visual stimuli elicit non-verbal associations (tactile, taste or smell) which are transmitted across the intact anterior part of the corpus callosum.

Destruction of the anterior part of the corpus callosum (e.g. due to infarction of the anterior cerebral artery (anterior cerebral artery syndrome), distal to the origin of the anterior communicating artery, prevents verbal information to be conveyed from language centers of the left hemisphere to the appropriate centers of the right (mute) hemisphere. This may produce left arm apraxia in which the patient is unable to identify numbers or letters written by a blunt object on the affected left extremity, or perform movements using the left arm and leg upon verbal or written commands, although normal spontaneous movements are maintained. Due to infarction of the rostral part of the corpus callosum, the patient with left arm apraxia is also unable to name an object placed in the left hand, or write or print with the left hand. Damage to the corpus callosum may also occur as a result of excessive consumption of red wine (Marchiafava-Bignami syndrome), producing subtle and variable manifestations.

Cerebral dysfunctions

Cerebral lesions occur in a variety of diseases and conditions such as Alzheimer's disease, post-encephalitis, Parkinsonism, and pseudobulbar palsy (associated with destruction of the corticobulbar tracts), and progressive supranuclear palsy. These diseases may produce speech and language disorders that may include speech derangement as in Alzheimer's disease, palilalia (compulsive repetition of a phrase with increasing speed and decreasing volume) as in progressive supranuclear palsy, and aphasia. Other cerebral lesions produce apraxia (inability to perform familiar motor activity without sensory or motor damage) or agnosia (inability to recognize objects and symbols despite intactness of sensory pathways). Cortical

Complete failure of the corpus callosum to develop, agenesis of the corpus callosum, may occur during the fourth to the twelfth week of development. Agenesis of the corpus callosum, a congenital anomaly, is accompanied by a partial or complete absence of the cingulate gyrus and septum pellucidum, or the appearance of ipsilateral longitudinal fibers, which include some that fail to cross the midline. This form of agenesis is not commonly associated with neurological deficits, although mild mental retardation, seizure, and motor deficits may be seen. Other form of this condition is associated with development of small, multiple gyri (micropolygyria) and heterotopias of the gray matter. In general, agenesis of the corpus callosum is associated with inherited metabolic disorders (pyruvate dehydrogenase deficiency, glutaric aciduria type II), and with chromosomal abnormalities as in Dandy-Walker, Aicardi's, and Cogan syndromes.

In Dandy-Walker syndrome, the cerebellar vermis fails to develop and the fourth ventricle is replaced by a cyst-like midline structure. Patients with this condition exhibit thinning of walls of the posterior cranial fossa and the roots of the cervical spinal nerves assume an ascending course in order to reach their corresponding foramina. As mentioned earlier, this syndrome may also be associated with agenesis (failure of development) of the corpus callosum and related manifestations.

Both Aicardi's syndrome, which is characterized by seizure, microcephaly, and vertebral defects such as hemivertebra; and Cogan syndrome that manifests keratitis (inflammation of the cornea) and vestibulo-auditory disorders, may show signs of agenesis of the corpus callosum.

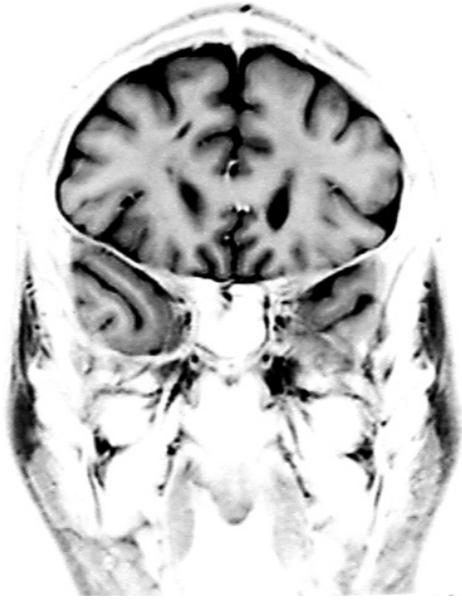


Figure 8.25 An inverted MRI scan (coronal section) of the brain through the anterior horn of the lateral ventricle. Observe the body and rostrum of the corpus callosum individual cerebral lobes, gyri and the septum pellucidum

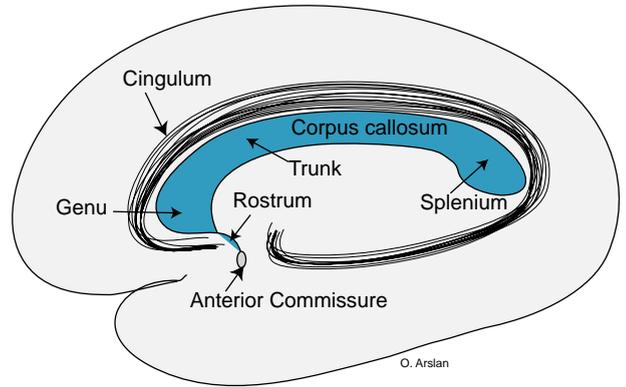


Figure 8.27 The cingulum within the cingulate gyrus. Observe its relationship to the corpus callosum

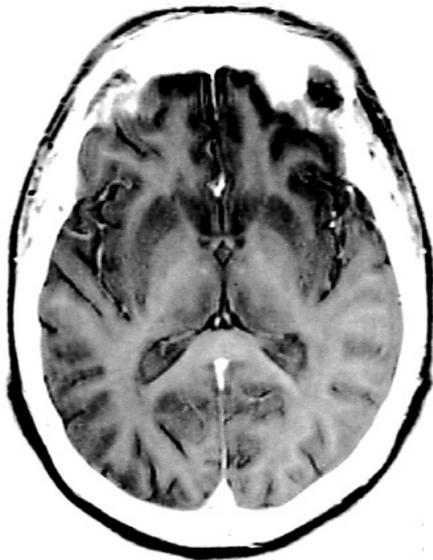


Figure 8.26 An inverted MRI scan (horizontal view) of the brain through the frontoparietal operculum. Note the curved midline anterior commissure rostral to the columns of the fornix. The splenium of the corpus callosum and the posterior horn of the lateral ventricle are also visible

dysfunctions may also produce dementia, and seizures which will be discussed later in this chapter.

In summary, the following sequences may be of value in determining the role by which each center plays in naming visual object:

Object—> optic nerve & tract—> lateral geniculate nucleus—> Brodmann's area 17 of the visual cortex—> Brodmann's area 18 —> Angular gyrus (Brodmann's area 39) —> Wernicke's area (area 22) – pattern is formed =>Arcuate fasciculus => Broca's motor speech center (Brodmann's areas 44 & 45) —> Facial area of the motor cortex —> muscles of speech via certain cranial nerves.

Cerebral dominance

Despite the similarity in the morphologic features of the two cerebral hemispheres and the symmetrical projections of the sensory pathways, each hemisphere maintains specialized in certain higher cortical functions. In most individuals, the posterior part of the superior temporal gyrus expands and shows greater length on the left cerebral hemisphere. A minority of brains exhibits this feature in the right hemisphere.

Identification of objects and comprehension of language may be accomplished by the right (mute, non-dominant or creative) hemisphere, utilizing visual and tactile information. This hemisphere also integrates visual impulses with spatial information and motor activities, as in drawing, and mediates musical tones, facial recognition, construction, and other non-verbal activities. Thus, the non-dominant hemisphere is holistic, concerned with perception of spatial (superior parietal lobule), gesturing

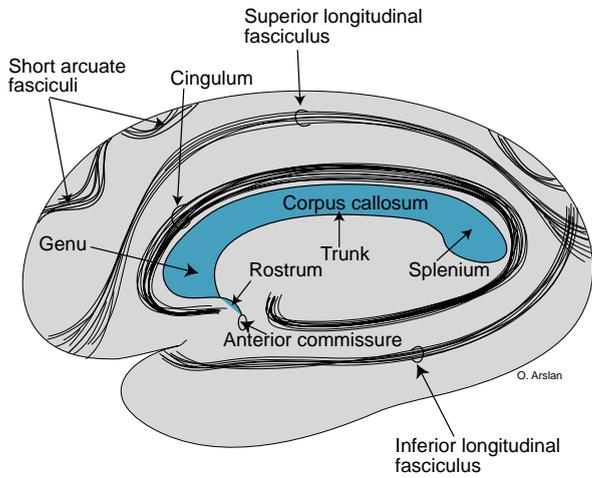


Figure 8.28 Mid-sagittal drawing of the brain. The superior and inferior longitudinal fasciculi are illustrated

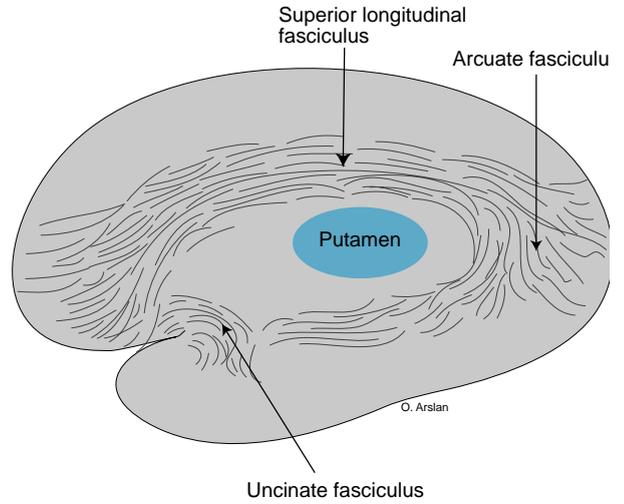


Figure 8.30 Schematic drawing of some of the association fibers within the cerebral hemisphere

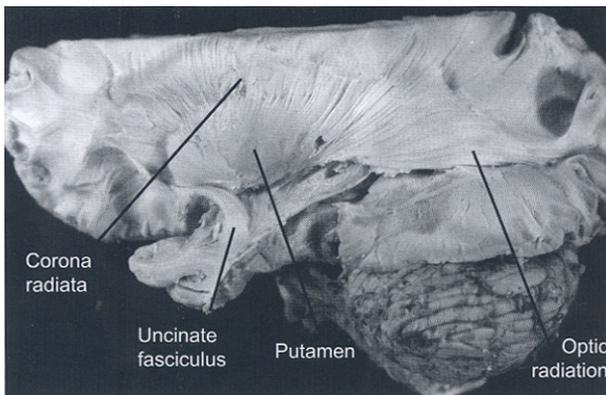


Figure 8.29 The lateral surface of the brain after removal of the frontal and temporal gyri. The fibers of the corona radiata are shown

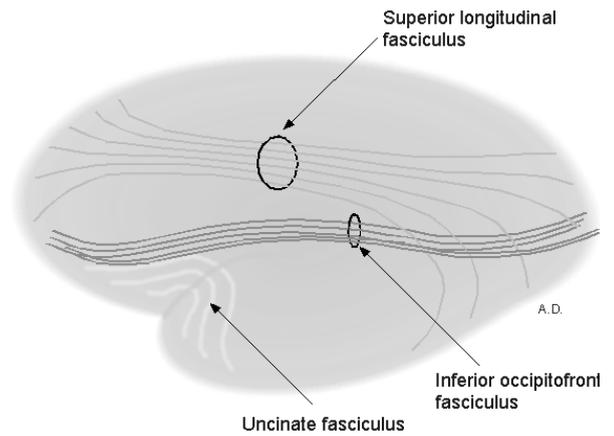


Figure 8.31 Diagram of the inferior occipitofrontal and superior longitudinal, and uncinate fasciculi are illustrated to emphasize their relative locations

Bilateral disruption of the superior longitudinal fasciculi may produce visual agnosia, which is characterized by the inability to name an object or describe its function.

that accompanies speech (prosody), and recognition of familiar objects. In another word, this hemisphere is holistically creative, lacks details, and defies rules and logic.

In 95% of males and 80% of females, the dominant hemisphere, usually the left hemisphere, is less creative and designed to carry out sequential analysis. It is conceived to comprehend spoken and written languages and to express thoughts into words. Additionally, sequencing of phonemic and syntactical characteristics of language, mathematical calculations, analytical functions, and fine skilled motor activities are regulated by the left hemisphere. Right handed individuals (dextrals) constitutes 80% of the population, 10% are left handed, and the rest 10% of the population is ambidextrous. In approximately 90-97% of individuals who use primarily their right hands, the left hemisphere is dominant for language. The other 3-10% of right-handed persons have speech center in the right hemisphere. In 60-65% of left handed individuals (sinistrals) the speech center is located in the left hemisphere; 20-25% has speech center in right hemisphere; and in 15-20% of the population, the speech center is bilateral. In 60% of ambidextrous individuals the speech center is located in the left hemisphere, in 10% of this population it is positioned in the right hemisphere, and in 30% of these individuals it lies in both hemispheres. Recovery from aphasia in sinistrals is more complete than dextrals. Positron emission tomography (PET) may be used to detect the increased blood flow into the dominant hemisphere.

Basal nuclei

The basal nuclei are embedded in the white matter of the cerebral hemispheres. Together with the substantia nigra, red and subthalamic nuclei, reticular formation, and the claustrum, they comprise the subcortical motor system. This system is concerned with stereotyped movements, suppression of cortically induced movements, regulation of posture and adjustment of muscle tone. The basal nuclei influence the motor activity by projecting to specific nuclei of the thalamus which in turn deliver the received impulses to the cerebral motor and premotor cortices. Specifically, the basal nuclei consist of the corpus striatum and amygdala. The amygdala is a structure which maintains connections with the striatum, thalamus, cerebral cortex, and structures that constitute the limbic system (see the

limbic system- [chapter 17](#)). The corpus striatum comprises the globus pallidus, caudate nucleus, and the putamen. Both the caudate nucleus and putamen form the neostriatum, representing the afferent portion of the basal nuclei, whereas the lentiform nucleus refers to both the putamen and the globus pallidus. For further discussion of the basal nuclei, see the extrapyramidal motor system- [Chapter 21](#).

Blood supply of the cerebral hemispheres

Most of the neurological disorders, whether reversible or irreversible, are the result of vascular diseases or accidents. Knowledge of anatomy of the cerebral vessels is of utmost clinical importance, as it is essential in performing and interpreting angiographic imaging, understanding the deficits associated with vascular accidents, and in the developing a treatment plan. The blood supply to the brain tissue is maintained by the carotid and vertebro-basilar arterial systems. There are specific features of the capillaries associated with these two arterial systems. For instance, these capillaries, which are composed of non-fenestrated continuous endothelial cells, connected by tight junctions and encased by perivascular end feet of astrocytes, possessing large number of mitochondria and pinocytotic vesicles. Approximately 15 percent of cardiac output, equivalent to 750 ml per minute, is directed to the brain. The gray matter of cerebral cortex receives blood far greater than the white matter. The difference between the arterial and venous pressure may determine the cerebral blood flow. In addition, intrinsic factors such as the condition of the cerebral vessels, changes in the tension of carbon dioxide, and alteration in pH will also affect the blood flow to the brain. Due to the small size of frontal lobes in infants, the cerebral vessels are concentrated within the Sylvian triangle.

As mentioned earlier, the branches of the internal carotid and basilar arteries supply the brain. The internal carotid artery ([Figures 8.34, 8.35, 8.38, 8.39 & 8.40](#)) arises from the common carotid artery at the level of the upper border of the thyroid cartilage, coursing in the neck in close proximity to the sympathetic trunk. This vessel supplies the rostral two thirds of the brain hemispheres, diencephalon, nasal cavity, forehead, eye and orbit. Initially it ascends in the neck within the carotid sheath (cervical part), entering the carotid canal to gain access to the cranial cavity. Within the carotid canal (petrous part), it lies anterior to the cochlea and tympanic cavity, separated by a thin bony lamella ([Figure 8.36](#)). This petrous part courses near the trigeminal ganglion, separated from it by the roof of the carotid canal. During its intracranial course the internal carotid artery passes over the cartilaginous plate of foramen lacerum and continue

Aphasia is the inability to comprehend the spoken and written language, or express thoughts via words despite the fact that sensory systems, mechanisms of articulation and the associated structures (Figures 8.32 & 8.33) are intact. This disorder should not be confused with other speech abnormalities that occur in cerebellar dysfunctions, hypoglossal or vagus nerve damage (changes in speech tone) or upper motor neuron palsy. Generally, the severity of aphasia depends upon the site of cortical damage and duration of the disorder. Although complete recovery does not always occur, the earlier the onset, the better the chance of recovery. Speech areas are comprised of the angular and opercular parts the inferior frontal gyrus (Broca's motor speech center), posterior part of the superior temporal gyrus (Wernicke's receptive speech center), and the fibers that connect these centers in the ipsilateral and contralateral hemisphere. The following disorders involve cognitive functions (prepositional features) of language in the dominant hemisphere (usually the left) hemisphere.

- Broca's (non-fluent, expressive, motor, verbal) aphasia (Figures 8.32 & 8.33) is seen in individuals with lesions of Broca's speech center (Brodmann's areas 44 and 45). This condition involves disorders of speech and written language. It is characterized by difficulty initiating or repeating words, restricted vocabulary and grammar, and labored and awkward speech with a tendency to delete adverbs and adjectives as well as connecting words (telegraphic speech). Although comprehension of the spoken and written language is usually preserved, writing is severely affected. Due to disruption of the ipsilateral corticospinal, corticobulbar and optic radiation, Broca's aphasia often is associated with right sided hemiplegia, supranuclear facial (lower facial palsy), and right sided homonymous hemianopsia. Tongue and lip movements are usually impaired. Involvement of the frontal eye field may result in conjugate deviation of both eyes to the left side.

- Wernicke's (receptive, fluent, sensory, syntactic, acoustic) aphasia results from destruction of the association cortex, that occupies the posterior portion of the superior temporal gyrus (Brodmann's area 22) of the dominant hemisphere (Figures 8.32 & 8.33). Since Wernicke's area integrates verbal memory, visual and sound patterns with the correct word phonemes that are essential elements for reading and writing, destruction of this area may impair the comprehension of spoken language, ability to read or write, and find appropriate words (circumlocution). Patients also exhibit enormous verbal output, and a tendency to enhance speech by irrelevant word substitution such as "fen for pen" known as verbal paraphasia. Sound transpositions (phonemic paraphasias) or substitution of phoneme (literal aphasia),

and increased rate and pressure of speech (logorrhea), as well as unwillingness to terminate speech may also be observed. Although the grammar of the spoken language is not correct, the free usage of a variety of tenses in an unusual combination gives the impression of a speech with proper syntax. For an examiner who does not speak the patient's language, observing any speech dysfunctions may not be an easy task. Since patients remain unaware of the deficit, their speech conveys little meaning. For example, patients with Wernicke's aphasia have trouble repeating statements.

Patients with Wernicke's aphasia may be labeled psychotic because of the similar nature of their speech to a thought disorder of frontal lobe origin. Patients may tend to develop a mania-like psychosis characterized by hyperactivity, rapid speech, euphoria or irritable mood. Some patients with Wernicke's aphasia may exhibit superior quadrantanopsia (one-fourth blindness), indicating involvement of the geniculo-calcarine pathway (Meyer's loop) as it courses through the temporal lobe. Individuals with Wernicke's aphasia may also exhibit a striking lack of concern (a finding that is not seen in individuals with Broca's aphasia) that may be replaced by paranoid behavior.

- Anomic (semantic, amnesic) aphasia (Figure 8.33) may occur at the end of Wernicke's aphasia or may be present as a distinct disorder. It is characterized by the inability to find words with relatively intact comprehension. Individuals with this condition do not exhibit paraphasia, but lack substantive words in the speech. It is associated with alexia and agraphia, and occasionally with right superior quadrantanopsia. It can be caused by an injury to the parieto-occipital cortex, which may extend to involve the angular gyrus in the left dominant hemisphere. This condition may be an early language disturbance detected with expanding brain tumors.

A lesion that disrupts the arcuate fasciculus connecting Wernicke's zone to Broca's speech center causes conduction (central) aphasia (Figure 8.33). The main deficit in this type of aphasia is the inability to repeat words, choose and sequence phonemes. Comprehension of silent reading remains intact, but the ability to read aloud is lost. Reading aloud requires intactness of the association visual cortex, splenium of the corpus callosum, angular gyrus, Wernicke's area, Broca's speech area, arcuate fasciculus, and the motor cortex. Patients clearly become aware of their language deficit, especially when they entangle a key word. Some degree of apraxia may also be observed in the limb and facial muscles.

- Transcortical aphasia (Figure 8.33) occurs as a result of compromise of the blood supply to the watershed areas surrounding the speech centers in the frontal and parietal

lobes. These areas are supplied by the middle, anterior, and posterior cerebral arteries.

- Transcortical sensory aphasia (isolated speech area syndrome) is a rare type of fluent aphasia which may result from a cerebrovascular accident in the watershed areas of the parieto-occipital cortex, and at the junctions of the middle, anterior, and posterior cerebral arteries. This vascular lesion disrupts the connection between Broca's and Wernicke's centers and other parts of the brain. Patients are unable to start conversation, and the response to a question generally contains confabulatory, automatic, irrelevant and repetitious paraphasia. Repetition may take the form of echoing (parrot-like), word phrases, and melodies (echolalia). Although reading and writing abilities are abolished, articulation of memorized materials remains intact.

- Transcortical motor (dynamic) aphasia (Figure 8.33) is a form of non-fluent aphasia (speech is reduced to less than 50 words per minute) in which repetition is unaffected, and the speech is grammatically accurate. Inability to initiate conversation is the primary deficit, although comprehension of sounds and written language remains functional. Anoxia or multiple infarctions that disrupts the connections of Broca's area to the rest of the frontal lobe may be responsible for this disorder.

- Transcortical motor and sensory aphasias are produced by lesions of the area surrounding the lateral cerebral fissure. Automatic repetition of words (echolalia) is the main speech-related function performed by these types of individuals.

- Global aphasia results from a lesion, which destroys Broca's and Wernicke's centers, and the connecting arcuate fasciculus. There is loss of ability to comprehend, articulate, read, write, and name a viewed object. It is usually associated with right homonymous hemianopsia, right hemiplegia, and right hemianesthesia.

- Aphemia (subcortical motor aphasia) is characterized by the inability to imitate, repeat or produce sounds, with preservation of the ability to read and write. Auditory comprehension and word finding also remain intact. This condition may result from destruction of the output from Broca's speech center.

- Subcortical sensory aphasia (pure word deafness) results from destruction of the primary auditory cortex and the transcallosal fibers that carry information from the non-dominant hemisphere. Since Heschl gyrus is damaged on the left (dominant) hemisphere and no sound is able to reach Wernicke's zone from the opposite hemisphere, comprehension and repetition of the spoken word are not possible.

- Alexia with agraphia is seen in individuals with a lesion involving the angular gyrus in the inferior parietal lobule. It is characterized by impairment of the ability to read and write, and inability to comprehend symbols and words. Comprehension of sounds and the ability to articulate are not affected. Due to the proximity of the angular gyrus to the temporal lobe, as well as other areas of the parietal lobe, additional deficits may also be seen including anomic aphasia, loss of right-left recognition and ability to identify fingers.

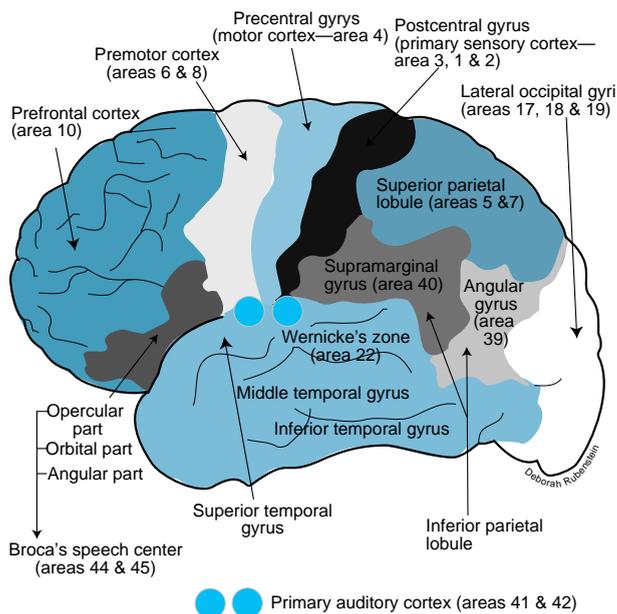


Figure 8.32 Prominent centers and gyri associated with the frontal, parietal, and temporal lobes. The Broca's speech center and Wernicke's zone are distinctly illustrated

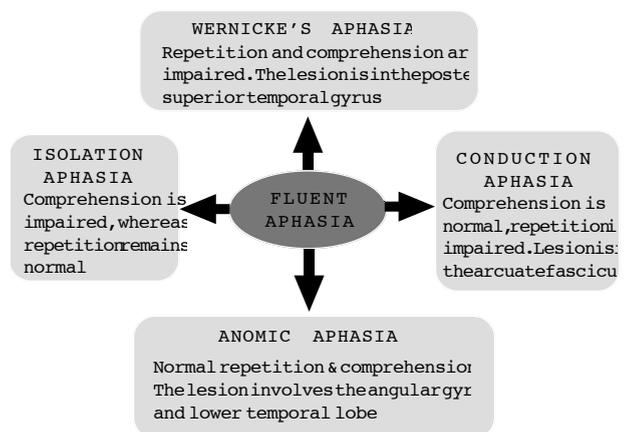


Figure 8.33 Schematic representation of various forms of fluent aphasia

- Pure alexia or alexia without agraphia (pure word blindness) is a rare condition that occurs as a result of disruption of the visual association cortex (Brodmann's areas 18 & 19) and the splenial fibers that convey visual information to the visual cortex and angular gyrus of the dominant hemisphere. It may be caused by occlusion of the left posterior cerebral artery. Patients exhibit right homonymous hemianopsia due to destruction of the left visual cortex. Disruption of the transcortical splenial fibers may result in the inability of patients to recognize words or letters, even their own. Since visually presented objects excite a variety of sensory systems in the mute hemisphere (tactile, taste, and olfactory) that are conveyed by the intact callosal fibers, naming these objects is possible. Generally, aphasics develop alexia because of the difficulty in comprehending the meaning of words, conversion of grapheme to phoneme (Wernicke's aphasia), or in formulating grammar (Broca's aphasia).
- Pure (aphasic) agraphia is a rare condition seen in individuals with lesions of the angular gyrus. Reading remains intact, but writing and spelling is severely affected. It may also be produced by a lesion of the motor association cortex of the frontal lobe.

- Disconnection syndromes, as discussed earlier, represent a constellation of deficits seen in complete transection of the corpus callosum. Patients with these syndromes may exhibit agraphia in the left hand, but not the right, as well as apraxia (ability to execute oral commands or perform familiar tasks is lost in the absence of sensory or motor deficits).
- Hemi-optic aphasia is characterized by the inability to name objects seen in the left visual field, while maintaining the ability to recognize these objects via the left hand which is guided by the right hemisphere. This syndrome is seen in individuals with bilateral epilepsy subsequent to surgical transection of the corpus.
- Tactile aphasia is a condition in which the patient is unable to identify objects placed in the left hand, but is able to do so when the object is placed in the right hand. As the right non-dominant hemisphere, which has lost its connection to the left hemisphere (due to disruption of the callosal fibers) is responsible for the recognition of an object; identification of an object placed in the left hand will not be possible.

through the carotid sulcus to the cavernous sinus. In this sinus (cavernous part), it reposes adjacent to the abducens, oculomotor, trochlear, ophthalmic, and maxillary nerves, giving rise to the cavernous, meningeal, and hypophysial arteries. As it leaves the sinus, it turns anteriorly, ventral to the optic nerve and dorsal to the oculomotor nerve. At this point (cerebral part), it gives rise to the ophthalmic, anterior cerebral, middle cerebral, posterior communicating, and anterior choroidal arteries.

The cavernous and the cerebral parts of the internal carotid artery are collectively known as the carotid siphon (Figure 8.34 & 8.36). Occlusion of one or both internal carotid arteries (at the level of carotid siphon) activates the collateral circulation between the meningeal branches of the external and the internal carotid arteries. Collateral circulation also develops between branches of the lenticulostriate arteries. As a result of this anastomosis one cerebral hemisphere is supplied with blood through a network of vessels (transdural anastomosis) resembling the "rete mirabile" of lower mammals. This anastomosis may be detected in Moya-Moya syndrome via angiography as a puff of smoke.

Many arterial branches arise from the cerebral part of the internal carotid artery, including the ophthalmic, anterior cerebral, middle cerebral, anterior choroidal, and the posterior communicating arteries. As the first branch of the internal carotid artery, the ophthalmic artery pierces the optic nerve and supplies the four quadrants of the retina through its central retinal branch (an end artery that lacks

any anastomosis), and the choroid and the sclera via the ciliary branches. It also supplies the orbit, nasal cavity, ethmoidal sinuses, dura mater, and the scalp (Figure 8.35).

One of the terminal branches of the internal carotid artery is the anterior cerebral artery (ACA) that runs above the corpus callosum, coursing on the medial surface of the brain (Figures 8.34, 8.35, 8.37, 8.38, 8.39 & 8.42). It is connected to the corresponding artery of the opposite side via the anterior communicating artery. It supplies the medial surface of the brain hemisphere, including the cingulate, medial frontal gyrus, upper parts of the precentral and postcentral gyri, and the paracentral lobule. Orbital and frontopolar branches supply the orbitofrontal cortex, and the rostral and medial parts of the frontal lobe, respectively. Within the cingulate sulcus, the cingulate branch makes its appearance, supplying the corresponding gyrus. Additionally, the callosomarginal branch supplies the paracentral lobule, whereas the pericallosal artery, a terminal branch of the anterior cerebral artery, supplies the precuneus, assuming a typical "sausage" configuration in syphilitic endarteritis. There are smaller, yet important branches that arise from the ACA such as the medial striate (recurrent artery of Heubner) which supplies head of the caudate nucleus, putamen, and anterior limb of the internal capsule. The latter branch is absent in about 3% of the population.

Most of the lateral surface of the brain is supplied by branches of the middle cerebral artery (Figures 8.34, 8.35, 8.38, 8.39 & 8.40) which travels in the lateral cerebral

- Aprosodia is a condition in which the affective component of language, such as musical rhythm, facial expression, and comprehension of these gestures is lost or impaired. These disturbances accompany lesions of the non-dominant hemisphere (usually the right). A lesion that involves the inferior frontal gyrus of the right hemisphere (mirror image of Broca's area) produces a speech which is monotonous, a gestural (lacks gestures), and lacks melody, timing, and other affective content (motor aprosodia). These individuals tend to have difficulty in conveying tune, singing, and understanding emotional reactions. They exhibit hemiplegia and lower facial palsy on the left side. A lesion, which destroys the

posterior part of the superior temporal gyrus in the right hemisphere (mirror image of the Wernicke's zone), may result in the inability to recognize and comprehend the emotional content of the spoken language (sensory aprosodia). The emotional gestures produced will not be appropriate for the occasion or the content of the speech.

- Alexithymia, frequently seen in patients with psychosomatic disorders, is characterized by the inability to express emotion through words. Disruption of the connection between the affective (right) hemisphere and the expressive left hemisphere may account for this deficit.

Apraxia is a disorder characterized by the inability to execute, learned voluntary functions without any detectable motor or sensory deficits, mental disability or comprehension deficits. It is classified into kinetic, ideomotor, parietal, callosal, sympathetic, Ideational, constructional, and Bucco-facial apraxia.

- Kinetic apraxia is characterized by the inability to perform fine, skilled movements in one extremity, often due to a lesion of the contralateral primary motor cortex (Brodmann's area 4).

- Ideomotor apraxia is a disorder in which patients exhibit an inability to perform a given task upon command, despite retaining aptness to execute acts automatically such as opening or closing the eyes. This deficit may be categorized into parietal, callosal, and sympathetic apraxia.

- Parietal apraxia is due to destruction of the arcuate fasciculus that establishes connection between the motor centers in the frontal lobe and the centers that formulate motor activities in the parietal lobe. This form of apraxia is bilateral and may be associated with conduction aphasia.

- Callosal apraxia, as the name indicates, is produced by disruption of the genu of the corpus callosum that connects the premotor areas of both hemispheres. Thus, information generated in the upper extremity area of the premotor cortex of the left frontal lobe would not reach the corresponding area of the right frontal lobe. Since

motor activity is conveyed via the corticospinal tract (which is crossed), this deficit will be seen in the left arm.

- Sympathetic apraxia is another form of ideomotor apraxia, resulting from damage to the premotor area of the left frontal lobe, an area adjacent to Broca's speech center. As discussed earlier, the premotor area of the left lobe provides motor commands to the corresponding area on the right side via the corpus callosum. Since the corticospinal tract is partly derived from the premotor area, the generated motor impulses will be conveyed to the spinal levels on the contralateral side. Therefore, destruction of the left premotor area produces a paralyzed right limb and an apractic left limb (in sympathy for the affected right limb). Patients with this lesion may also exhibit similar deficits in the buccofacial muscles, and possible aphasia due to proximity of the lesion to Broca's center in the left hemisphere.

- Ideational apraxia is characterized by the inability to perform a complex task or series of acts in a purposeful manner and in a proper sequence. It is caused by a lesion in the parietal lobe of the dominant hemisphere or as a result of a diffuse brain disorder (dementia). It stems from the loss of ability to appreciate and formulate the idea necessary to carry out a complex task, although individual acts within the task can be executed without any difficulty.

Agnosia refers to the failure to recognize and understand the symbolic significance of sensory stimuli, despite the presence of the learned skill, intactness of the sensory receptors and pathways, and the absence of mental disorders or dementia. This deficit is commonly associated with disruption of the connection of the primary, secondary or tertiary sensory cortices with the association cortical areas that store memories for the stimulus. Agnosias are classified into visual, auditory and tactile agnosia, simultanagnosia, anosognosia, Babinski's agnosia, reduplicative par-amnesia, asymbolia, and apractognosia.

- Visual agnosia is the inability to recognize objects by vision, while retaining the capability to identify the same objects with other sensory modalities. Individuals with this condition do not have defects in the visual apparatus or pathway, and can recognize people. This disability may change in severity from time to time. Lesions are generally confined to the visual association cortex of the temporal and parietal lobes and the connecting fibers to this cortex. Visual agnosia, a primary characteristic of Klüver Bucy syndrome, may take the form of alexia, protopagnosia, facial and finger agnosia, graphagnosia, color, auditory, and tactile agnosia.
- Alexia is a form of visual agnosia that is characterized by the inability to read as a consequence of failure to recognize the written words.
- Protopagnosia is a disability, resulting from bilateral destruction of the occipito-temporal gyri. Patients with this condition are unable to identify familiar people, or they may identify them as impostors (Capgras syndrome), or as strangers (Reverse Fergoli syndrome), or as strangers mistaken for familiar people (Fergoli syndrome). Patients also are unable to identify familiar objects removed from their common visual context.
- Facial agnosia is the inability to identify people by their faces, although identification of these individuals is possible via their voice, demeanor, or dress.
- Finger agnosia (anomia) is a deficit characterized by the incapacity to identify and name fingers. This dysfunction is often seen in Gertsman syndrome, and is associated with anarithmetria (loss of arithmetic concept), agraphia or dysgraphia, and left-right disorientation of the body parts and objects. This syndrome is a combination of agnosia and apraxia, and is produced by a lesion of the

angular and supramarginal gyri of the dominant cerebral hemisphere.

- Graphagnosia refers to the inability to recognize letters or numbers written on the palm.
- Color agnosia refers to inability to identify the color of an object, despite retaining the capacity to match cards of different colors. It is not a sex-linked deficit and lesions commonly affect the inferomedial parts of the occipital and temporal lobes. Patients with this deficit do not have color blindness.
- Auditory agnosia occurs as a result of bilateral or unilateral destruction of the Wernicke's zone in the dominant hemisphere, and is characterized by the inability to recognize familiar sounds with no detectable deficits in the auditory system or pathway.
- Tactile agnosia is characterized by the inability to recognize objects through touch without impairment of the tactile receptors, spinal nerves, or ascending sensory pathways. The primary lesion is in the supramarginal gyrus of the dominant hemisphere (left), and to a lesser degree in the postcentral gyrus. Astereognosis refers to the loss of ability to recognize the texture, form and shape of an object by tactile sensation (e.g. inability to recognize a coin placed in the palm of the hand).
- Simultanagnosia (spelling dyslexia) refers to the inability to recognize sensory stimuli received simultaneously and the inability to read except for the shortest words. This condition is a manifestation of a lesion of Brodmann's area 18, or dysfunctions in scanning of the visual images. It may be associated with visual deficits.
- Anosognosia (asomatognosia), an important part of "hemispatial neglect", is characterized by indifference to or rationalization of the symptoms, or denial of an illness of serious nature. Patients appear inattentive and experience allocheira, which refers to an individual's experience of a stimulus, applied to one side of the body and being felt on the opposite side. Allocheira results from lesion of the superior parietal lobule of the right (non-dominant) hemisphere.
- Babinski's agnosia refers to the neglect or even the denial of existence of a paralyzed limb in a paralytic patient.

Dementia refers to a progressive, diffuse, and multifocal decline in the intellectual and cognitive abilities that impairs daily functioning in the presence of normal consciousness. These include loss of memory accompanied by dysfunction in at least one other mental function such as memory, language, emotion or behavior and cognition (judgement, abstract thinking, etc.) This may be classified into cortical and subcortical dementia.

- Cortical dementia may be seen in Alzheimer's disease (discussed in [Chapter 16](#)) which accounts for approximately fifty percent of cases of dementia. Cortical dementia also occurs in multiple sclerosis (discussed in [Chapter I](#)), normal pressure hydrocephalus (discussed later in this chapter), Pick's disease, neurosyphilis, Lyme disease, subacute sclerosing panencephalitis, Jakob-Creutzfeld disease, and in individuals with frontal and temporo-parietal lobe lesions.

- Pick's disease (lobar atrophy or sclerosis) is an extremely rare condition that shows severe signs of frontal or temporal lobe dysfunctions. It is a slowly progressing disease that initially manifests behavioral disorders, lack of insight, and poor mental functions. These are followed by loss of retentive memory, language impairment, and appearance of primitive reflexes such as grasp and sucking reflexes. Dementia in this disease has a slow presenile course that resembles Alzheimer's dementia.

- In neurosyphilis, which is caused by the spirochete *Treponema pallidum*, dementia develops as a result of brain infection and is seen as a late manifestation. It may be preceded by amnesia and certain personality changes. Patients with syphilitic dementia may also exhibit paresis, dysarthria, tremor, Argyll-Robertson pupils, and locomotor ataxia.

- Dementia (pugilistica) may also occur as a result of repeated head trauma or cerebral concussions in professional boxers "punch-drunk state". Cortical dementia is manifested in the inability to recall events, but patients remain conscious and fully aware of their intellectual dysfunction.

- Lyme disease, which is caused by the spirochete *Borrelia burgdorferi*, may manifest dementia in the second stage of the disease weeks or months after the onset of infection. Dementia may be detected in association with sleep and emotional disorders, slowing of memory, irritability, facial nerve palsy, and some degree of poor concentration.

- Cortical dementia may also occur in subacute sclerosing panencephalitis (SSPE), a particularly fatal disease that affects children and young adults before the age of 20, months or years after measles attack. The probable etiology

is altered rubeola virus. It initially manifests mood disorders, insomnia, hallucinations, lack of concentration, which is eventually followed by myoclonic jerks, and dementia. Patients may also exhibit choreiform movements, rigidity, dysphagia, and cortical blindness.

- Jakob-Creutzfeld disease is a progressive neurodegenerative condition that manifests as cortical dementia, and commonly assumes sporadic or familial forms. In the sporadic form, the transmission of the disease may occur as a result of contaminated neurosurgical instruments, injection of human growth hormone, infected corneal transplant, and handling of cadaveric dura mater. Patients with the sporadic form may also show elevated levels of brain protein known as 14-3-3 in the cerebrospinal fluid. Myoclonic jerking, and periodic EEG complexes (sharp wave pattern superimposed on the slow background rhythm) accompany dementia. Patients may also develop a sleep disorder, ataxia, hemiparesis, aphasia, and hemianopsia. The familial form is thought to be an autosomal dominant inheritance condition with point mutations, deletions, or insertions in the coding sequence of the gene for PrP on the short arm of chromosome 20. The most common mutation that produces the clinical picture of this form of the disease is at codon 200. It has an earlier onset and its course is more protracted. The EEG changes are often missing and the 14-3-3 protein is not detected in the cerebrospinal fluid, as is the case with the sporadic form. Different phenotypic manifestations may develop as a result of these mutations. Some may exhibit cerebellar ataxia, spastic paresis, and dementia at a later stage. Progressive insomnia, dementia, and dysautonomia that prove to be fatal, may also be seen in association with mutation in the gene for PrP in this form of the disease.

- Subcortical dementia, which is associated with lesions of the brainstem, cerebellum, or basal nuclei, may be observed in individuals with Parkinson's and Huntington's diseases (which are described with the Extrapyramidal System in [Chapter 21](#)), AIDS patients, and in progressive supranuclear palsy. In this type of dementia speech dysfunction, motor deficits, and generalized slowing of cognitive function (mental akinesia) are prominent.

- AIDS dementia occurs in the late stages of the disease subsequent to meningitis and encephalitis, whereas progressive supranuclear palsy also known as 'stele-Richardson-Olszewski syndrome' exhibits parkinsonian manifestations including impairment of voluntary eye movements, prolongation of thought processes, irritability, and apathy.

Seizures are irregular, brief, sudden, and excessive and repeated activation and depolarization of neurons within the brain that produce hypersynchrony, where large cell group fires together, creating an electrical storm. The location of neuronal activity and the length of activation determine the eventual manifestations, including disturbance of sensation and consciousness, convulsive motor activity, behavior, or some combination of these disorders. Increased neuronal excitability may lead to neuronal synchrony and recruitment as well as accumulation of extracellular potassium or decline of postsynaptic GABAergic inhibition. Seizures are viewed in two categories: partial and generalized.

- Partial seizures manifest abnormal movements or sensations and/or stereotyped behavioral patterns on one side. These focal seizures result from localized lesions such as scars, tumors or arteriovenous malformations, head trauma, infection, prenatal injury, fever, hypo/hyperglycemia, stroke, alcohol withdrawal, or congenital or metabolic disorders. They either remain localized or spread to adjacent cortical areas depending on the extent of glutamate mediated excitation combined with the decrease in GABAergic inhibition. Partial seizures are classified into simple and complex partial seizures.

- A simple partial seizure is characterized by the relative localization of the abnormal discharge in the brain, usually to one hemisphere. It may arise from activation of foci in the primary motor, premotor, supplementary motor, or prefrontal cortices. Auras are very common and may be the only manifestation in this condition. It may involve the motor, sensory, and autonomic systems, and consciousness usually remains unaffected. Partial motor seizure may be manifested in turning the head and eyes to the contralateral side. Jacksonian "march" seizure is a motor seizure in which rhythmic and clonic twitching starts on the contralateral hand and "marches" up the arm, to the face, and down the leg in seconds and the patient commonly becomes unconscious. However, it may be localized and may affect the foot, thumb, or mouth angle on the contralateral side.

- Partial sensory seizure is associated with variety of sensations depending upon the selective involvement of certain parts of the sensory homunculus. These sensations may include epigastric rising sensation, tingling in the lips, fingers, or toes that spreads to adjacent areas. It may also be associated with vertigo, olfactory hallucinations, or visual disorders such as sensations of darkness and light flashes.

- Complex partial seizure occurs infrequently and irregularly, and is marked by impaired but not loss of consciousness, exhibiting widely varied clinical characteristics. Automatic behaviors such as chewing, lip

smacking, fumbling with clothes, scratching genitalia, thrashing of arms or legs, or loss of postural tone may be seen in the complex partial seizure. "Aura" may precede this type of seizure. Dyscognitive states, which include increased familiarity (deja vu) or unfamiliarity (jamais vu), autonomic responses, exhaustion, and illusions, may also be observed. However, these disorders are often more indicative of anxiety attacks than seizures.

- Generalized seizures, which result from involvement of both cerebral hemispheres (mostly with no apparent structural damage), are inherited for the most part. Many of the generalized seizures begin during childhood or adolescence. The two main categories of generalized seizures are the convulsive and non-convulsive forms. The common convulsive type is the tonic-clonic (formerly known as grand mal) seizure, whereas the non-convulsive forms include absence seizures (petit mal). Convulsive type may also include less common varieties such as purely tonic, atonic or clonic generalized seizure. Non-convulsive seizures also encompass atypical absence seizures. In summary, convulsive generalized seizures include tonic-clonic seizures, status epilepticus, tonic, atonic and clonic seizures.

- The tonic-clonic seizures (grand mal epilepsy) occur in 4-10% of all cases of epilepsy and is viewed in two types: a) awakening clonic-tonic-clonic seizures, which are provoked by sleep deprivation, excessive fatigue, and alcohol consumption; b) tonic clonic seizures, which occur both during sleep and wake periods, and maintains better remission rate following drug therapy than the first type. In general, patients with tonic-clonic seizures may or may not sense the approach of convulsions (prodrome phase) in the forms of apathy or ecstasy, movement of the head, abdominal pain, headache, palor or redness of the face, or unusual sensations. These experiences (aura) that last for few seconds, may represent an impending simple partial seizure. In the ictal phase (lasts 10-30 seconds), sudden loss of consciousness and fall to the ground, a brief period of flexion of the trunk and elbow, followed by a longer extension of the back and neck, jaw clamping, and stiffness of the limbs may occur. Suspension of breathing, dilatation of the pupil, cyanosis, and possible urinary incontinence are also observed. This tonic stage is followed by a clonic phase in which mild generalized tremor is followed by violent flexor spasm, facial grimaces and tongue biting. At this stage increase of blood pressure, pulse rate; salivary secretion, and sweating occur.

When the clonic phase terminates, movements cease, and the patient remains apneic, lethargic, confused, and often falls asleep (postictal phase). The EEG shows characteristic initial desynchronization, lasting for few

seconds, followed by a 10-second period of 10Hz spikes. In the clonic phase, the spikes become mixed with slow waves and then the EEG shows a polyspike-and-wave pattern. The EEG tracing becomes nearly flat when all movements have ceased.

Status epilepticus refers to the condition in which seizures last longer than 30 minutes or follow one another in a rapid fashion that a new wave of seizures begins before the previous one has ceased, with no recovery of consciousness or behavioral function. This condition is commonly caused by abrupt withdrawal of anticonvulsant medications, high fever, metabolic disorder, or cerebral lesions. There are two types of status epilepticus: convulsive and non-convulsive. Non-convulsive type affects behavior but does not produce tonic or clonic movements, which may be evident in the continuous lethargic and clouded state that a patient experiences with a prolonged absence seizure or a series of complex partial seizures. The convulsive type may be life threatening and may be fatal due to the sequence of events that may include circulatory collapse and hyperthermia.

Repeated nature of epileptic seizures may be explained experimentally on the basis of kindling theory. Induction of seizure activity in experimental animals increases in intensity subsequent to the increase in stimulus repetitions. Therefore, an intense seizure can be produced, after long period (months), by the application of relatively mild electrical stimulus. It has been suggested that prolonged electrical stimulation trigger a series of events in neural circuitry that enables repeated seizure activity to be produced by an appropriate stimulus. This theory may be similar to long-term potentiation (LTP) in which a brief period of intense activity may elicit a persistent change in the synaptic property of the neuron.

- Tonic seizures are characterized by sudden bilateral tonic (stiffening) muscle contractions of the entire body, accompanied by altered consciousness, without being followed by a clonic phase. They are brief and range from a few seconds to a minute and occur more commonly during sleep. This condition is usually caused by cerebral lesion and can occur at any age.
- Atonic seizures exhibit several forms, but classically, it is characterized by loss of postural muscle tone and responsiveness, and fall of the patient to the ground. Loss of muscle tone may be less severe, producing nodding of the head or drooping of the eyelids. These seizures occur at any age as brief episodes with sudden onset followed by immediate recovery.
- Clonic seizures are characterized by generalized clonic (jerking) movements that are not preceded by a tonic phase. These movements are often asymmetric and

irregular, and although rare, they usually occur in children.

- Non-convulsive generalized seizures comprise both absence and atypical absence seizures.
- Absence seizures are brief episodes (2-15 seconds) of staring (simple absence), accompanied by impairment of awareness and responsiveness. During the episode patients may stop talking or responding briefly. In a more complex absence seizure blinking or synchronized mouth or hand movements accompany the staring episode. They occur suddenly and leave the patient postictally alert and responsive. These seizures may be so brief that patients themselves are sometimes unaware of them and to the observer it appears as a moment of absent-mindedness or day dreaming. They usually begin between the age of 4 and 14, and often resolve by the age of 18. Approximately fifty percent of individuals with this type of seizure develop generalized tonic-clonic convulsions by the end of the second decade.
- Atypical absence seizures usually start and end gradually. They are not produced by hyperventilation, often last more than ten seconds, and like the typical absence, they also begin at an early age. In contrast to the typical absence seizures, these episodes are often seen in individuals with mental retardation and other neurologic disorders. In this condition, staring is accompanied by partial diminution in responsiveness (i.e. able to respond to questions and remember events). Blinking or jerking movements and tonic or atonic seizures may also occur.

fissure and across the insular cortex. These areas of distribution include the precentral, postcentral, angular, supramarginal, superior temporal, middle frontal, and the inferior frontal gyri, as well as the transverse gyri of Heschl. Numerous branches arise from this artery including the anterior temporal, orbitofrontal, prerolandic, rolandic, anterior and posterior parietal, angular, posterior temporal, and lenticulostriate branches. Brodmann's area 8 (frontal eye field) which controls horizontal saccadic eye movements toward the contralateral visual field, lies within the vascular domain of the ascending frontal branch "candelabra" of this artery, a branch formed by contribution of the prerolandic, rolandic and the anterior parietal branches. The middle cerebral artery also gives off the lateral striate (lenticulostriate or Charcot's artery of cerebral hemorrhage), and possibly the medial striate artery which enters the anterior perforated substance and supply the globus pallidus, putamen, the anterior limb of the internal capsule.

In addition to cerebral branches, the internal carotid artery gives rise to the anterior choroidal artery (Figure 8.35) which supplies the choroid plexus of the inferior horn of the lateral ventricle, hippocampal and dentate gyri, internal capsule, and the optic tract.

Another vessel that arise from the internal carotid artery and contribute to the arterial circle of Willis is the posterior communicating artery, which provides blood supply to the hypothalamus, optic tract, and tuber cinereum. It runs superior to the oculomotor nerve, a relationship that bears clinical significance. An aneurysm that develops in this artery may produce signs of oculomotor palsy (see cranial nerves-Chapter 11).

The posterior cerebral arteries (Figures 8.37, 8.39 & 8.41) which commonly emanate from the basilar artery also supply the brain hemispheres. However, in 25% of individuals one of the posterior cerebral arteries may arise from the internal carotid artery, replacing the posterior communicating branch. In 5% of individuals the posterior cerebral arteries on both sides gain origin from the internal carotid arteries.

After providing blood to the midbrain and portions of the occipital and temporal lobes, the posterior cerebral artery divides into posterior temporal and internal occipital branches. The latter branch gives rise to the calcarine and parieto-occipital arteries. The calcarine artery runs within the calcarine fissure and supplies the primary visual cortex, establishing anastomosis with the middle cerebral artery. Aside from its distribution to the cuneus and precuneus, the parieto-occipital branch of the also supplies the splenium of the corpus callosum (Figures 8.15 & 8.16). There are additional branches from the posterior cerebral artery including the thalamogeniculate and thalamoperforating arteries that supply the thalamus. Macular sparing in individuals with cerebrovascular

Wada test, in which sodium amobarbital is injected into each internal carotid artery, may be utilized to establish dominance of the cerebral hemisphere. Brief aphasia, which accompanies injection into the internal carotid artery, may determine the dominant hemisphere.

accident involving either the middle or posterior cerebral arteries may be attributed to the rich vascular anastomosis around the occipital pole between these two vessels.

Venous drainage of the cerebral hemispheres

Venous drainage of the brain is maintained by superficial and deep cerebral veins. The superficial set of veins (Figure 8.43 & 8.44) include the superior and inferior cerebral, superficial middle cerebral, and the anastomotic (connecting) veins. Venous blood from the superior, upper lateral and medial surfaces of the cerebral hemispheres is drained via numerous superior cerebral veins that open into the superior sagittal sinus.

It is extremely significant to note that the anterior group of superior cerebral veins open at a right angle to the superior sagittal sinus while the posterior group assumes a more oblique direction and against the current created by the blood in the dural sinuses. The inferior cerebral veins drain the orbital, frontal, and temporal gyri and open into the transverse sinus or the cavernous sinus, whereas the superficial middle cerebral vein runs across the lateral cerebral fissure to open into the cavernous or sphenoparietal sinus, draining the area around the lateral fissure. Two anastomotic veins interconnect the above mentioned superficial cerebral veins.

These connecting veins are comprised of the superior anastomotic vein of Trolard connecting the superior cerebral and superficial middle cerebral veins to the superior sagittal sinus, and the inferior anastomotic vein of Labbe that connects the middle cerebral vein to the transverse sinus.

Examination of the deep cerebral veins (Figures 8.43, 8.44, 8.45, 8.46 & 8.47) reveals the internal cerebral veins, great cerebral vein of Galen, basal and the occipital veins. Near the foramen of Monro, the internal cerebral vein, is formed by the choroidal, septal, epithalamic, lateral ventricular, and thalamostriate veins. Each internal cerebral vein runs medial to the thalamus on the dorsal aspect of the third ventricle, courses inferior to the splenium of corpus callosum.

- The choroidal vein drains the venous blood of the hippocampal gyrus, fornix, corpus callosum, and the choroid plexus of the lateral ventricle.
- The septal vein drains the septum pellucidum and corpus callosum.

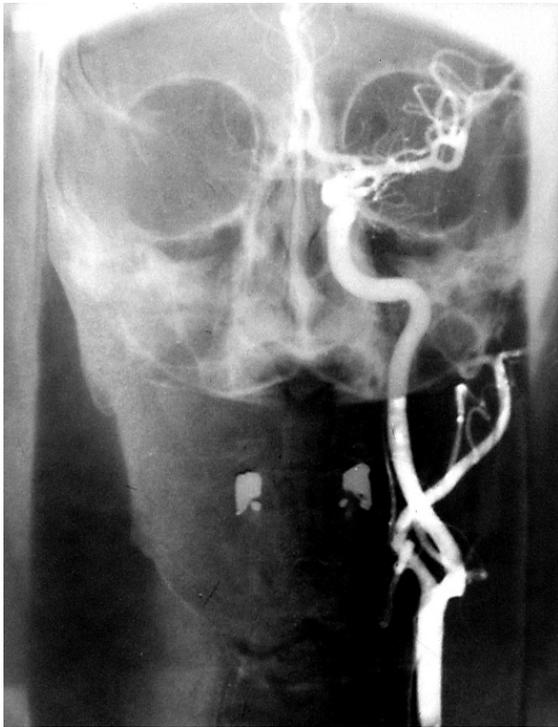


Figure 8.34 Anteroposterior arteriogram showing the common carotid artery, and various parts of the internal carotid artery and its branches. The course of the internal carotid artery within the carotid sheath, petrous temporal bone, and cavernous sinus are illustrated

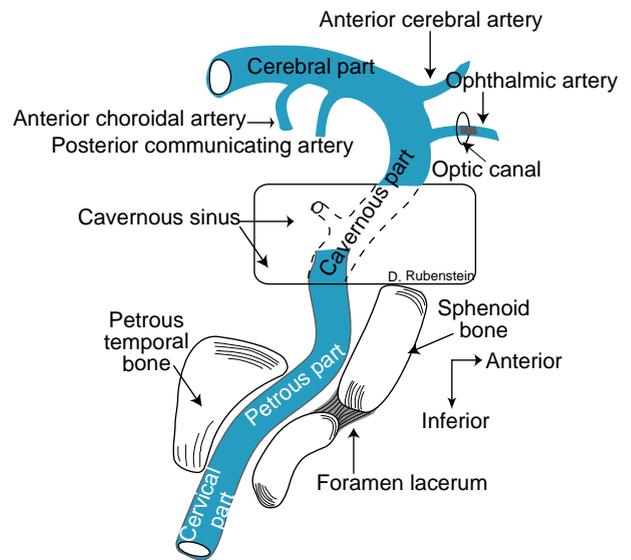


Figure 8.35 In this schematic drawing the course of the internal carotid artery and principle branches are indicated

into the straight sinus at the junction of the tentorium cerebelli and the falx cerebri. At this site, it receives the occipital, posterior callosal veins, and the basal vein of Rosenthal.

The occipital vein drains the venous blood of the occipital and the temporal lobes, whereas

The posterior callosal vein carries the venous blood from the caudal portion of the corpus callosum to the great cerebral vein of Galen. Near the anterior perforated substance, the basal vein (of Rosenthal) is formed by contributions from the deep middle cerebral, anterior cerebral, inferior striate, and occipital veins.

- The deep middle cerebral vein drains the insular cortex and follows the lateral cerebral sulcus.
- The anterior cerebral vein drains the medial surface of brain accompanied by the anterior cerebral artery.
- The inferior striate vein exits from the anterior perforated substance and drains the inferior surface of striatum.

Meninges

The brain is enveloped by the meninges that form coverings for the brain, contribute to the formation of the dural sinuses, brain barriers, and the cerebrospinal fluid. These coverings send partitions that separate the cerebral hemispheres from each other and from the cerebellum and the brainstem. Meninges consist of the dura mater (pachymeninx), the arachnoid and pia mater (leptomeninges). Since meninges continue with the epineurium and perineurium of peripheral nerves, meningitis may produce irritation of the meninges around the brain, spinal cord, and peripheral nerves.

The dura mater (Latin for tough mother), a collagenous membrane which covers the brain and spinal cord. It

Vascular disorders are occlusive in nature, in which the dysfunction is a sequel to ischemia or hemorrhage. Cerebral emboli may occur at anytime, but it is especially common during daytime. They may originate from the pulmonary veins, cardiac valves or chambers, and from plaques in the aortic arch or its branches. Ulceration and occlusion increase the likelihood of stenosis in the affected vessels.

- The epithalamic vein receives venous blood from the habenula and pineal gland.
- The lateral ventricular vein receives venous tributaries from the caudal thalamus, parahippocampal gyrus, and the lateral ventricle.
- The thalamostriate (terminal) vein courses caudally between the caudate nucleus and thalamus, draining both these structures.

The great cerebral vein of Galen (Figures 8.43, 8.44, 8.45, 8.46 & 8.47) is formed caudal to the pineal gland by the union of the two internal cerebral veins. This vein is located inferior to the splenium and within the cisterna ambiens (a dilatation of the subarachnoid space superior to the cerebellum). It joins the inferior sagittal sinus to open

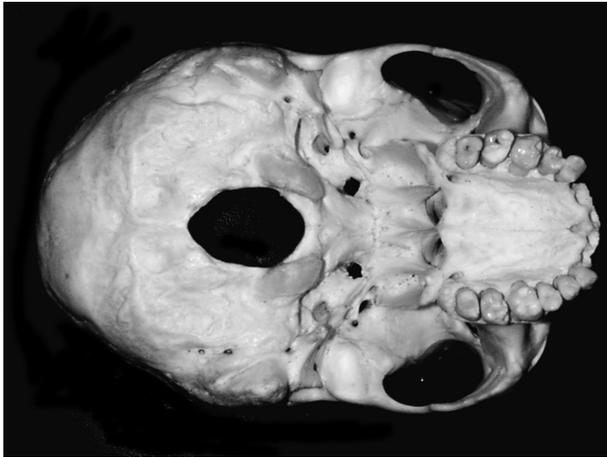


Figure 8.36 Inferior surface of the cranial base. The carotid canal and foramen lacerum are illustrated

consists of meningeal and endosteal layers (Figure 8.52). At certain locations, the gap between these two layers results in the formation of the dural sinuses. This layer is the most sensitive of all meninges to painful stimuli. Dural innervation within the anterior cranial fossa is maintained by the meningeal branches of the ophthalmic and maxillary nerves. The meningeal branches of maxillary nerve also contribute to the innervation of the dura mater in the middle cranial fossa. Within the posterior cranial fossa, the dura is supplied by the meningeal branches of the upper cervical spinal nerves. A recurrent branch of the ophthalmic nerve supplies the tentorium cerebelli. In the same manner the blood supply of the dura mater is secured by branches of the ophthalmic and middle meningeal arteries in the anterior cranial fossa. Dura of the middle cranial fossa is supplied by the middle meningeal, accessory meningeal, ascending pharyngeal, and lacrimal arteries. Whereas the meningeal branches of the occipital, vertebral, and the ascending pharyngeal arteries provide blood supply to the dura in the posterior cranial fossa. Dural sinuses and eventually the internal jugular vein receive the venous blood of the dura mater .

Epidural and subdural spaces, which lie superficial and deep to the dura mater, respectively, may be the sites of hematoma that produce serious manifestations. The clinical aspects of epidural and subdural hematomas are discussed below in detail.

Extensions of the dura mater divide the cerebral, separating the cerebellar hemispheres from each other and from the brain. It also forms a covering of the diaphragma sella, a covering of the pituitary gland in the hypophysial fossa. These dural partition include the falx cerebri, tentorium cerebelli, and falx cerebelli.

- The falx cerebri (Figure 8.45) is a dural partition which arches over the corpus callosum, extending between the two cerebral hemispheres. It stretches from the crista galli

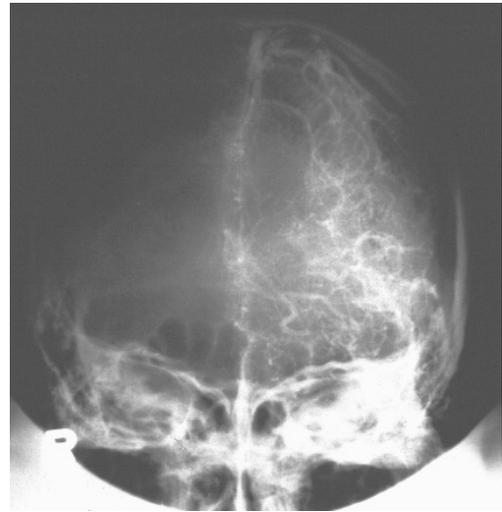


Figure 8.37 This angiogram of an individual with Moya-Moya syndrome illustrates the site of transdural anastomosis

Moya-Moya syndrome (Figure 8.37), a rare condition which is seen particularly in children and young adults and commonly in females. It was originally described in Japan and later in the west in individuals suffering from occlusive or stenotic diseases of the major branches of the arterial circle of Willis, and in association with neurofibromatosis, Sickle cell anemia, retinitis pigmentosa, Down's syndrome, and fanconi's anemia. Individuals with this condition exhibit convulsions associated with subarachnoid hemorrhage, alternating hemiplegia, and other variable neurological disorders. Ischemic events are commonly observed in the younger individuals, whereas subarachnoid or cerebral hemorrhage may be seen in the adults.

of the ethmoid bone, rostrally to the tentorium cerebelli, caudally. Along attachment of its superior border to the superior sagittal sulcus lies the superior sagittal sinus. This partition has a free inferior border that contains the inferior sagittal sinus.

- The tentorium cerebelli (Figure 8.45 & 8.47) occupies the space between the occipital lobes of the brain and the cerebellum. It contains the transverse sinus in its attached border, and the straight sinus at its junction with the falx cerebri (Figure 8.45). Both the great cerebral vein of Galen and the inferior sagittal sinus drain into the straight (rectus) sinus. Rostrally, the tentorium forms the tentorial notch, which allows the brainstem to pass through and join the diencephalon. This dural extension produces supratentorial and infratentorial compartments, respectively. In the supratentorial compartment lies the occipital lobes and diencephalon, whereas in the



Figure 8.38 Another angiogram of the internal carotid artery showing branches of the middle and anterior cerebral arteries. A branch of the posterior circulation (posterior cerebral artery) is also shown

infratentorial compartment the cerebellum and part of the brainstem are lodged.

- The falx cerebelli is a sickle-shaped dural partition, located in the posterior cerebellar notch, separating the cerebellar hemispheres. It attaches posteriorly to the occipital crest, extending from the internal occipital protuberance to the foramen magnum, containing the occipital sinus.

Dural sinuses

Dural sinuses (Figures 8.43, 8.45, 8.47, 8.55, 8.56 & 8.57) are valveless venous channels, which are devoid of muscular tissue and are commonly located between the meningeal and endosteal layers of the dura mater. These sinuses, which drain intracranial structures, are classified into postero-superior and antero-inferior groups. The postero-superior group includes the superior and inferior sagittal sinuses, straight sinuses, confluence of sinuses,

Tumors of the temporal lobe may display the middle cerebral artery upward. Also, an interesting correlation exists between the extensive area of distribution of this artery and the increase in the vulnerability to infection. Lacunar infarcts and possible death due to rupture of the lenticulostriate artery may occur in hypertensive individuals. However, these lacunar infarcts do not usually cause headache, and transient ischemic attacks, prior to the infarction, are infrequent.



Figure 8.39 In this angiogram branches of the internal carotid artery, branches of the middle cerebral artery are shown. Some branches of the posterior circulation are also visible

transverse (lateral) sinuses, sigmoid sinuses, and the occipital sinus. Other sinuses such as the sphenoparietal, cavernous, intercavernous, and the superior and inferior petrosal sinuses, form the antero-inferior group.

Posterosuperior group of dural sinuses

The superior sagittal sinus (Figures 8.43, 8.44, 8.45, 8.54 & 8.55) runs in the inner surface of the frontal bone from the crista galli, where it is connected to the emissary veins and to the veins of the nasal cavity, to the internal occipital protuberance, where it continues with the right transverse sinus. The connection to the nasal cavity is usually maintained via the foramen 'cecum' if it is patent, The dilated posterior extremity of this sinus continues with the confluence of the sinuses. The superior sagittal sinus occupies the upper border of falx cerebri and receives the diploic veins, arachnoid villi, and the superior cerebral veins. The superior sagittal sinus receives venous lacunae, parietal emissary veins, and superior cerebral veins.

- Venous lacunae are irregular venous pockets located on each side of the superior sagittal sinus, which receive the meningeal veins and the arachnoid granulations. They also communicate with each other as well as with the superior sagittal sinus.

- Emissary veins are small veins, which pierce the skull, establishing a connection between dural sinuses (e.g. superior sagittal sinus) and the extra-cranial veins. They

When the posterior cerebral arteries are derived from the internal carotid artery, transient ischemic attack (TIA) seen in occlusion of the internal carotid artery may also involve areas of distribution of the vertebral arteries.

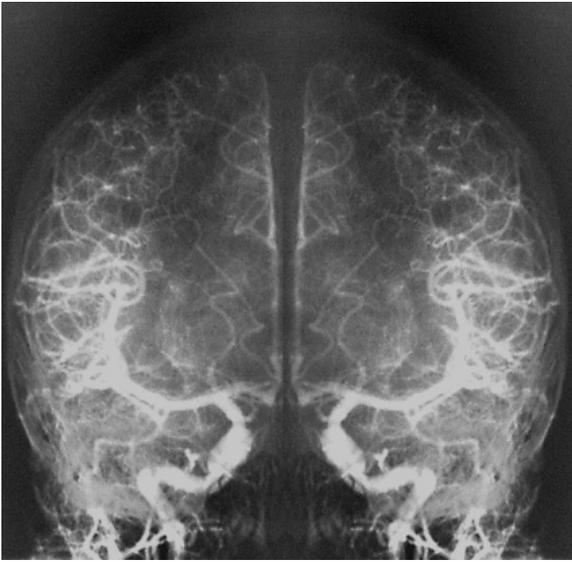


Figure 8.40 Angiogram of the internal carotid artery and its main cerebral branches. Branches of the middle cerebral artery are clearly visible

serve as another route by which infection may spread to the cranial cavity from areas outside the skull. Emissary veins are classified into frontal, parietal, temporal, and mastoid veins.

- Diploic veins, which are contained in the cancellous tissue between the compact layers of the calvaria, are connected to the emissary veins. These veins are devoid of valves and are absent in the newborn and well developed in adults.

- The inferior sagittal sinus (Figures 8.44 & 8.45) occupies the inferior margin of the falx cerebri dorsal to the corpus callosum. It continues with the straight sinus at the junction of the falx cerebri and tentorium cerebelli.

- The straight sinus (Figure 8.44, 8.45, 8.47 & 8.56) extends from the site of junction of the tentorium cerebelli and falx cerebri to the left transverse sinus. It receives the inferior sagittal sinus, superior cerebellar veins, and the great cerebral vein of Galen.

- The confluence of sinuses (Figures 8.45, 8.47 & 8.56) is formed at the site of union of the superior sagittal, straight, occipital and transverse sinuses near the internal occipital protuberance.

- The transverse sinus (Figures 8.45, 8.47 & 8.56) occupy the transverse sulci and the lateral and posterior

Vulnerability to ischemia in hypertensive individuals is greater in watershed areas, which represent the cerebral zones supplied by the terminal branches of the anterior, posterior, and middle cerebral arteries that lack adequate blood supply and efficient perfusion pressure.



Figure 8.41 Angiogram of the posterior cerebral circulation. The vertebral artery and its branches are illustrated. 1. Vertebral artery; 2. Basilar artery; 3. Anterior inferior cerebellar artery

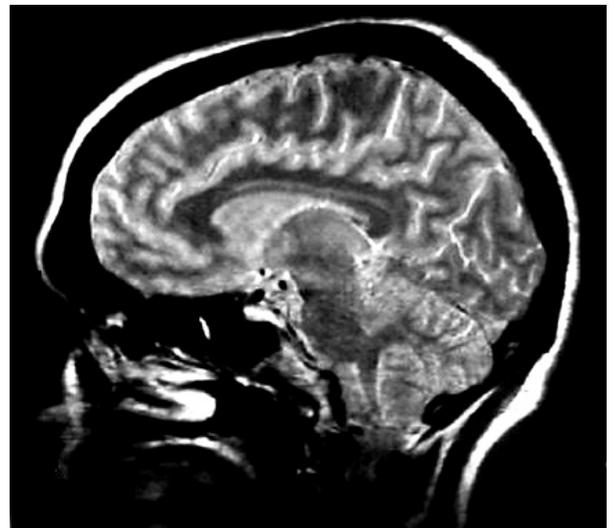


Figure 8.42 An MRI of the brain in the sagittal plane. Note the main branches of the anterior and posterior cerebral circulation

borders of the tentorium cerebelli. It appears that the right transverse sinus is continuous with the superior sagittal sinus, while the left sinus continues with the straight sinus. As the transverse sinus drains into the sigmoid sinus, it receives the superficial middle cerebral, inferior cerebral, inferior cerebellar, and some of the diploic veins. Anastomatic veins of Labbe (inferior anastomatic vein) and Trolard (superior anastomatic vein) connect the superficial middle cerebral veins to the transverse and superior sagittal sinuses, respectively. Occasionally, the transverse sinus also receives arachnoid villi.



Figure 8.43 Angiogram of the superficial and cerebral deep veins and associated sinuses. Note the bridging and their drainage sites into the superior sagittal sinus

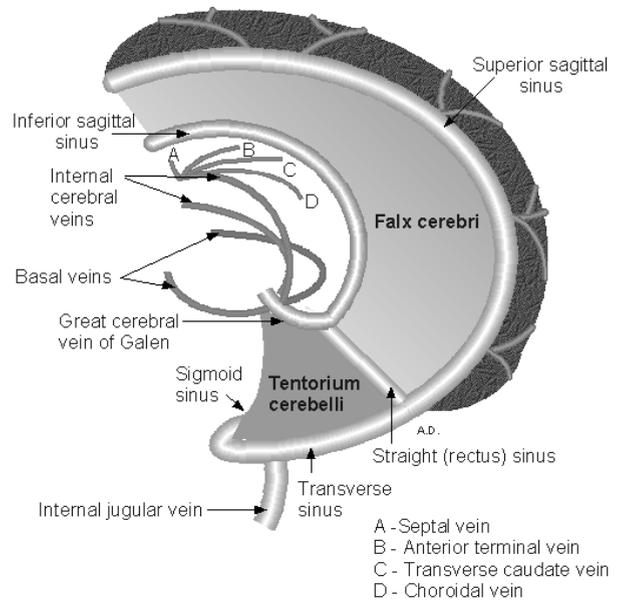


Figure 8.45 Tributaries of the internal cerebral vein and great cerebral vein of Galen are shown in this figure. The straight sinus, which receives the deep cerebral veins, is illustrated in relation to the tentorium cerebelli and falx cerebri

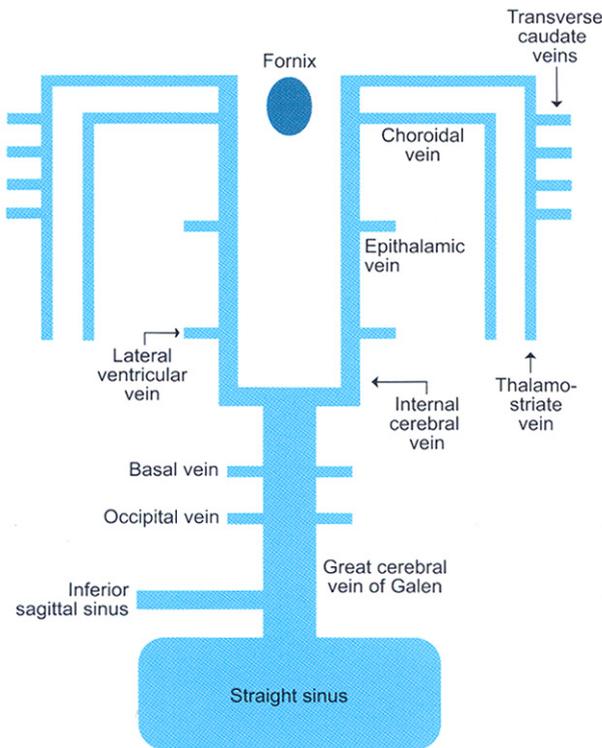


Figure 8.44 Schematic diagram of the deep cerebral vein. The great cerebral vein of Galen joins the venous blood from the inferior sagittal sinus to drain into the straight sinus

- The sigmoid sinuses (Figure 8.56) form a curve on the medial surface of the mastoid part of the temporal bone and are separated from the mastoid antrum of the middle ear by a thin plate of bone. They are connected both sides to the occipital and posterior auricular veins, as well as to the veins of the suboccipital triangle via the emissary veins.

- The occipital sinus is contained in the posterior border of the falx cerebelli and lies anterior to the occipital crest, joining the confluence of sinuses near the occipital protuberance. It is connected to the occipital vein and the internal vertebral venous plexus, which serves as a collateral venous route upon blockage of the internal jugular vein. As the smallest of all dural sinuses, the occipital sinus begins near the margin of the foramen magnum and terminates in the confluence of sinuses.

Anteroinferior group of dural sinuses

- The sphenoparietal sinus (Figures 8.56) runs along the inferior surface of the lesser wings of the sphenoid bone, joining the cavernous sinus on both sides. It receives the anterior temporal diploic veins and a branch of the middle meningeal vein.

- The cavernous sinuses (Figures 8.55 & 8.56) are located on both sides of the sella turcica, sphenoidal body, and the pituitary gland. Each sinus extends from the superior orbital fissure to the apex of the petrous temporal bone, and is connected to the pterygoid venous plexus via the emissary veins of the foramen ovale. It is interesting to note that this sinus contains the abducens, oculomotor, trochlear, ophthalmic, and maxillary nerves, as well as the internal carotid artery and associated sympathetic plexus.

- The superior petrosal sinus (Figure 8.56) follows the corresponding sulci, connecting the cavernous sinus to the

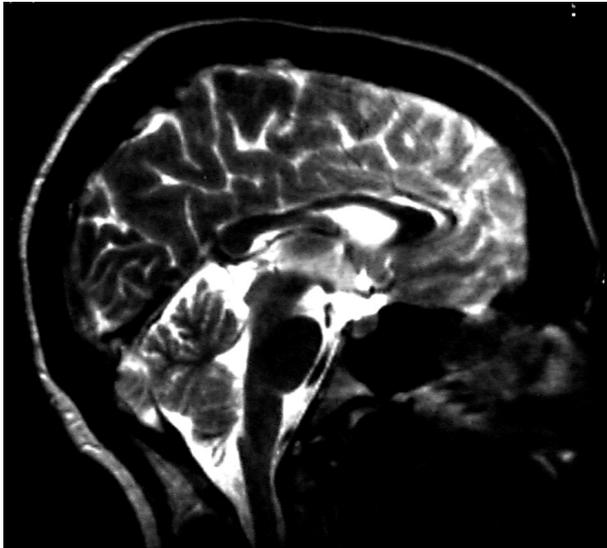


Figure 8.46 In this MRI scan the internal cerebral vein and the great cerebral vein of Galen, as well as the straight sinus are shown. Branches of the vertebrobasilar system are also illustrated

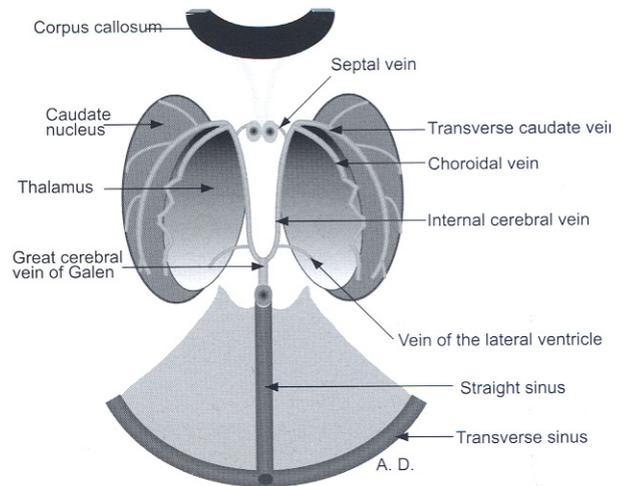


Figure 8.47 A detailed drawing of the various tributaries of the deep cerebral vein

Thinness of the wall of the great cerebral vein of Galen may predispose the vessel to rupture. Additionally, aneurysm of this vessel as a result of congenital arteriovenous malformation may produce hydrocephalus. The latter condition may be associated with congestive heart failure.

transverse sinus. It receives the inferior cerebral as well as the superior cerebellar veins.

- The inferior petrosal sinus occupies the inferior petrosal sulcus and connects the cavernous sinus to the internal jugular veins. It receives the superior cerebellar and labyrinthine veins and venous tributaries from the pons and medulla. It courses between the petrous temporal bone and the basilar part of the occipital bone.

- The arachnoid (spidery) mater ([Figure 8.58](#)), a delicate trabecular layer that covers the exterior of the brain without following the sulci, and lies between the dura and pia mater. Leptomeninges is a common term that refers to combined pia-arachnoid layer. It is separated from the pia and dura mater via the subarachnoid and subdural spaces, respectively. Dilatations of the subarachnoid space around the brain and brainstem that contains the cerebral vessels

A lesion of the parietal lobe may cause widening of the posterior part of falx cerebri and a "square shifting" of the anterior cerebral vein.

- Thrombosis of the cerebral veins may occur as a result of mycotic or pyogenic infections, or due to non-infectious conditions (e.g. malnutrition, hypercoagulable states). It may also be associated with trauma, administration of contraceptives, otitis media, and sinusitis. Thrombosis of the cerebral veins occurs as a result of primary or secondary lesions elsewhere in the body. Headache, vomiting or convulsions due to cerebral edema may be seen with or without a focal motor deficit.

- Superficial cerebral veins in particular are prone to rupture at the points of their entry into the superior sagittal sinus (bridging veins), resulting in subdural hematoma. This is characterized by sudden and severe headache, vomiting, and dilatation of the facial veins, focal seizures, hemiplegia, dyskinesia, and possibly papilloedema (discussed in detail later in this chapter).

are termed as cisterns. These cisterns occupy strategic locations around the brain and brainstem, which include the cerebello-medullary cistern, cisterna ambiens, pontine and interpeduncular cistern, the cistern of the lamina terminalis, and the supracallosal cistern.

- The cerebello-medullary cistern (cisterna magna) establishes communication with the fourth ventricle via the foramina of Luschka and Magendie, containing the terminal branches of the posterior inferior cerebellar artery.

- Arteriovenous malformations (FIGURE 8.48) are congenital connections between arteries and veins that develop between the fourth and fifth weeks of embryonic life and are commonly seen in the cerebral vessels. The most frequently afflicted vessel with this malformation is the middle cerebral artery. AV malformations are responsible for hemorrhage, focal or generalized seizures. They may mimic signs and symptoms of multiple sclerosis or tumors. Headache and intellectual deterioration are some of the manifestations of these anomalies.



Figure 8.48 An internal carotid artery angiogram showing the general pattern of arteriovenous malformation involving the frontopolar branch of the middle cerebral artery

- The cisterna ambiens is located posterior to the pineal gland and contains the great cerebral vein of Galen.
- The pontine cistern is located on the ventral surface of the pons, containing the basilar artery.
- The interpeduncular cistern encircles the arterial circle of Willis, mammillary bodies, and tuber cinereum.
- The cistern of the lamina terminalis and supracallosal cistern bridge the anterior cerebral artery.

Numerous minute arachnoid projections or villi, guarded by one way valves, enter the superior sagittal and/or transverse sinuses. These one-way valves allow CSF to pass from the subarachnoid space to the systemic circulation, while preventing fluid movement in the opposite direction. It is important to note that the low pressure of the dural sinuses relative to the intracranial pressure also dictates the flow of cerebrospinal fluid.

Irritation of the epineurium and perineurium may account for the distinctive features of Kernig's sign which is characterized by nuchal rigidity, pain and strong passive resistance upon attempt to extend the knee while the thigh is in flexed position. It may also account for automatic flexion of the hip and knee joints (Brudzinski's sign) upon abrupt flexion of the neck in meningitic patients (Figure 8.49).

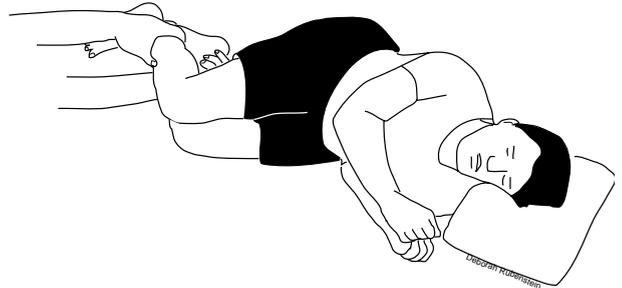


Figure 8.49 This diagram illustrates Brudzinski's sign

Arachnoid villi, which are present in the fetus and newborn, form the macroscopic arachnoid granulations (Pacchionian bodies) around 18 months of age that exert pressure on the inner surfaces of the calvarium, producing pressure atrophy and visible depressions. Extensive contacts with the ependymal lining of the ventricles, pia mater, adjacent glial cells, and the capillary endothelium of the choroid plexus, may be secured by the long path followed by the cerebrospinal fluid.

The pia (faithful) mater, the innermost of the meninges, is a delicate layer that follows the architecture of the sulci and contributes to the formation of the blood-brain barrier. When the pia mater (containing small blood vessels) and ependyma join, they form the tela choroidea, which gives attachment to the choroid plexus. The pia mater consists of an outer epi-pial layer and an inner intima pia layer. As the cerebral arteries course within the subarachnoid space, they become isolated from the pia-arachnoid layer by a space which is continuous with the intrapial periarterial space, a gap between the smooth muscle of arterial capillary and pia mater. At the point of entrance of the arterial capillaries into the pia mater, one pia layer forms the pia-adventitial layer around the

Dura mater may be associated with tumors (e.g. meningioma), epidural or subdural hemorrhages.

Epidural (extradural) hematoma refers to a localized accumulation of blood between the bony skull and the endosteal layer of the dura (Figure 8.50). It occurs most commonly as a result of rupture of the anterior division of the middle meningeal artery or vein. Epidural hematoma may be due to a minor trauma to the side of the head that produces fracture of the antero-inferior portion of the parietal bone. Epidural hematoma may lead to a rise in intracranial pressure, a condition which must be relieved before irreversible brain damage and herniation occur. Unsuccessful treatment of this condition may lead to death. It is a rapidly progressive condition, which may involve the posterior cranial fossa, resulting in ipsilateral cerebellar dysfunctions, headache, and upper motor neuron palsy. This is generally a unilateral condition that results in the majority of cases from temporal bone fractures associated with mild head trauma. This condition is usually associated with transient loss of consciousness and contralateral spastic palsy, requiring immediate surgical intervention. Due to the increased arterial blood pressure in epidural hematoma, MRI appears more rounded and isolated.

A subdural hematoma refers to the accumulation of venous blood in the subdural space (Figure 8.51). It results from rupture of the bridging superficial cerebral veins as they drain into the dural sinuses. Most often this condition occurs as a result of severe trauma to the front or back of the head, producing excessive anteroposterior displacement of the brain within the skull. Subdural hematoma is much more common than epidural hematoma and tends to have a poorer prognosis. The progression of this condition is relatively slower than that

of an epidural hematoma. Often symptoms do not appear until months after the initial head injury. Displacement of the pineal gland to the contralateral side, a radiographic finding, may be an initial sign of subdural hematoma. It is classified as an acute condition when it occurs within three days, subacute or chronic condition when it shows manifestations between three days and three weeks. This condition is characterized by loss or altered state of consciousness, unilateral pupillary dilatation (anisocoria-unequal pupils), and contralateral spastic palsy. However, spastic palsy may be seen ipsilaterally if the subdural hematoma is associated with compression of the midbrain (e.g. against the tentorial or Kernohan's notch). Progression of this condition is more insidious with symptoms appearing weeks or sometimes months after head injury. A sustained headache and mental obtundation are the most common symptoms. Imaging techniques that elucidate a brain shift may be useful in the diagnosis and assessment of asymptomatic cases. CT scans must be interpreted cautiously, since at certain stages (within weeks following injury) the hematoma itself becomes isodense with the surrounding brain tissue. MRI, which is less cost-effective method of scanning, overcomes this diagnostic problem. Subdural bleeding, that follows the contour of the lateral surface of the brain, appears flat.



Figure 8.50 This radiographic image clearly illustrates sites of epidural hematoma

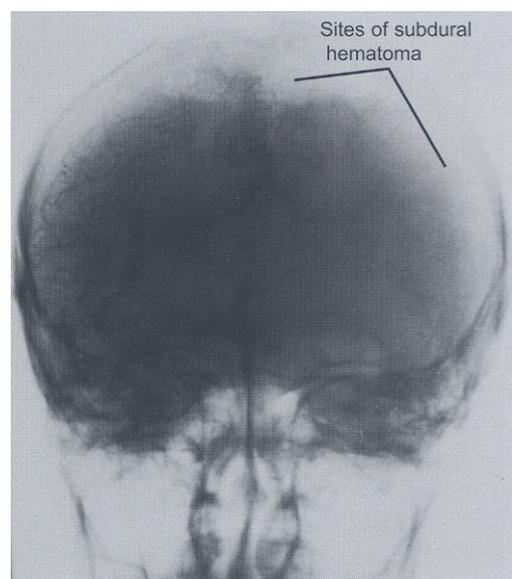


Figure 8.51 Radiographic image of the skull showing the extent of subdural hematoma

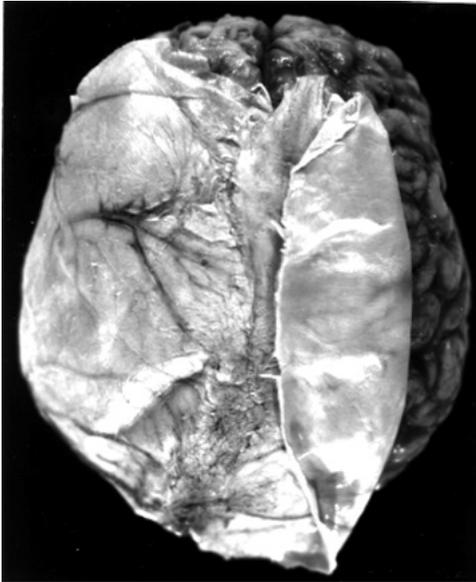


Figure 8.52 Photograph of the dura mater covering the brain. Notice the branches of the meningeal vessels

capillaries, which is separated from the external glial membrane by the periarterial subpial space. This layer follows the vessels into the brain forming a perivascular sheath which becomes discontinuous and eventually disappear as the vessels become capillaries. In this manner, leptomeningeal cells separate and form a regulatory interface between the arteries and the brain tissue, preventing the neurotransmitters released from nerves that supply the cerebral vessels from affecting the brain.

- Brain barriers that maintain the ionic composition of brain tissue by selectively allowing or excluding certain substances from entering the brain or nerve tissue, are formed by contribution from the pia mater. They (Figure 8.61) are classified into blood brain-barrier, brain-cerebrospinal fluid barrier, and blood nerve barrier. These barriers are essential for the optimum functions of the central and peripheral nervous systems. However, small lipophilic molecules can gain access to the brain, utilizing specific transport systems and are not affected by the barrier system. There are independent transporters for D-glucose, acidic, basic, and neutral aminoacids.

Blood brain barrier (BBB) is formed by the tight junctions of endothelial cells of the cerebral capillaries that prevent transcapillary movements and selectively impede the diffusion of large molecules, while allowing substances with high lipid solubility (Figure 8.53). It has been suggested that this barrier system depends upon the close inter-relationship of the astrocytic end-feet with the basement membrane of the capillary endothelial cells. These endothelial cells contain large number of mitochondria, and harbor enzymes that govern transport of ions to and from the CSF. They are non-contractile and do not contain actomyosin filaments that respond to

Increased pressure in a tentorial compartment, due to a developing mass, may eventually lead to herniation of part of the brain into the compartment with the lower pressure. Bilateral supratentorial masses (Figure 8.53) which is produced by rostro-caudal displacement and compression of the midbrain, pons, and associated structures such as the tectum, reticular formation, oculomotor nerve, and the diencephalon, may result in trans-tentorial or central herniation. In this condition, the undue pull of the displaced posterior cerebral artery upon the anterior choroidal artery, paramedian and pontine branches of the basilar artery, produces stretching and shearing of these vessels. Stupor (due to compression of the fibers of the ascending reticular activating system), and irregular and/or Cheyne-Stokes respirations (due to compression of the descending pathways to the respiratory center) are the main features of this condition. Due to its entrapment between the superior cerebellar and posterior cerebral arteries, the oculomotor nerve is most likely to be affected at the early stage of this disease. The supratentorial structures may also enlarge as a result of obstruction of the cerebral aqueduct. As a result of compression of the cerebral peduncle against the edge of the tentorium on the opposite side of herniation, the upper motor neuron dysfunctions will be seen on the side of herniation. Signs of decortication and decerebration will follow, leading to stiff posture and later rigidity. Additionally, paralysis of both vertical and horizontal (doll's eyes) movements, and conjugate gaze to the contralateral side (due to destruction of the tectum, pontine tegmentum, and the corticofugal fibers) may also be seen. Uncal herniation occurs as a result of supratentorial mass and is characterized by displacement of the uncus into and inferior to the tentorial notch. More detailed account on this condition is documented with temporal lobe and uncus.

histamine. This fact may account for the unresponsiveness of brain capillaries to allergic disorders associated with histamine release. Although local release of norepinephrine may result in reduction of blood flow into the brain capillaries via its action on the pericytes around these capillaries. In the newborn, the endothelium of the cerebral capillaries of the BBB, allows large molecules like albumin to be carried by their pinocytotic vesicles. This explains the high level of albumin in the CSF in neonates

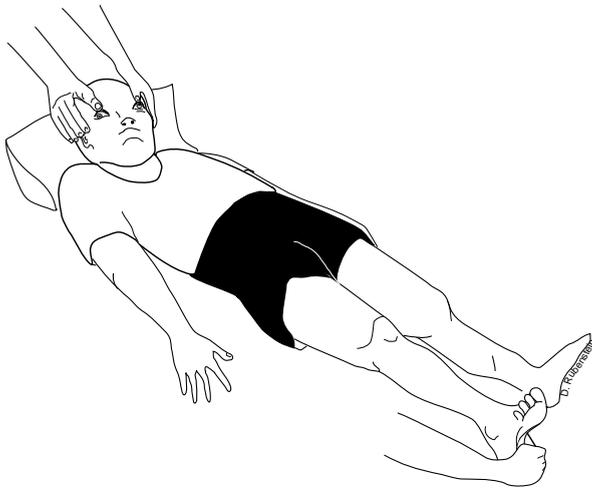


Figure 8.53 This is a depiction of an individual with transtentorial herniation

compared to infants. BBB may be disrupted as a result of brain tumors, or as a sequel to bacterial meningitis. Stroke induced cerebral edema may also impair the function of the blood brain barrier.

In general, the BBB prevents substances circulating in the blood stream from gaining access to the brain and also play a role in their modification and metabolism. Diffusion of large concentration of D-glucose (2-3 times more than normally metabolized by the brain) through the BBB is facilitated by an insulin-dependent GLUT-1 glucose transporter. Reduced GLUT-1 transporter may be associated with seizures, impaired brain development, and mental retardation. Passage of structurally related essential aminoacids (precursors of catecholamines and indolamines) through the cerebral capillaries to the brain is mediated by a single transporter. This allows an intense competition among neutral L-aminoacids; thus elevation in the plasma concentration of a rival aminoacid may account for the inhibition of uptake of others. Therefore, high plasma levels of phenylalanine, as in phenylketonuria, may remarkably reduce the uptake of the competing essential aminoacids. However, aminoacids that are synthesized in the brain (such as aminoacid neurotransmitter) are actively transported in a reverse direction outside the brain. CO₂, O₂, N₂O and volatile anesthetics diffuse rapidly into the brain.

Blood-cerebrospinal fluid barrier (BCB) is formed by the epithelial cells of the choroid plexus, which are connected by tight junctions, and the overlying pia-glial and ependyma-glial membranes. Thus, ventricular CSF diffuses into brain extracellular fluid and eventually into

The venous communications between the superior sagittal sinus and the extra-cranial veins may serve as a route for spread of infection from the nose and scalp to the dural sinuses and eventually the systemic circulation.

Obstruction of the superior sagittal sinus (Figure 8.53) as a result of thrombosis may impede absorption of cerebrospinal fluid and cause increased intracranial pressure.

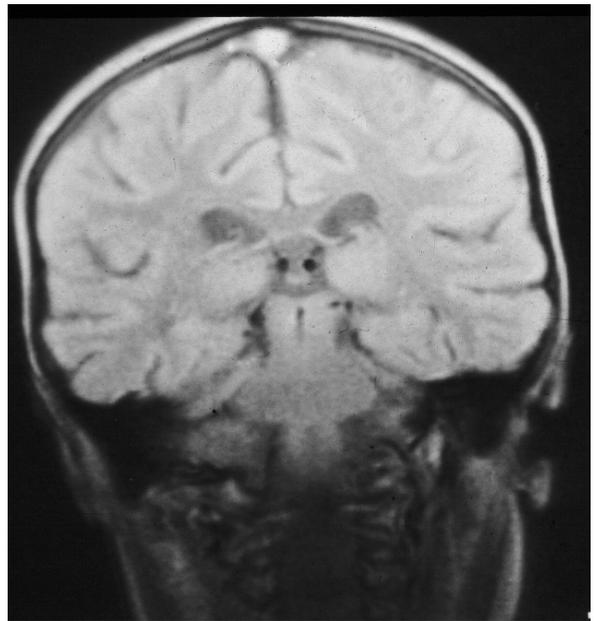


Figure 8.54 This MR image illustrates an obstructed superior sagittal sinus

the subarachnoid space. This barrier system is well illustrated in patients with Jaundice where the bile is selectively excluded from entering the CSF or brain. The presence of yellowish bile stain only in the stroma of the choroid capillaries substantiates the activity of this barrier. Sodium-potassium-ATPase system, which provides a pump allowing sodium into CSF and potassium into the plasma, is contained in the choroid epithelium. This ionic movement assists the passage of large amount of plasma water from the capillary bed.

- Blood nerve barrier (BNB) comprises the perineurium and the capillaries of endoneurium. The wall of these capillaries is non-fenestrated and the endothelial cells establish tight junctions. This barrier is functionally a much more effective in the dorsal root ganglia and autonomic ganglion.

It must also be remembered that the optimal function of cerebral neurons depends upon the stability of glucose

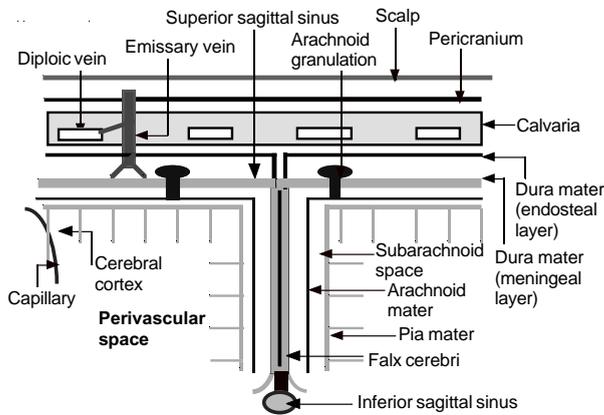


Figure 8.55 Schematic drawing of the scalp, calvaria, and superior sagittal sinus. The emissary veins and arachnoid granulations are shown to indicate the connection of the CSF and extracranial veins to the superior sagittal sinus

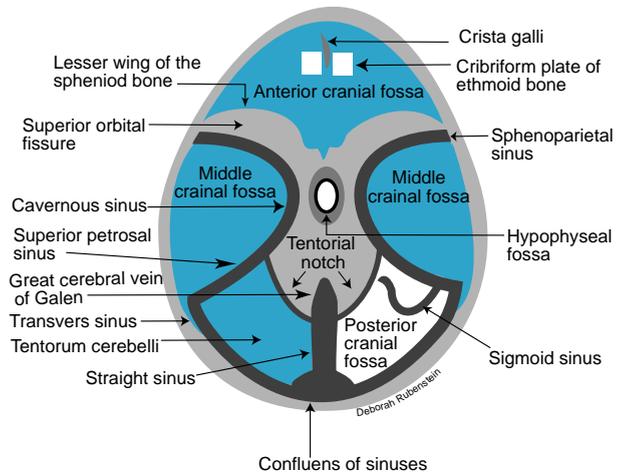


Figure 8.56 Diagram of the dural sinuses in the base of the cranium. Note the S-shaped configuration of certain dural sinuses on both sides of the cranial base

level in the extracellular space, brain potassium concentration, as well as transmitters' levels in the CSF and the brain, which are maintained by the barrier system. Normal CSF and extracellular fluid levels of potassium are maintained via active transport systems that operate in the choroid plexus and brain capillaries. A rise in the level of blood potassium renders the transport systems non-operational, whereas excess of potassium in the CSF is removed via active transport into the blood.

Not all areas of the brain harbor the barrier systems, in fact structures which occupy positions near the ventricles, surrounding the brainstem and the diencephalon known as the circumventricular organs (Figure 8.62) lack the barrier system and operate as points of contact between certain brain receptors and blood. These specialized areas, which may utilize the neurohumoral mechanism to exert their influences, include the subfornical organ, area postrema, and organ vasculosum of the lamina terminalis, neurohypophysis and intermediate lobe of the pituitary gland, medial eminence, pineal gland, and the subcommissural organ.

- The subfornical organ is located near the anterior pole of thalamus and the interventricular foramen of Monro, maintaining massive projections to the supraoptic and paraventricular nuclei and the lateral hypothalamic area. Through these connections, it plays an important role in homeostasis, osmoregulation and the circulation of blood in the choroid plexus. It binds angiotensin II and receives input from the hypothalamus, regulating water intake and inducing vasopressin secretion.

Cavernous sinus communicates with the facial (angular) veins and pterygoid venous plexuses via the superior and inferior ophthalmic veins, respectively. Thus, thrombosis of the cavernous sinus may occur as a result of spread of infection from the face (e.g. infected acne near the medial canthus), scalp, or infratemporal fossa.

A fistula between the internal carotid artery and cavernous sinus may occur spontaneously or as a result of trauma, presenting with retrobulbar pain, pulsating exophthalmos, double vision, visual deficits, audible orbital or cranial bruit, and dilatation of the conjunctival vessels. Cavernous sinus thrombosis is associated with swelling of the orbital soft tissue, which eventually leads to proptosis (forward displacement or bulging of the eyeball), disturbances of consciousness, hypersomnia, and often headache, chills, diplopia, visual impairment, and eye pain. Exophthalmos is the most frequent presenting sign, while papilloedema, facial edema, and subdural hematoma are less frequent findings. Retinal hemorrhage may also occur. This condition may prove to be fatal if it is left untreated.

- The area postrema (AP), an emetic chemoreceptor center, is located near the obex at the point of junction of the lateral walls of the caudal half of the fourth ventricle, receiving projection from the spinal cord and solitary nucleus. AP is intimately interconnected with the solitary tract nucleus. It is sensitive to apomorphine and digitalis

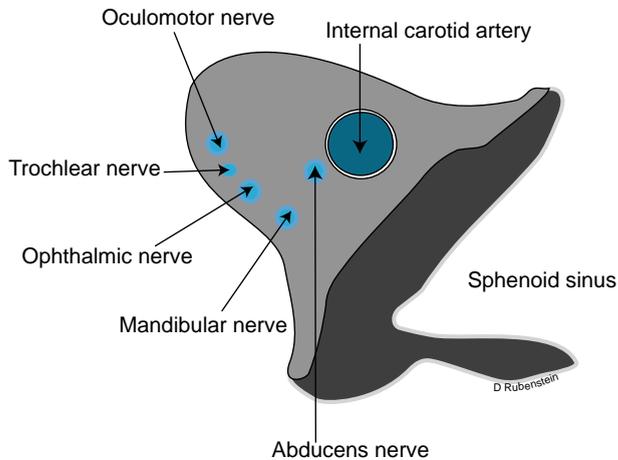


Figure 8.57 Content of the cavernous sinus. This dural sinus is unique in that it contains the internal carotid artery. The abducens nerve is the closest cranial nerve to the internal carotid artery

glycosides, regulating food and water intake and cardiovascular functions.

- The vascular organ of the lamina terminalis is a highly vascular structure, which lies superior and rostral to the optic chiasma and carries hypothalamic peptides (such as somatostatin, angiotensin II, and atrial natriuretics). Structurally, it is similar to the medially, maintaining functional relationship with the preoptic area and preserving fluid balance.

- The neurohypophysis receives terminals of the hypothalamic neurons that convey oxytocin, neurophysin, and vasopressin via the hypothalamo-hypophyseal tract.

- The medial eminence serves as a link and transducer between the hypothalamic neurons that secrete the hormone regulating factors, and the portal-hypophysial system. It also deals with the transduction of hypothalamic neuronal impulses.

- The pineal gland is discussed in detail with the epithalamus.

- The subcommissural organ is located ventral to the posterior commissure and at the site of junction of the third ventricle and cerebral aqueduct. It secretes proteinaceous materials into the cerebrospinal fluid; however, its role in salt and water balance is not yet confirmed.

Since both the ventricular system and the subarachnoid space contain the cerebrospinal fluid, a brief review of the ventricles with major emphasis on CSF, its pathway and associated clinical conditions will be needed.

The ventricular system (Figures 8.62, 8.63 & 8.65), a derivative of the neural canal, is comprised of the lateral,

Occlusion or atresia of the foramina Lushka or Magendie may produce a non-communicating hydrocephalus, which is characterized by enlargement of the ventricles, compression of the brain, and the subsequent thinning of the cerebral cortex (cortical atrophy). Varying degrees of mental retardation and skull enlargement may also occur.

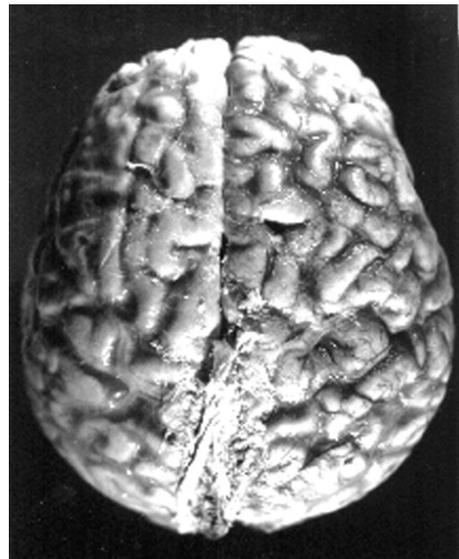


Figure 8.58 This photograph illustrates the arachnoid mater and arachnoid granulations

third, and fourth ventricles, cerebral aqueduct, and the central canal. This system communicates with the venous blood via the subarachnoid space. The ependymal cells that selectively allow certain substances to gain access to the brain line the ventricles.

Secretion of the cerebrospinal fluid is maintained at a rate of 0.3-0.4 ml/min by the choroid plexus (Figures 8.63 & 8.65) and to a much lesser degree by the ependyma. The choroid plexus is formed by the vascular epithelium of pia mater and the ependyma that invaginates through the choroidal fissure, containing mostly simple cuboidal ependymal cells with microvilli of the brush border type. This plexus is innervated by the postsynaptic sympathetic fibers that emanate from the superior cervical ganglion of the sympathetic trunk. Selective prevention of the free entrance of protein and electrolytes from the blood to brain tissue is maintained by the ependymal cells that form tight junctions. Secretion and transport of certain hormones such as transthyretin, a carrier of thyroxine and retinol and insulin-like growth factor-II into CSF may also be accomplished by the choroid plexus. Hardened bodies called psammoma (sand-like), which are composed of concentric rings of calcium carbonate, calcium and

Meningiomas (Figure 8.59), which are the most common benign primary intracranial tumors, are believed to arise from the arachnoid villi along the course of the superior sagittal and sphenoparietal sinuses. These tumors compress the brain and produce focal seizures often as an early sign. Also occlusion of the arachnoid villi due thrombosis, infection or tumors may produce a communicating hydrocephalus.

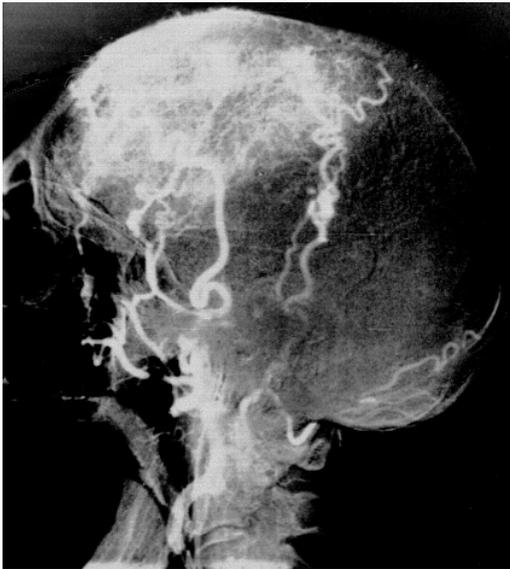


Figure 8.59 An angiogram of the internal carotid artery showing meningeoma in the parietofrontal area

magnesium phosphate, occur normally in the adult choroid plexus. CSF is circulated about three times in 24 hours, and the absorption rate can be 4-6 times the normal rate of formation. Secretion of cerebrospinal fluid may occur through a variety of processes that include filtration across the endothelial wall, hydrostatic pressure dependent activity, and enzymatically-controlled active process by the choroidal epithelium. The latter process is activated by ATPase and carbonic anhydrase. Cardiac glycosides produce inhibition of CSF secretion by uncoupling the mitochondrial oxidative phosphorylation. The steady secretion and absorption of the cerebrospinal fluid is essential for maintaining a uniform pressure within the ventricles and the cranial vault. Vast number of 5-hydroxytryptamine receptors may influence the blood flow in the choroid plexus.

Cerebrospinal fluid regulates ionic transport to and from the extracellular space (sink action), maintaining low concentrations of certain substances in the CSF and brain relative to plasma concentrations. This allows the creation of an efficient milieu for the conduction of nerve impulses. It also acts as a buffer to lessen the impact of head trauma

Subarachnoid hemorrhage and/or hematomas are commonly caused by rupture of the congenital berry aneurysm of the arterial circle of Willis. These saccular or oval-shaped, berry-like dilatations frequently occur near the proximal branches of the cerebral arteries (e.g. middle cerebral and posterior communicating arteries) where the muscular and elastic layers are deficient. They are associated with aortic coarctation and polycystic kidney. Compression of the optic, oculomotor, and trigeminal nerves by these aneurysms may occur prior to their rupture. Bleeding into the subarachnoid space produces symptoms that are frequently sudden in onset and include nuchal rigidity, severe ipsilateral headache, nausea, vomiting, transient vertigo, and occasional syncope (transient loss of consciousness that is preceded by light headedness). Hearing and visual impairment, as well as seizures (which occur in less than 20% of patients) may also be detected. Consciousness usually remains unaffected, however, disorders of concentration and attention, amnesia, visual and hearing impairment may be observed. Signs of oculomotor nerve palsy and possible hemiplegia are also seen in-patients with subarachnoid hemorrhage. CT scan and lumbar puncture (LP) may diagnose this condition. Neurologic complications may also include hydrocephalus, resulting from clot that blocks the CSF pathway in the posterior fossa, and vasospasm that produces cerebral infarctions.

Arachnoidal (leptomeningeal) cysts (Figure 8.60) are congenital lesions that develop from splitting of the arachnoid mater. Intrasellar cysts occupy extradural positions. They are divisible into simple and complex arachnoid cysts. In the simple cysts maintain the ability to actively secrete CSF, and are commonly found in the middle cranial fossa. Complex cysts may contain neuroglia and ependyma. Presentations of arachnoid cysts show variation according to their location. Increased intracranial pressure (ICP), visual deficits, developmental

Retardation, precocious puberty, hydrocephalus, and signs of bobble-head doll syndrome are seen in suprasellar arachnoid cysts. Cysts in the middle cranial fossa may manifest with hemiparesis, convulsions, and headache. Diffuse supra-or infratentorial cysts may also produce growth retardation, craniomegaly, and increased intracranial pressure.

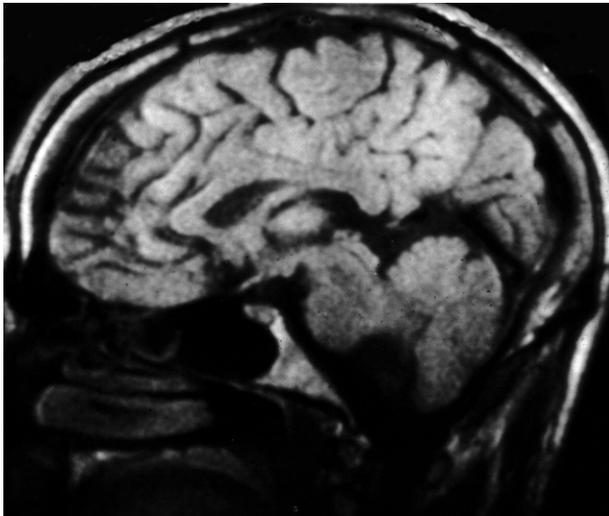


Figure 8.60 This an MR image illustrates an arachnoid cyst in the posterior cranial fossa, inferior and ventral to the cerebellum

(buoyancy effect), provides nutrients to the leptomeninges, and dramatically reduces the weight of the brain. Increases intracranial pressure and brain volume, as a result of vasodilatation of cerebral vessels or parenchymal swelling, may be counteracted by displacement of the CSF. The role of CSF in signal transduction, transport of hormones, and immune reaction has also been suggested.

Respiratory movements influence circulation of the cerebrospinal fluid, cardiac systole associated changes in the intracranial blood volume, current created by ependymal cilia, and by arterial pulsation of the choroid plexus. The normal pressure of CSF ranges between 6-14 cm water, which could be monitored by a manometer, attached to the lumbar puncture needle. This pressure remains constant at 50-200 mm of water unless an increase or decrease in brain size or blood volume occur (e.g. compression of the internal jugular veins increases the venous return of dural sinuses and subsequently produces increased intracranial pressure).

In general, the circulation of the CSF involves the following paths:

Lateral ventricle—> foramen of Monro —> third ventricle —> cerebral aqueduct —> fourth ventricle —> foramen of Luschcka and Foramen of Magendie —> cerebellomedullary cistern (cisterna magna) —> superior sagittal. The cerebrospinal fluid is also absorbed at the levels of spinal nerve root sheaths.

Clinical significance of barriers can be illustrated in (1) kernicterus, (2) cerebral edema, (3) brain scans, (4) the therapy of Parkinsonism, (5) epinephrine surge, and (6) hyperglycemia and/or hypoglycemia. Other conditions that exhibit the role of the brain barrier are ischemia, and certain viral or autoimmune diseases.

(1) In infants, the immature liver can not conjugate large amounts of bilirubin to serum albumin, leading to an increase of the unconjugated bilirubin. Inability of the blood-brain-barrier to block the unconjugated bilirubin from entering the CNS may be followed by its deposition in the basal and brainstem nuclei. Deposition of unconjugated bilirubin in the CNS is commonly detected in kernicterus or erythroblastosis (neonatorum) fetalis, a condition that develops as a consequence of Rh incompatibility between the mother and the fetus. It may also be associated with hemolytic diseases (low albumin reserve), reduced amount of glucuronyl transferase in the preterm infant, biliary atresia, low pH and hepatitis. Infants with this predicament, initially exhibit hypotonia, followed by rigidity and gaze palsies. They are likely to die and autopsy may reveals discoloration of the brain tissue particularly of the basal nuclei. Survivors show signs of mental retardation and some forms of choreiform movements. Bilirubin toxicity may also occur as a result of lack or ineffective of CNS bilirubin oxidase system due birth trauma or incomplete development.

(2) Cerebral edema may be caused by bradykinin, which stimulate the influx of protein into the brain and subsequent enlargement of the extracellular space of the white matter.

(3) Brain scans also utilize the blood-brain barrier concept, and contrast medium injected into the blood breaks down the barrier, allowing visualization and localization of lesions (gray matter contains large number of capillaries that greatly exceeds the white matter) via various imaging techniques.

(4) Administration of L-dopa, a precursor of dopamine, which is able to cross the blood brain barrier by a neutral aminoacid carrier, may be used in the treatment of Parkinson's disease.

(5) Neuronal function is maintained and released from the disastrous consequence of epinephrine surge by the blood brain barrier.

(6) Neuronal activities may be inhibited and coma may result in individuals with hyperglycemia that eventually lead to accumulation of ketone bodies in the brain. Overactivity of the CNS and mental confusion may occur in hypoglycemia. Lack of glucose in this condition may lead to insulin coma.

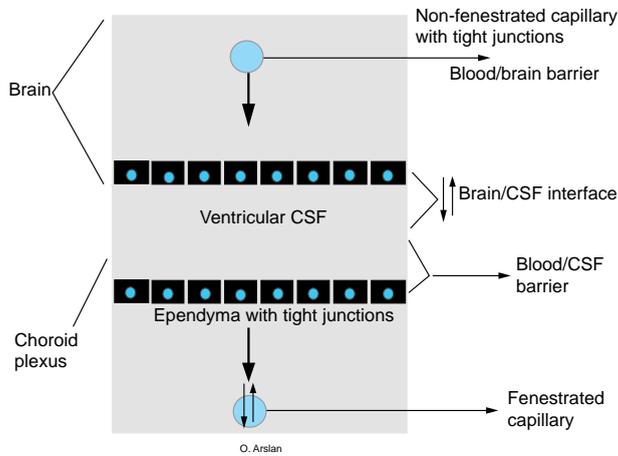


Figure 8.61 Diagram of the neural and vascular elements involved in the formation of the blood-brain and blood-CSF-barriers



Figure 8.63 The floor of the lateral ventricle and the choroid plexus. Foramen of Monro, third ventricle, and the floor of the fourth ventricle are also illustrated. The cerebral hemispheres, corpus callosum and part of the cerebellum are removed

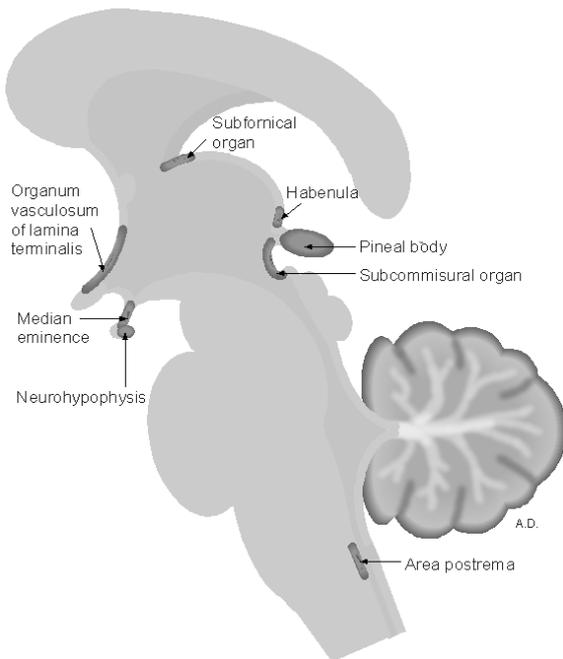


Figure 8.62 Drawing of the mid-sagittal brain illustrating the sites where blood brain barriers are absent

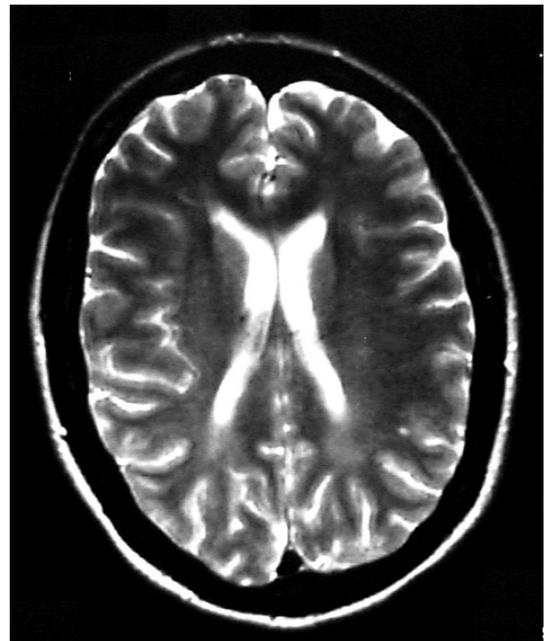


Figure 8.64 MRI scan of the brain showing some of the components of the lateral ventricles

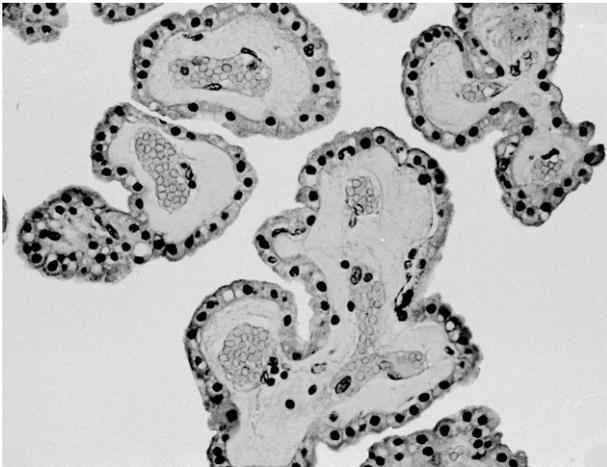


Figure 8.65 Photograph of the choroid plexus. Note the cuboidal cells of the choroid epithelium and associated capillary network

The cerebrospinal fluid (CSF) is a clear, colorless fluid that maintains an alkaline pH of 7.3. Turbidity or pinkish discoloration may be associated with presence of fresh blood from subarachnoid hemorrhage; yellowish discoloration of CSF (xanthochromia) may result from disintegrated blood or increased amount of protein and/or bilirubin. It contains trace amount of protein mainly immunoglobulin and to a lesser extent albumin. It also contains a few leukocytes and a small amount of glucose (80-120 mg per deciliter) and potassium (2.9 mEq/l), with greater concentration of sodium and chloride. This is in contrast to serum, which contains lower sodium concentration and higher potassium and calcium. The arachnoid mater, which forms part of the blood-CSF barrier, may also play a role in changing the composition of the CSF. Numerous peptides are also found in the CSF, which include luteinizing hormone releasing factor, cholecystokinin, angiotensin II, substance P, somatostatin, thyroid releasing hormone, oxytocin, vasopressin, etc. Alterations in the CSF concentrations of peptides may be used for the diagnosis of certain neurological diseases. The cerebrospinal fluid maintains an alkaline pH of 7.3. The changes in the composition of the CSF may serve as a tool in the diagnosis of certain diseases. A low pH value may occur in conditions associated with acidosis, hypercapnia, and in certain pulmonary diseases. Increased protein concentration is observed in spinal shock (complete transection of spinal cord) and in cases of extra- and intramedullary spinal cord tumors. Immunoglobulin G (IgG) is generally elevated in multiple sclerosis. Glucose levels decrease in bacterial, fungal, and viral meningitis. The CSF may contain neoplastic cells in primary and secondary neoplasms.

Intracranial pressure (ICP) increase may be associated with an abnormal increase in the cerebrospinal fluid volume, cerebral edema, intracranial hemorrhage, or impairment of venous drainage. ICP may produce papilloedema, nausea and vomiting (due to activation of the vomiting center in the upper medulla), bradycardia (slowing of the heart due to vagal activation), and coma.

Accumulation of cerebrospinal fluid in the ventricles produces hydrocephalus (Figures 8.67 & 8.68). This condition that commonly results from obstruction of CSF pathways as in ependymoma; over-secretion of the CSF as in a papilloma of the choroid plexus, venous insufficiency as in dural sinus thrombosis; or defective absorption due to occlusion the arachnoid villi as in arachnoiditis. Hydrocephalus may also be produced as a result of atrophy or reduction in the total volume of the brain (hydrocephalus ex vacuo) as is seen in Alzheimer's disease.

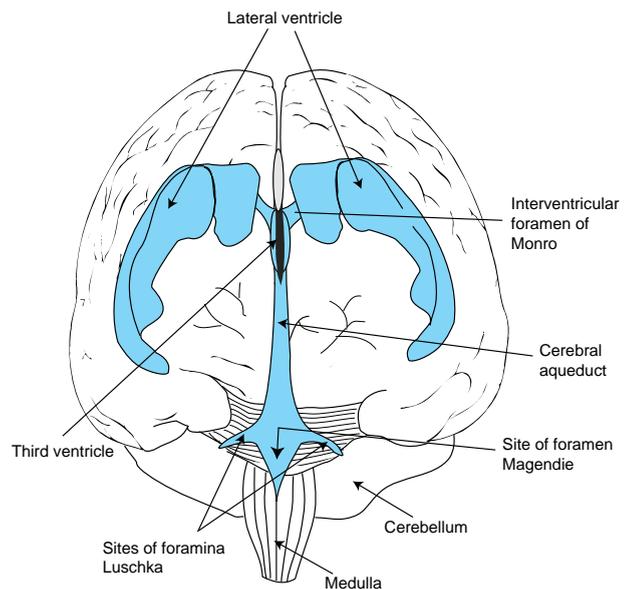


Figure 8.66 The ventricular system (posterior view)

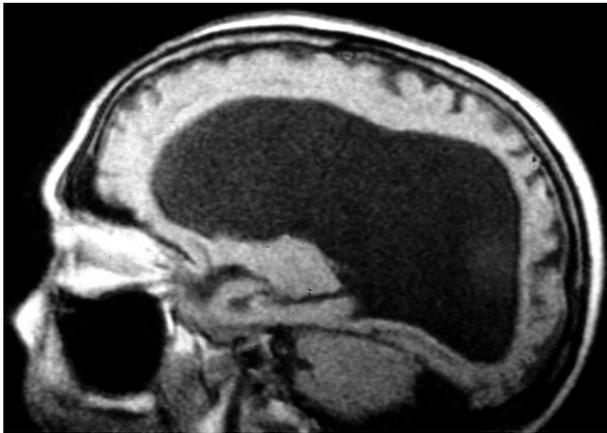


Figure 8.67 This MR image shows the massive dilatation of the lateral ventricle in an individual with obstructive hydrocephalus. Note the remarkable thinning of the cerebral cortex

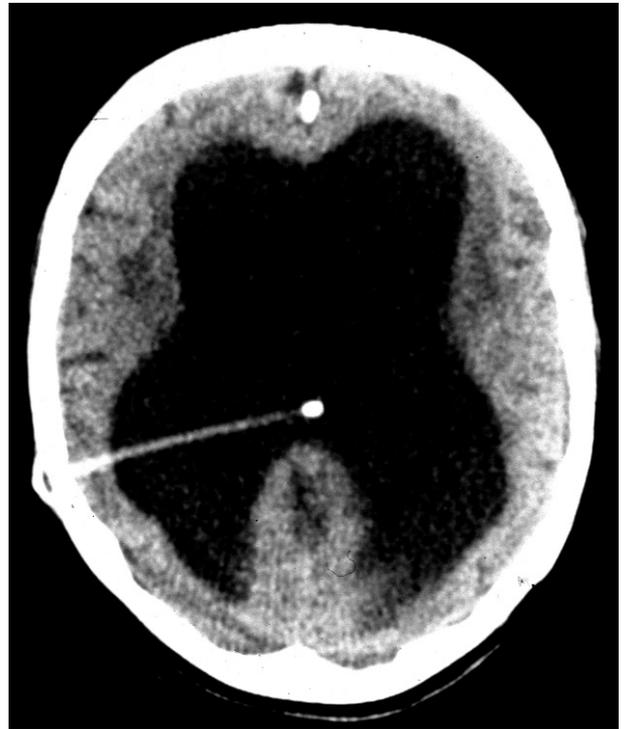


Figure 8.68 This image demonstrates a massive dilatation of the lateral ventricle in an individual with hydrocephalus. A surgical shunt placed to drain the excess CSF

Hydrocephalus may be (A) congenital or (B) acquired:

(A) Congenital (overt-infantile) hydrocephalus occurs usually in the first few months of life or inside the uterus. It rarely extends to the fifth decade of life. It is commonly associated with stenosis of the cerebral aqueduct; obstruction of the foramina Luschka and Magendie (Dandy Walker syndrome) or obliteration of foramen Magendie and cisterna magna (as in Arnold Chiari Type II malformation). It may also result from asymmetrical fusion of cervical vertebrae, imperfect fusion or non-union of the vertebral arches, meningomyelocele and closure of the foramina Magendie and Luschka (Klippel-Feil deformity). Congenital hydrocephalus commonly presents with meningomyelocele, increased intracranial pressure, separation of the sutures (diastasis), and protrusion of the fontanelles. It is also associated with enlargement of the head, thinning of the scalp, visible superficial vessels, and downward (setting sun sign) position of the eyes. Parinaud's syndrome, which exhibits vertical gaze palsy, may also be seen as a result of the pressure exerted on the pretectal area. Disorders of respiration (apneustic episodes), abducens nerve palsy, and "cracked pot sound" upon percussion of the enlarged lateral ventricles (Macewen's sign) are also observed in hydrocephalic young children. It is interesting to note that the cerebral cortex is less affected than the white matter and many patients survive this condition because of the capacity of the skull to expand. Signs of upper motor neuron palsy may also be seen. Although impairment of vision and paleness of the optic disc may be observed upon examination of the fundus, papilloedema will not be seen in these individuals.

(B) Acquired (occult) hydrocephalus may be caused by subarachnoid hemorrhage, post-meningitis, cysticercosis, vascular malformation, as well as tumors of the third ventricle, thalamus, and cerebral hemispheres. It is characterized by visible papilloedema, and less prominent frontal and occipital headache. It exhibits signs of frontal lobe dysfunctions such as inattentiveness, marked slowness in response, and easy distractibility. Memory impairment and reduction in mental and physical capacity are also noted. In older children and adults with rigid calvaria, gait apraxia and amnesia followed by dementia and slowing of thought process and later urinary incontinence may also occur. Imaging of the brain may reveal herniation of the third ventricle, erosion of the sella turcica, and atrophy of the corpus callosum. The onset of this condition is subacute and can cause intellectual deterioration followed by a restriction of movement. Manifestations of upper motor neuron palsy, which include deep tendon hyperreflexia of the lower extremities, and Babinski sign, may be detected along with gait disturbances. Surgical treatment involves ventriculo-peritoneal shunting, which is the most commonly used technique in adults.

It may also involve subcutaneous shunting, and draining the CSF into a systemic vein through the internal jugular vein. While improvement of gait is less likely, urinary incontinence is the most likely symptom to improve with shunting, while dementia is the least likely to undergo any changes. Hydrocephalus may also be classified into obstructive and non-obstructive forms:

- Obstructive hydrocephalus, the most common type of hydrocephalus, results from obstruction of the flow of CSF inside the ventricular system or at its drainage site into the dural sinuses. It may occur as a result of stenosis of the cerebral aqueduct, atresia of foramina Magendie and Luschka, obstruction of the fourth ventricle (as in Arnold Chiari Syndrome), or obstruction of the interventricular foramen of Monro. Obstructive hydrocephalus may be divided into communicating and non-communicating types.

- Communicating hydrocephalus occurs as a result of obstruction of the CSF pathway outside the ventricular system (e.g. in the cisterns and arachnoid villi), while normal connection between the ventricular system and the subarachnoid space via the foramina Magendie and Luschka is maintained. It is a slowly developing condition, which is characterized by ventricular enlargement, deterioration of mental faculties, and bilateral upper motor neuron palsy. It is seen in Arnold-Chiari malformation and leptomeningitis.

- Normal pressure hydrocephalus (NPH) is one form of the communicating hydrocephalus which develops over weeks or months as a result of a subarachnoid hemorrhage, post-traumatic events, post-meningitic conditions, or posterior cranial fossa tumors. NPH is a reversible condition, which exhibits no signs of increased

intracranial pressure, papilloedema or cranial nerves dysfunctions. It is presumed to be due to partial obliteration of the subarachnoid space around the cerebral hemispheres, combined with defective reabsorption of the cerebrospinal fluid through the arachnoid villi. It is seen in 15% of Alzheimer's patients and may be associated with basilar artery ectasia and fluctuations in cerebrospinal pressure. Radiographic imaging (CT and MRI scans) may show expansion of the temporal lobe and ventricles with minimal or no cortical atrophy. The prominent clinical manifestations of this condition includes gait apraxia, dementia, and urinary incontinence. With treatment, gait apraxia is the first sign to improve. Urinary incontinence may involve urgency and frequency of urination, but in severe cases, patients are totally incontinent. Dementia, which includes psychomotor and cognitive impairment, is unusual.

- Non-communicating hydrocephalus is caused by an obstructive process within the ventricular system, producing loss of communication between the ventricular system and the subarachnoid space. Obstruction sites may include foramina Monro, Magendie, or Luschka or the cerebral aqueduct. This form of hydrocephalus is often fatal and progresses very rapidly.

- Non-obstructive hydrocephalus is a sequel to papilloma of the choroid plexus that results in over-secretion of cerebrospinal fluid. It may also be caused by defective absorption at the arachnoid villi subsequent to hemorrhage, infections, dural fibrosis, or thrombosis of the superior sagittal sinus.

Section 3

Peripheral nervous system

The peripheral nervous system (PNS) consists of somatic, visceral (autonomic), sensory, and motor nerve fibers. These fibers are contained within the spinal and cranial nerves. Virtually all spinal and cranial nerves, with the exception of the olfactory and optic nerves, are integral parts of the peripheral nervous system. However, the neuronal cell bodies which form the PNS are located within the central nervous system. This system is further classified into autonomic (visceral) and somatic nervous systems.

9 [Autonomic nervous system](#)

The autonomic nervous system (ANS) consists of neurons that extend in the peripheral and central nervous systems, regulating visceral motor and reflex activities, as well as emotional behavior. It is not a fully autonomous entity, as the name may imply, but rather an interdependent system that functions under massive input from the cerebral cortex. The ANS maintains, through its diverse connections with the somatic nervous system, a stable internal environment or milieu (homeostasis), which is essential for normal physiological functions. It consists of efferent and afferent fibers and central neurons in the spinal cord, brainstem, diencephalon, and the brain. The afferent component transmits visceral pain and organic visceral sensations (e.g. hunger, malaise, nausea, libido, bladder, and rectal fullness). The efferent component innervates the smooth muscles, glandular tissue, and sweat glands.

Autonomic neurons and ganglia

Sympathetic system

Paravertebral ganglia

Prevertebral ganglia

Course of the sympathetic fibers

Parasympathetic (cranial) system

Sacral part

Autonomic centers

Autonomic reflexes

Autonomic plexuses

Enteric nervous system

Afferent components of the autonomic dysfunction

Disorders of the autonomic nervous system

Autonomic neurons and ganglia

The autonomic nervous system (ANS) (Figures 9.1 & 9.2) regulates visceral motor activity, contraction of the blood vessels, glandular secretions and transmission of visceral sensations. This system maintains homeostasis, an essential element for the physiological functions of the visceral organs. As an interdependent entity, the ANS functions under the influence of the cerebral cortex and hypothalamus. In contrast to the somatic nervous system, the innervation of the ANS occurs through two sets of neurons; preganglionic and postganglionic neurons. Preganglionic neuronal cell bodies are located within the central nervous system (spinal cord and the brainstem), whereas the postganglionic neurons lie within the peripheral nervous system within the paravertebral, prevertebral or the intramural ganglia.

The multipolar neurons of these ganglia (Figure 9.3) establish facilitatory or inhibitory synapses with the adjacent neurons, interneurons, or afferent cholinergic fibers. Multiplicity and pattern of the synaptic connections between the preganglionic and postganglionic neurons are aimed at intensifying autonomic response.

The axons of the preganglionic neurons consist of thinly myelinated (group B) fibers, whereas axons of the postganglionic neurons are of the unmyelinated type (C-group), rendering the conduction of generated response much slower. In contrast, axons of somatic nerves are principally myelinated.

Terminals of the autonomic fibers in the smooth muscles contain varicosities and synaptic vesicles that resemble that of the somatic nerves. However, these terminals show diffuse and extensive branching in which a terminal nerve fiber may innervate several smooth muscle fibers. This branching is limited and well localized in the fast acting muscles such as the dilator and constrictor pupillae. The synaptic gaps in the ANS are much wider than that of the skeletal (somatic) muscles, which allow far greater diffusion capacity and account for the delayed response associated with this system relative to the somatic nervous system. The greater the synaptic gap the slower the degradation processes of the neurotransmitter and the resultant prolonged action.

Due to the direct and uninterrupted connections between the somatic neuronal axons and their targets (e.g.

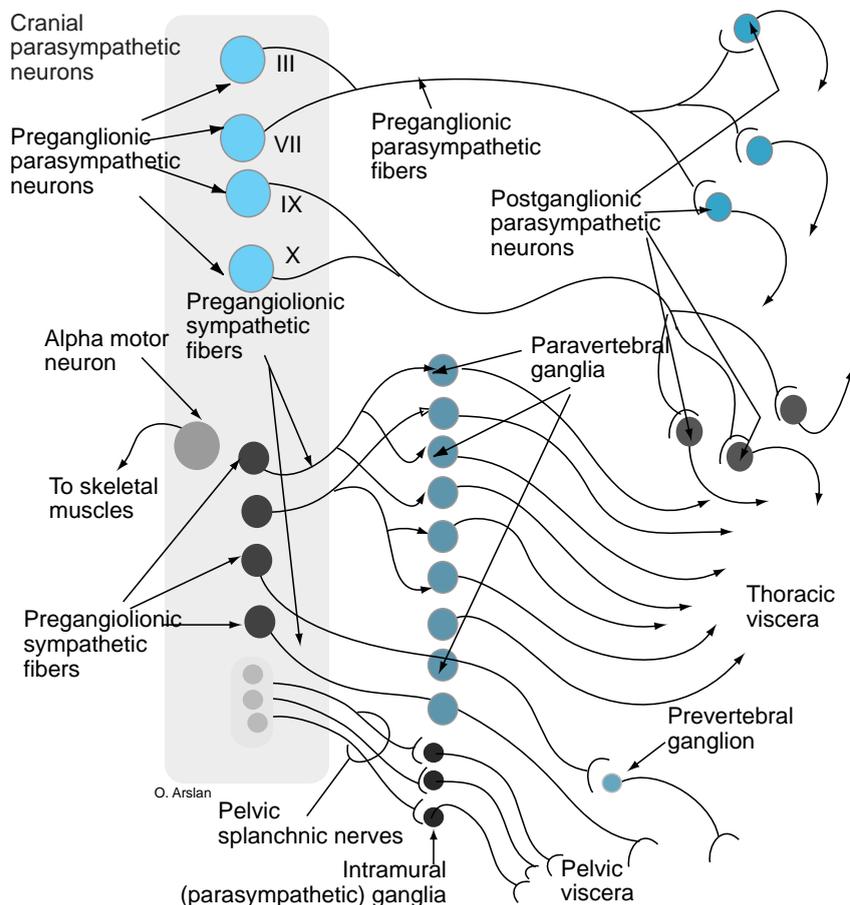


Figure 9.1 Schematic representation of the pre-ganglionic and post-ganglionic neurons of the sympathetic and parasympathetic systems

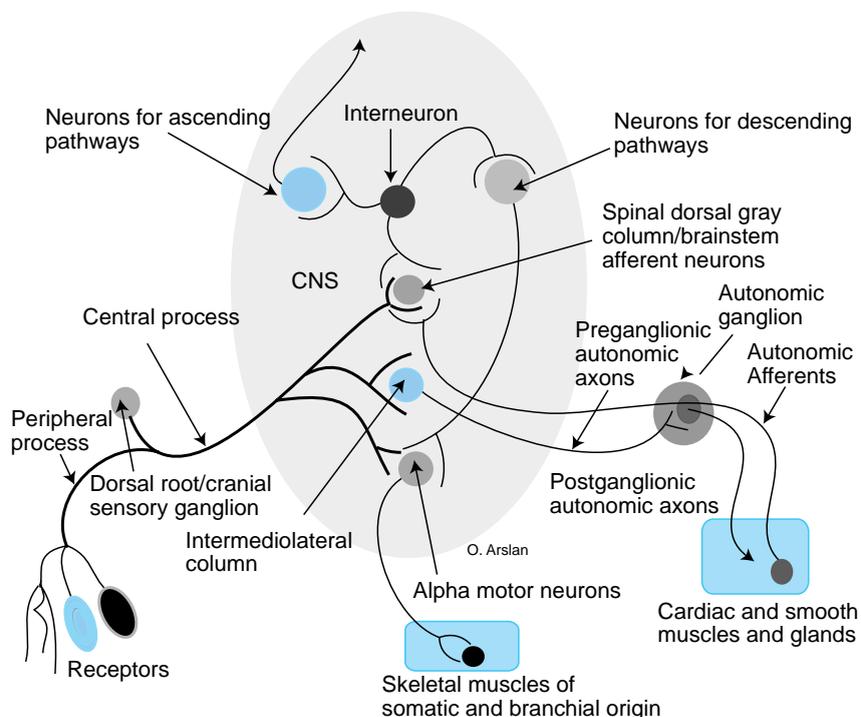


Figure 9.2 General differences between autonomic and somatic innervation, showing both efferent and afferent connections

skeletal muscles), the generated response is immediate and rapid.

Excision of the autonomic fibers may not produce atrophy of the denervated organ, as is the case with the somatic denervation.

Autonomic afferents carry a variety of sensations such as visceral pain, thirst, hunger, cramps, and sensations of well-being or malaise, somatic afferents primarily transmits signals associated with tactile, thermal, painful, joint and vibratory sensations.

Additional differences between these two main components of the peripheral nervous system also exist in regard to receptors and type of stimuli.

Visceral receptors are mainly free nerve endings, whereas somatic system comprises a variety of capsulated and uncapsulated receptors.

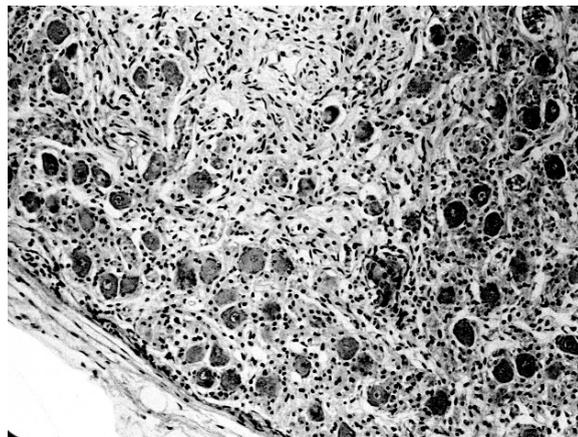


Figure 9.3 Photomicrograph of the multipolar autonomic neurons and associated glial cells

Table 9.1 Ganglia of the peripheral nervous system

<i>General characteristics</i>	<i>Sensory ganglia</i>	<i>Autonomic ganglia</i>
Location	1. Cranial nerves V, VI, VII & IX 2. Dorsal root ganglia	1. Sympathetic a. Paravertebral ganglia b. Prevertebral ganglia 2. Parasympathetic a. Submandibular, otic, ciliary & pterygopalatine ganglia b. intramural ganglia
Type of neurons	Pseudounipolar or bipolar neurons	multipolar neurons
Synaptic connections	None	Paravertebral, prevertebral & intramural ganglia

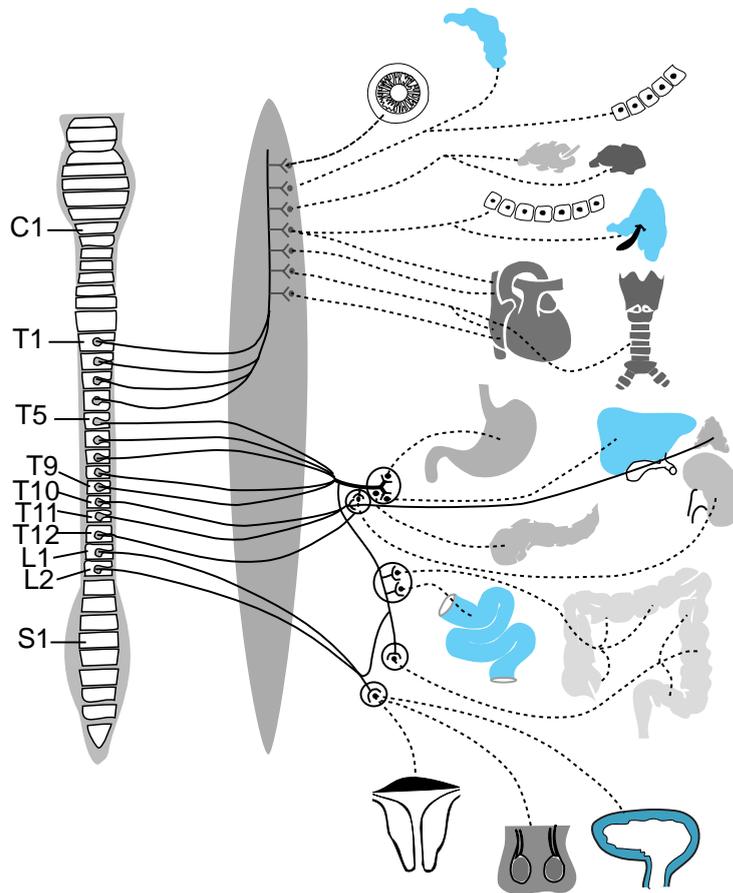


Figure 9.4 The preganglionic and postganglionic neurons of the sympathetic nervous system is illustrated. The splanchnic nerves and their associated ganglia are clearly marked

Conventional somatic stimuli may not elicit any visceral response; however, ischemia and tension within the wall of a viscus may activate the visceral receptors, eliciting pain.

Despite these difference both visceral and somatic afferent maintain neurons in the dorsal root ganglia. Specifically, cranial somatic sensory neurons constitute the trigeminal, geniculate, and superior ganglia of the glossopharyngeal and vagus nerves, whereas the neurons for visceral afferents are located in the geniculate, and the inferior ganglia glossopharyngeal and vagus of nerves. Additionally, both somatic and autonomic nerves form plexuses. Autonomic plexuses are scattered in the thoracic, abdominal, and pelvic cavities to form the pulmonary and aortic plexuses. Somatic nerve plexuses are formed regionally such as the cervical, brachial, and lumbosacral plexuses.

The ANS utilizes norepinephrine, dopamine, and acetylcholine as primary neurotransmitters, producing either an excitatory or inhibitory response. Modulators, such as hormones or tissue metabolites may exert influences upon the transmitter release or their action.

There are two functionally diverse and antagonistic systems within the ANS which operate in conjunction

with the enteric nervous system. These are the sympathetic and parasympathetic systems.

Sympathetic system

The sympathetic is a system brought into action during emergency and under stressful situations which releases energy by increasing the level of blood sugar and blood pressure, and intensifying the rate of cardiac contractility and output (positive inotropic and chronotropic effects). It is a system that directs blood flow to the voluntary musculature at the expense of viscera and skin. Excitation of a disproportionate number of postganglionic neurons (great degree of divergence) and high concentration of the circulating epinephrine in the blood stream are responsible for the mass-response of the sympathetic system. This system utilizes acetylcholine at the preganglionic level and norepinephrine at the postganglionic level. However, there are exceptions to this rule, acetylcholine may be utilized at the postganglionic level in the innervation of the blood vessels of skeletal muscle and the sweat glands. This may not be true in the case of sweat glands of the palm, which receive adrenergic fibers.

Other cotransmitters also play important roles in this system such as ATP and neuropeptide Y (NPY). Sympathetic (adrenergic) receptors are integral membrane glycoprotein, which are classified into presynaptic and postsynaptic groups.

Presynaptic receptors are categorized at least into α_2 and β_2 groups. Additional groups and subtypes are discussed in detail in [chapter 12](#).

Group α_2 receptors are found on both cholinergic and adrenergic nerve terminals. They act on pancreatic islets (b) cells and on platelets, resulting in reduction of insulin secretion and platelets aggregation, respectively. The latter effect is due to inhibition of adenylyl cyclase and activation of K^+ channels via G_i protein. On the adrenergic endings, α_2 (autoreceptors) receptors inhibit the release of norepinephrine by inhibiting of neuronal Ca^{2+} channels.

Group β_2 (hormonal) receptors are found on the vascular, pupillary, ciliary, bronchial, gastrointestinal, and genitourinary tract smooth muscles, initiating relaxation of coronary vessels, bronchi and skeletal arterioles, as well as the ciliary and constrictor pupilla muscles. These series of actions are produced by activation of adenylyl cyclase, mediated by G_s protein. They also produce glycogenolysis in the skeletal muscles and liver. β_2 agonists relax the bronchial smooth muscles and therefore can be used in the treatment of asthma. β_2 antagonists are not essential.

Postsynaptic receptors are categorized into α_1 and β_1 groups. α_1 agonists cause contraction of the smooth muscles of the arterioles and sphincters, whereas α_1 antagonists may counteract this effect in individuals with hypertension and peripheral vascular disease.

Group α_1 produces vasoconstriction and enhances glandular secretion (odoriferous apocrine sweat glands) via stimulation of phospholipase with formation of IP₃ (inositol-1,4,5-triphosphate) and diacylglycerol, and increased cytosolic Ca^{2+} .

β_1 receptors act particularly on the cardiac muscles, producing increased rates and force of contraction and atrioventricular nodal velocity via activation of adenylyl cyclase and Ca^{2+} channels. The role of β_1 agonists in the stimulation of the nodal and ventricular muscles of the heart may be utilized in the treatment of heart failure. In the same manner β_1 antagonists' (beta blockers) role in reducing cardiac rate and force of contractility may be utilized in the treatment of angina pectoris.

Sympathetic innervation of the skin encompasses adrenergic and cholinergic fibers. Cholinergic fibers act upon the muscarinic receptors, enhancing the secretion of the eccrine sweat glands, while adrenergic fibers produce vasoconstriction of the cutaneous arterioles and activate the secretion of the odoriferous apocrine sweat glands.

Activation of the sympathetic nervous system, which may mimicked by sympathomimetics, produces:

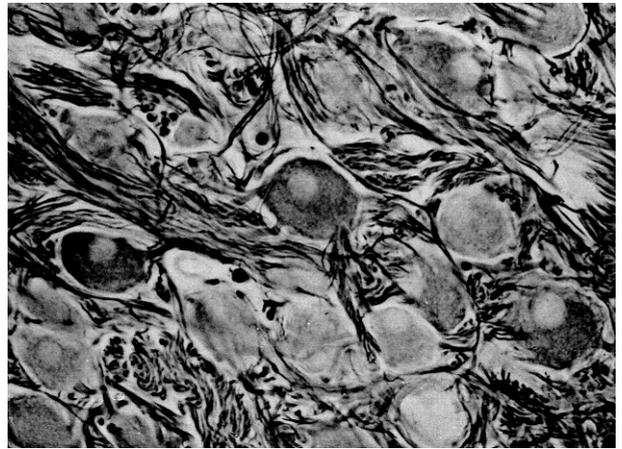


Figure 9.5 Photomicrograph of the multipolar neurons of the sympathetic ganglia and associate satellite cells

- Mydriasis (dilation of the pupils) by inducing contraction of the dilator pupillae muscles.
- Relaxation of the ciliary muscle.
- Increased contractility and rate of heart beat (positive inotropic and chronotropic effects).
- Vasodilatation of the skeletal and coronary arteries.
- Vasoconstriction of the bronchial arteries, as well as arteries of the digestive system and skin.
- Dilatation of bronchi and inhibition of bronchial secretion.
- Inhibition of gastrointestinal motility and contraction of the sphincters.
- Increased secretion of the sweat glands.
- Contraction of the erector pilorum muscles.
- Vasoconstriction of the genital arteries and contraction of the vas deferens, seminal vesicle, and prostate.
- Inhibition of the detrusor muscle of the bladder and contraction of the urethral sphincters.

The preganglionic sympathetic neurons ([Figures 9.1 & 9.4](#)) of the intermediolateral column of the thoracic and upper two or three lumbar spinal segments are connected to the postganglionic sympathetic neurons via the myelinated fibers of the white communicating rami. Postganglionic neurons form two sets of ganglia; paravertebral and prevertebral.

Paravertebral ganglia

The paravertebral ganglia ([Figures 9.1, 9.4, 9.5, 9.8 & 9.9](#)) form the sympathetic trunk, consisting of two symmetrical chains parallel to the vertebral column that unite anterior to the coccyx at the ganglion impar. Multipolar neurons of the paravertebral ganglia receive presynaptic fibers from the intermediolateral columns of the thoracic and upper two or three lumbar segments via myelinated white communicating rami, and provide postsynaptic fibers that



Figure 9.6 This is a depiction of manifestations of Horner's syndrome

join the spinal nerves via the unmyelinated gray communicating rami. The paravertebral ganglia are divided into cervical, thoracic, lumbar and sacral parts.

The cervical part of the sympathetic trunk (Figure 9.8) consists of the superior, middle, and inferior ganglia. Since these ganglia do not receive white communicating rami, the presynaptic fibers, which emerge from the upper thoracic spinal nerves, have to travel through the corresponding thoracic ganglia to reach their destination in the cervical ganglia. However, gray communicating rami do arise from these ganglia, supplying the upper four cervical spinal nerves.

The superior cervical ganglion, largest cervical ganglion, formed by fusion of the upper four cervical ganglia. It lies anterior to the longus capitis and posterior to the carotid sheath. This ganglion supply fibers to the carotid body and the pharyngeal plexus and cardiac branch (superior cardiac nerve) which contains efferent but NOT afferent nociceptive fibers. Most of emerging postganglionic fibers form the external and internal carotid plexus around the corresponding arteries. Fibers of the internal carotid plexus enter the cranial cavity supplying dura mater and dilator pupilla, superior tarsal, and orbital muscles. Fibers within the external carotid plexus supply vasoconstrictor and sudomotor fibers to the face and neck, as well as secretomotor fibers to the salivary gland via the otic and submandibular ganglia. It also provides gray communicating rami to the upper four cervical spinal nerves. Since the presynaptic fibers from the T1-T2 spinal segments project to the superior cervical ganglion, which innervates the structures in the head, removal of this ganglion may deprive the ipsilateral side of the head of sympathetic innervation.

- Ipsilateral disruption of the sympathetic fibers to head produces manifestations of Horner's syndrome (Figure 9.6) which comprises ptosis (drooping of the upper eyelid), mydriasis (dilatation of the pupil), enophthalmos (sunken eyeball), and anhydrosis (lack of sweating).
- Activation of the preganglionic sympathetic neurons at T1-T2 spinal segments requires descending autonomic input from the hypothalamus that travels in the lateral medulla and the lateral funiculus of the cervical spinal. Therefore, destruction of the lateral part of the medulla may also produce signs of Horner's syndrome, which are seen as a component of lateral medullary (Wallenberg's) syndrome.

The middle cervical ganglion (Figure 9.7) is an inconstant ganglion, which is located anterior to the inferior thyroid artery at the level of the sixth thoracic vertebra. It is formed by the fusion of the fifth and sixth cervical ganglia. It provides innervation to the heart, as well as furnishes gray communicating rami to the fifth and sixth cervical ventral rami. It is connected to the cervicothoracic ganglion via the ansa subclavia (see below). It provides thyroid branches and a (middle) cardiac nerve, which is the largest sympathetic contribution, to the deep cardiac plexus.

The inferior cervical ganglion joins the first thoracic ganglion to form the stellate ganglion.

The cervicothoracic (stellate) ganglion (Figure 9.7) lies posterior to the initial part of the vertebral artery, apex of the lung and cervical pleura, occupying the area between the transverse process of C7 and the neck of the first rib. It contributes gray communicating rami to the seventh and eighth cervical, and to the first thoracic spinal nerves. It also supplies postganglionic branches to the subclavian artery and its branches, and to the vertebral plexus, which extends into the cranial cavity. The preganglionic fibers

Pancoast tumor is a tumor of the apex of the lung, which may result in compression, or destruction of the stellate ganglion and the inferior trunk of the brachial plexus, producing pain and numbness in C8-T1 dermatomes. Phrenic nerve may also be affected in this tumor producing diaphragmatic palsy. Additional manifestations such as cardiac arrhythmias, obstruction of the superior vena cava, and hoarseness due to left recurrent laryngeal nerve palsy may also be seen. Signs of spinal cord compression may occasionally be seen due to erosion of the vertebral laminae by extension of the tumor. The stellate and middle cervical ganglia are connected via the ansa subclavia, a nerve loop that encircles the subclavian artery on both sides and courses medial to the origins of the internal thoracic and vertebral arteries.

that pass through the stellate ganglion, for the most part, project to the to the head and neck. However, vasomotor and sudomotor fibers are not contained in the white ramus to the cervicothoracic ganglion. Postganglionic fibers from the stellate ganglion also travel within the inferior trunk of the brachial plexus above the first rib, and then within the ulnar, radial and median nerves. In the hand, the postganglionic fibers leave these nerves and travel with the corresponding arteries. Occasionally a vertebral ganglion may be present near the origin of the vertebral artery, which provides gray communicating rami to the fourth and fifth cervical spinal nerves.

The thoracic part of the sympathetic trunk consists of eleven or twelve ganglia arranged anterior to the costal heads, and are covered by the costal pleura. These ganglia are connected to the thoracic spinal nerves via the white and gray communicating rami. Frequently, the first thoracic and the inferior cervical ganglia join to form the cervicothoracic (stellate) ganglion. The second through the fifth thoracic ganglia provide sympathetic fibers to the posterior pulmonary and deep cardiac plexuses, while the upper five thoracic ganglia provide sympathetic fibers to the aortic plexus. Presynaptic fibers, mainly from the T1-T6 (T7), which are destined to the cervical ganglia en route to the head, neck, and upper extremity, also travel within the cervical ganglia. Since vasoconstrictors to the upper extremity primarily emerge from the second and third spinal segments, excision of the corresponding thoracic ganglia (second and third) may denervate the vessels of the upper extremity. Presynaptic sympathetic fibers from the fifth through the ninth ganglia form the greater splanchnic nerve (Figure 9.4), presynaptic fibers from the tenth and eleventh ganglia form the lesser splanchnic nerve, whereas fibers that emanate from the twelfth thoracic ganglion form the least splanchnic nerve.

The lumbar part of the sympathetic trunk is connected to the thoracic part via the gap posterior to the medial arcuate ligament. The lumbar sympathetic ganglia receive white communicating rami from the upper four lumbar spinal nerves. These ganglia, which are located medial to the psoas major muscle and anterior to the lumbar vertebrae, give rise to the lumbar splanchnic nerves (preganglionic sympathetic fibers) that join the celiac, intermesenteric and the superior hypogastric plexuses.

Pain relief from the upper extremity, alleviation of vascular spasm in the hands (seen in Raynaud's disease) or hyperhidrosis (excessive sweating) may be achieved by injection of anesthetic solution into the stellate ganglion (stellate block). Success of this procedure may be ascertained by the appearance of signs of Horner's syndrome and increase temperature of the ipsilateral upper extremity.

The sacral part of the sympathetic trunk lies anterior to the sacrum and medial to the pelvic sacral foramina. It joins the sacral ganglia of the opposite side via the ganglion of impar. These ganglia receive preganglionic fibers from the lower thoracic and upper two lumbar spinal segments, giving rise to gray rami that join the sacral and coccygeal plexuses.

Prevertebral ganglia

The prevertebral ganglia (Figures 9.1 & 9.4) lie anterior to the lumbar part of the vertebral column, comprising the celiac, aorticorenal, superior mesenteric, and the inferior mesenteric ganglia. The celiac ganglia, the largest prevertebral ganglia, are located on both sides of the celiac trunk and medial to the suprarenal glands. The caudal (lower) part of each celiac ganglion is known as the aorticorenal ganglion. Much smaller ganglia, such as the superior and inferior mesenteric, are lodged within the corresponding plexuses.

Course of the sympathetic fibers

Axons of the sympathetic preganglionic neurons that project to the paravertebral ganglia usually follow an orderly course through the ventral root, spinal nerve and the white communicating rami. This is not true in the cervical and sacral segments which lack the corresponding white communicating rami that connect the spinal nerves to the paravertebral ganglia. Postganglionic axons of the sympathetic ganglia may follow diverse course which depends upon the site of termination (Figures 9.4 & 9.8). Most fibers return to the spinal nerves via the gray communicating rami. This route is followed by fibers that innervate the sweat glands, erector pilorum muscles, and the vessels of the extremities, thoracic and abdominal walls. Other fibers, which ascend to synapse in the superior cervical ganglion, form plexuses around major blood vessels destined to the head and neck region (e.g. sweat glands of the face and the dilator pupillae muscles). The sympathetic postsynaptic fibers to the lower face arise from the external carotid plexus, a network of sympathetic fibers that encircle and follow the course of the corresponding artery. Sympathetic fibers to the sweat glands of the supraorbital region are contained within the

Postganglionic fibers from the prevertebral plexuses travel in the femoral and obturator nerves, supplying vasoconstrictor fibers to the femoral and obturator arteries and their branches. Therefore, surgical removal of the upper three or four lumbar ganglia or their preganglionic neurons may completely denervate the lower extremity vessels.

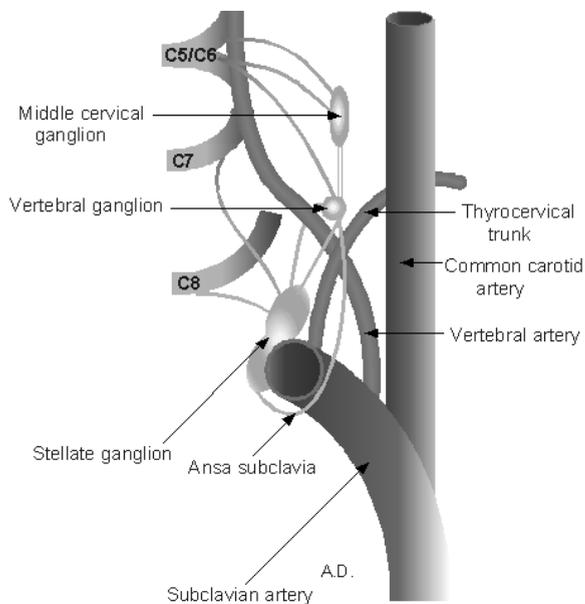


Figure 9.7 Drawing of the middle cervical and stellate ganglia and the connecting ansa subclavia

supraorbital and supratrochlear branches of the frontal nerve. The latter, a branch of the ophthalmic nerve, receives its sympathetic fibers by communicating with nasociliary nerve. Innervation of the dilator pupillae muscle is maintained by the postsynaptic sympathetic fibers that travel within the long ciliary branch of the nasociliary nerve. Sympathetic postsynaptic fibers to the superior tarsal muscle of the upper eyelid originate from the internal carotid plexus, as it travels within the cavernous sinus, and are contained within oculomotor nerve. An interesting point to bear in mind is the fact that both the sympathetic postsynaptic fibers to the superior tarsal and the somatic fibers to the levator palpebrae muscles course within the oculomotor nerve. Sympathetic postganglionic fiber to the thoracic viscera originates from the cervical and upper five thoracic paravertebral ganglia. Some fibers that are destined to the abdominal viscera bypass the sympathetic trunk to terminate in the prevertebral ganglia as the splanchnic nerves (Figures 9.1 & 9.4). The greater splanchnic nerve consists of preganglionic efferent and visceral afferent fibers that penetrate the crus of the diaphragm to enter the abdomen, establishing synaptic connections primarily with the celiac ganglion and partially with the aorticorenal ganglion. The lesser splanchnic nerve synapses in the aorticorenal ganglion, whereas the least splanchnic nerve (renal nerve) contributes to the renal plexus. Fibers that bypass both the paravertebral and prevertebral ganglia remain preganglionic and terminate in the chromaffin tissue of the adrenal medulla.

Parasympathetic (cranio-sacral) system

The parasympathetic is a local-response system, consisting of pre- and postganglionic neurons that act on the smooth muscles and viscera. The preganglionic parasympathetic fibers are contained in the pelvic splanchnic nerves and certain cranial nerves (Figures 9.1, 9.9 & 9.10). These preganglionic fibers establish connections with the postsynaptic parasympathetic neurons of the intramural ganglia (on pelvic and abdominal viscera) or with parasympathetic ganglia in the head. Parasympathetic responses are manifested in miosis (constriction of the pupil), contraction of the ciliary muscle, decreased contractility and cardiac output (negative inotropic and chronotropic effect), and constriction of the bronchi and bronchioles. Other manifestations include increased gastrointestinal tract motility, constriction of the coronary arteries and vasodilatation of the vessels of the external genitalia, and gastrointestinal tract, and contraction of the muscular wall of the urinary bladder (dilation of cerebral vessels are primarily due to change in CO₂ concentration).

Acetylcholine, the main neurotransmitter at parasympathetic terminals, is contained in the clear-spherical vesicles, acting primarily in conjunction with cotransmitters such as VIP (vasoactive intestinal peptide) and to a lesser degree ATP. Due to the rapid degradation of acetylcholine and the lesser degree of divergence (low ratio of preganglionic to postganglionic neurons), the action of the parasympathetic system remains localized and of short duration. Cholinergic receptors, which are activated by acetylcholine, are classified into nicotinic and muscarinic types.

Nicotinic receptors are further subdivided into nicotinic muscle receptor and nicotinic neuronal receptor.

Nicotinic muscle receptors (C-10 receptor) are pentameric protein, activation of which produce rapid increase in permeability of cells to sodium and calcium ions and subsequent depolarization and contraction of the skeletal muscle. Phosphorylation by cAMP protein kinase, protein kinase C, or trypsin kinase increases the desensitization of these receptors. Muscle receptor contains α , β , γ , and δ or α , β , δ , and ϵ subunits in a pentameric complex. The reason for the difference is because ϵ subunit replaces the γ in the adult. Subunit γ is particularly detected in the embryo or denervated muscle.

Neuronal nicotinic receptors are categorized into two subunits α and β with the α occurring in at least seven different forms and β in three forms. They exist in the autonomic ganglia, adrenal medulla and CNS. Neuronal nicotinic receptors are classified into bungarotoxin-insensitive (C-6) and bungarotoxin-sensitive nicotinic receptors. The former exists in the autonomic ganglia and produce depolarization and firing of the postganglionic neurons in the autonomic ganglia via opening of the

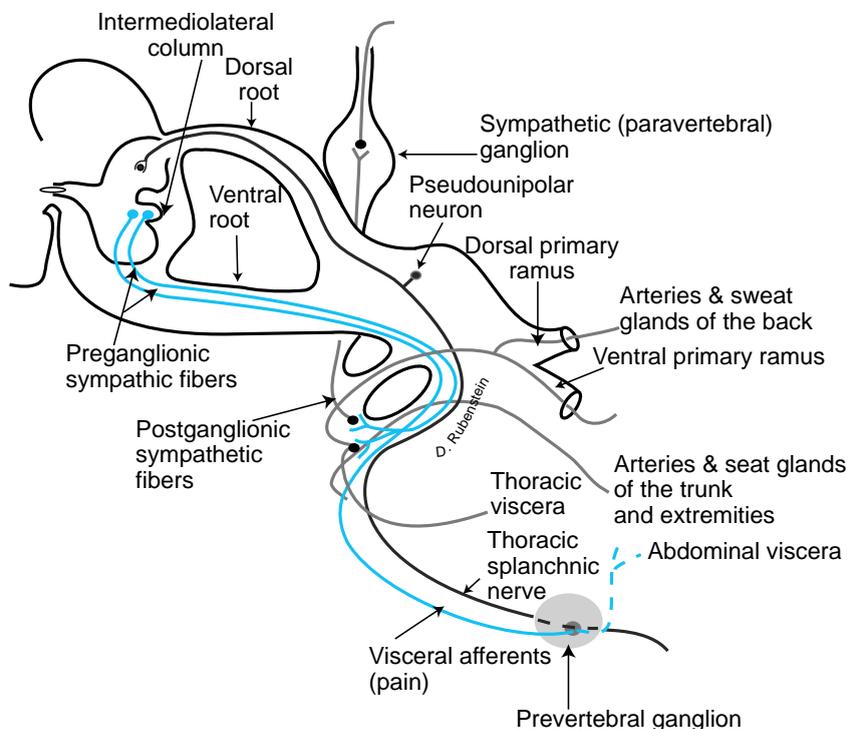


Figure 9.8 The functional components of a spinal nerve including general somatic afferent, general visceral afferent, general somatic efferent and general visceral efferent are shown

cation channel. There are numerous agonists for these receptors such as nicotine, phenyltrimethyl-ammonium, methylisoarecolone, cytisine, and dimethylphenylpiperazinium, as well as plethora of antagonists such as tubocurarine, lophotoxin, and dihydro-b-erythroidine.

Muscarinic receptors are coupled to G-proteins, and either acts directly or indirectly on ion channels or linked to second messenger systems. They are classified on pharmacological basis into M1-M3, and on the basis of molecular cloning into M4-M5 subtypes. All five subtypes exist in the central nervous system. M1 receptors show great affinity to pirenzepine and are found in the autonomic ganglia and glands. AFDX-116 shows high affinity to M2 receptors in the myocardium and smooth muscles, whereas 4-DAMP displays high affinity to M3 receptors in the smooth muscles and secretory glands. M₁, M₃, and M₅ are coupled to PI hydrolysis and M₂ and M₄ are coupled to cAMP.

Activation of the muscarinic receptors produces depolarization or hyperpolarization by opening or closing the potassium, calcium or chloride channels. Activation of M₁ receptors produces depolarization in the neurons of the autonomic ganglia. Stimulation of the M₂ receptors elicits hyperpolarization in the SA node, and a decrease in the atrial contractile force and conduction velocity in the AV node, and a slight decrease in the ventricular contractile force. Activation of the M3 receptors produces

contraction of the smooth muscles and increased glandular secretion.

Acetylcholine acts upon the muscarinic receptors on the exocrine glands, heart, and smooth muscles. Cholinergic receptors are nicotinic in the autonomic ganglia and muscarinic at the postganglionic parasympathetic nerve endings. In the central nervous system both muscarinic and nicotinic receptors exist. The combined effect of the muscarinic autoreceptors on the nerve endings (comparable to the α_2 autoreceptors of the sympathetic system) and acetylcholinesterase may prevent accumulation of acetylcholine in the synaptic cleft.

The parasympathetic system consists of cranial and sacral parts. The cranial part (Figures 9.9 & 9.10) consists of preganglionic neurons that course within the oculomotor, facial, glossopharyngeal, and vagus nerves.

The oculomotor nerve (III) contains preganglionic parasympathetic fibers, which are derived from the Edinger-Westphal subnucleus of the oculomotor nuclear complex. These fibers synapse in the ciliary ganglion, giving rise to postsynaptic fibers eventually innervate the constrictor pupillae and the ciliary muscles. CN III- (inferior branch) ———> ciliary ganglion ———> constrictor pupillae & ciliary muscle.

The facial nerve (VII) contains preganglionic parasympathetic fibers that emanate from the neurons of the lacrimal and superior salivatory nuclei, establishing

Cholinergic agents like carbachol (stimulates the bladder and bowel) and pilocarpine (produces constriction of the pupil) have similar effects to acetylcholine. Some of these agents act by inhibiting the enzyme cholinesterase and subsequently increasing the concentration of acetylcholine in the synaptic clefts. These cholinesterase inhibitors include physostigmine and diisopropylfluorophosphate (DFP). Others, such as tubocurarine act as an antagonist by competing with natural mediators at the synaptic site. Anticholinergic medications may be used clinically to: a) induce dryness of the bronchi during surgery, b) maintain dilatation of the pupil for in-depth ophthalmologic examination, c) block the vagal inhibition in case of cardiac arrest, d) prevent vomiting (antiemetic), e) counteract the spastic effect of morphine on the gastrointestinal tract, f) treat poisoning by overdose of cholinergic drugs, and g) cause relaxation of the urinary bladder in individuals with cystitis.

synapses in the pterygopalatine (sphenopalatine) and the submandibular ganglia, respectively. The postsynaptic parasympathetic fibers from the pterygopalatine ganglion supply the lacrimal gland, mucus glands of the palate, nasal cavity, and pharynx. On the other hand, the postsynaptic parasympathetic fibers from the submandibular ganglion innervate the submandibular and sublingual glands. CN VII → greater petrosal nerve → pterygopalatine ganglion → lacrimal gland, mucus glands of the palate, and nasal cavity and pharynx. CN VII- chorda tympani → submandibular ganglion → sublingual & submandibular glands.

The glossopharyngeal nerve (IX) contains preganglionic parasympathetic fibers from the medullary inferior salivatory nucleus that synapse in the otic ganglion. This ganglion sends postsynaptic secretomotor fibers to the parotid gland via the auriculotemporal nerve. CN IX → lesser petrosal nerve → otic ganglion → parotid gland.

The vagus nerve (X) contains preganglionic parasympathetic fibers, which are derived from the medullary dorsal motor nucleus of vagus. These fibers synapse in the terminal (intramural) ganglia scattered along the thoracic and abdominal viscera (e.g. the pulmonary, myenteric, and submucosal plexuses). Intramural ganglia contain in abundance neurons, which are non-adrenergic and non-cholinergic. They may also contain excitatory transmitters such as serotonin and substance P or inhibitory transmitters such as VIP, ATP or enkephalin. The vagal parasympathetic contributions to the abdominal viscera terminate at the junction of the right 2/3 and left 1/3 of the transverse colon.

Sacral part

The sacral part (Figure 9.1) of the parasympathetic system includes the parasympathetic preganglionic axons, emanating from the intermediolateral column of the second, third, and fourth sacral spinal segments. The axons of these neurons leave through the ventral roots of the corresponding segments and form the pelvic splanchnic nerves, which supply the pelvic viscera and part of the abdominal viscera. The pelvic splanchnic nerves are excitatory to the muscular wall of the descending colon, sigmoid, rectum and anal canal, as well as to a portion of the transverse colon. These splanchnic nerves are inhibitory to the urethral sphincters and vasodilator to the erectile tissue of the external genitalia.

Autonomic centers

Higher autonomic centers represent specific areas in the cerebral cortex, diencephalon, and the brainstem that closely regulate the ANS. This is based on the fact that stimulation or inhibition of these centers produces a variety of visceral changes. Autonomic centers in the cerebral cortex are scattered in the cingulate gyrus and hippocampal formation. In the diencephalon parasympathetic (anteromedial) and sympathetic (posterolateral) centers are located in the hypothalamus.

Hypothalamic control of the brainstem and spinal autonomic neurons is achieved via the dorsal longitudinal fasciculus (DLF), the mammillotegmental tract, and the medial forebrain bundle (MFB). The DLF connects the medial hypothalamus to the dorsal motor nucleus of vagus, nucleus ambiguus, salivatory and Edinger-Westphal nuclei, as well as the intermediolateral columns of the spinal cord. Medial hypothalamic neurons also send fibers to the dorsal motor nucleus of vagus, locus ceruleus, and raphe nuclei via the MFB. Brainstem raphe nuclei project to the prefrontal cortex, septal area, and cingulate gyrus also via the MFB.

The mammillotegmental tract are formed by the axons of the mammillary neurons that project to the raphe nuclei and other nuclei of the mesencephalic and pontine reticular formation.

In the brainstem, the pontine autonomic is comprised of a cardiovascular center in the caudal pons between the superior olivary nucleus and the root of the facial nerve. The medullary autonomic (respiratory) is comprised of the inspiratory center around the solitary nucleus that contains opiate receptors upon which morphine acts as a depressant, and an expiratory center around the ambiguus nucleus. The latter projects to the motor neurons of the thoracic spinal segments, innervating the internal and innermost intercostals. The pneumotoxic center is

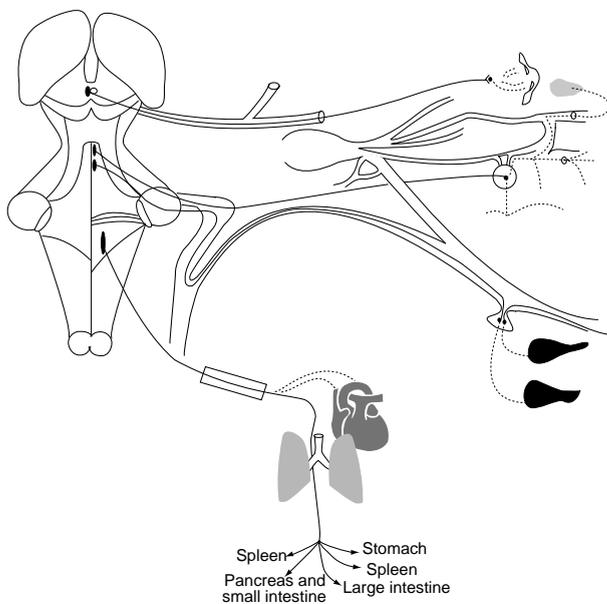


Figure 9.9 Cranial part of the parasympathetic nervous system. Note the associated nuclei, preganglionic fibers, and related ganglia

comprised of the parabrachial nuclei of the pons, which influences the rate of breathing by shortening the respiratory cycle.

Autonomic reflexes

A reflex is an innate, automatic response to a stimulus that occurs as a basic defense mechanism. It may be inherited or primitive, present at birth, and is common to all human beings. It may also be conditioned, which is acquired as a result of experience. Intactness of the receptor, sensory (afferent) neuron and a motor (efferent) neuron are essential for typical reflex to occur. Afferent fibers deliver the generated impulses from a receptor to the central nervous system where it may be inhibited, facilitated, or modified, while the efferent fibers transmit the processed information to the effector organ. An interneuron may exist between the afferent and efferent neurons. Reflexes do not always operate independently; in fact descending supraspinal pathways (somatic and visceral) modulate and regulate the neurons, which form the reflex arc. Conditions that affect the neural elements of a reflex arc or their supraspinal input may produce a variety of deficits. A lesion, which disrupts the reflex arc, may result in hyporeflexia or areflexia depending on the number of the involved segments. In peripheral neuropathy and

Transection of the lower pons disrupts the descending fibers from the pneumotaxic center, resulting in a deep respiratory cycle (apneustic breathing).

poliomyelitis, the receptor, afferent or the efferent neurons of a reflex arc may be damaged, producing hyporeflexia or areflexia.

Damage to the supraspinal pathways may produce, hyperreflexia, hyporeflexia, or areflexia (e.g. upper motor neuron palsy manifests both deep tendon hyperreflexia, and areflexia or hyporeflexia in the superficial abdominal reflexes).

Reflexes are categorized into superficial reflexes associated with the skin and mucus membrane and deep reflexes pertaining to the muscles and tendons. Reflexes may be mediated by cranial nerves (cranial reflexes) or spinal nerves (spinal reflexes). Additional classifications into visceral and somatic reflexes are based upon the nature of the innervated structure.

Visceral reflexes include visco-visceral and visco-somatic reflexes, while somatic reflexes comprise somato-somatic and somato-visceral reflexes. Visceral reflexes facilitate automatic adjustments of the entire organism to the internal and external environments. In order to promote digestion, some of these reflexes produce an increase in blood flow to the digestive tract following food ingestion, and decrease in absorption. Other reflexes may increase the rate and depth of respiration to meet the body's demand for oxygen in response to physical activity. Visceral reflexes are classified into visco-visceral, visco-somatic, and somato-visceral reflexes.

Visco-visceral reflexes include the carotid sinus, Bainbridge, and carotid body reflexes.

- Carotid sinus reflex is mediated by the carotid sinus (receptor), the carotid sinus branch of the glossopharyngeal (afferent limb), reticular formation, and the vagus nerve (efferent limb). An increase in blood pressure will stimulate the carotid sinus and activates the neural mechanism that adjusts the blood pressure to normal level.
- Bainbridge reflex monitors the central venous pressure through afferent nerve endings in the right atrium. These endings are represented by the peripheral processes of the neurons of the inferior ganglion of the vagus nerve. Distention of the right atrium produces reflex tachycardia due to vagal inhibition and sympathetic stimulation.
- Carotid body reflex is initiated by an increase in carbon dioxide and a decrease in oxygen tensions of the blood. These changes stimulate the carotid body (chemoreceptor) and eventually the respiratory center through the vagus nerve.

Visco-somatic reflexes comprise Hering Breuer, and vomiting reflexes.

- Hering Breuer reflex initiates expiration upon excitation of the terminals of the bronchial tree of the inflated lung. These excited terminals stimulate the expiratory center and the solitary nucleus. The expiratory center inhibits the

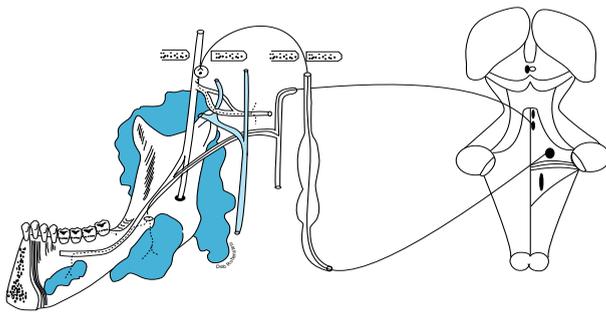


Figure 9.10 The sympathetic neurons associated with innervation of the thoracic viscera (heart, lungs and bronchi)

inspiratory center, eliciting passive and elastic recoil of the lung.

- Vomiting reflex is mediated by receptors, which are located in the mucosa of the stomach, gall bladder, or the duodenum. Activation of these receptors results in transmission of the generated impulses via the vagus nerve (afferent limb) to the solitary nucleus, medullary vomiting center, reticulo-spinal tracts, and neurons of the anterior horn and the intermediolateral columns of cervical and thoracic spinal segments.
- Somato-visceral reflexes are comprised of pupillary light, pupillary-skin (ciliospinal), accommodation, bladder and rectal reflexes, and mass reflex of Riddoch.
- The pupillary light reflex produces constriction of the pupil of the stimulated eye (direct light reflex) and the contralateral eye (consensual light reflex) in response to direct light applied to one eye. This reflex is mediated by the optic and the oculomotor nerves. The optic nerve, the optic tract, and the brachium of the superior colliculus form the afferent limb of this reflex. The pretectal nucleus, Edinger-Westphal nucleus, oculomotor nerve, ciliary ganglion, and the short ciliary nerves comprise the efferent limb.
- The pupillary-skin (ciliospinal) reflex is characterized by pupillary dilatation in response to painful stimuli. It may be elicited by a simple scratch, pinch, or a cutaneous wound, especially involving the facial skin. The afferent limb, (depending upon the site of the stimulus) may include neurons of the dorsal root ganglia or the trigeminal nerve, as well as neurons of the posterior horn or the spinal trigeminal nucleus. The efferent limb includes the reticular formation, reticulospinal tracts, intermediolateral columns of the first thoracic spinal segment, and the sympathetic pathway to the dilator pupillae muscle of the eye.
- The accommodation reflex adjusts both eyes to near vision, involving convergence (adduction) of the eyes, constriction of the pupils, and increase curvature of the

Pupillary light reflex is lost in the Argyll Robertson pupil, which results from destruction of the area medial to the lateral geniculate nucleus and is associated with neurosyphilis. In this condition the pupil remains unresponsive to atropine. Loss of light reflex may also be seen in diabetes mellitus, epidemic encephalitis, and alcoholism.

lens in both eyes. The input for this reflex is carried from the retina by the optic nerve, optic tract, lateral geniculate body, and optic radiation to the visual cortex. The efferent impulses travel and eventually via the short ciliary nerves to the ciliary body and the constrictor pupillae muscle.

The bladder and rectal reflexes regulate the sphincteric control of micturition and defecation via the pelvic splanchnic nerves. Incontinence may occur as a result of disruption of this reflex arc. The urge to urinate or defecate may be lost upon interruption of the afferent fibers.

The mass reflex of Riddoch is characterized by sudden evacuation of the bladder and bowel, flexion of the lower extremity, and sweating in response to emotional stimulus.

Autonomic plexuses

Autonomic plexuses represent network of visceral nerve fibers, which innervate structures in the thoracic, abdominal, and pelvic cavities. They are formed by sympathetic and parasympathetic nerve fibers and associated ganglia. They derive their names from the corresponding arteries that are associated with. These comprise the cardiac, celiac, suprarenal, renal, ureteric, superior mesenteric, aortic, inferior mesenteric, and superior and inferior hypogastric plexuses.

The cardiac plexus (Figures 9.4 & 9.10) provides innervation to the heart and the coronary arteries, consisting of deep and superficial parts. The superficial part of the cardiac plexus lies below the aortic arch and is formed by the cardiac branch of the left superior cervical ganglion, and by the parasympathetic fibers of the vagus nerve. The deep part of this plexus lies anterior to the bifurcation of the trachea and is formed by the cardiac branches of the cervical (with the exception of the left superior cardiac branch) and upper four or five thoracic ganglia. In contrast branches of the vagus and the recurrent laryngeal nerves form the parasympathetic component. Postganglionic fibers from the right vagus nerve establish synaptic connection with the sinoatrial node and with both atria. On the other hand, the postsynaptic fibers from the left vagus nerve act on the ventricular myocardium and the AV bundle. Reduction of the contractile force of the heart and rate of contraction are achieved by stimulation of the vagus nerves that act upon the muscarinic receptors of the cardiac nodal tissue and atria.

The mass reflex of Riddoch may be elicited in individual with spinal shock by stimulating the skin below the level of the spinal lesion.

The presynaptic muscarinic receptors on the sympathetic fibers are also inhibited by stimulation of the vagus nerves. Sympathetic postganglionic fibers act upon the β_1 and to lesser degree α receptors in the sinoatrial and atrioventricular nodes, atrioventricular bundle and ventricular myocardium. Activation of the β_2 receptors in the coronary arteries, by the circulating epinephrine, produces relaxation of the vessels. Cholinergic presynaptic α_2 receptors on branches of the vagus nerve may also be inhibited by the sympathetic postganglionic fibers.

Subsidiaries of the cardiac plexus are the coronary plexuses that surround the coronary arteries.

The left coronary plexus is an extension of the deep cardiac plexus, supplying the left atrium and left ventricle. The right coronary plexus innervates the right chambers of the heart, and is formed by the fibers of the deep and superficial parts of the cardiac plexus. The sympathetic fibers of this plexus, upon activation, produce coronary vasodilatation, while the parasympathetic fibers elicit vasoconstriction. The cardiac plexus continues with the pulmonary plexuses (Figure 9.11) around the corresponding arteries.

The pulmonary plexus, which lies partly anterior and partly posterior to the pulmonary hilus, receives parasympathetic fibers from the vagus nerve and sympathetic fibers from the second through the fifth thoracic spinal segments. This plexus innervates the pulmonary arteries, bronchi, and bronchial arteries.

The celiac plexus (Figures 9.4 & 9.12) surrounds the celiac trunk, and lies anterior to the diaphragmatic crura and medial to the suprarenal glands. It receives sympathetic fibers via the greater splanchnic (T5-T9 spinal segments) and the lesser splanchnic (T9-T11 spinal segments) nerve. The parasympathetic fibers are derived from the vagus nerve. This plexus which also receives somatic fibers via the phrenic nerves, contains the celiac ganglia (visceral brain) where the greater and lesser splanchnic nerve establish synaptic connections. Due to the proximity of the lower part of the celiac ganglion (aorticorenal ganglion) to the renal artery, it contributes postsynaptic parasympathetic fibers to the renal plexus. The celiac, as the mother of all abdominal plexuses, has subsidiary plexuses which innervate the liver, gallbladder, diaphragm, stomach, duodenum, spleen, adrenal glands, kidneys, and testes or ovaries (Figure 9.9).

Hepatic plexus, a continuation of the celiac plexus, surrounds the common hepatic artery and its branches and supplies the liver and gallbladder. Activation of the vagal parasympathetic fibers produces contraction of the gallbladder, bile duct, and relaxation of the sphincter of

Cardiac pain (e.g. due to myocardial ischemia) is transmitted by the C fibers of pseudounipolar neurons of the upper four or five thoracic spinal nerves that run in the middle and inferior cardiac branches of the sympathetic trunk. These fibers enter the dorsal horns of the corresponding spinal segments, synapse in certain laminae that form the anterolateral system. These connections may explain the referred pain to dermatomes of T1-T5, which is experienced by individual with acute myocardial infarction.

Oddi. This plexus receives sympathetic contribution from the seventh through the ninth spinal segments.

The gastric plexus consists of right and left plexuses; the right plexus, an extension of the hepatic plexus, innervates the pylorus. The sympathetic fibers produce contraction of the pyloric sphincter and inhibition of the gastric muscles, while the parasympathetic fibers maintain opposing effect. The left gastric plexus, another extension of the celiac plexus, surrounds the left gastric artery. It exerts similar effects upon the stomach and pylorus. The sympathetic fibers, which supply the stomach, are derived from the T6 to the T10 thoracic spinal segments.

The suprarenal plexus is formed largely by the preganglionic sympathetic fibers of T8-L1 spinal segments that synapse in the chromaffin cells of the adrenal medulla.

The renal plexus surrounds the renal arteries and is formed by the sympathetic fibers of the lesser splanchnic nerve (T10-T11), least splanchnic nerve (T12), and the first lumbar splanchnic nerve (L1), primarily exerting a vasomotor action. The vagal parasympathetic fibers serve as afferents, terminating in the wall of the kidney. This plexus also contribute to the ureteric and the gonadal plexuses.

The ureteric plexus receives sympathetic fibers from (T11-L1) spinal segments and parasympathetic fibers from the vagus and pelvic splanchnic nerves. Due to its close relationships to the abdominal and pelvic viscera, the ureteric plexus receives fibers from diverse sources including the aortic, renal, vesical and hypogastric plexuses.

The superior mesenteric plexus (Figures 9.4 & 9.12) is a continuation of the celiac plexus which is formed by sympathetic fibers of the ninth, tenth, eleventh, and twelfth thoracic and the first lumbar (T10-L1) spinal segments, and by the parasympathetic fibers of the vagus nerve. This plexus supplies part of the duodenum, jejunum, ileum, and approximately the right 2/3 of the large intestine.

The aortic (intermesenteric) plexus (Figures 9.4 & 9.12) encircles the aorta between the superior and inferior mesenteric arteries. It contributes to the testicular, inferior mesenteric, and the hypogastric plexuses.

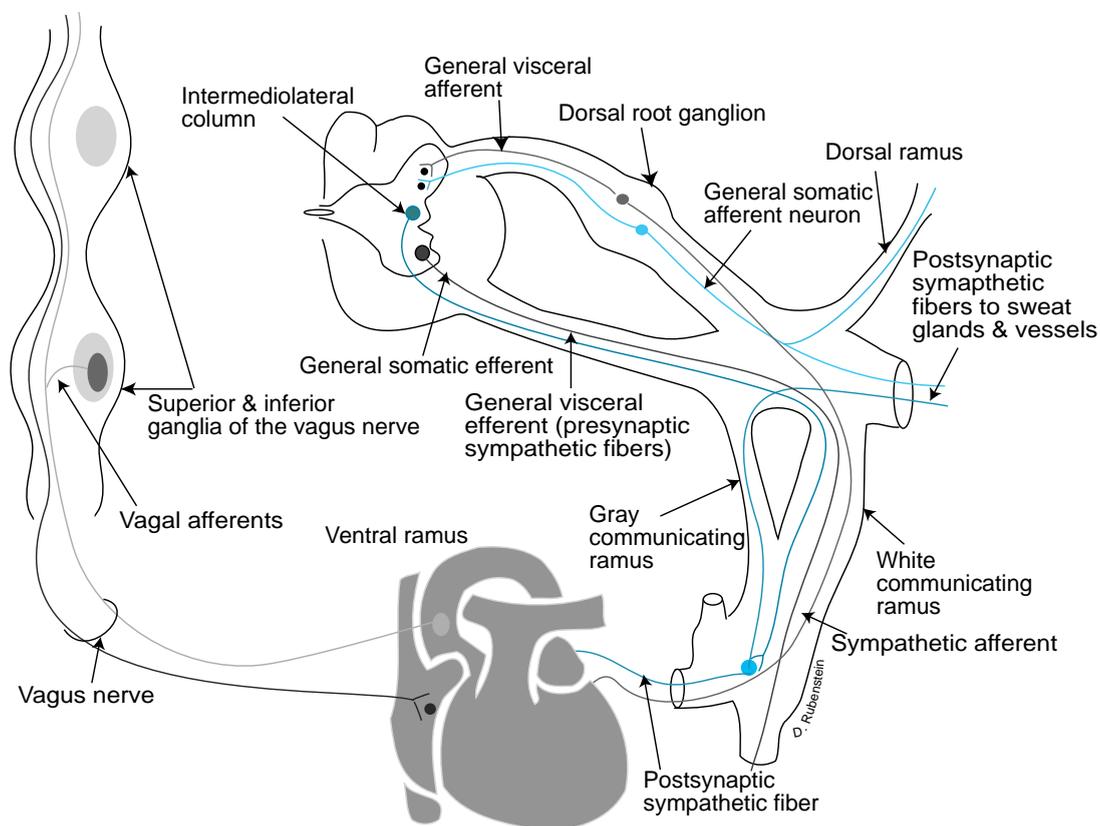


Figure 9.11 Diagram of the sympathetic neurons associated with innervation of the thoracic viscera (heart, lungs, and bronchi)

The inferior mesenteric plexus (Figures 9.4 & 9.12) surrounds the inferior mesenteric artery, containing sympathetic and parasympathetic fibers. The sympathetic fibers, which are inhibitory to the muscular walls of the descending colon, sigmoid colon, and upper part of the rectum, are derived from the first and second lumbar (L1 & L2) spinal segments. The parasympathetic fibers of the pelvic splanchnic nerves are excitatory, originating from the second, third, and the fourth (S2-S4) sacral spinal segments.

The superior hypogastric (presacral) plexus (Figure 9.4) is a continuation of the inferior mesenteric plexus. It receives sympathetic fibers from the eleventh thoracic through the second lumbar (T11-L2) spinal segments, and parasympathetic fibers from the pelvic splanchnic nerves (S2-S4 spinal segments). It runs anterior to the sacrum, sacral promontory and sacral plexus. It then divides into the right and left inferior hypogastric (pelvic) plexuses, supplying the pelvic structures.

The inferior hypogastric (pelvic) plexus (Figure 9.4) runs on both sides of the rectum, the uterus, and bladder, and gives rise to the vesical, middle rectal, prostatic, and the uterovaginal plexuses. It contains parasympathetic fibers from the pelvic splanchnic nerves and sympathetic

fibers from the lower thoracic and the upper lumbar (T12-L1 spinal segments). The uterovaginal part of the pelvic plexus supplies the serosa, myometrium, and the endometrium, as well as the vagina. The sympathetic fibers derived from the T12-L1 spinal segments produce uterine contraction and vasoconstriction, while the parasympathetic fibers produce relaxation of the myometrium and vasodilatation.

The vesical plexus, a subsidiary of the inferior hypogastric plexus, causes contraction of the detrusor muscles via the pelvic splanchnic nerves (parasympathetic), mediating micturition. The sympathetic component is derived from T11-L2 spinal segments, which also supplies motor fibers to the vas deferens and the seminal vesicle.

The prostatic plexus, another subsidiary of the inferior hypogastric plexus, supplies the urethra, bulbourethral glands, corpora cavernosa, and corpus spongiosum via the lesser and greater cavernous nerves. The sympathetic part of the prostatic plexus controls ejaculation, inhibits detrusor musculature of the bladder, and induces vasoconstriction. The parasympathetic part is formed by the pelvic splanchnic nerves, producing vasodilatation and erection.

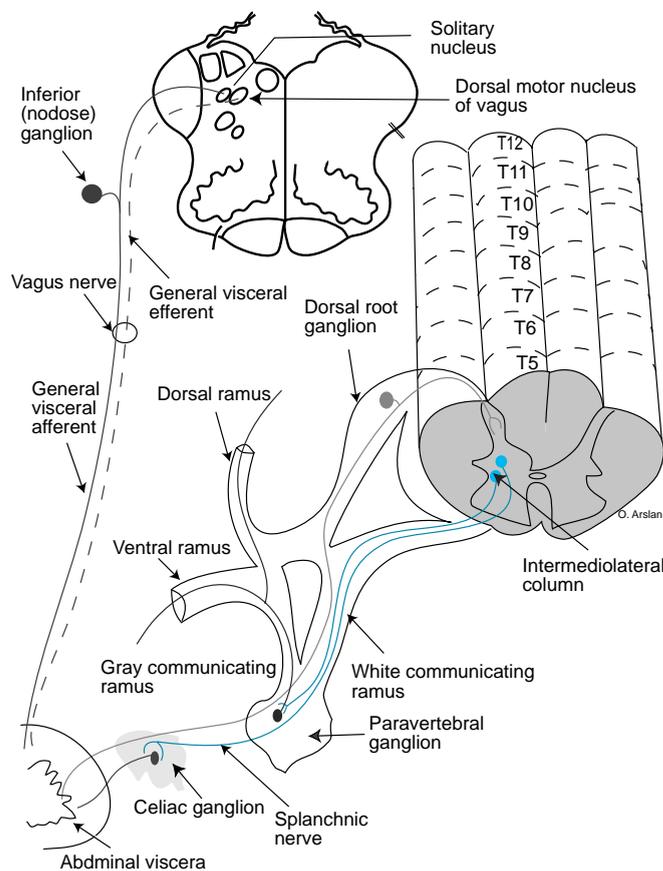


Figure 9.12 Schematic drawing of the sympathetic innervation of the abdominal viscera. Note the role of the celiac ganglia in mediating this innervation

Enteric nervous system

The enteric nervous system, an integral part of the autonomic nervous system, consists of a group of neurons within the myenteric plexus of Auerbach and the submucosal plexus of Meissner's and Henle's, as well as the pancreatic and cystic plexuses, which are derived from the neural crest cells. The myenteric plexus is located between the circular and longitudinal muscle layers, extending from the esophagus to the level of the internal anal sphincter. On the other hand, the submucosal plexus lies between the circular muscle and muscularis mucosa, stretching from the stomach to the anal canal. This system exerts a local reflex activity independent from the control of the brain and spinal cord. It is important to note that enteric nerves have more common features with the central nervous system than with the peripheral nerves. In fact, enteric nerves do not have collagenous coats, as is the case in the PNS. Further more, they lack the endoneurium and are supported by glial cells that resembles the astrocytes that contain glial fibrillary acidic protein (GFAP). Upon this network of neurons the motility and the secretory functions of the gastrointestinal tract from the middle third of the esophagus to the anorectal junction remain

dependent. The number of neurons associated with this system may be equivalent or exceeds the entire population of spinal neurons. This system of ganglia and plexuses is responsible for the induction of reflex peristalsis, independent of the direct commands of the brain. These ganglia maintain a blood-ganglion-barrier and are not pierced by vessels or connective tissue septa. Some neurons of this system may subservise sensory function, respond to changes in the morphology of bowel shape. Others are simply interneurons that receive input from sensory neurons and project to the parasympathetic postganglionic neurons.

Division of the sympathetic fibers of the superior hypogastric plexus (presacral neurectomy) may be performed in attempt to relieve pain associated with diseased pelvic viscera. However, dual transmission of pelvic pain via sympathetic and parasympathetic fibers may render complete analgesia an impossible task to achieve. In the male, removal of the superior hypogastric plexus may lead to loss of contraction of the seminal vesicles, prostate and the vas deferens, and eventual sterility.

Numerous neuropeptides have been identified within this system of neuronal network. This peptide may act to enhance or suppress the effects of transmitters or maintain a trophic role. Intrinsic motor neurons within this system may assume an excitatory role, utilizing acetylcholine and substance P as cotransmitters; others may project inhibitory effect using ATP (co-transmitter in the large and small intestine), vasoactive intestinal polypeptide (VIP), and NO (nitric oxide) as cotransmitters.

Somatostatin is widely distributed in the gastrointestinal tract and the δ cells of the pancreas where it inhibits the secretion of glucagon and insulin, a fact may prove significant in diabetic patients. It is present in the dorsal root ganglia and autonomic plexuses. In the CNS, it is concentrated in the hypothalamus, amygdala, and neocortex, where it facilitates responsiveness to acetylcholine. In Alzheimer's disease, formation of somatostatin neuritic processes and depletion of its SS-28 from the cortex are detected. Somatostatin-14, another form of this peptide may show reduction upon the administration of cysteamine as a treatment for the metabolic disease known as cystinosis.

Vasoactive intestinal peptide (VIP) is distributed in the pancreas, autonomic plexuses, and central nervous systems. It is also contained in the parasympathetic cholinergic neurons of the salivary glands. Secretion of this peptide increases the glandular secretion (enhances the secretory function of acetylcholine) and blood flow to the intestine (as a result of vasodilatation). VIP-related peptides include the growth hormone releasing hormone (GHRH) and pituitary adenylate cyclase activating peptide (PACAP). GHRH is isolated from the intestine, and PACA, as the name indicates, from the pituitary gland.

Afferent components of the autonomic nervous system

The peripheral processes of the dorsal root ganglia or certain cranial nerve ganglia usually accompany Autonomic (visceral) fibers. These afferent fibers, which are myelinated and unmyelinated, follow the course of the pre- and postganglionic neurons, terminating as capsulated receptors in the visceral and vascular walls. In addition to visceral pain, they also mediate visceral reflexes, and transmit organic visceral sensations, libido, distention, hunger, and nausea. Stimuli for visceral pain do not encompass cutting, burning, or crushing, but rather obstruction, and/or ischemia and distention of the visceral

Pain from the fundus and body of the uterus is received by the lower three thoracic spinal segments, while nociceptive stimuli from the cervix are received by the second, third, and fourth sacral spinal segments.

Lack of the parasympathetic ganglia in these plexuses, as a result of failure of migration of the neural crest cells, is responsible for congenital megacolon of Hirshsprung's disease, which is characterized by dilatation of the affected segment and constipation. Since constipation in patients with Parkinson's disease may also exhibit deficiency in dopaminergic neurons of the enteric system, a possible correlation between the migration of neural crest cells and dopamine may require further investigation. It may also be possible to use these enteric dopaminergic neurons as donor grafts. Other diseases that affect the PNS may also involve the enteric nervous system such as herpes simplex, diabetes mellitus, amyloidosis, Chaga's disease, etc.

wall. Visceral afferents utilize mechanoreceptors, chemoreceptors, thermoreceptors, and osmoreceptors.

Disorders of the autonomic nervous system

Autonomic disorders occur in a variety of diseases and condition which affect the autonomic centers in the central nervous system, descending autonomic pathways, or the preganglionic neurons in the spinal cord. They are also seen as a result of disruption of the postganglionic neurons in the paravertebral and prevertebral ganglia. These dysfunctions are comprised of the Hirschsprung's disease, hyperhidrosis, Raynaud's disease or phenomenon, spinal cord lesions, Horner's syndrome, stellate ganglion syndrome, Shy-Drager syndrome, botulism, Riley-Day Syndrome, reflex sympathetic dystrophy, achalasia, and Chagas disease.

Pain from viscera is predominantly carried by the sympathetic fibers and will be felt in the cutaneous areas of the spinal segments that originally provided the presynaptic neurons to the diseased viscus. Pain fibers from the bladder and anterior urethra is conducted by the pelvic splanchnic nerves and the superior and inferior hypogastric plexuses, as well as the lumbar splanchnic nerve. The hypogastric plexuses and the lumbar splanchnic nerves convey uterine pain, with the exception of the cervix, to the lower thoracic and upper lumbar spinal segments. Dysmenorrhea (intractable pain associated with menses) may be alleviated by excision of the superior hypogastric plexus. Nociceptive impulses from the uterine cervix is transmitted via the pelvic splanchnic nerves to the 2nd, 3rd, and 4th spinal segments. Afferents from the testis and ovary run through the gonadal plexuses that terminate in the 10th and 11th spinal segments. General visceral afferents are found in the glossopharyngeal and vagus nerves.

- Hirschsprung's disease (congenital megacolon) as previously described, is a condition which results from absence of the parasympathetic ganglia in the myenteric plexus of Auerbach. Loss of the peristaltic movement and subsequent constriction of the affected segment and retention of feces above the aganglionic segment characterize this disorder. This condition, which frequently involves the sigmoid colon and the rectum, is more common in males (see also developmental aspects).
- Hyperhidrosis (disorders of sweating) is characterized by increased sweating due to over-stimulation of the sympathetic postganglionic neurons which innervate the sweat glands. It may be associated with peripheral neuropathy and reflex sympathetic dystrophy. Palm sweating, due to social or situational nervousness, may be relieved, upon patient's consent, by removal of the second and third thoracic sympathetic ganglia.
- Raynaud's disease or phenomenon may be a primary idiopathic vascular disorder or secondary to other conditions. It is characterized by spasmodic vasoconstriction of the digital arteries of the extremities in response to cold or emotional stress. This phenomenon may occur secondary to a cervical rib, scleroderma, thoracic outlet syndrome, atherosclerosis of the brachial artery and connective tissue disease. It may be attributed to a lack of histamine induced vasodilatation subsequent to a lack of the neural mechanism for histamine release in individuals with intact hypothalamic sympathetic center. Emotional stimuli and cold may activate the sympathetic system, lowering the threshold for vasospastic response. It is characterized by intermittent pallor due to depletion of the blood in the capillary beds of the digits and cyanosis as a result of deoxygenation of the stagnant blood in the capillary beds. Color changes may involve redness of the affected digits (reactive hyperemia) as a result of dilation of the digital arteries and engorgement of the capillary beds with oxygenated blood may also be observed. This will confer a ruddy complexion to the skin of the digits. Small painful ulcers may appear on the tips of the digits. This condition may be treated by the oral administration of mild sedatives (e.g. phenobarbital) and reserpine. Prazosin and Ca antagonist nifedipine are known to be effective medications for this condition. Phenoxybenzamine and prostaglandins (thromboxane) are also indicated as a therapeutic measure.
- Spinal cord lesions produce autonomic disturbances, which vary with the level of injury. Lesions of the cervical and upper thoracic spinal segments are most likely to produce combined sympathetic and parasympathetic

dysfunctions, whereas damage to the lower thoracic segments are only associated with parasympathetic dysfunctions. Transection of the cervical part of the spinal cord may result in loss of all sensory and motor activities below the level of affected segment(s), as well as autonomic dysfunctions including loss of sweating, piloerection, loss of micturition, impotence, and hypotension (spinal shock). Recovery of autonomic functions may occur as a result of the release from cortical and hypothalamic control. Since changes in blood pressure in individuals with this condition may no longer be mediated by autonomic centers in the brainstem, cutaneous stimulation below the level of the lesion may produce a rise in blood pressure, mydriasis and sweating. Bladder function becomes automatic and urination may occur when it is full. Following these changes, patients may manifest a triple or mass reflex in which a mild cutaneous stimulus may produce flexion in all joints of the lower extremity (triple reflex) which disappears approximately four months following transection of the spinal cord.

- Horner's syndrome is characterized by miosis (constriction of the pupil), ptosis (drooping of the upper eyelid due to paralysis of the superior tarsal muscle), anhidrosis (lack of sweating) and apparent enophthalmos (sinking of the eyeball due to paralysis of the orbital muscle). Heterochromia, which refers to the diversity of colors in part or parts that should normally be one color, is a characteristic of congenital form of Horner's. In infants, Horner's syndrome may be associated with unpigmented iris that assumes a bluish or mixed gray and blue appearance. It may be caused by a lesion of the intermediolateral column of the first thoracic spinal segment or emerging ventral root, degeneration of the lateral medulla, lesion of the descending autonomic pathways from the hypothalamus, superior cervical gangliotomy, or syringomyelia. It may also be caused by percutaneous carotid puncture for cerebral angiography, intracavernous lesions, birth trauma, enlargement of the cervical lymph nodes, thoracic tumors, destruction of the internal carotid plexus, or hypothalamic lesion.

- Stellate ganglion syndrome is produced by compression of the stellate ganglion (as seen in Pancoast tumor of the apical lobe of the lung), exhibiting signs of Horner's syndrome and reflex sympathetic dystrophy. The latter manifests dryness of the skin of the upper extremity and vasodilatation.

- Achalasia refers to failure or incomplete relaxation of the lower esophageal sphincter, which is more common

in males. In this condition the normal peristalsis of the esophagus is replaced by abnormal contractions. It is classified into vigorous and classic achalasia. Vigorous achalasia resembles diffuse esophageal spasm, exhibiting simultaneous and repetitive contractions with large amplitude, whereas classic achalasia shows contractions of small amplitude. Secondary achalasia may result from infiltrating gastric carcinoma. Dysphagia, chest pain, regurgitation and pulmonary aspiration, and projectile vomiting characterize it. Emotional disorders and hurried eating may predispose the individual to this condition. Although esophageal myenteric plexus lack ganglia, the pathogenesis of this dysfunction is not well understood. Treatment may include administration of anticholinergics and calcium channel antagonists, or balloon dilatation. Surgical intervention in which the lower esophageal sphincter is incised may prove to be effective.

- Chagas disease is an infectious and zoonotic disease caused by *Trypanosoma Cruzi* and is transmitted from infected animals to humans by Reduviid bugs. Chagoma, an inflammatory lesion, is often seen at the site of entry of parasite. When the parasite enters through the conjunctiva, edema of the palpebrae and periocular tissue is a characteristic feature (Romana's sign). Heart is the most commonly affected organ, exhibiting cardiomyopathy, ventricular enlargement and thinning of their walls, mural thrombi and apical aneurysm. Right branch of His bundle is frequently damaged, producing AV block. Patients show signs of malaise, fever, and anorexia, which are associated with swelling of the face and lower extremities. This infectious parasitic agent may also cause destruction of the myenteric plexus in the esophageal, duodenal, colonic, and ureteric wall, producing megacolon, megaduodenum and megaureter. Lymphadenopathy, meningoencephalitis and increased incidence of esophageal varicosities are the main characteristics of this disease. This condition may be treated by nifurtimox, an effective drug against *Trypanosoma Cruzi* during acute phase of the disease.

- Shy-Drager Syndrome (idiopathic orthostatic hypotension) is a multisystem disorders which includes autonomic dysfunctions, ataxia, and upper motor neuron palsy. Autonomic dysfunctions comprise anhidrosis (lack of sweating), impotence, postural hypotension, mydriasis and pupillary asymmetry, bowel and bladder dysfunctions. The hallmark of this disease is postural hypotension, which is greater than 30/20 mm Hg on standing from a supine position. Patients also

exhibit Parkinsonian manifestations in which rigidity and bradykinesia are very conspicuous. Neuronal loss has been shown in the intermediolateral column of the thoracic spinal segments, peripheral autonomic ganglia, substantia nigra, locus ceruleus, olivary nuclei, caudate nucleus, and the dorsal motor nucleus of vagus. These cellular losses are accompanied by gliosis and in some cases with Lewy bodies, which are typical of Parkinson's disease. Men are more frequently affected than women are and the disease exhibits an insidious onset. Postural hypotension may be treated by medications that increase blood volume and by pressure (antigravity) stockings. Parkinsonian symptoms may be treated by the administration of sinemet or bromocriptine as well as a agonists.

- Botulism is caused by ingestion of food contaminated with *Clostridium botulinum* (anaerobic gram-positive organism), ingestion of spores and production of toxin, or as a result of wound infection with the same bacteria. It is a paralytic disease, which initially affects the cranial nerves, and expands to involve the limbs.

- Symptoms of botulism include autonomic disturbances such as nausea, vomiting, dysphagia, extremely dry throat, blurred vision, loss or diminished light reflex and ptosis, in addition to skeletal muscle paralysis. Descending paralysis which is symmetric involving the head, neck, arm and thorax is characteristic of this disease. Deep tendon reflexes are not generally affected, although gag reflex may be depressed. Patients may die from respiratory failure. Patients may be given antitoxin (equine antitoxin) as well as cathartics and enemas to eliminate the toxin supplemented with antibiotics.

- Riley-day syndrome (familial dysautonomia) is a familial recessive disorder of infants, which is characterized by a constellation of sensory and motor deficits. These deficits include hypopathia, hearing deficits and loss of taste. The autonomic disturbances in this syndrome include loss of lacrimation and loss of the mechanisms, which regulate blood pressure and temperature.

- Reflex sympathetic dystrophy exhibits pain and autonomic changes, occurring as a result of bone fracture, trauma to soft tissue, or myocardial infarction. The autonomic changes include increased sweating and vasoconstriction. Causalgia, a burning pain that is often accompanied by trophic cutaneous changes, is a form of reflex sympathetic dystrophy, occurring in partial lesion of a peripheral nerve such as the median or sciatic nerve.

Section 3

Peripheral nervous system

The peripheral nervous system (PNS) consists of somatic, visceral (autonomic), sensory, and motor nerve fibers. These fibers are contained within the spinal and cranial nerves. Virtually all spinal and cranial nerves, with the exception of the olfactory and optic nerves, are integral parts of the peripheral nervous system. However, the neuronal cell bodies which form the PNS are located within the central nervous system. This system is further classified into autonomic (visceral) and somatic nervous systems.

9 [Autonomic nervous system](#)

The autonomic nervous system (ANS) consists of neurons that extend in the peripheral and central nervous systems, regulating visceral motor and reflex activities, as well as emotional behavior. It is not a fully autonomous entity, as the name may imply, but rather an interdependent system that functions under massive input from the cerebral cortex. The ANS maintains, through its diverse connections with the somatic nervous system, a stable internal environment or milieu (homeostasis), which is essential for normal physiological functions. It consists of efferent and afferent fibers and central neurons in the spinal cord, brainstem, diencephalon, and the brain. The afferent component transmits visceral pain and organic visceral sensations (e.g. hunger, malaise, nausea, libido, bladder, and rectal fullness). The efferent component innervates the smooth muscles, glandular tissue, and sweat glands.

Autonomic neurons and ganglia

Sympathetic system

Paravertebral ganglia

Prevertebral ganglia

Course of the sympathetic fibers

Parasympathetic (cranial) system

Sacral part

Autonomic centers

Autonomic reflexes

Autonomic plexuses

Enteric nervous system

Afferent components of the autonomic dysfunction

Disorders of the autonomic nervous system

Autonomic neurons and ganglia

The autonomic nervous system (ANS) (Figures 9.1 & 9.2) regulates visceral motor activity, contraction of the blood vessels, glandular secretions and transmission of visceral sensations. This system maintains homeostasis, an essential element for the physiological functions of the visceral organs. As an interdependent entity, the ANS functions under the influence of the cerebral cortex and hypothalamus. In contrast to the somatic nervous system, the innervation of the ANS occurs through two sets of neurons; preganglionic and postganglionic neurons. Preganglionic neuronal cell bodies are located within the central nervous system (spinal cord and the brainstem), whereas the postganglionic neurons lie within the peripheral nervous system within the paravertebral, prevertebral or the intramural ganglia.

The multipolar neurons of these ganglia (Figure 9.3) establish facilitatory or inhibitory synapses with the adjacent neurons, interneurons, or afferent cholinergic fibers. Multiplicity and pattern of the synaptic connections between the preganglionic and postganglionic neurons are aimed at intensifying autonomic response.

The axons of the preganglionic neurons consist of thinly myelinated (group B) fibers, whereas axons of the postganglionic neurons are of the unmyelinated type (C-group), rendering the conduction of generated response much slower. In contrast, axons of somatic nerves are principally myelinated.

Terminals of the autonomic fibers in the smooth muscles contain varicosities and synaptic vesicles that resemble that of the somatic nerves. However, these terminals show diffuse and extensive branching in which a terminal nerve fiber may innervate several smooth muscle fibers. This branching is limited and well localized in the fast acting muscles such as the dilator and constrictor pupillae. The synaptic gaps in the ANS are much wider than that of the skeletal (somatic) muscles, which allow far greater diffusion capacity and account for the delayed response associated with this system relative to the somatic nervous system. The greater the synaptic gap the slower the degradation processes of the neurotransmitter and the resultant prolonged action.

Due to the direct and uninterrupted connections between the somatic neuronal axons and their targets (e.g.

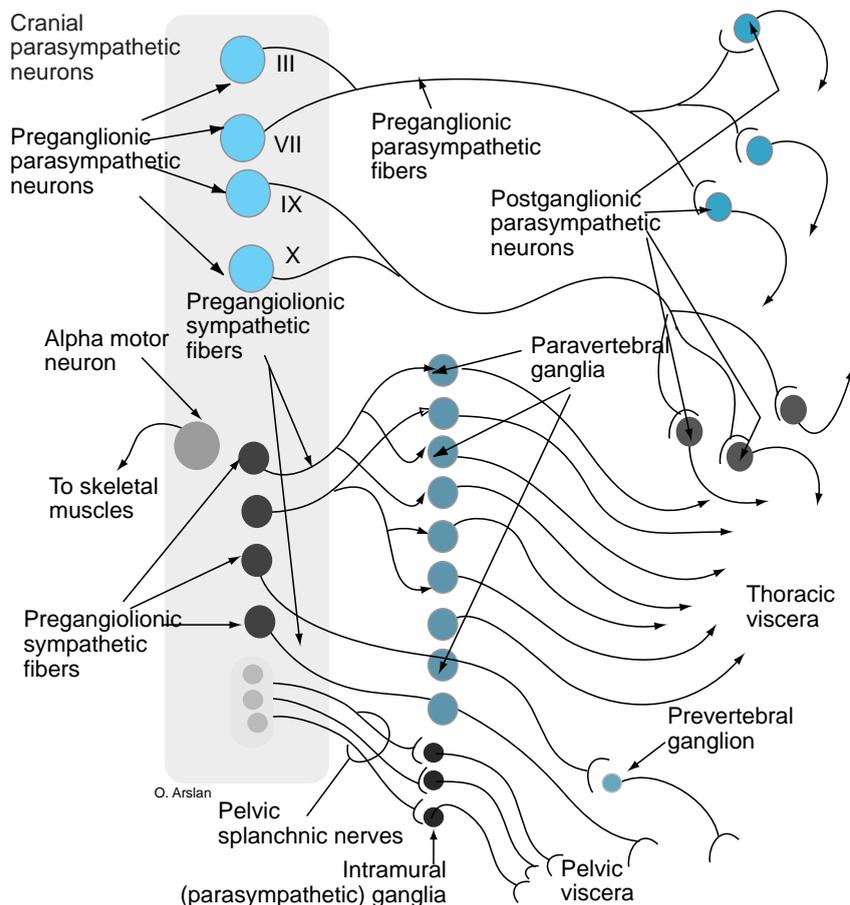


Figure 9.1 Schematic representation of the pre-ganglionic and post-ganglionic neurons of the sympathetic and parasympathetic systems

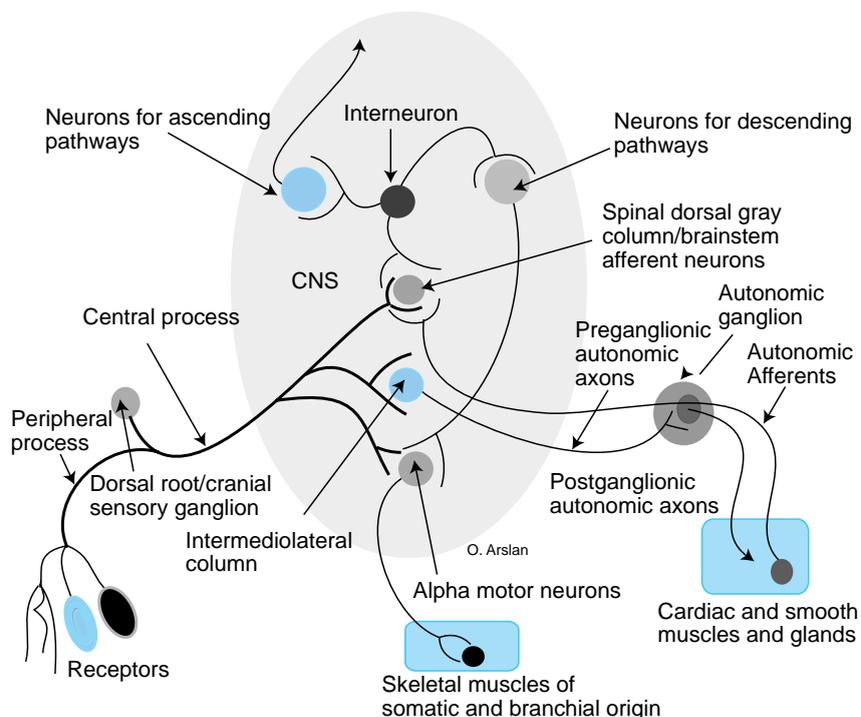


Figure 9.2 General differences between autonomic and somatic innervation, showing both efferent and afferent connections

skeletal muscles), the generated response is immediate and rapid.

Excision of the autonomic fibers may not produce atrophy of the denervated organ, as is the case with the somatic denervation.

Autonomic afferents carry a variety of sensations such as visceral pain, thirst, hunger, cramps, and sensations of well-being or malaise, somatic afferents primarily transmits signals associated with tactile, thermal, painful, joint and vibratory sensations.

Additional differences between these two main components of the peripheral nervous system also exist in regard to receptors and type of stimuli.

Visceral receptors are mainly free nerve endings, whereas somatic system comprises a variety of capsulated and uncapsulated receptors.

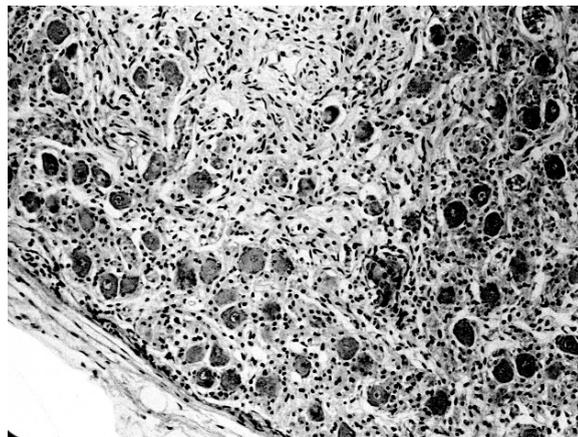


Figure 9.3 Photomicrograph of the multipolar autonomic neurons and associated glial cells

Table 9.1 Ganglia of the peripheral nervous system

<i>General characteristics</i>	<i>Sensory ganglia</i>	<i>Autonomic ganglia</i>
Location	1. Cranial nerves V, VI, VII & IX 2. Dorsal root ganglia	1. Sympathetic a. Paravertebral ganglia b. Prevertebral ganglia 2. Parasympathetic a. Submandibular, otic, ciliary & pterygopalatine ganglia b. intramural ganglia
Type of neurons	Pseudounipolar or bipolar neurons	multipolar neurons
Synaptic connections	None	Paravertebral, prevertebral & intramural ganglia

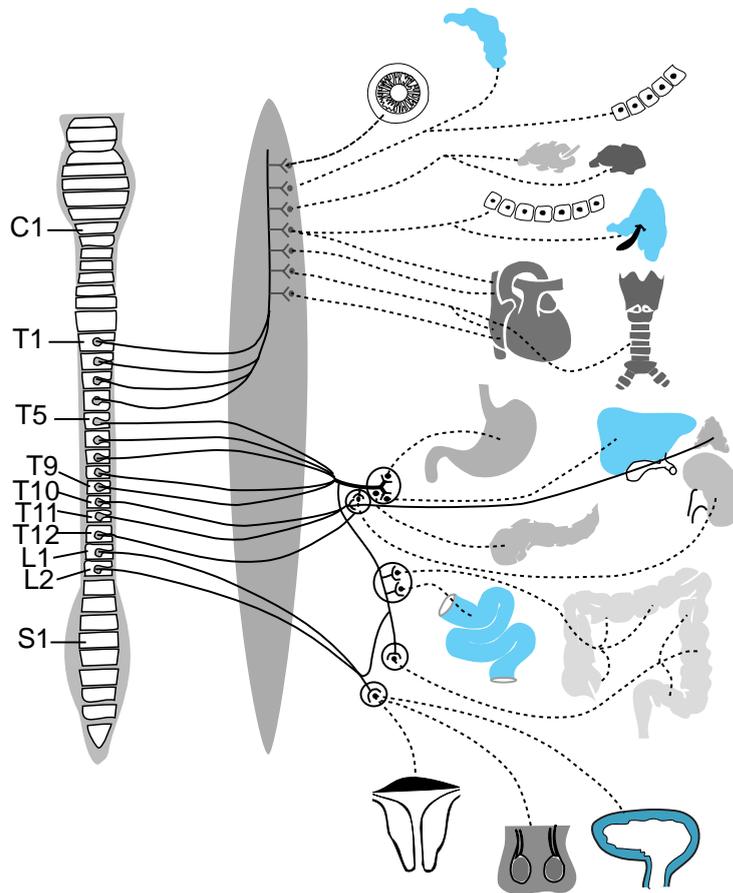


Figure 9.4 The preganglionic and postganglionic neurons of the sympathetic nervous system is illustrated. The splanchnic nerves and their associated ganglia are clearly marked

Conventional somatic stimuli may not elicit any visceral response; however, ischemia and tension within the wall of a viscus may activate the visceral receptors, eliciting pain.

Despite these difference both visceral and somatic afferent maintain neurons in the dorsal root ganglia. Specifically, cranial somatic sensory neurons constitute the trigeminal, geniculate, and superior ganglia of the glossopharyngeal and vagus nerves, whereas the neurons for visceral afferents are located in the geniculate, and the inferior ganglia glossopharyngeal and vagus of nerves. Additionally, both somatic and autonomic nerves form plexuses. Autonomic plexuses are scattered in the thoracic, abdominal, and pelvic cavities to form the pulmonary and aortic plexuses. Somatic nerve plexuses are formed regionally such as the cervical, brachial, and lumbosacral plexuses.

The ANS utilizes norepinephrine, dopamine, and acetylcholine as primary neurotransmitters, producing either an excitatory or inhibitory response. Modulators, such as hormones or tissue metabolites may exert influences upon the transmitter release or their action.

There are two functionally diverse and antagonistic systems within the ANS which operate in conjunction

with the enteric nervous system. These are the sympathetic and parasympathetic systems.

Sympathetic system

The sympathetic is a system brought into action during emergency and under stressful situations which releases energy by increasing the level of blood sugar and blood pressure, and intensifying the rate of cardiac contractility and output (positive inotropic and chronotropic effects). It is a system that directs blood flow to the voluntary musculature at the expense of viscera and skin. Excitation of a disproportionate number of postganglionic neurons (great degree of divergence) and high concentration of the circulating epinephrine in the blood stream are responsible for the mass-response of the sympathetic system. This system utilizes acetylcholine at the preganglionic level and norepinephrine at the postganglionic level. However, there are exceptions to this rule, acetylcholine may be utilized at the postganglionic level in the innervation of the blood vessels of skeletal muscle and the sweat glands. This may not be true in the case of sweat glands of the palm, which receive adrenergic fibers.

Other cotransmitters also play important roles in this system such as ATP and neuropeptide Y (NPY). Sympathetic (adrenergic) receptors are integral membrane glycoprotein, which are classified into presynaptic and postsynaptic groups.

Presynaptic receptors are categorized at least into α_2 and β_2 groups. Additional groups and subtypes are discussed in detail in [chapter 12](#).

Group α_2 receptors are found on both cholinergic and adrenergic nerve terminals. They act on pancreatic islets (b) cells and on platelets, resulting in reduction of insulin secretion and platelets aggregation, respectively. The latter effect is due to inhibition of adenylyl cyclase and activation of K^+ channels via G_i protein. On the adrenergic endings, α_2 (autoreceptors) receptors inhibit the release of norepinephrine by inhibiting of neuronal Ca^{2+} channels.

Group β_2 (hormonal) receptors are found on the vascular, pupillary, ciliary, bronchial, gastrointestinal, and genitourinary tract smooth muscles, initiating relaxation of coronary vessels, bronchi and skeletal arterioles, as well as the ciliary and constrictor pupilla muscles. These series of actions are produced by activation of adenylyl cyclase, mediated by G_s protein. They also produce glycogenolysis in the skeletal muscles and liver. β_2 agonists relax the bronchial smooth muscles and therefore can be used in the treatment of asthma. β_2 antagonists are not essential.

Postsynaptic receptors are categorized into α_1 and β_1 groups. α_1 agonists cause contraction of the smooth muscles of the arterioles and sphincters, whereas α_1 antagonists may counteract this effect in individuals with hypertension and peripheral vascular disease.

Group α_1 produces vasoconstriction and enhances glandular secretion (odoriferous apocrine sweat glands) via stimulation of phospholipase with formation of IP₃ (inositol-1,4,5-triphosphate) and diacylglycerol, and increased cytosolic Ca^{2+} .

β_1 receptors act particularly on the cardiac muscles, producing increased rates and force of contraction and atrioventricular nodal velocity via activation of adenylyl cyclase and Ca^{2+} channels. The role of β_1 agonists in the stimulation of the nodal and ventricular muscles of the heart may be utilized in the treatment of heart failure. In the same manner β_1 antagonists' (beta blockers) role in reducing cardiac rate and force of contractility may be utilized in the treatment of angina pectoris.

Sympathetic innervation of the skin encompasses adrenergic and cholinergic fibers. Cholinergic fibers act upon the muscarinic receptors, enhancing the secretion of the eccrine sweat glands, while adrenergic fibers produce vasoconstriction of the cutaneous arterioles and activate the secretion of the odoriferous apocrine sweat glands.

Activation of the sympathetic nervous system, which may mimicked by sympathomimetics, produces:

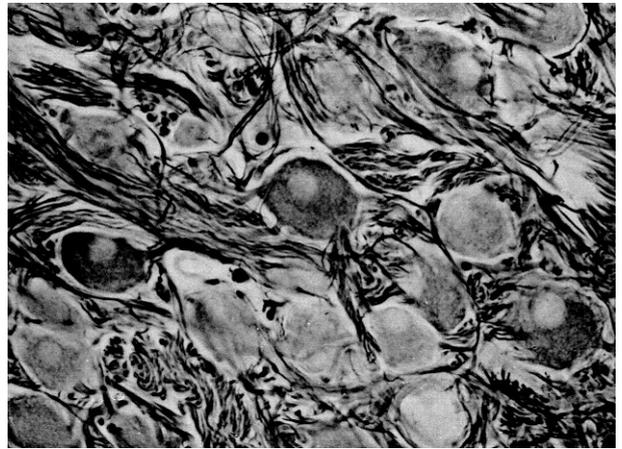


Figure 9.5 Photomicrograph of the multipolar neurons of the sympathetic ganglia and associate satellite cells

- Mydriasis (dilation of the pupils) by inducing contraction of the dilator pupillae muscles.
- Relaxation of the ciliary muscle.
- Increased contractility and rate of heart beat (positive inotropic and chronotropic effects).
- Vasodilatation of the skeletal and coronary arteries.
- Vasoconstriction of the bronchial arteries, as well as arteries of the digestive system and skin.
- Dilatation of bronchi and inhibition of bronchial secretion.
- Inhibition of gastrointestinal motility and contraction of the sphincters.
- Increased secretion of the sweat glands.
- Contraction of the erector pilorum muscles.
- Vasoconstriction of the genital arteries and contraction of the vas deferens, seminal vesicle, and prostate.
- Inhibition of the detrusor muscle of the bladder and contraction of the urethral sphincters.

The preganglionic sympathetic neurons ([Figures 9.1 & 9.4](#)) of the intermediolateral column of the thoracic and upper two or three lumbar spinal segments are connected to the postganglionic sympathetic neurons via the myelinated fibers of the white communicating rami. Postganglionic neurons form two sets of ganglia; paravertebral and prevertebral.

Paravertebral ganglia

The paravertebral ganglia ([Figures 9.1, 9.4, 9.5, 9.8 & 9.9](#)) form the sympathetic trunk, consisting of two symmetrical chains parallel to the vertebral column that unite anterior to the coccyx at the ganglion impar. Multipolar neurons of the paravertebral ganglia receive presynaptic fibers from the intermediolateral columns of the thoracic and upper two or three lumbar segments via myelinated white communicating rami, and provide postsynaptic fibers that



Figure 9.6 This is a depiction of manifestations of Horner's syndrome

join the spinal nerves via the unmyelinated gray communicating rami. The paravertebral ganglia are divided into cervical, thoracic, lumbar and sacral parts.

The cervical part of the sympathetic trunk (Figure 9.8) consists of the superior, middle, and inferior ganglia. Since these ganglia do not receive white communicating rami, the presynaptic fibers, which emerge from the upper thoracic spinal nerves, have to travel through the corresponding thoracic ganglia to reach their destination in the cervical ganglia. However, gray communicating rami do arise from these ganglia, supplying the upper four cervical spinal nerves.

The superior cervical ganglion, largest cervical ganglion, formed by fusion of the upper four cervical ganglia. It lies anterior to the longus capitis and posterior to the carotid sheath. This ganglion supply fibers to the carotid body and the pharyngeal plexus and cardiac branch (superior cardiac nerve) which contains efferent but NOT afferent nociceptive fibers. Most of emerging postganglionic fibers form the external and internal carotid plexus around the corresponding arteries. Fibers of the internal carotid plexus enter the cranial cavity supplying dura mater and dilator pupilla, superior tarsal, and orbital muscles. Fibers within the external carotid plexus supply vasoconstrictor and sudomotor fibers to the face and neck, as well as secretomotor fibers to the salivary gland via the otic and submandibular ganglia. It also provides gray communicating rami to the upper four cervical spinal nerves. Since the presynaptic fibers from the T1-T2 spinal segments project to the superior cervical ganglion, which innervates the structures in the head, removal of this ganglion may deprive the ipsilateral side of the head of sympathetic innervation.

- Ipsilateral disruption of the sympathetic fibers to head produces manifestations of Horner's syndrome (Figure 9.6) which comprises ptosis (drooping of the upper eyelid), mydriasis (dilatation of the pupil), enophthalmos (sunken eyeball), and anhydrosis (lack of sweating).
- Activation of the preganglionic sympathetic neurons at T1-T2 spinal segments requires descending autonomic input from the hypothalamus that travels in the lateral medulla and the lateral funiculus of the cervical spinal. Therefore, destruction of the lateral part of the medulla may also produce signs of Horner's syndrome, which are seen as a component of lateral medullary (Wallenberg's) syndrome.

The middle cervical ganglion (Figure 9.7) is an inconstant ganglion, which is located anterior to the inferior thyroid artery at the level of the sixth thoracic vertebra. It is formed by the fusion of the fifth and sixth cervical ganglia. It provides innervation to the heart, as well as furnishes gray communicating rami to the fifth and sixth cervical ventral rami. It is connected to the cervicothoracic ganglion via the ansa subclavia (see below). It provides thyroid branches and a (middle) cardiac nerve, which is the largest sympathetic contribution, to the deep cardiac plexus.

The inferior cervical ganglion joins the first thoracic ganglion to form the stellate ganglion.

The cervicothoracic (stellate) ganglion (Figure 9.7) lies posterior to the initial part of the vertebral artery, apex of the lung and cervical pleura, occupying the area between the transverse process of C7 and the neck of the first rib. It contributes gray communicating rami to the seventh and eighth cervical, and to the first thoracic spinal nerves. It also supplies postganglionic branches to the subclavian artery and its branches, and to the vertebral plexus, which extends into the cranial cavity. The preganglionic fibers

Pancoast tumor is a tumor of the apex of the lung, which may result in compression, or destruction of the stellate ganglion and the inferior trunk of the brachial plexus, producing pain and numbness in C8-T1 dermatomes. Phrenic nerve may also be affected in this tumor producing diaphragmatic palsy. Additional manifestations such as cardiac arrhythmias, obstruction of the superior vena cava, and hoarseness due to left recurrent laryngeal nerve palsy may also be seen. Signs of spinal cord compression may occasionally be seen due to erosion of the vertebral laminae by extension of the tumor. The stellate and middle cervical ganglia are connected via the ansa subclavia, a nerve loop that encircles the subclavian artery on both sides and courses medial to the origins of the internal thoracic and vertebral arteries.

that pass through the stellate ganglion, for the most part, project to the to the head and neck. However, vasomotor and sudomotor fibers are not contained in the white ramus to the cervicothoracic ganglion. Postganglionic fibers from the stellate ganglion also travel within the inferior trunk of the brachial plexus above the first rib, and then within the ulnar, radial and median nerves. In the hand, the postganglionic fibers leave these nerves and travel with the corresponding arteries. Occasionally a vertebral ganglion may be present near the origin of the vertebral artery, which provides gray communicating rami to the fourth and fifth cervical spinal nerves.

The thoracic part of the sympathetic trunk consists of eleven or twelve ganglia arranged anterior to the costal heads, and are covered by the costal pleura. These ganglia are connected to the thoracic spinal nerves via the white and gray communicating rami. Frequently, the first thoracic and the inferior cervical ganglia join to form the cervicothoracic (stellate) ganglion. The second through the fifth thoracic ganglia provide sympathetic fibers to the posterior pulmonary and deep cardiac plexuses, while the upper five thoracic ganglia provide sympathetic fibers to the aortic plexus. Presynaptic fibers, mainly from the T1-T6 (T7), which are destined to the cervical ganglia en route to the head, neck, and upper extremity, also travel within the cervical ganglia. Since vasoconstrictors to the upper extremity primarily emerge from the second and third spinal segments, excision of the corresponding thoracic ganglia (second and third) may denervate the vessels of the upper extremity. Presynaptic sympathetic fibers from the fifth through the ninth ganglia form the greater splanchnic nerve (Figure 9.4), presynaptic fibers from the tenth and eleventh ganglia form the lesser splanchnic nerve, whereas fibers that emanate from the twelfth thoracic ganglion form the least splanchnic nerve.

The lumbar part of the sympathetic trunk is connected to the thoracic part via the gap posterior to the medial arcuate ligament. The lumbar sympathetic ganglia receive white communicating rami from the upper four lumbar spinal nerves. These ganglia, which are located medial to the psoas major muscle and anterior to the lumbar vertebrae, give rise to the lumbar splanchnic nerves (preganglionic sympathetic fibers) that join the celiac, intermesenteric and the superior hypogastric plexuses.

Pain relief from the upper extremity, alleviation of vascular spasm in the hands (seen in Raynaud's disease) or hyperhidrosis (excessive sweating) may be achieved by injection of anesthetic solution into the stellate ganglion (stellate block). Success of this procedure may be ascertained by the appearance of signs of Horner's syndrome and increase temperature of the ipsilateral upper extremity.

The sacral part of the sympathetic trunk lies anterior to the sacrum and medial to the pelvic sacral foramina. It joins the sacral ganglia of the opposite side via the ganglion of impar. These ganglia receive preganglionic fibers from the lower thoracic and upper two lumbar spinal segments, giving rise to gray rami that join the sacral and coccygeal plexuses.

Prevertebral ganglia

The prevertebral ganglia (Figures 9.1 & 9.4) lie anterior to the lumbar part of the vertebral column, comprising the celiac, aorticorenal, superior mesenteric, and the inferior mesenteric ganglia. The celiac ganglia, the largest prevertebral ganglia, are located on both sides of the celiac trunk and medial to the suprarenal glands. The caudal (lower) part of each celiac ganglion is known as the aorticorenal ganglion. Much smaller ganglia, such as the superior and inferior mesenteric, are lodged within the corresponding plexuses.

Course of the sympathetic fibers

Axons of the sympathetic preganglionic neurons that project to the paravertebral ganglia usually follow an orderly course through the ventral root, spinal nerve and the white communicating rami. This is not true in the cervical and sacral segments which lack the corresponding white communicating rami that connect the spinal nerves to the paravertebral ganglia. Postganglionic axons of the sympathetic ganglia may follow diverse course which depends upon the site of termination (Figures 9.4 & 9.8). Most fibers return to the spinal nerves via the gray communicating rami. This route is followed by fibers that innervate the sweat glands, erector pilorum muscles, and the vessels of the extremities, thoracic and abdominal walls. Other fibers, which ascend to synapse in the superior cervical ganglion, form plexuses around major blood vessels destined to the head and neck region (e.g. sweat glands of the face and the dilator pupillae muscles). The sympathetic postsynaptic fibers to the lower face arise from the external carotid plexus, a network of sympathetic fibers that encircle and follow the course of the corresponding artery. Sympathetic fibers to the sweat glands of the supraorbital region are contained within the

Postganglionic fibers from the prevertebral plexuses travel in the femoral and obturator nerves, supplying vasoconstrictor fibers to the femoral and obturator arteries and their branches. Therefore, surgical removal of the upper three or four lumbar ganglia or their preganglionic neurons may completely denervate the lower extremity vessels.

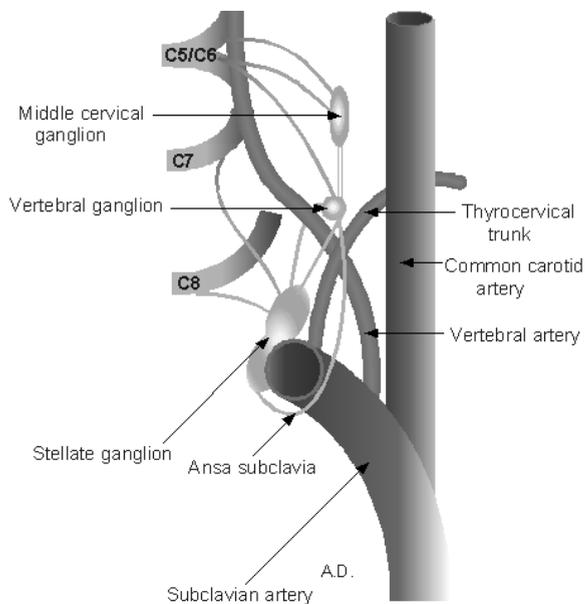


Figure 9.7 Drawing of the middle cervical and stellate ganglia and the connecting ansa subclavia

supraorbital and supratrochlear branches of the frontal nerve. The latter, a branch of the ophthalmic nerve, receives its sympathetic fibers by communicating with nasociliary nerve. Innervation of the dilator pupillae muscle is maintained by the postsynaptic sympathetic fibers that travel within the long ciliary branch of the nasociliary nerve. Sympathetic postsynaptic fibers to the superior tarsal muscle of the upper eyelid originate from the internal carotid plexus, as it travels within the cavernous sinus, and are contained within oculomotor nerve. An interesting point to bear in mind is the fact that both the sympathetic postsynaptic fibers to the superior tarsal and the somatic fibers to the levator palpebrae muscles course within the oculomotor nerve. Sympathetic postganglionic fiber to the thoracic viscera originates from the cervical and upper five thoracic paravertebral ganglia. Some fibers that are destined to the abdominal viscera bypass the sympathetic trunk to terminate in the prevertebral ganglia as the splanchnic nerves (Figures 9.1 & 9.4). The greater splanchnic nerve consists of preganglionic efferent and visceral afferent fibers that penetrate the crus of the diaphragm to enter the abdomen, establishing synaptic connections primarily with the celiac ganglion and partially with the aorticorenal ganglion. The lesser splanchnic nerve synapses in the aorticorenal ganglion, whereas the least splanchnic nerve (renal nerve) contributes to the renal plexus. Fibers that bypass both the paravertebral and prevertebral ganglia remain preganglionic and terminate in the chromaffin tissue of the adrenal medulla.

Parasympathetic (cranio-sacral) system

The parasympathetic is a local-response system, consisting of pre- and postganglionic neurons that act on the smooth muscles and viscera. The preganglionic parasympathetic fibers are contained in the pelvic splanchnic nerves and certain cranial nerves (Figures 9.1, 9.9 & 9.10). These preganglionic fibers establish connections with the postsynaptic parasympathetic neurons of the intramural ganglia (on pelvic and abdominal viscera) or with parasympathetic ganglia in the head. Parasympathetic responses are manifested in miosis (constriction of the pupil), contraction of the ciliary muscle, decreased contractility and cardiac output (negative inotropic and chronotropic effect), and constriction of the bronchi and bronchioles. Other manifestations include increased gastrointestinal tract motility, constriction of the coronary arteries and vasodilatation of the vessels of the external genitalia, and gastrointestinal tract, and contraction of the muscular wall of the urinary bladder (dilation of cerebral vessels are primarily due to change in CO₂ concentration).

Acetylcholine, the main neurotransmitter at parasympathetic terminals, is contained in the clear-spherical vesicles, acting primarily in conjunction with cotransmitters such as VIP (vasoactive intestinal peptide) and to a lesser degree ATP. Due to the rapid degradation of acetylcholine and the lesser degree of divergence (low ratio of preganglionic to postganglionic neurons), the action of the parasympathetic system remains localized and of short duration. Cholinergic receptors, which are activated by acetylcholine, are classified into nicotinic and muscarinic types.

Nicotinic receptors are further subdivided into nicotinic muscle receptor and nicotinic neuronal receptor.

Nicotinic muscle receptors (C-10 receptor) are pentameric protein, activation of which produce rapid increase in permeability of cells to sodium and calcium ions and subsequent depolarization and contraction of the skeletal muscle. Phosphorylation by cAMP protein kinase, protein kinase C, or trypsin kinase increases the desensitization of these receptors. Muscle receptor contains α , β , γ , and δ or α , β , δ , and ϵ subunits in a pentameric complex. The reason for the difference is because ϵ subunit replaces the γ in the adult. Subunit γ is particularly detected in the embryo or denervated muscle.

Neuronal nicotinic receptors are categorized into two subunits α and β with the α occurring in at least seven different forms and β in three forms. They exist in the autonomic ganglia, adrenal medulla and CNS. Neuronal nicotinic receptors are classified into bungarotoxin-insensitive (C-6) and bungarotoxin-sensitive nicotinic receptors. The former exists in the autonomic ganglia and produce depolarization and firing of the postganglionic neurons in the autonomic ganglia via opening of the

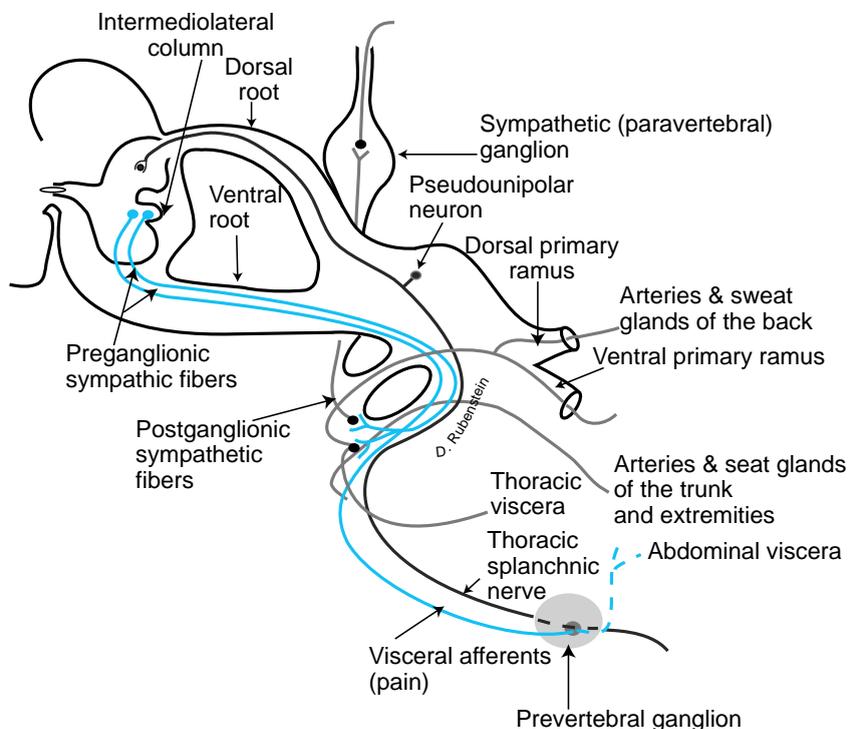


Figure 9.8 The functional components of a spinal nerve including general somatic afferent, general visceral afferent, general somatic efferent and general visceral efferent are shown

cation channel. There are numerous agonists for these receptors such as nicotine, phenyltrimethyl-ammonium, methylisoarecolone, cytisine, and dimethylphenylpiperazinium, as well as plethora of antagonists such as tubocurarine, lophotoxin, and dihydro-b-erythroidine.

Muscarinic receptors are coupled to G-proteins, and either acts directly or indirectly on ion channels or linked to second messenger systems. They are classified on pharmacological basis into M1-M3, and on the basis of molecular cloning into M4-M5 subtypes. All five subtypes exist in the central nervous system. M1 receptors show great affinity to pirenzepine and are found in the autonomic ganglia and glands. AFDX-116 shows high affinity to M2 receptors in the myocardium and smooth muscles, whereas 4-DAMP displays high affinity to M3 receptors in the smooth muscles and secretory glands. M₁, M₃, and M₅ are coupled to PI hydrolysis and M₂ and M₄ are coupled to cAMP.

Activation of the muscarinic receptors produces depolarization or hyperpolarization by opening or closing the potassium, calcium or chloride channels. Activation of M₁ receptors produces depolarization in the neurons of the autonomic ganglia. Stimulation of the M₂ receptors elicits hyperpolarization in the SA node, and a decrease in the atrial contractile force and conduction velocity in the AV node, and a slight decrease in the ventricular contractile force. Activation of the M3 receptors produces

contraction of the smooth muscles and increased glandular secretion.

Acetylcholine acts upon the muscarinic receptors on the exocrine glands, heart, and smooth muscles. Cholinergic receptors are nicotinic in the autonomic ganglia and muscarinic at the postganglionic parasympathetic nerve endings. In the central nervous system both muscarinic and nicotinic receptors exist. The combined effect of the muscarinic autoreceptors on the nerve endings (comparable to the α_2 autoreceptors of the sympathetic system) and acetylcholinesterase may prevent accumulation of acetylcholine in the synaptic cleft.

The parasympathetic system consists of cranial and sacral parts. The cranial part (Figures 9.9 & 9.10) consists of preganglionic neurons that course within the oculomotor, facial, glossopharyngeal, and vagus nerves.

The oculomotor nerve (III) contains preganglionic parasympathetic fibers, which are derived from the Edinger-Westphal subnucleus of the oculomotor nuclear complex. These fibers synapse in the ciliary ganglion, giving rise to postsynaptic fibers eventually innervate the constrictor pupillae and the ciliary muscles. CN III- (inferior branch) ———> ciliary ganglion ———> constrictor pupillae & ciliary muscle.

The facial nerve (VII) contains preganglionic parasympathetic fibers that emanate from the neurons of the lacrimal and superior salivatory nuclei, establishing

Cholinergic agents like carbachol (stimulates the bladder and bowel) and pilocarpine (produces constriction of the pupil) have similar effects to acetylcholine. Some of these agents act by inhibiting the enzyme cholinesterase and subsequently increasing the concentration of acetylcholine in the synaptic clefts. These cholinesterase inhibitors include physostigmine and diisopropylfluorophosphate (DFP). Others, such as tubocurarine act as an antagonist by competing with natural mediators at the synaptic site. Anticholinergic medications may be used clinically to: a) induce dryness of the bronchi during surgery, b) maintain dilatation of the pupil for in-depth ophthalmologic examination, c) block the vagal inhibition in case of cardiac arrest, d) prevent vomiting (antiemetic), e) counteract the spastic effect of morphine on the gastrointestinal tract, f) treat poisoning by overdose of cholinergic drugs, and g) cause relaxation of the urinary bladder in individuals with cystitis.

synapses in the pterygopalatine (sphenopalatine) and the submandibular ganglia, respectively. The postsynaptic parasympathetic fibers from the pterygopalatine ganglion supply the lacrimal gland, mucus glands of the palate, nasal cavity, and pharynx. On the other hand, the postsynaptic parasympathetic fibers from the submandibular ganglion innervate the submandibular and sublingual glands. CN VII → greater petrosal nerve → pterygopalatine ganglion → lacrimal gland, mucus glands of the palate, and nasal cavity and pharynx. CN VII- chorda tympani → submandibular ganglion → sublingual & submandibular glands.

The glossopharyngeal nerve (IX) contains preganglionic parasympathetic fibers from the medullary inferior salivatory nucleus that synapse in the otic ganglion. This ganglion sends postsynaptic secretomotor fibers to the parotid gland via the auriculotemporal nerve. CN IX → lesser petrosal nerve → otic ganglion → parotid gland.

The vagus nerve (X) contains preganglionic parasympathetic fibers, which are derived from the medullary dorsal motor nucleus of vagus. These fibers synapse in the terminal (intramural) ganglia scattered along the thoracic and abdominal viscera (e.g. the pulmonary, myenteric, and submucosal plexuses). Intramural ganglia contain in abundance neurons, which are non-adrenergic and non-cholinergic. They may also contain excitatory transmitters such as serotonin and substance P or inhibitory transmitters such as VIP, ATP or enkephalin. The vagal parasympathetic contributions to the abdominal viscera terminate at the junction of the right 2/3 and left 1/3 of the transverse colon.

Sacral part

The sacral part (Figure 9.1) of the parasympathetic system includes the parasympathetic preganglionic axons, emanating from the intermediolateral column of the second, third, and fourth sacral spinal segments. The axons of these neurons leave through the ventral roots of the corresponding segments and form the pelvic splanchnic nerves, which supply the pelvic viscera and part of the abdominal viscera. The pelvic splanchnic nerves are excitatory to the muscular wall of the descending colon, sigmoid, rectum and anal canal, as well as to a portion of the transverse colon. These splanchnic nerves are inhibitory to the urethral sphincters and vasodilator to the erectile tissue of the external genitalia.

Autonomic centers

Higher autonomic centers represent specific areas in the cerebral cortex, diencephalon, and the brainstem that closely regulate the ANS. This is based on the fact that stimulation or inhibition of these centers produces a variety of visceral changes. Autonomic centers in the cerebral cortex are scattered in the cingulate gyrus and hippocampal formation. In the diencephalon parasympathetic (anteromedial) and sympathetic (posterolateral) centers are located in the hypothalamus.

Hypothalamic control of the brainstem and spinal autonomic neurons is achieved via the dorsal longitudinal fasciculus (DLF), the mammillotegmental tract, and the medial forebrain bundle (MFB). The DLF connects the medial hypothalamus to the dorsal motor nucleus of vagus, nucleus ambiguus, salivatory and Edinger-Westphal nuclei, as well as the intermediolateral columns of the spinal cord. Medial hypothalamic neurons also send fibers to the dorsal motor nucleus of vagus, locus ceruleus, and raphe nuclei via the MFB. Brainstem raphe nuclei project to the prefrontal cortex, septal area, and cingulate gyrus also via the MFB.

The mammillotegmental tract are formed by the axons of the mammillary neurons that project to the raphe nuclei and other nuclei of the mesencephalic and pontine reticular formation.

In the brainstem, the pontine autonomic is comprised of a cardiovascular center in the caudal pons between the superior olivary nucleus and the root of the facial nerve. The medullary autonomic (respiratory) is comprised of the inspiratory center around the solitary nucleus that contains opiate receptors upon which morphine acts as a depressant, and an expiratory center around the ambiguus nucleus. The latter projects to the motor neurons of the thoracic spinal segments, innervating the internal and innermost intercostals. The pneumotoxic center is

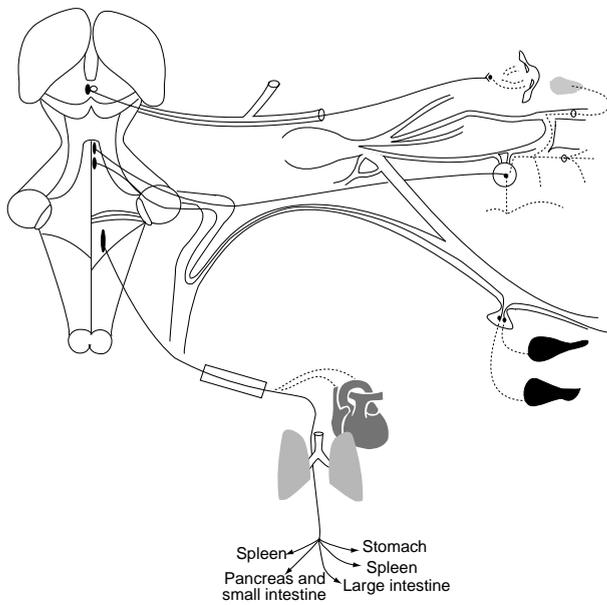


Figure 9.9 Cranial part of the parasympathetic nervous system. Note the associated nuclei, preganglionic fibers, and related ganglia

comprised of the parabrachial nuclei of the pons, which influences the rate of breathing by shortening the respiratory cycle.

Autonomic reflexes

A reflex is an innate, automatic response to a stimulus that occurs as a basic defense mechanism. It may be inherited or primitive, present at birth, and is common to all human beings. It may also be conditioned, which is acquired as a result of experience. Intactness of the receptor, sensory (afferent) neuron and a motor (efferent) neuron are essential for typical reflex to occur. Afferent fibers deliver the generated impulses from a receptor to the central nervous system where it may be inhibited, facilitated, or modified, while the efferent fibers transmit the processed information to the effector organ. An interneuron may exist between the afferent and efferent neurons. Reflexes do not always operate independently; in fact descending supraspinal pathways (somatic and visceral) modulate and regulate the neurons, which form the reflex arc. Conditions that affect the neural elements of a reflex arc or their supraspinal input may produce a variety of deficits. A lesion, which disrupts the reflex arc, may result in hyporeflexia or areflexia depending on the number of the involved segments. In peripheral neuropathy and

Transection of the lower pons disrupts the descending fibers from the pneumotaxic center, resulting in a deep respiratory cycle (apneustic breathing).

poliomyelitis, the receptor, afferent or the efferent neurons of a reflex arc may be damaged, producing hyporeflexia or areflexia.

Damage to the supraspinal pathways may produce, hyperreflexia, hyporeflexia, or areflexia (e.g. upper motor neuron palsy manifests both deep tendon hyperreflexia, and areflexia or hyporeflexia in the superficial abdominal reflexes).

Reflexes are categorized into superficial reflexes associated with the skin and mucus membrane and deep reflexes pertaining to the muscles and tendons. Reflexes may be mediated by cranial nerves (cranial reflexes) or spinal nerves (spinal reflexes). Additional classifications into visceral and somatic reflexes are based upon the nature of the innervated structure.

Visceral reflexes include viscerovisceral and viscerosomatic reflexes, while somatic reflexes comprise somatosomatic and somatovisceral reflexes. Visceral reflexes facilitate automatic adjustments of the entire organism to the internal and external environments. In order to promote digestion, some of these reflexes produce an increase in blood flow to the digestive tract following food ingestion, and decrease in absorption. Other reflexes may increase the rate and depth of respiration to meet the body's demand for oxygen in response to physical activity. Visceral reflexes are classified into viscerovisceral, viscerosomatic, and somatovisceral reflexes.

Viscerovisceral reflexes include the carotid sinus, Bainbridge, and carotid body reflexes.

- Carotid sinus reflex is mediated by the carotid sinus (receptor), the carotid sinus branch of the glossopharyngeal (afferent limb), reticular formation, and the vagus nerve (efferent limb). An increase in blood pressure will stimulate the carotid sinus and activates the neural mechanism that adjusts the blood pressure to normal level.
- Bainbridge reflex monitors the central venous pressure through afferent nerve endings in the right atrium. These endings are represented by the peripheral processes of the neurons of the inferior ganglion of the vagus nerve. Distention of the right atrium produces reflex tachycardia due to vagal inhibition and sympathetic stimulation.
- Carotid body reflex is initiated by an increase in carbon dioxide and a decrease in oxygen tensions of the blood. These changes stimulate the carotid body (chemoreceptor) and eventually the respiratory center through the vagus nerve.

Viscerosomatic reflexes comprise Hering Breuer, and vomiting reflexes.

- Hering Breuer reflex initiates expiration upon excitation of the terminals of the bronchial tree of the inflated lung. These excited terminals stimulate the expiratory center and the solitary nucleus. The expiratory center inhibits the

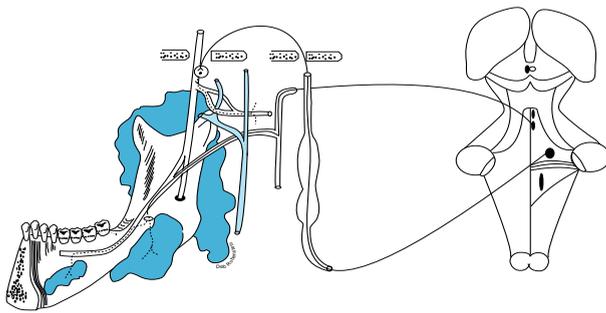


Figure 9.10 The sympathetic neurons associated with innervation of the thoracic viscera (heart, lungs and bronchi)

inspiratory center, eliciting passive and elastic recoil of the lung.

- Vomiting reflex is mediated by receptors, which are located in the mucosa of the stomach, gall bladder, or the duodenum. Activation of these receptors results in transmission of the generated impulses via the vagus nerve (afferent limb) to the solitary nucleus, medullary vomiting center, reticulo-spinal tracts, and neurons of the anterior horn and the intermediolateral columns of cervical and thoracic spinal segments.
- Somato-visceral reflexes are comprised of pupillary light, pupillary-skin (ciliospinal), accommodation, bladder and rectal reflexes, and mass reflex of Riddoch.
- The pupillary light reflex produces constriction of the pupil of the stimulated eye (direct light reflex) and the contralateral eye (consensual light reflex) in response to direct light applied to one eye. This reflex is mediated by the optic and the oculomotor nerves. The optic nerve, the optic tract, and the brachium of the superior colliculus form the afferent limb of this reflex. The pretectal nucleus, Edinger-Westphal nucleus, oculomotor nerve, ciliary ganglion, and the short ciliary nerves comprise the efferent limb.
- The pupillary-skin (ciliospinal) reflex is characterized by pupillary dilatation in response to painful stimuli. It may be elicited by a simple scratch, pinch, or a cutaneous wound, especially involving the facial skin. The afferent limb, (depending upon the site of the stimulus) may include neurons of the dorsal root ganglia or the trigeminal nerve, as well as neurons of the posterior horn or the spinal trigeminal nucleus. The efferent limb includes the reticular formation, reticulospinal tracts, intermediolateral columns of the first thoracic spinal segment, and the sympathetic pathway to the dilator pupillae muscle of the eye.
- The accommodation reflex adjusts both eyes to near vision, involving convergence (adduction) of the eyes, constriction of the pupils, and increase curvature of the

Pupillary light reflex is lost in the Argyll Robertson pupil, which results from destruction of the area medial to the lateral geniculate nucleus and is associated with neurosyphilis. In this condition the pupil remains unresponsive to atropine. Loss of light reflex may also be seen in diabetes mellitus, epidemic encephalitis, and alcoholism.

lens in both eyes. The input for this reflex is carried from the retina by the optic nerve, optic tract, lateral geniculate body, and optic radiation to the visual cortex. The efferent impulses travel and eventually via the short ciliary nerves to the ciliary body and the constrictor pupillae muscle.

The bladder and rectal reflexes regulate the sphincteric control of micturition and defecation via the pelvic splanchnic nerves. Incontinence may occur as a result of disruption of this reflex arc. The urge to urinate or defecate may be lost upon interruption of the afferent fibers.

The mass reflex of Riddoch is characterized by sudden evacuation of the bladder and bowel, flexion of the lower extremity, and sweating in response to emotional stimulus.

Autonomic plexuses

Autonomic plexuses represent network of visceral nerve fibers, which innervate structures in the thoracic, abdominal, and pelvic cavities. They are formed by sympathetic and parasympathetic nerve fibers and associated ganglia. They derive their names from the corresponding arteries that are associated with. These comprise the cardiac, celiac, suprarenal, renal, ureteric, superior mesenteric, aortic, inferior mesenteric, and superior and inferior hypogastric plexuses.

The cardiac plexus (Figures 9.4 & 9.10) provides innervation to the heart and the coronary arteries, consisting of deep and superficial parts. The superficial part of the cardiac plexus lies below the aortic arch and is formed by the cardiac branch of the left superior cervical ganglion, and by the parasympathetic fibers of the vagus nerve. The deep part of this plexus lies anterior to the bifurcation of the trachea and is formed by the cardiac branches of the cervical (with the exception of the left superior cardiac branch) and upper four or five thoracic ganglia. In contrast branches of the vagus and the recurrent laryngeal nerves form the parasympathetic component. Postganglionic fibers from the right vagus nerve establish synaptic connection with the sinoatrial node and with both atria. On the other hand, the postsynaptic fibers from the left vagus nerve act on the ventricular myocardium and the AV bundle. Reduction of the contractile force of the heart and rate of contraction are achieved by stimulation of the vagus nerves that act upon the muscarinic receptors of the cardiac nodal tissue and atria.

The mass reflex of Riddoch may be elicited in individual with spinal shock by stimulating the skin below the level of the spinal lesion.

The presynaptic muscarinic receptors on the sympathetic fibers are also inhibited by stimulation of the vagus nerves. Sympathetic postganglionic fibers act upon the β_1 and to lesser degree α receptors in the sinoatrial and atrioventricular nodes, atrioventricular bundle and ventricular myocardium. Activation of the β_2 receptors in the coronary arteries, by the circulating epinephrine, produces relaxation of the vessels. Cholinergic presynaptic α_2 receptors on branches of the vagus nerve may also be inhibited by the sympathetic postganglionic fibers.

Subsidiaries of the cardiac plexus are the coronary plexuses that surround the coronary arteries.

The left coronary plexus is an extension of the deep cardiac plexus, supplying the left atrium and left ventricle. The right coronary plexus innervates the right chambers of the heart, and is formed by the fibers of the deep and superficial parts of the cardiac plexus. The sympathetic fibers of this plexus, upon activation, produce coronary vasodilatation, while the parasympathetic fibers elicit vasoconstriction. The cardiac plexus continues with the pulmonary plexuses (Figure 9.11) around the corresponding arteries.

The pulmonary plexus, which lies partly anterior and partly posterior to the pulmonary hilus, receives parasympathetic fibers from the vagus nerve and sympathetic fibers from the second through the fifth thoracic spinal segments. This plexus innervates the pulmonary arteries, bronchi, and bronchial arteries.

The celiac plexus (Figures 9.4 & 9.12) surrounds the celiac trunk, and lies anterior to the diaphragmatic crura and medial to the suprarenal glands. It receives sympathetic fibers via the greater splanchnic (T5-T9 spinal segments) and the lesser splanchnic (T9-T11 spinal segments) nerve. The parasympathetic fibers are derived from the vagus nerve. This plexus which also receives somatic fibers via the phrenic nerves, contains the celiac ganglia (visceral brain) where the greater and lesser splanchnic nerve establish synaptic connections. Due to the proximity of the lower part of the celiac ganglion (aorticorenal ganglion) to the renal artery, it contributes postsynaptic parasympathetic fibers to the renal plexus. The celiac, as the mother of all abdominal plexuses, has subsidiary plexuses which innervate the liver, gallbladder, diaphragm, stomach, duodenum, spleen, adrenal glands, kidneys, and testes or ovaries (Figure 9.9).

Hepatic plexus, a continuation of the celiac plexus, surrounds the common hepatic artery and its branches and supplies the liver and gallbladder. Activation of the vagal parasympathetic fibers produces contraction of the gallbladder, bile duct, and relaxation of the sphincter of

Cardiac pain (e.g. due to myocardial ischemia) is transmitted by the C fibers of pseudounipolar neurons of the upper four or five thoracic spinal nerves that run in the middle and inferior cardiac branches of the sympathetic trunk. These fibers enter the dorsal horns of the corresponding spinal segments, synapse in certain laminae that form the anterolateral system. These connections may explain the referred pain to dermatomes of T1-T5, which is experienced by individual with acute myocardial infarction.

Oddi. This plexus receives sympathetic contribution from the seventh through the ninth spinal segments.

The gastric plexus consists of right and left plexuses; the right plexus, an extension of the hepatic plexus, innervates the pylorus. The sympathetic fibers produce contraction of the pyloric sphincter and inhibition of the gastric muscles, while the parasympathetic fibers maintain opposing effect. The left gastric plexus, another extension of the celiac plexus, surrounds the left gastric artery. It exerts similar effects upon the stomach and pylorus. The sympathetic fibers, which supply the stomach, are derived from the T6 to the T10 thoracic spinal segments.

The suprarenal plexus is formed largely by the preganglionic sympathetic fibers of T8-L1 spinal segments that synapse in the chromaffin cells of the adrenal medulla.

The renal plexus surrounds the renal arteries and is formed by the sympathetic fibers of the lesser splanchnic nerve (T10-T11), least splanchnic nerve (T12), and the first lumbar splanchnic nerve (L1), primarily exerting a vasomotor action. The vagal parasympathetic fibers serve as afferents, terminating in the wall of the kidney. This plexus also contribute to the ureteric and the gonadal plexuses.

The ureteric plexus receives sympathetic fibers from (T11-L1) spinal segments and parasympathetic fibers from the vagus and pelvic splanchnic nerves. Due to its close relationships to the abdominal and pelvic viscera, the ureteric plexus receives fibers from diverse sources including the aortic, renal, vesical and hypogastric plexuses.

The superior mesenteric plexus (Figures 9.4 & 9.12) is a continuation of the celiac plexus which is formed by sympathetic fibers of the ninth, tenth, eleventh, and twelfth thoracic and the first lumbar (T10-L1) spinal segments, and by the parasympathetic fibers of the vagus nerve. This plexus supplies part of the duodenum, jejunum, ileum, and approximately the right 2/3 of the large intestine.

The aortic (intermesenteric) plexus (Figures 9.4 & 9.12) encircles the aorta between the superior and inferior mesenteric arteries. It contributes to the testicular, inferior mesenteric, and the hypogastric plexuses.

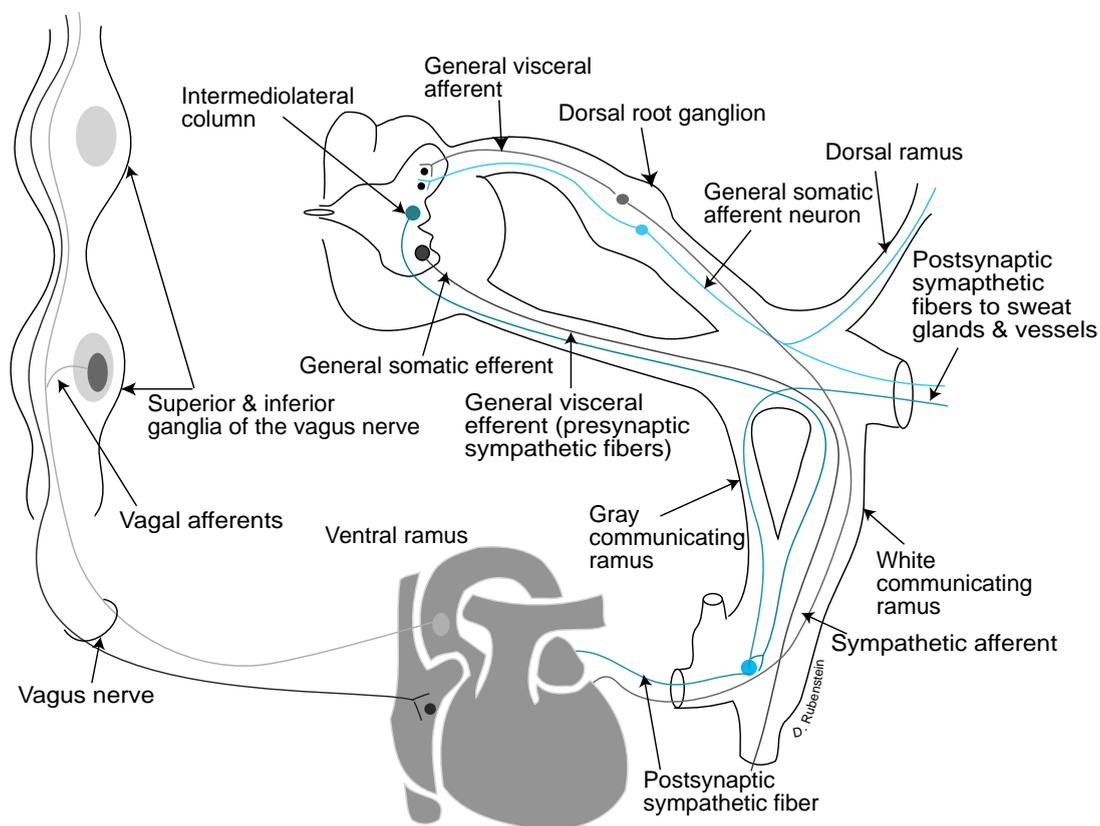


Figure 9.11 Diagram of the sympathetic neurons associated with innervation of the thoracic viscera (heart, lungs, and bronchi)

The inferior mesenteric plexus (Figures 9.4 & 9.12) surrounds the inferior mesenteric artery, containing sympathetic and parasympathetic fibers. The sympathetic fibers, which are inhibitory to the muscular walls of the descending colon, sigmoid colon, and upper part of the rectum, are derived from the first and second lumbar (L1 & L2) spinal segments. The parasympathetic fibers of the pelvic splanchnic nerves are excitatory, originating from the second, third, and the fourth (S2-S4) sacral spinal segments.

The superior hypogastric (presacral) plexus (Figure 9.4) is a continuation of the inferior mesenteric plexus. It receives sympathetic fibers from the eleventh thoracic through the second lumbar (T11-L2) spinal segments, and parasympathetic fibers from the pelvic splanchnic nerves (S2-S4 spinal segments). It runs anterior to the sacrum, sacral promontory and sacral plexus. It then divides into the right and left inferior hypogastric (pelvic) plexuses, supplying the pelvic structures.

The inferior hypogastric (pelvic) plexus (Figure 9.4) runs on both sides of the rectum, the uterus, and bladder, and gives rise to the vesical, middle rectal, prostatic, and the uterovaginal plexuses. It contains parasympathetic fibers from the pelvic splanchnic nerves and sympathetic

fibers from the lower thoracic and the upper lumbar (T12-L1 spinal segments). The uterovaginal part of the pelvic plexus supplies the serosa, myometrium, and the endometrium, as well as the vagina. The sympathetic fibers derived from the T12-L1 spinal segments produce uterine contraction and vasoconstriction, while the parasympathetic fibers produce relaxation of the myometrium and vasodilatation.

The vesical plexus, a subsidiary of the inferior hypogastric plexus, causes contraction of the detrusor muscles via the pelvic splanchnic nerves (parasympathetic), mediating micturition. The sympathetic component is derived from T11-L2 spinal segments, which also supplies motor fibers to the vas deferens and the seminal vesicle.

The prostatic plexus, another subsidiary of the inferior hypogastric plexus, supplies the urethra, bulbourethral glands, corpora cavernosa, and corpus spongiosum via the lesser and greater cavernous nerves. The sympathetic part of the prostatic plexus controls ejaculation, inhibits detrusor musculature of the bladder, and induces vasoconstriction. The parasympathetic part is formed by the pelvic splanchnic nerves, producing vasodilatation and erection.

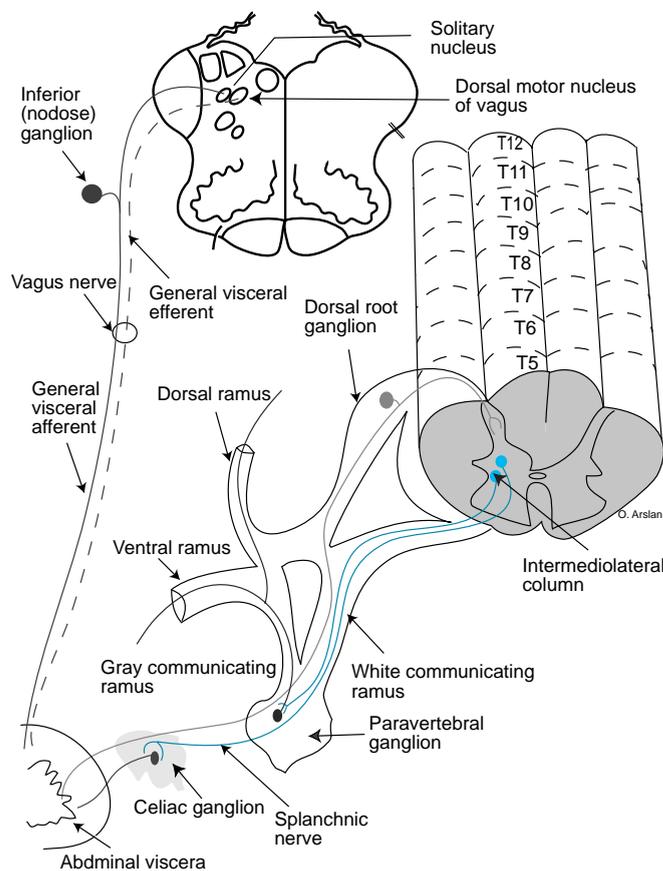


Figure 9.12 Schematic drawing of the sympathetic innervation of the abdominal viscera. Note the role of the celiac ganglia in mediating this innervation

Enteric nervous system

The enteric nervous system, an integral part of the autonomic nervous system, consists of a group of neurons within the myenteric plexus of Auerbach and the submucosal plexus of Meissner's and Henle's, as well as the pancreatic and cystic plexuses, which are derived from the neural crest cells. The myenteric plexus is located between the circular and longitudinal muscle layers, extending from the esophagus to the level of the internal anal sphincter. On the other hand, the submucosal plexus lies between the circular muscle and muscularis mucosa, stretching from the stomach to the anal canal. This system exerts a local reflex activity independent from the control of the brain and spinal cord. It is important to note that enteric nerves have more common features with the central nervous system than with the peripheral nerves. In fact, enteric nerves do not have collagenous coats, as is the case in the PNS. Further more, they lack the endoneurium and are supported by glial cells that resembles the astrocytes that contain glial fibrillary acidic protein (GFAP). Upon this network of neurons the motility and the secretory functions of the gastrointestinal tract from the middle third of the esophagus to the anorectal junction remain

dependent. The number of neurons associated with this system may be equivalent or exceeds the entire population of spinal neurons. This system of ganglia and plexuses is responsible for the induction of reflex peristalsis, independent of the direct commands of the brain. These ganglia maintain a blood-ganglion-barrier and are not pierced by vessels or connective tissue septa. Some neurons of this system may subserv sensory function, respond to changes in the morphology of bowel shape. Others are simply interneurons that receive input from sensory neurons and project to the parasympathetic postganglionic neurons.

Division of the sympathetic fibers of the superior hypogastric plexus (presacral neurectomy) may be performed in attempt to relieve pain associated with diseased pelvic viscera. However, dual transmission of pelvic pain via sympathetic and parasympathetic fibers may render complete analgesia an impossible task to achieve. In the male, removal of the superior hypogastric plexus may lead to loss of contraction of the seminal vesicles, prostate and the vas deferens, and eventual sterility.

Numerous neuropeptides have been identified within this system of neuronal network. This peptide may act to enhance or suppress the effects of transmitters or maintain a trophic role. Intrinsic motor neurons within this system may assume an excitatory role, utilizing acetylcholine and substance P as cotransmitters; others may project inhibitory effect using ATP (co-transmitter in the large and small intestine), vasoactive intestinal polypeptide (VIP), and NO (nitric oxide) as cotransmitters.

Somatostatin is widely distributed in the gastrointestinal tract and the δ cells of the pancreas where it inhibits the secretion of glucagon and insulin, a fact may prove significant in diabetic patients. It is present in the dorsal root ganglia and autonomic plexuses. In the CNS, it is concentrated in the hypothalamus, amygdala, and neocortex, where it facilitates responsiveness to acetylcholine. In Alzheimer's disease, formation of somatostatin neuritic processes and depletion of its SS-28 from the cortex are detected. Somatostatin-14, another form of this peptide may show reduction upon the administration of cysteamine as a treatment for the metabolic disease known as cystinosis.

Vasoactive intestinal peptide (VIP) is distributed in the pancreas, autonomic plexuses, and central nervous systems. It is also contained in the parasympathetic cholinergic neurons of the salivary glands. Secretion of this peptide increases the glandular secretion (enhances the secretory function of acetylcholine) and blood flow to the intestine (as a result of vasodilatation). VIP-related peptides include the growth hormone releasing hormone (GHRH) and pituitary adenylate cyclase activating peptide (PACAP). GHRH is isolated from the intestine, and PACA, as the name indicates, from the pituitary gland.

Afferent components of the autonomic nervous system

The peripheral processes of the dorsal root ganglia or certain cranial nerve ganglia usually accompany Autonomic (visceral) fibers. These afferent fibers, which are myelinated and unmyelinated, follow the course of the pre- and postganglionic neurons, terminating as capsulated receptors in the visceral and vascular walls. In addition to visceral pain, they also mediate visceral reflexes, and transmit organic visceral sensations, libido, distention, hunger, and nausea. Stimuli for visceral pain do not encompass cutting, burning, or crushing, but rather obstruction, and/or ischemia and distention of the visceral

Pain from the fundus and body of the uterus is received by the lower three thoracic spinal segments, while nociceptive stimuli from the cervix are received by the second, third, and fourth sacral spinal segments.

Lack of the parasympathetic ganglia in these plexuses, as a result of failure of migration of the neural crest cells, is responsible for congenital megacolon of Hirschsprung's disease, which is characterized by dilatation of the affected segment and constipation. Since constipation in patients with Parkinson's disease may also exhibit deficiency in dopaminergic neurons of the enteric system, a possible correlation between the migration of neural crest cells and dopamine may require further investigation. It may also be possible to use these enteric dopaminergic neurons as donor grafts. Other diseases that affect the PNS may also involve the enteric nervous system such as herpes simplex, diabetes mellitus, amyloidosis, Chaga's disease, etc.

wall. Visceral afferents utilize mechanoreceptors, chemoreceptors, thermoreceptors, and osmoreceptors.

Disorders of the autonomic nervous system

Autonomic disorders occur in a variety of diseases and condition which affect the autonomic centers in the central nervous system, descending autonomic pathways, or the preganglionic neurons in the spinal cord. They are also seen as a result of disruption of the postganglionic neurons in the paravertebral and prevertebral ganglia. These dysfunctions are comprised of the Hirschsprung's disease, hyperhidrosis, Raynaud's disease or phenomenon, spinal cord lesions, Horner's syndrome, stellate ganglion syndrome, Shy-Drager syndrome, botulism, Riley-Day Syndrome, reflex sympathetic dystrophy, achalasia, and Chagas disease.

Pain from viscera is predominantly carried by the sympathetic fibers and will be felt in the cutaneous areas of the spinal segments that originally provided the presynaptic neurons to the diseased viscus. Pain fibers from the bladder and anterior urethra is conducted by the pelvic splanchnic nerves and the superior and inferior hypogastric plexuses, as well as the lumbar splanchnic nerve. The hypogastric plexuses and the lumbar splanchnic nerves convey uterine pain, with the exception of the cervix, to the lower thoracic and upper lumbar spinal segments. Dysmenorrhea (intractable pain associated with menses) may be alleviated by excision of the superior hypogastric plexus. Nociceptive impulses from the uterine cervix is transmitted via the pelvic splanchnic nerves to the 2nd, 3rd, and 4th spinal segments. Afferents from the testis and ovary run through the gonadal plexuses that terminate in the 10th and 11th spinal segments. General visceral afferents are found in the glossopharyngeal and vagus nerves.

- Hirschsprung's disease (congenital megacolon) as previously described, is a condition which results from absence of the parasympathetic ganglia in the myenteric plexus of Auerbach. Loss of the peristaltic movement and subsequent constriction of the affected segment and retention of feces above the aganglionic segment characterize this disorder. This condition, which frequently involves the sigmoid colon and the rectum, is more common in males (see also developmental aspects).
- Hyperhidrosis (disorders of sweating) is characterized by increased sweating due to over-stimulation of the sympathetic postganglionic neurons which innervate the sweat glands. It may be associated with peripheral neuropathy and reflex sympathetic dystrophy. Palm sweating, due to social or situational nervousness, may be relieved, upon patient's consent, by removal of the second and third thoracic sympathetic ganglia.
- Raynaud's disease or phenomenon may be a primary idiopathic vascular disorder or secondary to other conditions. It is characterized by spasmodic vasoconstriction of the digital arteries of the extremities in response to cold or emotional stress. This phenomenon may occur secondary to a cervical rib, scleroderma, thoracic outlet syndrome, atherosclerosis of the brachial artery and connective tissue disease. It may be attributed to a lack of histamine induced vasodilatation subsequent to a lack of the neural mechanism for histamine release in individuals with intact hypothalamic sympathetic center. Emotional stimuli and cold may activate the sympathetic system, lowering the threshold for vasospastic response. It is characterized by intermittent pallor due to depletion of the blood in the capillary beds of the digits and cyanosis as a result of deoxygenation of the stagnant blood in the capillary beds. Color changes may involve redness of the affected digits (reactive hyperemia) as a result of dilation of the digital arteries and engorgement of the capillary beds with oxygenated blood may also be observed. This will confer a ruddy complexion to the skin of the digits. Small painful ulcers may appear on the tips of the digits. This condition may be treated by the oral administration of mild sedatives (e.g. phenobarbital) and reserpine. Prazosin and Ca antagonist nifedipine are known to be effective medications for this condition. Phenoxybenzamine and prostaglandins (thromboxane) are also indicated as a therapeutic measure.
- Spinal cord lesions produce autonomic disturbances, which vary with the level of injury. Lesions of the cervical and upper thoracic spinal segments are most likely to produce combined sympathetic and parasympathetic

dysfunctions, whereas damage to the lower thoracic segments are only associated with parasympathetic dysfunctions. Transection of the cervical part of the spinal cord may result in loss of all sensory and motor activities below the level of affected segment(s), as well as autonomic dysfunctions including loss of sweating, piloerection, loss of micturition, impotence, and hypotension (spinal shock). Recovery of autonomic functions may occur as a result of the release from cortical and hypothalamic control. Since changes in blood pressure in individuals with this condition may no longer be mediated by autonomic centers in the brainstem, cutaneous stimulation below the level of the lesion may produce a rise in blood pressure, mydriasis and sweating. Bladder function becomes automatic and urination may occur when it is full. Following these changes, patients may manifest a triple or mass reflex in which a mild cutaneous stimulus may produce flexion in all joints of the lower extremity (triple reflex) which disappears approximately four months following transection of the spinal cord.

- Horner's syndrome is characterized by miosis (constriction of the pupil), ptosis (drooping of the upper eyelid due to paralysis of the superior tarsal muscle), anhidrosis (lack of sweating) and apparent enophthalmos (sinking of the eyeball due to paralysis of the orbital muscle). Heterochromia, which refers to the diversity of colors in part or parts that should normally be one color, is a characteristic of congenital form of Horner's. In infants, Horner's syndrome may be associated with unpigmented iris that assumes a bluish or mixed gray and blue appearance. It may be caused by a lesion of the intermediolateral column of the first thoracic spinal segment or emerging ventral root, degeneration of the lateral medulla, lesion of the descending autonomic pathways from the hypothalamus, superior cervical gangliotomy, or syringomyelia. It may also be caused by percutaneous carotid puncture for cerebral angiography, intracavernous lesions, birth trauma, enlargement of the cervical lymph nodes, thoracic tumors, destruction of the internal carotid plexus, or hypothalamic lesion.

- Stellate ganglion syndrome is produced by compression of the stellate ganglion (as seen in Pancoast tumor of the apical lobe of the lung), exhibiting signs of Horner's syndrome and reflex sympathetic dystrophy. The latter manifests dryness of the skin of the upper extremity and vasodilatation.

- Achalasia refers to failure or incomplete relaxation of the lower esophageal sphincter, which is more common

in males. In this condition the normal peristalsis of the esophagus is replaced by abnormal contractions. It is classified into vigorous and classic achalasia. Vigorous achalasia resembles diffuse esophageal spasm, exhibiting simultaneous and repetitive contractions with large amplitude, whereas classic achalasia shows contractions of small amplitude. Secondary achalasia may result from infiltrating gastric carcinoma. Dysphagia, chest pain, regurgitation and pulmonary aspiration, and projectile vomiting characterize it. Emotional disorders and hurried eating may predispose the individual to this condition. Although esophageal myenteric plexus lack ganglia, the pathogenesis of this dysfunction is not well understood. Treatment may include administration of anticholinergics and calcium channel antagonists, or balloon dilatation. Surgical intervention in which the lower esophageal sphincter is incised may prove to be effective.

- Chagas disease is an infectious and zoonotic disease caused by *Trypanosoma Cruzi* and is transmitted from infected animals to humans by Reduviid bugs. Chagoma, an inflammatory lesion, is often seen at the site of entry of parasite. When the parasite enters through the conjunctiva, edema of the palpebrae and periocular tissue is a characteristic feature (Romana's sign). Heart is the most commonly affected organ, exhibiting cardiomyopathy, ventricular enlargement and thinning of their walls, mural thrombi and apical aneurysm. Right branch of His bundle is frequently damaged, producing AV block. Patients show signs of malaise, fever, and anorexia, which are associated with swelling of the face and lower extremities. This infectious parasitic agent may also cause destruction of the myenteric plexus in the esophageal, duodenal, colonic, and ureteric wall, producing megacolon, megaduodenum and megaureter. Lymphadenopathy, meningoencephalitis and increased incidence of esophageal varicosities are the main characteristics of this disease. This condition may be treated by nifurtimox, an effective drug against *Trypanosoma Cruzi* during acute phase of the disease.

- Shy-Drager Syndrome (idiopathic orthostatic hypotension) is a multisystem disorders which includes autonomic dysfunctions, ataxia, and upper motor neuron palsy. Autonomic dysfunctions comprise anhidrosis (lack of sweating), impotence, postural hypotension, mydriasis and pupillary asymmetry, bowel and bladder dysfunctions. The hallmark of this disease is postural hypotension, which is greater than 30/20 mm Hg on standing from a supine position. Patients also

exhibit Parkinsonian manifestations in which rigidity and bradykinesia are very conspicuous. Neuronal loss has been shown in the intermediolateral column of the thoracic spinal segments, peripheral autonomic ganglia, substantia nigra, locus ceruleus, olivary nuclei, caudate nucleus, and the dorsal motor nucleus of vagus. These cellular losses are accompanied by gliosis and in some cases with Lewy bodies, which are typical of Parkinson's disease. Men are more frequently affected than women are and the disease exhibits an insidious onset. Postural hypotension may be treated by medications that increase blood volume and by pressure (antigravity) stockings. Parkinsonian symptoms may be treated by the administration of sinemet or bromocriptine as well as a agonists.

- Botulism is caused by ingestion of food contaminated with clostridium botulinum (anaerobic gram-positive organism), ingestion of spores and production of toxin, or as a result of wound infection with the same bacteria. It is a paralytic disease, which initially affects the cranial nerves, and expands to involve the limbs.

- Symptoms of botulism include autonomic disturbances such as nausea, vomiting, dysphagia, extremely dry throat, blurred vision, loss or diminished light reflex and ptosis, in addition to skeletal muscle paralysis. Descending paralysis which is symmetric involving the head, neck, arm and thorax is characteristic of this disease. Deep tendon reflexes are not generally affected, although gag reflex may be depressed. Patients may die from respiratory failure. Patients may be given antitoxin (equine antitoxin) as well as cathartics and enemas to eliminate the toxin supplemented with antibiotics.

- Riley-day syndrome (familial dysautonomia) is a familial recessive disorder of infants, which is characterized by a constellation of sensory and motor deficits. These deficits include hypopathia, hearing deficits and loss of taste. The autonomic disturbances in this syndrome include loss of lacrimation and loss of the mechanisms, which regulate blood pressure and temperature.

- Reflex sympathetic dystrophy exhibits pain and autonomic changes, occurring as a result of bone fracture, trauma to soft tissue, or myocardial infarction. The autonomic changes include increased sweating and vasoconstriction. Causalgia, a burning pain that is often accompanied by trophic cutaneous changes, is a form of reflex sympathetic dystrophy, occurring in partial lesion of a peripheral nerve such as the median or sciatic nerve.

Section 4

Somatic nervous system

The somatic nervous system (SNS) utilizes acetylcholine as a neurotransmitter. It forms plexuses such as cervical, brachial, and lumbosacral. Excision of somatic nerve fibers may result in atrophy and paralysis of the denervated structure. The response of SNS to a stimulus is immediate, fast, and of short duration. This is due to the fact that the synaptic gap between the presynaptic and postsynaptic membranes of the innervated structure is very narrow, allowing lesser diffusion distance. It is also attributed to the short distance of the synaptic gap between the presynaptic and postsynaptic membranes of the innervated structure is very narrow, allowing lesser diffusion distance. It is also attributed to the short distance of the synaptic gap, rendering the degradation of the neurotransmitter more efficient. The somatic afferents transmit pain, temperature, touch, and movement sensations from the skin, muscles, and tendons. The neurones of the somatic afferents are located in the dorsal root, trigeminal, geniculate, and the superior ganglia of the glossopharyngeal and vagus nerves.

10 [Spinal nerves](#)

11 [Cranial nerves](#)

12 [Neurotransmitters](#)

Spinal nerves are formed by the union of the dorsal and ventral roots which later divide into dorsal and ventral rami. The dorsal rami supply the skin and muscles of the back, while the ventral rami contribute to the formation of the cervical, brachial, and lumbosacral plexuses. Each plexus consists of ventral rami from a series of spinal segments, giving rise to branches that supply muscles and cutaneous areas. Some of these branches are motor, others are sensory, and most carry both sensory and motor fibers. Damage to these branches may occur in certain conditions, producing a constellation of disorders that involve muscles and/or dermatomes. These conditions and associated deficits are discussed in an elaborate fashion in this chapter.

Formation, distribution and components of the spinal nerves

Cervical spinal nerves

Cervical plexus

Thoracic spinal nerves

Brachial plexus

Branches of the roots

Branches of the superior trunk

Branches of the lateral cord

Branches of the medial cord

Branches of the posterior cord

Lumbar spinal nerves

Lumbar plexus

Sacral spinal nerves

Sacral plexus

Spinal reflexes

Superficial reflexes

Deep reflexes

Formation, distribution and components of the spinal nerves

The spinal nerves are formed by the union of the dorsal and ventral roots. Both of these roots run in the subarachnoid space to reach their points of exit at the intervertebral foramina. The central processes of the unipolar neurons of the spinal ganglia (Figures 10.1 & 10.3) form the dorsal roots.

Dorsal root fibers enter the posterolateral sulcus of the spinal cord as medial and lateral bundles, receiving coverings from the pia mater, arachnoid and the dural sheath.

These roots consist of thickly and thinly myelinated, as well as unmyelinated fibers. The thickly myelinated fibers comprise group Ia (annulospiral) and group II (flower spray endings) fibers that convey information from muscle spindles, as well as group Ib fibers of the Golgi tendon organs. The thickly myelinated fibers of the dorsal roots can selectively be blocked by the application of pressure on the dorsal roots. These thick fibers also show selective degeneration in combined system disease (associated with pernicious anemia), tabes dorsalis, and arsenic poisoning. Smaller, thinly myelinated (Ad) fibers, and the unmyelinated C fibers that carry nociceptive impulses may be blocked more effectively by local anesthetics and can selectively be affected in beriberi disease (associated with vitamin B1 deficiency). The skin area supplied by one dorsal root is known as dermatome. Dermatomes (Figure 10.2) of successive dorsal roots show extensive overlap, which may be limited along the axial line. The ventral roots are comprised of axons of the α and δ motor neurons (GSE) of the ventral horn of the spinal cord which supply the extrafusal and intrafusal muscle fibers, respectively. They also contain general visceral efferents (GVE), emanating from the intermediolateral columns of the thoracic and upper lumbar segments (sympathetic fibers) or arising from the second through the fourth sacral segments (parasympathetic fibers). In the intervertebral foramina, the dorsal and ventral roots unite to form the spinal nerves, which are accompanied by the meningeal and spinal branches of the segmental arteries. There are thirty one pair of spinal nerves, eight cervical, twelve thoracic, five lumbar, five sacral, and one coccygeal. All spinal nerves emerge via the intervertebral foramina (bounded anteriorly by the intervertebral discs and vertebral bodies, posteriorly by zygapophyseal joints, superiorly and inferiorly by the vertebral notches), with the exception of the first cervical (suboccipital) and the fifth sacral spinal nerves. The first cervical spinal (suboccipital) nerve leaves the vertebral column between the occiput and the atlas, whereas the fifth sacral spinal nerve exits through the sacral hiatus. The eight cervical spinal nerve emerges inferior to the first thoracic vertebra.

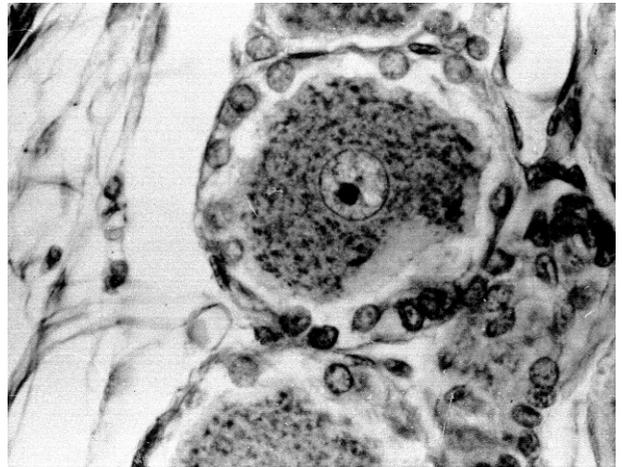


Figure 10.1 Photomicrograph of section of the dorsal root ganglion showing its main components

Proximity of the dorsal roots to the intervertebral discs may render them more prone to compression by a herniated intervertebral disc in which the nucleus pulposus extrudes posterolaterally into the vertebral canal.

The sympathetic ganglia are connected to all spinal nerves via the gray communicating rami. The thoracic and upper two or three lumbar spinal nerves have additional connection to the sympathetic ganglia via the white communicating rami (Figure 10.3).

Spinal nerves also give rise to recurrent meningeal branches to the spinal and cerebral dura mater, periosteum, blood vessels, posterior longitudinal ligament, as well as the intervertebral discs. Recurrence of pain in diseases associated with the vertebral column or spinal nerves may be attributed to irritation of these meningeal branches. There is considerable overlap in the innervation of the spinal dura mater, which accounts for the perception of pain over several dermatomes upon irritation of a small area of the dura mater that receives innervation via a single spinal nerve.

In general, the peripheral nerves are arranged in bundles or fasciculi that join together to form nerve trunks. The

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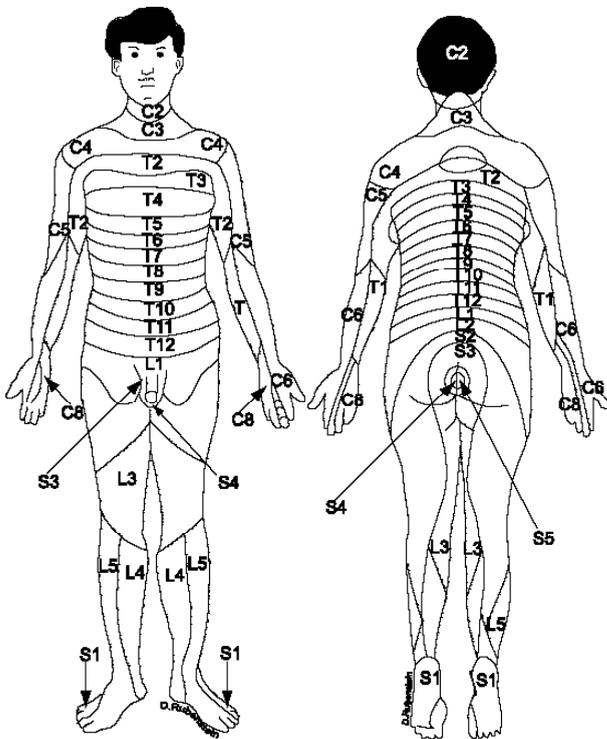


Figure 10.2 Dermatomes are mapped according to the band of skin innervated by dorsal roots of a single spinal segment

epineurium is a collagenous layer with variable amount of fat that invests the nerve trunk. The fat content of the epineurium plays a protective role against injuries, and loss of this fatty layer may produce pressure palsies in bed-ridden chronic patients. Each fasciculus within a nerve trunk is encircled by the perineurium, a relatively thicker connective tissue sheath that exhibits epitheloid and myoid characteristics. The perineurium consists of collagen and cells derived from fibroblasts that continue with the coverings of the encapsulated receptors. Individual fibers are surrounded by the endoneurium, a loose connective tissue layer that is derived from the mesoderm. It consists of collagenous fibers, fibroblasts, Schwann cells, and endothelial cells that are immersed in a fluid, maintaining a higher pressure than the surrounding.

The nerve fibers and the connective tissue coverings are vascularized by intraneural capillaries called vasa nervorum. These vessels are categorized into extrinsic epineurial vessels

This pressure difference, which is maintained by the perineurium, may be critical in preventing toxic contamination of the endoneurium. In addition, host neurons may send sprouts into the tubes formed by the endoneurium within the donor skin graft, allowing the re-innervation of the graft tissue to proceed.

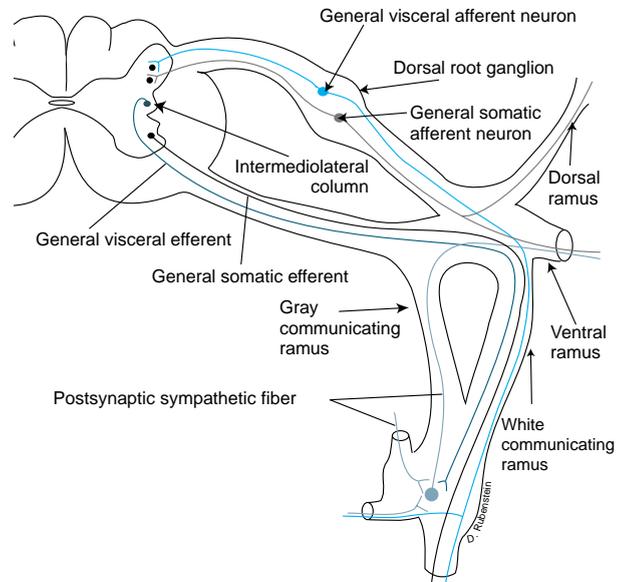


Figure 10.3 The spinal nerve, associated rami, and its functional components

and intrinsic longitudinal endoneurial microvessels. The unique course of these vessels may account for the relative resistance of peripheral nerve to ischemia. In addition to these coverings, nerve fibers may be ensheathed by myelin or remain unmyelinated. Thickness of the coverings also varies with the relative site of the nerve fiber and speed of conduction. Generally speaking, thickly myelinated fibers exist in high pressure sites, innervating targets that require fast conduction. Unmyelinated nerve fibers are relatively thin, and display a slower rate of conduction. They remain invested by the cytoplasm of the Schwann cells, in which each nerve fiber is enfolded by a single Schwann cell to form the Remak bundle. The unmyelinated fibers form the postganglionic autonomic, olfactory, and the nociceptive C fibers. Following their formation, the spinal nerves divide into a large ventral and smaller dorsal rami (Figure 10.3).

The ventral rami are mostly larger than the dorsal rami and supply the extremities, thoracic and abdominal walls. They form elaborate connections within the cervical, brachial and lumbosacral plexuses. These connections enable one spinal segment to contribute to the formation of more than one spinal nerve and also make it possible for one muscle to be innervated by more than one spinal segment. The thoracic spinal nerves, for the most part, retain their segmental arrangement and form the intercostal nerves.

The dorsal rami supply the skin and intrinsic muscles of the back and neck. They usually divide into medial and lateral branches (with the exception of the dorsal rami, the C1, C4, S5, and CC1 spinal nerves). In general, the medial branches of the dorsal rami of the cervical and upper thoracic spinal nerves provide primarily sensory

Pathological conditions involving the a motor neurons in the spinal cord (poliomyelitis) or brainstem, or their axons (polyneuropathy) may produce spinal nerves dysfunctions via demyelination, followed by muscle denervation, and paresis or paralysis.

- Paresis or paralysis may be preceded by visible involuntary contractions of the muscle fibers (fasciculation) involving a motor unit. Fibrillation involves a single muscle fiber, may not be visible through skin, and may only be detected through electromyography.

The extent and severity of neuronal damage may determine the degree of dysfunctions. On that basis trauma or neurological diseases may produce disorders that are classified into neuropraxia, axonotmesis and neurotmesis.

- Neuropraxia is an incomplete, transient and reversible loss of conduction without the loss of anatomic integrity. It results from transient ischemia or paranodal demyelination subsequent to severe compression. Neuropraxia may produce loss of deep tendon reflexes, and sensory dissociation with preservation of pain and thermal sensations, but with no detectable autonomic dysfunctions.

- Axonotmesis refers to a complete interruption of an axon and its myelin sheath with preservation of the connective tissue stroma. It is characterized by immediate and complete loss of all sensory, motor, and autonomic functions. The degree of recovery of injured nerve fibers (commonly from a closed crushed injury) is dependent upon the length of the damaged segment and its distance from the innervated structure. The part of the axon distal to the site of injury undergoes Wallerian degeneration. After a latent period of approximately one-month downward directed nerve regeneration may occur.

- Neurotmesis refers to the complete anatomic disruption of neural and connective tissue elements of an axon. It is caused by injuries that penetrate nerves such as stab or gunshot wounds. Fibrosis and loss of continuity of endoneurial tubules render spontaneous recovery and regeneration almost impossible, and neurosurgical repair a necessity.

while the lateral branches provide motor innervation. This pattern is reversed in the lower thoracic and lumbar spinal nerves. The dorsal rami of the sacral spinal nerves exit through the dorsal sacral foramina with the exception of the fifth, dividing into medial and the lateral branches. The dorsal ramus of the coccygeal nerve joins the lower two sacral dorsal rami to supply the coccygeal skin.

Spinal nerves may be affected in entrapment neuropathies, by a localized injury or inflammation caused by mechanical irritation from impinging anatomical

structure. Burning pain felt at rest and associated with altered sensation, is characteristic of these types of nerve injury. Injury to the spinal nerves or roots may also occur as a result of herniated intervertebral discs, tumors, osteoarthritis, spina bifida cystica, or cauda equina syndrome. These clinical conditions are generally dependent upon the extent of damage and the number of affected roots or nerves. Nerve root compression, e.g. as a result of disc prolapse, commonly occurs at sites where the vertebral column is most mobile. The lower cervical and lower lumbar vertebrae are the frequent sites of root compression. Paresthesia or pain may result from compression of the dorsal roots.

Cervical spinal nerves

There are eight cervical spinal nerves with the dorsal and ventral ram. The first cervical spinal nerve form the suboccipital nerve, which runs in the suboccipital triangle and provide innervation to the rectus capitis posterior major and minor and the inferior and superior capitis oblique muscles. The medial branch of the dorsal ramus of the second cervical spinal nerve forms the greater occipital nerve, which encircles the inferior oblique muscle and ascend to supply the skin of the posterior scalp as far as the vertex. The ventral rami of the cervical spinal nerves form the cervical plexus and contribute partly to the brachial plexuses.

Cervical plexus

The cervical plexus (Figures 10.4 & 10.5) is formed by the ventral rami of the upper four cervical nerves, with a small contribution from the fifth cervical segment. It lies deep to the internal jugular vein and anterior to the middle scalene muscle. This plexus gives rise to sensory and motor nerves. It also provides segmental motor innervation to the geniohyoid, rectus capitis anterior and lateralis, longus capitis, and longus colli muscles. This plexus gives rise to ansa cervicalis, phrenic, lesser occipital, great auricular, transverse (colli) cervical, and supraclavicular nerves.

Ansa cervicalis (C1, 2, 3) is a nerve loop formed by the union of the ventral ramus of the first cervical spinal nerve (descendens hypoglossi or superior root) and the ventral rami of the second and third cervical spinal nerves (descendens cervicalis or inferior root). The ansa cervicalis pierces the carotid sheath and runs superficial to the internal jugular vein, innervating the infrahyoid (strap) muscles (omohyoid, sternohyoid and sternothyroid), with the exception of the thyrohyoid muscle which is innervated by the ventral ramus of the first cervical spinal nerve.

Phrenic nerve (C3, 4, 5) is formed by the ventral rami of the third, fourth, and fifth cervical spinal nerves, with the

Prolapse of the lumbar intervertebral discs commonly occurs between the fourth and fifth lumbar vertebrae or between the fifth lumbar and the first sacral vertebrae. Prolapse of the fourth intervertebral disc (between L4-L5) is most likely to compress the fifth lumbar spinal root. In general disc herniation may be precipitated by flexion injuries and is often seen in middle-aged people who exhibit degenerative changes in the intervertebral discs and the posterior longitudinal ligament. It produces back pain that projects to the leg (sciatica), and movement disorders such as weakness of dorsiflexion of the foot and toes and sensory loss in lateral leg and dorsal surface of the foot (L5). Prolapse of the fourth intervertebral disc may also exhibit weakness of plantar flexion and eversion, pain or loss of sensation in the posterior leg and lateral plantar surface of the foot (S1). The hamstring muscles may show spasm when attempt is made to flex the thigh at the hip joint while the leg is extended (Lasegue's sign). Central protrusion of the herniated disc between L4 and L5 is commonly accompanied by urinary or bowel dysfunctions.

- Cervical disc herniation commonly occurs between the sixth and seventh cervical vertebrae. This is due to the fact that C6 is the fulcrum for cervical movements. Degeneration of the intervertebral discs (cervical spondylosis) results in motor deficits and pain in the arm or the neck. Prolapse of the intervertebral disc between the fifth and sixth vertebrae is most likely to compress the sixth cervical root. Cervical disc prolapse may protrude centrally to compress the spinal cord and

produce combined signs of upper motor neuron palsy and sensory deficits in the lower extremity.

- Thoracic spinal nerve roots are rarely affected due to the restricted rotatory movement between the thoracic vertebrae. However, direct trauma or cancer metastasis may cause collapse of the thoracic vertebrae and subsequent compression of the thoracic spinal nerve roots. Violent drawing of the entire body along the ground with one hand may specifically injure the dorsal root of the first thoracic spinal nerve, producing signs of Horner's syndrome and atrophy of the intrinsic muscles of the hand.

- Involvement of sympathetic fibers adjacent to the affected spinal nerve may occur as a result of trauma to soft tissue or bony fracture. This may result in burning pain in a wider territory than the area of distribution of the affected spinal nerve (causalgia) accompanied by autonomic disturbances such as sweating and vasoconstriction (reflex sympathetic dystrophy).

- Pain associated with compression of spinal nerves is generally confined to the area of distribution of the affected nerves and may or may not be accompanied by motor dysfunctions. Certain movements such as flexion, extension, or rotation aggravate root pain associated with a lesion or prolapsed disc of one or more spinal roots. Since the ventral rami are the primary contributors to the cervical, brachial, lumbar, and sacral plexuses, a detailed discussion of these plexuses will be appropriate at this point.

largest contribution comes from the fourth cervical spinal segment. This nerve runs on the anterior surface of the anterior scalene muscle and posterior to the prevertebral fascia. It courses within the superior and middle mediastina, between the

mediastinal pleura and fibrous pericardium. This nerve runs anterior to the pulmonary root, separating it from the vagus nerve. It supplies sensory fibers to the central part of diaphragmatic pleura and peritoneum, pericardium, mediastinal pleura, and to the hepatic plexus. It also provides motor fibers to the muscular diaphragm.

The accessory phrenic nerve is frequently derived from the fifth cervical spinal nerve. The superficial branches of the cervical plexus (listed below) exit at the midpoint of the posterior border of the sternocleidomastoid muscle (SCM) accompanied by the spinal accessory nerve.

Lesser occipital nerve (C2) curves around the sternocleidomastoid muscle and supplies the upper part of the medial surface of the ear and the area of the posterior scalp.

Great auricular nerve (C2-3) ascends toward the parotid gland, accompanied by the external jugular vein, carrying sensation from the facial skin that covers the parotid gland,

mastoid process, and the ear lobule. It is the only cutaneous nerve to the face, which is not derived from the trigeminal nerve.

Transverse (colli) cervical nerve (C2-3) arises from the ventral rami of the second and third cervical spinal segments, supplying cutaneous fibers to the anterior and lateral neck.

Supraclavicular nerves (C3-4) are derived from the ventral rami of the third and fourth cervical spinal nerves and descend deep to the platysma. They divide into lateral, intermediate, and medial branches, supplying the lower neck and the upper part of the anterior thorax.

Thoracic spinal nerves

The thoracic spinal nerves emerge from the intervertebral foramina distal to the corresponding vertebrae. Due to the difference between the length of the vertebral canal and the length of the spinal cord, the lower thoracic spinal nerves pursue a longer course in order to exit through the corresponding foramina. The medial branches of the dorsal rami of the upper six thoracic spinal nerves are primarily cutaneous to the back, while the lateral branches

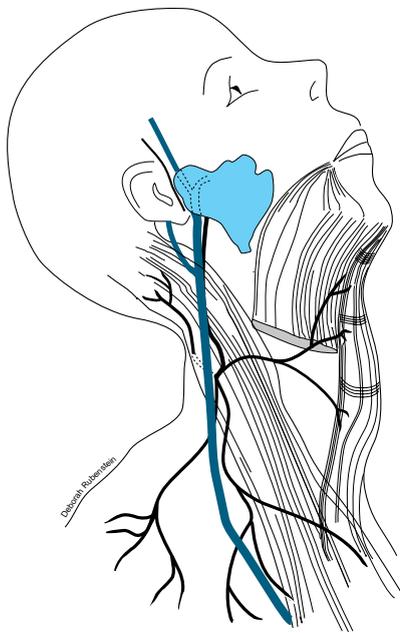


Figure 10.4 Schematic diagram of the superficial branches of the cervical plexus

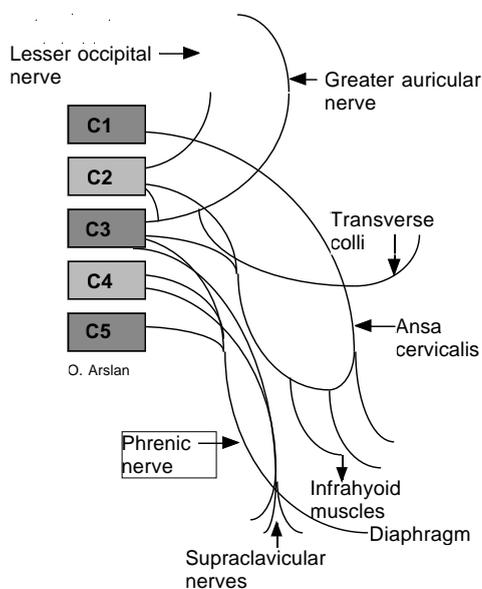


Figure 10.5 Components of the cervical plexus and its area of distribution

Pathological conditions involving the mediastinal and/or diaphragmatic pleura and peritoneum or the gall bladder may result in pain radiating to the dermatomes of third, fourth and fifth cervical spinal nerves which correspond to the back and upper part of the shoulder. Paralysis of the hemi-diaphragm may result from excision of the phrenic nerve in the neck unless an accessory phrenic nerve exists.

Anesthetics may be injected into the midpoint of the posterior border of SCM to achieve complete cervical nerve block in radical neck dissection.

of these rami are principally muscular to the iliocostalis and levator costarum muscles. On the other hand, the medial branches of the lower six thoracic spinal nerves innervate the multifidi and the longissimus muscles, and the lateral branches remain sensory. Continuation of the ventral rami of the thoracic spinal nerves form the intercostal nerves that run in the intercostal sulci and innervate the upper extremity, thoracic wall, anterior abdominal, and the gluteal region. The ventral ramus of the first thoracic nerve contributes to the brachial plexus and to several other nerves such as the ulnar and median nerves. A particular branch, the intercostobrachial nerve, arises from the second intercostal nerve (sometimes the third intercostal nerve) that joins the brachial plexus and supplies the skin of the upper part of the medial arm. The upper six intercostal nerves supply the thoracic wall, costal pleura, the diaphragm, and the diaphragmatic pleura and peritoneum, while the lower five intercostal (thoracolumbar) nerves course between the internal oblique and transverse abdominis muscles, innervating the skin and muscles of the anterior abdomen, as well as the peritoneum. In particular, the tenth intercostal nerve, supplies the skin of the umbilicus, whereas the seventh, eighth, and ninth intercostal nerves supply the supra-umbilical region. Lower two intercostal nerves supply the infra-umbilical region. The subcostal nerve courses posterior to the lateral arcuate ligament, anterior to the quadratus lumborum, and distal to the twelfth rib, accompanied by the subcostal vessels. It pierces the abdominal wall posterior to the anterior iliac spine and innervates the skin of the anterolateral gluteal region.

Brachial plexus

The brachial plexus (Figure 10.6) is formed by the union of the ventral primary rami of the C5-T1 spinal nerves (with a small contribution from the ventral ramus of C4

The origin, course, and the area of distribution of the intercostal nerves may explain the mechanism of projected pain to the thoracic wall associated with inflamed costal or diaphragmatic pleura. It may also account for the pain sensation in the anterior abdominal wall as a result of subluxation of the interchondral joints and compression of the lower intercostal nerves (clicking rib syndrome). Tuberculosis of the thoracic vertebrae may produce pain in the anterior abdominal as a result of compression of the intercostal nerves.

- Herpes zoster (shingles) commonly affects the dorsal root ganglia of the thoracic spinal nerves producing pain in the thoracic wall. In addition, involvement of the of the first thoracic spinal segment in the transmission of cardiac pain is responsible for the referred pain felt in the medial arm, medial forearm and medial fifth digit. The first thoracic spinal segment provides both sympathetic fibers to the cardiac plexus and cutaneous fibers to the medial arm and forearm via the medial antebrachial and brachial cutaneous branches (T8-T1) of the brachial plexus. It has been suggested that painful impulses from the heart are conveyed to T1 spinal segments via the sympathetic fibers lowering the threshold of the cutaneous neurons within that particular segment.

- Contraction of the abdominal muscles in response to cutaneous stimulation of the abdomen confirms the fact that the intercostal nerves subserve dual function of cutaneous and muscular innervation of the anterior abdominal wall.

spinal nerve). This plexus lies in the posterior triangle, posterior to the clavicle, and between the anterior and middle scalene muscles. It may be prefixed when it is formed by the ventral rami of the C4-C8 spinal nerves or postfixed when the ventral rami of C6-T2 spinal form it. The ventral rami of C5 and C6 join to form the superior trunk. The ventral ramus of C7 continues as the middle trunk, whereas the ventral rami of C8 and T1 spinal nerves form the inferior trunk. These individual trunks run in the axilla and then divide into anterior and posterior divisions. Union of the posterior divisions forms the posterior cord. The anterior divisions of the upper and middle trunks form the lateral cord while the anterior division of the inferior trunk continues as the medial cord. The roots of the brachial plexus give rise to the dorsal scapular and long thoracic nerves. The superior trunk gives origin to the suprascapular nerve; the lateral cord provides the

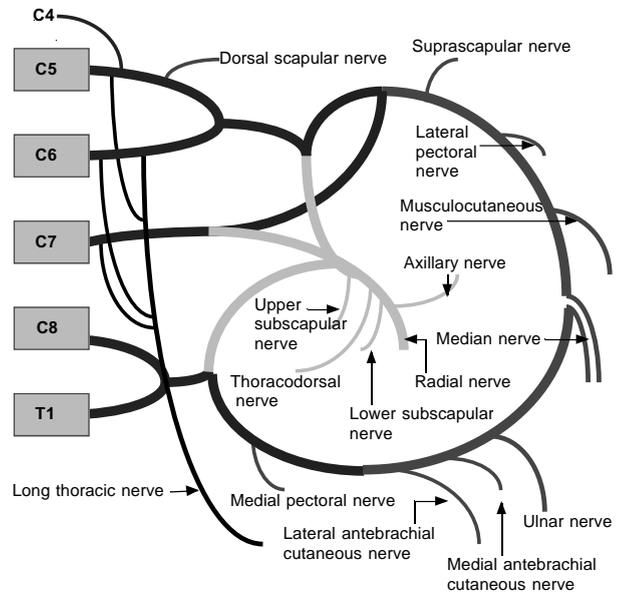


Figure 10.6 Formation of the brachial plexus. Observe the segmental contribution of the spinal cord to the trunks, divisions, cords, and peripheral branches

musculocutaneous and lateral pectoral nerves, as well as the lateral root of the median nerve. Numerous branches arise from the medial cord which include the medial pectoral, ulnar, and medial brachial and antebrachial cutaneous nerves, the nerve to subclavius, and the medial root of the median nerve. Branches of the posterior cord are the axillary, radial, upper and lower subscapular, and thoracodorsal nerves.

Branches of the roots

Dorsal scapular nerve (C5) (Figure 10.6) arises from the ventral ramus of the fifth cervical spinal nerve, pierces the

Summary

5	Roots:	Ventral rami of C5-T1, give rise to the dorsal scapular and long thoracic nerves.
3	Trunks:	Superior trunk (C5 & C6) gives rise to the suprascapular nerve and nerve to the subclavius, middle trunk (C7), inferior trunk (C8 & T1)
6	Divisions: 3 anterior & 3 posterior	
3	Cords:	Lateral, posterior, medial
16	Branches	Posterior cord: axillary, radial, thoracodorsal, upper & lower subscapular nerves Lateral cord: musculocutaneous and lateral pectoral nerves, and the lateral root of the median nerve Medial cord: medial pectoral, medial brachial and antebrachial cutaneous, and ulnar nerves, and medial root of the median nerve.

The roots (ventral rami), trunks, divisions, cords, and branches of the brachial plexus may be simplified by the following mnemonic: Robert Taylor Drinks Cold Beer.

Injury to the superior trunk (Erb-Duchenne's paralysis) may be caused by hyperextension of the neck which increases the angle between the shoulder and neck, or undue pull on the suprascapular nerve that anchors to the margins of the suprascapular notch. A fall from a motorcycle, a careless forceps delivery in breech position, or traction on the head may also precipitate this type of injury.

Patients present with an adducted (deltoid and supraspinatus are inoperative), extended and a medially rotated arm hanging limply at the side (coracobrachialis, infraspinatus and teres minor are no longer functioning). The forearm is extended and pronated (biceps brachii and brachialis are non-functional) and the wrist is slightly flexed, forming the typical configuration of Waiter's tip hand (Figure 10.7). Due to the extensive overlap between the cutaneous fibers of the contiguous nerves, sensory loss associated with this type of injury will be confined to a small region of the shoulder.



Figure 10.7 This diagram illustrates the manifestations of Erb's Duchenne Palsy

middle scalene, and supplies the levator scapula, as well as the major and minor rhomboids.

Long thoracic nerve (C5, C6, C7) (Figure 10.6) arises from the ventral rami of the C5, C6, and C7 spinal nerves and supplies the serratus anterior muscle, accompanied by the lateral thoracic vessels. Initially, the upper two roots (C5, C6) pierce the middle scalene muscle and later unite with the lower root from seventh (C7) cervical spinal segment.

Injury to the inferior trunk may be caused by excessive abduction of the arm which may occur in individual who clutches himself to an object while falling from a height (Klumpke's palsy). It may also occur during a difficult breech delivery (birth palsy or obstetric paralysis), or upon a sharp angulation of the inferior trunk over the cervical rib (cervical rib syndrome). It may be seen in individuals with abnormal insertion or spasm of the anterior and middle scalene muscles (scalene anterior syndrome), or as a result of anomalous fibrous band that extends to the first rib. This condition is characterized by paralysis of the intrinsic muscles of the hand, especially the thenar muscles, as well as the long flexors of the hand and the digits. Pain and numbness is felt along the medial border of the forearm, hand, and medial two digits. Horner's syndrome (ptosis, miosis, and anhidrosis) may also be seen in this condition due to involvement of the first thoracic spinal segment. Klumpke's palsy also exhibits "claw-hand" configuration.

When it is caused by a cervical rib or a fibrous band that extend to the first rib the subclavian artery may also be compressed in conjunction with the inferior trunk, producing combined neuronal and vascular disorders (thoracic outlet syndrome). In this syndrome the inferior trunk is damaged and the blood flow to the upper extremity within the subclavian artery is substantially decreased, producing coldness, cyanosis and pain in the arm. Patients manifest a positive Adson's test, a clinical finding in which the radial pulse becomes weaker on deep inspiration and also upon turning the head to the affected side.

Branches of the superior trunk

Suprascapular nerve (C5, C6) (Figure 10.6) runs deep to the omohyoid muscle, accompanied by the suprascapular vessels. It enters the suprascapular foramen, inferior to the suprascapular ligament. Then, it courses in the suprascapular and infraspinous fossae, innervating the supraspinatus and the infraspinatus muscles.

Nerve to the subclavius (C5, C6) as the name implies supplies the subclavius muscle, which acts a cushion that prevents rupture of the subclavian artery in clavicular fracture.

Branches of the lateral cord

Musculocutaneous nerve (C5, C6, C7) (Figures 10.6 & 10.8) is formed by the ventral rami of the fifth, sixth, and seventh spinal nerves. It pierces the coracobrachialis muscle and continues to the forearm as the lateral antebrachial cutaneous nerve. This nerve supplies the

Overactivity and fibrosis of the middle scalene muscle as a result of ischemic hypertrophy may damage the dorsal scapular nerve. Entrapment of this nerve within the middle scalene muscle hinders its ability to accommodate changes in position during movement of the head and arm. These movements exacerbate the pre-existing weakness, atrophy, and pain in the rhomboids and levator scapula muscles.

Proximity of the long thoracic nerve to the axillary lymph nodes, and its location superficial to the serratus anterior muscle and lateral to the mammary gland may account for the vulnerability of this nerve to injury in radical mastectomy. Carrying heavy objects on the shoulder or entrapment within the middle scalene may also damage the nerve. Unlike the dorsal scapular nerve, entrapment of this nerve within the middle scalene muscle does not produce pain in the upper extremity. Protrusion of the inferior angle of the scapula (winged scapula), which becomes evident upon protraction, is the main characteristic of long thoracic nerve dysfunction. This is due to paralysis of the serratus anterior and the inability of the muscle to hold the scapula against the thoracic wall. Weakened protraction and lateral rotation of the scapula are also common manifestations of this condition.

flexors of the elbow such as coracobrachialis, brachialis and biceps brachii. It also provides cutaneous innervation to the lateral side of the forearm.

Lateral pectoral nerve (C5, 6, 7) (Figure 10.5) supplies the pectoralis major muscle. Lateral root (C5, 6, 7) contributes to the formation of the median nerve.

Branches of the medial cord

The medial cord gives rise to the medial pectoral, medial brachial, medial antebrachial, and ulnar nerves, as well as to the medial root to the median nerve. Medial pectoral nerve (C8, T1) (Figure 10.6) pierces the pectoralis minor muscle and innervates both the pectoralis major and minor muscles. Medial brachial cutaneous nerve (C8, T1) is the smallest branch of the brachial plexus that supplies the distal one third of the medial surface of the arm (Figure 10.9). It may join the intercostobrachial nerve, or it may be replaced by the combination of the intercostobrachial nerve and a branch from the third intercostal nerve.

Medial antebrachial cutaneous nerve (C8, T1) (Figure 10.9) supplies the anterior and posterior surfaces of the medial side of the forearm as far down as the wrist.

The suprascapular nerve may be injured as a result of fibrosis and subsequent narrowing of the suprascapular foramen. Rupture of the rotator cuff and shoulder dislocation may also contribute to suprascapular nerve dysfunction. Fixation within the suprascapular foramen in the immobilized upper extremity of individual with frozen shoulder and repeated compensatory motion of the scapula may endanger this nerve. Traction exerted on this nerve may eventually produce a pull on the upper trunk of the brachial plexus leading to Erb's palsy. Compression of the suprascapular nerve may result in atrophy of the supraspinatus and infraspinatus muscles and associated weakness in lateral rotation and abduction of the arm, as well as pain sensation confined to the posterior shoulder. The suprascapular nerve may also be damaged in Colle's fracture as a result of downward movement of the thorax with the scapula is fixed and the arm is extended.

Ulnar nerve (C8, T1)-(Figure 10.10) runs medial to the axillary and brachial arteries, coursing in the corresponding sulcus on the medial epicondyle of the humerus. Later, it pierces the flexor carpi ulnaris near its origin and runs toward the wrist, deep to muscle. At the wrist, it crosses the flexor retinaculum between the pisiform bone and the hook of the hamlet (Canal of Guyon), a common site of entrapment of the ulnar nerve. Then, the ulnar nerve divides into motor and sensory branches in the hand.

No muscle in the arm receives innervation from the ulnar nerve. In the forearm, it innervates the flexor carpi ulnaris and medial half of the flexor digitorum profundus.

After exiting Guyon canal, it innervates all the hypothenar muscles, the abductor, flexor and opponens digiti minimi, the palmar and dorsal interossei, the

Injury to the musculocutaneous nerve, although rare, may result from a fracture of the humerus, shoulder dislocation, positioning of the arm during surgery, or entrapment inside a hypertrophied coracobrachialis muscle. Common manifestations of this injury are weakened flexion of the arm, markedly weakened flexion of the forearm, weakened supination and instability of the shoulder joint. Impairment of the cutaneous sensation in the lateral half of the forearm will also be observed in this injury. Heavy objects placed on the forearm and supported by the elbow may particularly compress the lateral antebrachial cutaneous branch of this nerve.

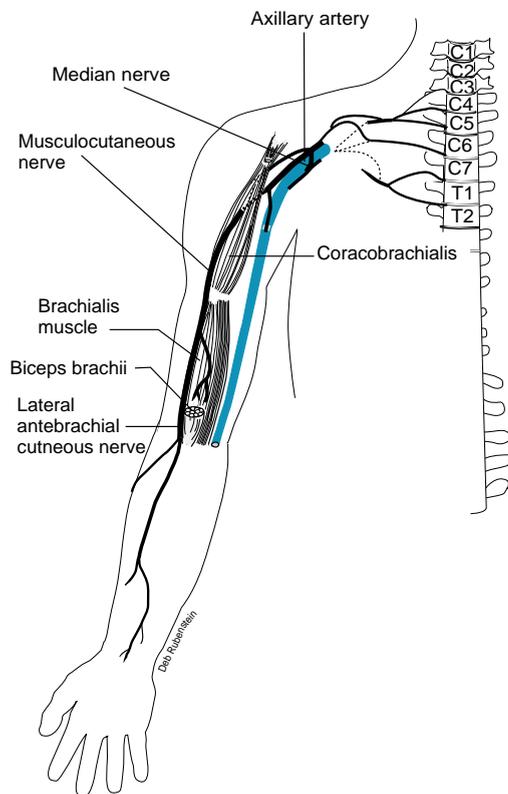


Figure 10.8 Musculocutaneous nerve and its branches

adductor pollicis (in about 55% of individuals), and the two medial lumbricals. The ulnar nerve also provides cutaneous innervation to one and a half of the medial portion of the palm and dorsum of the hand, via the palmar and dorsal cutaneous branches. However, these cutaneous branches to the hand may leave the ulnar nerve proximal to the canal and flexor retinaculum, bearing significant clinical importance in anesthetic block associated with hand injuries.

Median nerve (C6, 7, 8, T1) (Figures 10.13 & 10.14) is formed by the union of the corresponding roots from the lateral and medial cords, anterior to the axillary artery. Sometimes, the musculocutaneous may also join the medial root when the lateral root is smaller than usual. This nerve runs in the middle of the arm with the brachial artery, anterior to the brachialis tendon, and within the cubital fossa. It courses between the humeral and ulnar heads of the pronator teres muscle, descending with the anterior interosseous vessels, on the posterior surface of the flexor digitorum superficialis. At this point, it gives rise to the anterior interosseous branch, which supplies the pronator quadratus, the lateral, half of flexor digitorum profundus, and the flexor pollicis longus. It enters the hand, deep to the flexor retinaculum, within carpal tunnel. This tunnel, which is formed by the flexor retinaculum (transverse carpal ligament) between the scaphoid and

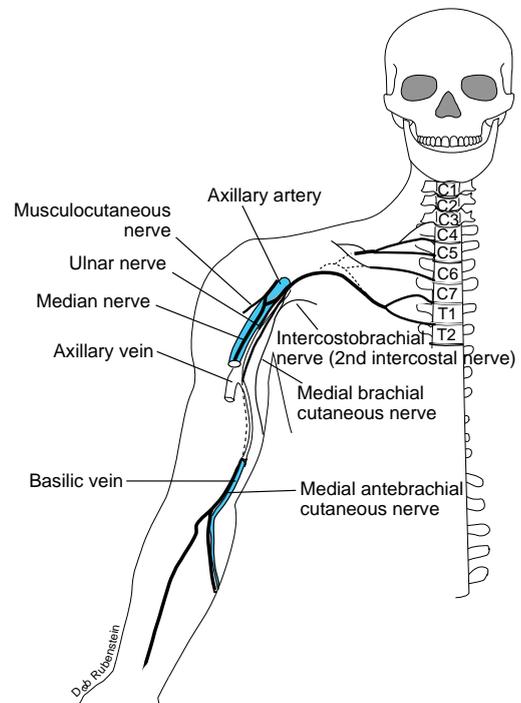


Figure 10.9 The course and areas of distribution of the medial brachial and antebrachial cutaneous nerves

trapezium on the radial side and the pisiform and hamlet on the ulnar side. It gives passage to the median nerve and tendons of the flexor digitorum superficialis, flexor digitorum profundus and the flexor pollicis longus. The ulnar artery and nerve, radial artery and nerve, palmaris longus, flexor carpi ulnaris and the palmar cutaneous branch of the median nerve lie outside of the carpal tunnel, anterior to the flexor retinaculum. It supplies the thenar muscles and provides cutaneous innervation to the hand and digits. Proximal to the flexor retinaculum, the median nerve gives rise to the palmar cutaneous branches to the skin of the thenar eminence. It also innervates the skin of the palmar surfaces of the lateral three and half digits and the dorsal surfaces of the distal phalanges of these digits. It also supplies all muscles of the anterior forearm with the exception of the flexor carpi ulnaris and the medial half of the flexor digitorum profundus. Additionally, it innervates the thenar muscles and the lateral two lumbricals, with the exception of the adductor pollicis.

Fibers of the ulnar nerve which supply the intrinsic muscles of the hand may run within the median nerve in about 20% of individuals and leave the nerve distal to the elbow to join the ulnar nerve again (Martin-Gruber anastomosis).

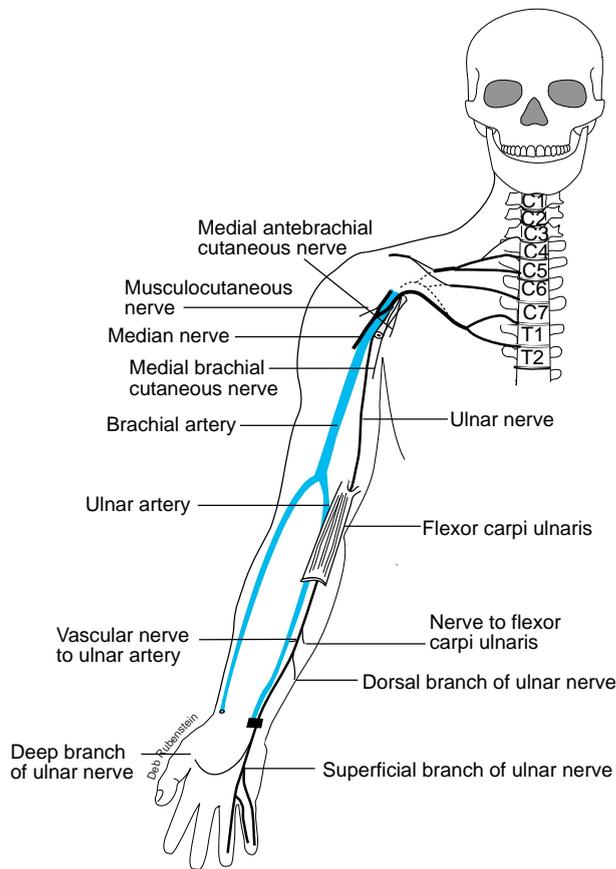


Figure 10.10 Ulnar nerve, its course and areas of distribution are illustrated in this diagram

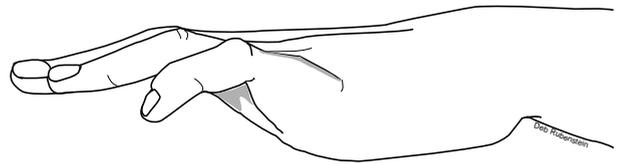


Figure 10.11 The hand and digit disorders associated with ulnar nerve damage at the elbow. Note abnormal posture of the fourth and fifth digits and flattening of the dorsal interossei with normal hypothenar muscle

Ulnar nerve injuries occur in fractures involving the medial epicondyle, dislocation of the elbow, entrapment within the Guyon canal. It may also be compressed as a result of entrapment between the two heads of the flexor carpi ulnaris, prolonged leaning on the elbow (Vegas Neuropathy), sustained flexion of the elbow, cubitus valgus deformity (tardy ulnar palsy), or entrapment within the cubital fossa (cubital tunnel syndrome). Injury to the ulnar nerve at the wrist results in atrophy of the hypothenar muscles and subsequent loss of thumb adduction which makes scraping the thumb across the palm and formation of the letter "O" by the second digit and the thumb an impossible task. Loss of abduction and adduction of the digits is exemplified by the inability of a patient to hold a piece of paper between the digits.

Ulnar claw hand (Figures 10.11 & 10.12), a characteristic configuration of the ulnar nerve damage at the wrist, is due to hyperextension at the metacarpophalangeal joints particularly of the ring and fifth digits and hyperflexion at the interphalangeal joints. Weakened extension and flexion at the interphalangeal joints (IP) of the fourth and fifth digits, hollowing of the palm (empty purse) and guttering of the grooves between the metacarpal bones may also be seen in this type of injury. Impaired sensation, paresthesia and nocturnal pain in the medial one third of the palm and dorsum of the hand may also be experienced by the patient.

Injury to the ulnar nerve at the axilla is rare, however its predisposition to injury is more common at the elbow due to its superficial position in the condylar sulcus of the medial epicondyle (ulnar nerve sulcus).

This innervation can be abbreviated by the mnemonic, loaf, denoting 1/2 of lumbricals, opponens pollicis, abductor pollicis, and flexor pollicis brevis are supplied by the ulnar nerve.

Branches of the posterior cord

Axillary nerve (C5, C6) (Figure 10.6) runs in the quadrangular space accompanied by the posterior humeral circumflex artery and vein. The anterior branch of this nerve supplies the deltoid muscle and the skin that covers the muscle, whereas the posterior branch supplies the teres minor and the posterior part of the deltoid, carrying sensations from the lower lateral part of the arm.

Radial nerve (C5, C6, C7, C8 & T1) is formed by the ventral rami of the fifth, sixth, seventh cervical, and first thoracic spinal nerves (Figure 10.18). This nerve runs in the radial sulcus of the humerus accompanied by the deep

Damage to the nerve at the elbow may occur as a result of recurrent trauma or subluxation and subsequent displacement of the nerve anterior to the epicondyle. It may also occur in gouty tophus or as a result of entrapment in the aponeurosis between the flexor digitorum profundus and the superficialis, producing cubital tunnel syndrome. This syndrome is characterized by numbness or paraesthesia (abnormal sensations such as tingling, prickling, burning, and itching) in the area of distribution of the ulnar nerve, extending to the forearm with possible involvement of the precondylar or intracapsular region. Impaired hand adduction, lateral deviation of the hand upon flexion, loss of flexion at the distal interphalangeal joints of the ring and fifth digits and relatively mild form claw hand may also be observed.

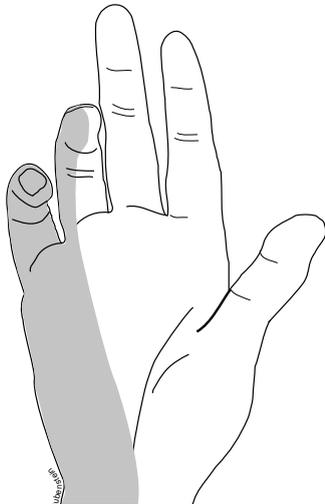


Figure 10.12 Manifestations of ulnar claw-hand due to an injury to the ulnar nerve at the wrist. The shaded zone indicates the area of sensory loss

brachial vessels. It innervates the triceps brachii by a branch that arise within this sulcus, and proximal to the mid-diaphysis of the humerus. The site of innervation of this muscle accounts for intactness of triceps brachii muscle in a fracture involving the distal third of the humerus. The radial nerve also innervates the anconeus, a weak extensor of the elbow. Anterior to the lateral epicondyle of the humerus, it divides into superficial and deep branches. The superficial branch supplies sensory fibers to the radial side of the thumb and adjacent area of the thenar eminence, as well as the three and half digits of the dorsum of the hand as far as the mid-portions of the middle phalanges of the index, middle and ring fingers. The deep branch pierces the supinator muscle and

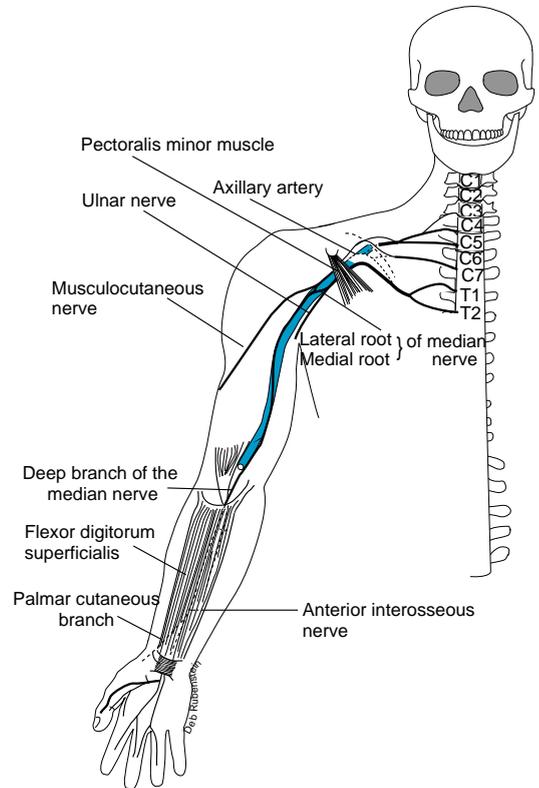


Figure 10.13 Course of the median and its terminal branches

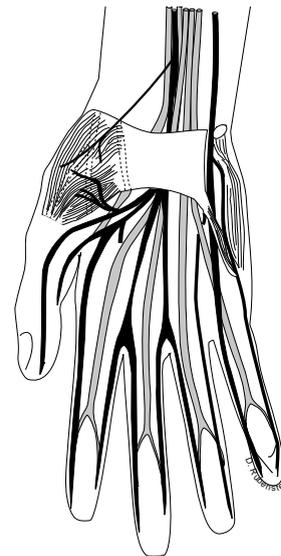


Figure 10.14 The course of the median nerve in the carpal tunnel, its branches in the hand. Notice the origin and course of the palmar branch of the median nerve

continues as the posterior interosseous nerve to supply the brachioradialis, supinator, extensor digitorum, extensor carpi radialis longus and brevis. It also innervates the abductor pollicis longus, all extensors of the thumb (extensor pollicis brevis and longus) and extensors of the

Damage to the median nerve may occur as a result of fractures of the humerus, antecubital catheterization, elbow dislocation, or low grade pressure to the upper arm as it occurs in honeymooners (honeymoon paralysis). It may also be compressed as a sequel to sustained muscular force (e.g. against a guitar) while the forearm is pronated. It may also occur during its course between the ulnar and humeral heads of the pronator teres muscle. Volkmann's ischemic contracture may also lead, if untreated, to compression of the median nerve by the pressure of the swollen muscles of the forearm or pressure buildup by the accumulated fluid and blood under the flexor digitorum superficialis. Cuts across the wrist, anterior dislocation of the lunate bone, or compression in the carpal tunnel may also damage the nerve. Occasionally, both the median nerve and the brachial artery may be entrapped unilaterally or bilaterally by the ligament of Struthers, which extends from the medial epicondyle of the humerus to a bony spur at the distal humerus (seen in 2% of people). It is equally important to note that compression of the brachial artery may simultaneously be accompanied by compression of the median nerve, producing vascular and neuropathic changes.

Damage of the median nerve at the wrist produces loss of thumb opposition as in thumb pinching, atrophy of most thenar muscles and loss of cutaneous sensation from the lateral two thirds of the palm. There may also be anesthesia in the palmar surfaces of the thumb, index and middle fingers, as well as the lateral one half of the ring finger and the dorsal surfaces of the medial four digits as far as the middle phalanges. Weakened flexion at the metacarpophalangeal joints, weakened extension at the interphalangeal joints of the index and middle and impaired thumb abduction are also observed. Weakened thumb abduction and inadequate thumb rotation may produce "bottle sign", a deficit in which the subject is unable to maintain a grip of a round object. Flattening and atrophy of the thenar eminence and the counter pull of the extensor and the abductor pollicis longus muscles on the thumb result in pulling the thumb to the same

level with the other digits and producing the ape hand configuration.

Compression of the median nerve at the wrist may also occur inside the carpal tunnel producing signs of carpal tunnel syndrome. This syndrome, a unilateral and sometimes bilateral condition that often involves the dominant hand, is common in pregnancy and in middle aged women during the premenstrual period. It may be caused by fluid retention, Colle's fracture, acromegaly, hypothyroidism, congestive heart failure, tenosynovitis of the flexor tendons, mucopolysaccharidosis, or tuberculosis of the synovial sheaths. Since repetitive movements at the wrist displace the flexor tendons against the palmar side of the carpal tunnel, continuous and sustained flexion and extension of the wrist may be a predisposing factor for this condition. Transducers inserted into the canal may measure the increase in intracarpal pressure.

Carpal tunnel syndrome (Figure 10.15), the most common neuropathy of the hand, is characterized by acroparesthesia (tingling, numbness), pain in the radial three digits that increases at night or early morning and is frequently relieved by firm grasp of the hand. Demyelination of the median nerve, subsequent atrophy of the thenar muscles, and associated autonomic disturbances such as swelling and alteration in the texture of the skin, are also common manifestations of this disease. Opposition, and to a lesser degree abduction of the thumb may eventually be affected. Carpal tunnel syndrome is confirmed by the application of Tinel's sign and Phalen's maneuver.

Tapping the wrist produces Tinel's Sign, characterized by tingling and electrical sensation in the area of the sensory distribution of the median nerve. Forced flexion of the wrist (Phalen's maneuver) or forced extension of the wrist (Reverse Phalen's maneuver) produces pain and tingling in the cutaneous distribution of the median nerve (Figure 10.16). Anomalous innervation, as in Martin-Gruber Anastomosis, must be ruled out in order to confirm the diagnosis of this condition.

digits at the interphalangeal joints. This branch ends at the dorsal surfaces of the carpal bones as pseudoganglion, a swelling which provides articular branches to the wrist joint. The cutaneous fibers of the radial nerve also innervate the skin of the lower lateral and posterior surfaces of the arm and forearm via the posterior cutaneous branches.

Upper subscapular nerve (C5, 6) supplies the subscapular muscle. Lower subscapular nerve (C5, 6) supplies the teres major and distal part of the subscapular muscles.

Thoracodorsal nerve (C6, 7, 8) (Figure 10.6) descends between the upper and lower

branches of the subscapular nerve accompanied by the corresponding branch of the subscapular vessels (thoracodorsal artery and vein), supplying the latissimus dorsi muscle.

Lumbar spinal nerves

As is the case with other spinal nerves, the dorsal rami of the lumbar spinal nerves divide into medial branches that

In addition to "ape hand" configuration and the dysfunctions listed with damage at the wrist, injury to the median nerve at the elbow results in greater sensory loss in the palm. Loss of pronation and loss of flexion of the thumb are also experienced by the affected individuals. Loss of flexion at the interphalangeal joints of the index and middle fingers and the subsequent inability to make a fist are also seen in this condition. Inability to make a fist, allowing the patient to flex the digits supplied by the ulnar nerve produces preacher's hand position. Weakened flexion at the elbow and at the wrist and radial abduction of the hand is additional manifestations of this lesion.

Compression of the median nerve as it courses between the ulnar and humeral heads of the pronator teres or as it runs posterior to the fibrous arch of the flexor digitorum profundus produces pronator teres syndrome. This syndrome, which may also be precipitated by repeated pronation and supination, manifests similar dysfunctions to those seen with median nerve lesion proximal to the elbow. Pronation may be weakened, but not totally lost. Pain in the palmar surface of the hand aggravated by either pronation or elbow flexion, and paraesthesia in the proximal forearm, which is elicited by forced supination of the forearm and extension of the hand at the wrist, are characteristics of this syndrome.

The median nerve may also be entrapped in the bicipital aponeurosis, producing signs of lacertus fibrosus syndrome. This type of entrapment produces pain upon forced pronation of the flexed and supinated hand. Damage to the median nerve at the midpoint of the forearm produces partial paralysis of the flexor digitorum superficialis muscle, which results in pointing of the index finger (Figure 10.17). This is due to the uncountered action of the extensors of the index finger. In general, injury to the median nerve is commonly associated with a burning and tearing pain sensation in the digits and palm of the hand, which is accompanied by vasomotor and sudomotor changes on cutaneous areas wider than the area of distribution of the median nerve (causalgia). The affected part of the hand and digits become extremely sensitive to touch, including

contact with clothes or air. Causalgia is attributed to over stimulation of sensory fibers at their point of interruption by the sympathetic fibers. Sympathectomy or blockade of the corresponding sympathetic ganglia may relieve it. Causalgia may be also associated with ulnar and sciatic nerves injury.

Compression of the anterior interosseous branch of the median nerve (anterior interosseous nerve syndrome) may result from humeral fracture, percutaneous puncture of the median cubital vein, or fibrous bands extending from the flexor digitorum superficialis across the median nerve. It is characterized by weakened flexion at the distal interphalangeal joints of the thumb and index finger accompanied by an impaired pinch maneuver. Weakened pronation, and more importantly loss of flexion at the distal interphalangeal joints of the index and middle finger, are the primary deficits of this syndrome.

Muscles that are innervated by the ulnar nerve may also be affected if the motor fibers to these muscles run within anterior interosseous nerve before joining the ulnar nerve (Martin-Gruber anastomosis).

Combined damage to the median and ulnar nerves at the wrist results in true claw hand, which is characterized by hyperextension of the metacarpophalangeal joints and hyperflexion of the distal interphalangeal joints of the digits, unopposed by the action of interossei and lumbricals. Thumb opposition and adduction as well as atrophy of the thenar and hypothenar muscles are additional deficits of this injury.

Combined ulnar and median nerves damage at the elbow or at a more proximal site produces "ape hand" configuration (but no apparent clawing) and hyperextension of the hand at the wrist (unopposed by the flexors). It also results in forearm supination (due to paralysis of the pronators), and hyperextension digits at the metacarpophalangeal joints (due to paralysis of the interossei and lumbricals).

supply the multifidi and lateral branches, innervating the erector spinae. Lateral branches of the upper three dorsal rami form the superior clunial nerves and supply the skin of the gluteal region. The ventral rami accompany the lumbar arteries, receiving the gray communicating rami from the sympathetic ganglia. Upper two or three ventral rami may also receive white communicating rami, conveying presynaptic sympathetic fibers. They form the lumbar plexus and innervate the muscles in the posterior abdominal wall and the lower extremity.

Lumbar plexus

The ventral rami of all lumbar spinal nerves form the lumbar plexus, running posterior to the psoas major muscle. The ventral ramus of the fourth lumbar spinal segment contributes to both the lumbar and sacral plexuses (nervus furcalis). It is considered a prefixed plexus when the ventral rami of the third and fourth lumbar spinal nerves contribute to both the lumbar and sacral plexus. However, when the fifth lumbar ventral ramus split

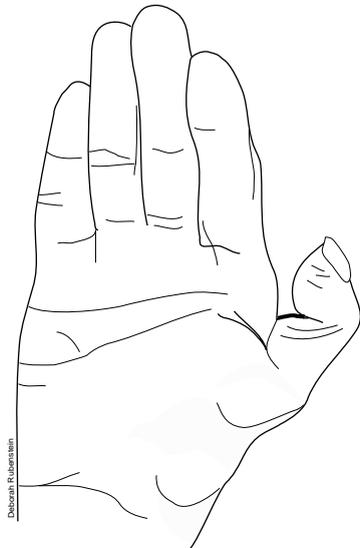


Figure 10.15 Manifestations of carpal tunnel syndrome. Note the wasting of the thenar muscles and ape-hand configuration

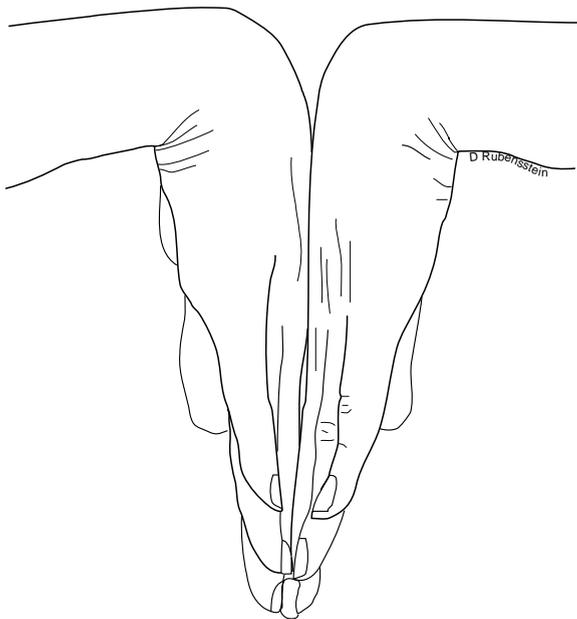


Figure 10.16 This diagram depicts the Phalen's test. Observe the acute flexion at the wrist

between the lumbar and sacral plexuses, the lumbar plexus is considered a postfixed plexus. This plexus (Figure 10.20) is commonly formed by the ventral rami of the upper lumbar spinal nerves which run anterior to the transverse processes of the lumbar vertebrae, giving rise to the iliohypogastric, ilioinguinal, genitofemoral, lateral femoral

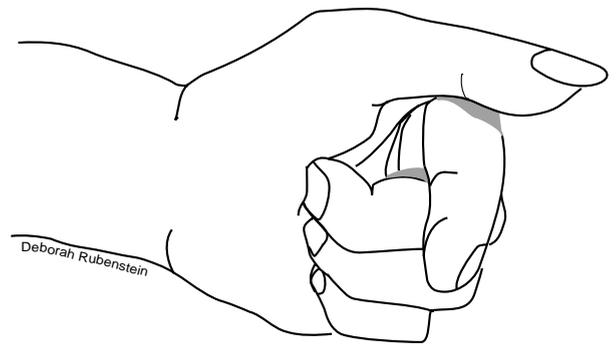


Figure 10.17 This is a drawing depicting the major manifestations of anterior interosseous nerve syndrome

cutaneous, femoral, obturator and possibly the accessory obturator nerves.

Iliohypogastric nerve (L1)- (Figures 10.20) arises from the entire ventral ramus of the first lumbar spinal nerve with a smaller contribution from the subcostal nerve. It courses initially between the kidney and the quadratus lumborum, then it pierces the transverse abdominis, running between the transverse and internal oblique muscles. It divides into branches that supply the skin of the anterolateral gluteal region and the skin and muscles of the anterior abdominal wall, proximal to the superficial inguinal ring.

The Ilioinguinal nerve (L1)-(Figure 10.20) maintains similar origin to the iliohypogastric nerve, running between the internal oblique and the transverse abdominis muscles, and through the inguinal canal with the spermatic cord or the round ligament. It emerges from the superficial inguinal ring to supply the lower portions of the internal oblique and transverse abdominis muscles, the skin of the upper medial thigh, and the anterior part of the external genitalia.

Damage to the axillary nerve may occur as a result of inferior dislocation of the humeral head or fracture of the humeral neck, manipulation to reduce dislocation of the humerus, intramuscular injections, or pressure from the use of crutches. Axillary nerve palsy is characterized by loss of shoulder contour and severe weakness of arm abduction (due to intactness of the supraspinatus, upper fibers of the trapezius, and serratus anterior muscles). Weakened lateral rotation (due to paralysis of the teres minor) and limited loss of cutaneous sensation from the shoulder are additional deficits of this condition.

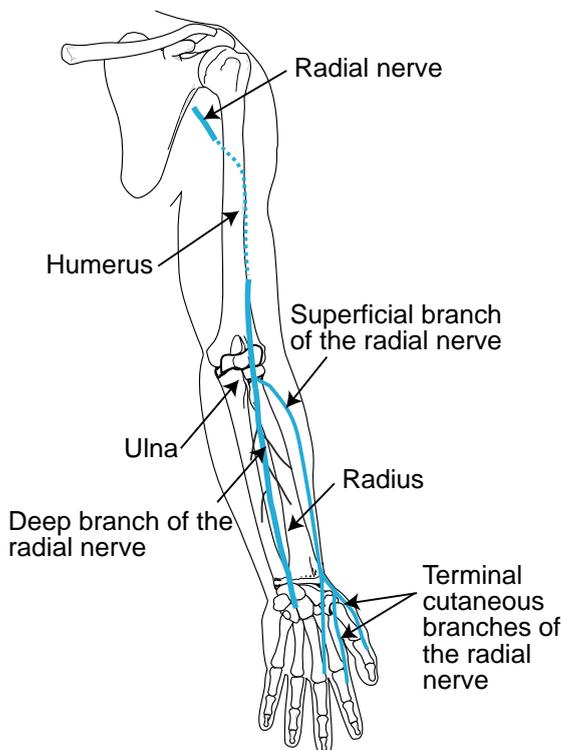


Figure 10.18 The course, branches, and distribution of branches of radial nerve

Radial nerve is commonly injured in fractures that involve the midshaft of the humerus. Sleeping while inebriated with the arm hanging over the edge of a chair (sleep, or Saturday night palsy), crutch misuse (crutch palsy), or misplaced pacemaker catheter may compress and injure the radial nerve. Arcade of Frohse, a fibrous band associated with flexor digitorum superficialis muscle may entrap the radial nerve. In Parkinson's disease and Guillian-Barre Syndrome, the radial nerve may be compressed as a result of fibrosis of the triceps brachii muscle. Damage to the radial nerve in the axilla may result in loss of extension of the elbow (due to paralysis of the triceps brachii and anconeus). Loss of extension of the hand at the wrist (wrist drop) and extension of thumb and the metacarpophalangeal joints, and loss of sensation in the cutaneous area of distribution of the radial nerve (Figure 10.19) are also occur. Weakened flexion of the elbow, abduction of the thumb, radial and ulnar deviation of the hand, and weakened extension of the interphalangeal joints are additional manifestations of this type of injury. Since the triceps muscle receives innervation proximal to the midpoint of the humerus, damage to the radial nerve immediately distal to this point will spare extension of the elbow.

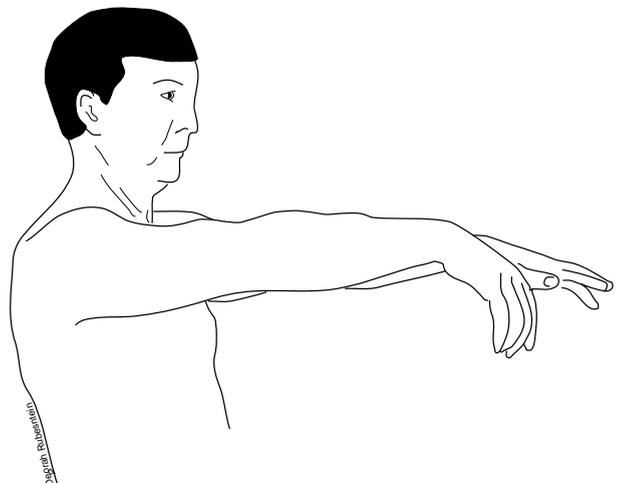


Figure 10.19 This drawing illustrates right hand wrist drop as a result of radial nerve damage

Compression or injury to the posterior interosseous nerve (PIN) distal to the supinator muscle spares the extensor carpi radialis, resulting in radial deviation of the hand upon extension, wrist drop, and weakened extension at the interphalangeal joints. Sensory changes are not expected to occur since the PIN is purely motor, however some radial paresthesia may be observed. Compression of the superficial branch of the radial nerve by tight watchbands or handcuffs may produce isolated numbness, loss of pain, and more importantly numbness with no motor deficits (cheiralgia paresthetica or Wartenberg's disease). Prolonged orchestral drumming has been implicated in the entrapment of the posterior cutaneous nerve of the arm.

Genitofemoral nerve (L1 and L2)- (Figure 10.20) is derived from the anterior branches of the ventral rami of the first and second lumbar spinal nerves. It pierces the psoas major muscle, passes posterior to the ureter, and then divides into genital and femoral branches. The genital branch enters the deep inguinal ring, supplying the cremasteric muscle, skin of the scrotum, mons pubis, and the labia majora. The femoral branch pierces the femoral sheath and supplies the skin anterior to the upper part of the femoral triangle.

Lateral femoral cutaneous nerve (L2 and L3) originates from the posterior branches of the ventral rami of the second and third lumbar spinal nerves (Figures 10.20 & 10.21). This nerve crosses the iliacus muscle, providing sensory fibers to the parietal peritoneum. It then pierces the skin near the anterior superior iliac spine to distribute to the lateral thigh.

Damage to the subscapular nerve may produce weakened medial rotation and adduction of the arm (due to paralysis of the subscapularis and teres major muscles).

The Iliohypogastric nerve may be damaged by a surgical incision in the lower anterior abdominal wall, which weakens the anterior abdominal wall, predisposing the patient to direct inguinal hernia.

The lateral femoral cutaneous nerve may be damaged in individuals with lumbar lordosis, as a result of entrapment within the inguinal ligament, or compression against the anterior superior iliac spine. Constant adduction (e.g. sitting with crossed legs for prolonged period of time), compensatory stretching of the fascia and muscles around the nerve, and disorders in the ligaments that stabilize the vertebral column may all contribute to damage to the lateral femoral cutaneous nerve.

Femoral nerve (L2, L3 and L4) is formed by the posterior branches of the ventral rami of the second, third and fourth lumbar spinal nerves (Figures 10.20 & 10.22). It runs deep to the psoas major, anterior to the iliacus, and then descends posterior to the inguinal ligament. It enters the femoral triangle where it innervates the sartorius, pectineus and quadriceps femoris. It provides sensory fibers to the hip joint, anterior thigh via the intermediate femoral cutaneous branch, and to the skin of the lower medial thigh via the medial femoral cutaneous branch.

The saphenous nerve (Figure 10.23) considered the longest branch of the femoral nerve, runs in the femoral triangle and adductor canal. It leaves the canal by piercing the deep fascia medial to the knee joint, giving rise to the infrapatellar branch. It supplies the medial surface of the leg and the medial border of the foot.

Obturator nerve (L2, 3, 4) arises from the anterior branches of the ventral rami of the second, third, and fourth lumbar spinal nerves (Figure 10.24). It descends posterior to the psoas major muscle, crosses the pelvic brim, and enters the obturator canal. It exits the obturator canal, dividing into anterior and posterior branches, which are separated by the adductor brevis muscle. It supplies the adductor longus and brevis, part of the adductor magnus, and pectineus muscles. It also provides sensory fibers to the medial side of the thigh and hip joint.

Accessory obturator nerve (L3, L4) is an inconstant nerve, which gains origin from the anterior branches of the ventral rami of the third and fourth lumbar spinal nerves. It travels posterior to the pectineus and supplies the obturator muscle and the hip joint.

Sacral spinal nerves

The dorsal rami of the sacral spinal nerves emerge from the dorsal sacral foramina with the exception of the fifth sacral nerve. Each dorsal ramus gives off medial branches that terminate in the multifidi and lateral branches that join the dorsal ramus of the fifth lumbar spinal nerve to form the middle clunial nerves, that supply the skin of the posterior gluteal region. Dorsal rami of the fourth and fifth sacral nerves also innervate cutaneous fibers to the skin overlying the coccyx. Visceral efferent fibers of the sacral plexus form the pelvic splanchnic nerves. These parasympathetic efferents arise from the intermediolateral columns of the second, third and fourth sacral spinal segments, and run in the ventral rami. Due to the vasodilator effect upon the penile arteries and the important role they play in erection, these fibers are also known as *nervi erigentes*. They also control micturition by inducing contraction of the detrusor muscles and relaxation of the urethral sphincters. Additionally, these nerves provide parasympathetic fibers to the left one third of the transverse colon, descending colon, sigmoid colon and the rectum.

Sacral plexus

The sacral plexus is formed by the union of the lumbosacral with the ventral rami of the first, second, third, and part of the fourth sacral spinal nerves (Figures 10.25 & 10.26). The lumbosacral trunk results from union of part of the ventral ramus of fourth lumbar spinal nerve and the entire ventral ramus of fifth lumbar spinal nerve. It is embedded in the digitations of the piriformis muscle on the posterolateral wall of the pelvis, anterior to the sacrum and posterior to the rectum. Branches of the sacral plexus leave through the greater sciatic foramen, proximal and/or distal to the piriformis muscle. A pregnant uterus, malignancies involving the rectum and other pelvic structures may compress the sacral plexus.

The Ilioinguinal nerve may be endangered in surgical repair of a direct inguinal hernia, or as a result of a low incision in the anterior abdominal wall while performing an appendectomy operation. It may be compressed by constant and violent contraction of the muscles of the anterior abdominal wall as a result of a fall from a height, abnormalities in the hip joints, or ligamentous disorders of the vertebral column. Weakness in the abdominal muscles innervated by the ilioinguinal nerve may precipitate a direct inguinal hernia. Pain associated with entrapment of the ilioinguinal nerve may mimic urinary tract or gastrointestinal disorders.

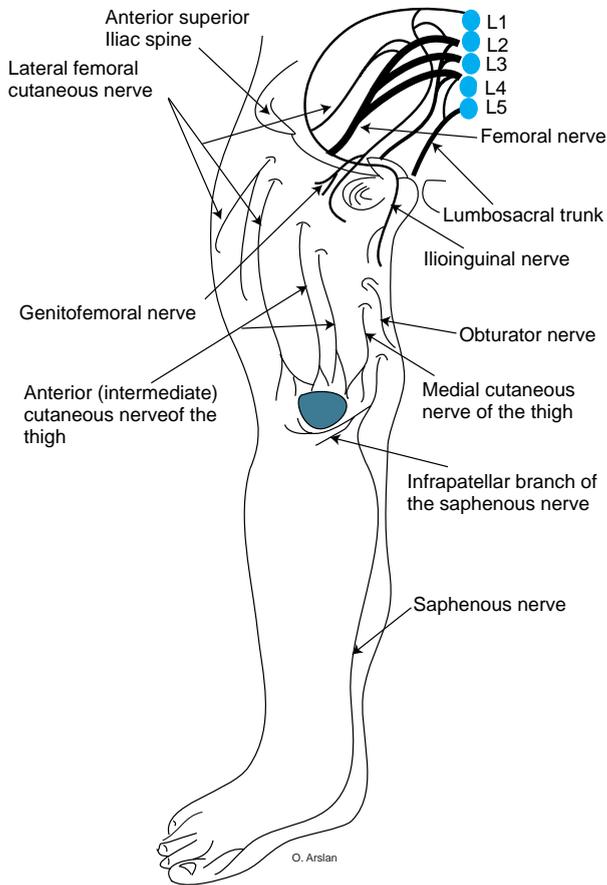


Figure 10.20 Lumbar plexus showing segmental contributions to the individual branches

Compression of this plexus produces pain that radiates to the posterior thigh and leg. Aneurysm of the superior gluteal artery may specifically affect the lumbo-sacral trunk.

The sacral plexus gives rise to branches, which supply the gluteal region, posterior leg, and foot. These branches are the superior gluteal, inferior gluteal, posterior femoral cutaneous, pudendal, sciatic nerve, and the pelvic splanchnic nerves. The latter has already been described earlier.

Superior gluteal nerve (L4, L5, S1) is formed by the posterior branches of the fourth and fifth lumbar and the first sacral ventral rami (Figures 10.25 & 10.26). It leaves the pelvis through the greater sciatic foramen and proximal to the piriformis muscle. It supplies the abductors and the medial rotators of the thigh (gluteus medius, gluteus minimus, and tensor fascia lata).

Inferior gluteal nerve (L5, S1, S2)- (Figures 10.25 & 10.26) arises from the posterior branches of the fifth lumbar and first and second sacral ventral rami. This nerve exits the pelvis via the greater sciatic foramen, proximal to the piriformis muscle, innervating the gluteus maximus muscle.

Attempts to extend the leg while the thigh is abducted, particularly following parturition, may produce excessive angulation of this nerve and subsequent compression, resulting in meralgia paresthetica. Individuals with this condition may exhibit numbness and tingling or burning sensation in the lateral thigh and knee. This condition is more common in obese individuals following substantial weight loss. It may occasionally be seen after abdominal operations. However, despite its course behind the cecum on the right side and sigmoid colon on the left, no apparent relationship to abdominal disorders have been shown.

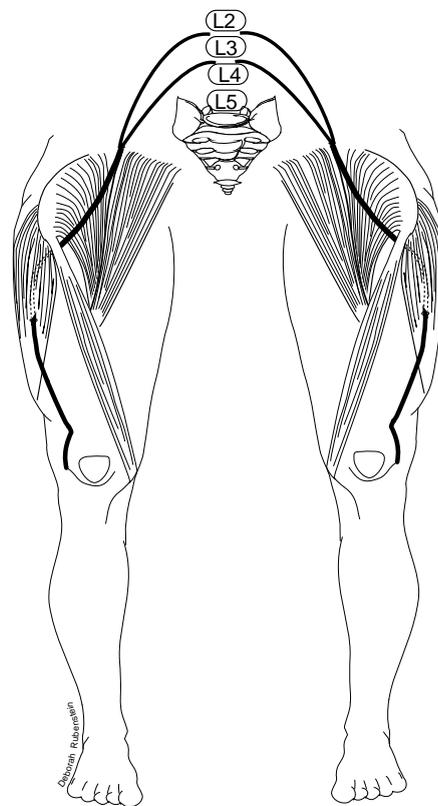


Figure 10.21 Lateral femoral cutaneous nerve. Observe its close relationship to the inguinal ligament

Posterior femoral cutaneous nerve (S1, S2, S3) comes from the posterior branches of the first and second sacral and the ventral branches of the second and third sacral ventral rami (Figure 10.25). This nerve leaves the pelvis via the greater sciatic foramen, distal to the piriformis muscle. It supplies sensory fibers to the posterior thigh, as far down as the popliteal fossa. It gives rise to the inferior clunial branches, which innervate the skin of the lower gluteal region. It also supplies the posterior part of the external genitalia via the perineal branch.

The femoral nerve may be damaged in dislocation of the hip joint, as a result of stab or gun shot wound, or as a sequel to fractures of the coxa or proximal femur. Retroperitoneal abscesses or tumors, and complication of femoral angiography may also injure the femoral nerve, producing paralysis of the quadriceps femoris and subsequent loss of the patellar reflex and impairment of knee extension. Extension of the knee may still be possible via the iliotibial tract. The patient may be able to stand and walk, experiencing difficulty in going up and down stairs. Patients cannot climb stairs and are unable to swing the lower extremity forward during walking. Complete paralysis of the sartorius, rectus femoris and partial paralysis of pectineus muscle may also occur, leading to weakened thigh flexion. However, the iliopsoas, which is the main flexor of the thigh, remains intact. Sensory loss on the anterior and lower medial thigh and the medial surface of the leg and foot are also observed in femoral nerve damage.

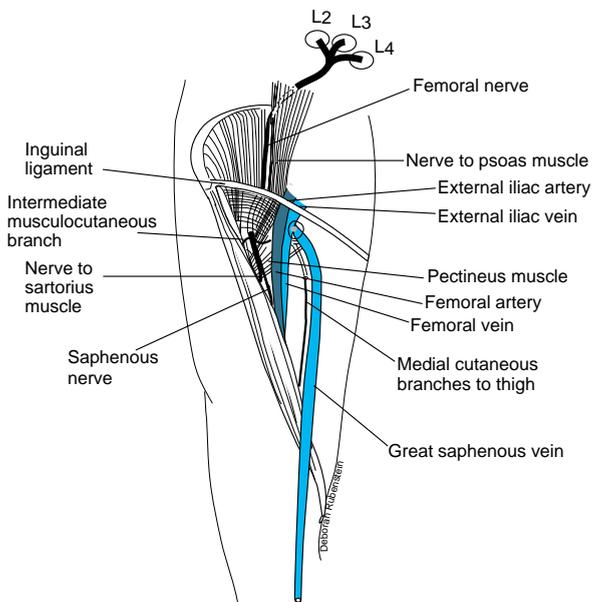


Figure 10.22 In this drawing the origin of the femoral nerve and its innervation in the thigh are illustrated

Pudendal nerve (S2, S3, S4) (Figures 10.25 & 10.27) originates from the anterior divisions of the ventral rami of the second, third and fourth sacral ventral rami. It leaves the pelvis via the greater sciatic foramen and enters the gluteal region, accompanied by the internal pudendal vessels. It then crosses the ischial spine, the sacrospinous ligament, and enters the ischiorectal fossa through the lesser sciatic foramen. It travels in the pudendal canal on

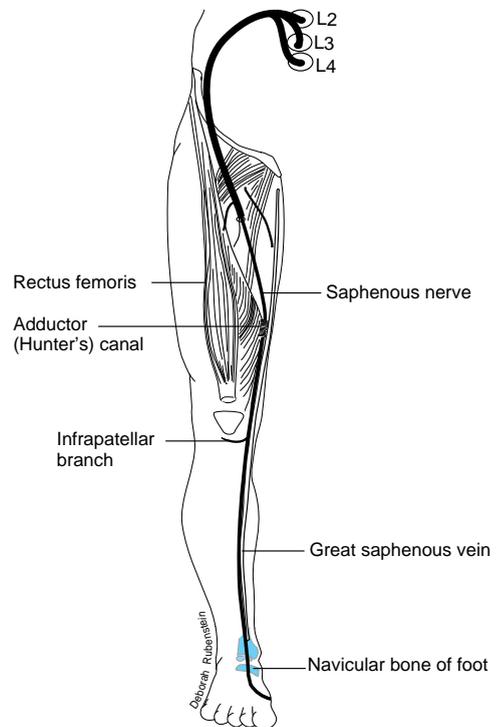


Figure 10.23 The course and termination of the saphenous branch of the femoral nerve. Note the infrapatellar branch

The saphenous nerve, in particular, may be entrapped as it exits the adductor canal, producing numbness or anesthesia in the medial surface of the leg and medial border of the foot. Accidental excision of the infrapatellar branch of the saphenous nerve during arthroscopic knee surgery may result in the formation of neuroma, eliciting excruciating pain in the area of its distribution.

the lateral wall of the ischiorectal fossa, giving rise to the inferior rectal branch. The inferior rectal nerve supplies motor fibers to the external anal sphincter and sensory fibers to the lining of the ectodermal part of the anal canal. The pudendal nerve divides into perineal branch and dorsal nerve of the penis or clitoris. The perineal branch gives rise to the posterior scrotal (labial) branches, which are sensory to the scrotum or labia majora, and to muscular branches to the urogenital muscles. The dorsal nerve of the penis or clitoris runs in the urogenital diaphragm, then within the suspensory ligament of the penis or the clitoris, accompanied by the corresponding artery and vein. This nerve provides sensory fibers to the penis and clitoris.

Sciatic nerve (L4, L5, S1, S2, S3) is the largest nerve in the body, emerging from the greater sciatic foramen distal to the piriformis (Figures 10.25, 10.28 & 10.29). This nerve is derived from the ventral rami of the fourth and

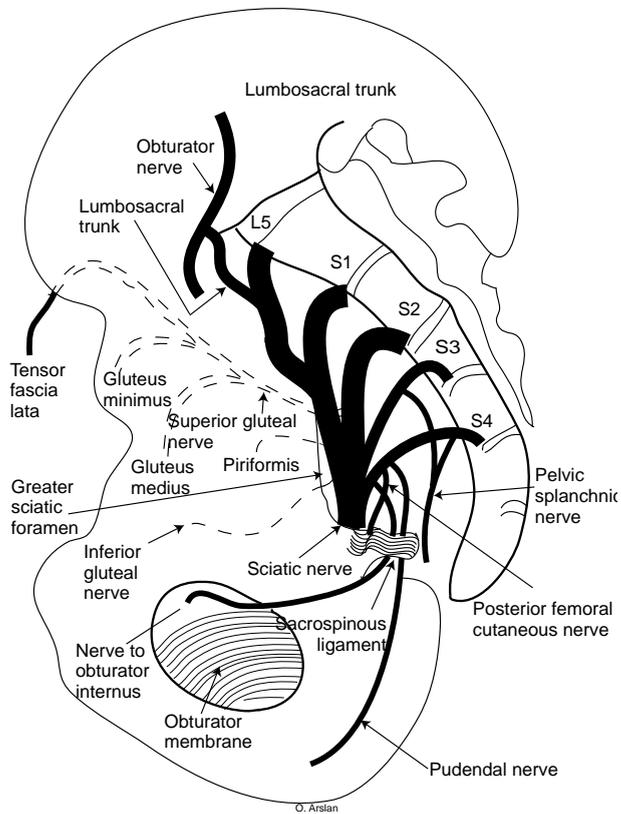


Figure 10.25 Sacral plexus, showing segmental contributions, divisions, and individual branches



Figure 10.26 The roots of the sacral plexus in relation to the piriformis muscle showing the lumbar sacral trunk

two heads of the gastrocnemius muscle, accompanied by the short saphenous nerve. In the lower third of the leg, the tibial nerve becomes superficial and courses posterior to the medial malleolus and deep to the flexor retinaculum, where it bifurcates into the medial and lateral plantar nerves (Figures 10.31 & 10.32). The medial plantar nerve innervates the abductor hallucis, flexor digitorum brevis, flexor hallucis brevis, and the first



Figure 10.27 The course and branching of the pudendal nerve

Damage to the posterior femoral cutaneous nerve produces anesthesia primarily in the posterior thigh with no motor deficits. Recurrence of pain after successful pudendal nerve block may be attributed to intactness (not affected by the anesthetic) of the perineal branch of the posterior femoral cutaneous nerve which also supplies the external genitalia.

lumbrical muscles. It carries sensation from the medial two third of the plantar surface of the foot. The lateral plantar nerve innervates the rest of the plantar muscles of the foot and receives cutaneous sensation from the lateral one third of the plantar surface of the foot.

Spinal reflexes

Spinal reflexes are locally mediated neuronal events, which are constantly modulated by the facilitatory and inhibitory influences of the descending supraspinal pathways. However, the ascending influences from the lower spinal segments are also exerted upon higher spinal levels. The dramatic intensity in the extensor rigidity of the forelimb muscles in a spinal (decerebrate) animal, whose spinal cord has been transected at the level of the sixth thoracic spinal cord segment, is thought to be dependent upon the ascending inhibitory pathways (Shiff-Sherrington Reflex). Spinal reflexes may be classified into superficial and deep reflexes.

The pudendal nerve may be injured or compressed within the pudendal canal during horse back riding, as a result of a pressure from a mass or exudate in the ischiorectal fossa, pressure of a pregnant uterus, or fracture of the ischial spine. Damage to the pudendal nerve produces loss of sensation from the posterior part of the external genitalia and the ectodermal anal canal. It may also result in paralysis of the perineal muscles including the external urethral sphincter and the external anal sphincters.

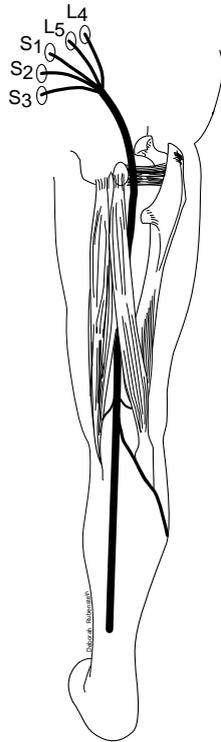


Figure 10.28 Segmental origin of the sciatic nerve, its course, and its division into the tibial and common peroneal nerves

Superficial group of reflexes

The superficial group of reflexes is comprised of the interscapular, superficial abdominal, cremasteric, gluteal superficial, plantar, anal, and bulbocavernous reflexes.

- Interscapular reflex refers to the reflex contraction of the rhomboideus muscles and bilateral retraction of the scapula, upon stroking the skin of the interscapular (T2-T4) area.
- Superficial abdominal reflex is elicited by stroking the skin of the abdomen from the periphery toward the umbilicus, stimulating the seventh through the twelfth thoracic (T7-T12) spinal segments. It results in contraction of the oblique abdominal muscles and

The sciatic nerve may be entrapped within the greater sciatic foramen or compressed by an anomalous ligament or fibrous tissue within the greater sciatic foramen. Posterior dislocation of the hip joint, fractures of the femur, and aneurysm of the inferior gluteal artery may also impair the function of this nerve. Signs and symptoms associated with sciatic nerve damage are equivalent to a combination of damage to the tibial and common peroneal nerves. When the sciatic nerve is affected near its origin, or as it crosses within the greater sciatic foramen, or at any site proximal to midposterior thigh, weakened knee flexion and loss of plantar flexion of the foot will ensue. The patient is able to stand and walk, but exhibits foot drop and toe drop, and inability to move the foot. Trophic and vasomotor changes may also be seen. Sensations from the posterior thigh, posterior leg and dorsum and plantar surfaces of the foot are lost, while sensations from the medial surface of the leg and medial border of the foot remain unaffected. Projection of pain (usually of episodic nature) to the posterior thigh and posterior leg, as a result of overstretching of the irritated or inflamed sciatic nerve, is commonly referred to as sciatica.

The patient may present with low back pain or sciatic pain or both. Backache may be acute, severe, and incapacitating. It may also be gradual in onset and diffuse in nature. Lumbar spasm and abnormalities of posture and restriction of spinal movement are usually seen. Complete recovery may be possible, however the tendency for recurrence of symptoms always exists. Lying down or standing may relieve pain, but it is aggravated by coughing, sneezing or stooping. This condition is diagnosed by either tapping the sciatic nerve or flexing the thigh at the hip while the leg is extended and the patient is in a supine position (Lasegue sign). Patients attempt to relieve the pain by flexing the leg at the knee (Kernig's sign). Kernig's sign may be encountered in the absence of nuchal rigidity. Trauma to the sciatic nerve may result in a severe persistent burning pain (causalgia) which may be accompanied by vasoconstriction and sweating in an area larger than the area of distribution of the nerve itself (reflex sympathetic dystrophy). This may be due to possible involvement of the sympathetic nerves that accompany the neighboring arteries.

movement of the umbilicus toward the side of the stimulus. However, obese and pregnant individuals usually do not exhibit this response.

- Cremasteric reflex, on the other hand, is characterized by contraction of the cremasteric muscle, followed by retraction of the ipsilateral testicle, upon a light stroke in a

The common peroneal nerve is prone to damage in a spiral fracture of the neck of fibula, or by the pressure exerted by a cyst on the lateral side of the popliteal fossa. It may also be affected in individuals with an improperly fitting cast or as a result of squatting. These conditions produce (foot drop), a common deficit, due to paralysis and atrophy of the dorsiflexors (extensors) and evertors of the foot. It is also associated with limited loss of sensation from the dorsum of the foot and the upper lateral leg. This limited sensory loss is due to the overlap of the cutaneous innervation of the affected areas.

downward direction to the upper medial thigh. This reflex is mediated by the ilioinguinal nerve (L1) as the afferent limb and the genitofemoral nerve (L1, L2) as the efferent limb.

- Gluteal superficial reflex (L4-S1) is characterized by contraction of the gluteus maximus in response to examiner's stroke of the skin of the buttock.
- Plantar reflex (L5-S2) is produced by stroking the lateral aspect of the foot, eliciting either plantar flexion of all the toes or no response at all. Anal reflex (S4, S5, CC1) is elicited by stroking the perianal region with a pinwheel, producing puckering of the anal orifice. It is abolished in tabes dorsalis, cauda equina and conus medullaris syndromes.
- The bulbocavernosus reflex (S2, S3, S4) may be utilized to reveal the intactness of the bladder, and is particularly important in upper motor neuron diseases. This reflex is characterized by contraction of the bulbospongiosus muscle, upon compressing the glans penis or clitoris or pinching the prepuce. Interruption of the efferent motor fibers of this reflex produces incontinence, while disruption of the afferent limb abolishes the urge to urinate and defecate.

Deep reflexes

Deep group of reflexes the myotatic, inverse myotatic (clasp knife), flexor, and crossed extension reflexes.

The superficial peroneal nerve may be compressed in lateral compartment syndrome, resulting in numbness and burning sensation on the dorsum of the foot. Weakened eversion but not total loss due intactness of the extensor digitorum longus and peroneus tertius may also be observed. Plantar flexion is also affected due to paralysis of the peroneus longus and brevis. Injury to the superficial peroneal nerve may also occur as it pierces the deep fascia of the distal leg to innervate the dorsum of the foot. In this instance the dysfunction is limited to a burning sensation in the area of distribution of the nerve.

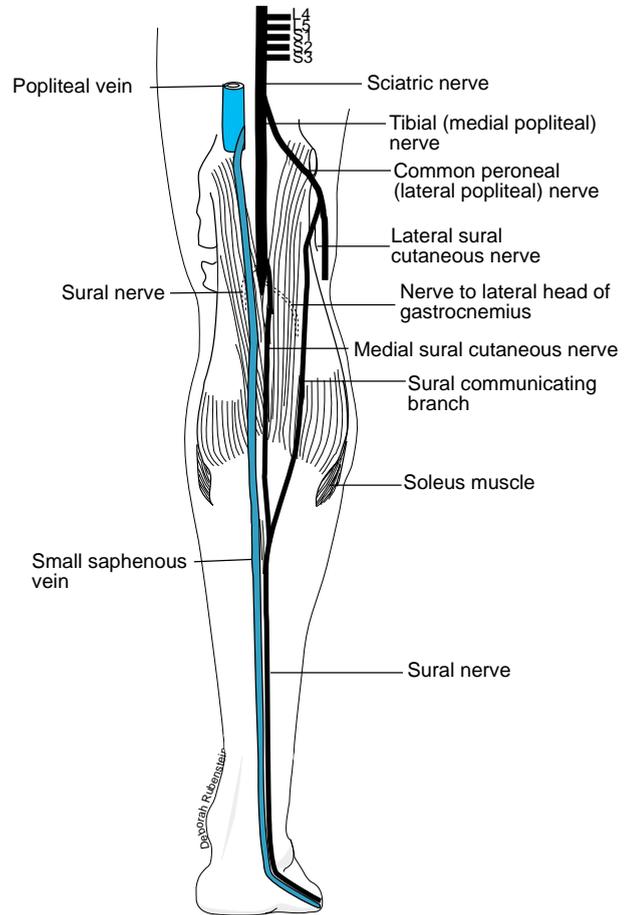


Figure 10.29 The sural nerve, its relationships and its course

Trauma to the dorsum of the foot, poorly fitting casts or shoes, or violent plantar flexion or eversion of the foot may easily damage the deep peroneal nerve. Since, the anterior compartment is a confined space sealed by a bony wall and connective tissue septum which allows no expansion, leg cast (shin splint) may result in compression of the associated vessels and nerves with resultant edema. The pressure from the developed edema may be sufficient to produce ischemic necrosis of the structures and signs of anterior compartment syndrome. An intense pain, redness and swelling confined anterior to the tibia characterize this syndrome. Dorsiflexion of foot and toes becomes very painful. Paralysis of the tibialis anterior and extensor digitorum longus may also occur, producing foot drop (Figure 10.30). In addition to the above deficits weakened eversion and inversion of the foot may also seen.

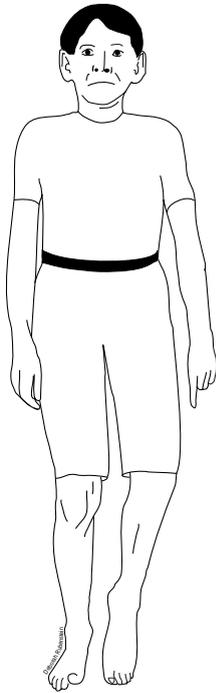


Figure 10.30 This drawing is a depiction of left foot drop in an individual with a damage to the common peroneal nerve

Stretch (myotatic) reflex (Figure 10.33) is elicited by tapping the tendon of a muscle, producing increased length of the muscle fibers and subsequent activation of the muscle spindle. Contraction of the muscle spindle activates the annulospiral (Ia) fibers, which in turn monosynaptically stimulate the ipsilateral alpha motor neurons, producing contraction of the stretched muscle. Annulospiral afferents establish excitatory monosynaptic connections with alpha motor neurons of the synergists and disynaptic inhibitory connections to the motor neurons of the antagonistic muscle (reciprocal inhibition). Myotatic stretch reflexes are produced by tapping the patellar ligament in patellar reflex (L2, L3 & L4) and Biceps brachii tendon in biceps reflex (C5, C6). It is also elicited upon tapping the tendon of the triceps in triceps reflex (C7, C8), tendon of the brachioradialis in radial reflex (C7, C8)), Gastrocnemius (Achilles) tendon in gastrocnemius or Achilles reflex (S1, S2) etc. Periosteal reflex produces flexion and supination of the forearm upon tapping the radial styloid process, while periosteal-ulnar reflex produces extension and ulnar abduction upon striking the ulnar styloid.

- Contraction of a muscle can also be elicited by activation of the muscle spindle via the gamma loop, without stretching the muscle. In gamma loop, the contraction of the muscle spindle activates the primary Ia (annulospiral) endings, which in turn monosynaptically activates the alpha motor neurons. The firing of these alpha neurons result in contraction of the extrafusal muscle fibers. Thus,

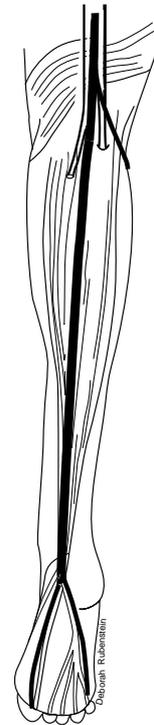


Figure 10.31 The tibial nerve and its terminal branches, the medial and lateral plantar nerves are illustrated

Damage to the tibial nerve may occur in a fracture of the distal end of the femur, as a result of trauma to the popliteal fossa, or entrapment within the tarsal tunnel. Demyelination of fibers of this nerve may also be caused by thiamine deficiency as in Beriberi disease. Loss of flexion in all joints of the toes (due to paralysis and atrophy of the intrinsic plantar muscles of the foot) with the resultant pes cavus, an exaggerated plantar arch, may occur when the tibial nerve is damaged. Loss of abduction and adduction of all toes, weakened flexion of the leg at the knee, weakened inversion and impaired plantar flexion may also occur. Due to the extensive overlap of the cutaneous innervation of the foot sensory deficits are not prominent, although numbness and burning pain may be felt in the sole of foot, especially upon standing. In general, compression of the tibial nerve may be suspected in individuals exhibiting a burning pain and paresthesia in the foot.

under normal conditions, the cerebral cortex can trigger muscle contraction and initiate postural changes and movement via two mechanisms, a) activating the alpha motor neuron directly and b) indirectly via the gamma loop. The role of the gamma loop is illustrated when

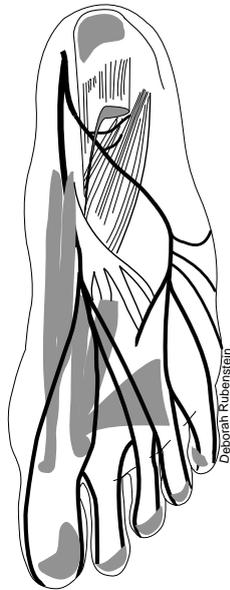


Figure 10.32 The medial and lateral plantar nerves

assuming an erect posture. Standing stretches the quadriceps muscle, which causes activation of the stretch receptor and subsequent contraction of the quadriceps femoris. However, the muscle begins to relax as soon as the tension in the muscle spindle is reduced, and the rate of discharge from alpha motor neurons is diminished. In order to maintain erect posture, the gamma loop comes into action and activates the muscle spindle. Voluntary and precise movements are executed by the simultaneous activation of both systems, which are complementary. In general, activation of the alpha system predominates when a quick response is desired, whereas activation of the gamma system predominates when a smooth and precise movement is desired.

- Inverse myotatic reflex comes into action upon stimulation of the Golgi tendon organ and the Ib fibers as a result of the tension developed in the contracted muscle. The Ib fibers establish disynaptic inhibitory (autogenic inhibition) contacts with the agonist neurons, and excitatory synapses with the antagonistic neurons. The sum of these actions produces relaxation of the agonistic muscles.

- Flexor (withdrawal) reflex enables an individual to avoid harm by withdrawing from nociceptive or injurious stimuli. This reflex is mediated by the free nerve endings (and to a lesser extent by the tactile receptors), and group III nerve fibers, conveying the impulses to the spinal cord. These afferent fibers establish polysynaptic excitatory and inhibitory connections with the motor neurons. The net effect of this circuitry is facilitation of ipsilateral flexor

Prolonged paralysis of the plantar flexors may cause shortening of the calcaneal tendon (achilles tendon), producing equinovarus deformity, which is characterized by plantar hyperflexion, inversion of the foot and medial rotation of the tibia. Patients attempt to walk on the lateral border of the foot and may develop slapping-gait. This condition may also arise from intrauterine compression of the spinal segments that contribute to the tibial nerve. Damage to the tibial nerve distal to the middle third of the leg may occur as a result of fractures of the medial malleolus, calcareous, or talus. It may also occur in dislocation of the ankle joint and compression within the flexor retinaculum (tarsal tunnel syndrome). This syndrome is associated with post-traumatic deformities of the knee, tight shoes and Pott's (Dupuytren's) fracture which involves the distal end of the fibula and the medial malleolus. Deficits may include, depending upon the extent of nerve damage, paresis of the plantar muscles of the foot with no detectable dysfunctions in the muscles of the leg. The metacarpophalangeal joints of the lateral four toes may exhibit hyperextension (extensors are not counteracted by the lumbricals and interossei), whereas the interphalangeal joints show hyperflexion (flexors are not opposed by the lumbricals and interossei). Sensory disturbances are restricted to a burning sensation in the sole of the foot, which may be aggravated by walking. Neuromas of the digital branches of the medial and lateral plantar nerves cause a condition known as Morton metatarsalgia, in which pain is felt in the anterior part of the sole of the foot. Damage to the sural branch of the tibial nerve may result from a Baker's cyst (a synovial cyst of the popliteal fossa) or fracture of the base of the fifth metatarsal bone. Impairment of sensation in the lower lateral leg and lateral border of the foot characterize this injury.

(agonists) motor neurons and inhibition of ipsilateral extensor (antagonist) motor neurons.

- Crossed extension reflex is characterized by flexion of the ipsilateral limb and extension of the contralateral limb in response to a strong nociceptive stimulus. This reflex is a byproduct of the flexion reflex, whereby the afferent fibers establish multisynapses at many levels of the spinal cord with the ipsilateral flexor neurons, and with the contralateral extensor neurons (via the anterior white commissure).

Unilateral absence of the superficial abdominal reflex may be seen in both upper and lower motor neuron disorders. Upper motor neuron lesions that produce this reflex disorder usually involve the cerebral cortex and the descending autonomic pathways, whereas lower motor neuron lesions must affect the lower three thoracic spinal segments in order to produce loss of this reflex.

No significance is attached to the bilateral absence of this reflex, however unilateral absence may indicate upper motor neuron palsy.

The cremasteric reflex is brisk in young adults and is usually absent in conus medullaris syndrome, varicocele, upper motor neuron palsy, and in damages involving the upper lumbar roots.

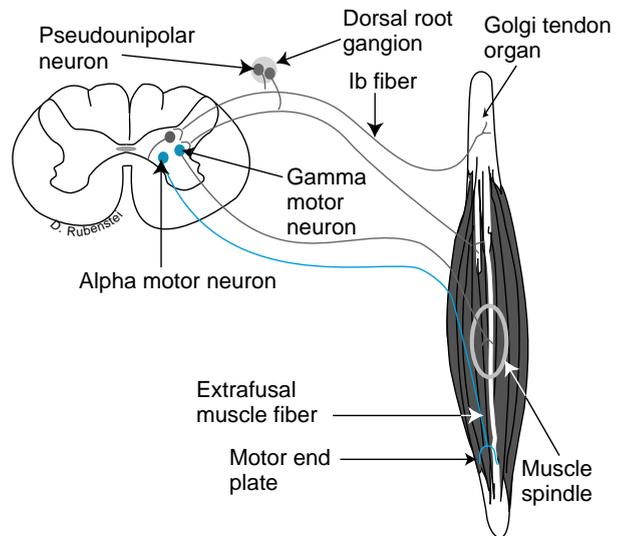


Figure 10.33 Diagram illustrates the components of myotatic reflex. Observe the gamma neurons and afferents of the muscle spindle

Diminished or absence of myotatic reflex may occur in peripheral neuropathies, tabes dorsalis, poliomyelitis, diabetes mellitus, Holmes-Adie syndrome, sciatica, syringomyelia and cervical spondylosis. Spinal shock, coma, and certain types of hydrocephalus may also diminish or abolish the myotatic reflexes. Upper motor neuron disorders such as stroke, multiple sclerosis, and spinal cord tumors or in strychnine poisoning and anxiety disorders may render this reflex hyperactive (intensified). Westphal's sign, failure to produce the patellar (myotatic) reflex may be reversed by the reinforcement method of Jendrassik which requires the patient to clench his hands while the patellar tendon is tapped.

The inverse myotatic reflex is thought to underlie the mechanism of "clasp knife" phenomenon, which is observed in upper motor neuron palsy. In this reflex passive stretching of the spastic muscle is met initially with great resistance to an extent, after which the muscle suddenly gives away. Sherrington named this phenomenon because of its similarity to the action of a jack or a switchblade knife.

Topographically, cranial nerves occupy the cranial cavity, though some may extend to the neck, thorax, and abdomen. They are classified according to their functions and connections to various parts of the central nervous system. Some of these nerves are sensory (olfactory, optic), others subservise motor functions (oculomotor, trochlear, abducens, accessory, and hypoglossal), while others carry both sensory and motor components (e.g. trigeminal, facial, glossopharyngeal, and vagus nerves). The facial, glossopharyngeal, and vagus nerves carry taste sensations, innervating structures both in the head and neck. The nerve fibers that subservise sensory function are the central extensions of the unipolar neurons (e.g. facial, glossopharyngeal, and vagus nerves), or the axons of bipolar neurons (e.g. olfactory and vestibulocochlear nerve), or the axons of multipolar retinal neurons (e.g. optic nerve). The olfactory and optic nerves are extensions of the central nervous system. Certain cranial (oculomotor, facial, and glossopharyngeal) nerves contain presynaptic parasympathetic fibers. Others such as the trigeminal, facial, glossopharyngeal, and vagus nerves innervate muscles of branchial origin.

I. Olfactory nerve

II. Optic nerve

III. Oculomotor nerve

IV. Trochlear nerve

V. Trigeminal nerve

VI. Abducens nerve

VII. Facial nerve

Nuclei associated with the facial nerve

VIII. Vestibulocochlear nerve

IX. Glossopharyngeal nerve

Nuclei of the glossopharyngeal nerve

X. Vagus nerve

Nuclei associated with the vagus nerve

XI. Accessory nerve

XII. Hypoglossal nerve



Figure 11.1 Inferior surface of the brain illustrating the associated cranial nerves



Figure 11.2 Cranial fossae with associated foramina and openings

I Olfactory nerve

The olfactory nerve (SVA) (Figure 11.3) represents the axons of the bipolar neurons of the olfactory mucosa. The filaments of this nerve (fila olfactoria) pass through the cribriform plate of the ethmoid bone (Figures 11.2) and enter the olfactory bulb, establishing synapses in the mitral cells. The olfactory bulb (Figures 11.1 & 11.2), located inferior to the frontal lobe, contains the second order neurons within the olfactory tract. It is an allocortex and consists of three layers, containing mitral and tufted cells, as well as inhibitory granular and periglomerular cells. Periglomerular cells, which are GABAergic, receives excitatory fibers from the bipolar neurons and establish inhibitory connections with the surrounding mitral cells. Inhibition is also accomplished by the dendro-dendritic synaptic connections between the dopaminergic and granule cells. Centrifugal fibers from the contralateral anterior olfactory nucleus may activate the inhibitory internuncial neurons. Mitral cells also provide collateral fibers to the anterior olfactory nucleus. Impulses in the olfactory tract pass through the medial, intermediate and lateral olfactory striae.

The lateral olfactory stria terminates in the uncus (Figure 11.1), which constitutes the primary olfactory cortex. The medial and intermediate olfactory striae terminate in the septal area and the anterior perforated substance, respectively.

The olfactory nerve is tested by the application of a mild, non-irritating scent (coffee or herb) to one nostril at a time while the eyes are closed. Smell sensation may be reduced in Paget's disease, diabetes mellitus, and post laryngotomy. Head trauma may lead to contusion of the olfactory nerves, producing anosmia (complete loss of the sense of smell). Post-traumatic anosmia may be detected weeks or months after the insult and may last as long as the post-traumatic amnesia. Unilateral anosmia of non-rhinogenic origin may be a sign of a subfrontal lobe tumor, meningiomas of the sphenoidal ridge, and hypophysial tumors affecting the sella turcica. It may also occur a sequel to a fracture of the anterior cranial fossa, which is frequently accompanied by leakage of CSF through the nostrils. Bilateral anosmia may occur as a result of nasal infection (e.g. rhinitis sicca) or common cold, excessive smoking and cocaine use, and is commonly associated with loss of taste. Smaller proportion of individuals with viral influenza-induced anosmia may completely recover the sense of smell. Damage or irritation of the uncus by a developing mass may produce olfactory hallucination with phantom smells.

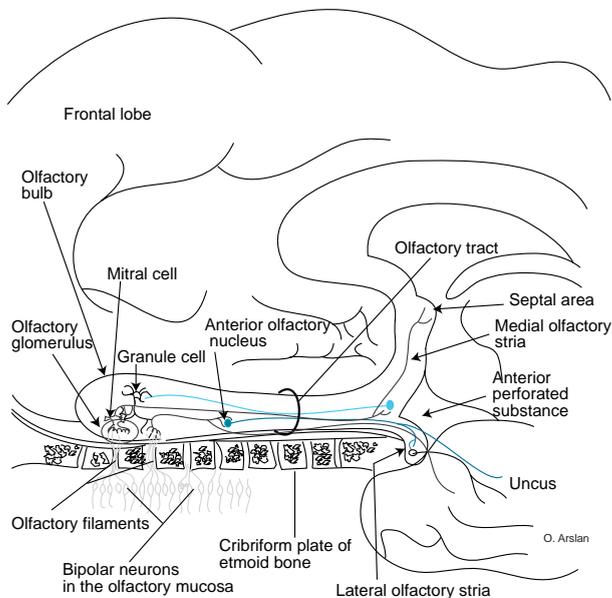


Figure 11.3 Olfactory nerve filaments, synaptic connection, and olfactory stria are followed in this diagram to their terminations in the septal area and uncus

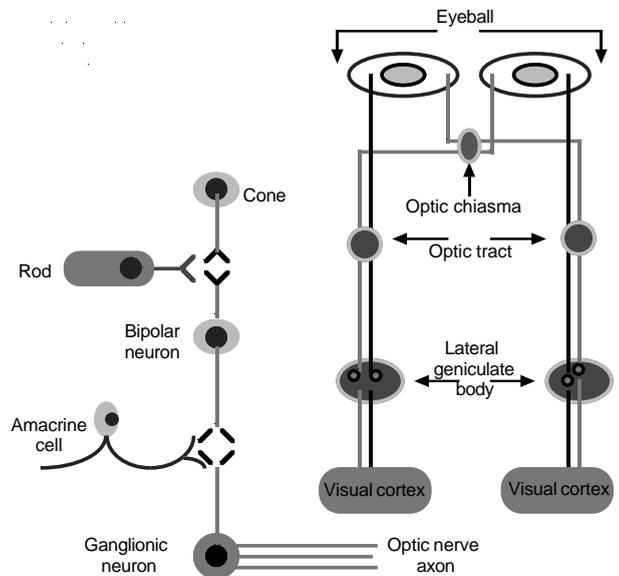


Figure 11.4 Impulses carried by the optic nerve are followed through the optic chiasma and optic tract to their final destination in the visual cortex

In Kallmann's syndrome, which is characterized by secondary hypogonadism and associated dwarfism and occasional color blindness, anosmia may be caused by aplasia (lack of development) of the olfactory bulb and agenesis of the olfactory lobes. Anosmia is often accompanied by ageusia (impaired sense of taste). This combined disorder may be seen in an individual following head trauma, and in patients with scleroderma who underwent treatment with histidine.

Presence of the central retinal artery and vein inside this nerve may account for the reduction of the arterial and retardation venous blood flow in these vessels upon compression of this nerve by a growing tumor or by increased intracranial pressure. Additionally, since meningeal coverings of the brain, associated subarachnoid space and cerebrospinal fluid continue around the optic nerve, conditions that affect the circulation of the CSF may eventually translate into pressure build-up on this nerve.

II Optic nerve

The optic nerve (SSA) is formed by the axons of retinal ganglion cells (Figures 11.1 & 11.4). It is considered an extension of the brain for two main reasons, first, it is surrounded by myelin from the oligodendrocytes, second, it is an embryological derivative of the forebrain diverticulum. Due to these reasons patches of demyelination along the course of the optic nerve are seen in multiple sclerosis. Optic nerve acquires myelin in the orbit, otherwise, myelinated axons in the retina may cause light reflection and blurred vision. Visual information from the temporal and nasal halves of the corresponding retina, as well as impulses concerned with pupillary light and accommodation reflexes is carried by the optic nerve. Fibers of the optic nerve leave the retina medial to the fovea centralis and converge on the optic disc, piercing the

choroid layer, sclera, and entering the orbit. In the orbit, it is crossed by the ophthalmic artery. Then, it leaves the orbit and gains access to the cranial cavity through the optic canal (Figure 11.2). Posterior to the optic canal, the nasal fibers decussate to form the optic chiasma (Figures 11.1 & 11.4). In the cranial cavity, the internal carotid artery lies lateral to the optic nerve, and ventral to the anterior cerebral artery.

III Oculomotor nerve

The oculomotor nerve (GSE, GVE) emerges from the ventral surface of the midbrain within the interpeduncular fossa, in close relationship to the crus cerebri (Figures 11.1, 11.5, 11.6 & 11.7). This nerve runs between the superior cerebellar and the posterior cerebral arteries, and inferior to the posterior communicating artery. It courses within

Integrity of the optic nerve is determined by examination of the visual fields and visual acuity. This is accomplished by confrontational visual field testing which involves closure of the examiner's right eye and patient's left eye while standing at eye level opposite each other. This is followed by the examiner's simultaneous show of one or two fingers in each hand and his request that the patient ascertain the fingers that he has seen. The other eye will be tested the same way from upper to lower quadrants. In normal individuals the fingers will be seen at the same time by the examiner and patient. Scotoma (focal blindness) which occurs in glaucoma and tumors of the central nervous system may be detected upon widening of the visual field of a patient by pulling the examiner's hand away from the patient. Flashing light beam or a pencil may also be used and the patient is asked to state the timing of its appearance and direction. Visual acuity may be assessed by using the Snellen eye chart, positioned approximately 20 feet from the patient. Each eye is tested separately and the first number in the standard ratio 20/20 denotes the actual distance of the patient from the chart, while the second number represents the distance at which a person with normal vision can read the chart. Visual acuity of each eye, which reflects the macular function, should be tested independently with and without glasses. For this purpose the examiner may use a newspaper article, or attempt to present a picture or small objects to be identified by the patient. Visual acuity may vary by environmental factors such as illumination and degree of contrast.

To detect the differences between both eyes in response to afferent stimuli, the swinging light test is employed. In this test the patient is asked to look at a distant object while the examiner rapidly swings a light beam from one eye to the other. When directing the light into the blind eye, neither eye will show constriction. However, upon moving the light back to the intact eye, the blind eye shows apparent pupillary dilatation due to the lack of afferents to the retina and optic nerve (Marcus Gunn Pupil).

the cavernous sinus and leaves the middle cranial fossa via the superior orbital fissure. It enters the orbit as a component of the tendinous annulus of Zinn, where it divides into superior and inferior rami. The superior ramus (GSE) supplies the superior rectus and levator palpebrae, whereas the inferior ramus provides innervation (GSE) to the medial and inferior recti, and the inferior oblique. There are preganglionic parasympathetic fibers (GVE) to the ciliary ganglia that run within the inferior ramus. These autonomic fibers constitute the efferent limb for

Complete destruction of the optic nerve results in total blindness on the affected side. Due to the bilateral connections of the visual fibers of the optic nerve, pupillary light and accommodation reflexes are lost on both sides when the affected eye is stimulated.

Prolonged elevation of intracranial pressure produces uniform compression of the optic nerve leading to blindness. Papilloedema (choked disc) is a condition in which the optic disc protrudes anteriorly as a result of dilatation of the subarachnoid space around the optic nerve, subsequent to increased intracranial pressure. This condition may also be associated with compression of the central retinal artery and vein, and may be observed in hypertensive individuals.

both pupillary light and accommodation reflexes. Oculomotor nerve is formed by neuronal axons of the oculomotor nucleus; a-V- shaped nucleus, which lies medial to the medial longitudinal fasciculus at the level of the superior colliculus. It consists of somatic and visceral nuclear columns. In the somatic component of this nucleus (Figures 11.5 & 11.7) dorsal, intermediate, ventral, caudal central and medial cellular columns exist. The dorsal column innervates the ipsilateral inferior rectus muscle; the intermediate column supplies the ipsilateral inferior oblique muscle; and the ventral column provides innervation to the ipsilateral medial rectus. The latter neuronal column is controlled by the internuclear neurons of the abducens nucleus in lateral gaze. The caudal central column provides bilateral innervation to the levator palpebrae muscle, whereas the medial column innervates the contralateral superior rectus muscle. Preganglionic parasympathetic fibers to the ciliary ganglion, which innervate the constrictor pupilla and ciliary muscles, arise from the Edinger Westphal nucleus visceral, the visceral column of the oculomotor nucleus (Figure 11.7).

Descending cortical fibers to the oculomotor nucleus, which form the corticobulbar fibers, are crossed and uncrossed and establish contact with the nucleus via the reticular formation. Additionally, vestibular fibers also project to the oculomotor nucleus through the MLF, regulating movements of the head and fixation of gaze. Fibers from the accessory oculomotor nuclei (interstitial nucleus of Cajal, nucleus of Darkschewitsch, and nucleus of the posterior commissure), project to the oculomotor nuclei by crossing in the posterior commissure.

IV Trochlear nerve

The trochlear nerve (GSE) is the only cranial nerve which exits from the dorsal surface of the pons, caudal to the level of the inferior colliculus (Figures 11.9 & 11.10). This nerve, which represents the axons of the trochlear nucleus,

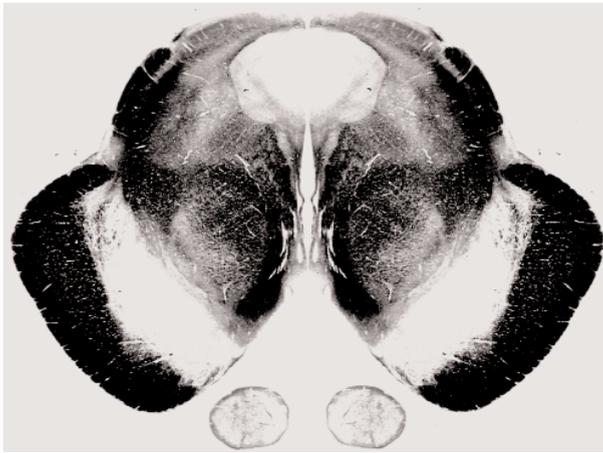


Figure 11.5 The oculomotor nuclear complex is illustrated and its location is identified in reference to the MLF and the periaqueductal gray matter

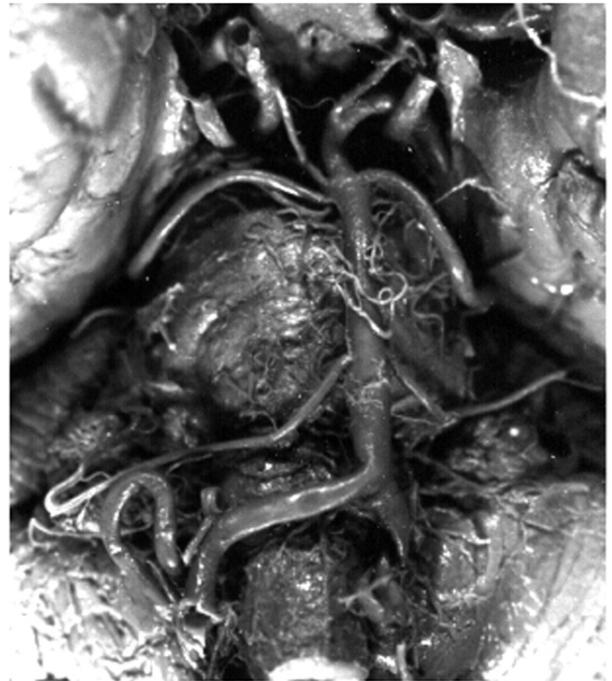


Figure 11.6 The course of the oculomotor nerve between the superior cerebellar and posterior cerebral arteries is illustrated

Destruction of the oculomotor nerve may occur in combination with the corticospinal tract in Weber's Syndrome or in conjunction with the red nucleus, spinothalamic tracts, medial lemniscus, and superior cerebellar peduncle in Benedikt's Syndrome. It may also be damaged together with the red nucleus in Claude's (lower red nucleus) syndrome, exhibiting contralateral hemiataxia, but with no apparent hyperkinesia. Oculomotor nerve palsy with contralateral cerebellar ataxia, tremor, and signs of spastic palsy are seen in Nothnangel syndrome. Since the oculomotor nerve courses immediately rostral to the superior cerebellar artery, caudal to the posterior cerebral artery and inferior to the posterior communicating artery, an aneurysm of any of these individual vessels (occasionally may produce signs of oculomotor palsy. Transtentorial herniation may also pose undue stretch on these vessels, resulting in oculomotor nerve dysfunction that almost always involve the pupil. Thrombosis of the cavernous sinus, fractures of the middle cranial fossa or superior orbital fissure, parasellar neoplasm, and demyelinating diseases may also produce deficits associated with the oculomotor nerve. In ALS and poliomyelitis, the oculomotor nerve remains intact despite involvement of the motor neurons. Some of the above syndromes are discussed with the motor system or under the heading of combined motor and sensory lesions.

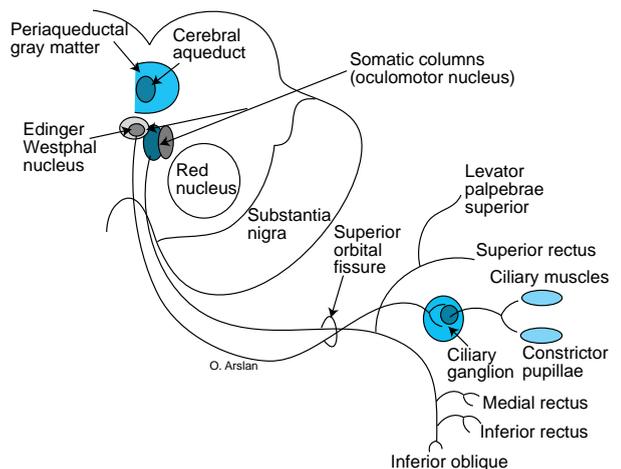


Figure 11.7 The functional components of the oculomotor nerve from their origin in the oculomotor nuclear complex to their site of innervation is shown in this drawing.

Injury to the oculomotor nerve may be partial or complete and the recovery may occur unevenly. In diabetes-induced oculomotor nerve damage is painful and the parasympathetic fibers may be spared. However, these fibers may be damaged in brainstem lesions. Fibers, which mediate accommodation reflex, may be damaged in diphtheria. An acute isolated painful oculomotor nerve palsy is most commonly associated with aneurysm of the branches of the internal carotid artery. Damage to the oculomotor nucleus may occur in multiple sclerosis and produces identical deficits to oculomotor nerve palsy and if complete, also result in contralateral superior rectus palsy. Unilateral lesion of the lateral tegmentum of the midbrain may produce signs of oculomotor palsy on the same side and trochlear nerve palsy on the opposite side.

Oculomotor palsy (Figure 11.8) is characterized by ipsilateral:

- Ptosis (drooping of the upper eyelid due to paralysis of the levator palpebrae superior). This deficit should be distinguished from the ptosis observed in Horner's syndrome. In the latter condition, ptosis is less pronounced and occurs as a result of paralysis of the superior tarsal muscle, subsequent to disruption of the postsynaptic sympathetic fibers.
- Mydriasis (dilatation of the pupil) is due to paralysis of the constrictor pupillae muscle and the unopposed action of the dilator pupillae muscle.
- Diplopia (double vision) is seen in all direction except in lateral gaze and the distance between true and false images is maximal in the direction of the gaze. The false image will always be peripheral to the true image.
- Lateral strabismus (lateral deviation) and downward deviation of the eye due to activation of unopposed lateral rectus and the superior oblique muscles.
- Enophthalmos (inward displacement of the eyeball), possibly an illusionary feature due to drooping of the upper eyelid.
- Loss of pupillary and accommodation reflexes.

Examining the light reflex and observing movement of the eyes tests integrity of the oculomotor nerve. To test the light reflex, the patient is asked to look at a distance, while the examiner shines a bright light into one eye of the patient; the examiner then observes the pupils in both eyes (direct and consensual light reflexes). In normal individuals, both pupils will constrict in response to the light applied to one eye. In lesions of the oculomotor nerve, the affected eye remains unreactive regardless of which eye is stimulated. Since both the optic and oculomotor nerves mediate accommodation reflex, evaluation of near vision may reveal the condition of these nerves. In order to accomplish this task, the patient is asked to look alternately at distant and close objects and observe convergence of both eyes. The functional integrity of the extraocular muscles which receive innervation from the oculomotor nerve may be tested by asking the patient to follow the examiner's finger as it traces an "H" configuration, first, moving to patient's right, then up, then down, then back to the midline.

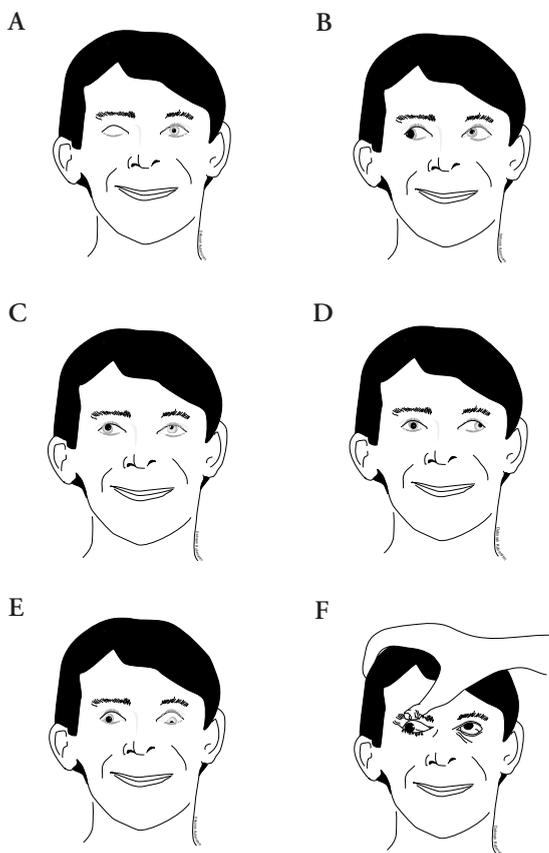


Figure 11.8 Manifestations of right oculomotor nerve palsy are depicted in diagrams A to G. (A) Ptosis, (B) intact lateral gaze to the right side, (C) inability to gaze in an upward direction, (D) inability to adduct the right eye upon left lateral gaze, (E) inability to look downward on the right eye, (F) Paralyzed eyelid is raised, exhibiting lateral strabismus

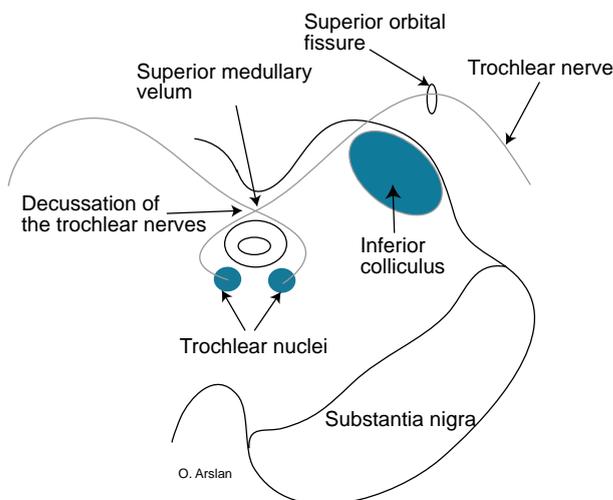


Figure 11.9 The course of the trochlear nerve and its complete decussation in the superior medullary velum is shown in this drawing

Lesions of the trochlear nerve may occur in multiple sclerosis, cavernous sinus thrombosis, and superior orbital fissure syndrome that also involves the oculomotor (CN III) nerve. It may also occur in orbital apex syndrome, affecting the optic (CN II), oculomotor (CN III), and abducens (CN VI) nerves in addition to the trochlear nerve. Trochlear nerve palsy is characterized by impairment of downward gaze of the adducted eye (Figures 11.11 & 11.12). The eye on the affected side remains elevated and assumes higher position in the adducted position than when the eye is abducted, and decreases with abduction. Elevation of the eye on the affected side assumes maximal position when the neck is bent toward the affected side, maintaining normal position upon bending of the neck toward the intact side (Bielschowsky's head-tilt test). Vertical diplopia will be more evident as the patient looks down and inward.

completely decussate within the superior medullary velum. Following its exit from the cavernous sinus, the trochlear nerve runs between the superior cerebellar and posterior cerebral arteries, making it vulnerable to damage by an aneurysm of these arteries. It enters the orbit via the superior orbital fissure, innervating the superior oblique muscle. The trochlear nucleus receives ipsilateral vestibulo-

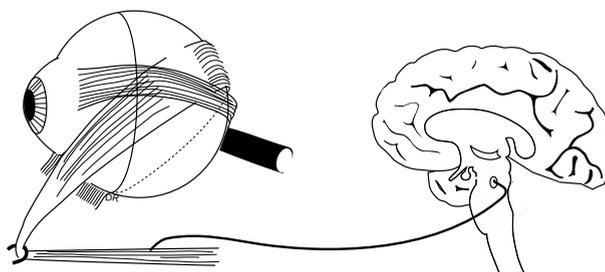


Figure 11.10 The origin, course and final destination of the trochlear nerve

Patients adopt a characteristic posture, tilting the head toward the opposite side so that the face will be directed toward the affected side (Beilshowsky sign). Maintenance of such a posture for an extended period will lead to torticollis (Wry Neck), which refers to the spasmodic contracture of the neck. Bilateral trochlear nerve palsy may occur in superior medullary velum syndrome as a result of a lesion that disrupts the decussating fibers of this nerve within the superior medullary.

ocular fibers and bilateral fibers from the accessory oculomotor nuclei.

V Trigeminal nerve

The trigeminal nerve (GSA, SVE)-(Figures 11.1 & 11.18), the largest of all cranial nerves, exits the pons through the middle cerebellar peduncle. It has a sensory (trigeminal, Gasserian, semilunar) ganglion which is formed by the unipolar neurons of the sensory fibers. This ganglion lies anterior to the apex of the petrous temporal bone and resides in Meckel's Cave. The trigeminal nerve gives off the ophthalmic (V1), maxillary (V2), and the mandibular (V3) divisions. Functionally, the ophthalmic and sensory, while the mandibular division remains mixed. There are postsynaptic sympathetic and postsynaptic parasympathetic fibers within the sensory fibers.

The ophthalmic division (V1) runs in the cavernous sinus and reaches the orbit through the superior orbital fissure (Figure 11.15). It supplies the frontal and ethmoidal sinuses, eyeball, the dura of the anterior cranial fossa, nasal cavity, upper eyelid, and the skin of the forehead region and scalp as far as the lambdoid suture. This division has a frontal, nasociliary, and lacrimal branches. The frontal nerve provides sensory fibers to the

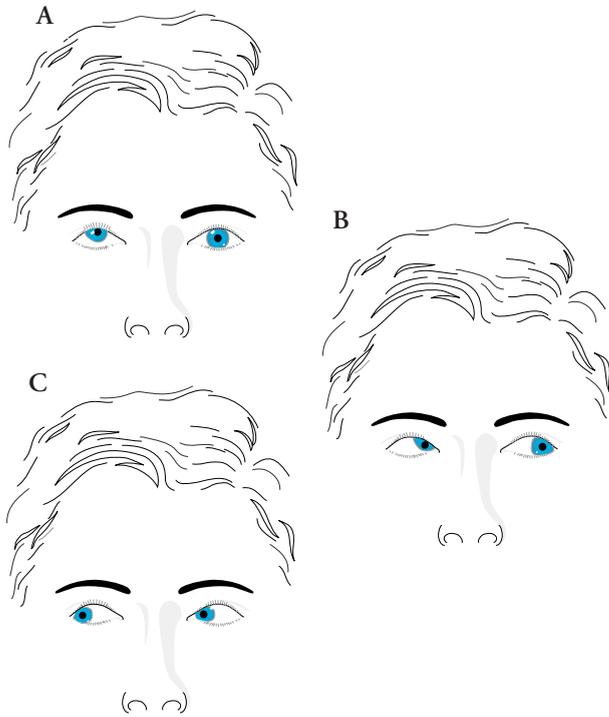


Figure 11.11 The deficits associated with trochlear nerve palsy. Note in (A) the right eye is elevated upon forward gaze, in (B) Elevation of the eye is increased with adduction, and in (C) decreased with abduction

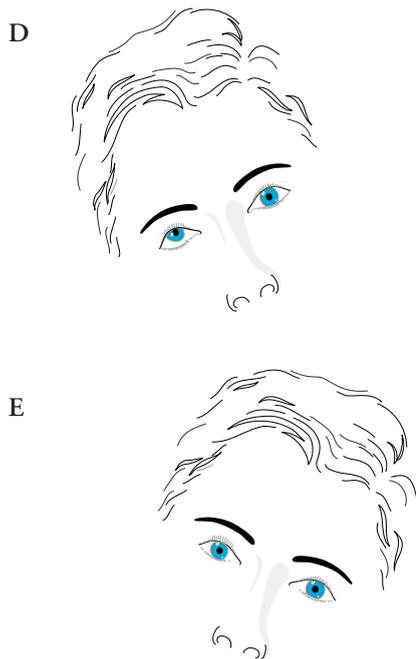


Figure 11.12 Diagrams of manifestations of trochlear nerve palsy. In (D) maximal elevation upon tilting the head to the affected side, while in (E) eye elevation disappears upon head tilting in the opposite direction

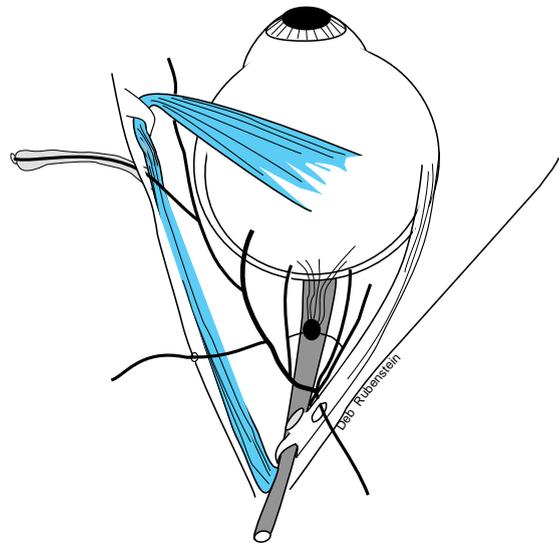


Figure 11.13 The course and branches of the nasociliary nerve

forehead, upper eyelid, and scalp via its supratrochlear and supraorbital branches (Figure 11.14). The lacrimal nerve also transmits postsynaptic parasympathetic fibers to the lacrimal gland (Figure 11.18). The nasociliary branch of the ophthalmic nerve (Figure 11.13) runs with the ophthalmic artery, giving rise to sensory fibers to the lateral nose and the eyeball. It also carries presynaptic parasympathetic fibers that eventually run through the short ciliary branches to the ciliary body and the constrictor pupilla muscle.

The ophthalmic nerve mediates both corneal and lacrimal reflexes. The corneal reflex, a somatic reflex which is elicited by a light touch of the cornea or conjunctiva with a wisp of cotton, as the patient looks to the opposite side. As a result of contraction of the orbicularis oculi muscles produces blinking in both eyes. This reflex is mediated by the indirect bilateral connections of the ophthalmic nerve (afferent limb) to the facial (efferent limb) motor neurons via interneurons of the pontine reticular formation.

Lacrimation (tearing) reflex is also mediated by the ophthalmic nerve (afferent limb), which conveys the signals to the superior salivatory nucleus in the reticular formation of the pons. The latter projects via the intermediate and the greater petrosal nerves to the pterygopalatine ganglion that provides postsynaptic parasympathetic fibers to the lacrimal gland via the zygomatico-temporal branch of the maxillary and the lacrimal branches of the ophthalmic nerve.

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Nasociliary neuralgia is an episodic or prolonged pain sensation in the medial canthus of the eye, eyeball, and external nose. Redness of the forehead, congestion of the nasal mucus membrane, lacrimation, and conjunctivitis usually accompany this condition. This may be triggered by stimulation of the medial canthus. Antibiotics, cortisone, and local anesthetic (5% solution of cocaine) may be used to treat this condition.

fossa, nasal cavity, upper eyelid, and the skin of the forehead region and scalp as far as the lambdoid suture. This division has a frontal, nasociliary, and lacrimal branches. The frontal nerve provides sensory fibers to the forehead, upper eyelid, and scalp via its supratrochlear and supraorbital branches (Figure 11.14). The lacrimal nerve also transmits postsynaptic parasympathetic fibers to the lacrimal gland (Figure 11.18). The nasociliary branch of the ophthalmic nerve (Figure 11.13) runs with the ophthalmic artery, giving rise to sensory fibers to the lateral nose and the eyeball. It also carries presynaptic parasympathetic fibers that eventually run through the short ciliary branches to the ciliary body and the constrictor pupilla muscle.

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The maxillary division (V2) runs in the cavernous sinus, leaves the middle cranial fossa through foramen rotundum (Figure 11.15), and enters the pterygopalatine fossa, where it is attached to the pterygopalatine ganglion (Figure 11.16). It provides sensory fibers to the following areas:

- (a) Skin overlying the maxilla, upper lip, lower eyelid and side of the nose, as well as upper canine teeth via the infraorbital branch.
- (b) Molar and premolar maxillary teeth and maxillary sinuses via the superior alveolar branches.

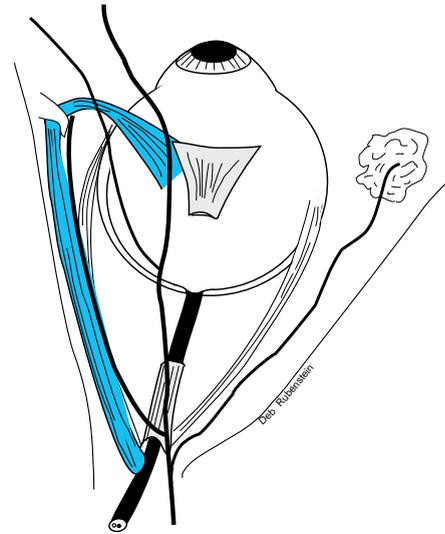


Figure 11.14 Frontal and lacrimal branches of the ophthalmic nerve

Damage to the ophthalmic, facial nerve, or their central connections in the pons may produce loss of corneal reflex. Loss of the corneal reflex due to ophthalmic nerve lesion may be observed in both eyes when the affected side is stimulated. However, this reflex may still be elicited in both eyes when the unaffected side is stimulated (Figure 11.19).

- (c) Mucosa of the palate via the greater and lesser palatine branches.
- (d) Meningeal branches to the dura of the middle cranial fossa,
- (e) nasal branches to the nasal cavity and nasopharynx.
- (f) Temporal region via the zygomatic branch, which further divides into zygomaticofacial and zygomaticotemporal, branches.

The latter communicates with the lacrimal nerve, conveying postganglionic parasympathetic fibers to the lacrimal gland. It also gives rise to ganglionic branches to the pterygopalatine ganglion. The nasal branches form the afferent limb of the nasal (sneeze) reflex, which is characterized by contraction of the muscles of the soft palate, pharynx and larynx, diaphragm and intercostal muscles, in response to irritation of the nasal mucosa. Afferent limb of this reflex conveys these impulses to the spinal trigeminal nucleus which are transmitted in turn to the trigeminal motor and ambiguus nuclei, as well as the intercostal and motor neurons of the phrenic nerves.

The mandibular branch (V3) is sensory to the mandibular teeth, floor of the mouth, anterior 2/3 of the



Figure 11.15 Main foramina and fissures that transmit the branches of the trigeminal nerve

Sluder's neuralgia is a condition, which is associated with a lesion of the pterygopalatine ganglion. This disorder is characterized by pain in the areas of distribution of the nasal, pharyngeal, and palatine branches of the maxillary nerve that pierce the pterygopalatine ganglion. Frequent sneezing is common in many cases. Paranasal infection may also induce this condition.

tongue, and skin of the jaw and chin (Figure 11.17). It innervates to the muscles of mastication, and the tensor palatini and tympani. It leaves the middle cranial fossa via the foramen ovale (Figure 11.15) and enters the infratemporal fossa to course lateral to the otic ganglion. It divides into a primarily motor anterior trunk (with the exception of the buccal branch) and a principally sensory posterior trunk (with the exception of the mylohyoid nerve).

The posterior trunk of the mandibular nerve gives rise to the lingual, inferior alveolar, auriculotemporal, and mylohyoid branches.

The lingual nerve is sensory to the anterior 2/3 of the tongue, floor of the mouth and lingual gingiva. In the infratemporal fossa, it joins the chorda tympani branch of the facial nerve, which carries taste sensation from the anterior 2/3 of the tongue, and proceeds to attach to the submandibular ganglion.

The inferior alveolar nerve (Figure 11.17) runs in the mandibular canal, supplies the mandibular teeth, and gives

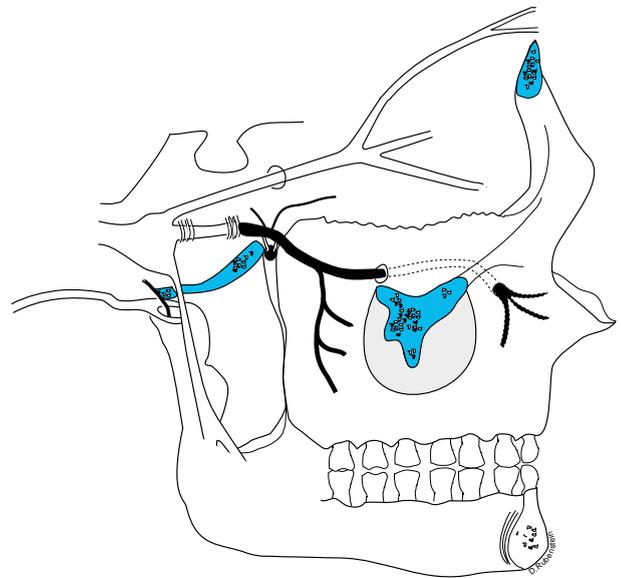


Figure 11.16 The origin, general course, and branches of the maxillary nerve

rise to the mental and incisive nerves. The mental nerve supplies the skin of the chin and is involved in the jaw-jerk reflex. This reflex is monosynaptic characterized by sudden closure of the mouth (as a result of bilateral contraction of the masseter and temporalis muscles), following a downward tap on a finger placed on the jaw when the mouth is slightly open. It is mediated by the mandibular nerve, through the mesencephalic and the motor trigeminal nuclei.

The auriculotemporal nerve (Figure 11.17) is the only branch that courses posteriorly, arising by two roots that encircle the middle meningeal artery. It carries postganglionic parasympathetic fibers to the parotid gland, and sensory fibers to the temporomandibular joint, anterior temporal region, auricle, and the external acoustic meatus. The mylohyoid nerve innervates the mylohyoid muscle and the anterior belly of the digastric muscle.

The anterior trunk of the mandibular nerve gives rise to nerves that supply the temporalis, lateral and medial pterygoid, masseter, tensor tympani, and tensor palatini muscles. Buccal nerve, the only sensory branch of the anterior trunk, supplies the skin and mucosa of the cheek.

The trigeminal nerve has three sensory and a single motor nucleus (Figures 11.18 & 11.20). The sensory

Division of the lingual nerve distal to the site of union with chorda tympani may produce loss of general and taste sensations from the anterior 2/3 of the tongue and impairment of salivary secretion from the submandibular and sublingual glands.

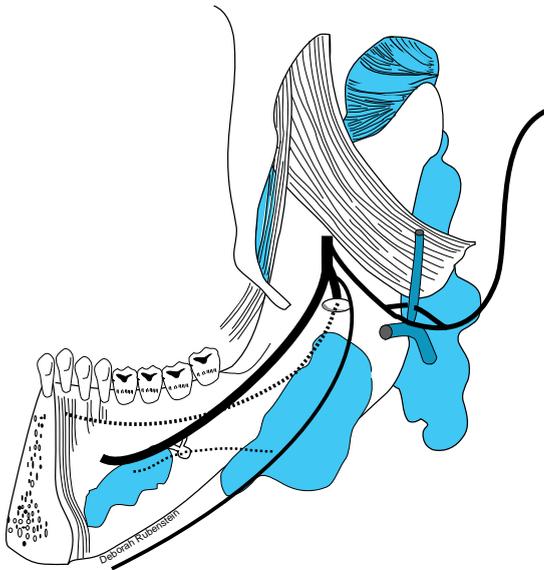


Figure 11.17 The principal branches of the mandibular nerve are shown

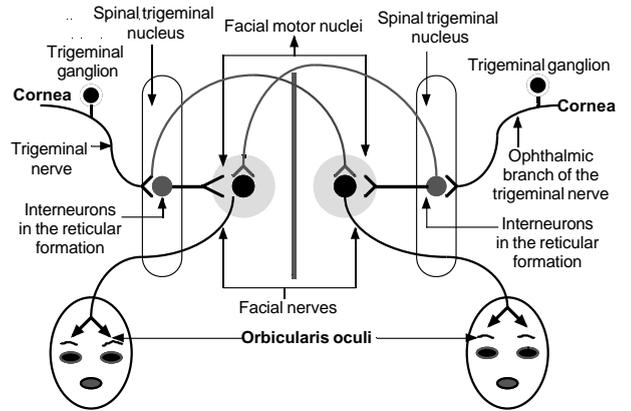


Figure 11.19 Corneal reflex. The trigeminal and facial nerves, as illustrated in this diagram, mediate this reflex

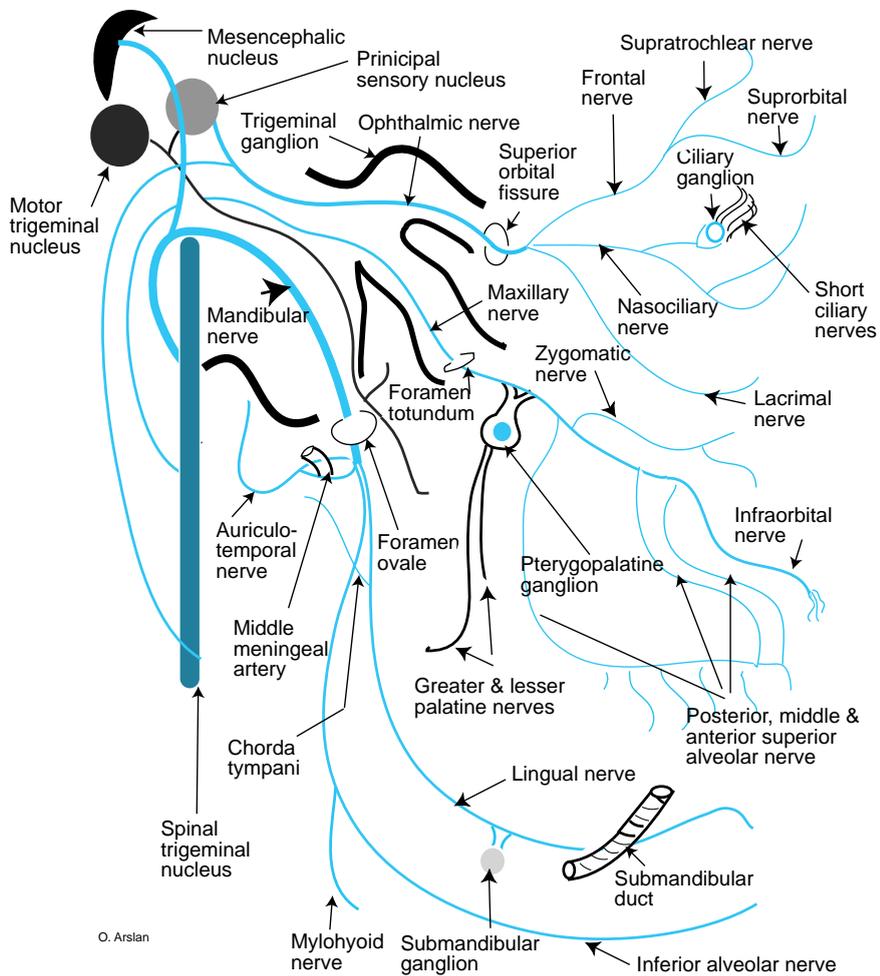


Figure 11.18 Functional components, branches, and associated nuclei of the trigeminal nerves. The course of these branches and their areas of distribution are documented to facilitate the understanding of the central and peripheral course of this nerve

Failure to elicit Jaw-jerk reflex may indicate a pontine lesion involving the trigeminal nerve, mesencephalic or motor trigeminal nuclei. Hyperactive jaw reflex is a manifestation of corticobulbar tract damage.

nuclei of the trigeminal nerve are the spinal, principal sensory, and mesencephalic trigeminal nuclei.

The spinal trigeminal nucleus (GSA) extends from the midpons to the upper segments of the spinal cord, representing the rostral extension of the substantia gelatinosa. It receives thermal, painful, and tactile sensations from the head region within branches of the trigeminal, facial, glossopharyngeal, and vagus nerves. As they terminate in this nucleus, they form the spinal trigeminal tract, which is positioned lateral to the nucleus. Within the spinal trigeminal nucleus and tract, the ophthalmic fibers occupy a caudal position to the more rostral mandibular fibers, while the maxillary fibers maintain an intermediate position. Since pain and thermal fibers terminate in the most caudal portions of this nucleus and tract, within the caudal medulla, excision of the spinal trigeminal tract (tractotomy), if it is performed at this level, may alleviate the intractable pain associated with trigeminal neuralgia.

In the midpons, the principal (pontine or chief) sensory nucleus (GSA) lies lateral to the trigeminal nerve fibers. It transmits tactile and pressure sensation, showing identical somatotopic distribution to that of the spinal trigeminal nucleus.

Neurons of the spinal trigeminal nucleus and the ventral part of the principal sensory nucleus give rise to axons regarded as secondary trigeminal fibers. These fibers cross the midline and run through the reticular formation, forming the ventral trigeminal lemniscus on the opposite side. Fibers from the dorsal part of the principal sensory nucleus are virtually derived from the mandibular nerve, ascend ipsilaterally as the dorsal trigeminal lemniscus. Both of the trigeminal lemnisci are associated topographically with the medial lemniscus and project to the VPM nucleus of the thalamus. The secondary trigeminal fibers have collaterals that establish contact with specific nuclei in the reticular formation, mediating various trigeminal reflexes.

The mesencephalic nucleus (GSA) receives fibers, transmitting proprioceptive input from the temporomandibular joint, muscles of mastication, hard palate, mandibular and maxillary alveoli, and possibly from the extraocular muscles. It projects to the cerebellum and superior colliculi, and mediates the jaw-jerk reflex.

The motor trigeminal nucleus (SVE), is located medial to the entering trigeminal nerve fibers in the rostral pons. It is the source of motor fibers to the muscles of

Injury to the trigeminal nerve or its branches may occur as a result of a tumor of the ponto-cerebellar angle, otitis media, cavernous sinus thrombosis, fractures involving the middle cranial fossa, or metastatic carcinomas. Multiple sclerosis may produce trigeminal neuralgia and transient facial anesthesia in young adults. In particular, the ophthalmic branch may be damaged as it courses within the superior orbital fissure in conjunction with the oculomotor, trochlear, and abducens nerves. It may also be injured in orbital apex syndrome together with the optic, oculomotor, trochlear, and abducens nerves. A fracture confined to the ramus of mandible may put the mandibular nerve out of function.

Destruction of the trigeminal nerve produces combined sensory and motor, as well as reflex disorders. These dysfunctions include unilateral anesthesia in the area of distribution of the trigeminal nerve, loss of corneal reflex on both sides when the affected eye is stimulated, and also atrophy of the muscles of mastication, tensor tympani, and tensor palatini muscles. Additional deficits include loss of sensation from the facial region, oral and nasal cavities, and the anterior two thirds of the tongue. Sensations from the temporomandibular joint, paranasal sinuses, and anterior part of the external acoustic meatus may also be lost. The jaw-jerk, oculo-cardiac (a reflex that mediates slowing of heart rate upon compression of the eyeball), sneezing, and lacrimation reflexes are impaired. Impairment of the postsynaptic parasympathetic innervation to the head region may also be noticed. Referred (projected) pain to the area of distribution of branches of the trigeminal nerve is common. For example pain from carious tooth may project pain to the ear, or an ulcer of the tongue may produce pain that is felt in the ear and temporal region that corresponds to the area of distribution of the auriculotemporal nerve.

mastication, tensor tympani, and tensor palatini muscles. It receives bilateral corticobulbar fibers, and forms the efferent limb of the jaw-jerk reflex.

VI Abducens nerve

The abducens nerve (GSE)-(Figures 11.1 & 11.23) is formed by the axons of the motor neurons of the abducens nucleus, which lies deep to the ependyma of pontine part of the fourth ventricle. As the abducens nucleus is surrounded by the motor fibers of the facial nerve, forming

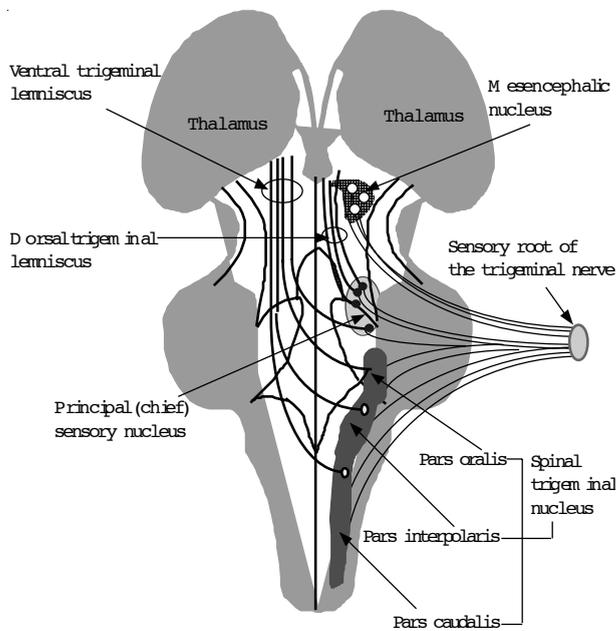


Figure 11.20 Trigeminal nuclei and their projections via the trigeminal lemnisci

Anomalous connections between the postsynaptic parasympathetic fibers of the auriculotemporal nerve which are destined to the parotid gland and the sympathetic postsynaptic fibers that supply the sweat glands of the face may occur following infection, trauma, and although rarely after surgical operation involving the parotid gland. These aberrant connections produce signs of Frey Syndrome (gustatory sweating) which is characterized by sweating induced by salivatory stimuli. Patients with Frey syndrome exhibit flushing and sweating on the face, along the distribution of the auriculotemporal nerve in response to tasting or eating. Auriculotemporal neuralgia may accompany this condition. Although a rare form of neuralgia, this disorder may exhibit burning pain in the preauricular and temporal, triggered by chewing or tasting spicy food.

the facial colliculus (Figure 11.22). This nucleus is unique among all other cranial nerve motor nuclei as it contains a population of alpha motor neurons that give rise to the abducens nerve, and a smaller population of interneurons that send axons through the contralateral MLF to the motor neurons of the oculomotor nucleus. These axons control the oculomotor neurons that innervate the medial rectus muscle. This functionally dual population of neurons may account for the distinct deficits produced by a lesion of the abducens nerve versus the abducens nucleus. During its course in the tegmentum and basilar pons, the

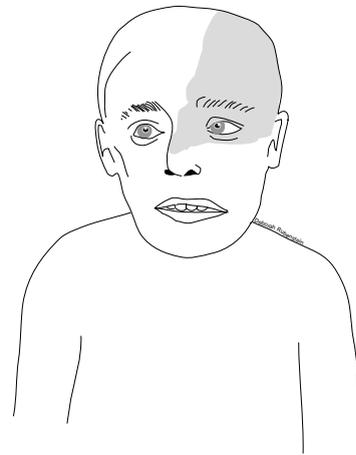


Figure 11.21 Port-wine discoloration (cutaneous vascular nevus) of the territory of the ophthalmic nerve. The patient is retarded and suffers from epileptic seizures

A lesion confined to the motor trigeminal nucleus may only result in atrophy of the muscles of mastication and deviation of the mandible toward the lesion side.

Trigeminal neuralgia (tic douloureux), a common idiopathic condition, exhibits a lightning or lancinating facial pain on the affected side which lasts for a few seconds. This lifelong recurring disorder affects women twice as often as men and develops relatively late in life between the age of 50 and 60. The paroxysmal pain associated with this condition is frequently elicited by mild stimuli (e.g. touch, application of cold, etc.) in one or more area of distribution of the trigeminal nerve. Patients may also exhibit signs of autonomic disorders (lacrimation, salivation, and flushing of the face), reflex facial muscle spasm, and sensory loss. Aberrant superior cerebellar or cerebral arteries may produce this condition by compressing the root of the trigeminal nerve. Multiple sclerosis accounts for most cases of trigeminal neuralgia in young adults. This condition may be treated by injection of glycerol into the root of the trigeminal nerve or by relieving the compression by placing a barrier between the trigeminal nerve and the anomalous vessel.

abducens nerve run adjacent to the corticospinal tract. It leaves the brainstem at the ponto-bulbar sulcus and maintains a long intracranial course. It forms a bend over the apex of the petrous temporal bone and enters the cavernous sinus, where it lies adjacent to the internal carotid artery, oculomotor, trochlear, ophthalmic, and maxillary nerves.

Proximity of the abducens nerve to the internal carotid artery may account for the initial signs of abducens nerve palsy in individuals with an aneurysm of the internal carotid artery. Also, due to its long intracranial course and sharp bend over the petrous temporal bone, this nerve is more prone to injury than any other cranial nerve. Damage to this nerve may also occur in cavernous sinus thrombosis, fracture of the superior orbital fissure, and aneurysm of the internal carotid artery. Medial strabismus or convergent squint in which the patient is unable to direct both eyes toward the same object characterizes abducens nerve palsy (Figure 11.24). This occurs due to paralysis of the lateral rectus muscle. Patients also experience horizontal diplopia (in acute stage) on attempted gaze to the affected side. Chronic abducens nerve palsy may not exhibit diplopia as the image from the affected eye is suppressed psychologically.

Destruction of the abducens nerve and the adjacent fibers of the corticospinal tract on one side may produce signs of middle alternating hemiplegia in which hemiplegia is manifested on the contralateral side while signs of abducens nerve palsy remains ipsilateral. A lesion of the abducens nucleus results in disruption of the abducens nerve and the internuclear neurons that emanate from the abducens nucleus and project to the contralateral medial rectus, producing lateral gaze which is characterized by adductor paresis on the lesion side and abductor palsy on the opposite side.

vestibulocochlear and labyrinthine artery. It runs dorsal to the cochlea within the facial canal, emerging through the stylomastoid foramen. It supplies the occipitalis, posterior belly of the digastric, and the mylohyoid muscles. It pierces the parotid gland and then divides into temporal, zygomatic, buccal, marginal mandibular, and cervical branches. The facial nerve has a motor and intermediate roots.

The motor root (SVE) is derived from neurons of the facial motor nucleus that provide innervation to the muscles of facial expression. These fibers ascend toward the midline and encircle the abducens nucleus, forming the facial colliculus. These motor fibers mediate both glabellar and corneal reflexes. Corneal reflex (also discussed with the trigeminal nerve (Figure 11.19) is characterized by contraction of the orbicularis oculi and the resultant blinking upon stimulation of the cornea by a wisp of cotton. Damage to the facial nerve also results in loss of this reflex on the side of lesion.

The intermediate (root) nerve contains general and special sensory, as well as preganglionic parasympathetic fibers. The sensory neurons of the facial nerve are located in the geniculate ganglion, a collection of unipolar neurons at the junction of the vertical and horizontal parts of the facial nerve.

The somatic sensory fibers of this root terminate in the spinal trigeminal nucleus, while the special visceral afferent (taste) fibers establish synaptic connections with neurons of the solitary nucleus. This root also contains preganglionic parasympathetic fibers run within the greater petrosal nerve and chorda tympani, providing secretomotor fibers to the submandibular, sublingual, and lacrimal glands. The facial nerve gives rise to the greater petrosal, chorda tympani, stapedius, posterior auricular nerve, and muscular branches.

Greater petrosal nerve (GVE, GVA, SVA)-(Figure 11.28) arises from the facial nerve at the level of the geniculate ganglion, carrying preganglionic parasympathetic fibers (GVE) from the superior salivatory nucleus to the pterygopalatine ganglion. It also conveys taste (SVA) and general sensory (GVA) fibers from the soft

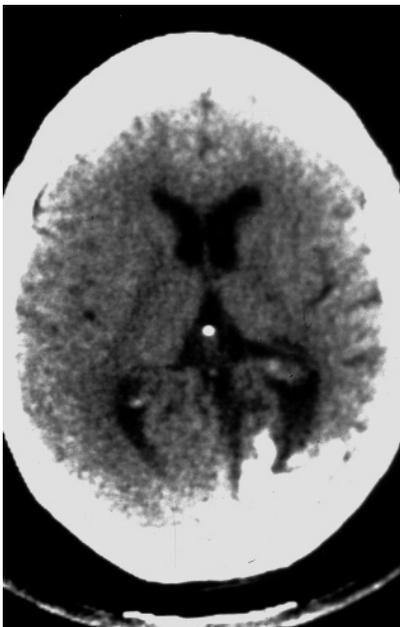


Figure 11.22 This Image shows a prominent calcification in an individual with Sturge-Weber Syndrome

Then, it leaves the cavernous sinus to enter the orbit via superior orbital fissure, innervating the lateral rectus muscle.

VII Facial nerve

The facial nerve (GSA, GVE, SVA, SVE)- (Figures 11.1, 11.25, 11.26 & 11.28) leaves the brainstem at the cerebello-pontine angle, enters the internal acoustic meatus (Figure 11.2), accompanied by the

Table 11.1 Cranial nerves I-VI

<i>Cranial nerve</i>	<i>Component</i>	<i>Location of cell bodies</i>	<i>Course</i>	<i>Distribution</i>	<i>Function</i>
I. Olfactory	S.V.A.	Neuroepithelial cells in nasal cavity	Cribriform plate of ethmoid	Olfactory mucus membrane	Olfaction
II. Optic	S.S.A.	Ganglion cells in the retina	Optic canal	Retina	Vision & visual reflexes
III. Oculomotor	G.S.E.	Somatic column of oculomotor nucleus	Superior orbital fissure	Levator palpebrae & all extraocular muscles with the exception of lateral oblique	Elevates the upper eyelid; adducts, elevate or depresses the eyeball.
	G.V.E.	Edinger Westphal nucleus		Ciliary & constrictor pupillae muscles	Mediates light and accommodation reflexes
IV. Trochlear	G.S.E.	Trochlear nucleus	Superior orbital fissure	Superior oblique	Abducts, intorts & depresses the eyeball
V. Trigeminal	G.S.A.	Trigeminal (Gasserian) ganglion	V1-superior orbital fissure V2 -foramen rotundum V3- foramen ovale.	Skin of face, scalp, gingiva, anterior 2/3 of tongue, oral and nasal cavities, eye, paranasal sinuses & meninges	Cutaneous and proprioceptive information
	S.V.E.	Trigeminal motor nucleus	Foramen ovale	Muscles of mastication, anterior belly of digastric, tensor tympani & mylohyoid muscle	Mastication, mandibular movements & deglutition
VI. Abducens	G.S.E.	Abducens nucleus	Superior orbital fissure	Lateral rectus	Lateral deviation of the eye

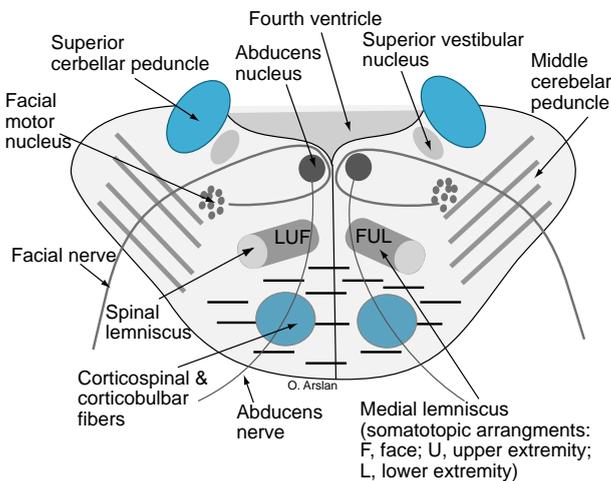


Figure 11.23 The abducens nucleus and nerve are shown in this section of the caudal pons. The relationship of the facial nerve to the abducens nucleus is also illustrated

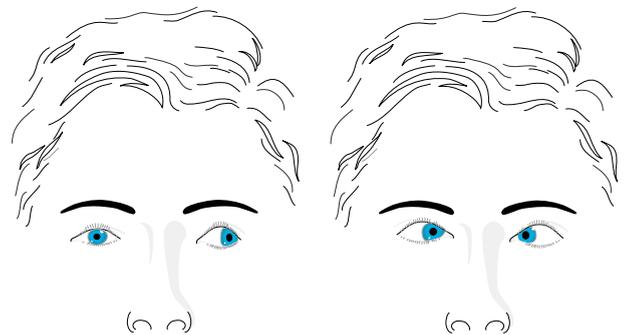


Figure 11.24 Deficits associated with right abducens nerve palsy. Note the affected eye is adducted at rest (left diagram), and can not abduct when attempt to look to the right (right diagram)

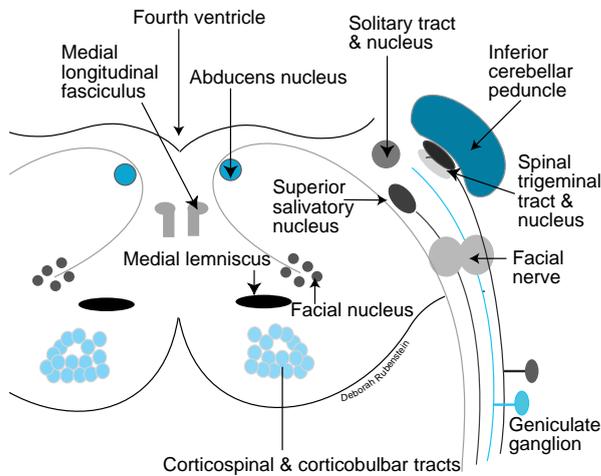


Figure 11.25 The functional components of the facial nerve, course, and associated nuclei are shown in this diagrammatic section of the pons

The glabellar (McCarthy's) reflex or Myerson sign exhibits forceful, persistent, involuntary and repeated contraction of the orbicularis oculi muscle, which is elicited by repetitive finger taps on the forehead and supraorbital margin in a downward direction to the glabella. Damage to the facial nerve or its nucleus produces glabellar hyporeflexia, a disorder seen in Parkinson's disease and in patients with bilateral frontal lobe lesion, and occasionally in tense and overly stressed individuals.

palate to the solitary nucleus. This nerve should not be confused with the lesser petrosal branch of the glossopharyngeal nerve.

Chorda tympani (SVE, GVE)-(Figure 11.28) runs in the upper quadrant of the tympanic membrane medial to the malleus and incus, leave the skull via the petrotympanic fissure and enters the infratemporal fossa. It carries preganglionic parasympathetic (GVE) fibers from the superior salivatory nucleus and conveys taste sensation (SVA) from the anterior two thirds of the tongue to the solitary nucleus.

Stapedius nerve (SVE) is formed by fibers of the facial motor nucleus, supplying the stapedius muscle. This muscle contracts in response to loud noises.

The posterior auricular branch (SVE) innervates the occipitalis muscle, and derives its axons from the facial motor nucleus (Figure 11.25). Other muscular branches of the facial nerve supply the stylohyoid (SVE) posterior belly of the digastric muscles. Five muscular branches arise from

Ramsay-Hunt syndrome, a condition that results from herpetic viral infection of the geniculate ganglion may result in auricular pain followed by vesicular eruptions in the area of distribution of the auricular branch of the facial nerve in the concha of the ear.

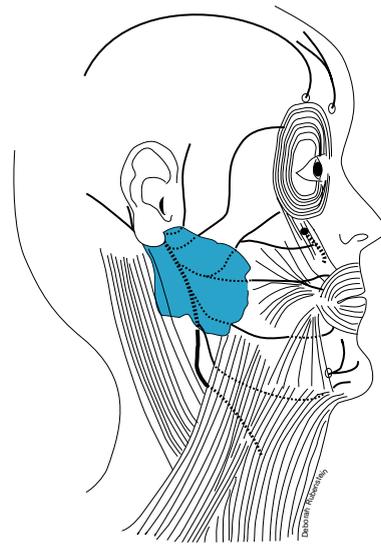


Figure 11.26 The course and branches of the facial nerve, outside the facial canal, are illustrated

Anomalous connection between the preganglionic parasympathetic fibers of the chorda tympani and the presynaptic parasympathetic fibers of the greater petrosal nerve may result in salivation induced by lacrimation (crocodile-tear syndrome).

the trunk of the facial nerve within the parotid gland, which include the temporal, zygomatic, buccal, marginal mandibular, and cervical branches (Figure 11.26). It is important to distinguish between the buccal branch of the facial nerve and that of the mandibular nerve. The buccal branch of the facial nerve is motor to the muscles around the mouth and runs with the parotid duct, supplying the masseter muscle, while the buccal branch of the mandibular nerve is sensory to the skin and mucosa of the cheek. The auricular branch (GSA) transmits general sensory impulses from the concha of the ear to the spinal trigeminal nucleus.

Nuclei associated with the facial nerve

These nuclei are comprised of the facial motor, superior salivatory, solitary, and the spinal trigeminal (Figures 11.25 & 11.28).

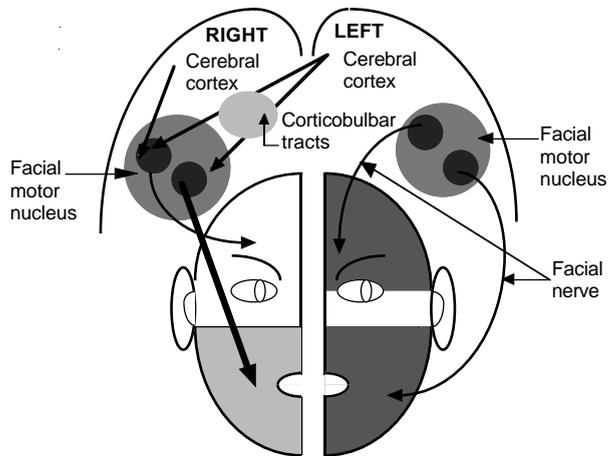


Figure 11.27 Schematic drawing of the preferential distribution of the corticobulbar tract in the facial motor nuclei. Note the bilateral distribution of the corticobulbar fibers to the neurons of the upper face and contralateral projection to the neurons of the lower face

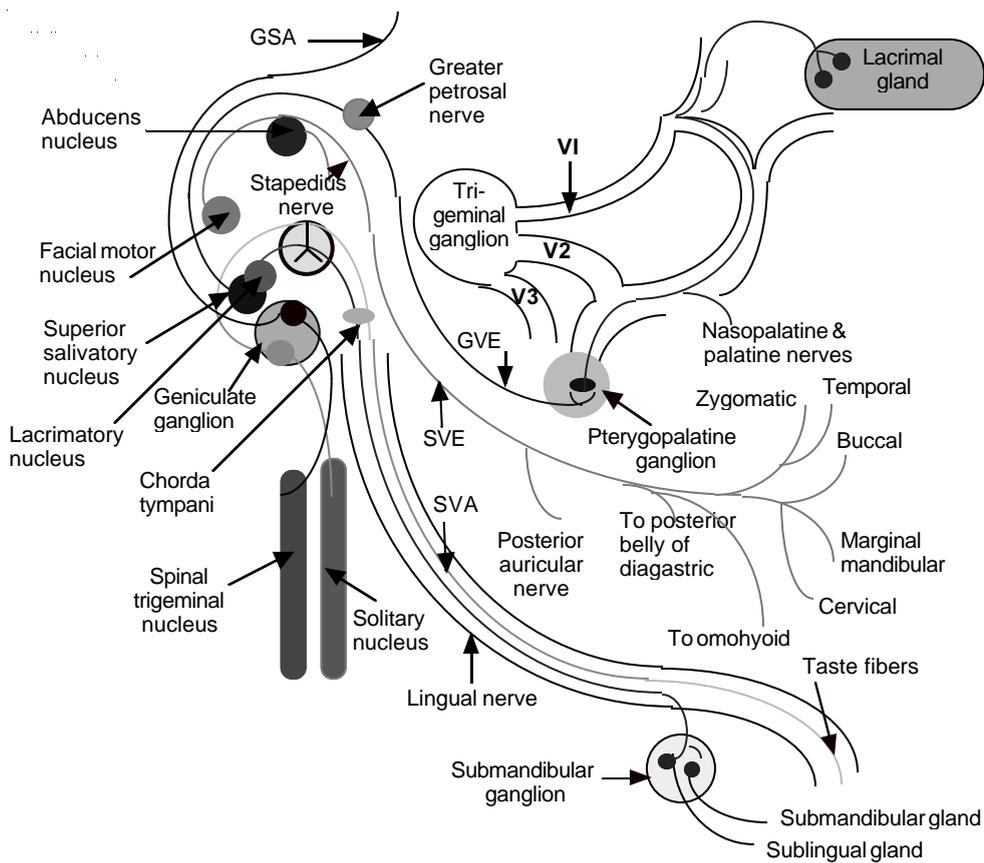


Figure 11.28 The individual fibers of the facial nerve, functional components, and sensory and motor nuclei of the facial nerve are marked with colors

Facial palsy occurs as a result of lesions involving the corticobulbar fibers, facial motor nucleus, or the facial nerve. These lesions, as documented below, are categorized into supranuclear and infranuclear lesions. Supranuclear lesions (Figure 11.29) involve the corticobulbar fibers that emanate from the cerebral cortex and project to the facial motor nucleus. These lesions, as seen in multiple sclerosis, produce upper motor neuron signs in the muscles around the mouth on the contralateral side. Patients cannot voluntarily move the affected muscles (voluntary facial palsy), however; they remain responsive to emotional stimuli.

Supranuclear lesions that affect the projections of the limbic system to the facial motor nucleus may result in mimetic facial palsy. In this condition, patient remains unresponsive to emotional stimuli, while preserving the ability to produce contraction of the affected muscles upon command. Infranuclear lesions (Figure 11.30) are caused by damage to the facial nerve and/or the facial motor nucleus. These lesions may be the result of mumps, acoustic neuroma, parotid tumors, geniculate herpes (herpes zoster oticus), leprosy, leukemia, sarcoidosis, or remain idiopathic. In the newborn, absence of the mastoid processes render the facial nerves on both sides unusually exposed and vulnerable to damage by careless use of obstetrical forceps. Facial nerve damage produces ipsilateral symptoms, which vary dependent upon the site of the lesion. A lesion at or above the level of the geniculate ganglion (as in tumors of the cerebello-pontine angle or in fractures of the internal acoustic meatus) results in the ipsilateral loss of lacrimation and loss of general and special visceral (taste) sensations from the palate. These deficits are due to disruption of the greater petrosal nerve). Taste sensation from the anterior two thirds of the tongue and secretion of the submandibular and sublingual are also lost, due to destruction of the chorda tympani. Hyperacusis (lower hearing threshold) as a result of the destruction of the stapedius nerve and paralysis of all facial muscles of expression, the posterior belly of the digastric, and the stylohyoid muscles may also be visible. Paralysis of muscles of facial expression results in asymmetry of the face, widening of the palpebral fissure, inability to close the eye, loss of the corneal reflex, sagging of the angle of the mouth, and smoothing of facial sulci.

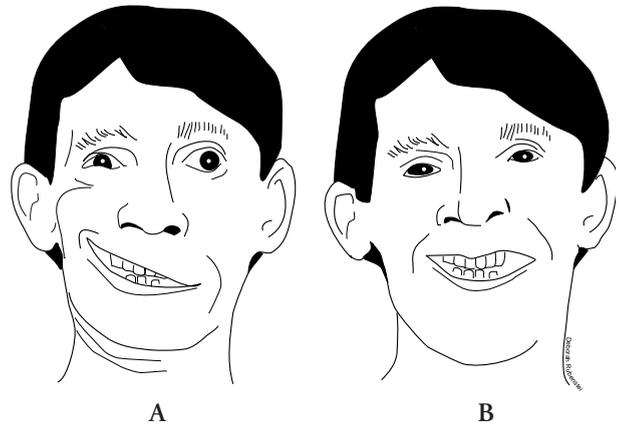


Figure 11.29 Manifestations of supranuclear facial palsy. Note the prominent weakness in the muscles around the mouth when the patient is asked to open the mouth (A) and the retention of these muscles in response to emotional condition (B)

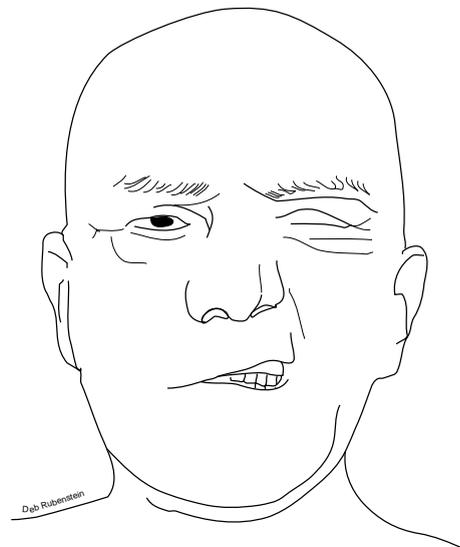


Figure 11.30 Left infranuclear facial palsy. Note the smoothing of the sulci, including the nasolabial sulcus, sagging of the labial commissure on the affected side

The facial motor nucleus (SVE) is located in the tegmentum of the caudal pons, giving rise to the special visceral efferent fibers that encircle the abducens nucleus, forming the facial colliculus. Uniqueness of this nucleus is illustrated in its highly distinctive corticobulbar connections. The part of the facial motor nucleus that provides innervation to the muscles around the mouth and lower face receives only crossed corticobulbar fibers, whereas the part of the nucleus that supplies the muscles around the orbit and the forehead region receives bilateral

Unilateral destruction of the facial motor nucleus produces similar deficits to the lesion that disrupts the facial nerve at or proximal to the geniculate ganglion.

A lesion, immediately distal to the geniculate ganglion, produces all of the above mentioned deficits while preserving lacrimation and taste sensation from the palate. Paralysis of the facial muscles of expression is the only deficit seen in individuals with damaged facial nerve at the stylomastoid foramen. Loss of corneal reflex due to facial nerve damage is observed only on the side of the lesion, regardless of which side is stimulated. Inability to close the eye by the unopposed action of the levator palpebrae superioris, and loss of blinking may increase the potential of corneal irritation or ulceration and may lead to keratitis and possible blindness. This complication may be avoided by placing a patch over the affected eye. The oculo-auricular reflex, which is characterized by posterior movement of the ear when the patient directs his or her gaze as far laterally as possible, is lost in Bell's palsy. Prognosis of this condition depends on the severity of ear pain and the degree of paralysis, and it is poorer in individuals with ear pain and extensive facial palsy.

Bell's palsy is an inflammatory disease of unknown etiology, which results from compression, or inflammation of the facial nerve. It may occur following exposure to cold or a viral infection. This condition, which accounts for about 80% of all cases of facial palsy, may accompany otitis media, mastoiditis and petrositis. It may occur in diabetic patients and pregnant woman. Patients exhibit abrupt or progressive unilateral paralysis of the facial muscles, which may be preceded or accompanied by earache. Glandular secretion, stapedius muscle function, and taste sensation often remain unaffected.

corticobulbar projections. This diverse cortical input accounts for the selective paralysis of the contralateral muscles around the mouth in individuals with unilateral corticobulbar damage, while sparing the muscles around the eye and orbit (Figure 11.27).

Spinal trigeminal nucleus (GSA) receives general somatic sensations from the concha, to be delivered to the ventral posteromedial nucleus of thalamus.

Superior salivatory nucleus (GVE) lies adjacent to the caudal end of the facial motor nucleus in the caudal pons and provides preganglionic parasympathetic fibers to the pterygopalatine and the submandibular ganglia via the greater petrosal and chorda tympani branches, respectively.

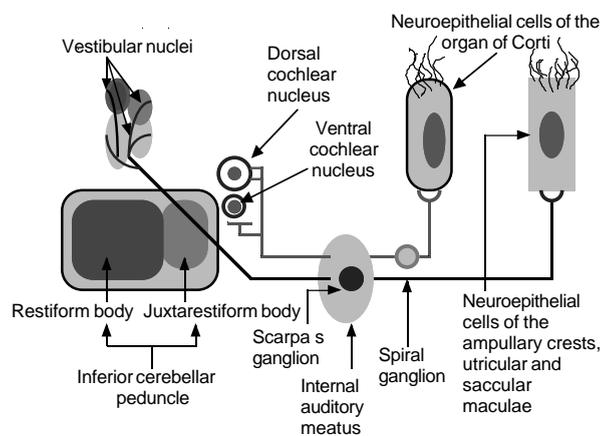


Figure 11.31 In this diagram the vestibular and auditory receptors, associated ganglia, and course of individual nerves are illustrated. The connection of the vestibular nerve to the vestibular nuclei is also shown

Intactness of the vestibular nerve and its connections may be evaluated by instilling cold or warm water (caloric test) or by rotating in the Barany chair. Dysfunction of the vestibular nerve produces ataxia, vertigo, and nystagmus, which are briefly explained below (see also the vestibular system, Chapter 15).

- Ataxia (incoordination of motor activity) is due to vestibular nerve dysfunction and is gravity dependent, severe, and often an intermittent incoordination of limb movement. It becomes apparent during walking and standing.
- Vertigo is a severe sense of rotation of the environment which is frequently intermittent and may be accompanied by oscillopsia (a back and forth movements of the visual objects with downbeat nystagmus), nausea, and vomiting. Vertigo may result in pallor, depression, and falling.
- Nystagmus, an abnormal rhythmic oscillation of the eyeball, is produced visually by watching stationary targets from a moving vehicle (optokinetic nystagmus), or by extreme gaze to one side. It may also be produced iatrogenically by instilling cold or warm water into the ear (caloric test), or rotating in the Barany Chair. Clinically, it may result from peripheral or central vestibular lesions (see the vestibular system).

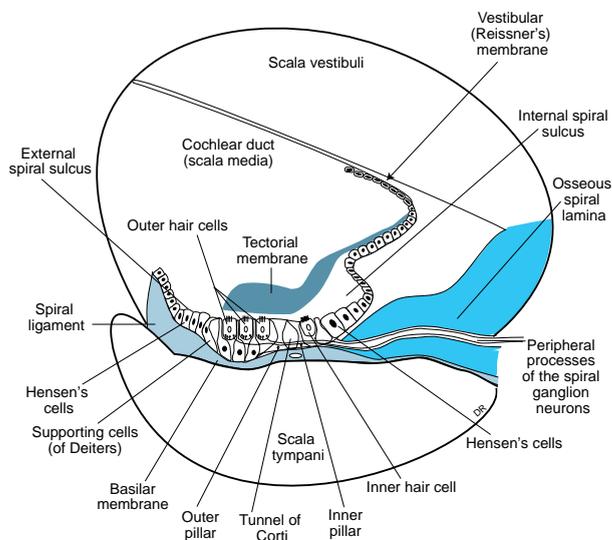


Figure 11.32 In this drawing the neuroepithelial cells within the organ of Corti, spiral ganglia, and course of the cochlear nerve are illustrated

Damage to the cochlear nerve, as a result of acoustic neuroma, Meniere's disease, or fracture involving the petrous temporal bone, produces nerve deafness on the side of the lesion. This type of deafness may be accompanied by tinnitus (ringing of the ear), and is distinguished from conduction deafness by Rinne and Weber tests (see the auditory system, Chapter XIV). Tinnitus, a unilateral or bilateral continuous or intermittent hissing sound, is an important manifestation of cochlear nerve damage. It is often severe enough to interfere with the normal daily activities. Fractures of the posterior cranial fossa, involving the internal acoustic meatus and tumors of the cerebello-pontine angle (acoustic neuroma) may result in combined vestibular, cochlear and facial nerve dysfunctions. This type of injury is characterized by deafness on the side of the lesion, vertigo (sense of rotation of the environment or self), nystagmus, ataxia, and signs of ipsilateral infranuclear facial palsy.

Postsynaptic fibers from these ganglia control the secretion of the lacrimal, submandibular, sublingual glands, and the mucus glands of the palate and pharynx.

Solitary nucleus (SVA) receives taste fibers via the central processes of the geniculate neurons that primarily originate from the anterior two thirds of the tongue. Postsynaptic

fibers from this nucleus terminate in the ventral posteromedial nucleus of thalamus.

VIII Vestibulocochlear nerve

The vestibulocochlear nerve (GSA)-(Figure 11.1) has cochlear (auditory) and vestibular components. The vestibular nerve (SSA)-(Figure 11.31) represents the axons of the bipolar neurons of the superior and inferior vestibular (Scarpa's) ganglia. The dendrites of these neurons pass through foramina in the internal acoustic meatus and eventually distribute to the vestibular receptors in a selective manner. For example, the neurons of the superior vestibular ganglion receive information from the ampullary crests of the anterior and lateral semicircular ducts and the macula of the utricle, whereas the inferior vestibular ganglion receives input from the ampullary crests of the posterior semicircular duct and the macula of the saccule. This nerve leaves the brainstem at the cerebello-pontine angle, accompanied by the facial, cochlear nerves, and the labyrinthine artery. Therefore, combined vestibular and auditory deficits, as well as facial palsy may be seen in pathological conditions involving the internal acoustic meatus or the cerebello-pontine angle (i.e. acoustic neuroma).

The cochlear nerve (SSA) is formed by the central processes of the bipolar neurons of the spiral ganglion, which are located in the modiolus of the cochlea (Figure 11.32). The site of entry of the cochlear nerve into the pons and its course within the internal acoustic meatus are identical to that of the vestibular nerve. The dendrites of the bipolar neurons of the spiral ganglia receive auditory impulses from the organ of Corti (site of auditory neuroepithelial cells) within the cochlea and convey these impulses to the cochlear nuclei in the brainstem.

IX Glossopharyngeal nerve

The glossopharyngeal nerve (GVA, GVE, GSA, SVA, SVE)-(Figures 11.1, 11.33 & 11.34) exits the medulla from the rostral portion of the post-olivary sulcus and leaves the skull through the jugular foramen. It has two ganglia, a superior somatic sensory and an inferior visceral sensory ganglia. This nerve gives off tympanic, carotid sinus, lingual, pharyngeal, tonsillar, muscular, and auricular branches.

The tympanic branch (Jacobson's nerve-GVA) arises from the glossopharyngeal nerve in the jugular foramen, and forms the tympanic plexus. This nerve conveys sensations from the mucosa of the middle ear, auditory tube, and mastoid air cells to the solitary nucleus. The lesser petrosal branch (GVE) carries presynaptic parasympathetic fibers from the inferior salivatory nucleus of the medulla to the otic ganglionic. The carotid sinus

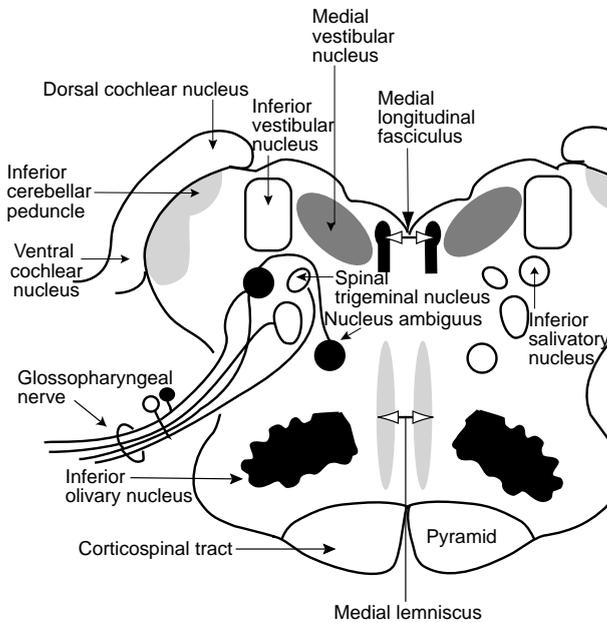


Figure 11.33 The functional components of the glossopharyngeal nerve and related nuclei are shown

branch (GVA) carries baroreceptor information from the carotid artery to the solitary nucleus, mediating the carotid sinus reflex in response to a rise in the blood pressure, an external massage of the carotid sinus in the neck. These stimuli activate the visceral afferent fibers of the glossopharyngeal nerve that establish contacts via interneurons in the reticular formation of the medulla with the dorsal motor nucleus of vagus and simultaneously, with the neurons of the reticulospinal tracts. The dorsal motor nucleus of the vagus sends preganglionic parasympathetic fibers to the cardiac plexus, reducing cardiac contractility (negative chronotropic effect). The medullary reticulospinal tract inhibits or reduces the firing rate of the preganglionic sympathetic neurons that supply the cardiac plexus and the cutaneous arterioles. The decrease in the sympathetic output combined with the vagal inhibition result in a decrease of cardiac rate and output. The decrease in the peripheral vascular resistance leads to a decrease in blood pressure. This reflex is hyperactive in some individuals with vasomotor instability, and in response to a mild stimulus (carotid sinus syncope). Lesions of the glossopharyngeal or the vagus nerves abolish this reflex.

The lingual branch carries special visceral afferents (SVA) and general sensory fibers (GVA) from the posterior one third of the tongue to the solitary nucleus. The pharyngeal (GVA) branch joins the corresponding branches of the vagus nerve to form the pharyngeal plexus that supplies the oropharyngeal mucosa, mediating the pharyngeal (gag) reflex through its connections to the solitary nucleus and nucleus ambiguus, and the vagus

The glossopharyngeal nerve may be damaged in fractures of the posterior cranial fossa and stenosis of the jugular foramen. Demyelination caused by multiple sclerosis, tumors of the posterior cranial fossa, aneurysm of the internal carotid artery, and injuries involving the retroparotid space may also damage this nerve. Occlusion of the posterior inferior cerebellar artery may affect the associated nuclei in the medulla, producing deficits that may also be shared by lesions of the vagus and accessory nerves. Although isolated injury to the glossopharyngeal nerve is rare, the following are some of the conditions associated with irritation, compression or damage to this nerve.

- A lesion that destroys the glossopharyngeal, vestibulocochlear, and vagus nerves, as well as the corticospinal tract may produce signs of Bonnier's syndrome, which is characterized by vertigo, nystagmus, hearing deficits, dysphonia, hoarseness of voice, contralateral hemiplegia, and tachycardia.
- Vernet's syndrome may occur as sequel to fractures of the base of the skull, involving the jugular foramen and its content, which includes the glossopharyngeal, vagus, and the spinal accessory nerves. Disorders of this condition are analogous to the combined deficits associated with these individual nerves.
- Villarreal's syndrome is a condition, which results from injury to the retroparotid space, which involves the glossopharyngeal, vagus, accessory, and hypoglossal nerves. Sympathetic postganglionic fibers may also be disrupted in this condition, resulting in Horner's Syndrome.
- Glossopharyngeal neuralgia is a rare condition, which is characterized by spontaneous attacks of excruciating pain in the tonsillar area, posterior third of the tongue, and the external acoustic meatus, radiating to the throat, side of the neck, and the back of the lower jaw. It is provoked by yawning, laughing, chewing, or by swallowing of particularly cold liquid, and may be associated with peritonsillar abscess, oropharyngeal carcinoma, and ossified stylohyoid ligament. It is rarely bilateral and it may accompany trigeminal neuralgia. When ear pain is felt without signs of middle ear disease, oropharyngeal cancer must also be considered. This condition may be associated with episodes of fainting, syncope, and reflex bradycardia as a result of involvement of the carotid sinus nerve.

Table 11.2 Cranial nerves VII-IX

<i>Cranial nerve</i>	<i>Component</i>	<i>Location of cell bodies</i>	<i>Course</i>	<i>Distribution</i>	<i>Function</i>
VII. Facial nerve	S.V.E.	Facial motor nucleus.	Internal auditory meatus, facial canal & stylomastoid foramen	Facial muscles of expression, stylohyoid, stapedius & posterior belly of digastric	Facial expression & increase hearing threshold & elevation of hyoid bone
	G.V.E.	Superior salivatory nucleus	Within the intermediate nerve via the internal auditory meatus; then via greater petrosal & pterygoid canal nerves to the pterygopalatine ganglion	Lacrimal gland, mucus glands of palate, pharynx & nasal cavity	Parasympathetic
	S.V.A.	Geniculate ganglion	Same as above	Via chorda tympani to anterior 2/3 of the tongue	Taste
	G.S.A.	Geniculate ganglion	Via auricular branch	Concha of ear	General somatic sensation
VII. Vestibulo-cochlear nerve					
Cochlear nerve	S.S.A	Spiral ganglion	Internal acoustic meatus	Organ of Corti	Audition
Vestibular nerve	S.S.A	Scarpa's ganglion	Same as above	Receptors in the semicircular canals, utricle & saccule	Balance, orientation in three dimensions & fixation of gaze
IX. Glosso-pharyngeal nerve	G.V.E.	Inf. salivatory nucleus	Jugular foramen	Parotid gland	Parasympathetic
	S.V.E.	Nucleus ambiguus	Jugular foramen	Stylopharyngeus	Swallowing
	G.V.A.	Inferior ganglion	Same as above	Carotid sinus & body; Posterior 1/3 of the tongue, oropharynx, palatine tonsils, and tympanic membrane	Baroreceptor & chemoreceptor; pain & temperature Sensations from the mucosa of these areas
	S.V.A.	Inferior ganglion	Same as above	Posterior 1/3 of the tongue	Taste
	G.S.A.	Superior ganglion	Same as above	Retro-auricular	General sensations

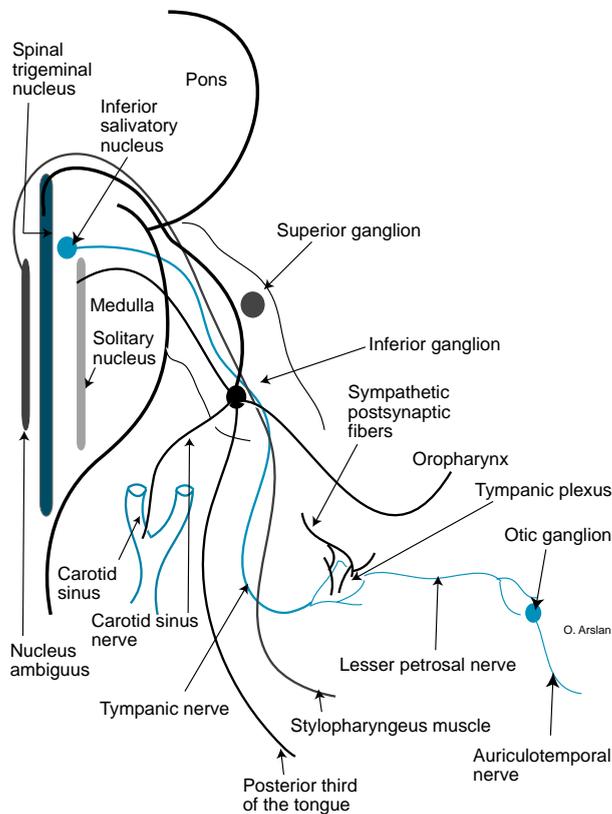


Figure 11.34 Functional components, branches, and associated nuclei of the glossopharyngeal nerve

nerve. The gag reflex is characterized by elevation of the stimulated part of the soft palate, and is elicited by light stimulation of the oropharynx and soft palate. Unilateral loss of gag reflex may indicate damage to the glossopharyngeal nerve or the vagus nerve and may be observed in lateral medullary syndrome. In the elderly, this reflex may be reduced on both sides or may be absent. The tonsillar branch (GVA) carries sensations from the palatine tonsils, fauces, and soft palate to the solitary nucleus. This branch may over-activate in glossopharyngeal neuralgia. The muscular branches (SVE) arise from the ambiguus nucleus and supply the stylopharyngeus muscle, while the auricular branch (GSA) carries general sensation from the retro-auricular area, terminating in the spinal trigeminal nucleus.

Nuclei of the glossopharyngeal nerve

The nuclei associated with the glossopharyngeal nerve (Figures 11.33 & 11.34) are comprised of the nucleus ambiguus, solitary, spinal trigeminal, and inferior salivatory nuclei.

The nucleus ambiguus (SVE) is located in the medulla and provides special visceral efferent fibers that supply the

stylopharyngeus muscle. It also provides fibers to the cranial part of the accessory nerve and to the vagus nerve, innervating the laryngeal, pharyngeal, and palatine muscles. Damage to these nucleus results in deviation of the uvula to the intact side, a unique feature of this lesion.

The solitary nucleus receives taste (SVA) sensations from the posterior 1/3 of the tongue and general visceral sensations (GVA) from the carotid sinus, and pain and temperature sensations from the middle ear, posterior 1/3 of the tongue, oropharynx, and the tonsils.

The spinal trigeminal nucleus (GSA) receives cutaneous sensation from the retro-auricular area.

The parasympathetic fibers from the inferior salivatory nucleus (GVE) are conveyed to the otic ganglion, which eventually innervate the parotid gland.

X. Vagus nerve

The vagus (Figures 11.1, 11.35 & 11.36), as in the case of the glossopharyngeal nerve, is a composite nerve with diverse functional entities. It travels ventrolaterally in the caudal medulla through the spinal trigeminal tract and nucleus and adjacent to the nucleus ambiguus and spinal lemniscus. Therefore, the vagus nerve and associated nuclei may be damaged by a single lesion in the lateral medulla, producing signs and symptoms of Wallenberg's or lateral medullary syndrome, which exhibits dysphagia, dysphonia, alternating hemianesthesia. This nerve leaves the medulla via the post-olivary sulcus, as a series of rootlets and exits the skull through the jugular foramen, accompanied by the glossopharyngeal and accessory nerves. Then, it runs through the neck as the posterior component of the carotid sheath. During its course in the superior and posterior mediastina, it gives rise to branches to the cardiac and pulmonary plexuses. Later, the vagus nerves on both sides contribute to the formation of the anterior and posterior vagal trunks around the abdominal part of the esophagus, entering the abdomen through the esophageal hiatus of the diaphragm. In the abdomen, it contributes presynaptic parasympathetic fibers to the celiac, superior mesenteric, and aortic plexuses. The vagal (parasympathetic) contribution to the abdominal viscera terminates at the junction of the right two-thirds and left one third of the transverse colon. The vagus nerve has a superior and inferior ganglia, containing neurons for somatic and visceral sensations, respectively. Within this nerve, the motor fibers belong to the cranial part of the accessory nerve, which distribute to the laryngeal, pharyngeal, and palatal muscles.

Through its course, the vagus nerve gives rise to branches in the cranial cavity, thorax, and abdomen, which include the meningeal, auricular, pharyngeal, carotid body, superior and inferior laryngeal, cardiac, pulmonary, esophageal, celiac, and superior mesenteric branches.

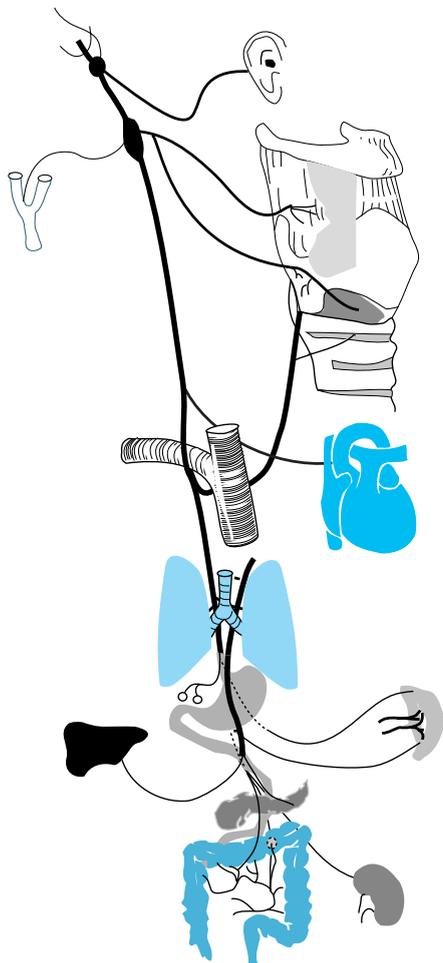


Figure 11.35 The origin, course, and distribution of branches of the vagus nerve

- The meningeal branch (GSA) conveys sensations from the dura mater of the posterior cranial fossa to the spinal trigeminal nucleus. In the same manner, the auricular branch (GSA) carries somatic sensations from the external acoustic meatus to be conveyed to the spinal trigeminal nucleus.
- The pharyngeal branch (SVE) consists of the cranial part of the accessory nerve that contributes to the formation of the pharyngeal plexus. Through this plexus the vagus nerve innervates most of pharyngeal muscles (with the exception of the stylopharyngeus) and palatine muscles with the exception of the tensor palatini. Branches that distribute to the epiglottic vallecula (SVA) convey taste sensations to the solitary nucleus.
- Branches to the carotid body (GVE) arise from the inferior ganglion and course as a component of the pharyngeal branch and very rarely run within the superior laryngeal branch, transmitting signals about the changes in the level of carbon dioxide and oxygen tension. These fibers join the pharyngeal branches of the

Vagal trunks may selectively be severed in vagotomy, a surgical procedure used in the treatment of chronic gastric or duodenal ulcers. This surgical approach is intended to greatly reduce hydrochloric acid secretion and thus enhance healing of the affected part of the gastrointestinal tract. It may be classified into truncal, selective and high selective vagotomy. Truncal vagotomy may not desirable due to the accompanied gastric stasis (dumping), atonia of the gallbladder, and impaired pancreatic secretion. In selective vagotomy, although the gastric branches of the vagus nerve, including nerves of Latarjet to the antrum, are specifically cut, gastric dumping occurs, requiring surgical bypass. In high selective vagotomy only the branches to the fundus and body of the stomach (acid secreting areas) are cut and gastric dumping is thus avoided. This procedure may also induce atrophy of the oxyntic cells, rendering it unresponsive to the circulating gastrin.

glossopharyngeal nerve and the cervical part of the sympathetic trunk, to form the pharyngeal plexus.

- The superior laryngeal branch (GVA, SVE) divides into an internal (sensory) and an external (motor) laryngeal branches. The internal laryngeal nerve (GVA, SVA) accompanies the superior laryngeal vessels in its course in the medial wall of the piriform recess, and distribute branches to the laryngeal mucosa of the vestibule, laryngeal sinus, and the epiglottic vallecula. This branch carries general sensations (GVA) from the laryngopharynx, piriform recess, and most of the laryngeal mucosa to the solitary nucleus. Taste sensation from the extreme posterior part of the tongue and the epiglottic vallecula is also conveyed by this nerve to the solitary nucleus. The external laryngeal nerve (SVE) emanates from the nucleus ambiguus and provides motor fibers to the cricothyroid muscle.
- The inferior (recurrent) laryngeal nerve (GVA, SVE) encircles the subclavian artery on the right side and the aortic arch on the left side and courses medial to the ligamentum arteriosum. This nerve carries general visceral sensation (GVA) from the infraglottic part of the larynx. During its course within the tracheo-esophageal sulcus and medial to the thyroid gland, this nerve runs in close proximity to the inferior thyroid artery, a relationship that bears important clinical significance in thyroidectomies
 - The cardiac branches contribute parasympathetic fibers (GVE) to the deep and superficial cardiac plexuses, with the superficial part of the plexus receiving innervation from the left vagus, and the deep part receiving branches from the right vagus and the recurrent laryngeal nerves. These fibers slow the heart rate and produce constriction

The vagus nerve is prone to damage in fractures of the posterior cranial fossa, involving the jugular foramen, or by an aneurysm of the common or internal carotid artery. Unilateral lesion of the vagus nerve results in slight difficulty in swallowing (dysphagia) and breathing (dyspnea), accompanied by regurgitation of food through the nasal cavity. It also produces hoarseness and a voice with nasal quality, transient tachycardia, loss of gag reflex, and deviation of the uvula toward the intact side on phonation. In unilateral vagal dysfunction, no consistent deficits are associated with the heart, lungs, or bowel functions. Bilateral disruption of the vagus nerves results in a serious condition which manifests cardiac arrhythmia, severe difficulty in breathing, dysphagia, dysphonia, abdominal pain, and stomach distention.

Emotional stress, crowded environment, and warmth often precipitate a common condition known as vasovagal syncope. It is characterized by sweating, an aura of nausea, and loss of consciousness. It is similar to the reflex vasovagal syncope in which fainting spell is caused by venipuncture. Asking the patient to say "AH", producing elevation of the soft palate (uvular or palatal reflex) tests intactness of the vagus nerve. The uvular (palatal) reflex is characterized by equal and symmetrical movement of the soft palate and elevation of the uvula, upon stimulation of the mucosa of the soft palate or during phonation. It is mediated by the glossopharyngeal and vagus nerves.

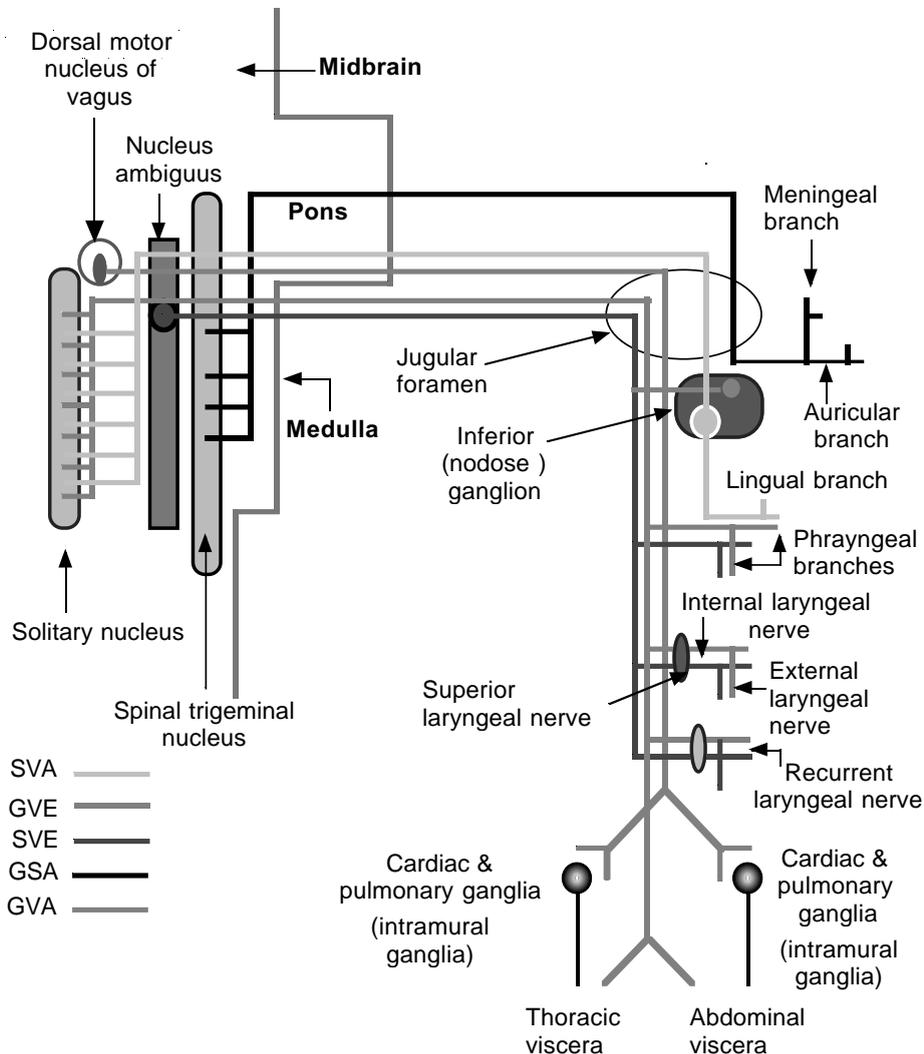


Figure 11.36 Complete descriptive diagram of the vagus nerve, nuclei, and areas of distribution

A specific lesion of the superior laryngeal nerve produces anesthesia in the mucus membrane of the vestibule and the laryngeal sinus. Tension in the affected vocal folds is lost, resulting in a monotonous voice. On the other hand, the recurrent laryngeal nerves are prone to damage in thyroidectomy upon ligation of the inferior thyroid arteries that maintain close relationships to these nerves. The left recurrent laryngeal nerve may also be damaged in an aneurysm of the aortic arch, as a result of bronchial and esophageal carcinoma, or in conditions which produce enlargement of the mediastinal lymph nodes. According to Semon's Law, progressive lesions of the recurrent laryngeal nerve produce dysfunction in the abductors of the vocal folds before any significant deficits in the adductors. In contrast, the recovery involves the adductor muscles first followed by the abductors of the vocal cords. Unilateral damage to the recurrent laryngeal nerve results in paralysis of the intrinsic laryngeal muscles with the exception of the cricothyroid, as well as ipsilateral loss of sensation from the infraglottic part of the larynx. Initially, the voice is weak and altered (like a whisper), but movement of the opposite vocal fold toward the midline may compensate for this deficit, rendering the voice fairly normal. The external laryngeal branch may be destroyed in ligation of the superior thyroid artery, producing paralysis of the cricothyroid muscle and monotonous voice.

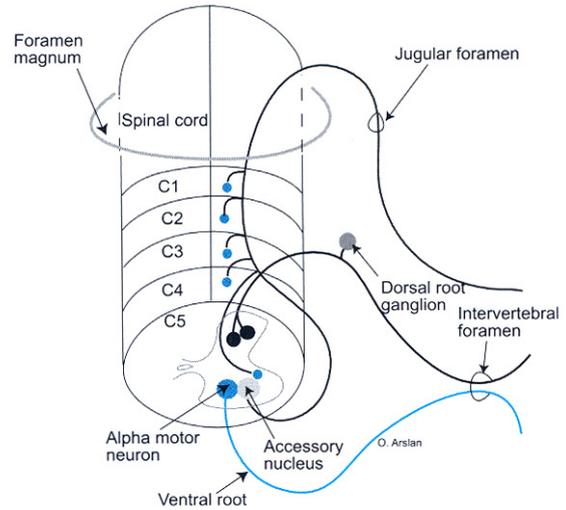


Figure 11.38 Drawing of the spinal accessory nerve, its origin, course and areas of distribution are visible

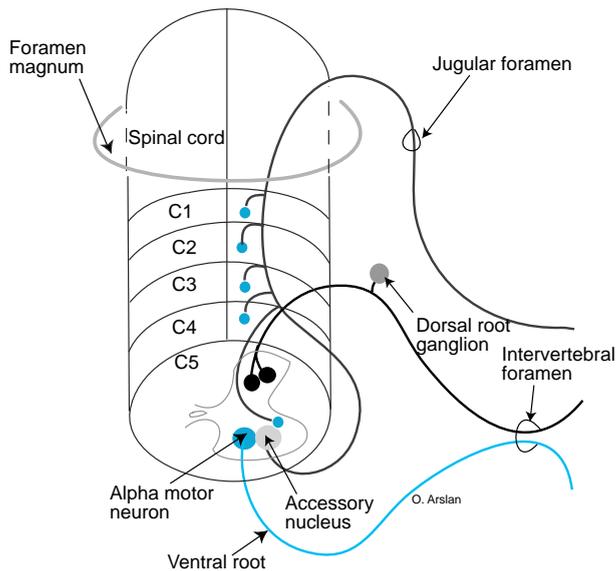


Figure 11.37 Drawing of the medulla at the level of the vagus nerve showing the associated nuclei and ganglia

The accessory nerve is vulnerable to damage in radical neck dissection; a fairly common surgical procedure employed in metastatic carcinomas of the neck. The pressure exerted by calcified tuberculous cervical lymph nodes, or surgical attempts to remove these nodes may also damage the spinal accessory nerve. A stab wound in the neck, fractures of the foramen magnum or jugular foramen may also injure the accessory nerve. In addition, it may be damaged when the facemask of a football player is suddenly pulled laterally. Irritation of the spinal accessory nerve may lead to torticollis (Figure 11.39), a spasmodic contracture of the sternocleidomastoid muscle. Damage to the spinal accessory nerve may lead to paralysis of the trapezius and sternocleidomastoid muscles. Paralysis of the trapezius muscle results in winging of the scapula, which becomes more prominent upon attempt to abduct the arm on the affected side. This fact distinguishes winging of the scapula observed in long thoracic nerve damage versus accessory nerve damage. Paralysis of the sternocleidomastoid produces inability to turn the face to the opposite side.



Figure 11.39 This is a depiction of a patient with right side torticollis due to spasmodic contracture of the sternocleidomastoid muscle

To test the integrity of the spinal accessory nerve, the trapezius and sternocleidomastoid functions are tested. To check intactness of the trapezius muscle, the patient is asked to shrug his shoulders against resistance. To test the sternocleidomastoid muscle, the patient is asked to turn his head to one side against resistance by the examiner.

of the coronary arteries. They also carry general visceral sensation (GVA) from the heart.

- The pulmonary branches are broncho-constrictors and secretomotor (GVE) to the bronchial mucus glands, which run within the pulmonary plexus. They also carry information from stretch receptors (GVA) from the pulmonary bronchi.

- The esophageal branches carry parasympathetic preganglionic (GVE) fibers that facilitate esophageal motility, as well as general visceral sensation (GVA) from the esophagus. These branches form the esophageal plexus and continue to the abdomen around the esophagus as the anterior and posterior vagal trunks. The anterior vagal trunk is formed primarily by the left vagus, while the posterior vagal trunk is principally derived from the right vagus.

- Branches to the celiac and superior mesenteric plexuses provide parasympathetic (GVE) fibers to the stomach, small intestine, cecum, ascending colon, and the right two

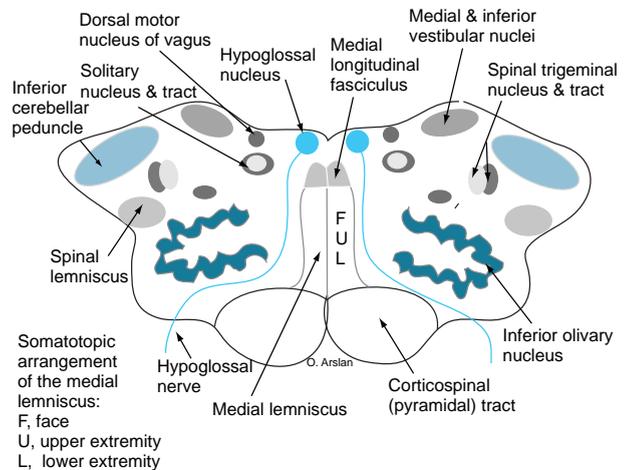


Figure 11.40 In this section of the medulla at the mid-olivary level, the hypoglossal nuclei and nerves are shown. Observe the course of the hypoglossal nerve lateral to the medial lemniscus and between the pyramid and the inferior olivary nucleus

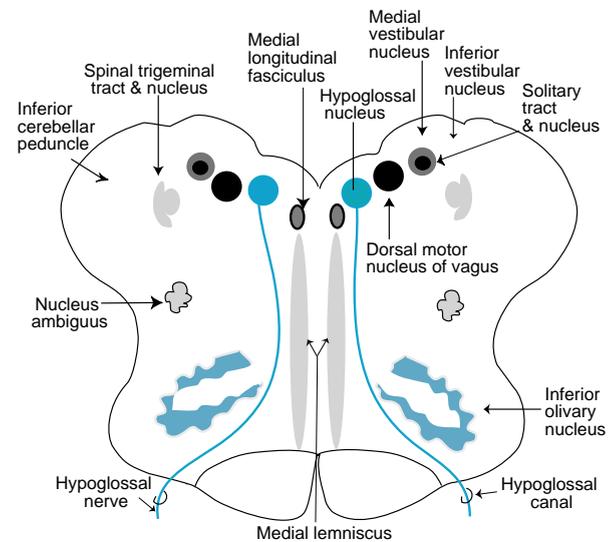


Figure 11.41 This is a drawing of an individual with right hypoglossal nerve palsy

thirds of the large intestine. It also provides general visceral afferent (GVA) fibers, conveying sensory modalities of hunger, nausea, thirst, and bowel fullness to the solitary nucleus.

Nuclei associated with the vagus nerve

The vagal nerve nuclei include the dorsal motor nucleus of vagus, nucleus ambiguus, solitary nucleus, and the spinal trigeminal nucleus (Figures 11.36 & 11.37).

A unilateral lesion of the hypoglossal nerve (Figure 11.42) may produce ipsilateral atrophy of the lingual muscles and deviation of the tongue toward the lesion side upon protrusion. On retraction, the atrophied part of the tongue rises up higher than the other parts. Bilateral lesion of the hypoglossal nerves results in defective speech and difficulty in chewing. The tongue lies motionless and thus swallowing becomes very difficult, forcing the patient to extend his head back and push the bolus of food into the pharynx with the aid of his or her fingers. The hypoglossal and ambiguus nuclei may selectively be damaged in individuals with Tapia syndrome, which is characterized by paralysis of the muscles of the soft palate, posterior pharyngeal wall, vocal cords, and lingual muscles.



Figure 11.42 This is a drawing of an individual with right hypoglossal nerve palsy

- The dorsal motor nucleus of the vagus (GVE) occupies the area dorsolateral to the hypoglossal nucleus, forming the vagal trigone in the floor of the fourth ventricle. This nuclear column maintains similar dimensions to the hypoglossal nucleus both caudally and rostrally, providing parasympathetic preganglionic (GVE) fibers to the thoracic and abdominal viscera.

- The nucleus ambiguus (SVE) provides special visceral motor fibers that innervate the muscles of pharynx, larynx and soft palate.

The solitary nucleus receives general visceral (GVA), which constitute nearly 80% of the entire vagus nerve, from the bronchi, gastrointestinal tract, and the carotid

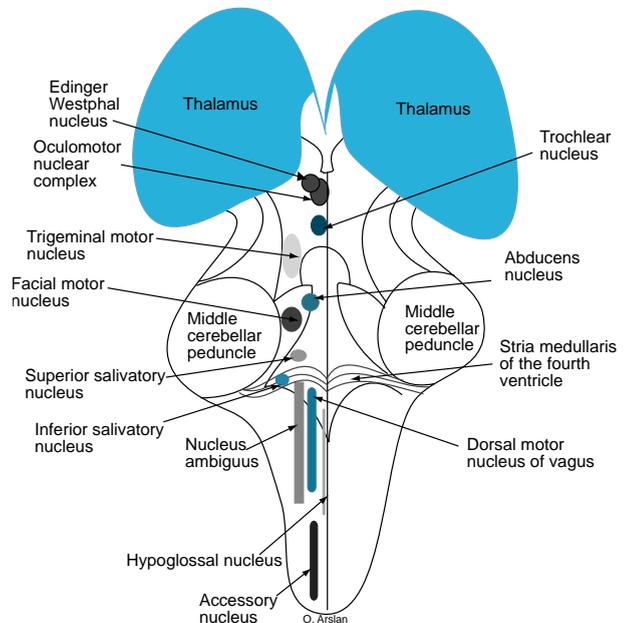


Figure 11.43 Diagram of the somatic and autonomic efferent nuclei of the cranial nerves

body. It also receives special visceral afferents (SVA-taste) from root of the tongue and epiglottic vallecula. These afferents are conveyed to the ventral posteromedial nucleus of thalamus en route to the sensory cortex.

- The spinal trigeminal nucleus (GSA) receives general somatic sensations from the external acoustic meatus, concha of the ear, and the dura mater of the posterior cranial fossa.

XI Accessory nerve

The accessory nerve (Figure 11.38) has a cranial part (SVE), which is derived from the ambiguus nucleus (Figures 11.42), and a spinal part that originates from the upper five spinal segments (Figure 11.37). The cranial part joins the vagus nerve, distributing through its branches to the muscles of the larynx and pharynx. The spinal part forms the spinal accessory nerve, enters the cranial cavity through the foramen magnum (Figure 11.15), and leaves the skull through the jugular foramen. It courses through the posterior triangle and innervates the sternocleidomastoid and the trapezius muscles.

XII Hypoglossal nerve

The hypoglossal nerve (Figures 11.40), which is derived from neuronal axons of the hypoglossal nucleus (GSE) of the medulla, descends within the reticular formation, lateral to the medial lemniscus, and between the inferior

Table 11.3 Cranial nerves X-XII

<i>Cranial nerve</i>	<i>Component</i>	<i>Location of cell bodies</i>	<i>Course</i>	<i>Distribution</i>	<i>Function</i>
X. Vagus	G.V.E.	Dorsal motor nucleus of vagus	Jugular foramen	esophageal, bronchial & muscles of the small intestine & right half of the large intestine	Secretomotor to the glandular tissue and motor to the intestinal wall
	S.V.E.	Nucleus ambiguus	Same as above	most muscles of the soft palate, pharynx & larynx	Movements of muscles of the soft palate, pharynx & larynx during deglutition. respiration & phonation.
	G.V.A.	Inferior (nodose) ganglion	Same as above	Visceral sensations from the pharynx, larynx, bronchi, aortic arch & body, most of the digestive tract including the right 2/3 of large intestine	Visceral sensations; chemo-receptor & pressure changes
	G.S.A.	Superior (jugular) ganglion	Same as above	External auditory meatus & auricle	Cutaneous sensibility
	S.V.A.	Inferior (nodose) ganglion	Same as above	taste sensation from epiglottic vallecula	Taste
XI. Accessory nerve	S.V.E.	Nucleus ambiguus	Jugular foramen	within branches of the vagus to pharyngeal & laryngeal muscles	Swallowing & phonation
	G.S.E.	Upper five spinal segments	Foramen magnum rostrally; exit via jugular foramen	Trapezius & sternocleidomastoid muscles	Elevation of scapula & shoulder point; turning the face upward & to the opposite side
XII. Hypoglossal	G.S.E.	Hypoglossal nucleus	Hypoglossal canal	Intrinsic & extrinsic muscles of the tongue	Change the shape of the tongue & maintain its movement

olivary and the pyramidal tract. The hypoglossal nucleus (Figures 11.40, 11.42) extends from the level of the stria medullaris to an area near the upper pole of the inferior olivary nucleus. Due to its proximity to the medial lemniscus and the pyramids, a single lesion may producing signs of medial medullary syndrome or inferior alternating hemiplegia, dependent upon the extent of the damage. It emerges from the medulla at the preolivary sulcus leaves the skull through the hypoglossal canal and runs in the occipital and carotid triangles, encircling the occipital branch of the external carotid artery. In the neck, a branch

of the first cervical spinal segment joins the hypoglossal to later leave as the superior root of the ansa cervicalis. All intrinsic and extrinsic lingual muscles, with the exception of the palatoglossus (innervated by the pharyngeal plexus), receive motor innervation from the hypoglossal nerve.

Table 11.4 Cranial nerves somatic and autonomic components

<i>Nerve</i>		<i>Afferent</i>		<i>Efferent</i>		
				<i>Parasympathetic ganglia</i>	<i>Somatic</i>	<i>Brachial</i>
I	Olfactory	+	Bipolar neurons in the olfactory mucosa	None	None	None
II	Optic	+	Extension of CNS	None	None	None
III	Oculomotor		None	Ciliary	+	None
IV	Trochlear		None	None	+	None
V	Trigeminal		Trigeminal, (semilunar or Gasserian) ganglion	None	None	+
VI	Abducens		None	None	+	None
VII	Facial	+	geniculate	Pterygopalatine & submandibular ganglia	None	+
VIII	Vestibulo-cochlear	+	Scarpa's & spiral ganglia	None	None	+
IX	Glossopharyngeal	+	Superior & inferior ganglia	Otic ganglion	None	+
X	Vagus	+	Superior & inferior ganglia	Intramural ganglia	None	+
XI	Accessory		None	None	None	+
XII	Hypoglossal	XII	None	None	+	None

Classical neurotransmitters are small molecules of neuroactive agents actively involved in synaptic transmission and modulation. They are synthesized in the neurons and are released at the presynaptic terminals in sufficient amounts to affect the membrane potential or conductance of the postsynaptic neurons, producing inhibition or excitation. Their effect is commonly associated with the selective opening of specific ion channels in the postsynaptic membrane/and or phosphorylation of intracellular protein. They may bind directly to a receptor and cause second messenger mediated changes in the neurotransmission. Exogenous administration of neurotransmitters may mimic the actions of the endogenous transmitters. Certain neurotransmitters may be released after a more sustained activation. Inactivation of these agents may occur locally at the terminals by enzymatic uptake and degradation, or diffusion and release. Some neurotransmitters do not act upon postsynaptic membrane but affect its response to other neuromediators by enhancing or inhibiting their activities. Classical (small-molecule) neurotransmitters are comprised of amino acid neurotransmitters, acetylcholine and biogenic amines.

Peptidergic neurotransmitters are scattered in the peripheral, central, and enteric nervous systems, and their synthesis is regulated by mRNA and ribosomes at the soma or dendrites. They are derived from inactive prohormone which is cleaved by certain proteolytic enzymes. Peptidergic neurotransmitters are organized structurally into families and many are neurohormones which are synthesized in neurons and released into the blood circulation, CSF, or into the intercellular space by exocytosis.

Amino acid neurotransmitters

GABA

Glycine

Glutamic acid

Acetylcholine

Monoamines

Catecholamines

Indolamines

Neuropeptides

Amino acid neurotransmitters

Amino acid neurotransmitters comprise gamma-aminobutyric acid (GABA) and glycine as proven inhibitory neurotransmitters, glutamate and aspartate as putative stimulatory neurotransmitters. Others such as proline, serine, and taurine, await further study to be considered as neurotransmitters. For our purposes we will be dealing with the first group only.

Gamma-amino-butyric acid (GABA)

Gamma-Amino-Butyric Acid (GABA) is the major inhibitory neurotransmitter in the brainstem, spinal cord and Purkinje neurons of the cerebellum. It induces depolarization predominantly in the spinal cord and hyperpolarization in the cortical cells. It acts by increasing the permeability of postsynaptic membrane to chloride. GABA is produced via an irreversible reaction of L-glutamic acid and glutamic acid decarboxylase (GAD), utilizing pyridoxal phosphate (a form of vitamin B6) as a cofactor. Substantial increase in the postmortem level of GABA may be attributed to the transient activation of the glutamic acid decarboxylase.

GABA is metabolized principally by GABA transaminase (GABA-T), an extensively distributed enzyme, which binds to pyridoxal phosphate, and may be inhibited by gabaculine. Transamination of GABA produces succinic semialdehyde, which is later reduced to g-hydroxybutyrate (GHB).

GABAergic neurons are scattered in high concentrations in many brain areas such as the lateral geniculate nucleus, Purkinje cell axons that project to the lateral vestibular and the cerebellar nuclei, and also in the striatal neurons that convey impulses to the substantia nigra and cortical neurons. Most interneurons are GABAergic such as the amacrine and horizontal cells of the retina. GABAergic neurons are lacking or found in trace amounts in the peripheral nervous system. The highest concentrations of GABA are found in diencephalon, whereas lower

Substances that decrease the amount of pyridoxine (hydrazides) or inhibits its action (e.g. sulfhydryl reagents, chloride, etc.) may repress the action of GABA and subsequently induce reversible epileptic seizures. Experimentally, localization of glutamic acid decarboxylase may be of value in determining the concentration of GABA. Development of autoantibodies against glutamic acid decarboxylase may be associated with Stiff-man syndrome, a rare chronic neurological condition that exhibits progressive, and fluctuating muscle spasm and atrophy.

Increased levels of GHB subsequent to a deficiency of succinic semialdehyde dehydrogenase may occur as a manifestation of congenital disorder of GABA metabolism, producing dementia and ataxia.

Deficiency of succinic semialdehyde dehydrogenase may produce mental retardation, cerebellar disorders including hypotonia. These patients excrete copious amounts of both succinic semialdehyde and 4-hydroxybutyric acid. Deficiency of GABA-T produces deep tendon hyperreflexia, psychomotor retardation and increased height. The latter effect may be attributed to the ability of GABA to enhance release of growth hormones.

concentrations are localized in the cerebral hemispheres and brainstem.

Depolarization of the presynaptic neurons stimulates the release of GABA at the synaptic clefts. Reuptake into both presynaptic terminals and surrounding neuroglial cells terminate the action of GABA. Temperature and ion-dependent transport systems maintain this reuptake. In contrast to nerve terminals, GABA taken up into glial cells can not be utilized, but instead it may be metabolized to succinic semialdehyde by GABA-T. The semialdehyde is oxidized to succinate via succinic semialdehyde dehydrogenase.

Glial GABA may be recovered via the Krebs cycle where it is converted to glutamine. Glutamine is transferred to

Blockage of GABAergic cortical neurons may be responsible for inducing convulsions and maintaining myoclonus. It has been suggested that lack of GABA in the substantia nigra, putamen, and caudate nucleus, subsequent to degeneration of the GABAergic neurons, may be associated with the involuntary choreiform movements observed in Huntington's disease. Additionally, overactivity of GABAergic neurons, which exert inhibitory effect on dopaminergic nigral neurons, is thought to have a role in producing some of the signs and symptoms of Parkinson's disease. Also, the toxin of clostridium tetani may bind to the presynaptic GABAergic cells of the alpha motor neurons of the spinal cord and brainstem, blocking the release of GABA. Inactivation of GABA blocks the inhibitory influences on the motor neurons, resulting in muscle spasm, rigidity, locked-jaw, dysphagia, and opisthotonos.

GABA-a receptors show binding sites for benzodiazepine and comprises a group of anxiolytic drugs that act particularly on GABA-a-g2. Barbiturates (e.g. phenobarbital) and anti-epileptic drugs act on GABA-a-a and GABA-a-b receptors. These drugs increase chloride current and the duration of channel opening induced by GABA. GABA-a receptors are also the major molecular target for the volatile anesthetics and possibly ethanol. Neuroactive steroids (analogs of the progesterone and corticosterone derivatives) may exert anti-anxiety, sedative and hypnotic effects via their potent modulatory effects of GABA-a receptors.

neurons where it is converted by glutaminase to glutamate, which re-enters the GABA shunt.

Overactivity of GABA produces an inhibitory effect on dopaminergic neurons by producing hyperpolarization at the postsynaptic level in the cerebral cortex and hyperpolarization at the presynaptic level in the spinal cord.

GABA receptors are localized in the neuronal cell membranes as well as astrocytes and are classified into GABA-a and GABA-b. The GABA-a receptors are more common than GABA-b and belong to the same superfamily of ligand-activated receptors as the nicotinic-acetylcholine receptors. They are G-protein coupled ionotropic receptors that comprise a, b, g, d, and r subunits with additional subtypes. The r subunit in particular is abundant in the retina.

GABA-b receptors encompass two principal types of receptors that differ in regard to location. They are coupled indirectly to calcium and potassium channels via second messenger systems (G-proteins). Inhibitory response of these receptors is produced, at both presynaptic and postsynaptic levels by increased potassium or decreased calcium conductance and inhibition of cAMP production. Receptor antagonists such as picrotoxin block GABA-b receptors, which mediate postsynaptic inhibitory potentials (IPSPs). They have selective affinity to baclofen, a GABA-analog (b-(4-chloro-phenyl)-g-aminobutyric acid), which releases intracellular GABA but not to bicuculline, and are not affected by benzodiazepine (e.g. Valium & Librium) or barbiturates (e.g. phenobarbital). Both groups of drugs increase GABA-induced chloride current either by intensifying the frequency of channels opening or prolonging its duration.

Some investigators suggest that improved cognitive ability may be achieved by blocking the GABA-b receptors that increase GABA and neuronal excitability of hippocampal neurons and thus improve memory encoding.

Glycine

Glycine, the simplest of all amino acids in structure, is formed from serine in a reaction catalyzed by serine trans-hydroxy-methylase. It may also be formed by transaminase reaction with glutamate. Glycine is an essential component in the metabolism of peptides, proteins, nucleic acids, and porphyrins. Transmitter glycine potentiates synaptic activity by hyperpolarizing the membrane and increasing chloride permeability. Its inhibitory action is similar to that of GABA, but mainly restricted to the spinal motor neurons and interneurons. It can be blocked by strychnine and not by bicuculline or picrotoxin. Glycine is found in high concentrations within the interneurons of the ventral horn of the spinal cord. It is released from the presynaptic terminals of primary afferent fibers of retina, pons, and medulla. It has been shown that glycine has a role in both increasing the frequency of NMDA (N-Methyl-D-Aspartate) receptor channel opening and also preventing desensitization of these receptors, without involving the glycine receptors. b-Alanine, taurine, L-alanine, L-serine and proline activate glycine receptors.

Glutamic Acid

Glutamic acid, the most abundant amino acid in the central nervous system, is a precursor for GABA, and a short acting excitatory neurotransmitter. This neurotransmitter is involved in the formation of peptides, and proteins as well as detoxification of ammonia in the cerebral cortex. The L-glutamate form of this neurotransmitter is synthesized in the nerve terminals via the Krebs cycle and transamination of a-oxyglutarate and also from glutamine in the glial cells. Glial cells and nerve endings release glutamic acid via a calcium dependent exocytotic process. It has been found to have a powerful depolarizing effect on the neurons in all areas of the central nervous system. The sensitivity of glutamate receptors to glutamate agonists N-methyl D-aspartate (NMDA) is utilized as a basis in the classification of ionotropic glutamate receptors into NMDA and non-NMDA receptors. There are also metabotropic glutamate

The delay in muscle relaxation following voluntary contraction or percussion is seen in myotonia, a condition that exhibits abnormally slow relaxation of the skeletal muscles following active contraction. These changes are ascribed to the decrease in chloride conductance caused by reduction of glycine at synaptic clefts and its excretion in urine. Spasticity in antigravity muscles and hyperreflexia observed in upper motor neuron palsies are also thought to be mediated by glycine.

receptors, which exerts effects via G-protein. Neuronal dysfunctions associated with anoxia, seizures or hypoglycemia may be due to the disproportionate inflow of calcium ions through the NMDA receptor channels and dramatic sustained increase in the level of glutamate (excitotoxicity). Anoxia impairs the sodium/potassium pump by reducing the ATP, which is followed by excessive increase in the level of potassium concentration in the extracellular space, promoting depolarization of neurons and inhibiting glutamate uptake and its release by reversing the glutamate transporter. This positive feedback system leads to a dramatic increase in the extracellular glutamate concentration. During this process vast influx of sodium ions via both NMDA and NON-NMDA receptor channels may enhance cellular necrosis by increasing the water content of the neuron (cytotoxic edema). Calcium ions gain access through NMDA receptors and voltage-dependent calcium channels and possibly via AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid). Therefore, glutamate receptor antagonists, calcium channel blockers, and antioxidants can achieve suppression of calcium influx. Glutamate produces neuronal necrosis by utilizing calcium and free radicals as mediators. Calcium ions role in neuronal death occurs initially upon activation of proteases and endonucleases, which lead to proteolysis of the microfilaments and eventual destruction of DNA. These ions also induce neuronal damage by enhancing the release of toxic hydroxyl free radicals via stimulation of NO synthetase (NOS) and phospholipase A2. Glutamate is also released at synaptic sites where long-term potentiation (LTP), a sustained increase in amplitude of excitatory potentials, occurs. LTP, which is thought to be associated with long-term memory, may be facilitated by the depolarization, calcium influx in the hippocampal neurons. It may also be associated with calcium-calmodulin dependent protein kinase and protein kinase C.

Acetylcholine

Acetylcholine is the first neurotransmitter to have been identified in the central nervous system. Extensive

AMPA and NMDA receptor agonists may become excitotoxic in the presence of bicarbonate. This observation is based on individuals with Guam disease, manifesting clinical signs of ALS, Parkinsonism and senile dementia complex. This disease occurs in the inhabitants of island of Guam (Chamorros) who consume seeds of cycad-cycas circinalis (false sago) as a food source. The latter contains the neutral amino acid b-N-methyl-amino-L-alanine (BMAA) which exhibits an affinity for NMDA receptors, but does not display in vitro toxicity or direct excitatory effect.

- Some scientific views indicate that the biochemical changes observed in Huntington's chorea may be directly or indirectly related to the glutamate actions as a neurotransmitter. This observation is based upon the experimental injection of NMDA agonists into the striatum and the subsequent neuronal loss that seems similar to that of Huntington's chorea. This is supported by the fact that NMDA receptor-mediated neurotoxicity may result from presynaptic and postsynaptic abnormalities that affect glutamate synapses and render some cells prone to toxicity by the normal glutamate levels. Lower concentrations of glutamate transporters may lead to toxic extracellular glutamate levels. Inhibition of glutamate release and blockage of NMDA-and kainate-mediated processes are the mechanisms utilized by medications for ALS such as Riluzole.

- Substance that act like an AMPA agonist, stimulating its receptors, can selectively produce destruction of the upper and lower motor neurons. This is evident in individuals with neurolethyrism, an upper motor neuron disorder that occurs in the inhabitants of certain parts of Africa and Asia subsequent to a dietary reliance on chickpea (*Lathyrus sativus*). The toxin that produces this deficit is b-N-Oxalylamino-L-alanine (BOAA).

- In global ischemia, which occurs in individuals with cardiac arrest, neuronal death (e.g. in the CA1 pyramidal neurons of the hippocampal gyrus) may also be significantly reduced, when AMPA receptor antagonists are administered within the first 24 hours of ischemic episodes. Combination of therapeutic hypothermia and the administration of an NMDA antagonist may achieve neuroprotection in instances of global ischemia. Neuronal protection of the penumbra (area in the immediate surrounding of the site of focal ischemia) can be accomplished to a remarkable degree by the administration of NMDA antagonists in the first few hours of the insult. Experimental evidence points to the significant role that AMPA antagonists can play in neuronal protection following focal ischemic insult.

- Since NMDA receptor antagonists appears to prevent the induction of epileptic seizures, the role of NMDA receptor in induction of epilepsy has been strongly suggested.

- Reproduction of the positive and negative symptoms of schizophrenia by PCP and other NMDA receptor antagonists and altered postmortem levels of glutamate in schizophrenic brains may support the role of glutamate in this psychiatric disorder.

distribution of this neurotransmitter in the limbic system, interneurons of the neostriatum, alpha motor neurons of the spinal cord and basal nucleus of Meynert has been subsequently confirmed. In the brainstem, the parabrachial nuclear complex, which is located dorsolateral to the superior cerebellar peduncle, contains high concentration of the cholinergic neurons. A prominent subnucleus of this complex, the pedunculopontine nucleus, is involved in the generation of rhythmic movements by projecting to the spinal cord. This neurotransmitter is also found in the retina, cornea, motor nuclei of the cranial nerves, and autonomic ganglia. In general the function of acetylcholine varies with the site of its activity. It maintains an excitatory function in the central and the peripheral nervous systems (with the exception of its inhibitory effect upon the cardiac muscles). Acetylcholine is formed in the cytosol by the reversible reaction of acetylCoA and choline and conversion of acetyl CoA to CoA which is catalyzed by choline acetyl transferase (ChAT). Choline is derived from the degradation of acetylcholine by acetylcholinesterase within the synaptic cleft and also from the breakdown of phosphatidyl choline from other membrane sources. Lecithin produces a greater and longer lasting rise in plasma choline levels. In general, the amount of acetylcholine at any given moment is dependent upon the amount of calcium influx and the duration of the action potential. Acetylcholinesterase, which is widely distributed in neuronal and non-neuronal tissues, exists in several molecular forms and catalyzes the hydrolysis of acetylcholine.

Cholinergic receptors, which are found in the brain and spinal cord and, are classified into antagonistic muscarinic and nicotinic receptors.

The muscarinic receptors have several transmembrane spanning regions that are linked to GTP-binding protein (G-protein coupled receptors) which respond slowly, stimulated by muscarine and are blocked by atropine or scopolamine. They cause inhibition of adenylyl cyclase, stimulation of phospholipase C and regulation of ion channels. There are five muscarinic receptors, which display relatively slow response times to Ach binding. They are categorized into m1-m5. The m1 receptors are postsynaptic, excitatory, and remain particularly unaffected in Alzheimer's disease. On the other hand, m2 receptors are presynaptically inhibitory, regulating the release of acetylcholine. This group of receptors is reduced in Alzheimer's disease and their binding sites in the hippocampal gyrus, cerebral cortex and striatum show appreciable age-related decrease. However, major impairments were detected with m2 control of DA release.

Nicotinic receptors respond quickly, excitatory, and are activated by nicotine. These receptors are blocked by curare drugs or excess of nicotine or acetylcholine, and are

Cholinergic neurons are thought to have crucial role in learning, memory, and cognitive ability. The role of cholinergic neurons in short term memory is also assumed on the fact that centrally acting muscarinic blockers such as atropine and scopolamine may produce loss of memory and inability to execute learned tasks. On the contrary, chemicals that inhibit acetylcholinesterase (e.g. physostigmine) may elicit the opposite responses.

found in the neuromuscular junction, autonomic ganglia, cortex and thalamus. They are desensitized by continued exposure to agonists. Nicotinic receptors have distinct subunits which include two α , β , γ , and δ containing four membrane spanning α helices. It has been suggested that these subunits are arranged around an ion channel that remain closed at rest, but opens when the ACh binds to a subunit of these receptors. Neuronal nicotinic receptors that contain $\alpha 2$ - $\alpha 6$ subunits are distinct from non-neuronal receptors, showing resistance to α -bungarotoxin and related α -neurotoxin.

Cholinergic neurons within the nucleus basalis of Meynert, which project to wide areas of cerebral cortex, receive afferents from the limbic system and the hypothalamus and are involved in the ascending reticular activating system.

Monoamines

Monoamines (biogenic amines) are comprised of the catecholamines and the indolamines

Monoamine transmitters are stored in synaptic vesicles, their release is a calcium- dependent processes, and may be

- Cholinergic over-activation, which may be responsible for the clinical signs of Parkinson's disease, occurs as a result of either decreased dopaminergic activity or increased amount of acetylcholine. Administration of physostigmine increases the striatal acetylcholine concentration and often contributes to the exacerbation of Parkinson's disease.
- Treatment of pre-eclampsia (hypertension-induced nervous disorders, e.g. seizure coma, etc.) is based upon the fact that magnesium sulfate, the drug of choice, acts by inhibiting acetylcholine release.
- Inhibition of the release of acetylcholine by the toxin of clostridium botulinum, a calcium dependent substance, occurs peripherally by binding to the external receptors at the synapse sites. Botulinum toxin cannot penetrate the central nervous system or exert any direct influence upon the central cholinergic neurons. Excessive inhibition of acetylcholinesterase produces surplus of acetylcholine that binds to receptors, leading to exhaustion.

metabolized by monoamine oxidase (MAO). Plasma membrane transporter terminates synaptic action of the monoamine transmitters.

Catecholamines

Catecholamines are derivatives of beta-phenyl ethylalanine, with hydroxy groups on the third and fourth positions. They are synthesized by tyrosine, a common precursor for norepinephrine, epinephrine, and dopamine. In the central and peripheral nervous systems, transformation of tyrosine via a series of chemical changes may lead to the formation of norepinephrine, dopamine, or epinephrine, a process which is dependent upon tyrosine hydroxylase and dopamine- β hydroxylase. Release of catecholamines is stimulated by the influx of calcium.

Catecholamines are formed by L-tyrosine, which is converted to L-dopa (Levodopa), via hydroxylation by tyrosine hydroxylase (rate limiting enzyme). L- dopa is converted to dopamine following decarboxylation by an aromatic aminoacid decarboxylase. Dopamine is either stored in the vesicles or hydroxylated to L-norepinephrine by dopamine- β -hydroxylase. L-epinephrine is formed in the adrenal medulla from norepinephrine by the enzyme phenyl-ethanolamine-N-methyltransferase. Norepinephrine and dopamine are metabolized (inactivated) by monoamine oxidase (MAO) and catechol-o-methyl transferase (COMT). Inactivation of norepinephrine occurs by the re-uptake mechanism into the presynaptic nerve terminals.

Catecholamines are found in the brain, chromaffin tissue of the adrenal medulla, and the sympathetic nervous system maintaining massive projections throughout the brain. Amine transmitters have slow modulatory influences and most of their receptors are part of the G-protein coupled family. They may play a role in the regulation of visceral activities, emotion and attention. Norepinephrine is the primary neurotransmitter in the sympathetic (peripheral nervous) system, while dopamine, serotonin, and norepinephrine act primarily in the central nervous system.

Adrenergic receptors are classified into alpha (α) and beta (β) receptors. Although activation of both receptors produces inhibition of gastrointestinal tract motility, their classification in general is based on their respective excitatory and inhibitory effects on smooth muscles. These receptors are further subdivided into α_1 and α_2 and β_1 , β_2 & β_3 . Activation of α_1 noradrenergic postsynaptic receptors produces vasoconstriction, while activation of the presynaptic α_2 receptors may inhibit the release of norepinephrine, a process unaffected by pertussis toxin, which inhibits G-protein. α_1 Receptors are inhibited by Prazosin, a α_1 blocking substance. β receptors are closely linked to adenyl cyclase activation via G-protein.

Enzymes, which are involved in metabolic degradation of the catecholamines such as monoamine oxidase (MOA) and catechol-o-methyl transferase (COMT) maintain an important role in the expression of emotion. Lower levels of catecholamines may produce depression, while higher levels produce euphoria.

Stimulation of the β receptors results in changes, which include vasodilatation of the coronary and abdominal arteries, and relaxation of the ciliary, gastrointestinal, and detrusor muscles. They also produce activation of glycogenolysis, as well as dilatation of the bronchi. Activation of the β_1 receptors produces increased rate and strength of cardiac contractility as well as increased secretion of renin, whereas activation of β_3 enhances lipolysis. Low concentrations of epinephrine activate presynaptic β_2 receptors.

Norepinephrine

Norepinephrine in the CNS is concentrated in neurons of the locus ceruleus of the rostral pons and caudal medulla and the lateral tegmental nuclei. These noradrenergic neurons project to the entire cerebral cortex, hippocampus, cerebellum, and spinal cord as well as basilar pons and ventral medulla. It is released in small amounts from the adrenal gland during circulatory collapse. In dystonia, the level of norepinephrine drops in the red nucleus, hypothalamus, mammillary body, locus ceruleus, and subthalamic nucleus.

Norepinephrine has potent excitatory but weak inhibitory effects on smooth muscles. It has also stronger affinity than epinephrine to β_3 receptors. Noradrenergic neurons in the brainstem reticular formation are classified, according to Dahlstrom and Fuxe, into A1 through A8 groups. The A1 group projects to the spinal cord, solitary nucleus and hypothalamus and is located in the caudal

Norepinephrine regulates the degree of arousal, mood, memory and learning, and also modulates sound transmission (sharpening effect). An excess of norepinephrine has been shown to elicit euphoria, while its depletion may produce depression. The effects of mood elevating drugs (antidepressants) such as MAO inhibitors, re-uptake blockers such as reserpine (antidepressant) and amphetamines (sympathomimetics) is based upon the role of these agents in either increasing the concentration or depleting the endogenous norepinephrine. MOA action on norepinephrine results in the formation of vanilylmandelic acid (VMA), a readily detectable product in the urine. Measurement of VMA levels may bear diagnostic value in conditions such as pheochromocytoma and neuroblastoma.

Checking the levels of 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), a major CNS metabolite of norepinephrine that is found in the urine, blood, and CSF, may assess the functional activity of the central adrenergic neurons.

lateral medulla. A5 lies in the caudal pons near the superior olivary nucleus, and projects to the intermediolateral column of the spinal cord. The locus ceruleus, which is designated as group A6, occupies the rostral pons and caudal midbrain, projecting via the central tegmental tract, medial forebrain bundle, superior cerebellar peduncle, and the tectospinal tract.

Agonists and antagonists of a receptor exert influences on the firing rate of locus ceruleus neurons. α_2 agonists such as clonidine, inhibit the firing of locus neurons in contrast to yohimbine and idazoxane (α_2 antagonists) which facilitate these neuronal activity. The A7 group is located in the lateral pontine tegmentum of the isthmus sending projections to the spinal cord. In the peripheral nervous system, norepinephrine stimulates presynaptic and postsynaptic receptors.

Epinephrine

Epinephrine is released into the blood stream from chromaffin cells of the adrenal medulla. This neurotransmitter stimulates the vascular smooth muscles, and produces a rise in blood glucose concentration. Thus, arousal from insulin coma may be achieved by activation of glycogenolysis. Epinephrine has a stronger affinity for β adrenergic receptors in the smooth muscles of the vessels, bronchi, gastrointestinal tract and urogenital system. Similarly, it also has stronger affinity to α_1 and α_2 receptors than norepinephrine. Epinephrine-containing neurons are classified into group C1 in the lateral tegmentum, C2 in the dorsal medulla, and C3 in the medial longitudinal fasciculus. Certain noradrenergic neurons of the C1 and C2 groups project to the hypothalamus via the central tegmental tract and periventricular gray.

The extensive and global projection of the locus ceruleus to the intralaminar thalamic nuclei via the ascending reticular activating system may account for its role in paradoxical (REM) sleep.

Norepinephrine is thought to have a role in Stiff-man Syndrome, which is characterized by uncontrollable muscular spasm and stiffness. This suggestion is based upon the fact that increased level of 3-methoxy-4-hydroxyphenylethyleneglycol, a metabolite of norepinephrine, is detected in the urine of the affected individuals.

Dopamine

Dopamine, representing approximately 50% of the total catecholamines, is formed by conversion of tyrosine to L-dopa tyrosine hydroxylase and then to dopamine via L-aromatic amino acid decarboxylase. Orally administered tyrosine does not increase dopamine levels. However, orally administered levodopa (L-dopa-L-dihydroxyl phenylalanine) is absorbed from the small intestine by active transport and later converted in the dopaminergic nigral neurons into dopamine. Dopaminergic neurons are concentrated in the tuberal nuclei of hypothalamus, nucleus accumbens, olfactory tubercle, midbrain, carotid body and the superior cervical ganglion. The latter also contains both cholinergic and noradrenergic neurons. In general, the distribution of dopamine parallels that of norepinephrine, with dopaminergic neurons outnumbering the noradrenergic neurons at the ratio of 3 to 1. High concentrations of dopamine and low concentrations of norepinephrine exist in the caudate nucleus and putamen, whereas the reverse occurs in the hypothalamus.

Dopaminergic neurons in the pars compacta of the substantia nigra exert inhibitory influence. The pars compacta synthesizes dopamine and delivers it to the neostriatum (caudate and putamen) via the nigrostriatal fibers.

Dopaminergic neurons in the ventral tegmentum and substantia nigra form the mesocortical pathway that projects to the prefrontal cortex (involved in motivation, attention and social behavior) and entorhinal area. In contrast to the mesolimbic system, these neurons do not develop tolerance to continued usage of antipsychotic medications. Midbrain dopaminergic neurons, which are components of the mesocortical system, lack autoreceptors that regulate impulse traffic. They are generally presynaptic and respond to the same transmitter utilized by the neuron that contains them. They have faster firing rate than the mesolimbic dopaminergic neurons and are less affected by the dopamine receptor blocking agents such as haloperidol.

Dopaminergic receptors are classified on an anatomical and functional basis into D1, D2 receptors; within D1 group of receptors D3, D4, and D5 subtype exist. D5 and D1 have similar concentration in the hypothalamus and temporal lobes. D4 subtype is particularly identified in the brains of schizophrenics. D1 and D2 receptors in the caudate and putamen showed detectable increase in

Monoamine oxidase-B (MOA-B) oxidizes and selectively increases the level of dopamine. Inhibitors of this enzyme such as amphetamines have a profound mood elevating effect, and may even produce agitation.

Degeneration of the nigrostriatal fibers and depletion of dopamine accounts for the manifestations of Parkinson's disease. In Parkinson's disease, the mechanism of degradation of dopamine is maintained but its synthetic machinery is impaired. Dopaminergic neurons in the ventral tegmental nuclei of the midbrain, which are localized medial to the substantia nigra, form the mesolimbic system, a group of neurons that maintain a diffuse projections to the septal area, amygdala, entorhinal area, nucleus accumbens septi, olfactory tubercle, and the pyriform cortex. The role of these projections in controlling mood and emotion accounts for the psychiatric disorders that accompany L-dopa therapy.

It has been suggested that overactivity of the mesolimbic dopaminergic neurons may be associated with schizophrenia. Antipsychotic drugs may increase dopaminergic neuronal activity and dopamine synthesis by blocking the postsynaptic dopaminergic receptors. Prolonged usage of these medications may lead to tolerance development. On the same basis, the inhibitory action of neuroleptic drugs upon these neurons may explain the improvement seen in patients with these disorders, as well as the unwanted side motor disorders.

density in Parkinsonism and decrease in Huntington's chorea.

Indolamines

Indolamines are comprised of serotonin and histamine.

Serotonin

Serotonin (5-hydroxytryptamine) is synthesized by hydroxylation of tryptophan and carboxylation of the product of the reaction by tryptophan hydroxylase. The latter enzyme also catalyzes the carboxylation process that forms serotonin and converts dopa to dopamine. The level of tissue oxygen, pteridine, and tryptophan (cofactors or substrate) may also influence the rate of 5-HT formation.

Dopaminergic neurons located in the tuberal nuclei of the hypothalamus project to the median eminence via the tubero-infundibular tract and then to the adenohypophysis via the portal-hypophysial system. These projections are postulated to regulate the secretion of prolactin and melanocyte-stimulating hormone (MSH). Dopaminergic neurons in the retina and olfactory bulb may play a role in the phenomenon of lateral inhibition, which sharpen the visual and olfactory impulses and prevent neuronal cross talk.

Dopamine transporter (DAT), a sodium/calcium dependent plasma protein, may bind to drugs like cocaine and amphetamine, producing behavioral and psychomotor changes. Thus, cocaine overdose may be treated by antagonists that prevent this binding. Substances that show high affinity for DAT such as 1-methyl, 4-phenyl 1, 2,3,4, 6-tetra-hydropyridine (MPTP) may prove to be toxic to dopaminergic neurons. D1 receptors mediate the dopamine-stimulated increase of adenylate cyclase and subsequently intracellular cAMP. The role of D2 receptors in motor activity, independent of adenylate cyclase, is clearly illustrated in the reduction of both motor and vocal tics upon administering drugs that act upon these receptors.

Additionally, the newer generation of antipsychotics such as clozapine (Clozaril™) is thought to act upon D2 receptors, resulting in selective inactivation of the dopaminergic neurons in the ventral tegmentum, but not in the neurons of the substantia nigra. These drugs may also have fewer side effects than the older generation of anti-psychotics, which are known to produce tardive dyskinesia in some patients. D3 and D4 receptors maintain primary functional relationships to the limbic system and the telencephalon and secondary connections to the basal nuclei. The anti-psychotic drug clozapine's strong affinity to D3 and D4 receptors may account for the suppression of unwanted subcortical motor side-effects.

Although presence of this neurotransmitter in the central nervous system represents a small fraction of its total concentrations in the whole body, serotonin is found in high concentration in the raphe nuclei, spinal cord, and in the hypophysis cerebri, where it is converted into melatonin by acetylation and methylation. Serotonin is actively transported from the cytoplasm to the storage vesicles. The vesicular transport involves vesicular transporter-1 and -2 (VMAT1 and VMAT2) which also function as antiporters to eliminate cytoplasmic toxic materials. For this very reason, vesicular transporters are known as (Toxin Extruding Antiporters (TEXANs). Serotonin is stored in vesicles which do not contain ATP, but instead contain specific protein that binds to 5-HT (serotonin binding protein) with high affinity in the presence of Fe^{2+} . Release of serotonin is thought to occur via exocytosis and its rate is determined by the firing rate of serotonergic soma in the raphe nuclei. Synaptic actions of 5-HT are terminated by binding of these molecules to specific transporter proteins on the serotonergic neurons.

Serotonin receptors generally operate via a guanine nucleotide triphosphate (GTP)-binding (G) protein and are classified, according to their coupling to second

Dopamine's possible role in Gilles de la Tourette Syndrome (hereditary multiple tic disorder), a childhood neurological condition which exhibits multiple motor and vocal tics and compulsive utterance, is based upon the improvement seen in patients with this disease following administration of dopaminergic antagonists. In psychiatric patients using certain neuroleptic drugs, a reduction of dopamine concentration in the substantia nigra may occur as a result of manganese intoxication or ingestion of levodopa that produce hydrogen peroxide and hydroxyl free radicals, leading to involuntary motor activities.

messengers and their amino acids sequence homology. The 5-HT₁ group of receptors are negatively coupled to adenylate cyclase via Gi family of proteins, exhibiting high binding affinity to [3H] 5-HT and mediating inhibition.

The 5-HT₁ family of receptors is further classified into 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}. The 5-HT_{1A} receptors are localized mainly in the hippocampus (CA1 sector), amygdala, neocortex, hypothalamus, and raphe nuclei, mediating emotion. Neuronal hyperpolarization of this group of receptors is achieved by inhibiting adenylyl cyclase activity/and or opening of the potassium channels via G_i protein or by inhibition of calcium channels via G_O protein. 5-HT_{1A} autoreceptor agonists such as R(1)8-OH DPAT is effective in inhibiting the neuronal activities of the midbrain raphe nuclei and the CA1 pyramidal cells of the hippocampal gyrus. Other members of 5-HT_{1A} are also negatively coupled to adenylyl cyclase. 5-HT_{1B} also utilizes G_i protein and mediate inhibition of adenylate cyclase. The same principles apply to 5-HT_{1C}, 5-HT_{1D}, and 5-HT_{1E}. Binding sites for [3H] 5-HT in the choroid plexus is termed 5-HT_{1C} subtype, whereas the binding sites for [3H] 5-HT in the bovine brain is designated as 5-HT_{1D} subtype. Inositol phosphate is liberated by the activation of 5-HT_{1C}, which leads to the opening of the calcium-dependent chloride channel.

The 5-HT₂ group contains receptors that maintain amino acid homology and are coupled to phospholipase C possibly via G_q. They can selectively be blocked by ketanserin and ritanserin and may produce excitatory effects, displaying high affinity to H₃-spiperone. 5-HT₂ antagonists may block the excitatory effects of glutamate

Changes in the 5-HT function have been implicated in the affective disorders, schizophrenia, migraine, sleep and anxiety disorders. Neurotransmission at 5-HT receptors may be blocked by antidepressants (e.g. fluoxetine), hallucinogens (e.g. LSD), anxiolytics (e.g. buspirone), antiemetic (e.g. ondansetron), and antimigraine drugs (e.g. sumatriptan).

and 5-HT receptors in the facial motor nucleus. This group of receptors is comprised of 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. Prolonged stimulation of the 5-HT_{2B} and 5-HT_{2C} receptors may produce reduction in receptor density or sensitivity. Sustained administration of 5-HT antagonists may result in down-regulation of both HT_{2A} and 5-HT_{2C}.

5-HT₃ is a member of ligand-gated ion channel that function independent of G-protein. They are densely populated at the nerve terminals in the entorhinal and frontal cortices, hippocampus, and area postrema, as well as the peripheral nervous system. These receptors are excitatory in the peripheral, enteric and autonomic nervous systems, facilitating membrane depolarization to serotonin. They resemble the nicotinic cholinergic receptors, mediating fast synaptic transmission.

Additional receptors within the 5-HT family that are positively coupled to the adenylate cyclase include 5-HT₄, 5-HT₆, and 5-HT₇. 5-HT₄ receptor-binding sites are identified in the striatum, substantia nigra, olfactory tubercle, and atrium. They may mediate striatal dopamine release by s-hydroxytryptamine. However, 5-HT₅ receptors do not couple to adenylyl cyclase and consist of 5-HT_{5A} and 5-HT_{5B}. The 5-HT_{5A} mRNA transcripts are localized in the hippocampal gyrus, granule cells of the cerebellum, medial habenular nucleus, amygdala, thalamus, and olfactory bulb, whereas 5-HT_{5B} mRNA are found in the dorsal raphe nucleus, habenula and hippocampus. 5-HT₆ receptor mRNA has been detected in the striatum, olfactory tubercle, and nucleus accumbens.

5-HT₇ is identified as a receptor in the vascular smooth muscle cells and astrocytes of the frontal cortex.

Dahlstrom and Fuxe described nine groups of serotonergic neurons that are designated as B1 through B9. B6 and B7 represent the dorsal raphe nucleus; B8 corresponds to the median raphe (superior central) nucleus, whereas B9 forms part of the ventrolateral tegmentum of the pons and midbrain. B1-B4 groups are localized in the midpons through the caudal medulla and they project mainly to the spinal cord. B1, which is localized in the caudal part of the ventral medulla, has no known projections. B3, which corresponds to the raphe magnus, projects to the spinal laminae I & II and the intermediolateral lateral column. B2 (nucleus raphe obscurus) projects to lamina IX. B6-B9 nuclear groups project to the telencephalon and diencephalon. B8 group appears to project largely to the limbic system, whereas B7 maintains specific projections to the neostriatum, thalamus, cerebral and cerebellar cortices. Ascending serotonergic projections from the rostral midbrain form the dorsal periventricular tract and the ventral tegmental radiation, which join medial forebrain bundle and the dopaminergic and noradrenergic projections in the

5-HT₆ receptors exhibit high affinity for LSD, antipsychotic and tricyclic antidepressants such as clozapine, clomipramine, mianserin, and ritanserin, and positively couple to adenylate cyclase.

- Uptake of 5-HT is accomplished by an active process that utilizes Cl⁻ and Na⁺ and remains temperature-dependent. Therefore, inhibitors of Na/K ATPase may impair the uptake process of serotonin. Tricyclic antidepressants, such as imipramine and amitriptyline, inhibit reuptake of both serotonin and norepinephrine. Therefore, selective serotonin reuptake inhibitors (SSRIs) may also be used for the treatment of clinical depression. It has been suggested that serotonin reuptake inhibitors may alleviate symptoms of obsessive-compulsive disorder (OCD). Atypical antipsychotic drugs such as clozapine may inhibit central dopaminergic neurons but primarily maintain more powerful antagonistic action on 5-HT_{2A} and 5-HT_{2C} receptors. Agonists at 5-HT_{2A} and 5-HT_{2C} receptors may be responsible for the hallucinogenic activity of certain drugs such as LSD. Sumatriptan, an effective medication in the treatment of migraine, is thought to derive its therapeutic role from the agonist action at 5-HT_{1D} and 5-HT_{1F}. Depletion of 5-HT content of serotonin is correlated with the tranquilizing action of reserpine, a hypotensive drug, which also deplete norepinephrine and dopamine contents.

- Chemotherapeutic agents, such as cisplatin and dacarbazine induce severe forms of nausea and vomiting. This results from a series of events that involve release of 5-HT from the chromaffin tissue of the gastrointestinal tract and the enteric nervous system. Released 5-HT specifically activates 5-HT₃ receptors, which are ligand-gated ion channel receptors, producing depolarization of the afferent nerves and increasing their firing rates. This eventually leads to activation of the chemoreceptor (emetic) trigger area. Thus, antagonistic agents that act on 5-HT₃ receptors in the GI tract such as ondansetron and granisetron, and not on the emetic center, break these series of events and produce relief from nausea and vomiting.

hypothalamus. The dorsal raphe nucleus projects to the striatum, whereas the median raphe nucleus sends fibers to the hippocampus, septal area and hypothalamus. A somatotopic representation of the ascending serotonergic projections exists in which the rostral and

lateral parts of the dorsal raphe nucleus predominantly project to frontal cortex. It is well established that serotonergic neurons produce combination of depolarization and increased membrane resistance of the neurons of the facial motor nucleus, which enhance the response of these neurons to other excitatory input.

Serotonin is implicated in the regulation of the slow phase of sleep, pituitary functions and activities of the limbic system (behavior, thermoregulation, mood and memory). It also plays an important role in the inhibition of pain transmission. Medullary raphe nuclei exert analgesic influence via projections to the spinal cord, whereas pontine and mesencephalic neurons contribute to the ascending reticular activating system via its rostral projections.

Histamine

Histamine acts both as a neurotransmitter and neuromodulator in the central nervous system, mainly occupying the midbrain, tuberal and mammillary nuclei of the hypothalamus and their extensions in the principal mammillary and the tubero-infundibular tracts, respectively. In the hypothalamus, it coexists with substance P, met-enkephalin, and glutamic acid decarboxylase. Non-neuronal histamine is contained in a substantial amount in the mast cells, where it is depleted by mast-degranulating drugs. Histamine exerts its influences on autonomic activity, temperature regulation, food and water intake (suppressant), vestibular function (may mediate motion sickness), sleep-wake cycles, and neurohumoral mechanism (release of vasopressin, prolactin, adrenocorticotrophic, etc.) It maintains the ability to excite CNS neurons and may be involved in locomotor and exploratory behavior, as well as diurnal changes in other CNS functions. Learning and retention of information may be enhanced by histamine. Histamine release is mostly non-synaptic and widely diffuse, and release of neuronal histamine may be increased by stimulation of the D₂ dopaminergic and some serotonergic and NMDA receptors. Histaminergic neurons project to glial cells, blood vessels, neurons, as well as capillary networks. Histamine receptors are identified as H₁, H₂, and H₃ according to their order of detection. H₁ receptors are shown to be involved in hormonal release,

Destruction of the raphe nuclei and subsequent depletion of serotonin may produce reversible insomnia. The use of serotonin blockers such as ergotoin, tricyclic antidepressant, MOA inhibitors, and sumatriptan in the treatment of migraine headache may support the role of serotonin in this condition.

Neurons of the dorsal raphe nucleus seem to be more prone to neurotoxicity generated by certain amphetamine derivatives, such as d-fenfluramine, 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) or parachloamphetamine (PCA). 5-hydroxyindoleacetaldehyde (5-HIAA), a serotonin metabolite, shows reduction in the CSF of MDMA users. Blocking the serotonin transport systems may avert this neurotoxicity. In contrast median raphe nucleus appears to be unaffected by these neurotoxic effects.

food intake, increased free calcium ion concentration, contraction of the smooth muscles, and increase capillary permeability. In the ventrolateral hypothalamus, H₁ receptor is involved in wakefulness. Both H₁ and H₂ are involved in regulation of pituitary gland function, whereas H₂ receptors may mediate endogenous analgesia.

Neuropeptides

Neuropeptides are substances that arise from inactive precursors, their synthesis on ribosomes in the perikaryon or dendrites of a neuron that is regulated by mRNA, and packaged for release in the endoplasmic reticulum. Their eventual release is by calcium dependent process. Neuropeptides include the enkephalins, endorphins, Substance P, cholecystokinin (CCK) and hypothalamic peptides. Many peptides such as bradykinin, somatostatin,

It has been suggested that histamine may alter the blood-brain barrier, suppress the immune system and produce certain vascular changes, contributing via these neurotoxic effects to the development of certain neurodegenerative diseases, such as multiple sclerosis, Alzheimer's disease and Wernick's encephalopathy. H₁ receptor-mediated effect of histamine reduces seizure activity. Therefore, H₁ antagonists increase seizure onset and/or duration. H₁ antagonists that induce sedation include diphenhydramine and mepyramine, as well as meclizine (anti-motion sickness medication). H₂ receptors are involved in inhibition of gastric secretion, positive inotropic and chronotropic effects upon the cardiac muscles, and inhibition of contraction of the smooth muscles. Therefore, H₂ antagonists (cimetidine and ranitidine) reduce gastric secretion and thus can be used for the treatment of gastric and duodenal ulcers. On the other hand, H₃ receptors may be involved in the regulation of histamine release and inhibition of acetylcholine, dopamine, norepinephrine and other peptides.

gastrin, secretin, vasoactive polypeptide (VIP) are also shown to act upon the autonomic intestinal neurons and enteric nervous system, which will be discussed later with the autonomic nervous system. In view of the vast amount of information available in this area, the discussion will only be restricted to certain peptides.

Enkephalins are pentapeptides that are present in the interneurons of the substantia gelatinosa, nucleus raphe magnus and the small intestine. Enkephalinergic neurons modulate pain via presynaptic inhibition upon afferents in the brainstem and spinal cord. They are classified into methionine enkephalin and leucine enkephalin.

Endorphins are peptides (naturally occurring opiates) consisting of C-terminally extended forms of Leu-enkephalin that bind to opiate receptors in the brain, and induce analgesia similar to morphine. These receptors have the ability to bind to opiate agonists (e.g. morphine) or to antagonists (e.g. naloxone). Endorphins may be implicated in states of depression and generalized convulsions. They are derived from different genes and they are classified into dynorphin-A, dynorphin-B, and α and β -endorphins. β -endorphins are contained in neurons within the diencephalon and pons, and may be involved in the acquired intellectual deterioration in adults.

Substance P (SP) is an 11 amino-acid oligopeptide that is present in the nerve endings of the unmyelinated class C or myelinated Ad fibers which carry nociceptive (painful) stimuli to the substantia gelatinosa. Therefore, axotomy may reduce the level of this peptide. Substance P is found in the dorsal root ganglia, gastrointestinal tract, and sensory ganglia of cranial nerves, spinal trigeminal nucleus, basal nuclei, nucleus raphe magnus, periaqueductal gray, and the hypothalamus. Other peptides that relate closely to substance P are neurokinin A and neurokinin B with their specific receptors NK1 and NK2. The neurokinin A gene is located on chromosome 7, whereas the gene for neurokinin B is positioned on chromosome 12. Substance P exerts a more powerful effect than both neurokinins at NK1, however it remains less potent at NK2.

Cholecystokinin (CCK) is a neuromediator concentrated in the amygdala, hypothalamus, cerebral cortex, periaqueductal gray matter, and the spinal dorsal gray columns. It coexists with other peptides in the substantia nigra, ventrotectal area, and the medulla. CCKa and CCKb are known receptors for cholecystokinin, with CCKb being the predominant receptor in the brain. CCKa is found in the nucleus accumbens septi, posterior hypothalamus, and area postrema of the medulla.

Hypothalamic peptides are 3–14 amino acid peptides including thyrotropin releasing hormone, somatostatin, corticotropin releasing factor, melanocyte-stimulating factor, and luteinizing hormone releasing factor.

Section 5

Sensory Systems

The sensory systems transmit special somatic (vision, auditory and vestibular) sensations, general somatic (tactile, thermal, painful, and proprioceptive) sensations, general visceral sensations (visceral pain, changes in blood pressure, hunger, libido, etc), and special visceral (olfactory and taste) sensations. Most of these sensations project to the cerebral cortex while others are perceived at subcortical levels (e.g. cerebellum).

- 13 Visual system
- 14 Auditory system
- 15 Vestibular system
- 16 Olfactory system
- 17 Limbic system
- 18 Gustatory system
- 19 General somatic sensations

The visual system is a special somatic afferent system which receives, processes, and recognizes visual impulses. It forms binocular images and regulates reflexes associated with vision. It is the only sensory system which is totally dependent upon the cerebral cortex. In order for visual images and associated memory to be constructed, visual impulses must pass through a chain of structures and neurons which are located in the eye and visual pathway, encompassing the cornea, iris, anterior and posterior chambers of the eye, vitreous body, retina, optic nerve, optic tract, visual radiation, and visual cortex.

Peripheral visual apparatus

Eyeball

Visual Pathways

Ocular movements

Disorder of ocular movements

Ocular reflexes

Gaze centers

Peripheral visual apparatus

The eyeball is the peripheral visual organ, which is situated in the bony orbital cavity. It is surrounded by the orbital fat, separated by a thin fibrous (Tenon's) capsule.

Eyeball

The eyeball (Figure 13.1) consists of an outer fibrous, an intermediate vascular, and an inner neuronal layer.

Tunica fibrosa

Tunica fibrosa, the outermost layer of the eyeball, consists of the cornea and retina.

The cornea (Figure 13.1) is avascular structure that forms one sixth of the fibrous tunic and represents the main refractive medium of the eyeball. It has no lymphatics, receives a rich nerve supply by the long ciliary nerves, and is highly resistant to infection. It forms the anterior wall of the anterior chamber of the eye and joins the sclera at the corneal-scleral junction.

The sclera (Figure 13.1) is a fibrous structure which preserves the shape of the eyeball, resists intraocular pressure, and provides smooth surface for eye movements, giving attachment to the extraocular muscles. It is continuous anteriorly at the limbus with the connective tissue stroma of the cornea, posteriorly with the dural sheath of the optic nerve. At the lamina cribrosa sclera (weakest part of this layer), the sclera is pierced by fibers of the optic nerve as well as the posterior ciliary vessels.

Tunica vasculosa

The tunica vasculosa represents the intermediate layer of the eyeball, consisting of the choroid layer, ciliary body, and the iris (Figure 13.1). Arteries and veins are the main components of the vascular choroid layer. Within this layer, the veins join together and form 4 or 5 vorticoses veins. These vorticoses veins drain into the anterior ciliary veins. Arterial part of the choroid layer is formed by the ciliary arteries that extend to the iris, forming the major and minor arterial iridal circles. In addition to the central

- Kayser-Fleischer ring, a greenish gray pigmentation around the corneo-scleral junction, is formed by the deposition of copper in the Descemet's membrane and is seen in Wilson's disease (hepatolenticular degeneration). See also the subcortical motor system.
- At the corneo-scleral junction the Schlemm's canal, a venous channel, exists that receives the aqueous humor (fluid within the anterior and posterior chambers). Occlusion at this site may lead to accumulation of aqueous humor, increase intraocular pressure, and the resultant glaucoma.

In some individuals, the lens may be absent as a developmental anomaly (primary aphakia), or as a result of degeneration (secondary aphakia). Corneal opacity and cataracts of the anterior lens are seen in congenital anomaly of Peter's, in which gradual impairment of vision and diplopia are observed. The opacity may be confined to the nucleus of the lens (central cataract), producing myopia and poor vision during the day and better vision in dim light. Peripheral cataracts result in poor vision in dim light and better vision in bright daylight. Congenital cataracts may be seen at birth due to metabolic or chromosomal abnormalities, infection, or maternal diseases. The lens may be affected by a myriad of clinical conditions that include presbyopia and sunflower cataract.

- Presbyopia develops as a result of aging and by the conversion of the lens into a less pliable structure, rendering it less reactive to contraction of the ciliary muscles. Presbyopic patients are hyperopic, exhibit difficulty in reading fine print and endure the inconvenience of holding reading materials farther away to achieve optimum vision.

- Sunflower cataract (chalcosis lentis) is a condition, which is seen in Wilson's disease due to the impregnation of the subcapsular area of the lens with the radiating metallic green grayish opacity.

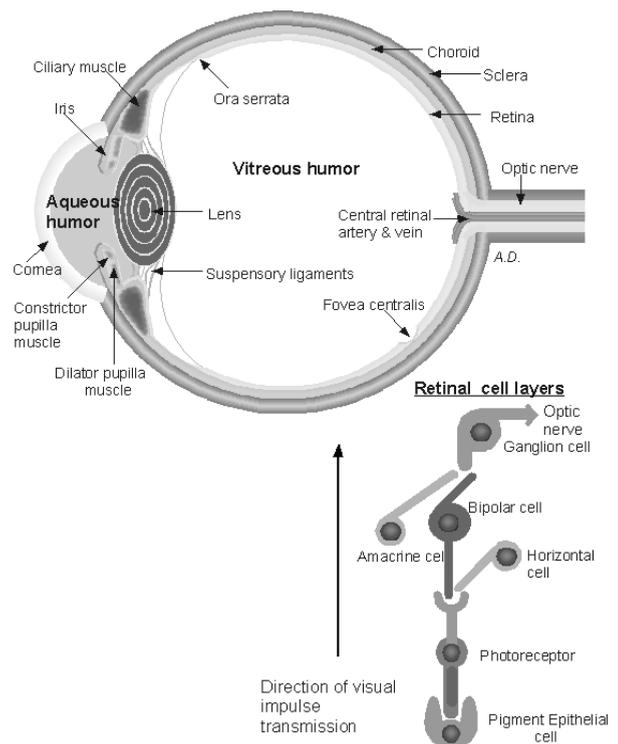


Figure 13.1 Section of the eyeball and associated layers. The neuronal organization of the retina is also illustrated

- Miosis refers to constriction of the pupil that is commonly seen in Horner's syndrome. Bilateral miotic pupils may result from metabolic encephalopathies, destructive pontine lesions or opiate use. Miosis of pontine origin may be due to disruption of the descending sympathetic pathways. Disruption of the efferent sympathetic fibers in the carotid sheath, near the apex of the lung or base of the neck may also produce unilateral miosis.
- Mydriasis (dilatation of the pupil) is manifested in oculomotor palsy as a result of the unopposed action of the dilator pupillae muscle. This sign may be seen subsequent to aneurysms of the posterior communicating, superior cerebellar, and posterior cerebral arteries, and also in uncal herniation. Traumatic mydriasis is usually unilateral, occurs in response to direct trauma, and may not be accompanied by ocular muscle dysfunction. Bilateral mydriasis may be seen in trauma patients with poor vascular perfusion subsequent to hypotension or increased intracranial pressure. Prompt restoration of pupillary response may follow adequate vascular perfusion. Patients with Cheyne-Stokes respiration may exhibit mydriasis in hyperventilation phase and miosis in apneustic phase.
- Anisocoria refers to the unequal pupils in which one eye may show constriction. physiological anisocoria occurs in 20% of the population, exhibiting mild difference (up to 2 mm) in pupil size. Determination of whether the smaller or larger pupil is abnormal may require comparing pupil size in the dark and the room light. Sympathetic anisocoria will be more marked in dim light due to the subnormal constriction of the affected (small) pupil. This may result from iritis, disruption of the cervical sympathetics or application of miotic (miosis inducing) medications. Parasympathetic anisocoria will be evident in room light since the affected (larger) pupil constricts subnormally. This type of anisocoria may be seen in individuals with oculomotor palsy, glaucoma or as a result of application of mydriatic (mydriasis inducing) drugs such as atropine.

- Argyll-Robertson pupil is characterized by the inability of the eye to constrict in response to light, while remaining responsive (constricts) in accommodation. This condition occurs in tabes dorsalis or tertiary syphilis, diabetes mellitus, and in severe vitamin B deficiency. The lesion is usually located medial to the lateral geniculate nucleus, disrupting the afferent limb of the pupillary light reflex, while preserving the afferent limb of the accommodation reflex. Reverse Argyll Robertson pupil is seen in syphilis and Parkinson's disease.
- Hippus is a phenomenon in which the pupil exhibits spontaneous, intermittent rhythmical constriction and dilatation. Although the diagnostic value is questionable, this condition may be associated with hysteria, multiple sclerosis, brain abscess, and Cheyne-Stokes respiration.
- Marcus Gunn Pupil is characterized by a slow reaction to light or the inability to constrict in response to direct light. It is observed in individuals with a lesion of the optic nerve or retina, and in ipsilateral retrobulbar neuropathy which produces relative afferent pupillary defect (RAPD). In RAPD, the presence of normal consensual reflex when the contralateral eye is stimulated indicates that the oculomotor nerve is intact. When the light is quickly passed from the intact to the affected eye, both eyes show dilatation (positive swinging flashlight test). The consensual reflex is preserved, but the depth of perception of moving and colored objects is lost. The visual deficits are exacerbated by exercise or by any efforts which increase the body temperature (Uthoff's sign). The latter sign is due to the possible change in the conduction of the affected nerve or variation in the sodium and potassium concentration around the myelin of the optic nerve following physical activity. The Gunn pupil, a congenital anomaly that is characterized by ptosis and retraction of the eyelid on the affected side in response to opening the mouth or deviation of the jaw, is not equivalent to Marcus Gunn.

retinal artery, these vessels provide a supplementary source of blood supply to the retina. The intermediate part of the tunica vasculosa is known as the ciliary body, which extends from the lateral end of the iris to the ora serrata (site of junction of the light sensitive and non-sensitive parts of the retina). It consists of ciliary muscles and processes, giving attachment to the suspensory ligaments of the lens (zonular fibers). When viewing distant objects, the ciliary muscle is relaxed and the zonular ligaments are stretched and become taut.

On the other hand, when viewing near objects, the ciliary muscle is contracted, accompanied by movement of the ciliary body toward the iris and relaxation of the

suspensory ligaments, which results in an increase in lens curvature. The ciliary processes secrete the aqueous humor into the posterior chamber by active transport and diffusion from the capillaries.

The lens ([Figure 13.1](#)), a main component of the eye chambers, is a biconvex, colorless, avascular structure, derived from the surface ectoderm, and positioned between the iris and the anterior chamber. It lies posterior to the iris, embedded in the hyaloid fossa, receiving the suspensory ligaments of the lens. It is functionally similar to the cornea with a less refractive (dioptric) power. It has a transparent elastic capsule, a cortical zone, and a nucleus. The anterior and posterior poles represent the most convex

Glaucoma, a condition in which the intraocular pressure is elevated independent from any other diseases of the eye (primary glaucoma) or as a result of ocular diseases (secondary glaucoma). Primary (chronic, or open angle) glaucoma may be congenital or acquired and may result from obstruction at the canal of Schlemm, aqueous veins, or the trabecular meshwork at the irideocorneal angle.

- Open angle glaucoma is the most common form of glaucoma, which is produced by a gradual increase in intraocular pressure, accompanied by a gradual loss of peripheral vision, ending in total blindness. It usually begins in the fourth or fifth decades of life in individuals with familial history of variety of glaucoma. Symptoms are absent at the onset, and its diagnosis may be confirmed by examination of the fundus of the eye and detection of increased intraocular pressure. In later stages of this disease, the optic cup is abnormally deep and permanently put out of function. Lack of clear symptoms in the initial stages of this disease is an important indication that regular ophthalmologic examination is highly recommended for individuals over the age of forty. Pilocarpine, which constricts the pupil and increases the outflow of the aqueous humor through the irideo-corneal angle, may be used topically to treat this condition. Timolol (Timoptic) may reduce the production of aqueous humor, but its side effects on the cardiovascular system may make it less desirable

medication. Marijuana may also lower intraocular pressure in this type of glaucoma.

- Closed angle glaucoma results from increased intraocular pressure subsequent to adhesion of the iris to the cornea and closure of the irideocorneal angle. It may not always be spontaneous, but iatrogenic, resulting from the application of medications that dilate the pupil and block the irideo-corneal (filtration) angle by the iris itself. Tricyclic antidepressants with anticholinergic properties may precipitate this condition. Patients are usually older than 40 years with family history of glaucoma. Few patients may complain of seeing halos around lights. This condition may be acute or chronic.

- (a) Acute (closed) angle glaucoma is produced by the sudden obstruction of aqueous humor circulation, which produces pain and visual impairment of the affected eye. In this condition, the eye appears red, the cornea seems hazy, and the blood vessels are dilated.

- (b) Chronic (closed) angle glaucoma occurs as a result of gradual obstruction of the irideocorneal angle, showing similar signs to the acute closed angle glaucoma. Topical and systemic treatments and even laser iridectomy may have to be promptly applied to reduce production of aqueous humor. Glaucomas may be associated with lesions involving the peripheral retina or the optic nerve, producing peripheral scotoma (focal blindness in the form of dark or colored spot).

parts of the lens. Changes in the lens curvature are regulated by the suspensory ligaments of the lens and the muscles of the ciliary body.

The iris ([Figure 13.1](#)) forms the adjustable diaphragm of the eye that encircles the pupil, consisting of circular muscle fibers (constrictor pupilla) and radial fibers (dilator pupilla muscle), pigment cells, and epithelium. Constrictor pupilla, which acts as a pupillary sphincter, is innervated by the postganglionic parasympathetic fibers, whereas the dilator pupilla receives innervation from the postganglionic sympathetic fibers. The iridal pigment is the same in all individuals; however, the amount of pigment and the pattern of its distribution determine the eye color. Malclosure of intraocular fissures results in a defect (coloboma) in the iris, choroid layer, retina, or optic disc. The pupil, an opening in the center of the iris, may exhibit abnormalities such as miosis, mydriasis, anisocoria, Argyll Robertson pupil, hippus, Adie's (tonic) pupil, and Marcus Gunn Pupil.

The anterior chamber ([Figure 13.1](#)) of the eye is located between the cornea anteriorly, iris and the lens posteriorly. It contains the aqueous humor, which crosses the trabecular network to gain access to the irideo-corneal angle and the canal of Schlemm. The area between the iris anteriorly and the lens and zonular fibers posteriorly

represents the posterior chamber. Both eye chambers communicate via the pupil, containing the aqueous humor, which maintains the intraocular pressure. Aqueous humor also serve as a path for metabolites from the cornea and lens, carries nutrients such as glucose, and plays a role in respiratory gaseous exchange. Failure of this communication may result in glaucoma.

The vitreous body ([Figure 13.1](#)) is a clear and colorless substance, occupying most of the eyeball posterior to the lens. It primarily consists of water, hyaluronic acid, trace amounts of mucoproteins, and some salts. It contains fibrils, which may be visible as floating objects. The hyaloid membrane surrounds the vitreous body, thickens at the ora serrata of the retina to form the ciliary zonule. The ciliary zonule forms the suspensory ligaments of the lens and the hyaloid membrane. The hyaloid canal pierces the vitreous body and stretches from the optic disc to the posterior pole of the lens.

Refractive disorders

In a normally relaxed eye (emmetropia), no optical defects exist and it is adapted to the far vision. The lens is flat and the suspensory ligaments of the lens (zonular fibers) are tense ([Figures 13.1 & 13.3](#)). However, near vision requires the use of accommodative power that includes an

increase in lens curvature, constriction of the pupil, and convergence. The increase in lens curvature shortens the focal distance and allows images from closer objects to fall on the retina. The changes in near vision occur when the eyeball has a normal antero-posterior dimension and functional refractive media within normal range. An abnormally long or short eyeball, an uneven curvature of the refractive media, or a nonfunctional or overly functional accommodative apparatus, may produce a variety of disorders, including myopia, hyperopia, astigmatism, presbyopia, and anisometropia.

Tunica nervosa

Tunica nervosa consists of the pigment epithelial layer and retina (Figure 13.1). The pigment epithelium is loosely bound to the retina that contains the photoreceptor layer. The pigment epithelial layer offers mechanical support, absorbs excess light, providing nutrients for photoreceptors.

The retina (Figure 13.1 & 13.2) is the inner layer of the tunica nervosa that develops as the optic vesicle from the diencephalon, consisting of the pars optica, pars ciliaris, and pars iridica. The pars optica joins the pars ciliaris at the ora serrata. The pars optica is the only light-sensitive part, which contains the photoreceptors, and it is loosely bound to the pigment epithelium. The pigment layer offers mechanical support, absorbs excess light, prevents or minimizes light reflection, and provides nutrients for the photoreceptors. The retina is incompletely fused to the pigment epithelium and is separated by a potential space.

The peripheral retina and ciliary body joins at the ora serrata. At the ora serrata, the sensory layers of the retina and the retinal pigment epithelium fuse thus limiting the spread of any pathological subretinal fluid. The tunica nervosa contains photoreceptors, which are divided into cones and rods. Cones vary in number from 6-7 million and are distributed among the rods except in the fovea centralize. They occupy a central position, whereas the rods are localized in the periphery. The optic disc is the site where axons of the ganglionic layer leave the eyeball, the optic nerve is formed, and the photoreceptors are absent. The physiologic cup is the lighter-colored central part of the disc which is penetrated by the retinal vessels. The macula lutea, a yellowish spot on the temporal side of the optic disc, contains the fovea centralis. The latter is for acute vision occupied only by cones. The physiologic cup is the lighter-colored central part of the disc, which is penetrated by retinal vessels. The normal cup to-disc ratio of 1:5 may be lost in glaucoma.

The cones possess a higher threshold of excitability and have a 1:1 synapse ratio with the dendrites of the bipolar neurons. Cones are specialized in day vision (photopic) and color discrimination.

- Myopia (near sightedness) is an optical disorder characterized by the inability to see far objects. It may be due to an abnormally long eyeball axis or a refractive power, which is too strong (Figure 13.2). Therefore, the image from a distant object falls anterior to the retina. As the object moves closer, the focal point moves back to the same degree until the image is spotted on the retina and clear vision is achieved. This condition may be associated with rhegmatogenous retinal detachment in which the retina is detached and break-up into pieces. Myopia is corrected by a concave lens.

- Hyperopia (far-sightedness) is the most common optical disorder associated with an abnormally short axis of the eyeball or weak refractive power (Figure 13.2). Due to shortness of the optical axis, images from distant objects fall behind the retina in the relaxed eye. However, accommodation focuses the images on the retina, allowing clear vision of distant objects. A convex lens corrects hyperopia.

- Astigmatism results from an uneven curvature of the refractive surfaces (egg-shaped), leading to a change in the angle of refraction of the horizontal and perpendicular light rays and subsequent focusing of these rays on different spots on the retina. As a result blurred vision ensues. A cylindrical lens, which is concave or convex on one axis and flat on other, corrects this disorder.

- Presbyopia, a condition that develops with aging, is characterized by an inelastic, hard and less pliable lens, which lacks or has limited power of accommodation. Individuals with this disorder are hyperopes (far-sighted).

- Anisometropia is a rare disorder in which the refractive powers between both eyes remain different.

Rods (Figure 13.2) are the most numerous, averaging between 100-130 million per retina. They are peripherally located and activated by lower illumination. Rods visualize black, white, and gray colors under twilight or scotopic (achromatic) vision. In dim light, rods contract to maximize the surface area exposed to the limited light. The outer segments of rods contain discs, which are sloughed and removed by pigment cells. Dendrites of horizontal cells in the inner nuclear layer interconnect cones and rods. The processes of the large glial (Müller) cells, which hold the retinal layers together, constitute the outer limiting membrane. The photoreceptors form synaptic linkage with the dendrites of the bipolar neurons at the outer plexiform layer.

Detachment of the retina from the pigment epithelium may be complete or focal, occurring as a result of trauma or disease processes. It may be associated with a break up of the retina (Rhegmatogenous detachment) subsequent to direct trauma. Retinal detachment, as is seen in diabetic vitreoretinopathy, is associated with intact retina that underwent undue traction by the fibrovascular bundles between the vitreous body and the retina. Retinal detachment may also occur when pathological processes allow exudate derived from the choroid layer to enter the subretinal space (exudative retinal detachment). Retinal detachment may cause blurred vision, light flashes or the appearance of floating bodies. Cherry red spots may be seen on fundoscopic examination of the retina in individuals with Tay-Sachs disease.

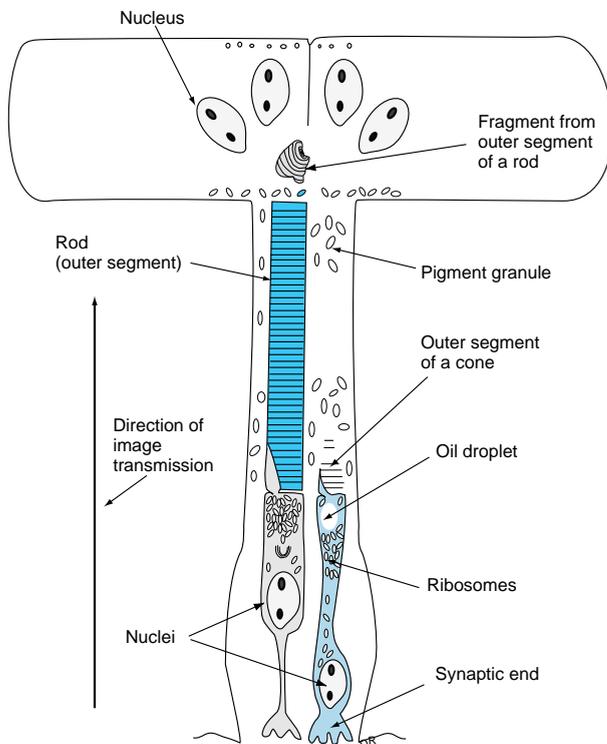


Figure 13.2 The structural organization of the photoreceptors

The bipolar neurons (Figure 13.1) are depolarizing or hyperpolarizing neurons that represent the primary (first order) neurons in the visual pathway. Depolarizing (invaginating) bipolar neurons are inhibited by darkness. They stimulate the “on” type ganglionic cells and are released from inhibition by illumination. Hyperpolarizing (flat) neurons are inhibited by light, excite the “off” type

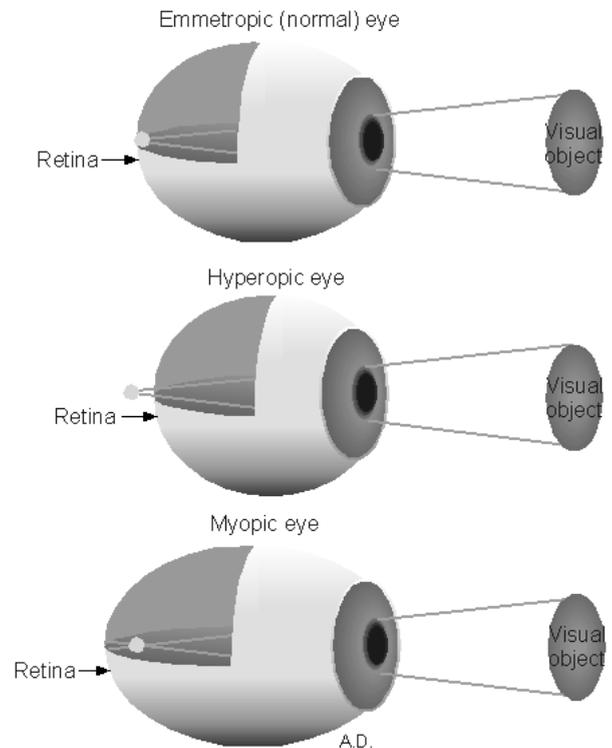


Figure 13.3 Refractive defects associated with vision

ganglionic neurons, maintaining different receptors. The nuclei of these neurons are located in the inner nuclear layer while the axons are spread in the inner plexiform layer, establishing contacts with the dendrites of the ganglion cells.

The amacrine cells (Figure 13.1), which resemble the granule cells of the olfactory bulb, form inhibitory synapses upon the dendrites of the ganglion cells, and maintain reciprocal connections with the bipolar neurons. These cells contain different transmitters and together with the ganglionic neurons, are the only excitable (produce action potentials) neurons of the retina. The horizontal cells establish inhibitory dendrodendritic synapses with the bipolar neurons, intensifying contrast by inactivating the bipolar and ganglionic neurons.

Ganglionic multipolar neurons (Figures 13.1 & 13.5) form the second order neurons in the visual pathway, which have the capacity to fire at a fairly steady rate even in the absence of visual stimuli. They are either “on” type or “off type”, dependent upon their synaptic connections with the bipolar neurons. They are classified into sustained X, transient Y, and intermediate W cells. Sustained X cells subserve constant on or off response, analyzing field in regard to their shapes and colors of objects in the visual field. Transient Y cells are relatively few in number, giving rise to momentary response to rapidly moving objects. Y cells project to the superior colliculus and thalamus to detect the movement of objects in the visual field. W cells

A lesion rostral to the optic chiasma involving the foveal part of the retina and the corresponding part of the optic nerve are commonly seen in multiple sclerosis. These lesions may be associated with optic neuritis (inflammation of the optic disc) or retrobulbar neuritis (inflammation of the optic nerve).

- Dark or colored spots in the center of the visual field are referred to as central scotoma. The point of exit of axons of the optic nerve from the eyeball marks the optic disc of the retina, commonly known as the blind spot. The focal blind spot attributed to the optic disc is termed physiological scotoma.

- Arcuate scotoma is a pathological focal visual deficit, which results from a lesion in the retina or optic nerve fibers. It occurs near the optic disc and arches superiority or inferiorly toward the nasal field of the retina and in the direction of the axons of the ganglionic multipolar neurons.

- Scintillating (flittering) scotoma (teichopsia) is characterized by floating of irregular and lucid spots, sometimes with a zigzag or wall-like outline, which may last for up to twenty to twenty five minutes. It usually occurs secondary to occipital lobe lesion. It may also be associated with migraine (migraine aura).

- Color blindness may be inherited (sex linked) or acquired. Patients may exhibit blindness toward all colors (achromatopia) or to one (monochromatopia) or two colors (dichromatopia). Color vision is mediated by the cones, segregated from other visual information in the retina, and eventually processed in a specialized pathway in the visual cortex utilizing the lateral geniculate nucleus and the optic radiation. The inherited variation in the amount of photopigments in the blue cones, green cones, and red cones may account for the sex-linked condition of color blindness. This condition affects 8 percent of males compared to 2 percent of females. This

is due to the fact that red and green genes exist as a recessive trait on the male X chromosome. One percent of males lack the red gene (protanopes-lack the long wave mechanism) and two to three percent lack the green gene (deuternopes-lack the medium length mechanism). The gene for the blue color is present on an autosome on the seventh chromosome, and is rarely affected by mutation. It is thought that all three-cone genes maintain a common ancestral red gene. The red gene may have given rise to the blue cone pigment which in turn have given origin to the red and green cone pigments. Trichromats are individuals with normal three-color vision or with one normal color vision and two feeble red vision (protanomaly). Trichromats may also have three feeble green vision (deutranomaly) or four weak blue vision (tritanomaly). These weaknesses are due to the reduction in the amount of cone pigment and are unrelated to neuronal circuitry associated with processing of the color vision. Dichromats, individuals with two-color vision (color blind) and who lack one of the pigments, may not perceive red (protanopes) due to lack of erythrolabe, green (deutanopes) as a result of absence of chlorolabe, or blue (tritanopes-lack the short wave length mechanism) due absence of cyanolabe. Deutanopia are much more common than protanopia in the ratio of 3 to 1.

Gene loss or recombination between genes, which produce a hybrid gene on the X chromosome, may occur in individuals with red-green color blindness. However, disorders of color vision may also be acquired. Pathological conditions that affect the outer layer of the retina may produce blindness to blue color (tritanopia) as a result of loss of the processing mechanism of short-wave length. In this manner, pathological elements that affect the optic nerve and the inner retinal layer may cause loss of red-green color vision.

are small and project to the pretectum to mediate the pupillary light reflex. The dendrites of the ganglionic neurons are connected with the axons of the bipolar neurons in the inner plexiform layer. Some ganglionic neurons in the nasal halves of the retina may fixate the visual image on the fovea centralis, preventing the image from slipping off. This occurs when axons of these specific ganglionic neurons project via the midbrain reticular formation to the inferior olivary nucleus. This is followed by projection of the olivocerebellar fibers to the same Purkinje neurons that receive input from the medial vestibular nucleus.

The axons of the ganglionic neurons leave the eyeball through the lamina cribrosa sclera, forming the optic nerve. The retina is divided by the optic axis into a medial (nasal) half and a lateral (temporal) half, a horizontal plane further divides the retina into upper and lower nasal and

upper and lower temporal quadrants. The object seen by the retina represents part of the visual field. The nasal half of the retina of each eye receives visual impulses from the temporal half of the visual field and vice versa. The upper quadrant of the retina of one eye sees the lower quadrant of the contralateral visual field and vice versa.

The retina is dependent upon the arterial supply of the ophthalmic artery (Figure 13.4). This artery arises from the cerebral part of the internal carotid artery medial to the anterior clinoid process. It enters the orbit via the optic canal accompanied by the optic nerve. It supplies the eye, forehead, dura matter, ethmoidal sinuses, and the nasal cavity. In the orbit, it frequently runs superior and then medial to the optic nerve, accompanied by the nasociliary nerve. It gives rise to the central retinal, anterior ciliary, and the long and short posterior ciliary arteries.

Accumulation of pigment cells and floating discs of the outer segments may account for the retinal degeneration and black colored lesions in the fundus seen in retinitis pigmentosa. Disc debris in the outer part of the retina may hinder the diffusion of nutrients from capillaries of the choroid layer to the photoreceptors, thus accounting for the retinal degeneration observed in this blinding disease. A small lesion or petechial hemorrhage in the retina near the optic disc produces a focal blindness or scotoma in which central visual acuity is impaired. Vitamin A plays a significant role in vision. Darkness causes vitamin A to undergo reverse changes into retinin, which bonds with opsin to form rhodopsin. Nyctalopia (night blindness) is associated with vitamin A deficiency.

The central retinal artery (Figure 13.4) penetrates the optic nerve near the eyeball and divides into four branches. These branches are end arteries that supply the four quadrants of the retina. The branches appear thinner and brighter red than the corresponding vein with a normal artery to vein ratio of 2:3. In hypertensive individuals, the central retinal artery may exhibit narrowing or spasm and become thickened or sclerotic, changing color to orange-metallic. The central retinal vein (Figure 13.5) may be concealed by the more superficial and widened arterial wall branches that give the appearance of a discontinuous venous column. The long and short posterior ciliary arteries that supply the choroid and ciliary processes and establish anastomosis with branches of the central retinal artery.

Visual pathways

The optic nerve (Figures 13.1, 13.6 & 13.11) is formed by the axons of the ganglionic layer of the retina, acquiring myelin outside the eyeball. Embryologically, it develops with the retina as an extension of the telencephalon. Fibers arising from the macula follow a straight course to the optic disc forming a spindle-shaped area termed the papillomacular bundle. Those fibers arising from the nasal retina follow a relatively straight course. Fibers of the temporal retina follow an arcuate path around the papillomacular bundle to reach the optic disc.

The optic tract (Figures 13.8, 13.9, 13.10, 13.11, 13.13, 13.14 & 13.15) is formed by the crossed nasal and ipsilateral temporal fibers of the optic nerve. Each optic tract carries impulses to the opposite visual field, and runs adjacent to the internal carotid artery, hypothalamus, cerebral peduncles, and thalamus. The fibers which originate from the macula lutea occupy an intermediate

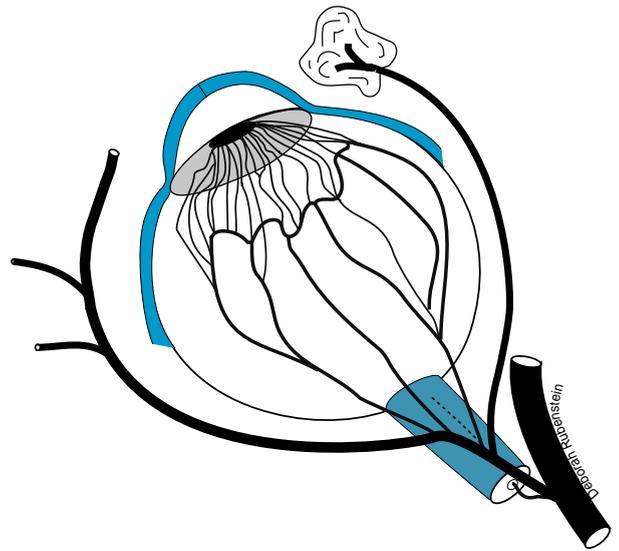


Figure 13.4 The ciliary and central retinal branches of the ophthalmic artery

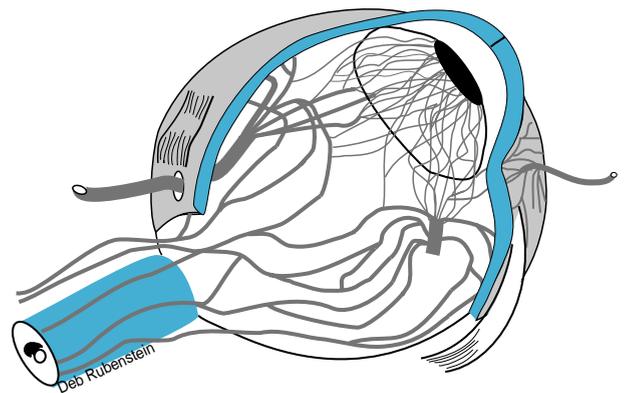


Figure 13.5 The central retinal vein and the anterior and posterior ciliary veins are illustrated

Occlusion of one branch of the central retinal artery may produce quadrantanopia. A decrease of blood flow within the central retinal artery may indicate possible occlusion of the internal carotid artery. Incomplete occlusion of the internal carotid artery exhibits sudden transient monocular blindness in the form of a blackout or misty vision appearing as a shade or curtain which covers the visual field from side to side or from above without permanent visual loss (amaurosis fugax). This transient visual attack, which lasts from seconds to minutes, may also result from compression of the ophthalmic artery by the intraocular pressure subsequent to reduction in the pressure of the carotid system. Bilateral reduction in the blood pressure of the ophthalmic artery, relative to the pressure of the brachial artery may indicate bilateral carotid disease.

Examination of the fundus of the eye may reveal in a normal person a more sharply defined temporal edge than the nasal edge. The optic disc appears pinkish in light-skinned persons and yellowish-orange in dark-skinned individuals. Pallor of the disc may suggest atrophy of the optic nerve. Retinal vessels radiate from the center of the optic disc and divide into branches that distribute to the retinal quadrants. Hypertension and arteriosclerosis alter the morphology of these vessels.

Essential or malignant hypertension may produce retinal exudate, hemorrhage into the plexiform layer of the retina, cotton wool patches, a lipid star in the macula, and irregular narrowing of the retinal arteries.

The physiologic cup is the lighter-colored central part of the disc, which is penetrated by retinal vessels. The normal cup-to-disc ratio of 1: 5 is genetically determined. Only 2% of normal eyes have a ratio more than 0.7. Unequal *c/d* ratios, in which the difference between the two eyes is more than 0.1, is seen in 8% of normal individuals and in 70% of patients with early glaucoma. A changing *c/d* ratio is significant because glaucomatous expansion of the optic cup is superimposed upon the amount of physiological cupping present before the onset of raised intraocular pressure. During the early stages of glaucoma the increase in size of a small cup may not be detected because of its dimensions may still be smaller than the physiological cup. Therefore, estimation of the cup size does not by itself carry diagnostic value, unless the increase is profound. Glaucomatous cups are usually larger than physiological cups, although a large cup may not pathological.

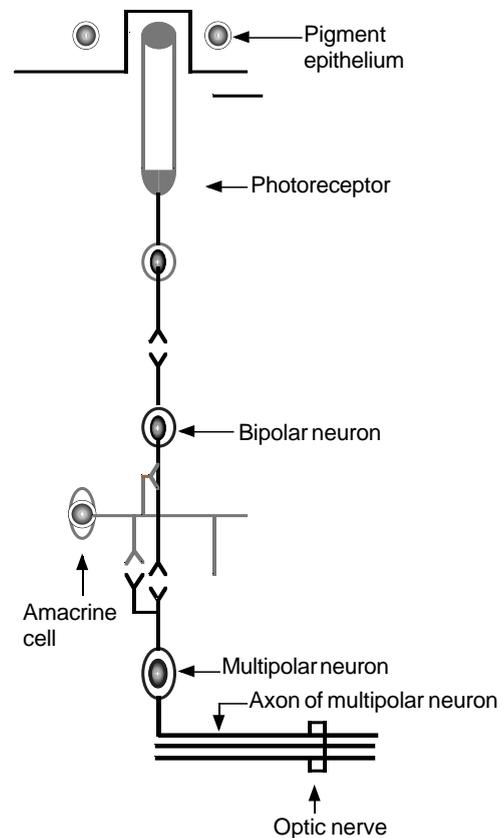


Figure 13.6 Neuronal series associated with transmission of visual image to the optic nerve

position, fibers from the upper quadrant of the retina reside in an anterior and medial location, while the fibers from the lower quadrant of the retina occupy a more lateral and posterior position in the optic tract. Most of the fibers of the optic tract project to the lateral geniculate body (LGB), a visual relay nucleus of the thalamus, where they establish synaptic links with its neurons. Some fibers of the optic tract bypass the LGB and terminate in the pretectum and tectum, containing the efferent neurons for the pupillary light reflex. The fibers that bypass the LGB enter the superior colliculus and the pretectum, activate the Edinger-Westphal nucleus of both sides via the posterior commissure. The Edinger-Westphal nucleus provides preganglionic parasympathetic fibers to the ciliary ganglia that control the curvature of the lens and the contraction of the sphincter pupillae muscle through the short ciliary nerves.

The lateral geniculate nucleus (LGB)- (Figures 13.9, 13.10, 13.11, 13.14, 13.15 & 13.16) is a visual relay nucleus which consists of six layers. Layers 1, 4, and 6 receive fibers from the contralateral retina, while layers 2, 3 and 5 receive fibers from the ipsilateral retina. Layers 1 and 2 form the ventral (magnocellular) subnucleus and

The arcuate fibers reaching the supero-temporal and infero-temporal aspects of the optic nerve head are most vulnerable to glaucomatous insult and the fibers of the papillo-macular bundle are the most resistant. The nasal fibers of the optic nerve partially decussate in the optic chiasma, while the temporal fibers continue on the same side as part of the optic tract. Fibers from the lower nasal quadrant form a short loop into the medial part of the contralateral optic nerve prior to joining the optic tract (anterior knee fibers of von Willebrand). This accounts for superior temporal quadrantanopia in the contralateral eye, which accompanies optic nerve lesion. Fibers from the superior nasal quadrant of the retina also form a short loop (posterior knee fibers of von Willebrand) extending into the ipsilateral optic tract. The optic nerve also forms the common afferent limb for both the pupillary light and accommodation reflexes. It enters the orbit through the optic canal and is invested by the meninges. Stenosis, Paget's disease, suprasellar tumors, or fractures involving the optic canal may damage the optic nerve.

The optic nerve may undergo inflammation outside the eyeball (retrobulbar neuritis), or intraocularly (papillitis). Retrobulbar (optic) neuritis produces unilateral visual deficits and may be caused by multiple sclerosis (MS), measles, mumps, or varicella viruses. Optic neuritis in MS patients may produce scotoma and defects in temporal halves of the visual fields. Papillitis produces swelling of the margins of the optic disc as a result of a local inflammatory process

- Papilloedema (Choked disc) is a condition characterized by bilateral passive elevation of the margins of the optic discs as a result of increased intracranial

pressure. Since the subarachnoid and subdural spaces of the brain also extend around the optic nerve, increased intracranial pressure can be transmitted along these spaces, producing edema around the nerve and retardation of venous drainage. Tumors which involve the optic nerve sheath, tectum, cerebellum, fourth ventricle (ependymoma), cerebral hemisphere and the corpus callosum may also produce papilloedema. Cerebellar tumors (e.g. medulloblastoma) may protrude into the fourth ventricle and obstruct the pathway of the cerebrospinal fluid, producing increased intracranial pressure and papilloedema earlier than any other tumors of the central nervous system. Cavernous sinus thrombosis as well as sinusitis may contribute to this condition by impeding the venous blood flow.

It is rarely seen in congenital cyanotic conditions of the heart or in Guillain-Barre syndrome (an idiopathic acute febrile inflammatory disease that produces polyneuropathy). Since pontine or medullary tumors do not generally interfere with the circulation of the cerebrospinal fluid, these masses do not usually induce papilloedema.

Therefore, patients may die from brainstem compression before developing papilloedema. Papilloedema can be detected by examining the dilated retinal veins in the fundus of the eye. Inflammation of the optic disc is suspected when exudate and hemorrhage with moderate elevation of the disc margin are present. Headache, nausea, vomiting, hemiparesis, hemianopsia, and diplopia due to involvement of the abducens nerve, may also be seen in individuals with papilloedema.

layers 3 to 6 comprise the dorsal (parvicellular) subnucleus. Most fibers of the optic tract terminate in the lateral geniculate body. Fibers bypass the LGB to synapse in the pretectal area and the superior colliculus. The synaptic connections between the optic tract and the neurons of the lateral geniculate nucleus are somatotopically arranged. The medial part of the lateral geniculate body receives fibers from the upper retinal quadrant, the lateral part receives fibers from the lower retinal quadrant; and the central part of the lateral geniculate body receives fibers from the macula. The axons of dorsal (parvicellular) subnucleus of the LGB neurons form the geniculo-calcarine tract (optic radiation). The medial part of this projection terminates in the superior bank of the calcarine fissure, whereas the lateral part projects in a similarly precise manner to the inferior bank of the visual cortex.

The optic radiation (Figures 13.9, 13.11, 13.1, 13.14 & 13.15) represents the postsynaptic fibers of neurons from the dorsal (parvicellular) subnucleus of the lateral

geniculate body. The optic radiation (geniculocalcarine tract), shaped like a crescent, has ventral and dorsal parts which courses within the retrolenticular part of the internal capsule en route to the visual cortex. Each part represents one fourth of the visual field of the contralateral side. The ventral part of the optic radiation known as Meyers loop terminates in the lower bank of the calcarine fissure (lingual gyrus). The upper fibers of the optic radiation end in the upper bank of the calcarine fissure, represented by the cuneus. Fibers derived from the upper retinal quadrant run in the superior part of the optic radiation, and fibers from the lower retinal quadrant fibers are shifted to the lower part of the optic radiation. The foveal fibers occupy the most lateral position of the optic radiation.

The primary visual or striate cortex (Brodmann's area 17) is the principal area for visual perception, integration, and formation of binocular image. It has a point to point connection with the lateral geniculate body (Figures 13.12, 13.15 & 13.16). Due to this precise connection, a

The optic chiasma (Figures 13.7, 13.12, 13.14 & 13.16) is formed by the nasal fibers of the optic nerve which decussate rostral to the hypothalamus and tuber cinereum and superior to the pituitary gland. Due to the close relationship of the optic chiasma to the adenohypophysis, adenomas of the pituitary or craniopharyngioma may compress the optic chiasma and disrupt the nasal fibers of the retina, producing bitemporal heteronymous hemianopsia tunnel vision). Bitemporal heteronymous hemianopsia (Figure 13.14) may be suspected if a patient can read left-hand letters only with the right eye, and the right-hand letters with the left eye. Binasal heteronymous hemianopsia may be produced by aneurysms of both internal carotid arteries. Unilateral nasal hemianopsia may possibly occur if the aneurysm of the internal carotid artery is ipsilateral. This type of aneurysm may mimic a pituitary tumor, producing visual deficits and radiographically detectable sellar enlargement. A chiasmal lesion may also produce junctional scotoma, superior or inferior bitemporal quadrantanopsia, or monocular temporal hemianopsia.

Tumors or lesions involving the optic tract near the optic chiasma may result in congruous or complete homonymous hemianopsia. A lesion, which involves the area medial to the lateral geniculate body, as is seen in tabes dorsalis or tertiary syphilis, may selectively disrupt the fibers that mediate constriction of the pupil in light reflex, leaving the accommodation reflex arc unaffected. Individuals with this type of lesion may exhibit pupillary response in accommodation but not in response to light (Argyll Robertson pupil).

small lesion in the visual cortex may result in scotoma (focal blindness). Area 17 includes portions of the lingual and cuneate gyri, extending to the lateral surface of the occipital lobe. It consists of a very thin granular cortex, in which layer IV is divided into densely packed upper and lower sublayers and a lighter middle layer with fewer small cells between the giant stellate cells. The light middle layer has a thickened outer band that is visible to the naked eye in sections of the fresh brain and is known as the band of Gennari. Area 17 receives information from all neurons of the lateral geniculate body and projects to Brodmann's areas 18 and 19.

The interconnection between areas 17 of both cerebral hemispheres is not well developed. Visual fibers which reach the pulvinar deal with the contralateral visual field and project to layers I, III and IV of the cortical areas 18 and 19 and to the supragranular layers of Brodmann's area 17. The latter projection constitutes the extrageniculate visual pathway.

Perception of visual images (e.g. individual may be able to read an article if brought into focus) remains intact even with bilateral damage to the striate cortex as long as the occipital pole is spared. Bilateral destruction of the occipital poles, on the other hand, markedly impairs the ability to clearly and accurately observe visual fields.

Dark bars against a light background, and straight edges separating areas of different degrees of brightness effectively stimulate the visual cortex. The primary visual cortex consisting of functional units arranged in columns of cells exhibiting different receptive fields. These functional units include the ocular dominance and orientation columns that are arranged perpendicular to the cortical surface.

The ocular dominance columns are partially formed at birth, receive visual information from both eyes, and are arranged in such a manner that one eye will be dominant. Segregation of the visual impulses into right and left laminae of the dominance column occurs in layer IV. However, no ocular dominance columns exist in the parts of the striate cortex which receive impulses from the optic disc, and the most peripheral temporal visual field of the ipsilateral eye. The orientation columns are smaller than

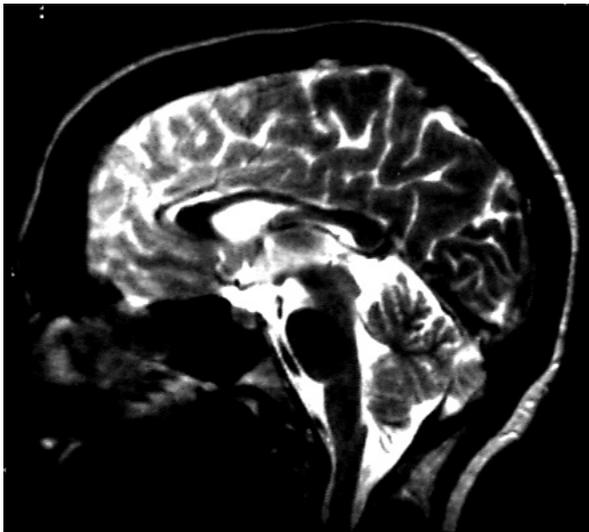


Figure 13.7 MRI Scan of the brain. Observe the course of the optic chiasma and its relationship to the lamina terminalis

Destruction of the optic tract produces homonymous hemianopsia on the contralateral visual field (Figure 13.12). Due to proximity of the internal carotid artery to the optic tract, aneurysm of this vessel may compress the ipsilateral (temporal) fibers of the optic tract, resulting in nasal hemianopsia (Figure 13.10).

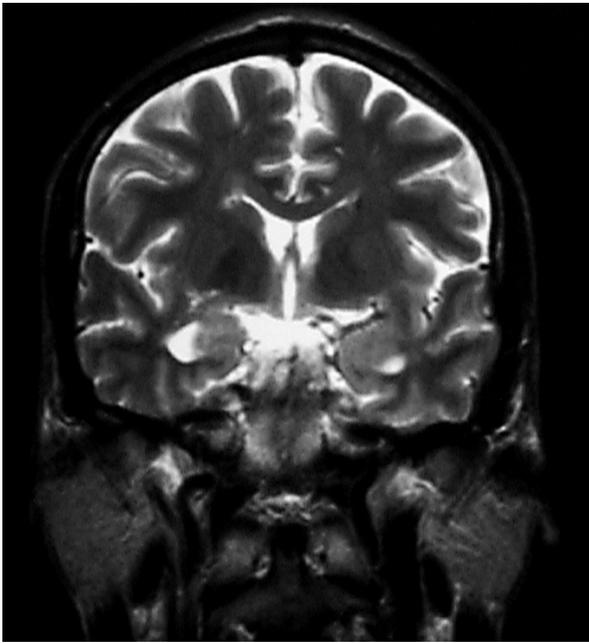


Figure 13.8 MRI Scan of the brain (coronal view). Note the course of the optic tract in relation to the third ventricle



Figure 13.9 Horizontal section of the brain. The optic tract, lateral geniculate body, and the optic radiation are prominently displayed

the dominance columns and extend from the white matter to the pial surface of the cerebral cortex. These orientation columns contain cells which possess the same receptive field axis of orientation and have 'on' and 'off' centers. The visual cortex is primarily supplied by the posterior cerebral

Since the ventral portion of the optic radiation (Meyer's loop) follows a separate course within the temporal lobe before joining the bulk of the geniculocalcarine tract, a selective damage to the optic radiation, a frequently occurring lesion, may produce quadrantanopia in the opposite visual field. Edema caused by bleeding from the medial striate artery (a branch of the middle cerebral artery) may also compress the optic radiation, resulting in transient homonymous hemianopsia which lasts until the edema subsides. Vascular lesions affecting the optic radiation may also be caused by occlusion of the anterior choroidal and posterior cerebral arteries. Also an abscess that develops in the temporal lobe, above the level of the auditory meatus, may compress and disrupt the fibers of Meyer's loop, producing quadrantanopia in the contralateral visual field. Homonymous visual field defects due to lesions of Meyer's loop tend to be incongruous. Those due to damage to the optic radiation near the visual cortex are congruous (edges of the visual field defect in each eye is identical in shape).

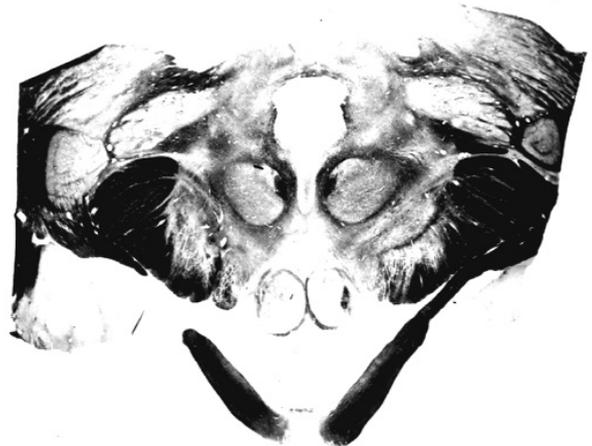


Figure 13.10 In this section the optic tract and the lateral geniculate bodies are also clearly visible

artery, although the middle cerebral artery also contributes blood supply through its anastomotic connections.

The secondary visual cortex (Brodmann's area 18) adjoins the striate cortex, deals with visual memories, and receives visual impulses from Brodmann's area 17. It is a mirror image representation of the Brodmann's area 17, which consists of a six-layered granular cortex. It interconnects areas 17 and 19 and does not contain the band of Gennari. This cortex, as in the case of area 17,



Figure 13.11 MRI Scan illustrates some of the elements associated with the visual system. Note the optic nerve, optic chiasma, optic tract, lateral geniculate nucleus, and the optic radiation

responds best to dark bars and edges. The majority of cells in Brodmann's area 18 are complex cells arranged in columns. Usually, in the dominant hemisphere the upper lateral portion of Brodmann's area 18 deals with memories for inanimate objects while the lower medial portion is concerned with memories for living parts or individuals. In order for the visual object to be recognized, information must project to Brodmann's area 18 of the dominant hemisphere (for fine feature analysis) via the splenium of the corpus callosum.

The tertiary visual cortex (Brodmann's area 19), a mirror image of Brodmann's area 18, occupies the area lateral to the secondary visual cortex. It is responsible for recalling (revisualizing) formerly seen images. The hypercomplex cells are the primary neurons in Brodmann's area 19 that receive visual input from both eyes. Stimulation of this area produces colorful visual images of moving events and objects. The middle part of area 19 relates to the macula and object sizes, whereas the inferior part of this area responds exclusively to color. Movement activates a small area, anterior to the macular zone of area 19. In order for the images to be recalled, visual information must project from Brodmann's areas 18 to area 19 where they are activated by various types of stimuli (e.g. auditory, tactile, olfactory, etc.). It is important to note that recalling symbols is a function of the angular gyrus.

It is important to remember that the inferior temporal gyrus serves as a visual association cortex, contains visual

Macular sparing is a phenomenon in which a lesion involving the occipital lobe or occipital pole results in no detectable deficit of the central vision. It is thought that sparing of central vision may either be due to efficient arterial anastomosis and collateral circulation between the middle and posterior cerebral arteries or bilateral representation of the macular area in both cerebral hemispheres. Although cortical blindness and contralateral incongruous homonymous hemianopsia may also be seen.



Figure 13.12 MRI scan (mid-sagittal view) of the brain illustrating the visual cortex within the lingual gyrus and cuneus

memory stores, and receives input from the entorhinal cortex (Brodmann's area 22) and Brodmann's areas 7, 18 and 19. These connections may explain the visual hallucination associated with temporal lobe epilepsy, as well as the vivid scenes experienced by patient undergoing brain operation. Beginning by the 5th postnatal month, the visual association cortices (Brodmann's areas 18 and 19) become involved in stereopsis, a mechanism that enables the brain to measure the incongruity between the two retinal images, thus constructing a complete three-dimensional image.

Ocular movements

Eye movements provide a significant index of the functional activity of the motor nuclei of the extraocular muscles and the neurons within the brainstem reticular

Unilateral or bilateral occlusion of the posterior cerebral artery (Figure 13.13) is commonly associated with a variety of deficits and syndromes. Infarction of the posterior cerebral artery is the most common etiology of visual deficits of occipital lobe origin (Figure 13.11). Transient occlusion of the vertebral arteries on both sides, which may occur as a result of cervical spondylosis and subsequent narrowing of the transverse foramina, may dramatically reduce the blood flow in the labyrinthine and posterior cerebral arteries. A patient with this condition may experience vertigo and transient blindness, which last for few seconds, without remembering that these disorders ever have happened.

- Anton's syndrome (cortical blindness) is an expression of psychological ramification of cortical blindness which is caused by disruption of the corticothalamic connection between area 17 and the thalamus, and also in individuals with non-dominant hemispheric damage. It commonly results from bilateral occlusion of the posterior cerebral arteries. Patients have normal sized and reactive pupils and may show indifference or pay no attention to half of the visual field of the same side. They are generally unaware of their blindness. Patients attempt to name objects in the visual field and describe the surrounding objects, though they can not tell illuminated from non-illuminated areas. They consistently deny their blindness and insist that poor lighting or disinterest is the causes for their visual problems.

- Occlusion of the posterior cerebral arteries may result in bilateral degeneration of the parieto-occipital cortex between Brodmann's areas 19 and 7, producing signs and symptoms of Balint syndrome. This syndrome is characterized by the inability to appreciate or scan the peripheral visual field (due to lack of coordination with the oculomotor system) or use visual cues to grasp an object. Infarction of the posterior cerebral artery may also produce a combination of hemianopsia or quadranopsia, macular sparing, and hemianesthesia with no muscle paralysis. If the infarct involves the dominant hemisphere, Charcot-Wilbrand Syndrome may develop, producing visual agnosia.

- Gertsmann's syndrome, transcortical sensory aphasia, and alexia without agraphia are also seen in posterior cerebral artery infarcts.

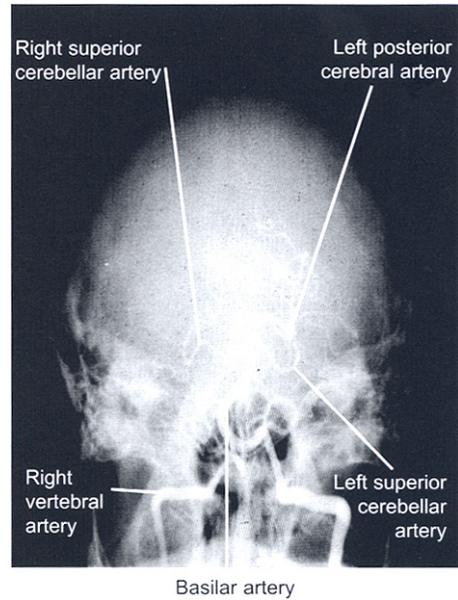


Figure 13.13 In this angiogram of the vertebro-basilar system, the right posterior cerebral artery is obstructed

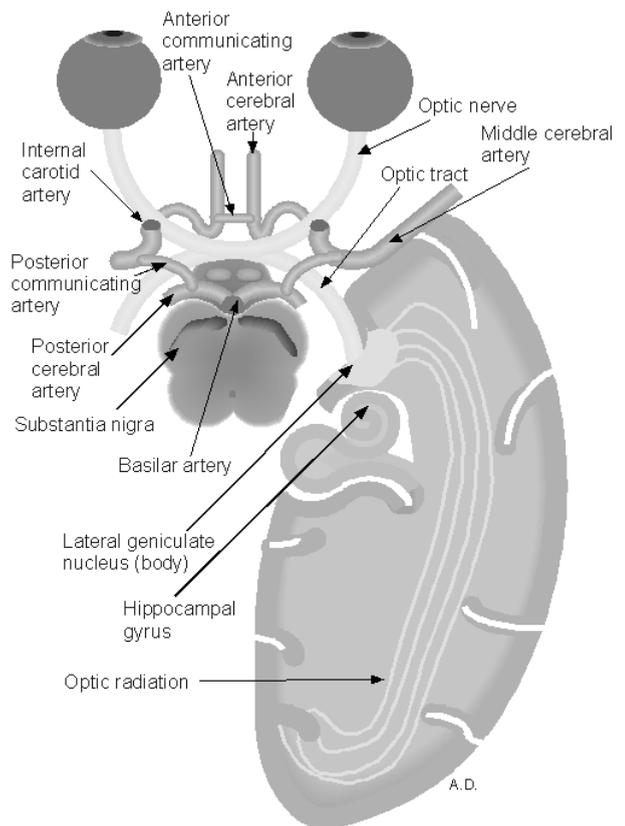


Figure 13.14 Drawing of the visual pathway from the optic nerve to the visual cortex in the occipital lobe. The relationship of the arterial circle of Willis to optic nerve, optic chiasm, and optic tract is shown

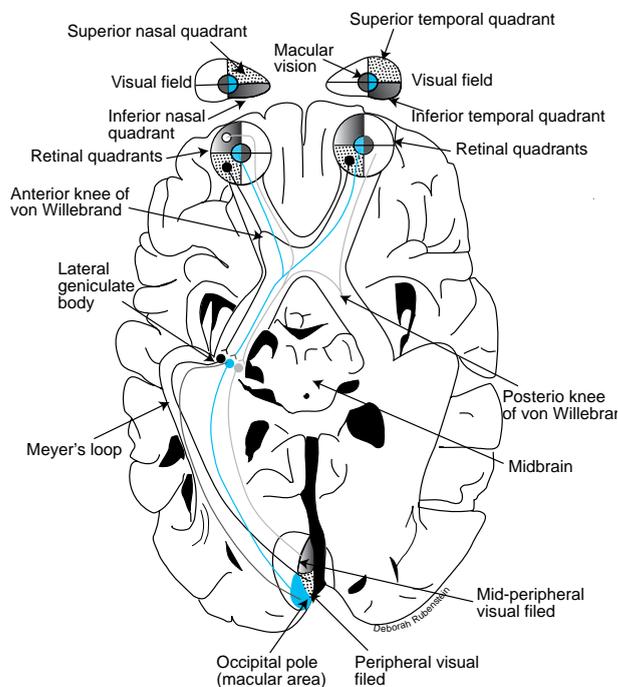


Figure 13.15 The course of the visual image from the retina through the optic nerve, optic tract, later geniculate body, optic radiation, to the visual cortex

- Amblyopia (lazy eye) is a disorder that develops from a prolonged suppression of an image in one eye between the second and fourth year of life. It may be the result of congenital strabismus and the inadequate stimulation of one eye by visual image. It occurs in children who exhibit diplopia as a sequel to functional imbalance between the extraocular muscles and subsequent attempts to eliminate the image in one eye by constantly utilizing the other eye. As the crossed-eyed child favors one eye over another, the unused eye eventually loses visual acuity and may permanently be blind. In this condition no deficits are recorded in the refractive media or ocular apparatus. Amblyopia may also occur as a result of nutritional deficiency and in alcoholics. This condition may be associated with damage to the optic nerves and bilateral scotoma. Blurred vision and optic atrophy may also occur in this condition.

formation. They are classified into conjugate (version) movements, where the visual axes of both eyes remain parallel (for far vision), and disconjugate (vergence) movement, in which the visual axes intersect (for near vision) by the contraction of the medial recti muscles (Figures 13.17 & 13.18 & 13.19). Disconjugate (vergence) movements deal with tracking of approaching

- Disruption of the connection between Brodmann's area 18 of both cerebral hemispheres may occur upon excision of the corpus callosum producing unilateral visual agnosia. Patients with this type of deficit are unable to recognize images received by the right (non-dominant) hemisphere of the brain. Bilateral visual agnosia results from a lesion of Brodmann's area 18 in the dominant cerebral hemisphere. Visually agnostic patients can not recognize objects without using tactile, auditory, gustatory, or olfactory clues.

- Lesions that damage the upper lateral or lower medial parts of the secondary visual cortex in the left dominant hemisphere may result in autopagnosia, which is characterized by failure of the patient to distinguish living people from objects. Lesions of the dominant hemisphere confined to the upper part of Brodmann's area 17 and the occipital association cortex adjacent to the angular gyrus produce finger agnosia. This condition manifests inability to name objects, identify fingers, write, do arithmetical calculations, or recognize left from right. Achromotopsia, the inability to recognize color in only one-half of the visual field, may occur independently. Stimulation of Brodmann's area 18 results in visual hallucinations in the form of sparkling lights.

(convergence) or receding (divergence) objects which require slow movements of the eyes in opposite directions. Conjugate movements depend upon the integrity of certain gaze centers and the medial longitudinal fasciculus (MLF). The MLF is the principal internuclear pathway that interconnects the motor nuclei of the extraocular muscles, coordinates eye movements, and ensures binocular vision.

Conjugate eye movements are further categorized into saccadic and smooth-pursuit movements. Saccadic movements of the eye are involuntary and rapid movements that include successive jumps of the eye from one point of visual fixation to another. These movements are mediated by the contralateral superior colliculus that project to the ipsilateral paraventricular reticular formation (PPRF) and the medial longitudinal fasciculus. The PPRF stimulates the ipsilateral abducens nucleus and contralateral medial rectus neurons of the oculomotor nuclear complex. It is the only conjugate movement that could be produced voluntarily.

Saccades occur virtually in all voluntary eye movements with the exception of smooth pursuit eye movements. In contrast to smooth pursuit movement, visual acuity is diminished during saccades. Saccadic movements are used to improve reading speed by increasing the numbers of

- Lesions involving the parietal lobe and Brodmann's area 19 of the occipital lobe may cause dysfunction similar to astereognosis. Therefore, the ability to recall objects by using tactile stimuli may be lost.
- Visual changes in migraine headaches include blurred vision, flashing lights, wavy lines and scotoma. Hemiparesis, ophthalmoplegia or aphasia may accompany these symptoms. Bilateral disruption of the connections between the association visual cortices and the entorhinal cortex (Brodmann's area 28) may occur as a result of basilar artery insufficiency that extends to involve the posterior cerebral arteries. This disconnection which is associated with degeneration of the occipito-temporal area result in anterograde visual amnesia and the difficulty in visually adapting to new and unfamiliar territory despite intactness of the visual apparatus.

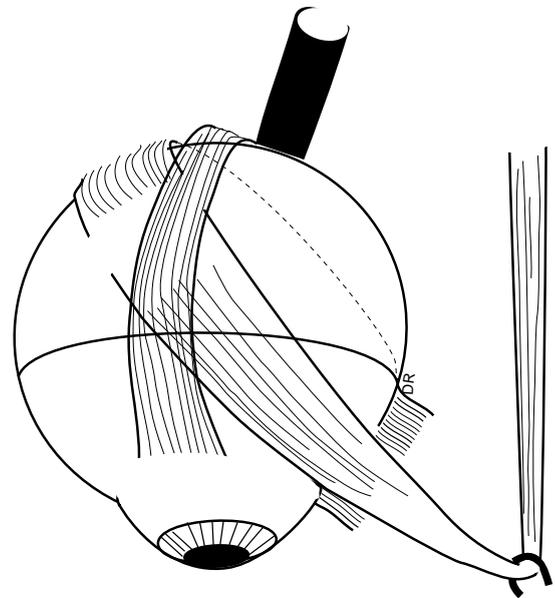


Figure 13.17 Diagram of the eyeball demonstrating the sites of attachment of the oblique muscles in relation to the optic axis

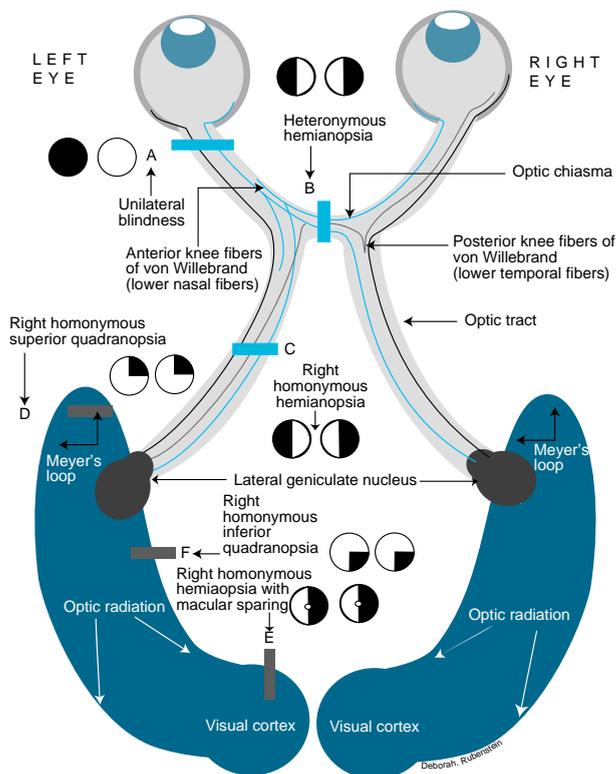


Figure 13.16 A detailed view of the lesions associated with the visual system and pertinent dysfunctions

words read in a single fixation. Smooth-pursuit movement is a slow conjugate eye movement that becomes active in tracking moving targets. Cerebellar dysfunctions, administration of sedatives and analgesics produce fragmentation of this movement into a series of saccades.

Corticotectal fibers that are derived from the occipital lobe (Brodmann's areas 17,18 & 19) control involuntary smooth pursuit eye movement.

Disorders of ocular movements

These disorders include nystagmus, conjugate gaze palsy, ocular dysmetria, oculogyric reflex, opsoclonus, ocular flutter, ocular bobbing, and ocular myoclonus.

- Nystagmus is an involuntary, rhythmic oscillation of the eye in response to an imbalance in the vestibular impulses (See also the vestibular system).
- Conjugate gaze palsy include lateral gaze and vertical gaze palsies. Lateral gaze palsy refers to the inability to look to the side of the lesion that results from destruction of the abducens nucleus. Vertical gaze palsy is characterized by the inability to look upward. This condition results from destruction of the vertical gaze center in the superior colliculus.
- Ocular dysmetria denotes an error in ocular fixation, producing overshooting the intended target followed by oscillation of the eyeball. This is commonly seen in cerebellar vermal lesion. .
- The oculogyric reflex is characterized by upward or side to side rolling movements of the eyes accompanied by abnormal contractions of the facial muscles. It is a manifestation of acute dysgenic condition, a disorder induced by neuroleptics. This reflex may be the result of metabolic disorders of dopamine and may be alleviated with anticholinergic medications.

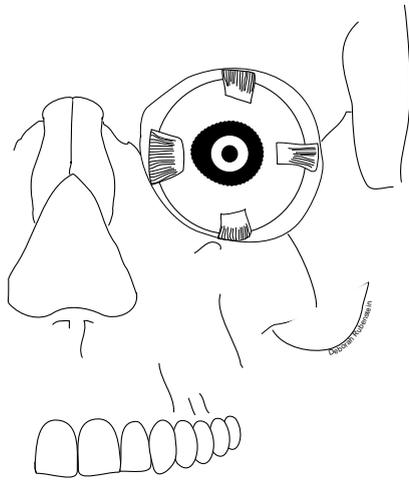


Figure 13.18 Diagram of the recti muscle

- Opsoclonus (dancing eyes in infants) is another ocular disorder that exhibits a random, conjugate saccadic movement of the eyes in all directions with unequal amplitudes. It is a manifestation of pretectal lesions or viral encephalitis.
- Ocular flutter, seen in individuals with cerebellar lesions, is characterized by sudden, rapid, and spontaneous to-and-fro oscillations of the eyes. It is associated with blurred vision and may be seen with changes in fixation regardless of the direction of the gaze.
- Ocular bobbing refers to the fast, spontaneous (not rhythmic) downward deviation of both eyes, followed by slow synchronous return of the eyes to the original position. This phenomenon may be seen in comatose individuals with lesions of the pons, cerebellum, or cerebral cortex.
- Ocular myoclonus is a term used to describe the rhythmic, rotatory or pendular movements of the eyes synchronously with similar movements of the palatal, pharyngeal, laryngeal, lingual, and diaphragmatic muscles.

Saccadic movements are controlled by the contralateral frontal cortex and are not affected by sedatives or analgesics. They are lost in Huntington's chorea and ophthalmoplegia of supranuclear origin. Cerebellar diseases may produce overshooting and undershooting of saccadic movements.

A lesion which destroys the contralateral pontine lateral gaze center, ipsilateral frontal eye field or the ipsilateral cortico-mesencephalic tract may result in the inability to look to the opposite side.

- Congenital ocular motor apraxia (Cogan syndrome) is a disorder of conjugate deviation of the eyes in which voluntary saccades are absent. The eye movements only occur when the head is in motion. The head, and not the eyes, abruptly turns to the side to visualize the object. The eyes move in the opposite direction of the movement.

Ocular reflexes

Ocular reflexes are comprised of the direct pupillary, consensual pupillary, accommodation, ciliospinal, oculo-cardiac, and oculo-auricular reflexes, as well as blink reflex of Descartes.

The direct pupillary light reflex (Figure 13.20) is produced by shining a beam of light into the eye and observing the pupillary constriction on the stimulated eye. This reflex is mediated by the optic nerve (afferent limb) and the oculomotor nerve (efferent limb). Information, which is carried by the optic nerve, is delivered to the optic tract, and bilaterally to the oculomotor nuclei. It is lost in Argyll Robertson pupil, a pupillary disorder that occurs in neurosyphilis, diabetes mellitus, and individuals with epidemic encephalitis and alcoholism.

The consensual pupillary light reflex (Figure 13.20) is characterized by constriction of both pupils in response to application of light to one eye. It is mediated by the bilateral connection of the optic tract to the oculomotor neurons via the central commissural connections. Disruption of the optic tract fibers which are destined to the oculomotor nuclei, as a result of a lesion medial to the lateral geniculate body, produces manifestations of Argyll-Robertson pupil. This exhibits loss of pupillary constriction in light reflex, while maintaining it in accommodation.

The accommodation reflex (Figure 13.20) exhibits certain changes in the eye which are associated with near vision. These changes include convergence (adduction of the eyes), miosis, and increased curvature of the lens. It requires the utilization of the visual cortex as well as the optic nerve, optic tract, and oculomotor nuclei.

The ciliospinal reflex exhibits pupillary dilatation in response to painful stimulation of a dermatomal area (e.g. pinching the neck or face). This reflex is dependent upon the integrity of the cervical postsynaptic sympathetic fibers as well as the presynaptic neurons of the first and second thoracic spinal segments.

The oculo-cardiac reflex is characterized by bradycardia (slowing of heart rate) in response to a pressure applied on the eyeball. It is mediated in the medulla by the ophthalmic nerve's (afferent limb) connections, via interneurons, to the spinal trigeminal nucleus, dorsal motor nucleus of vagus, and the cardiovascular center in the medulla (efferent limb).

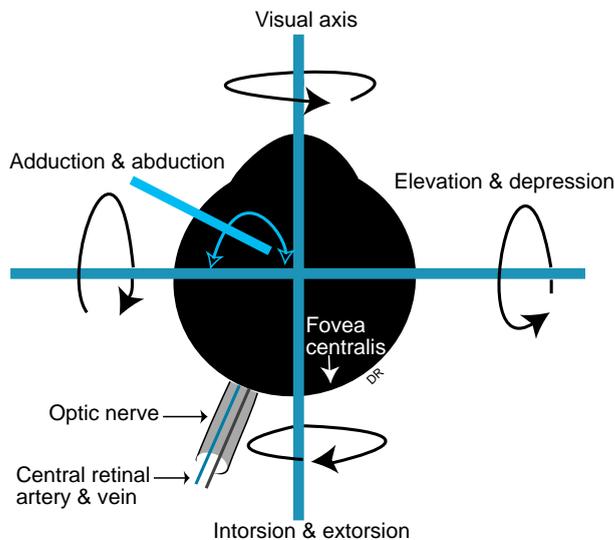


Figure 13.19 Diagram of the ocular movement around the visual axis. These movements encompass adduction, abduction, elevation, depression, intorsion, and extorsion

The oculocephalic reflex (Doll's eye movement) is produced by rotating the head to one side with the eyes held open. This abrupt head movement results in initial movements of both eyes contralaterally followed by movements to the midline, regardless of the direction of rotation. This movement is dependent upon the integrity of the vestibular, oculomotor and abducens nerves and nuclei, and the medial longitudinal fasciculus. This reflex is inhibited in the awake individual by the descending cortical influences. Closure of the eyelids facilitates this reflex by eliminating the cortical input. Patients, who have bilateral cortical lesions, as in the comatose individuals, with intact brainstem connections between the oculomotor nerve and the vestibulocochlear nuclei, exhibit a brisk doll's eye movement.

Loss of the oculocephalic reflex is an ominous finding which indicates metabolic depression or a lesion in the brainstem that disrupted the connection between the third and eighth cranial nerves. Suppression of the ascending reticular activating system and loss of consciousness occurs when the lesion is located rostral to the pontine and midbrain gaze centers. Therefore, loss of this reflex in comatose patients may indicate that the trauma has damaged the caudal pons and did not spare the lateral gaze center, requiring urgent intervention. Impaired oculocephalic response may also occur as a result of malpositioning or inadequate head rotation.

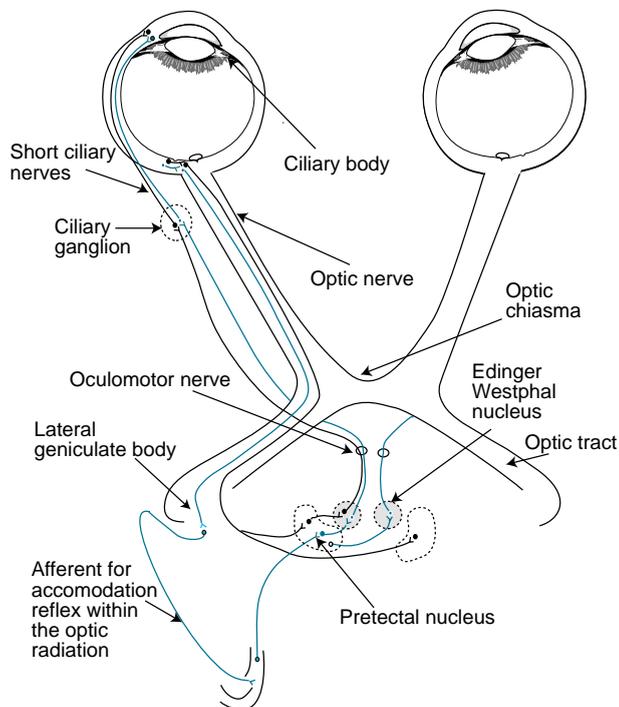


Figure 13.20 The reflex arcs of accommodation and pupillary light reflex

The oculo-auricular reflex is elicited by asking the patient to look to the extreme temporal side. It is characterized by contraction of the posterior auricular muscles and the subsequent movement of the ear posteriorly, contralateral to the stimulated side. This reflex is absent in Bell's palsy.

The blink reflex of Descartes is produced by an object that abruptly and unexpectedly approaches the eye. This reflex is mediated by the optic and facial nerves and is characterized by contraction of the orbicularis oculi in response to this stimulus.

Gaze centers

Gaze centers are represented by the lateral and vertical gaze centers in the pons and midbrain, respectively. The lateral gaze (horizontal) center (Figure 13.21) is located in the abducens nucleus and the adjacent parapontine reticular formation (PPRF). This region includes a pulse generator for fast eye movements and an integrator that determines the ultimate resting position of the eye. It controls the contralateral medial rectus muscle, and the ipsilateral lateral rectus muscle. Cortico-tectal tract, which is derived from the frontal eye field (Brodmann's area 8), carries information that projects to the contralateral gaze center,

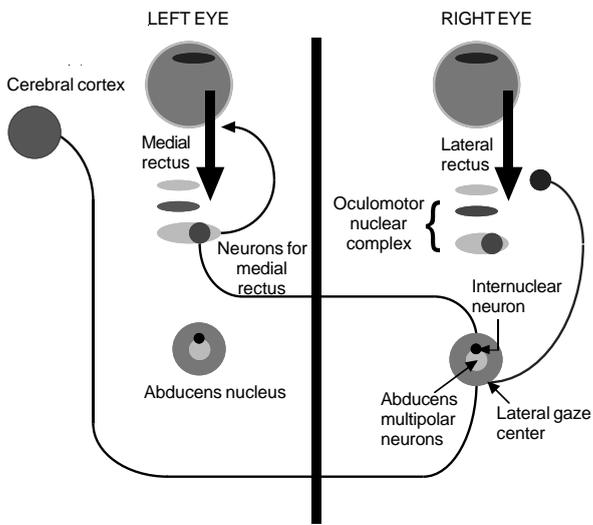


Figure 13.21 The role of the abducens nucleus as a lateral gaze center in adducting the contralateral eye and abducting the ipsilateral eye. The role of the cerebral cortex in influencing eye movement is also illustrated

regulating contralateral voluntary conjugate eye movements. Corticotectal fibers that are derived from the occipital lobe (Brodmann's areas 17,18 and 19) control involuntary smooth pursuit eye movement.

The vertical gaze center is located in the superior colliculus of the midbrain. Parinaud's syndrome ([Figure 13.22](#)) is characterized by the inability to gaze upward, manifesting weakness of convergence and sometimes loss of pupillary light reflex and mydriasis. It primarily occurs as a result of a lesion in the superior colliculi or the

Lesions of the contralateral pontine lateral gaze, the ipsilateral frontal eyefield, or the ipsilateral cortico-mesencephalic tract may produce gaze palsy to the opposite side.

posterior commissure, subsequent to a pineal gland tumor. The supranuclear mechanism for upward gaze is situated closer to the third ventricle than the center for downward gaze.

Posterior tumors of the third ventricle may result in paralysis of the upward gaze (not downward gaze). Upward gaze palsy may also be seen in individuals with subdural hemorrhage or hydrocephalus. Damage to the rostrally situated interstitial nucleus of Cajal, which lies dorsal and medial to the MLF, results selectively in downward gaze palsy. Posterior thalamic hemorrhage may be associated with downward deviation of the eye. Pretectal syndrome results from vascular occlusion or neoplasms that are confined to the pretectum or the tectum and is characterized by bilateral paralysis or paresis of vertical gaze, nystagmus and lid retraction.

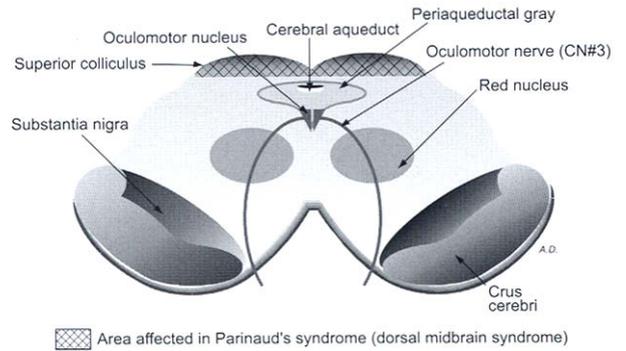


Figure 13.22 Section of the midbrain showing the lesion associated with parinaud's syndrome. In this syndrome the vertical gaze center which is represented in the superior colliculus is disrupted

Gonadal Hormones and Sexual Differentiation of Human Behavior: Effects on Psychosexual and Cognitive Development

Melissa Hines

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I. Introduction and Overview

Other chapters in this volume have discussed the powerful influences of gonadal steroids on sexual differentiation of brain and behavior in a wide range of mammals. This chapter will focus on the question of whether gonadal hormones exert similar influences on human neurobehavioral development. In other mammals, true experiments are possible, where animals are

randomly assigned to have hormones manipulated or not and where animals who do not experience a hormone manipulation are treated with a placebo or sham procedure. These types of experiments are generally not possible in human beings, because of ethical considerations. Therefore, information relevant to hormone influences on human development has come from studies of naturally occurring situations where hormonal aberrations occur. These include genetic disorders as well as situations where women have been prescribed hormones during pregnancy, usually for medical reasons. Of course, data obtained from these naturally occurring situations must be viewed more cautiously than data from true experiments, and the nonhormonal consequences of the genetic disorder or other situation resulting in hormonal abnormality must be considered in interpreting data. For this reason, as each situation involving hormonal abnormality is introduced, relevant details will be provided. Because of space constraints, these details will not be exhaustive and the reader interested in more extensive information should consult a basic text in pediatric endocrinology.

This chapter will not review in detail the extensive evidence that the gonadal hormones, androgen and estrogen, direct certain aspects of brain development during early critical periods, as these are described in other chapters. However, a few particular general points about these influences are worth reviewing before beginning the discussion of human studies. First, in general, hormones have two major types of influences on brain and behavior, activational and organizational, and these influences vary in their permanence and in the developmental time period during which they occur. Activational influences are temporary, waxing and waning as hormone levels rise and fall, and generally occur in sexually mature animals. An example would be behavioral changes that occur across the estrous cycle in rodents. In contrast, organizational influences of hormones typically occur during critical periods of early (prenatal or neonatal) development and are permanent. Although the hormone is present only briefly, its effect persists across the animal's life span. This is thought to occur because hormones direct basic processes of neural development, affecting, for instance, whether nerve cells live or die, which other cells they connect with anatomically, and which neurotransmitters they use.¹ This chapter will evaluate the possibility of similar organizational influences on human behavior. A second important point is that gonadal hormones influence behaviors that show sex differences. Therefore, in evaluating the hypothesis that gonadal hormones influence human neurobehavioral development, the focus will be on behaviors that show sex differences. In human beings, such behaviors fall into three general categories: (1) core gender identity, or the sense of self as male or female; (2) sexual orientation, or the direction of one's erotic interests, in persons of the same sex, the other sex, or both and (3) what are sometimes called gender role behaviors, or behaviors that have no obvious relation to sexuality or reproduction, but which differ on average in males and females. This chapter will discuss research in each of these three categories in turn. Third, in other species, particularly rodents, administration of estrogen to females during early

development has many of the same neurobehavioral influences as administration of androgen. This is because the androgen, testosterone, is normally converted to the estrogen, estradiol, within certain regions of the brain before it acts to masculinize and defeminize the normal developing male animals. For this reason exposure of girls and women to high levels of estrogen during development will be discussed with the expectation that results will resemble those seen following exposure to androgen. Finally, as other chapters have outlined, the early hormone environment influences the development of brain structures that show sex differences as well as behavioral outcomes. In addition, there are sex differences in the human brain. However, to date, there are no studies of these sexually differentiated brain structures in people who developed in atypical hormone environments. For this reason, this chapter will focus on behavioral outcomes following development in sex-atypical hormone environments.

II. Core Gender Identity

There is growing evidence that the early hormone environment contributes to the development of core gender identity and its disorders. Several studies have focused on genetic females with congenital adrenal hyperplasia (CAH), a genetic disorder that results in overproduction of adrenal androgens, beginning prenatally. The diagnosis of a physical intersex condition, including CAH, precludes the diagnosis of gender identity disorder.² Nevertheless, women with CAH appear to be at increased risk for the symptoms of gender identity disorder, which include a strong and persistent cross-gender identification, the desire to be, or insistence that one is, of the other sex, and a persistent discomfort with one's assigned sex and its associated gender role. For instance, a Canadian study³ found that one of a sample of 30 genetically female (XX) individuals with CAH who had been raised as females was now living as a male. The possibility that this occurred by chance was calculated to be one in 608. A second study⁴ reported on four XX CAH patients in the New York area who had been raised as females but who now chose to live as males. The possibility that this was a chance occurrence was calculated to be 1 in 420 million. Similarly, a study conducted in the Netherlands⁵ found that 2 of 18 girls with CAH also met the criteria for a diagnosis of gender identity disorder. So did 5 of 29 children with other diagnoses who had been exposed to high levels of androgen prenatally and raised as females. Reasons for the androgen exposure in these 29 children included partial androgen insensitivity syndrome (PAIS), cloacal extrophy, a transverse penis, gonadal dysgenesis, and true hermaphroditism. Others also have reported gender identity disorder in a true hermaphrodite raised as a female⁶ and in a person with PAIS raised as a female.⁷

So, hormones can influence core gender identity. But, can they determine it? Probably not. Most people exposed to high levels of androgen prenatally because of endocrine disorders and raised as females do not have gender identity disorder. This clearly is true of females with CAH, as evidenced by the two studies described above where 29 of 30 CAH women in one study and 16 of 18 CAH girls in a second were content in the female gender. However, the elevated androgen levels experienced by genetic females with CAH are likely to be lower and to differ in timing from those of normal males. For this reason, other disorders, such as those experienced by XY individuals with cloacal extrophy or transverse penises, may be more informative. Although information is limited to relatively few cases, it appears that for these patients also, despite an increased risk of gender identity disorder, female gender assignment and rearing usually lead to contentment with the female role.⁵ This despite the XY chromosome complement and presumed exposure to male-typical levels of testicular hormones prenatally and even during the early postnatal period until the testes are removed.

Perhaps the most stringent test of possible hormonal determination of gender identity is provided by situations where no underlying disorder is present, but other circumstances lead to gender reassignment. How likely is gender identity disorder in these cases? One well-publicized case involved a pair of identical twins, one of whom had his penis damaged during a phimosis repair at the age of 8 months. This twin was reassigned as female at the age of 17 months and surgically corrected to have female-appearing genitalia. Initial reports from early childhood suggested good adjustment to the female role,⁸ an outcome that was widely cited as support for socialization as the primary determinant of gender identity. As an adult, however, this twin lives as a man and was reportedly unhappy for many years with the female sex of assignment.⁹ This outcome could be seen as providing evidence that early exposure to testicular hormones determines male gender identity, despite female rearing. However, such a strong conclusion is unwarranted, partly because for the first 17 months of life, this child was socialized as a boy. Also, as in most intersex cases, no actual data on the rearing environment are available. Thus, we have no way of knowing how successful the parents were at changing the socialization of a child who had been their son for almost a year and a half to socialization that would be typical for a daughter. In addition, another case of a similar nature¹⁰ produced a somewhat different outcome. In this case, the penis of a male infant was damaged during electrocautery circumcision at the age of 2 months. By 7 months of age, when the child was hospitalized for reconstructive surgery of the genitalia, the child had been reassigned to the female sex. At the age of 16 and again at the age of 26 this woman was interviewed and found to have a female core gender identification with no sign of gender dysphoria at present or in the past. Differences between this individual and the prior case may relate to the age at sex reassignment (prior to 7 months vs. 17 months or later), or to other factors.

One question that has not been explored systematically is why some children with endocrine disorders are content with their sex of assignment and others are not. No single syndrome is particularly susceptible to problems. Factors suggested to be important include slowness to assign gender after birth, a change from the original gender assignment, ambiguity in the sex of rearing, failure to correct the genitalia surgically, poor postnatal hormonal control, problems in the parent-child relationship, and gender-atypical psychological and body image.^{4,5,10} However, no studies have directly addressed these possibilities. Resolution of this issue is important not only to increase our understanding of the basic science of gender development but also to assist in clinical decision making and patient management.

III. Sexual Orientation

The two cases of ablatio penis discussed above differed not only in outcomes for core sexual identity but also in outcomes for sexual orientation. The child reassigned as female after the age of 17 months had the sexual orientation of a heterosexual male as an adult,⁹ whereas the child reassigned as female by the age of 7 months was bisexual. During the period of assessment at age 26 she had sought additional vaginal surgery to facilitate sexual intercourse with a male partner. However, several months later she had switched from living with this man to living with a new partner, this time a woman.¹⁰ Both of these cases suggest that masculine-typical levels of testicular hormones during the prenatal and neonatal period predisposes away from a sexual orientation exclusively toward men, although the contribution of early rearing as a male, or of genitalia that require surgical correction for comfortable intercourse, cannot be ruled out.

What of other “experiments of nature”? These also suggest a hormonal contribution to sexual orientation. Once again, however, hormones appear to be a contributory rather than determining factor. Data have come from studies of genetic females exposed to high levels of androgen prenatally because of CAH, genetic females and males exposed to high levels of estrogen prenatally because their mothers were prescribed the synthetic hormone, diethylstilbestrol (DES) during pregnancy, and genetic males exposed to lower than normal levels of androgen because of defective receptors or deficiencies in enzymes needed to produce androgens.

A. Genetic Females

1. CAH

This chapter will focus on XX patients treated for CAH beginning early in life. The small number of studies examining sexual orientation in CAH

patients who were not treated until relatively late in life will be excluded, to avoid the problems of interpretation associated with postnatal exposure to high levels of androgen and attendant continued physical virilization.

Several studies have reported that women with CAH have decreased heterosexual interest, increased homosexual interest, or decreased sexual interest in general. An initial study from the United States compared 30 women with CAH to 27 control women, 15 of whom had complete androgen insensitivity syndrome (CAIS) and 12 of whom had Rokitansky syndrome. Women with these two syndromes were selected as controls because they were being followed at the same endocrine clinic as the CAH women and because, like the CAH women, they had an endocrine disorder requiring genital correction. Evaluations of sexual orientation, in imagery as well as behavior, were made by the women themselves and verified by investigator ratings based on clinic notes and an interview. Seven of the 30 CAH women were noncommittal about their sexual orientation. Of the remaining 23, 12 rated themselves as heterosexual. This was significantly different from controls, all 27 of whom were willing to indicate their sexual orientation and 25 of whom rated themselves as heterosexual. The remaining two women indicated that they were bisexual. A second study, from Germany,¹¹ compared 34 women with CAH to 14 of their unaffected sisters. Among those old enough to have had sexual experiences, 44% of the CAH group desired or had experienced homosexual relations, compared with 0% of controls. In addition, on inventories of sexual interests, the CAH group scored higher on a homosexual interest scale and lower on a heterosexual interest scale compared with the sister controls. The CAH group also reported decreased general sexual interest. A third study, from Canada,³ compared 30 women with CAH to unaffected sisters ($n = 12$), half-sisters ($n = 1$) and female cousins ($n = 2$). All women but three were interviewed face to face. Two were interviewed by telephone and one completed questionnaires. The interviews included an assessment of sexual orientation in fantasy and experience. Participants also completed a questionnaire assessing erotic response and orientation. The CAH group showed decreased general sexual activity as well as decreased heterosexual activity. A fourth study, from Germany,¹² assessed 45 CAH women (37 with classic CAH, the disorder studied in other reports, and 8 with late-onset CAH, meaning that the disorder was not apparent at birth or in infancy, but appeared later in life) and 46 controls matched for sex, age, education, and professional background. Both groups of women completed a questionnaire and the CAH women were also interviewed. The women with CAH were less sexually active, and reported fewer relationships than controls. However, self-report of homosexuality appeared similar. The authors stated: "Two patients and one control individual stated they were lesbians and lived with a female partner. One of the women stated in the questionnaires that she was a lesbian but denied it in the personal interview. Whether this was a sign of shyness or instability in her decision remains unclear."

This raises one difficulty in studying sexual orientation. Because it is such a personal issue, research participants may be reluctant to divulge detailed or accurate information. A second complication relates to the need for surgical correction of the genitalia and differences in the quality of the surgical outcome. Mulaikal,¹³ for instance, studied 80 women with CAH and found that heterosexual behavior was more frequent and lack of sexual experience less frequent in CAH patients with an adequate vagina than in those without an adequate vagina and that an adequate vagina was more likely in the simple-virilizing variant of CAH than in the salt-losing variant. He found 33 of 40 simple-virilizing patients compared to 19 of 40 salt-losing patients to have an adequate vagina. Typically, effects on gendered behavior, including sexual orientation, are more pronounced in salt-losing patients than in simple virilizers.^{3,11} Is this because they have had less successful surgical repair of the vagina? Alternatively, is the salt-losing form of the disorder more severe and thus more likely to lead both to alterations in sexuality and difficulties in vaginal repair? In their 1992 study, Dittman et al.¹¹ asked about insecurities based on genital problems and found no relationship to sexuality. Also, to the extent that measures of sexual orientation are based on fantasy as well as actual behavior, genital adequacy should be less important. However, the possibility that genital problems contribute to alterations in sexuality in CAH cannot be ruled out.

Thus, several types of studies would improve our understanding of sexual outcomes in CAH. First, it appears to be important to assess sexuality through in-depth interviews by trained sexual interviewers who can help participants comfortably divulge personal information about their sexuality. In addition, these interviews should cover information on fantasy as well as actual behavior. It also seems important to assess at least three dimensions of sexuality (heterosexual interest, homosexual interest, and sexual interest in general) since there is some evidence of alteration in each of these areas. Finally, the relationship between medical factors, such as salt-losing vs. simple-virilizing CAH (or even late-onset CAH) and the adequacy of the surgical repair of the genitalia, merit more-detailed examination to determine if alterations in particular dimensions of sexuality are more pronounced in some subgroups than in others or relate to physical problems associated with sexual function.

2. DES

On a more theoretical level, study of other hormone-exposed groups without physical problems related to surgical repair of the genitalia could shed light on the hypothesis that hormones during early development shape brain regions involved in determining sexual orientation. One group that could be particularly informative in this regard is women exposed to the synthetic estrogen, DES. In other species, early exposure to DES has masculinizing and defeminizing influences on certain aspects of brain and behavioral development, but not on development of the genitalia.¹⁴⁻¹⁷ Female offspring of these

pregnancies could reveal influences of hormones on sexual orientation in the absence of genital virilization and repair.

One group of researchers has studied sexual orientation in three samples of DES-exposed women. The first sample included 30 DES-exposed women, aged 17 to 30, compared with 30 unexposed women recruited from the same gynecological clinic.¹⁸ The controls resembled the DES-exposed women in age and in having abnormal PAP smear findings. (Although prenatal treatment with DES rarely causes genital virilization, it usually alters some aspects of genital development. A small proportion of DES-exposed women develop vaginal or cervical adenocarcinoma, and a large proportion develop vaginal adenosis. In most cases they have abnormal PAP smears.¹⁹) Twelve unexposed sisters of the DES-exposed women formed a second comparison group. Sexual orientation in fantasy and behavior was assessed by interview using seven-point rating scales, ranging from exclusively heterosexual (0), through bisexual to exclusively homosexual (6).^{20,21} Results suggested DES increased bisexuality or homosexuality. Approximately 24% of the DES-exposed women (vs. 0% of the control group) had a lifelong bisexual or homosexual orientation. Among the 12 sister pairs, 42% of the DES-exposed women (vs. 8% of their unexposed sisters) had a life-long bisexual or homosexual orientation.

This initial study was later reported along with two further studies.²² In one, a second sample of 30 DES-exposed women was compared with 30 demographically matched controls who did not have a history of DES exposure. Eight unexposed sisters also participated. Results resembled those of the first study. About 35% of the DES-exposed women (vs. about 13% of the matched controls) showed bisexual or homosexual responsiveness since puberty. For sister pairs, the percentages were 36 and 0%. In the third study, 37 women exposed to DES were identified from obstetrical files. Daughters of women treated with at least 1000 mg of DES were compared with age-matched daughters of untreated women identified from the files of the same obstetrical practice. Results again suggested an association between DES and homosexual or bisexual orientation, although the difference between hormone-exposed and unexposed women (16 vs. 5%) appeared less dramatic than in the first two samples.

B. Genetic Males

1. *Androgen Insensitivity Syndrome (AIS)*

The consequences for genetic males of developing in a hormone environment that could promote a female-typical sexual orientation are not well understood. This may be because such hormone environments are rare. AIS, a disorder in which the testes produce normal levels of androgens, but cells cannot respond to it because of receptor defects, occurs in only about 1 in 60,000 births, and very few AIS individuals have been studied. One study compared sexual orientation in CAH women to 15 AIS patients who had

been raised female. The AIS group had a more female-typical sexual orientation (i.e., toward males) than the CAH group,²³ but the AIS group was not compared with female controls with no endocrine disorder.

2. Enzymatic Deficiencies

Other syndromes that provide an opportunity to study the impact of reduced levels of androgen on gender development in genetic males include deficiencies in enzymes that are required for androgen synthesis, such as 5-alpha-reductase deficiency and 17-beta-hydroxysteroid dehydrogenase deficiency. In both syndromes, the physical appearance at birth is more female than male, and affected individuals are often raised as females. However, if the individual's testes are not removed, the dramatic elevation in androgen at puberty produces physical virilization. It has been reported that these individuals then adopt a male identity and social role and the sexual orientation of a heterosexual man (i.e., toward women).²⁴⁻²⁶ One interpretation of this outcome is that androgen exposure had programmed the brain in the male direction, despite rearing as a female.²⁴ Alternatively, it has been suggested that not enough data are available on rearing to know if it was unambiguously female,^{27,28} or that the change to a masculine physical appearance or the social advantages of being male (or disadvantages of being a sterile female) in the societies where these syndromes have been studied account for the change.^{27,29}

3. Exposure to DES or Progestins

The impact on sexual orientation of exposure of genetic males to estrogen, progestins, or a combination of estrogen and progestin has also been investigated. Neither prenatal estrogen or progesterone exposure appears to influence sexual orientation in men. One study compared two groups of men exposed prenatally to the synthetic estrogen, DES, with controls matched for sex, age, and maternal age at birth.³⁰ One group had been exposed to DES alone, and the other to DES plus natural progesterone. There were no differences between either hormone-exposed group and their respective controls. Of 16 DES-exposed men, 15 indicated their behavior was exclusively heterosexual, as did 16 of 16 control men. Similarly, 13 of 17 DES-exposed men and 13 of 16 controls indicated their fantasies were exclusively heterosexual. Of 21 men exposed to DES plus progesterone, 20, compared with 16 of 20 control men, indicated exclusively heterosexual behavior, while 15 of 21 in the hormone group and 14 of 21 in the control group indicated exclusively heterosexual fantasies. The study also included men exposed to natural progesterone or synthetic progestins without DES. They also showed no differences in either sexual experience or fantasy from matched controls. In the natural progesterone group, 8 of 10 were exclusively heterosexual in behavior (vs. 9 of 10 controls) and 6 of 10 were exclusively heterosexual in fantasy (vs. 6 of 10 controls). In the synthetic progestin group, 12 of 13 were

exclusively heterosexual in behavior (vs. 12 of 13 controls) and 10 of 13 were exclusively heterosexual in fantasy (vs. 11 of 13 controls).

A second set of studies of DES-exposed men also found no influence on sexual orientation. One study compared 31 hormone-exposed men with 29 unexposed controls, all recruited from one obstetrical practice that had prescribed DES. The second included 34 DES-exposed men and 15 controls, all recruited from one urological practice. Sexual orientation in behavior and fantasy was based on interviews and measured on a 7-point heterosexual to homosexual continuum. No consistent differences were seen between the DES-exposed men and controls.³¹

The absence of an influence of estrogen and progesterin on sexual orientation in men is not surprising. Animal models of hormonal influences suggest that neither estrogen nor progesterone have consistent demasculinizing or feminizing influences on development in genetic males when administered early in life (see, e.g., Reference 14, but also Reference 32).

IV. Gender Role Behaviors

Gender role behaviors are sometimes defined as behaviors that are culturally fixed or assigned to one sex or the other (e.g., Reference 33). However, this definition assumes enough knowledge of the causes of behavioral sex differences to determine which are culturally fixed or assigned. Perhaps a safer definition would be those behaviors, other than core sexual identity or sexual orientation, that differ on average for males and females. Even this definition, although safer, is not without problems. As Maccoby and Jacklin³⁴ pointed out as long ago as 1974, there is great debate and widespread misconception about psychological sex differences. In addition, they described problems associated with identifying sex differences, such as the increased probability of publishing when sex differences are significant and not when they are not, producing an overreporting of spurious effects. A second problem is a tendency for researchers, like others, to see behavior through the prism of their own preconceptions, a tendency that can result in observing sex differences if you expect them, but not if you do not. Although these problems cannot be avoided completely, there is general agreement that there are several sex differences in what are commonly viewed as gender role behaviors. These include juvenile play behavior (e.g., toy choices, sex of preferred play partners, and rough and tumble play), specific cognitive abilities (e.g., mental rotations ability, spatial perception ability, mathematical problem-solving ability, verbal fluency, and perceptual speed and accuracy), personality characteristics (e.g., aggression and nurturance), and manifestations of neural asymmetry (e.g., hand preferences and language lateralization). In some cases, sufficient data are available to estimate the size of these behavioral sex

differences. To put them in a familiar perspective, they are typically less than half the size of the sex difference in height, which is two standard deviation units. Nevertheless, by behavioral standards, where group differences of 0.8 standard deviation units are regarded as large, they are potentially important. The next section of this chapter will discuss data regarding hormonal influences on gender role behavior. Because of space limitations, the focus will be on two areas: childhood play behavior and cognitive functioning.

A. Childhood Play Behavior

The play behavior of girls exposed to high levels of androgen prenatally, because of CAH, has been assessed in several studies and found to be more masculine or less feminine than that of controls. These results have been reported based on interviews with the girls and their mothers, on questionnaires and even in direct observations of the toy choices of girls with CAH compared with unaffected sisters and female first cousins in the same age range.^{8,35-39} Questionnaire and interview data suggest that the influenced behaviors include increased rough-and-tumble play and interest in male playmates, as well as increased interest in male-typical toys, such as cars and trucks, and decreased interest in female-typical toys, such as dolls. However, the one study that involved direct observation of rough-and-tumble play⁴⁰ found no difference between 20 girls with CAH compared with 12 unaffected female relatives, despite seeing sex differences in the 12 unaffected girls compared with 15 unaffected male relative controls. Further research is needed to determine if this reflects a lack of a hormone effect on rough-and-tumble play. Alternatively, the testing situation may have been inadequate to detect an effect. Rough-and-tumble play requires a partner. Because most girls do not like this kind of play and boys prefer to play in this way with other boys, rough-and-tumble play in CAH girls could have been inhibited by the lack of a willing partner (see Reference 40 for additional discussion of this and other possibilities).

The play behavior of children whose mothers were prescribed hormones during pregnancy has also been studied. One investigation found that ten girls exposed to androgenic progestins prenatally showed increased preferences for male playmates, masculine-typical toys, and vigorous play.⁸ Thus, this source of exposure to androgenic hormones appears to have similar effects on girls to those seen after prenatal androgen exposure caused by CAH. Similarly, exposure of genetic females to the synthetic progestin, medroxyprogesterone acetate (MPA), which has some anti-androgenic action, has been reported to decrease some male-typical play behaviors and increase some female-typical ones. These effects appear to be more limited, and less consistent, than those of androgen exposure,⁴¹⁻⁴³ perhaps not surprisingly since there is less room for a meaningful decrease in feminine-typical behaviors in genetic females than for a meaningful increase in masculine-typical ones.

In contrast to the effects of androgen, prenatal exposure of genetic females to the synthetic estrogen DES does not appear to influence sexual differentiation of juvenile play. Three reports on women exposed prenatally to DES used interviews and questionnaires to assess childhood play retrospectively.⁴⁴⁻⁴⁶ The three reports were from a single research group and involved a total of 60 DES-exposed women compared with various control groups. Taken together with the results for girls exposed to androgens prenatally, these data suggest that masculine-typical play behaviors differentiate under the influence of androgen acting through androgen receptors, rather than following conversion to estrogen. This is consistent with data from experimental studies of rats, where sex differences in rough-and-tumble play, unlike sex differences in most other behaviors, have been suggested to result from direct action of androgen.⁴⁷ However, the only published study of the influences of DES on rough-and-tumble play in nonhuman primates suggests that prenatal exposure of genetic females to DES has some masculinizing effects.¹⁷ Female rhesus monkeys exposed to a long duration of DES treatment prenatally, but not those exposed to a short duration of treatment, initiated more rough play and initiated play with male partners more frequently than untreated females. In these respects their play behavior resembled that of male monkeys. These results suggest that certain aspects of play behavior might be sensitive to prenatal estrogen exposure, or that longer duration of exposure might be influential.

It is not clear if exposure to estrogen or progestin prenatally alters the development of play behavior in males. One study suggested that exposure of boys to the antiandrogenic progestin MPA decreased some, but not all, aspects of male typical play.^{43,48} However, a study of boys exposed to a different antiandrogenic progestin, 17-alpha-hydroxyprogesterone caproate (17 aHC), found no evidence of alterations in sex-typical play behavior.⁴⁹ A third study, of boys exposed to estrogen and progestin, found some evidence of decreased athleticism in a group of 6-year-olds, but no evidence of changes in other aspects of sex-typical play at this age and no evidence of changes in athleticism in a similar group of hormone-exposed boys at age 16.⁵⁰

B. Cognitive Abilities

Early reports on cognitive function in hormone-exposed patients suggested that prenatal exposure to androgenic hormones enhanced general intelligence. Patients exposed to androgenic progestins and patients with CAH had intelligence quotient (IQ) scores that were significantly higher than the population norm.^{51,52} Subsequently, individuals exposed to natural progesterone were reported to be rated by teachers as smarter and to have received more scholastic honors and progressed farther in school compared with matched controls.^{53,54} Because natural progesterone should have antiandrogenic activity, these results would appear to be in conflict.

Subsequent research revealed no IQ differences between CAH patients and relative controls, and no difference from predictions based on parental IQ.⁵⁵⁻⁵⁷ Intellectual attainment in CAH patients has also been reported to resemble that of carefully matched controls.⁵⁸ Similarly, studies of children exposed prenatally to estrogen and progestins (androgenic or antiandrogenic action unspecified)⁵⁹ and of women exposed to the synthetic estrogen DES^{60,61} have found no differences in general intelligence from unexposed relatives. Also, reevaluation of the data suggesting that progesterone enhanced intellectual attainments found little support for the original conclusions,⁶² suggesting instead that they resulted from questionable sampling and statistical analyses. Similarly, attempts at replication by reevaluation of some of the original participants, as well as new ones, found no evidence of an association between prenatal progesterone and academic achievement.⁶³ Thus, it now appears that exposure to high levels of sex hormones does not influence general intelligence. This is consistent with the absence of sex differences in general intelligence.

Although general intelligence appears to be similar for males and females, there are some sex differences in specific aspects of cognitive function. These include male advantages on tasks requiring mental rotation of two- or three-dimensional objects, spatial perception tasks, and mathematical problem solving and female advantages on verbal fluency and perceptual speed and accuracy. Although these differences have sometimes been conceptualized as a male advantage on spatial and mathematical tasks and a female advantage on verbal tasks, this is an overgeneralization. In all three areas there are some tasks that do not show sex differences. (See References 64 through 69 for meta-analyses in these areas.)

Thus the sex differences are specific to subtypes of ability. In addition, they vary in magnitude. The largest is that in three-dimensional mental rotations for which the difference between men and women is 0.92 standard deviation units (or "d" units). Effect sizes for group differences can be classified as large ($d = 0.8$ or greater), moderate ($d =$ about 0.5), or small ($d =$ about 0.2).⁷⁰ By using this approach, sex differences in mathematical problem solving, verbal fluency, and perceptual speed are moderate, those in spatial perception are small to moderate, and those in two-dimensional mental rotation are small (see, Reference 71) for further discussion and additional references regarding effect sizes).

The evidence that prenatal hormone levels influence sex differences in cognitive function is equivocal. One study reported enhanced performance on a three-dimensional mental rotations task in 17 CAH girls compared with 13 unaffected sisters and female first cousins.⁷² Similar differences between CAH and control girls were also seen on a two-dimensional mental rotations task and on a spatial visualization task which would not normally show a sex difference. There were no differences between female patients and controls on tests of perceptual speed and accuracy or on measures of verbal ability. There also were no significant differences between 8 boys with CAH and 14

unaffected male relatives on any of the cognitive measures. This is the only published study of CAH patients to date that has used the three-dimensional mental rotations task that shows a large sex difference. One other study of 7 girls and 5 boys with CAH compared to 6 unaffected sisters and 4 unaffected brothers reported enhanced performance in CAH girls and impaired performance in CAH boys on a two-dimensional mental rotations task,⁷³ but a separate study using the same task in a sample of 17 girls and 10 boys with CAH and 11 unaffected sisters and 16 unaffected brothers found no such differences.⁵⁵ Studies have also found no differences between CAH patients and controls on the block design subtest of the Wechsler scales, (Wechsler Adult Intelligence Scale, WAIS, Wechsler Intelligence Scale for Children, WISC, and the revised versions of these, WAIS-R and WISC-R) or on the embedded figures test (EFT),^{55,74} although one found CAH girls to perform worse than controls on the block design subtest,⁵⁸ a result opposite prediction based on the idea that visuospatial abilities generally show a male advantage. However, the block design subtest of the WAIS-R shows only a small sex difference ($d = 0.26$) and the same subtest of the WISC-R shows a negligible sex difference ($d = 0.15$). (Some studies may have used unrevised versions of these tests, but sex differences on subtests appear similar in the revised and unrevised versions^{75,76}). Similarly, the EFT shows variable sex differences ($d = 0.18$ overall and for the group EFT, but effect size may be as small as 0.01 for the children's EFT and as large as 0.42 for the individual EFT^{64,66}). As a consequence these tests are not ideal markers of hormonal influences.

Most studies of CAH patients have also found no differences on tasks measuring verbal abilities or perceptual speed and accuracy. As noted above, the Resnick et al.⁷² study finding enhancement in CAH females on several visuospatial measures found no differences between CAH girls or boys in perceptual speed or accuracy or on verbal measures. Baker and Ehrhardt⁵⁵ also reported no differences for CAH males or females on verbal measures. Similarly, two additional studies found no evidence of differences between CAH patients and controls on measures of verbal abilities or perceptual speed and accuracy. One included 15 female and 16 male CAH patients and matched controls.⁷⁴ The other included 7 female and 12 male patients compared with matched controls, but in this one study the results were not broken down by sex.⁷⁷

The most consistent finding regarding CAH and cognition has involved impaired computational ability. This has been reported in three studies.^{55,58,77} In one study the effect was seen for girls but not boys,⁵⁸ in one it was seen in both girls and boys separately⁵⁵ and in the third it was seen in the combined group of boys and girls.⁷⁷ This effect is puzzling. Although there is a sex difference favoring females in computational ability, it is small and apparent only in young children.⁶⁸

If androgens play a role in the development of sex differences in human cognition, they are unlikely to do so after conversion to estrogen. Two studies of DES-exposed women have found them to be highly similar to their unaffected sisters on verbal and visuospatial tasks that show sex differences as

well as on those that do not. The first study compared 25 women who had been exposed for at least 20 weeks prenatally to DES with 25 of their unexposed sisters. There were no differences on a two-dimensional mental rotations task and no differences on a verbal fluency task.⁶⁰ The second study included 42 women exposed prenatally to DES and 26 unexposed sisters.⁷⁸ The groups did not differ in performance on any of several measures that show sex differences, including a three-dimensional mental rotations task, measures of spatial perception, verbal fluency, and perceptual speed and accuracy. They also did not differ on verbal or spatial tasks that do not show sex differences. A third study of cognition following prenatal exposure to DES availed itself of a sample from a true experiment where women had been administered either DES or placebo during pregnancy to evaluate its efficacy for preventing miscarriage. American College Testing (ACT) scores were obtained for 325 female offspring, 175 exposed to DES and 150 exposed to placebo prenatally. There were no differences between the groups on any of four ACT subtests that show sex differences.⁷⁹ The absence of an effect of early estrogen exposure on cognitive development, at least in the area of spatial ability, appears to contrast with the situation in rodents where levels of estrogen during early development influence sex differences in spatial ability during later life.⁸⁰

What of cognitive abilities in other hormone-exposed groups? A syndrome that has been studied extensively is Turner syndrome (TS). This syndrome occurs when the second member of the 23 pairs of chromosomes (the sex chromosomes) is absent or imperfect. Consequences of TS include universal short stature and other more variable outcomes including gonadal failure in the great majority of cases.^{81,82} For patients with the XO karyotype this gonadal failure occurs prenatally.⁸³ It is possible, therefore, that TS patients experience lower than normal levels of ovarian hormones during critical developmental periods. Vocabulary scores are normal in TS females, but a variety of other cognitive abilities, including some that are typically performed better by males, some that are typically performed better by females, and some that are sex neutral, are impaired (see Reference 71). Published data are insufficient to determine if impairment is greater on tasks that show sex differences compared with tasks that do not.

Men with idiopathic hypogonadotropic hypogonadism (IHH) experience gonadal failure because of a deficiency in gonadotropins or hypothalamic releasing factors.⁸⁴ They are typically born with normal-appearing male genitalia, assumedly because maternal gonadotropins stimulate androgen production prenatally.⁸⁵ However, it is not known if prenatal androgen production is equivalent to that of normal males. In addition, men with IHH would not experience the neonatal elevation in androgen that occurs in normal males. IHH men have been reported to show visuospatial deficits on several tasks including a two-dimensional mental rotations task (the Space Relations subtest of the Differential Aptitude Test) and a measure of spatial perception (the Rod and Frame Test) as well as on tests that are less sensitive to gender, such as the EFT and Block Design, although this last result has not

been found consistently.⁸⁵⁻⁸⁷ One study also found that the severity of the disorder correlated with the degree of visuospatial impairment, that treatment with testosterone in adulthood did not improve performance, and that men who became hypogonadal after puberty did not show impaired visuospatial ability, all of which points to the importance of an androgen deficit during early development.⁸⁵ In regard to verbal abilities, IHH men do not differ from controls on tasks that do not show a sex difference, including Wechsler subtests and a vocabulary test.^{85,87} However, in one study they showed impairment on the Controlled Associations Test, a measure of verbal fluency.⁸⁷

A group of ten patients with CAIS have been reported to show deficiency on a number of spatial tasks, including Block Design and other performance subtests from the Wechsler scales compared with 26 female and 9 male relatives.⁸⁸ However, most of the tests on which impairment is seen show negligible or no sex differences. Similarly, one study of ten boys exposed to the synthetic estrogen DES prenatally found them to have reduced scores on a combination of Wechsler performance subtests compared with their unexposed brothers,⁸⁹ tests which again show small to negligible sex differences. The placebo controlled study of DES-exposed offspring found one difference between 172 DES-exposed males and 175 placebo-treated controls. The DES-exposed men scored higher on the Social Science subtest of the ACT. Since males typically score slightly higher than females on this subtest, the effect is in the direction of more masculine-typical performance. However, the effect was not predicted and, since it was the single significant finding from a number of statistical comparisons, the authors attributed it to chance.⁷⁹

V. Summary and Conclusions

Data on cognitive function in patients exposed to atypical hormone environments prenatally is inconclusive. Only the studies of DES-exposed offspring have used sample sizes large enough to be confident of detecting effects if they exist, and these studies are notable in providing no evidence of a hormonal influence. Studies of patient groups have relied on smaller samples. For some syndromes, findings are contradictory. In addition, for these syndromes as well as those producing more consistent findings, it is not clear if cognitive impairments are specific to abilities that show sex differences (or even more pronounced for these abilities compared with those that do not show sex differences). Inconsistencies could result from small sample size and reduced power to detect effects consistently. Alternatively, as noted in the discussion of research on gender differences, there is a tendency to publish results for small samples when they are significant but not when they are not, and this tendency could be operating in studies of hormonal influences as well. Conclusive information about whether or not hormones influence

sexual differentiation of human cognitive functions will require larger samples and attention to the magnitude of changes in abilities that show sex differences compared with those that do not.

Data suggesting hormonal contributions to core gender identity, sexual orientation and childhood play behavior, particularly toy choices, suggest that the early hormone environment has consistent influences in these areas. Girls exposed to high levels of androgens prenatally, either because of CAH or because their mothers were prescribed androgenic progestins during pregnancy, show increases in masculine-typical play behavior. Other research suggests that sex differences in play behavior, including toy choices, are also learned, through reinforcement and modeling (see Reference 90 for reviews). Thus, the early hormone environment appears to be one of several types of influences shaping sex differences in these childhood behaviors.

Both XX and XY individuals reared as females but exposed to levels of androgenic hormones that are higher than those experienced by normal females during prenatal and neonatal development show an increased likelihood of symptoms of gender identity disorder. Similarly, women exposed to high levels of either androgens or estrogens during development show increased homosexual or bisexual interest. However, for both sexual orientation and core gender identity, the effect of hormone exposure is not universal. Bisexuality and homosexuality are increased following prenatal exposure, as is the occurrence of symptoms of gender identity disorder. However, the majority of women exposed to high levels of hormones are heterosexual and content in their assigned gender. Thus, as for childhood play behavior, hormones appear to be one of a number of factors shaping these aspects of sexual identity.

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Sexual Differentiation of Spatial Functions in Humans

Elizabeth Hampson

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I. Introduction

Although the two sexes do not differ in intelligence, as measured by standard IQ tests, a number of specialized cognitive functions are sexually differentiated in humans. On average, women outperform men on tests of perceptual speed and accuracy, verbal fluency, and certain memory functions. Men outperform women in many spatial functions that require the formation of accurate mental representations of the positions or movements of objects in space. For example, men tend to excel on tasks which involve route-learning, or in which visual objects or parts of objects are mentally transformed in shape or

position, manipulated, rotated, visualized in motion or from an alternate orientation in space. In everyday life, men claim to rely more than women on dynamic mental representations to guide behavior, while women claim to engage in more static mental imagery than men.¹

Spatial abilities evolved to enable our hominid ancestors to solve spatial problems in the natural environment. Today, they are typically assessed in the laboratory setting using a variety of psychometric tests or synthetic problems. An example item from a test of spatial ability is shown in [Figure 15.1](#). The type of function assessed in this case is called “mental rotation” or “spatial orientation.” Factor analytic studies of mental test batteries have long identified spatial orientation as a separable form of spatial ability. In everyday life, mental rotation is required in many mechanical or building-related activities and is involved in recognizing one’s surroundings from different vantage points. Mental rotation tests are widely used to assess spatial ability in human research and reliably elicit a male advantage. The size of the sex difference varies, but on mental rotation tests with a high degree of difficulty, average scores for men and women differ by as much as one full standard deviation.

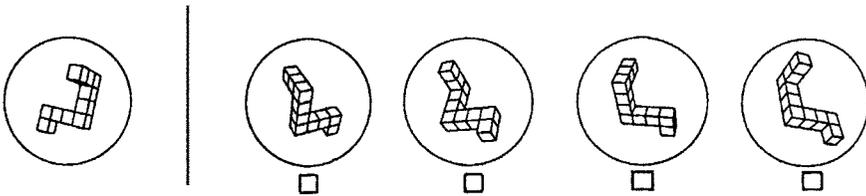


FIGURE 15.1

Example item from a test of mental rotation. The objective is to determine which two of four alternatives represent the same figure as the target figure shown at the left. (From Vandenberg, S.G., *Mental Rotations Test*, 1971. With permission.)

The proximate causes of sex differences in cognition are debated. In the early 1980s, I embarked on a series of studies to investigate whether gonadal steroids are involved in the sexual differentiation of cognitive function. At the time, there was emerging evidence in other species that sex steroids are the basis of a remarkable range of behavioral sex differences, but this was a radical or even heretical idea in humans. The popular wisdom of the day suggested that social and experiential factors, not biology, were the sole causes of cognitive sex differences. A close examination of the literature, however, provided clues that hormones might be involved, at least in spatial functions. For one thing, sex differences in a variety of spatial learning tasks had been demonstrated in nonhuman species, suggesting sexual differentiation in spatial functions is not a uniquely human phenomenon. The male advantage on spatial tasks was observed across a diverse range of human cultures with differing gender expectations and socialization practices. The observation that sex differences in spatial function are not expressed before puberty, or, if

present, are weaker than the sex differences seen in mature adults, raised the possibility of an activational component. Finally, spatial proficiency had been noted in earlier research to covary predictably with individual difference variables or biological markers suggestive of a hormonal influence.^{2,3} Of course, spatial functions in other species are now known to exhibit hormone sensitivity, but most of this work did not emerge until later (but see Reference 4).

In this chapter, we will review evidence from our own laboratory and elsewhere which supports the neuroendocrine hypothesis. We will also try to place hormonal modulation of spatial abilities within an evolutionary context. In general, evidence increasingly suggests that sex differences in spatial functions have a substantial basis in neuroendocrine events. Effects seen for spatial ability are important beyond these exact functions because they help build support for the more general view that the human central nervous system (CNS) is sexually differentiated and that sex steroids are important in the establishment and expression of sex-dependent neural and behavioral specializations.

II. Effects of Early Life Hormones on Spatial Functions

A difficulty facing human researchers is the inability, except under rare circumstances, to manipulate hormones experimentally in order to observe the effects on some dependent variable of interest. Researchers must rely on clinical conditions in which early life hormones differ from the norm, either being present in excess or in insufficient amounts or in which tissue responsiveness to specific steroids is reduced through a genetic error. Two of the most important sources of evidence for testing the role of early life hormones in sexual differentiation of cognitive function are people with congenital adrenal hyperplasia (CAH) and people born of pregnancies in which the mothers ingested the synthetic estrogen diethylstilbestrol (DES) during gestation.

A. Evidence from Congenital Adrenal Hyperplasia

The classical form of CAH due to 21-hydroxylase deficiency is a rare disorder of adrenal steroid biosynthesis that affects approximately 1 in 15,000 live births. In this condition, the 21-hydroxylase enzyme is deficient in the adrenal cortex as a result of a gene mutation on the short arm of chromosome 6. As a result, males or females with CAH are exposed during gestation to unusually high levels of androgens, beginning in the third month of fetal life. As soon as diagnosis is made, which usually occurs in the immediate newborn period, at least in females, replacement therapy with glucocorticoids

and, if necessary, mineralocorticoids is begun. With treatment, steroid concentrations can be normalized and further virilization prevented. In early diagnosed cases who receive effective treatment, the hormonal abnormalities are confined to the prenatal and early neonatal period. An interesting question, therefore, is whether females with CAH show evidence of increased spatial abilities, compatible with their male-like gestational environment. Such an observation would suggest that early androgens are important in the organization of spatial abilities in humans, because postnatal upbringing in girls with CAH is female. Thus, environmental factors do not likely account for any observed differences between girls with CAH and unaffected girls. Partial masculinization of other behavioral traits, including sexual orientation⁵ has been reported in females with CAH.

In our own research,⁶ we were fortunate to have the opportunity to assess a group of young children with the classical form of CAH (N = 12) and a control group of unaffected siblings (N = 10). We used a standard paper-and-pencil spatial test, Spatial Relations, plus a nonspatial test, Perceptual Speed, taken from the same set of aptitude tests (the *Primary Mental Abilities* battery). The two tests were closely matched on mode of responding and other extraneous features. The results were striking (Figure 15.2). On Spatial Relations, a test of spatial visualization that involves mentally fitting together sets of cutout shapes, girls with CAH scored a full standard deviation above the mean for control girls. In contrast, control girls achieved the higher score on Perceptual Speed. Thus, a double dissociation was found. Perceptual speed is a skill that shows a female superiority in adult samples, so defeminization of perceptual speed in girls with CAH is not implausible.

Confirmation of our findings comes from an earlier study by Resnick et al.⁷ who also found better spatial abilities in females with CAH. In the Resnick study, superior spatial scores in the CAH group relative to female controls were found on three different tests of spatial ability including two tests of mental rotation. This suggests the spatial improvement is likely to generalize to other types of spatial measures. Importantly, in both Resnick's study and our own, the effect was selective. No enhancement in the CAH group was found for other types of cognitive functions that were assessed, nor did they differ from controls in general intelligence. In Resnick's study, the effects were seen in adolescents and young adults, indicating the effects are likely to persist at older ages, although, obviously, this less clearly implicates an organizational mechanism than our own work, which was done in prepubertal children. Taken together, the two studies provide strong evidence in favor of an organizational effect of early androgens on spatial functions that ordinarily exhibit a male advantage.

Recent work by Grimshaw et al.⁸ in ordinary children who do not have CAH provides convergent evidence for a relationship between spatial ability and the androgen environment *in utero*. Testosterone concentrations at 14 to 20 weeks of gestational age were measured by radioimmunoassay in specimens of amniotic fluid and correlated with the later performance of the offspring of those pregnancies on a mental rotation task at age 7. In girls,

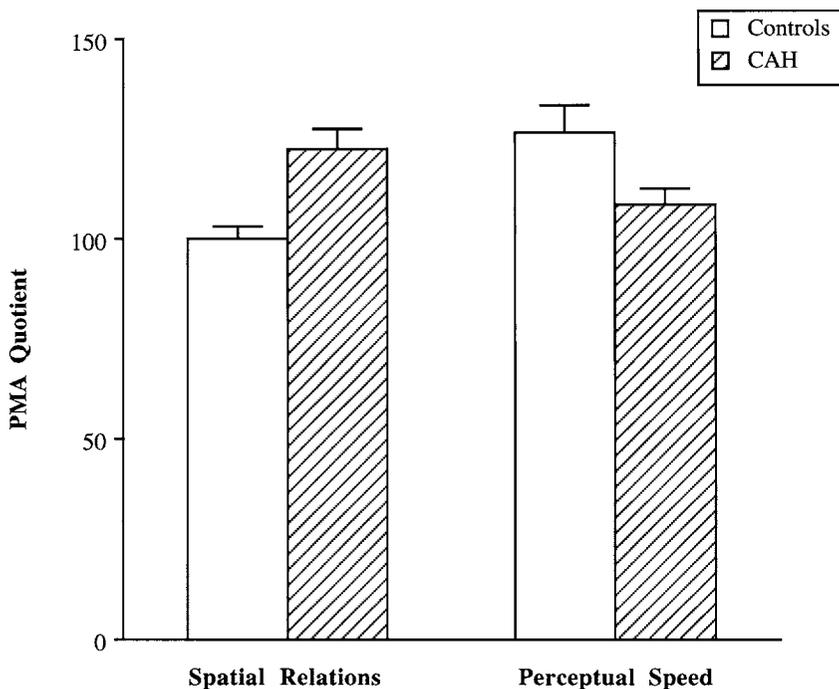


FIGURE 15.2

Girls with CAH outperformed same-sex sibling controls on a test of spatial visualization. The difference was reversed on a test of perceptual speed and accuracy.

Grimshaw et al. found a significant positive correlation ($r = 0.67$) between testosterone levels in second-trimester amniotic fluid and facility in the mental rotation task. In boys, if anything, the opposite pattern was seen ($r = -0.62$). This is consistent with our own CAH findings,⁶ in that in our study boys with CAH were discovered to have *lower* spatial visualization scores than control boys. It must be stressed that the Grimshaw data do not necessarily identify Weeks 14 to 20 as the critical period when sexual differentiation of spatial functions occurs. The second trimester is often considered the time when sexual differentiation of the human brain is most likely to occur, and the Grimshaw data are certainly consistent with that prospect. But if a fetus with higher testosterone at Weeks 14 to 20 is also characterized by relatively higher levels of androgens at other points in gestation, the same pattern of correlations with spatial scores could easily emerge at other time points as well. At present, we cannot exclude this possibility.

B. Evidence from Women Exposed to Diethylstilbestrol

An important corollary source of information about the sexual differentiation of spatial functions comes from studies of people exposed to the synthetic

estrogen DES during gestation. DES is a nonsteroidal estrogen that was widely prescribed for the prevention of miscarriage from the 1940s to the early 1970s. Spatial abilities along with other sexually differentiated cognitive functions have been investigated in women exposed to DES. As in the CAH work, a provisional hypothesis was that women exposed to DES might develop superior spatial abilities, relative to unexposed controls. The basis for expecting better spatial abilities in women exposed to DES is observations in laboratory rodents that exposure to DES during early development leads to masculinization and defeminization of several behavioral characteristics. Support for the masculinizing potential of DES in humans comes from work showing an increased incidence of bisexuality in women exposed to DES during gestation.⁹ It is important to note, however, that DES exerts its activities by binding to estrogen receptors and is capable of exerting masculinizing effects in the CNS only in those neural regions that normally undergo sexual differentiation via conversion of testicular androgens to estradiol.

In terms of spatial abilities, Hines and Shipley¹⁰ failed to find a difference between DES-exposed women and their unexposed sisters on a test requiring mental rotation of simple two-dimensional shapes. In a recent study, Hines and Sandberg¹¹ used a more extensive set of cognitive measures, including six spatial tests assessing a wide variety of different spatial functions, to investigate cognitive performance in women with a history of DES exposure. No evidence of superior spatial performance was found. DES-exposed women did not differ from their sisters who were not DES-exposed either in spatial ability or any other cognitive function. Scores were closely equivalent in the two groups of women. Both the Hines studies were well designed and well executed, so the failure to find significant differences is not likely due to methodological error. Hines concluded that prenatal DES exposure has little or no effect on women's cognitive development.

C. Conclusion

The hypothesis that there is an organizational effect of early androgens on spatial abilities in humans is supported by evidence from people with CAH and by the recent work by Grimshaw incorporating a direct assay of testosterone in amniotic fluid.⁶⁻⁸ Females exposed to higher levels of androgens showed better spatial processing than females exposed to lower levels of androgens. So far, the evidence from DES studies suggests that females exposed to DES do not exhibit an enhancement on traditional measures of spatial ability, relative to unexposed female controls. Far from being disappointing in their seeming lack of support for the organizational hypothesis, the DES results are quite important theoretically. The most straightforward interpretation is that spatial functions do not masculinize via the aromatization route. However, Hines and Sandberg¹¹ noted that women whose DES exposure ended later in gestation scored higher on a spatial composite measure than those whose exposure ended earlier in gestation. This was true

even though no group difference between the DES women and controls was found. Thus, an alternative possibility that cannot be completely ruled out at present is that sexual differentiation of brain areas mediating spatial processing does occur under the influence of estrogens, but occurs as a very late gestational event, possibly even extending into the early infant period (see References 12 and 13, for discussion of the possibility of a postnatal critical period). In that case, DES exposure might typically occur too early in gestation to have discernible effects on spatial abilities. Whether the DES data are telling us something about the sensitive period for differentiation of spatial functions or about the molecular endocrine mechanisms that subserve masculinization has yet to be resolved.

III. Reversible Effects of Sex Steroids in Adults

In the past few years, evidence has begun to accumulate suggesting that adult sex steroids might also affect the expression of spatial abilities. These effects are of considerable theoretical interest because they imply that ovarian hormones and, potentially, testicular androgens as well can act as regulators of neural function in brain regions outside the hypothalamic–pituitary area not classically thought to be steroid sensitive in adults.

A. Effects of Estrogens on Spatial Functions

Some of the earliest evidence for this position came from studies of the menstrual cycle, conducted by ourselves and others, in the mid- to late-1980s. Our work was explicitly designed to test the possibility that discernible changes in sexually differentiated cognitive functions might accompany changes in the concentrations of ovarian steroids. In an initial study, we examined a group of healthy young women at two different phases of the menstrual cycle on a battery of motor tests plus the Rod-and-Frame test. The Rod-and-Frame evaluates perceptual accuracy in aligning a rod to the true upright when it is presented against a visual background that is tilted and therefore spatially confusing. The Rod-and-Frame is considered a reliable and valid measure of a type of spatial function involving spatial perception. Males are typically slightly more accurate than females on the Rod-and-Frame, with an average sex difference of approximately 2 to 3° of error per trial. We discovered that healthy women were significantly more accurate on the Rod-and-Frame task during menses, which is characterized by low concentrations of estradiol and progesterone, than during the midluteal peak in estrogen and progesterone secretion.¹⁴ The same women showed a relative facilitation during the luteal testing on several of the motor tasks involving fine coordination of the fingers and hands. Thus, a dissociation in the two categories of tasks was

demonstrated. We followed up this work with further studies using a more extensive set of test measures to sample a wider variety of sexually differentiated cognitive functions.

Our first follow-up study assessed healthy women at the midluteal and menstrual phases using a repeated measures design.¹⁵ Order of testing was carefully counterbalanced and, where possible, alternate but equivalent versions of the tests were given on the two occasions. Besides the original tests of motor function, we included multiple measures of several sexually differentiated cognitive abilities — these included functions that show sex differences in favor of females (e.g., verbal fluency, perceptual speed, articulatory speed and accuracy) and functions that show sex differences in favor of males (spatial abilities). The Rod-and-Frame test was supplemented with a conventional paper-and-pencil measure of spatial visualization, Space Relations, which is part of a standard aptitude test battery used in vocational placement and counseling. A test of figural disembedding, the Hidden Figures test, was included because there were hints from other work¹⁶ that this type of spatial function, in which a simple figure must be discriminated when hidden within a more complex visual pattern, may be affected by the menstrual cycle. Thus, our set of spatial measures was diverse, deliberately being chosen to sample more than one type of spatial ability. The results of this study provided further evidence of menstrual cycle variability in spatial function. On initial exposure to the tests, women at the menstrual phase obtained higher scores on the set of spatial measures than women at the midluteal phase. Differences in accuracy between the two phases were small but consistent. Again, motor abilities including verbal articulation were if anything facilitated at higher estrogen and progesterone levels, relative to menses. The study provided modest support for the hypothesis that ovarian hormones can affect spatial functioning, but also had limitations. Notably, because estradiol and progesterone varied in parallel at the two phases of the menstrual cycle we chose to investigate, it was not possible to determine which of the two hormones was most closely associated with the cognitive and motor effects.

To remedy this, a third study was carried out. This time we assessed a new group of women twice: immediately before ovulation, when estradiol concentrations are greatly elevated, and at menses, when estradiol is low, in counterbalanced fashion.¹⁷ The same test battery was used as before. We discovered that women's spatial scores were diminished during the preovulatory estradiol peak, relative to their achievements on the same tests during menses. Phase of cycle was confirmed by serum radioimmunoassays (RIAs). Because progesterone is still low prior to ovulation, this finding suggested that high levels of estradiol alone are sufficient to induce the effect. Importantly, in none of our three menstrual cycle studies were the cognitive effects attributable to concurrent variations in mood state. A commonly used mood inventory sensitive to alterations in mood in both ordinary individuals and psychiatric populations that was given as part of our test battery enabled us to rule out this possibility. Furthermore, among the three spatial measures, scores on two of the three showed significant albeit modest correlations with

serum estradiol as quantified by the RIAs (Hidden Figures, Space Relations). The correlation for the Space Relations test was especially interesting because it was differentiated from the other spatial measures by having the form of an inverted U-shaped function.¹⁷ Thus, a distinct relationship to serum estradiol was suggested, both by the effects of phase of cycle and by the patterns of correlations obtained.

An effect of the menstrual cycle on spatial functions has since been replicated by many laboratories (e.g., References 18 through 21), but not all (e.g., Reference 22). For example, using the Vandenberg Mental Rotations test, Silverman and Phillips²¹ found strikingly consistent effects of menstrual cycle phase in studies assessing women at the menstrual and nonmenstrual phases of the cycle (Figure 15.3). It may be significant that the Vandenberg test elicits some of the largest and most reliable sex differences in the spatial abilities literature. However, not all studies have found menstrual cycle effects even when the Vandenberg Mental Rotations was used (e.g., Reference 23). In part,

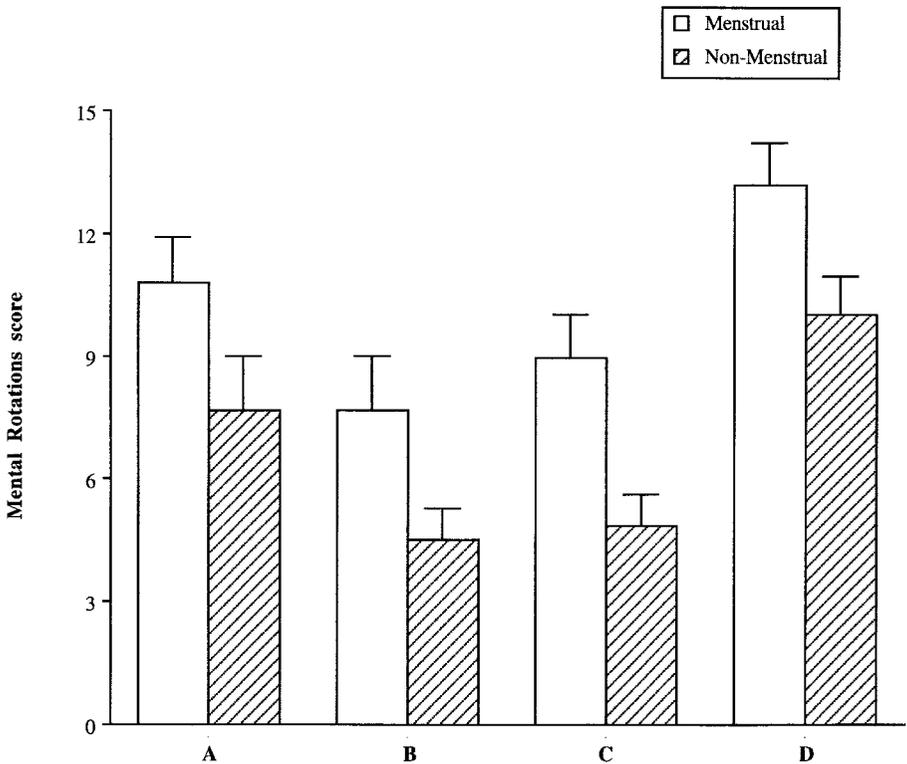


FIGURE 15.3

Several different studies by Silverman and colleagues using Vandenberg’s Mental Rotations test have confirmed our earlier finding of better spatial ability in women at menses relative to high-estrogen phases of the menstrual cycle. Means shown in A, B, and C are from Studies 2, 3, and 4 in Silverman and Phillips.²¹ D is from Phillips and Silverman.¹⁹

this reflects the relatively small size of the menstrual cycle fluctuations and their consequent vulnerability to methodological differences. Because women are notoriously unreliable in their verbal reports of their menstrual cycle length and last dates of onset, the validity of group testing is questionable. Nor can women's estimates be taken at face value without objective verification of phase of cycle, either through radioimmunoassays or indirect means (e.g., basal body temperature). Other factors might also be instrumental in determining whether menstrual cycle effects are seen but have not been systematically explored. As one example, in our own studies we typically excluded volunteers who were less than 21 years of age because the incidence of anovulatory cycles is high until women are in their early 20s²⁴ and because there is evidence that ovarian steroid production does not reach full adult levels until around the same age.²⁵ Researchers who rely on first year college students for their data may be less likely to detect significant menstrual cycle effects on cognition.

Recent support for an effect of estradiol on the expression of spatial abilities comes from studies using other methodologies. Evidence for an inhibitory influence of very high levels of estrogen or improvements in spatial abilities under reduced estrogen has come from studies of women using oral contraceptives,²¹ (but see Reference 26), women who are pregnant,²⁷ studies of women athletes with amenorrhea,²⁸ and studies of male-to-female transsexuals in whom exogenous estrogen treatment resulted in diminished scores on a rotated figure test and an increase in verbal fluency.²⁹ The cognitive effects of intermediate estrogen levels are less clear. Our own menstrual cycle work focused on phases of the cycle where estradiol is maximized or minimized so we have little data to speak to this issue. The fact that we found an inverted U-shaped function relating serum estradiol to women's scores on the Space Relations test suggests that, on at least some types of spatial tests, a drop in spatial scores may not occur until relatively high levels of estradiol are reached.

B. Evidence From Studies of Men

The expression of spatial abilities in adult men might also be regulated by concentrations of gonadal steroids.

As far back as the 1970s, Petersen³ and others reported that males with more masculinized somatotypes had relatively weaker spatial ability in relation to their verbal scores than males with less masculinized somatotypes. The studies were criticized on the grounds that somatotype is not reliably related to individual differences in androgen concentrations. Later studies employing direct radioimmunoassay measures of testosterone (T) or other androgens reported significant differences in spatial abilities between men with higher and lower circulating T concentrations. Young men with the highest androgens performed more poorly than young men with lower androgens on tests of spatial visualization,^{30,31} and on composite scores that

averaged across a mixed set of spatial³¹ or spatial and mathematical tests.³⁰ In recent work of our own, using a saliva measure of free T, we found significant negative correlations in young male university students between free T and accuracy on the Vandenberg Mental Rotation test.³² The fact that effects in all these studies were seen only on spatial tests and not on verbal fluency tests or other cognitive measures suggests that the effects are selective and not due to some generalized deleterious effect of very high androgens.

Negative correlations between T and spatial abilities in men have not always been found. Some studies have found positive correlations. For example, in a recent study of the !Kung San of Namibia, Christiansen³³ found positive correlations between levels of circulating androgens and scores on two spatial tests chosen to be cross-culturally valid. A salient feature of the Namibian sample was their relatively low concentrations of serum and salivary T. This may be relevant to the findings. In another group of low-T men, namely, aging men who had senescent decline in T levels, Janowsky et al.³⁴ found that double-blind placebo-controlled treatment with T (via the testosterone patch) produced an increase in performance after 12 weeks on a test of spatial function but not on other cognitive measures. In general, studies finding a positive relationship between T and spatial performance have involved populations in which T was relatively low (e.g., females, low T males due to age, illness, or constitutional factors), whereas studies finding a negative relationship involved young adult men in the prime of their lives. One possible way to integrate the seemingly divergent findings is to suggest that there might be a hypothetical optimum level of T for spatial functioning. In general, it might well be the case that increased T promotes better spatial ability, but that if T rises above the theoretical optimum, as it might in a proportion of young adult men, poorer rather than better spatial ability may be the result.

Because of the research designs that were used, most of the studies done so far are not able to differentiate between effects of T on spatial abilities that are due to lifelong exposure to higher vs. lower levels of T and reversible effects due to the immediate hormone environment (i.e., “activational” effects). That is, T has typically been measured at only one time point, providing a snapshot view of the relationship between T and spatial abilities across a set of individuals. Several studies now suggest that not all of the observed correlation is attributable to organizational factors. The recent studies by Janowsky et al.³⁴ and Van Goozen et al.^{29,35} are a case in point. Van Goozen studied female-to-male transsexuals undergoing treatment with testosterone esters preparatory to surgery for sex reassignment. Relative to a control group, treated females showed a greater increase from baseline in scores on a simple mental rotation test and a corresponding decline in verbal fluency, after 12 weeks of hormone treatment. If circulating androgens do have a reversible influence on the expression of spatial abilities, we might also expect to see changes in men’s spatial scores with biorhythm-based changes in levels of T secretion. In support of this possibility, we found preliminary evidence that

variations in spatial function might accompany diurnal and circannual variations in T. Men tested in the spring scored almost half a standard deviation higher on tests of spatial ability than men tested in the autumn, when circulating T levels were higher.³⁶ This effect was seen only on spatial tests and not other cognitive measures. In another study, we found that men tested in late morning achieved higher mental rotation scores than men tested in early morning, consistent with the diurnal change in T (Figure 15.4).³² In both studies, lower T concentrations were associated with better spatial performance, as one might expect in healthy young adult men.

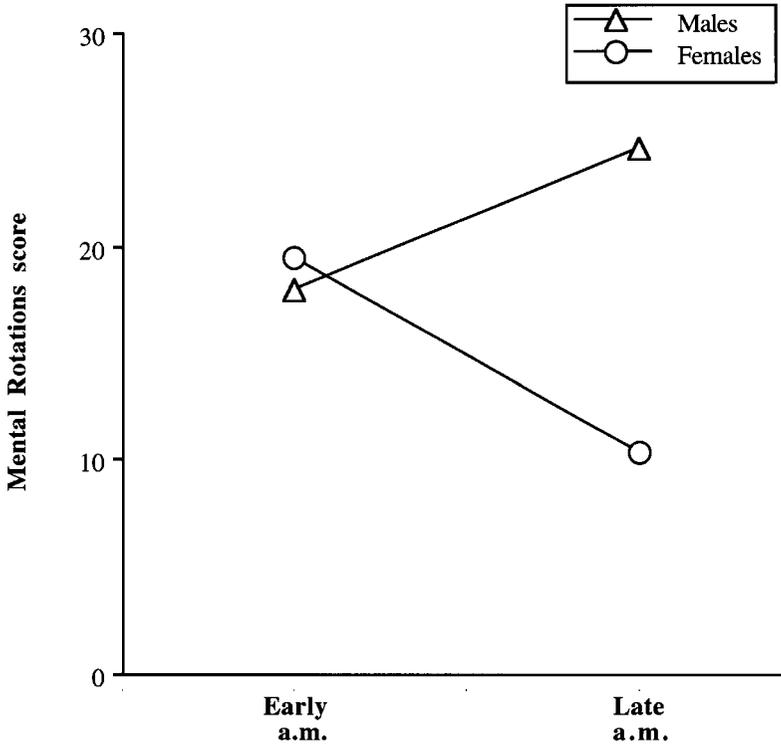


FIGURE 15.4 Diurnal changes in spatial performance in males and females. Males scored higher on the Mental Rotations test in late morning, while females scored lower. In both sexes, the pattern was consistent with the expected diurnal changes in circulating T concentrations. A salivary measure of free T confirmed that T was about 20% lower in late morning in males.

To summarize, there is preliminary evidence from a number of sources that spatial ability may vary with T levels in adult males. Although the observations must be regarded cautiously until further data come to light, so far the data suggest that increases in T when T is fairly low are associated with improvements in spatial performance, whereas increases in T when T is high may serve to diminish spatial performance. The mechanisms underlying

these effects are not yet understood. One possibility is that T exerts its effects through conversion to estradiol rather than acting on androgen receptors *per se* at the neural level. An appealing feature of this possibility is that it would allow us to integrate the findings in males and females to form a unified theory regarding the adult effects of sex steroids on spatial abilities.

IV. Convergent Evidence from Animal Studies

To shed further light on the neuroendocrine interactions that may underlie the effects of sex steroids on spatial functions, we must turn to work in other species.

A. Effects of Perinatal Hormone Manipulations

Experimental studies in the rat have shown that the male advantage normally observed on conventional spatial learning tasks like the Morris water maze (WM) or radial-arm maze (RAM) is powerfully dependent on sex steroids. Early studies involving neonatal hormone manipulations^{4,37,38} indicated a possible role for sex hormones in the organization of spatial learning. But these studies were not followed up in detail until nearly 1990. In an elegant set of experiments, Williams et al.³⁹ showed that exposing female rats to estradiol benzoate (EB) in the first few days of life led to male-typical levels of maze acquisition in adulthood and changes in the relative reliance on landmark vs. geometric cues for navigation in the RAM. Females exposed to neonatal estrogen showed improved performance relative to control females and increased reliance on geometry cues, a change toward the typical male pattern of performance. In later work using a different type of maze, Roof⁴⁰ found a dose-dependent improvement in both the RAM and WM in female rats treated neonatally with T propionate (TP), and also found evidence of a reverse effect in males, consistent with the optimal level hypothesis and with our own findings for spatial ability in boys with CAH. The hippocampal formation is often considered to be one important substrate for this form of spatial learning in the rat. It was therefore of interest that Roof and Havens⁴¹ observed morphological changes in the granule cell layer (GCL) of the dentate gyrus in response to neonatal TP. Females treated with TP showed a wider GCL than control females, as is more typical of males. A larger GCL predicted better maze acquisition in females. The Roof and Williams studies implicate the first few neonatal days as a sensitive period for masculinization of spatial function in the rat and suggest that this masculinization occurs via the aromatization route.

Studies of early hormone effects have focused almost exclusively on the neonatal period. Recent evidence, however, raises the possibility of a *prenatal*

contribution to sexual dimorphism in spatial function as well. Using a variety of hormonal manipulations from embryonic Day 16 to birth, Isgor and Sengelaub⁴² found that TP and dihydrotestosterone propionate (DHTP) had masculinizing effects on WM acquisition in female rats. Flutamide treatment followed by gonadectomy on postnatal Day 1 demasculinized WM acquisition in males. Although females did show some evidence of masculinization by prenatal treatment with EB, EB was not as effective as androgens in altering adult levels of WM performance. As in Roof's work, some effects of prenatal hormones on hippocampal morphology were seen, but in this case changes were localized to pyramidal cells of the CA1 and CA3 subfields of the hippocampus.

B. Effects of Adult Hormone Manipulations on Spatial Learning

Animal researchers have more recently begun to focus on the question of whether adult steroids have discernible effects on spatial learning, and the extent to which these effects model the findings of human studies. Most of the evidence suggests that ovarian hormones do have an influence on spatial learning in females, although a few studies failed to find significant effects (e.g., References 43 and 44). Evidence of T effects in males is also beginning to emerge, including some work supporting a deleterious effect of high levels of T (e.g., Reference 45). Most studies of adult hormones were stimulated either by human work showing changes in spatial proficiency related to the menstrual cycle or by reports from B. McEwen's laboratory of a remarkable degree of plasticity of hippocampal synapses in response to variations in ovarian steroids in the adult rat. Woolley and McEwen⁴⁶ discovered that the density of synapses in CA1 declined by as much as 30% over the 24-h period from proestrus to estrus in the female rat, and that the changes are estrogen dependent. This stimulated a burst of studies on hippocampally dependent spatial learning, on the premise that such remarkable plasticity must be functionally significant. Many researchers assumed that impairment on hippocampal learning and memory tasks would be observed in female rats at estrus as a result of decreased synaptic connectivity, but most studies have not found this effect. In fact, the inference itself is questionable. It assumes (1) that greater numbers of hippocampal synapses will necessarily correspond to behavioral improvements and (2) that changes in other neural regions subserving spatial learning either do not occur or are insignificant in driving the behavioral response. Stewart and Kolb⁴⁷ found that estrogen deprivation in female rats increased the dendritic arbor of pyramidal neurons in parietal cortex and produced modest increases in apical dendritic spine density in that region.

So far, the bulk of the empirical evidence favors a negative influence of high levels of estradiol on spatial learning, compatible with the human findings. Several studies of naturally cycling female rats have found better spatial learning at lower levels of circulating estradiol.^{48,50} In some studies, sex

differences in WM acquisition were found only when males were compared with females who were in a high-estrogen state (e.g., proestrus).^{48,51} In meadow voles, Galea, Kavaliers, Ossenkopp, and Hampson⁵¹ found better maze acquisition in nonbreeding females than in females housed in breeding pairs. Plasma estradiol levels were positively correlated with latencies to find the hidden platform (i.e., with poorer performance). The vole data are of special interest because voles are induced ovulators. Increased plasma estrogen levels and a prolonged state of behavioral estrus with no detectable cycling is induced in females by pairing them with males. This helps defuse one criticism that has been raised in studies in the rat, where rapid changes in hormones across the estrous cycle make it difficult to make inferences about hormone-behavior relationships. In deer mice, Galea et al.⁵² found that male WM acquisition was superior to females during the breeding season only, with female deer mice showing significant decreases in WM performance in the high-estrogen breeding season relative to the low-estrogen nonbreeding season. A few studies using hormone replacement methodologies in ovariectomized rats have reported that EB enhances performance in the RAM (e.g., Reference 53). But Korol et al.⁵⁴ found that estradiol treatment impaired acquisition in the WM. A further complication is that there might be a sex difference in the stress response to the WM which may interact in female rats with stage of the estrous cycle.⁵⁵ The role glucocorticoid responses might play in spatial learning has not been adequately explored.

One of the unresolved questions about of the effects estrogen on spatial learning and memory is whether the effects are mediated by the classical estradiol receptor, ER α , or some alternative genomic or nongenomic mechanism, perhaps involving the newly identified receptor ER β . A recent study by Fugger et al.⁵⁶ strongly implicates the ER α system. Using a WM measure of spatial learning, Fugger et al.⁵⁶ found that acute treatment with EB impaired performance of wild-type female mice in the WM but not transgenic knockout females lacking functional copies of the ER α gene. This result suggests that impaired performance under estradiol on the WM task requires ligand-dependent ER α activation.

To summarize, clear modulatory effects of estradiol levels on a least one form of spatial behavior have been demonstrated in laboratory rodents. On the whole, the evidence favors a negative effect of high levels of estradiol, at least for WM performance, but a few studies, mostly using the RAM, have found a positive influence of estradiol on female maze proficiency. Other studies failed to find any changes at all related to the estrous cycle (e.g., Reference 43). At this preliminary stage of the research, it is not possible to tell whether the discrepancies across studies are due to the use of physiological vs. pharmacological doses of estradiol, chronicity vs. acuteness of the estradiol exposure, misidentification in some studies of estrous phase, the time lag after treatment at which the behavioral effects of EB exposure are measured, the type of maze-learning task that is employed, presence or absence of non-spatial pretraining, strain of rats or species of rodent, or other as yet unknown factors.

An important issue is the validity of comparing human and nonhuman data on spatial function. While the nonhuman data increasingly take shape, and appear to support the inferences being made from human studies, there is still an inferential problem in that the type of spatial ability being assessed in laboratory rodents almost invariably involves spatial navigational learning (e.g., the Morris WM or RAM), whereas spatial abilities in humans are typically assessed using mental rotation or other non-navigational tasks. These tasks are worlds apart. Although different spatial functions in humans likely have somewhat different neurological substrates, reliance on the hippocampal formation has not been demonstrated for tasks such as mental rotation, which, if anything, appear to rely on parietal and, especially, right hemisphere cortical processes.⁵⁷ Therefore, the validity of generalizing from rats solving a maze to humans is open to question. Ideally, the same spatial functions could be examined comparatively across species. Since we cannot train a rat to do mental rotation, a reasonable alternative is to train humans to learn mazes instead. In a recent study from my laboratory, we devised a “virtual” maze task that can be administered to humans by computer.⁵⁸ Traversing the maze involves learning a route by trial and error over a series of learning trials through a complicated set of alleyways. Only one route through the alleyways leads out of the maze. An exciting outcome of our work is the extremely large size of the male advantage elicited by this task. In terms of either time to completion ($d = 1.6$) or spatial memory errors ($d = 1.4$), the sex differences we found are among the largest ever reported on a spatial task in human beings. We also found a respectably high correlation with scores on the Vandenberg Mental Rotation test, indicating that the two types of tasks, while superficially quite different, do share a significant proportion of common variance.

IV. Evolutionary Significance of the Modulatory Effects

Animal studies suggest that androgen and estrogen levels are the proximate mechanisms responsible in large part for sex differences in spatial behavior. In humans, too, the development and expression of spatial abilities appear to be susceptible to regulation by gonadal steroids. What evolutionary function is served by these modulatory effects?

A number of theories have sought to explain the male advantage in spatial ability in terms of ranging. One of the most influential theories to arise in recent years was proposed by Gaulin and Fitzgerald,^{59,60} who hypothesized that the sex difference in spatial abilities is not a universal characteristic among mammalian species, but rather evolved in proportion to navigational demands. A male advantage in spatial ability was hypothesized to evolve only in species where range expansion contributes differentially to the reproductive success of males and females, i.e., where range expansion is a male

reproductive tactic. In support of this, Gaulin showed in field studies using radiotelemetry to monitor ranging that a polygynous (*Microtus pennsylvanicus*) but not a monogamous species of vole (*M. ochrogaster* or *M. pinetorum*) showed a sex difference in range size, evident during the breeding season only. In polygynous voles, adult males but not females expanded their home ranges in the breeding season to overlap the home territories of several reproductive females. Because surplus ranging behavior entails energetic and risk costs that must be avoided in the absence of compensatory benefits (e.g., increased mating opportunities), it is not surprising that range expansion occurred in the breeding season only. Correspondingly, only the polygynous species of vole and not the monogamous ones exhibited male superiority on a set of laboratory-administered maze-learning tasks.

In humans, too, certain spatial abilities, notably the ability to form and manipulate mental representations of large-scale three-dimensional space, may have evolved as navigational adaptations. Anthropological data, patterns of wear in leg bones from fossil specimens as far back as the mid-Paleolithic, and other sources of evidence, support the view that we are a species with sexually dimorphic ranging patterns. In a recent review, Sherry and I⁶¹ concluded that of the various evolutionary theories put forth to explain the male advantage in human spatial abilities, sexual selection theories are most viable. These theories postulate greater ranging in males, in search of resources, to achieve status, to compete for mates, or to enhance mating opportunities. One can easily imagine how the organizational effects of steroids, possibly with activation by later hormones, could adapt the male brain for greater ranging. However, an interesting oversight that became apparent in our literature review is that none of the currently proposed evolutionary models predicts the effects of ovarian hormones on spatial abilities that have now been documented in both human and nonhuman species.

Sherry and I proposed a new hypothesis, which we called *Fertility and Parental Care Theory*. We suggested that ranging over long distances, with its associated costs in terms of energy expenditure and heightened risks of predation, may be especially disadvantageous for reproductive females. One important reason for this is that a threshold level of body fat is essential in females for maintaining menstrual cyclicity and optimum fertility and for supporting the caloric demands of lactation. Modern-day empirical data suggest that interference with optimum fertility occurs at surprisingly low levels of physical demands in women. For example, Ellison²⁵ has shown that ovarian insufficiency begins at moderate levels of exercise in ordinary women. Female athletes, especially those in highly aerobic sports, are prone to menstrual irregularities and oligo- or amenorrhea due to their reduced percentage of body fat. Oligo- and amenorrheic women were clustered among cross-country skiers, long- and middle-distance runners, and rowers in the Stokes and Kimura²⁸ study cited earlier. Panter-Brick et al.⁶² found a relatively high incidence of luteal-phase insufficiency and reduced fertility with seasonal changes in workload among Nepali women. If female foraging or navigation over long distances is disadvantageous, and certain spatial abilities evolved

specifically as adaptations to the demands of navigation, then spatial ability might be reduced in females under high estrogen conditions indicative of fertility or parental care investment (e.g., pregnancy) as an adaptation to promote reproductive success. In other words, spatial ability might be reduced in reproductively viable females compared with males because its metabolic costs do not justify its maintenance. If high estrogen levels during the reproductive years serve as a trigger for reduced spatial ability and mobility, then menstrual cycle fluctuations become comprehensible as a by-product of this effect. A similar argument applies to pregnancy where energy balance is also critical, both for optimum development of the fetus and for storing energy for subsequent lactation. At present, almost nothing is known in either humans or nonhuman species about whether spatial ability is in fact suppressed during the high estrogen period of pregnancy.

Sherry and I concluded that the Fertility and Parental Care hypothesis was necessary as an adjunct to traditional views based on sexual selection to account for all the endocrine data. In particular, the inhibitory effects of high estrogen on specific spatial abilities that show a male superiority are not otherwise accounted for by traditional evolutionary theories. We are therefore left with a more complex picture, in which spatial ability may have evolved as an adaptation to ranging but in which endocrine factors in both sexes modulate this function in order to maximize reproductive success.

In closing, I note that most attention in the research literature has been devoted to studying sexually differentiated spatial functions that favor males. Silverman and Eals⁶³ recently argued that other spatial abilities might have evolved which favor *females* because of greater female involvement in local foraging as part of the sexual division of labor. In fact, Silverman and Eals⁶³ discovered that women are more accurate than men at remembering the relative locations of static objects within a complex visual scene, a sex difference they suggest may reflect an evolved advantage in the ability to remember the relative positions of food sources or significant landmarks within local arrays of vegetation. This “female” spatial advantage reinforces the view that spatial ability consists of dissociable components that may have quite different evolutionary histories as well as different neurological substrates. Further study of spatial abilities that favor females, and of the possibility that endocrine factors are the proximate causes of these differences as well, is an important direction for future research.

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The Luteinizing Hormone–Releasing Hormone System in the Developing Monkey Brain

Ei Terasawa, Laurie A. Abler, and Nancy M. Sherwood

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I. Introduction

When Dr. Matsumoto contacted me regarding publication of a book entitled *Sexual Differentiation of the Brain* in honor of the retirement of Prof. Yasumasa Arai, I responded to him saying that although I am not currently engaged in research on the sexual differentiation of the brain, I would write a chapter

that would be related to Prof. Arai's recent work on the migration of luteinizing hormone-releasing hormone (LHRH) neurons. Perhaps I should explain why we started to study the origin and migration of LHRH neurons in nonhuman primates.

In early 1990, based on articles of Schwanzel-Fukuda and Pfaff,¹ Wray et al.,² and Ronnekleiv and Resko,³ we started to establish a culture system for LHRH neurons. We thought that it would be advantageous to harvest LHRH neurons from the olfactory placode before migration into the brain and culture them.⁴ However, because of our unfamiliarity with embryonic materials and the lack of detailed descriptions on the origin and migratory pathway of LHRH neurons in primates, we needed to conduct minimal developmental studies on LHRH neurons. Developmental studies in nonhuman primates, however, require time-mated monkey fetuses by cesarean section, which are very valuable. Thus, we felt that in addition to investigating the origin and the migratory pathway of LHRH neurons, we should study whether other forms of LHRH neurons are present in the primate brain during the early stage of development.

Since the LHRH molecule was first isolated from the pig brain and sequenced,⁵ more than a dozen LHRH isoforms have been found in the brain throughout the animal kingdom, and multiple forms of LHRH in the brain of a single species have been reported. Further, based on the amino acid sequence, several scientists have attempted to establish evolutionary relationships for LHRH molecules (see References 6 through 13 for a review).

At this time, we have found that in the developing monkey brain (1) there are two different types of mammalian LHRH neurons that originate at two different developmental stages, originate from probably two different locations, and migrate into different areas of the brain; and (2) in addition to mammalian LHRH (mLHRH) neurons, the chicken LHRH-II (cLHRH-II) form is present in the nonhuman primate brain.

II. Two Types of LHRH Neurons in the Forebrain of Monkey Embryos

Using the antibodies GF-6 (supplied by N.M. Sherwood), which is immunoreactive with many forms of LHRH including mammalian and salmon forms, and LR-1 (a gift from R. Benoit, University of Montreal, Canada), which is mainly immunoreactive with the mammalian form, we are able to discern two LHRH cell populations in the brain of monkeys at embryonic Day 36 (E36) and older by comparing adjacent stained sections.¹⁴ One population of cells is immunopositive with both GF-6 and LR-1, GF-6(+)/LR-1(+), whereas the other population of cells is immunopositive with GF-6 but not LR-1, GF-6(+)/LR-1(-); i.e., GF-6 stains both populations, whereas LR-1 stains only one of the populations.¹⁵

GF-6(+)/LR-1(-) cells first appear in the basal forebrain of embryos at E30, but GF-6(+)/LR-1(+) cells begin to arise in the basal epithelial layers of the medial olfactory pit of embryos at E32. The latter cells migrate along the terminal nerve and appear in the forebrain in embryos at E38. Since the appearance of GF-6(+)/LR-1(-) cells precedes that of GF-6(+)/LR-1(+) cells in embryonic tissues, we have decided to call GF-6(+)/LR-1(-) cells the “early” LHRH population and GF-6(+)/LR-1(+) cells the “late” LHRH cell population.¹⁵

There are morphological differences between “early” cells and “late” cells. Early LHRH cells are smaller in size (approximately $10 \times 7 \mu\text{m}$) and either oval or round in shape, whereas late LHRH cells are larger in size (approximately $15 \times 7 \mu\text{m}$) and have a fusiform shape. In addition, the majority of early LHRH cells have a single short neurite, whereas late LHRH cells are bipolar neurons with extensive fiber projections¹⁵ (Figure 16.1).

Late cells are also immunopositive with antisera 1076 and B-6, antibodies targeted to mLHRH, whereas early cells are immunonegative with 1076 and B-6. Similarly, late LHRH cells are weakly immunopositive to the hydroxyproline LHRH antiserum, 939, whereas early LHRH cells are immunonegative with the same antibody. Preabsorption of GF-6 with several different LHRH peptides (except lamprey LHRH-I and -III) blocks immunoreactivity with both LHRH cell populations, whereas preabsorption of LR-1 with mLHRH peptide blocks immunoreactivity with the late cell population.¹⁵

Late LHRH populations are *bona fide* mLHRH neurons previously described in embryos of the rhesus macaque, mouse, rat, and newt.^{1-3,16,17} This conclusion is based on the facts that late LHRH cells (1) are immunopositive to the antimammalian antisera LR-1¹, as well as 1076 and B-6; (2) originate from epithelial cells of the medial olfactory pit and migrate into the brain via the extracranial terminal nerve during early embryonic stages; and (3) complete migration in the septum, preoptic area, and hypothalamus during fetal development (see Section III), similar to the LHRH neuronal migration described by others.³

In contrast, early LHRH cells are not exactly mLHRH neurons. They (1) are not immunopositive with the antimammalian antisera LR-1, 1076, or B-6, but are immunopositive to antibody GF-6; (2) are different in shape from late LHRH cells; (3) originate from the olfactory placode prior to the formation of the olfactory pit; (4) migrate into the brain along the olfactory nerve, rather than the terminal nerve; and (5) eventually settle in the striatal and limbic structures of the fetal brain (see Section IV).

III. Distribution Pattern of the Late LHRH Neurons

At E32 to E36, late LHRH neurons differentiate from the olfactory pit and migrate toward the brain. At E34 to E36, late LHRH neurons extend their fibers along the base of the forebrain, reaching into anterior diencephalic areas, and a larger number of ‘late’ LHRH neurons are seen along the entire extent of the

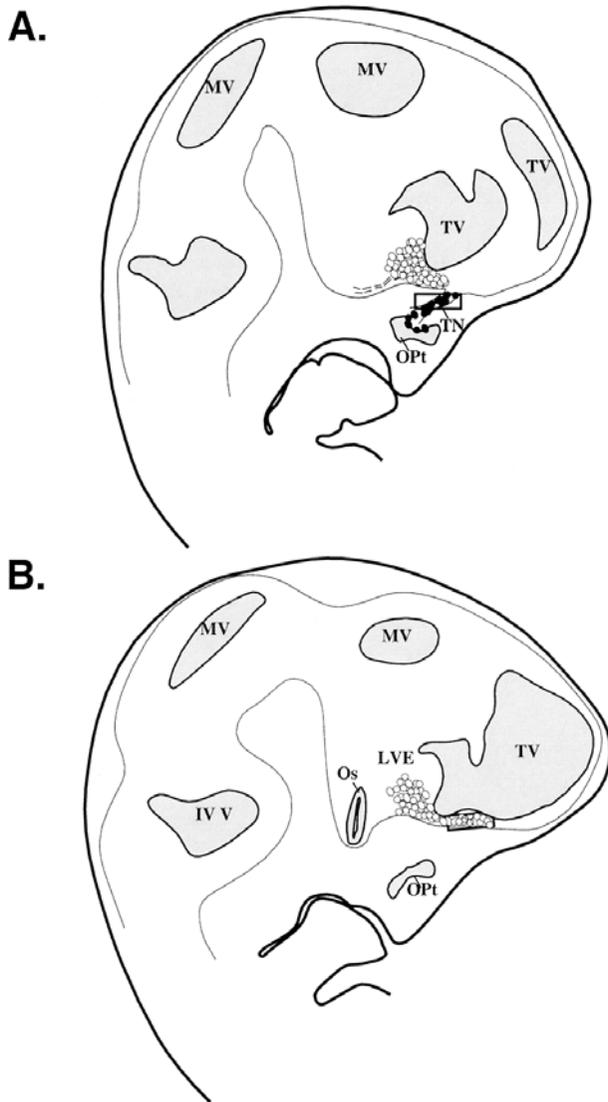


FIGURE 16.1

Schematic drawing of parasagittal sections from an embryo at E36 (A and B). Section A is medial to section B, separated by approximately 100 μm . Medially, a massive number of early LHRH cells (open circles) are found in the base of the forebrain at this age (A). Laterally, early LHRH cells are also found widely from preolfactory areas of the forebrain to more caudal regions, namely, the ventral telencephalon and the lateral ventricular eminence (B). Late LHRH cells (closed circles) migrate along the extracranial terminal nerve, and their fibers (dashed lines) advance caudally within the base of the brain, passing over early LHRH cells (open circles, A). (Modified from Quanbeck et al., *J. Comp. Neurol.*, 380, 293, 1997.)

extracranial terminal nerve. At E38, some late LHRH neurons move into the anterior forebrain, although the majority are still on the extracranial terminal nerve. Between E42 and E52 late LHRH neurons migrate towards their final destinations. In the brain, late LHRH neurons follow one of two (ventral or dorsal periventricular) migratory pathways. The majority of late LHRH neurons take a ventral migratory pathway: Shortly after entering the brain, late LHRH cells disperse the aggregate that they had maintained when migrating on the extracranial terminal nerve and appear to start extending their axons as they migrate individually toward their final destinations. However, most cells seem to maintain an indirect contact with LHRH fibers oriented toward the diencephalon. The minority of late LHRH neurons take the dorsal periventricular pathway: after entering the brain they also lose cell-to-cell contact, but keep migrating dorsally along the wall of the telencephalic vesicles and subsequently toward the third ventricle.

Migration of late LHRH neurons continues into late fetal development, although the basic distribution pattern is established as early as E52. Late LHRH neurons are found in the olfactory bulb, olfactory tubercle, pericommisural areas, the diagonal band of Broca, medial preoptic area, medial septal nucleus, regions around the lamina, suprachiasmatic area, lateral hypothalamus, medial basal hypothalamus, periventricular region of the third ventricle, the region ventrolateral to the arcuate nucleus, and median eminence. At the late fetal stage, densely stained late LHRH nerve fibers are present in the median eminence, and less dense but heavily stained fibers are seen in the organum vasculosum of the lamina terminalis. A detailed description of the migratory pattern and distribution pattern of late LHRH neurons has been reported previously.¹⁴ The final distribution of LHRH neurons in the late fetal age is similar to that described for fetal, juvenile, and adult monkeys.¹⁸⁻²⁰

IV. Origin and Distribution of the Early LHRH Neurons

The origin of early LHRH cells is unclear at this time. Although at E30 several neuroblastic cells, weakly stained with GF-6, are present along olfactory nerves, a large number of darkly stained early LHRH neurons with a mature appearance have already appeared in the area of the rostralateral forebrain. At E32 to E36, increasing numbers of early LHRH cells are distributed throughout wide regions of the ventral forebrain below the telencephalic vesicle.¹⁵ It is possible that a small number of undifferentiated early LHRH cells originate from the olfactory pit and migrate into the forebrain, after which they proliferate for several days, eventually generating thousands of early LHRH cells. Undifferentiated neurons dividing after the onset of migration are seen during neural crest ontogeny.²¹ However, it is more likely that the site of early LHRH neurogenesis is the ventricular zone of the telencephalon, since the number of neuroblastic cells observed in the olfactory areas is far

fewer than in the ventral forebrain. A recent report by Daikoku and Koide²² suggests that olfactory placode ablation in rats does not change the number of LHRH cells in the septal region, although it is unclear whether the population of LHRH cells described is equivalent to the early cells in the monkeys. Cell lineage tracer studies with placode ablation will answer the question regarding the origin of early LHRH cells.

At E38 and E42, thousands of early LHRH neurons are distributed medially across a wide area of the basal telencephalon, from septal areas, rostrally, to the preoptic sulcus, caudally. During this developmental stage, unlike the shape and distribution of late LHRH cells, early LHRH cells are small and oval in shape with short, unipolar processes and do not exhibit a morphology indicative of cell migration. By E51, early LHRH cells are scattered widely throughout areas of the telencephalon containing the basal nuclei, such as the lateral septum, stria terminalis, amygdala, internal capsule, putamen, globus pallidus, and claustrum of the fetal brain. Distribution of early LHRH cells in the E77 fetus is similar to that seen in the E51 to E62 fetuses.

If early cells are not moving themselves, how do early LHRH cells reach these locations? It is plausible, at least in part, that early LHRH cells move into these positions along with the development of the forebrain. For example, at E36, the medial and lateral ventricular eminences are the structures comprising the ventral forebrain where early LHRH cells are located. As development proceeds, the two eminences fuse to form one ventricular eminence, which then gives rise to the striatum and amygdala.^{23,24} Most of these events take place between E42 and E51 in the rhesus macaque embryo.^{25,26}

Additional morphological differentiation of early LHRH neurons occurs along with the formation of the mature telencephalic structures. The appearance of early LHRH cells seen in limbic and striatal structures in the brain of E50 and older fetuses differs from that of early LHRH cells seen at E42 and younger: Cells in striatal structures are large, unipolar, and round in shape with an extensive nucleus surrounded by a thin rim of weakly stained cytoplasm, whereas cells in the limbic system are small, bipolar, and fusiform in shape. Morphological differentiation during late development is well established in the cerebral cortex: e.g., final morphological appearance of neurons migrating from the ventricular zone in an undifferentiated state depends on intercellular interactions with neighboring cells and the surrounding extracellular matrix.²⁷ Similarly, in the peripheral nervous system after completion of migration, the neural crest cells undergo further morphological differentiation under the influence of growth factors, such as nerve growth factor (NGF).²⁸

V. The mLHRH Gene in Early and Late LHRH Neurons

What is the form of the LHRH molecule in early cells? First, it is not likely to be the mLHRH form with its full ten amino acids, since early LHRH cells are

not stained with the antibodies LR-1, 1076, or B-6. Further, it is not a post-transcriptionally modified LHRH form, such as hydroxyproline⁹. Hydroxyproline⁹ LHRH is found in many species of animals, especially in the fetal brain in rats,²⁹ and the presence of a relatively higher amount of hydroxyproline⁹ LHRH is reported in the hippocampus than in the hypothalamus of adult rats.³⁰ Although we find early LHRH cells in extrahypothalamic regions in our studies, the observation that early LHRH cells, but not late LHRH cells, are immunonegative with the hydroxyproline⁹ LHRH antiserum, 939, suggests that early cells do not contain hydroxyproline⁹ LHRH¹⁵. Second, it does not appear to be chicken-I, chicken-II, salmon, lamprey-I, or lamprey-III LHRH forms, since specific antibodies to those molecules are immunonegative with early LHRH cells. Third, it may not be a form of sea bream LHRH, in which only Arginine⁸ is replaced by Serine⁸.

In situ hybridization histochemistry with monkey and rat mLHRH cRNA riboprobes suggests that the distribution of late cells expressing mLHRH mRNA (Figure 16.2a) is essentially identical to those stained with GF-6

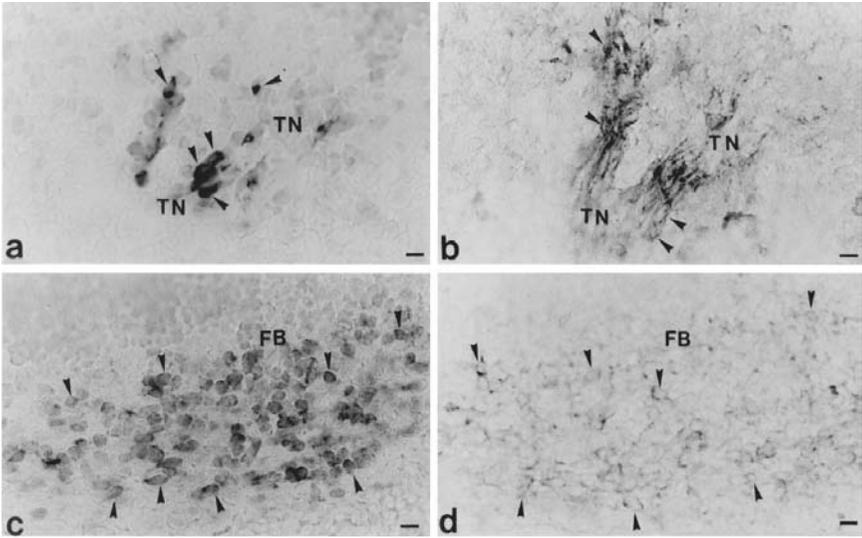


FIGURE 16.2

In situ hybridization for mammalian LHRH mRNA and immunocytochemistry of early and late LHRH neurons using GF-6 in the fetal monkey at E35 (a and b, sagittal sections). Immunopositive cells are visualized using diaminobenzidine, whereas *in situ* hybridization signals are visualized using digoxigenin-11-UTP and alkaline phosphatase. In the fetal head at E35 (a and b), late LHRH neurons (arrowheads) are seen on the terminal nerve (TN), with *in situ* hybridization (a) and immunocytochemistry (b) in adjacent tissue sections. Similarly, early LHRH neurons (arrowheads) are also seen in the ventral forebrain (FB), with both *in situ* hybridization (c) and immunocytochemistry (d) in adjacent sections. Cell size with *in situ* hybridization appears to be smaller, since *in situ* hybridization shrinks tissue sections more than those stained for immunocytochemistry. Approximate locations of a and b are indicated by a square box in Figure 16.1A, and approximate locations of c and d are indicated by a square box in Figure 16.1B. Scale bars: for all = 20 μm.

(Figure 16.2b). The results clearly indicate that late LHRH cells originating from the olfactory pit express mLHRH mRNA as expected. This observation is in agreement with those described by Wray et al.³¹ and Ronnekleiv and Resko.³ Early LHRH cells in the basal forebrain of young fetuses (E35 to E39) and in the striatum and amygdala in older fetuses (E50 to E78) also express mLHRH mRNA. The distribution of mLHRH mRNA positive early cells (Figure 16.2c) in the forebrain is very similar to that seen with GF-6 (Figure 16.2d). However, the expression of mLHRH mRNA in early cells is consistently less than that seen in late cells, suggesting that early cells contain low transcription levels of the mLHRH gene. A double-labeling study with GF-6 and antisense digoxigenin-labeled riboprobes suggest that both late and early LHRH neurons express mLHRH mRNA. In contrast, *in situ* hybridization using sense riboprobe does not hybridize with mLHRH mRNA. In addition, we have confirmed the specificity of the antisense riboprobe hybridization with early and late cells using a “random” digoxigenin-labeled riboprobe, as well as prehybridizing the sections with an excess of unlabeled antisense riboprobe to block antisense hybridization.

The presence of a second population of cells containing the mLHRH gene transcripts in the human brain has been also described by Rance et al.³² The distribution pattern of these LHRH cells in the adult human brain³² is strikingly similar to that seen in the rhesus monkey brain after E50, as shown in this and previous studies.¹⁵ Interestingly, the presence of a second population of cells containing the mLHRH gene does not appear to be limited to primates. Two different groups report a second population of neurons transcribing the mLHRH gene in the basal forebrain in fetuses and the septal region in adults using transgenic mice with an mLHRH promoter-driven β -galactosidase reporter gene.^{33,34}

VI. LHRH Fragments and the Cleavage Enzyme E.C.3.4.24.15 in Early LHRH Neurons

If early LHRH neurons contain mLHRH mRNA, why are they not stained with LR-1? Previously, we speculated that an N-terminal peptide might be present in early LHRH cells, since GF-6 is N-terminally directed, based on its cross-reactivities with many forms of the LHRH molecule,¹⁵ and on the absence of immunoreactivity with other antisera in early cells. In fact, this could be a product derived from proteolytic cleavage of LHRH, such as LHRH¹⁻⁵ and LHRH⁴⁻¹⁰. To determine the presence of LHRH fragments in the early and late LHRH neurons, the distribution pattern of early and late LHRH cells stained with GF-6 is compared with the distribution pattern stained with antisera raised against LHRH¹⁻⁵ or LHRH⁴⁻¹⁰ (both are gifts of L. Jennes).

The appearance, as well as the distribution, of late LHRH¹⁻⁵ positive neurons at E38 is very similar to late LHRH neurons stained with GF-6. However, late LHRH¹⁻⁵ positive neurons decrease their staining intensity in older fetuses (E50 to E78); i.e., they are immunostained very faintly, or often not at all. In contrast, early LHRH neurons are invariably immunopositive with LHRH¹⁻⁵ in both young and older fetuses. LHRH⁴⁻¹⁰ positive neurons, similar to the GF-6 positive late LHRH neurons, are consistently observed in all fetuses examined; i.e., late LHRH cells arising from the olfactory pit/placode and on the terminal nerve of young (E35 to E39) fetuses are immunopositive with the antibody to LHRH⁴⁻¹⁰. In contrast, staining of early LHRH⁴⁻¹⁰ positive neurons in the base of the telencephalon of younger (E35 and E36) fetuses is either absent or very faint. In older (E50 and older) fetuses, early LHRH⁴⁻¹⁰ positive neurons are distributed in the same regions where GF-6 positive early neurons are found.³⁵

Further, preabsorption tests for GF-6 with either the LHRH¹⁻⁵ peptide or LHRH¹⁻¹⁰ peptide indicate that both early and late LHRH cells are immunonegative (Table 16.1). In contrast, preabsorption of GF-6 with LHRH⁴⁻¹⁰ does

TABLE 16.1
Immunocytochemistry of Antibodies Preabsorbed with Various Peptides

Antibodies	Peptide for Absorption	Late Cells	Early Cells
GF-6	Control	Positive	Positive
	LHRH ¹⁻⁵	Negative	Negative
	LHRH ¹⁻¹⁰	Negative	Negative
	LHRH ¹⁻³	Positive	Positive
	LHRH ⁴⁻¹⁰	Positive	Positive
	LHRH ⁵⁻¹⁰	Positive	Positive
LHRH ¹⁻⁵	Guinea pig LHRH	Negative	Negative
	Control	Weakly positive	Positive
	LHRH ¹⁻⁵	Negative	Negative
	LHRH ⁴⁻¹⁰	Weakly positive	positive
	LHRH ¹⁻¹⁰	Weakly positive	Positive
LHRH ⁴⁻¹⁰	LHRH ⁵⁻¹⁰	Weakly positive	Positive
	Control	Positive	Weakly positive
	LHRH ⁴⁻¹⁰	Negative	Negative
	LHRH ¹⁻¹⁰	Negative	Weakly positive
	LHRH ¹⁻⁵	Positive	Weakly positive
LR-1	LHRH ⁵⁻¹⁰	Weakly positive	Weakly positive
	Control	Positive	Negative

not abolish the immunopositive staining of both early and late LHRH neurons. Similarly, preabsorption of GF-6 with either LHRH⁵⁻¹⁰ or LHRH¹⁻³ does not abolish the immunopositive staining of both early and late LHRH neurons (Table 16.1). In addition, LHRH¹⁻⁵ immunopositive early cells are blocked by preabsorption of the antibody with the LHRH¹⁻⁵ peptide, but not

with any of the other peptides examined, i.e., LHRH¹⁻¹⁰, LHRH⁴⁻¹⁰, or LHRH⁵⁻¹⁰ (Table 16.1), indicating that early LHRH neurons contain LHRH¹⁻⁵ peptide or a molecule similar to LHRH¹⁻⁵.³⁵

If early LHRH neurons contain LHRH¹⁻⁵, they may also contain metalloendopeptidase E.C.3.4.24.15 (EP24.15) peptide, an enzyme that cleaves LHRH at the Try⁵-Gly⁶ position. To examine this possibility, adjacent sections that immunostained for LHRH¹⁻⁵ and LHRH⁴⁻¹⁰ are exposed to an affinity-purified rabbit polyclonal antibody against EP24.15.³⁶ Specificity is also tested by exposing the tissues to the EP24.15 antibody after preabsorption with the EP24.15 peptide. By using single staining, late EP24.15 positive cells in fetuses at E35 and E38 are seen on the terminal nerve. However, late LHRH-type neurons, single-stained with the EP24.15 antibody in the older fetus brains (E50 to E78), are difficult to detect, since they are faintly stained, and the cells are mostly scattered. Early EP24.15 positive cells are observed in the basal forebrain of fetuses at E35 and E36 and are consistently seen in the brain of older fetuses at E50 to E78. Immunofluorescein double-labeling indicates that early GF-6 positive neurons are also LHRH¹⁻⁵ positive and EP24.15 positive,³⁵ and late GF-6 positive cells were faintly immunopositive with EP24.15. Moreover, both early and late LHRH¹⁻⁵ positive neurons are also EP24.15 positive. Therefore, immunopositive staining of early cells with the endopeptidase EP24.15 antibody suggests that early cells also contain the cleavage enzyme for the bond between Tyr⁵-Gly⁶ position of LHRH¹⁻¹⁰,³⁷ and therefore it is likely that early cells contain the LHRH¹⁻⁵ and LHRH⁶⁻¹⁰-like peptides.

VII. Possible Functions of LHRH Fragments and EP24.15

What is the role of neuropeptide breakdown products in modulating neural function? The fact that early LHRH cells express much higher levels of LHRH¹⁻⁵ than late cells, shown by immunocytochemistry and confocal imaging, is indicative of a possible function of early LHRH independent from late LHRH neurons. The existence of LHRH¹⁻⁵ in early LHRH cells in the extrahypothalamic region further suggests that they are not involved in control of LH/FSH release, since the medial basal hypothalamus is the only part of the brain responsible for the maintenance of pulsatile LHRH release and ovulatory LHRH release in primates.³⁸ A recent report suggests that the LHRH fragment, LHRH¹⁻⁵, alters LHRH release, since LHRH¹⁻⁵, but not LHRH²⁻¹⁰, suppresses pulsatile release of LHRH and *N*-methyl-d-aspartate (NMDA)-induced LHRH release.³⁹ These authors propose a hypothesis that LHRH¹⁻⁵ is an endogenous antagonist of NMDA receptors. This hypothesis is partly supported by a preliminary report by Moorjani et al.⁴⁰ showing that LHRH¹⁻⁵ competes with NMDA binding in membrane preparations from the rat hypothalamus and cortex using a ³H-L-glutamate displacement assay. Therefore,

it is possible that LHRH¹⁻⁵ is a neurotransmitter in early LHRH neurons. Additional functions of LHRH¹⁻⁵ in the fetal brain remain to be investigated.

It has been reported that mLHRH neurons in the adult rat hypothalamus express EP 24.15; i.e., EP24.15 is found in the perivascular space of the median eminence and is secreted into the portal circulation.⁴¹ These authors further show that a specific inhibitor of this enzyme increases the amplitude of the steroid-induced LH surge in ovariectomized rats. In sheep, however, EP24.15 activity does not fluctuate throughout the estrous cycle, and intraventricular infusion of an EP24.15 inhibitor does not block the LHRH release pattern.⁴² Nonetheless, the results of Wu et al.⁴¹ indicate a possible neuroendocrine role for EP24.15 in late LHRH neurons in the adult hypothalamus. In addition, it is possible that EP24.15 in late LHRH neurons plays a role in the degradation of other peptidergic inputs on LHRH neurons, since this enzyme also cleaves neuropeptides, such as angiotensin, neurotensin, dynorphin A, and bradykinin.⁴³ A functional role of EP24.15 in late LHRH neurons in the embryonic brain remains unknown.

VIII. The cLHRH-II Form in the Monkey Brain

cLHRH-II is the most ubiquitous second form of LHRH in the animal kingdom and is not believed to be crucial for the control of gonadotropin secretion.^{6,9,13,44,45} The presence of cLHRH-II has been reported in many species such as marsupials,⁴⁶ musk shrews,⁴⁷ rodents,⁴⁸ and humans.⁴⁹ The complementary (c) DNA or gene that encodes cLHRH-II has been reported in several fish (see Reference 50), tree shrews,⁵¹ and humans.⁴⁹ In contrast to the distribution pattern of mLHRH in the anterior portion of the brain, cLHRH-II cells are consistently found in the posterior portion of the brain, namely, midbrain, of most species.

Early in this series of studies, we started to collaborate with Nancy M. Sherwood. The initial aim was to determine the molecular structure of the early LHRH cells in the monkey fetal forebrain. However, instead, she and her graduate student, David Lescheid, isolated the cLHRH-II peptide by HPLC from the adult and fetal monkey brain.⁵² This was a big surprise, because when we were focusing on the forebrain area of monkey fetuses, we did not detect cLHRH-II positive cells with three polyclonal antibodies. Subsequently, we went back to reexamine immunocytochemically stained tissue sections from various developmental stages and found that there were cLHRH-II positive cells in the posterior hypothalamic region of an E34 embryo and in the periaqueductal region of older fetuses.

cLHRH-II positive neurons are round in shape with fine neurites and generally smaller than mLHRH neurons, which are fusiform in shape with thick neurites. They are most commonly distributed in the periventricular region of the posterior portion of the third ventricle to the periaqueductal region of

the midbrain, but a small number of cLHRH-II perikarya and fibers are present in the pituitary stalk.⁵²

The origin of cLHRH-II cells is currently unknown. However, studies of olfactory ablation suggest that these cells do not originate from the olfactory placode.^{23,53} It has been suggested that cLHRH-II neurons originate from the ventricular ependymal cells.^{54,55} In primates as well, cLHRH-II neurons appear to originate from precursor cells in the periventricular zone of the third ventricle and aqueduct, because immunopositive cLHRH-II cells in the area most proximal to the ventricle are more round than those away from the ventricle, and the shape becomes more irregular as the cells move distally from the ventricle (E. Terasawa, unpublished observation).

In order to determine the cDNA of cLHRH-II, we carried out RT-PCR on adult and fetal (E85) rhesus monkey brainstem mRNA⁵⁶ with primers based on a portion of the upstream signal peptide and the downstream processing region of human and tree shrew cLHRH-II cDNA.^{49,51} The resulting PCR product was cloned and sequenced.

The cDNA sequence encoding the cLHRH-II decapeptide in the monkey midbrain is identical to that reported in humans and only differs by one nucleotide substitution from that reported in the tree shrew. However, the cDNA region for the signal peptide in the rhesus monkey midbrain shows 90% sequence identity to that in humans, but only 81% sequence identity to that in tree shrews. The corresponding amino acids, deduced from the signal peptide cDNA of the rhesus monkey, show 88% sequence identity to that in humans and 75% sequence identity to that in tree shrews (Table 16.2). Further, the cDNA region for gonadotropin-releasing hormone associated peptide (GAP) in the monkey brain shows 81% sequence identity to that in humans and 77% sequence identity to that in tree shrews. The corresponding amino acid sequence identity of the GAP region is 70 and 64%, respectively (Table 16.2). From the perspective of cLHRH-II in humans, chicken preproLHRH-II in the rhesus monkey is more closely related to the human sequence than the tree shrew sequence. These data suggest that cDNA and amino acid sequences of the cLHRH-II decapeptide are well conserved, but the sequences of the signal peptide and the GAP region have been modified during evolution. Nonetheless, cLHRH-II is present in the midbrain in the rhesus monkey and this form of LHRH is well conserved throughout vertebrate evolution.

At this point there is little information on the function of cLHRH-II. In a previous study, we have shown that cLHRH-II stimulated LH release *in vivo* in rhesus monkeys.⁵² Although there are cLHRH-II fibers with a small number of perikarya present in the basal hypothalamus and the pituitary stalk, the fiber density and staining intensity of mLHRH neurons far exceed those of cLHRH-II. Further, the amount of cLHRH-II in the monkey hypothalamus detected by HPLC is much smaller than that of mLHRH.⁵² Therefore, cLHRH-II may not play a major role in stimulating pituitary gonadotropins.

TABLE 16.2

Comparison of the Chicken LHRH-II Amino Acid Sequence Among Human, Rhesus Monkey, and Tree Shrew

	-20	-10	+1	10	20
Human:	MASSRRG--LLLLLLLTAHLGPSEA QHWSHGWYPG GKRALSSAQD				
Rhesus Monkey:	MASSRRG-LLLLLMLLTAHPGPSEA QHWSHGWYPG GKRALSSAQD				
Tree Shrew:	MASSMLGFLLLLLLMAAHPGPSEA QHWSHGWYPG GKRASNSPQD				
	30	40	50	60	
Human:	PQNALRPPGRALDTAAGSPVQTAHGLPSHALAPLDDSMWPWEGRTT				
Rhesus Monkey:	PQNALRPPAGSPA-----QATYGLPSDALAHLEDSMPWEGRTT				
Tree Shrew:	PQSALRPPAPSAA-----QTAHSFRSAALASPEDSVPWEGRTT				
	70	80	90		
Human:	AQWSLHRKRHLARTLLTAAREPRPA				
Rhesus Monkey:	AWWSLRRKRYLAQTILTAAREPRPA				
Tree Shrew:	AGWSLRRKQHLMRLLSAAGAPRPA				

IX. Examination of the Guinea Pig Form of LHRH in the Monkey Brain

Recently, two transcripts, one which encodes a unique form of the decapeptide and another which encodes mLHRH, have been described in the guinea pig brain.⁵⁷ Since we have speculated in a previous study that the primary binding site of GF-6 is the N-terminus amino acids, especially LHRH¹⁻⁵, we have tested the cross-reactivity of GF-6 with guinea pig LHRH peptide and examined the immunoreactivity of GF-6 after preabsorption with the guinea pig LHRH peptide. Although guinea pig LHRH differs at the Tyr² and Val⁷ amino acid positions from His² and Leu⁷ in mLHRH¹⁻¹⁰, respectively, cross-reactivity of GF-6 with guinea pig LHRH peptide was equal to that of mLHRH¹⁻¹⁰ (N.M. Sherwood, unpublished observation). Further, guinea pig LHRH peptide canceled GF-6 immunopositive staining in both late and early cells (see Table 16.1). The His² to Tyr² change is especially interesting. In all other forms of LHRH discovered to date, His is at the second position. Apparently, this amino acid change suggests that histidine is not critical for binding of GF-6. Nonetheless, preliminary data suggest that the monkey brain does not have guinea pig LHRH; i.e., the cross-reactivity of GF-6 with guinea pig LHRH may not be significant, as brain extracts from an adult or fetal (E85) rhesus monkey did not have GF-6 immunoreactive peaks in the

HPLC fractions where guinea pig LHRH elutes (N.M. Sherwood, unpublished observation).

X. Conclusion

In this chapter we have described the observations in the fetal monkey brain that (1) there are two different types of mLHRH neurons which have the same gene, but originate at two different developmental stages and probably at two different locations and migrate into different areas of the brain, and (2) in addition, the cLHRH-II form is present in the non-human primate brain. The distribution pattern of early LHRH and cLHRH neurons in the extrahypothalamic region clearly suggests that they are not involved in control of gonadotropin release per se, and rather, that they may play a role as peptide neurotransmitters.

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