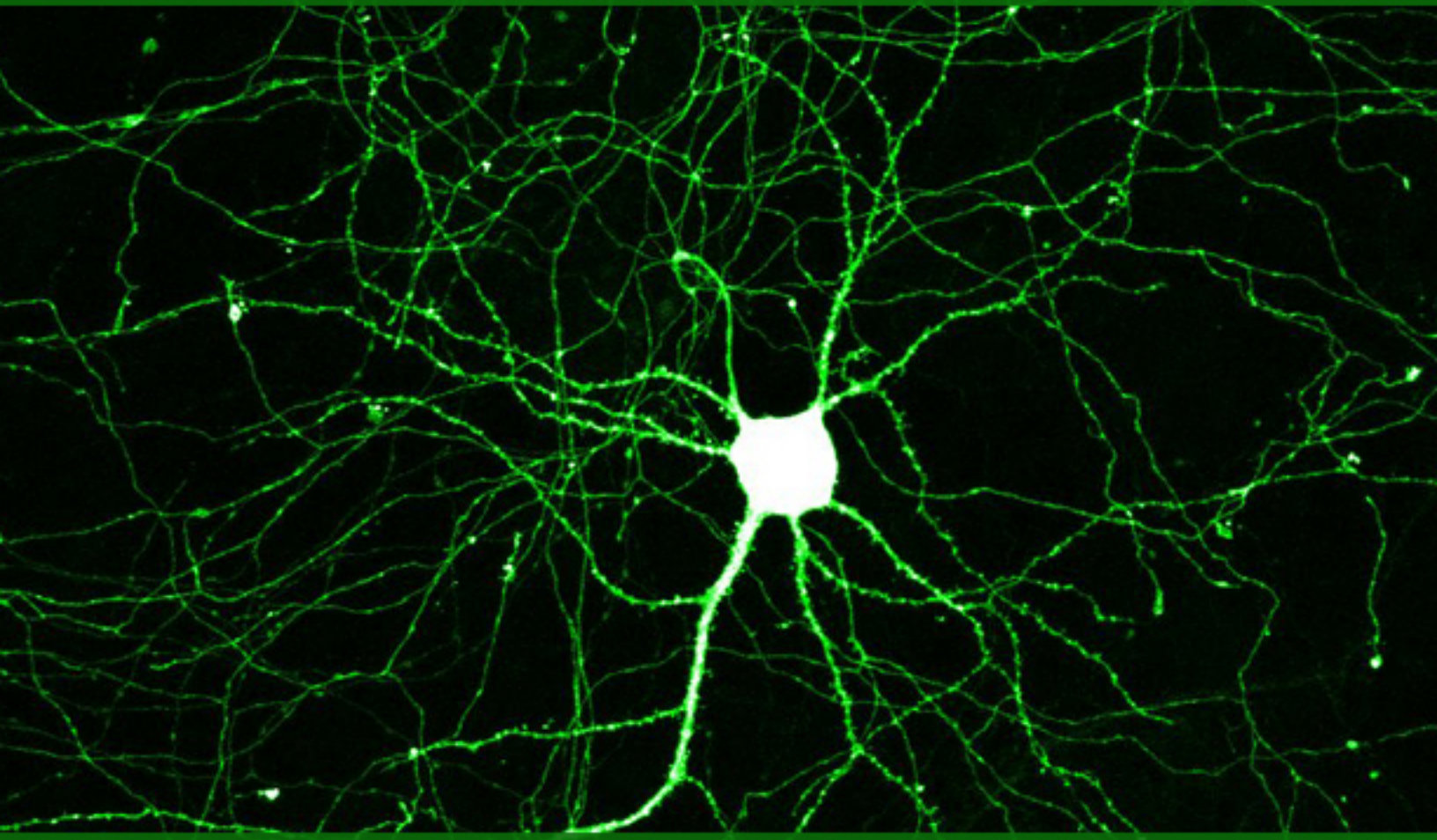
Autonomic and Peripheral Nervous System



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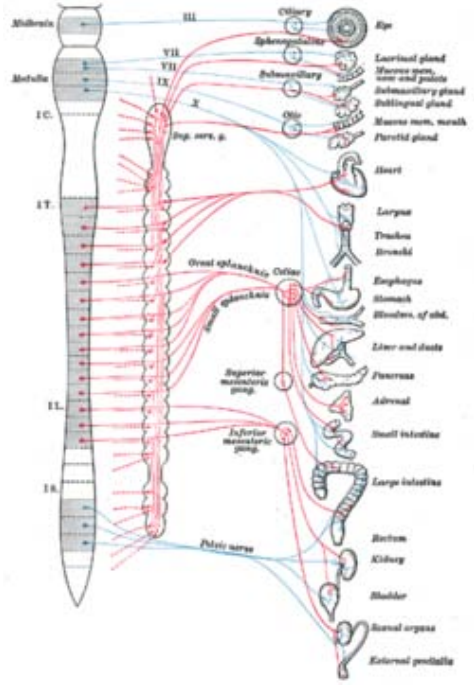
Chapter 1

Autonomic Nervous System

nervous system



The autonomic nervous system

Blue = parasympathetic

Red = sympathetic

Latin *divisio autonomica systematis nervosi peripherici*

The **autonomic nervous system** (**ANS** or **visceral nervous system**) is the part of the peripheral nervous system that acts as a control system functioning largely below the level of consciousness, and controls visceral functions. The ANS affects heart rate, digestion, respiration rate, salivation, perspiration, diameter of the pupils, micturition (urination), and sexual arousal. Whereas most of its actions are involuntary, some, such as breathing, work in tandem with the conscious mind.

It is classically divided into two subsystems: the parasympathetic nervous system and sympathetic nervous system. Relatively recently, a third subsystem of neurons that have been named 'non-adrenergic and non-cholinergic' neurons (because they use nitric oxide as a neurotransmitter) have been described and found to be integral in autonomic function, particularly in the gut and the lungs.

With regard to function, the ANS is usually divided into sensory (afferent) and motor (efferent) subsystems. Within these systems, however, there are inhibitory and excitatory synapses between neurons.

The enteric nervous system is sometimes considered part of the autonomic nervous system, and sometimes considered an independent system.

Anatomy

ANS innervation is divided into sympathetic nervous system and parasympathetic nervous system divisions. The sympathetic division has thoracolumbar “outflow”, meaning that the neurons begin at the thoracic and lumbar (T1-L2) portions of the spinal cord. The parasympathetic division has craniosacral “outflow”, meaning that the neurons begin at the cranial nerves (CN 3, CN7, CN 9, CN10) and sacral (S2-S4) spinal cord.

The ANS is unique in that it requires a sequential two-neuron efferent pathway; the preganglionic neuron must first synapse onto a postganglionic neuron before innervating the target organ. The preganglionic, or first, neuron will begin at the “outflow” and will synapse at the postganglionic, or second, neuron’s cell body. The post ganglionic neuron will then synapse at the target organ.

Sympathetic division

The sympathetic division (thoracolumbar outflow) consists of cell bodies in the lateral horn of spinal cord (intermediolateral cell columns) of the spinal cord from T1 to L2. These cell bodies are GVE (general visceral efferent) neurons , and are the preganglionic neurons. There are several locations upon which preganglionic neurons can synapse for their postganglionic neurons:

- Paravertebral ganglia of the sympathetic chain (these run on either side of the vertebral bodies)
- Prevertebral ganglia (celiac ganglia, superior mesenteric ganglia, inferior mesenteric ganglia)
- Chromaffin cells of adrenal medulla (this is the one exception to the two-neuron pathway rule: synapse is direct onto cell bodies)

These ganglia provide the postganglionic neurons from which innervation of target organs follows. Examples of splanchnic (visceral) nerves are:

- Cervical cardiac nerves & thoracic visceral nerves which synapse in the sympathetic chain
- Thoracic splanchnic nerves (greater, lesser, least) which synapse in the prevertebral ganglion
- Lumbar splanchnic nerves which synapse in the prevertebral ganglion
- Sacral splanchnic nerves which synapse in the inferior hypogastric plexus

These all contain afferent (sensory) nerves as well, also known as GVA (general visceral afferent) neurons.

Parasympathetic division

The parasympathetic division (craniosacral outflow) consists of cell bodies from one of two locations: brainstem (Cranial Nerves III, VII, IX, X) or sacral spinal cord (S2, S3, S4). These are the preganglionic neurons, which synapse with postganglionic neurons in these locations:

- Parasympathetic ganglia of the head (Ciliary (CN III), Submandibular (CN VII), Pterygopalatine (CN VII), Otic (CN IX)
- In or near wall of organ innervated by Vagus (CN X), Sacral nerves (S2, S3, S4))

These ganglia provide the postganglionic neurons from which innervations of target organs follows. Examples are:

- The preganglionic parasympathetic splanchnic (visceral) nerves
- Vagus nerve, which wanders through the thorax and abdominal regions innervating, among other organs, the heart, lungs, liver and stomach

Sensory neurons

The sensory arm is made of “primary visceral sensory neurons” found in the peripheral nervous system (PNS), in “cranial sensory ganglia”: the geniculate, petrosal and nodose ganglia, appended respectively to cranial nerves VII, IX and X. These sensory neurons monitor the levels of carbon dioxide, oxygen and sugar in the blood, arterial pressure and the chemical composition of the stomach and gut content. (They also convey the sense of taste, a conscious perception). Blood oxygen and carbon dioxide are in fact directly sensed by the carotid body, a small collection of chemosensors at the bifurcation of the carotid artery, innervated by the petrosal (IXth) ganglion. Primary sensory neurons project (synapse) onto “second order” or relay visceral sensory neurons located in the medulla oblongata, forming the nucleus of the solitary tract (nTS), that integrates all visceral information. The nTS also receives input from a nearby chemosensory center, the area postrema, that detects toxins in the blood and the cerebrospinal fluid and is essential for chemically induced vomiting or conditional taste aversion (the memory that ensures that an animal which has been poisoned by a food never touches it again). All these visceral sensory informations constantly and unconsciously modulate the activity of the motor neurons of the ANS

Motor neurons

Motor neurons of the ANS are also located in ganglia of the PNS, called “autonomic ganglia”. They belong to three categories with different effects on their target organs: sympathetic, parasympathetic and enteric.

Sympathetic ganglia are located in two sympathetic chains close to the spinal cord: the prevertebral and pre-aortic chains. Parasympathetic ganglia, in contrast, are located in close proximity to the target organ: the submandibular ganglion close to salivary glands, paracardiac ganglia close to the heart etc... Enteric ganglia, which as their name implies innervate the digestive tube, are located inside its walls and collectively contain as many neurons as the entire spinal cord, including local sensory neurons, motor neurons and interneurons. It is the only truly autonomous part of the ANS and the digestive tube can function surprisingly well even in isolation. For that reason the enteric nervous system has been called “the second brain”.

The activity of autonomic ganglionic neurons is modulated by “preganglionic neurons” (also called improperly but classically "visceral motoneurons") located in the central nervous system. Preganglionic sympathetic neurons are in the spinal cord, at thoraco-lumbar levels. Preganglionic parasympathetic neurons are in the medulla oblongata (forming visceral motor nuclei: the dorsal motor nucleus of the vagus nerve (dmnX), the nucleus ambiguus, and salivatory nuclei) and in the sacral spinal cord. Enteric neurons are also modulated by input from the CNS, from preganglionic neurons located, like parasympathetic ones, in the medulla oblongata (in the dmnX).

The feedback from the sensory to the motor arm of visceral reflex pathways is provided by direct or indirect connections between the nucleus of the solitary tract and visceral motoneurons.

Function

Sympathetic and parasympathetic divisions typically function in opposition to each other. But this opposition is better termed complementary in nature rather than antagonistic. For an analogy, one may think of the sympathetic division as the accelerator and the parasympathetic division as the brake. The sympathetic division typically functions in actions requiring quick responses. The parasympathetic division functions with actions that do not require immediate reaction. Consider sympathetic as "fight or flight" and parasympathetic as "rest and digest".

However, many instances of sympathetic and parasympathetic activity cannot be ascribed to "fight" or "rest" situations. For example, standing up from a reclining or sitting position would entail an unsustainable drop in blood pressure if not for a compensatory increase in the arterial sympathetic tonus. Another example is the constant, second to second modulation of heart rate by sympathetic and parasympathetic influences, as a function of the respiratory cycles. More generally, these two systems should be seen as permanently modulating vital functions, in usually antagonistic fashion, to achieve

homeostasis. Some typical actions of the sympathetic and parasympathetic systems are listed below.

Sympathetic nervous system

Promotes a "fight or flight" response, corresponds with arousal and energy generation, and inhibits digestion.

- Diverts blood flow away from the gastro-intestinal (GI) tract and skin via vasoconstriction.
- Blood flow to skeletal muscles and the lungs is enhanced (by as much as 1200% in the case of skeletal muscles).
- Dilates bronchioles of the lung, which allows for greater alveolar oxygen exchange.
- Increases heart rate and the contractility of cardiac cells (myocytes), thereby providing a mechanism for the enhanced blood flow to skeletal muscles.
- Dilates pupils and relaxes the ciliary muscle to the lens, allowing more light to enter the eye and far vision.
- Provides vasodilation for the coronary vessels of the heart.
- Constricts all the intestinal sphincters and the urinary sphincter.
- Inhibits peristalsis.
- Stimulates orgasm.
- Diabetes peristalsis

Parasympathetic nervous system

Promotes a "rest and digest" response, promotes calming of the nerves return to regular function, and enhances digestion.

- Dilates blood vessels leading to the GI tract, increasing blood flow. This is important following the consumption of food, due to the greater metabolic demands placed on the body by the gut.
- The parasympathetic nervous system can also constrict the bronchiolar diameter when the need for oxygen has diminished.
- Dedicated cardiac branches of the Vagus and thoracic Spinal Accessory nerves impart Parasympathetic control of the Heart or Myocardium.
- During accommodation, the parasympathetic nervous system causes constriction of the pupil and contraction of the ciliary muscle to the lens, allowing for closer vision.
- The parasympathetic nervous system stimulates salivary gland secretion, and accelerates peristalsis, so, in keeping with the rest and digest functions, appropriate PNS activity mediates digestion of food and indirectly, the absorption of nutrients.
- Is also involved in erection of genitals, via the pelvic splanchnic nerves 2–4.
- Stimulates sexual arousal.

Neurotransmitters and pharmacology

At the effector organs, sympathetic ganglionic neurons release noradrenaline (norepinephrine), along with other cotransmitters such as ATP, to act on adrenergic receptors, with the exception of the sweat glands and the adrenal medulla:

- Acetylcholine is the preganglionic neurotransmitter for both divisions of the ANS, as well as the postganglionic neurotransmitter of parasympathetic neurons. Nerves that release acetylcholine are said to be cholinergic. In the parasympathetic system, ganglionic neurons use acetylcholine as a neurotransmitter, to stimulate muscarinic receptors.
- At the adrenal cortex, there is no postsynaptic neuron. Instead the presynaptic neuron releases acetylcholine to act on nicotinic receptors.
- Stimulation of the adrenal medulla releases adrenaline (epinephrine) into the bloodstream which will act on adrenoceptors, producing a widespread increase in sympathetic activity.

The following table reviews the actions of these neurotransmitters as a function of their receptors.

Circulatory system

Heart

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
cardiac output	β1, (β2): increases	M2: decreases
SA node: heart rate (chronotropic)	β1, (β2) : increases	M2: decreases
Atrial cardiac muscle: contractility (inotropic)	β1, (β2): increases	M2: decreases
Ventricular cardiac muscle	β1, (β2): increases contractility (inotropic) increases cardiac muscle automaticity	---
at AV node	β1: increases conduction increases cardiac muscle automaticity	M2: decreases conduction Atrioventricular block

Blood vessels

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
vascular smooth muscle	α1: contracts; β2: relaxes	M3: relaxes

renal artery	α1: constricts	---
larger coronary arteries	α1 and α2: constricts	---
smaller coronary arteries	β2:dilates	---
arteries to viscera	α: constricts	---
arteries to skin	α: constricts	---
arteries to brain	α1: constricts	---
arteries to erectile tissue	α1: constricts	M3: dilates
arteries to salivary glands	α: constricts	M3: dilates
hepatic artery	β2: dilates	---
arteries to skeletal muscle	β2: dilates	---
Veins	α1 and α2 : constricts β2: dilates	---

Other

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
platelets	α2: aggregates	---
mast cells - histamine	β2: inhibits	---

Respiratory system

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
smooth muscles of bronchioles	β2: relaxes (major contribution) α1: contracts (minor contribution)	M3: contracts

The bronchioles have no sympathetic innervation, but are instead affected by circulating adrenaline

Nervous system

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
Pupil dilator muscle	α1: contracts (causes mydriasis)	M3: contracts circular muscle (causes miosis)
Ciliary muscle	β2: relaxes (causes long-range focus)	M3: contracts (causes short-range focus)

Digestive system

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
salivary glands: secretions	β: stimulates viscous, amylase secretions α1: stimulates potassium cation	M3: stimulates watery secretions
lacrimal glands (tears)	β: stimulates protein secretion	---
kidney (renin)	β1: secretes	---
parietal cells	---	M1: Gastric acid secretion
liver	α1, β2: glycogenolysis, gluconeogenesis	---
adipose cells	β1, β3: stimulates lipolysis	---
GI tract (smooth muscle) motility	α1, α2, β2: decreases	M3, (M1) : increases
sphincters of GI tract	α1 , α2 , β2: contracts	M3: relaxes
glands of GI tract	no effect	M3: secretes

Endocrine system

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
pancreas (islets)	α2: decreases secretion from beta cells, increases secretion from alpha cells	M3 increases stimulation from alpha cells and beta cells
adrenal medulla	N (nicotinic ACh receptor): secretes epinephrine and norepinephrine	---

Urinary system

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
Detrusor urinae muscle of bladder wall	β2: relaxes	M3: contracts
urethral sphincter (internal)	α1: contracts	relaxes
sphincter	α1: contracts; β2 relaxes	M3: relaxes

Reproductive system

Target	**Sympathetic** (adrenergic)	**Parasympathetic** (muscarinic)
uterus	α1: contracts (pregnant) β2: relaxes (non-pregnant)	---
genitalia	α1: contracts (ejaculation)	M3: erection

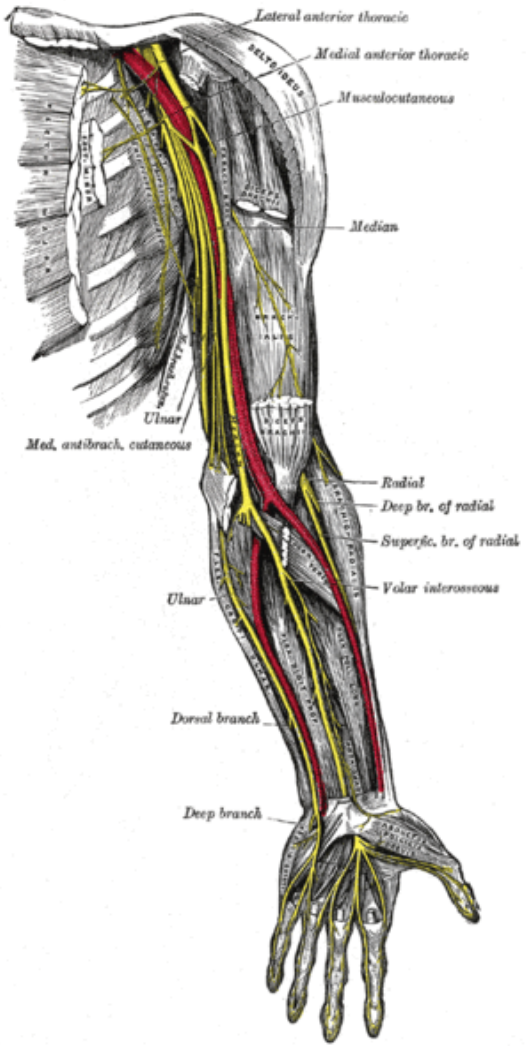
Integumentary system

Target	**Sympathetic** (**muscarinic** and adrenergic)	**Parasympathetic** (muscarinic has no effect on sweating)
sweat gland secretions	M: stimulates (major contribution); α1: stimulates (minor contribution)	---
arrector pili	α1: stimulates	---

Chapter 2

Peripheral Nerve and Spinal Nerve

Peripheral nerve



Nerves (yellow)

A **peripheral nerve**, or simply **nerve** is an enclosed, cable-like bundle of peripheral axons (the long, slender projections of neurons). A nerve provides a common pathway for the electrochemical nerve impulses that are transmitted along each of the axons. Nerves are found only in the peripheral nervous system. In the central nervous system, the analogous structures are known as tracts. Neurons are sometimes called *nerve cells*, though this term is potentially misleading since many neurons do not form nerves, and nerves also include non-neuronal Schwann cells that coat the axons in myelin.

Each nerve is a cordlike structure that contains many axons. These axons are often referred to as "fibres". Within a nerve, each axon is surrounded by a layer of connective tissue called the endoneurium. The axons are bundled together into groups called fascicles, and each fascicle is wrapped in a layer of connective tissue called the perineurium. Finally, the entire nerve is wrapped in a layer of connective tissue called the epineurium.

Anatomy

Nerves are categorized into three groups based on the direction that signals are conducted:

- *Afferent nerves* conduct signals from sensory neurons to the central nervous system, for example from the mechanoreceptors in skin.
- *Efferent nerves* conduct signals from the central nervous system along motor neurons to their target muscles and glands.
- *Mixed nerves* contain both afferent and efferent axons, and thus conduct both incoming sensory information and outgoing muscle commands in the same bundle.

Nerves can be categorized into two groups based on where they connect to the central nervous system:

- *Spinal nerves* innervate much of the body, and connect through the spinal column to the spinal cord. They are given letter-number designations according to the vertebra through which they connect to the spinal column.
- *Cranial nerves* innervate parts of the head, and connect directly to the brainstem. They are typically assigned Roman numerals from 1 to 12, although cranial nerve zero is sometimes included. In addition, cranial nerves have descriptive names.

Each nerve is covered externally by a dense sheath of connective tissue, the epineurium. Underlying this is a layer of flat cells, the perineurium, which forms a complete sleeve around a bundle of axons. Perineurial septae extend into the nerve and subdivide it into several bundles of fibres. Surrounding each such fibre is the endoneurium. This forms an unbroken tube which extends from the surface of the spinal cord to the level at which the axon synapses with its muscle fibers, or ends in sensory receptors. The endoneurium consists of an inner sleeve of material called the glycocalyx and an outer, delicate, meshwork of collagen fibres. Nerves are bundled along with blood vessels, since the

neurons of a nerve have fairly high energy requirements. Within the endoneurium, the individual nerve fibres are surrounded by a low protein liquid called endoneurial fluid. The endoneurium has properties analogous to the blood-brain barrier, in that it prevents certain molecules from crossing from the blood into the endoneurial fluid. In this respect, endoneurial fluid is similar to cerebro-spinal fluid in the central nervous system. During the development of nerve edema from nerve irritation or (injury), the amount of endoneurial fluid may increase at the site of irritation. This increase in fluid can be visualized using magnetic resonance neurography, and thus MR neurography can identify nerve irritation and/or injury.

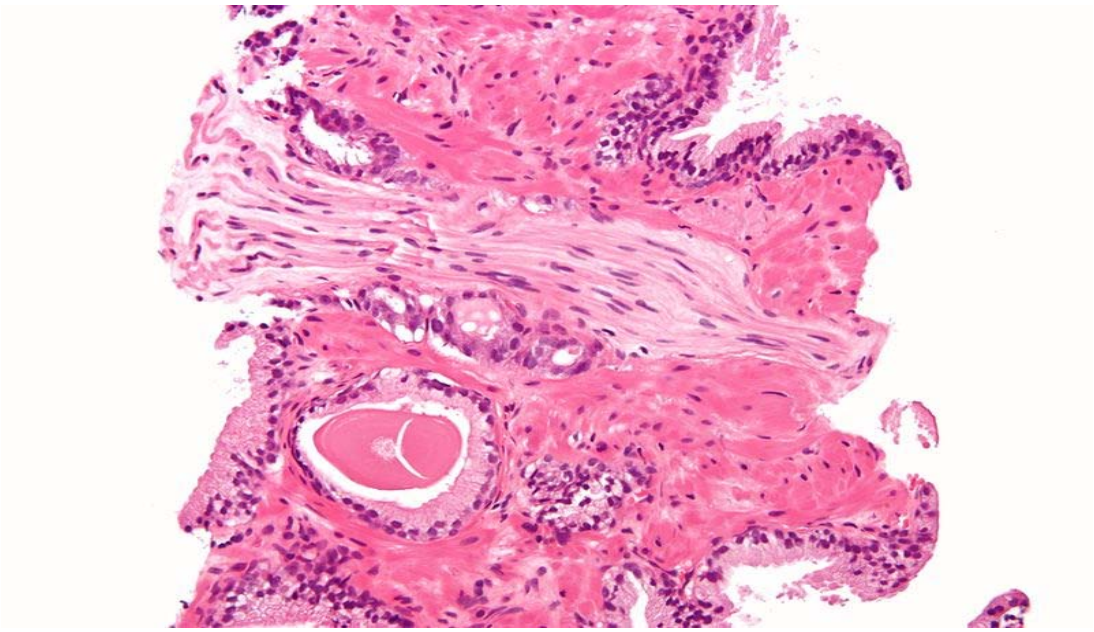
Physiology

A nerve conveys information in the form of electrochemical impulses (known as nerve impulses or action potentials) carried by the individual neurons that make up the nerve. These impulses are extremely fast, with some myelinated neurons conducting at speeds up to 120 m/s. The impulses travel from one neuron to another by crossing a synapse, the message is converted from electrical to chemical and then back to electrical.

Nerves can be categorized into two groups based on function:

- *Sensory nerves* conduct sensory information from their receptors to the central nervous system, where the information is then processed. Thus they are synonymous with *afferent nerves*.
- *Motor nerves* conduct signals from the central nervous system to muscles. Thus they are synonymous with *efferent nerves*.

Clinical importance



Micrograph demonstrating perineural spread of prostate cancer. H&E stain.

Damage to nerves can be caused by physical injury or swelling (e.g. carpal tunnel syndrome), autoimmune diseases (e.g. Guillain-Barré syndrome), infection (neuritis), diabetes or failure of the blood vessels surrounding the nerve. A *pinched nerve* occurs when pressure is placed on a nerve, usually from swelling due to an injury or pregnancy. Nerve damage or pinched nerves are usually accompanied by pain, numbness, weakness, or paralysis. Patients may feel these symptoms in areas far from the actual site of damage, a phenomenon called **referred pain**. Referred pain occurs because when a nerve is damaged, signalling is defective from all parts of the area from which the nerve receives input, not just the site of the damage. Neurologists usually diagnose disorders of the nerves by a physical examination, including the testing of reflexes, walking and other directed movements, muscle weakness, proprioception, and the sense of touch. This initial exam can be followed with tests such as nerve conduction study and electromyography (EMG).

Cancer

Cancer can spread along nerves; this is known as *perineural spread* and often is associated with a worse prognosis.

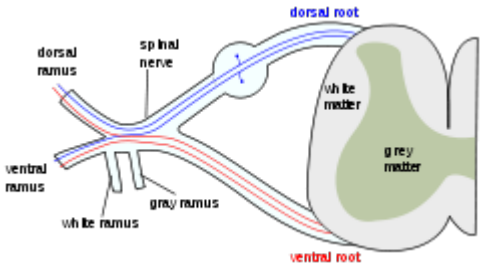
Nerve Growth & stimulation

Nerve growth normally ends in adolescence, but can be re-stimulated with a molecular mechanism known as "Notch signaling", working on a Notch receptor:

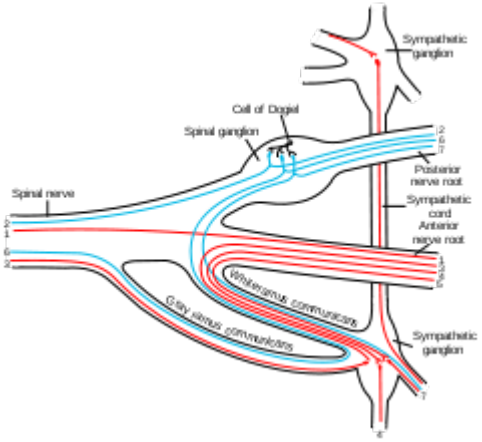
Yale Study Shows Way To Re-Stimulate Brain Cell Growth ScienceDaily (Oct. 22, 1999) — Results Could Boost Understanding Of Alzheimer's,

Spinal nerve

Nerve: Spinal nerve



The formation of the spinal nerve from the dorsal and ventral roots



Scheme showing structure of a typical spinal nerve.

1. Somatic efferent.
2. Somatic afferent.
3,4,5. Sympathetic efferent.
6,7. Sympathetic afferent.

Latin	*nervi spinales*
Gray's	*subject #208 916*
MeSH	*Spinal+nerves*

The term **spinal nerve** generally refer to a mixed spinal nerve, which carries motor, sensory, and autonomic signals between the spinal cord and the body. Humans have 31 left-right pairs of spinal nerves, each roughly corresponding to a segment of the vertebral column: 8 cervical spinal nerve pairs (C1-C8), 12 thoracic pairs (T1-T12), 5 lumbar pairs (L1-L5), and 5 sacral pairs (S1-S5) and 1 coccygeal pair. The spinal nerves are part of the peripheral nervous system (PNS).

Anatomy

Each spinal nerve is formed by the combination of nerve fibers from the dorsal and ventral roots of the spinal cord. The dorsal roots carry afferent sensory axons, while the ventral roots carry efferent motor axons. The spinal nerve emerges from the spinal column through an opening (intervertebral foramen) between adjacent vertebrae. This is true for all spinal nerves except for the first spinal nerve pair, which emerges between the occipital bone and the atlas (the first vertebra).

Outside the vertebral column, the nerve divides into branches. The dorsal ramus contains nerves that serve the dorsal portions of the trunk carrying visceral motor, somatic motor, and sensory information to and from the skin and muscles of the back. The ventral ramus contains nerves that serve the remaining ventral parts of the trunk and the upper and lower limbs carrying visceral motor, somatic motor, and sensory information to and from the ventrolateral body surface, structures in the body wall, and the limbs. The meningeal

branches (recurrent meningeal or sinuvertebral nerves) branch from the spinal nerve and re-enter the intervertebral foramen to serve the ligaments, dura, blood vessels, intervertebral discs, facet joints, and periosteum of the vertebrae. The rami communicantes contain autonomic nerves that serve visceral functions carrying visceral motor and sensory information to and from the visceral organs.

Some ventral rami merge with adjacent ventral rami to form a nerve plexus, a network of interconnecting nerves. Nerves emerging from a plexus contain fibers from various spinal nerves, which are now carried together to some target location. Major plexuses include the cervical, brachial, lumbar, and sacral plexuses.

Clinical significance

The muscles that one particular spinal root supplies are that nerve's myotome, and the dermatomes are the areas of sensory innervation on the skin for each spinal nerve. Lesions of one or more nerve roots result in typical patterns of neurologic defects (muscle weakness, abnormal sensation, changes in reflexes) that allow localization of the causeating lesion.

Chapter 3

Connective Tissue in the Peripheral Nervous System and Dorsal Root Ganglion

Connective tissue in the peripheral nervous system

A peripheral nerve contains two types of tissue:(1) nerve fibers, and (2) connective tissue. Dendrites and axons with schwann cells and myelin sheath are surrounded by connective tissue. A nerve fiber in the peripheral nervous system consists of an axon or long dendrite, myelin sheath (if existence) and their schwann cells. Peripheral sensory fibers contain long dendrites, but peripheral motor fibers have long axons. Long dendrites of sensory fibers have structural properties as motor axons.

Layers of connective tissue in the peripheral nerve

Three layers of connective tissue surround each peripheral nerve that include:

- Epineurium
- Perineurium
- Endoneurium

Epineurium

The epineurium surrounds the peripheral nerve trunk (i.e. Superficial epineurium). This is considered the outermost layer. The epineurium separates the nerve fascicles, but lies outside the perineurium (i.e. Interfascicular epineurium).

Perineurium

Each nerve fascicle is surrounded by the perineurium that includes a group of nerve fibers. The perineurium has very important role in the protection and support from nerve

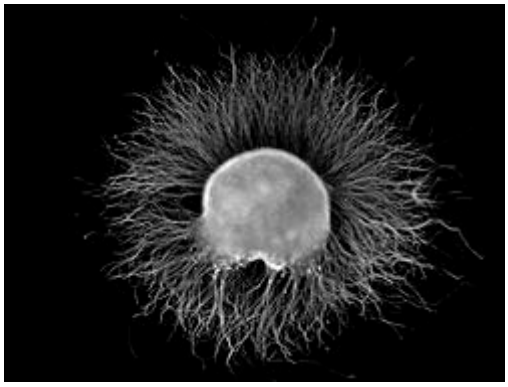
fibers. This section of connective tissue is an important factor in preventing the passing of large molecules from the epineurium into a fascicle.

Endoneurium

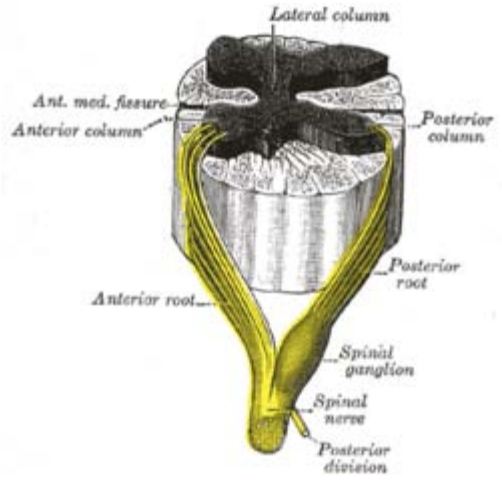
Each nerve fiber is surrounded by the endoneurium. This section is a thin layer of connective tissue. The endoneurium is the tube that places the components of a nerve fiber such as axon, the myelin sheath and Schwann cells into itself. Thus, the endoneurium separates nerve fibers of a fascicle.

Dorsal root ganglion

Dorsal root ganglion



This is a dorsal root ganglion (DRG) from a chicken embryo (around stage of day 7) after incubation overnight in NGF growth medium stained with anti-neurofilament antibody. Axons growing out of the ganglion are visible.



A spinal nerve with its anterior and posterior roots. The dorsal root ganglion is the "spinal ganglion", following the posterior/dorsal root.

Latin	*ganglion sensorium nervi spinalis*
Gray's	*subject #185 750*
Precursor	neural crest
MeSH	*Spinal+Ganglia*

In anatomy and neurology, a **dorsal root ganglion** (or **spinal ganglion**) is a nodule on a dorsal root that contains cell bodies of neurons in afferent spinal nerves.

Unique unipolar structure

The axons of dorsal root ganglion neurons are known as afferents. In the peripheral nervous system, afferents refer to the axons that relay sensory information into the central nervous system (i.e. the brain and the spinal cord). These neurons are of the pseudo-unipolar type, meaning they have an axon with two branches that act as a single axon, often referred to as a *distal process* and a *proximal process*.

Note: the neuron can consist of three parts:

1. Dendrite that receives the information and relays it to the Soma), or cell body.
2. Soma - the cell body of the neuron
3. Axon: which relays information from the soma.

In a neuron, the dendrite receives information from another neuron's axon at the synapse, and the axon sends information to the next neuron's dendrites, even though the dendrite may be covered with myelin.

Unlike the majority of neurons found in the central nervous system, an action potential in dorsal root ganglion neuron may initiate in the *distal process* in the periphery, bypass the cell body, and continue to propagate along the *proximal process* until reaching the synaptic terminal in the dorsal horn of the spinal cord.

Distal section

The distal section of the axon may either be a bare nerve ending or encapsulated by a structure that helps relay specific information to nerve. For example, a Meissner's corpuscle or Pacinian corpuscle may encapsulate the nerve ending, rendering the *distal process* sensitive to mechanical stimulation, such as stroking or vibration, respectively.

Location

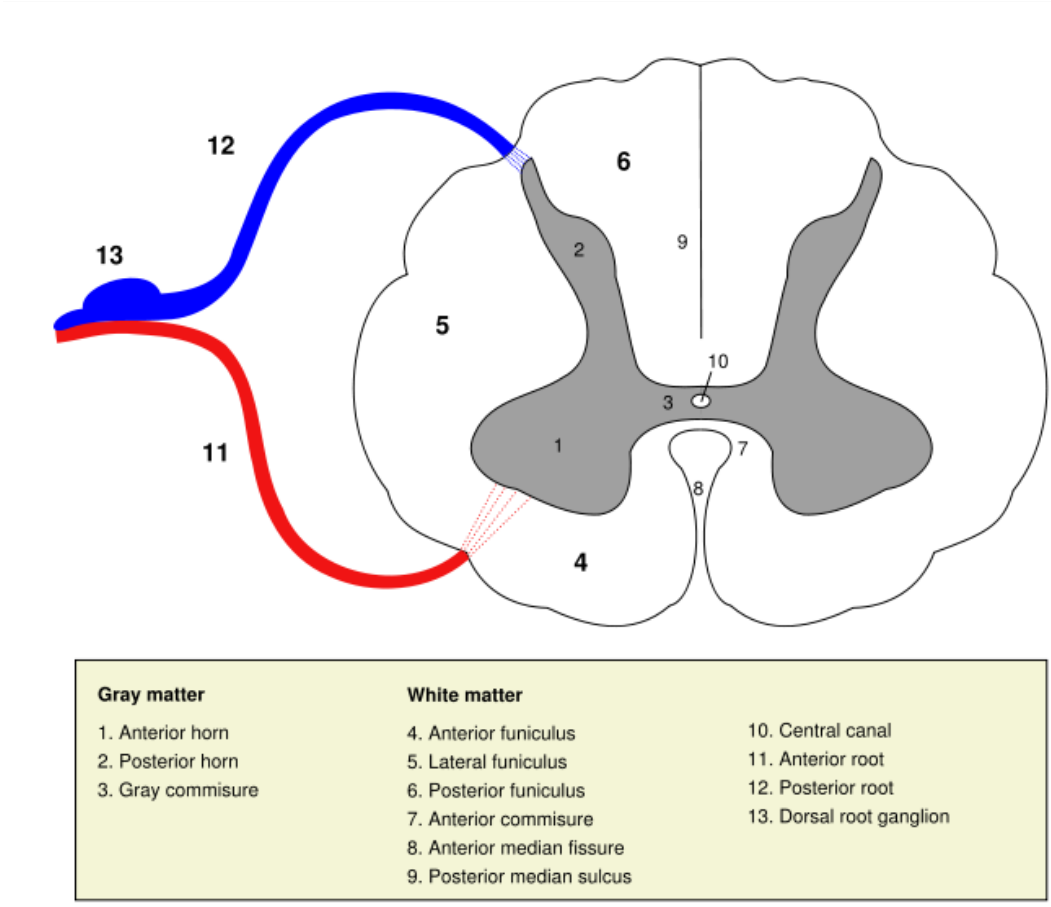
The dorsal root ganglia lie along the vertebral column by the spine.

Embryology

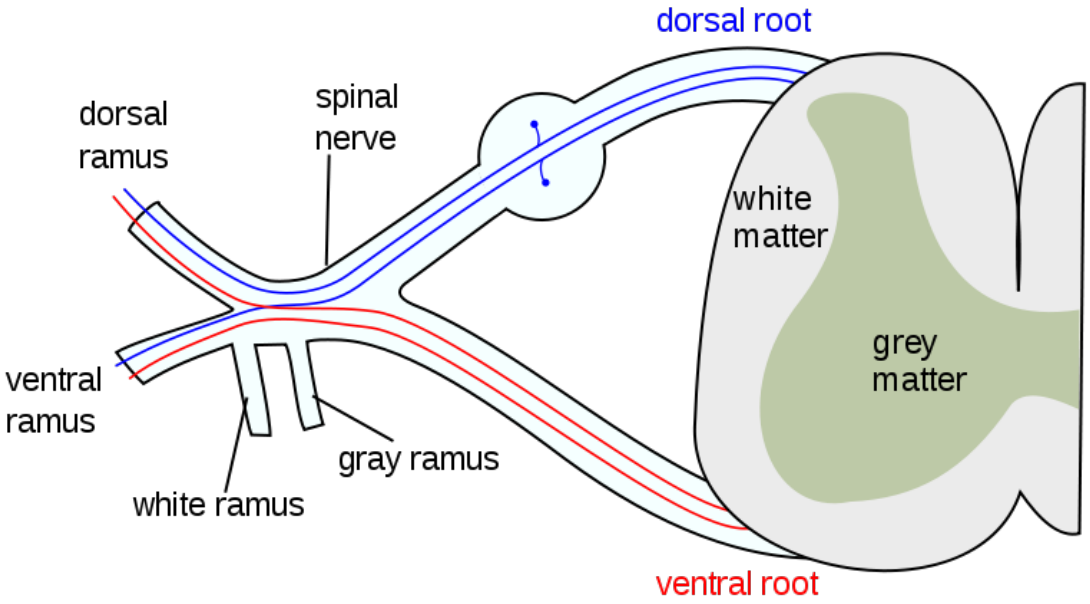
The dorsal root ganglia develops in the embryo from neural crest cells, not neural tube. Hence, the spinal ganglia can be regarded as gray matter of the spinal cord that became translocated to the periphery.

Nociception

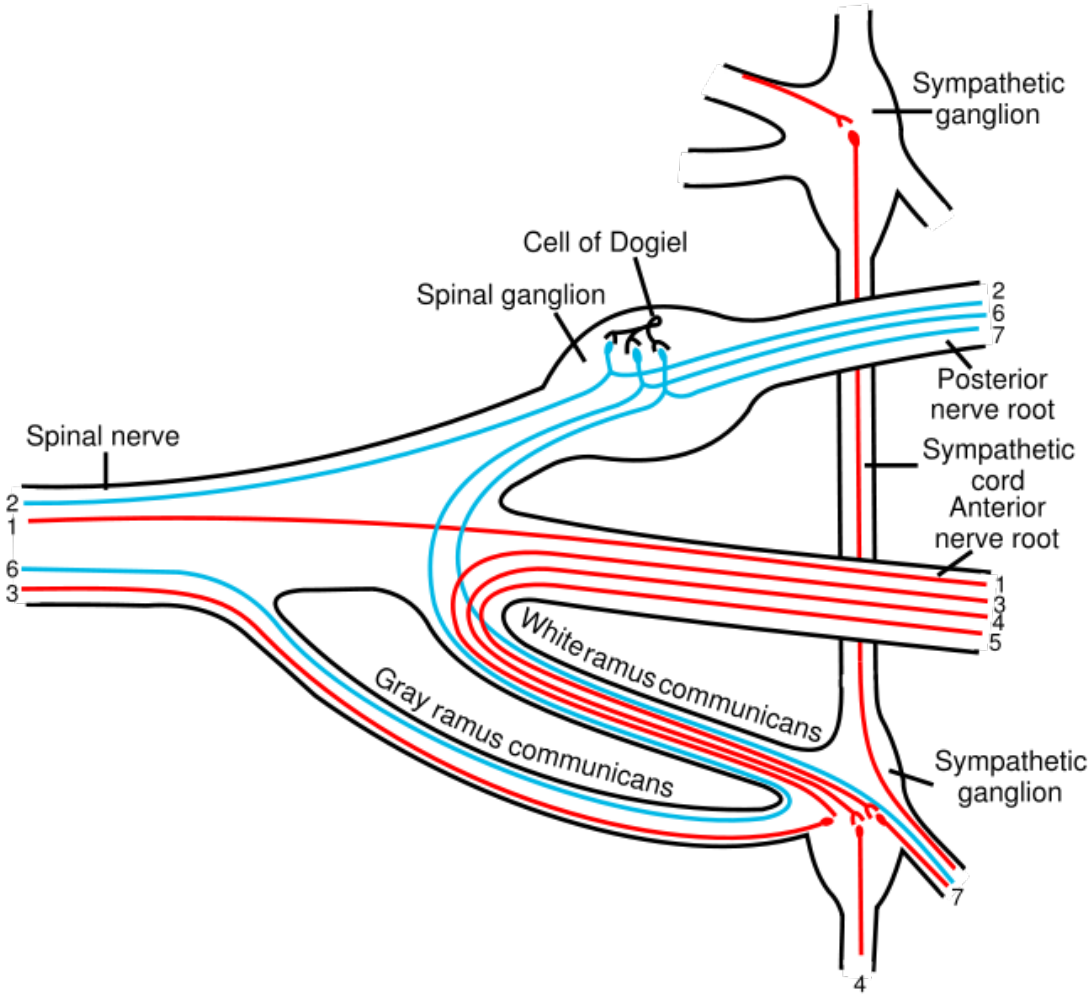
Proton-sensing G protein-coupled receptors are expressed by DRG sensory neurons and might play a role in acid-induced nociception.



Medulla spinalis



The formation of the spinal nerve from the dorsal and ventral roots



Scheme showing structure of a typical spinal nerve

Chapter 4

Efferent Nerve Fiber and General Visceral Afferent Fibers

Efferent nerve fiber

Nerve: Efferent nerve fiber

Latin *neurofibrae efferentes*

In the nervous system, **efferent nerves** – otherwise known as motor or effector neurons – carry nerve impulses *away* from the central nervous system to effectors such as muscles or glands (and also the ciliated cells of the inner ear). The term can also be used to describe relative connections between nervous structures (for example, a neuron's efferent synapse provides input to another neuron, and not vice-versa). The opposite activity of direction or flow is **afferent**.

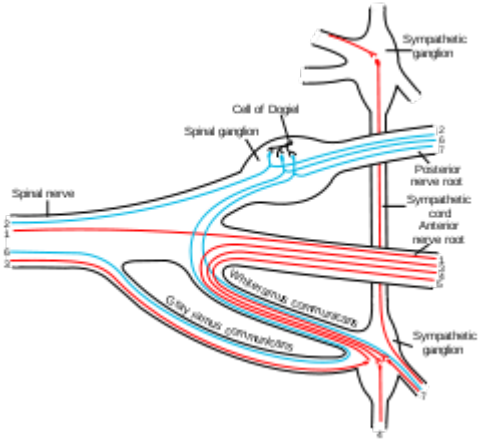
The motor nerves are efferent nerves involved in muscular control. The cell body of the efferent neuron is connected to a single, long axon and several shorter dendrites projecting out of the cell body itself. This axon then forms a neuromuscular junction with the effectors. The cell body of the motor neuron is satellite-shaped. The motor neuron is present in the grey matter of the spinal cord and medulla oblongata, and forms an electrochemical pathway to the effector organ or muscle. Besides motor nerves, there are efferent sensory nerves that often serve to adjust the sensitivity of the signal relayed by the afferent sensory nerve.

Etymology and Mnemonics

Both **afferent** and **efferent** come from French, evolved from Latin (the basis of many terms in medicine and biology) for the terms, respectively, *ad ferens* (Latin verb *ferre*: carry), meaning *carrying into*, and *ex ferens*, meaning *carrying away*. *Ad* and *ex* give an easy mnemonic device for remembering the relationship between *afferent* and *efferent*: ***a**fferent connection **a**rrives* and an ***e**fferent connection **e**xits*.

General visceral afferent fibers

General visceral afferent fibers



Scheme showing pathways (white/grey rami are spatially reverese, possibly for clarity?) of a typical spinal nerve.

1. Somatic efferent.

2. Somatic afferent.

3,4,5. Sympathetic efferent.

6,7. Parasympathetic afferent.

Note that this image merely depicts pathways in a schematic fashion - it is not anatomically correct. The efferent sympathetics exit in a loop - entering the more lateral white and either exiting the more medial grey or traveling up/down the chain to exit grey at other ganglia.

Gray's *subject #190 849*

The **general visceral afferent fibers** (**GVA**), conduct sensory impulses (usually pain or reflex sensations) from the viscera, glands, and blood vessels to the central nervous system. They are considered to be part of the autonomic nervous system. However, unlike the efferent fibers of the autonomic nervous system, the afferent fibers are not classified as either sympathetic or parasympathetic.

Examples of nerves containing GVA fibers include the glossopharyngeal nerve and the vagus nerve.

Pathway

Abdomen

In the abdomen, general visceral afferent fibers usually accompany sympathetic efferent fibers. This means that a signal traveling in an afferent fiber will begin at sensory receptors in the afferent fiber's target organ, travel up to the ganglion where the sympathetic efferent fiber synapses, continue back along a splanchnic nerve from the ganglion into the sympathetic trunk, move into a ventral ramus via a white ramus communicans, and finally move into the mixed spinal nerve between the division of the rami and the division of the roots of the spinal nerve. The GVA pathway then diverges from the sympathetic efferent pathway, which follows the ventral root into the spinal column, by following the dorsal root into the dorsal root ganglion, where the cell body of the sympathetic visceral afferent nerve is located. Finally, the signal continues along the dorsal root from the dorsal root ganglion to a region of gray matter in the dorsal horn of the spinal column where it is transmitted via a synapse to a neuron in the central nervous system.

The only GVA nerves in the abdomen that do not follow the above pathway are those that innervate structures in the distal half of the sigmoid colon and the rectum. These afferent fibers, instead, follow the path of parasympathetic efferent fibers back to the vertebral column, where the afferent fibers enter the S2-S4 sensory ganglia followed by the spinal cord.

Pelvis

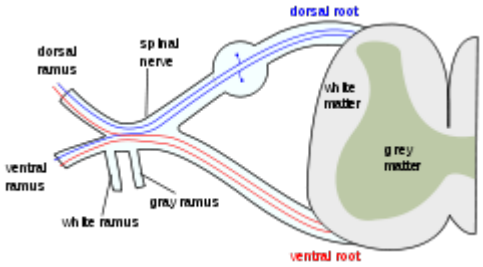
The course of GVA fibers from organs in the pelvis, in general, depends on the organ's position relative to the pelvic pain line. An organ, or part of an organ, in the pelvis is said to be "above the pelvic pain line" if it is in contact with the peritoneum, except in the case of the large intestine, where the pelvic pain line is said to be located in the middle of the sigmoid colon. GVA fibers from structures above the pain line follow the course of the sympathetic efferent fibers, and GVA fibers from structure below the pain line follow the course of the parasympathetic efferents. Pain from the latter fibers is less likely to be consciously experienced.

Chapter 5

Posterior Root of Spinal Nerve and General Somatic Efferent Fibers

Posterior root of spinal nerve

Posterior root of spinal nerve



The formation of the spinal nerve from the dorsal and ventral roots

Latin	*radix posterior*
Gray's	*subject #208 916*
MeSH	*Dorsal+Roots*

In anatomy and neurology, the **dorsal root** (or **posterior root**) is the afferent sensory root of a spinal nerve.

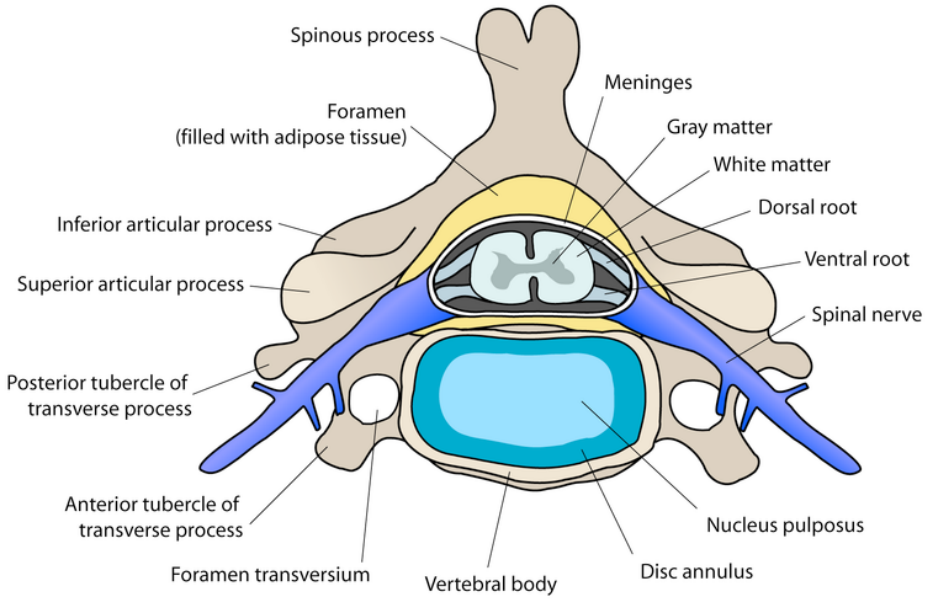
At the distal end of the dorsal root is the dorsal root ganglion, which contains the neuron cell bodies of the nerve fibres conveyed by the root.

If the dorsal root of a spinal nerve were severed it would lead to numbness in certain areas of the body.

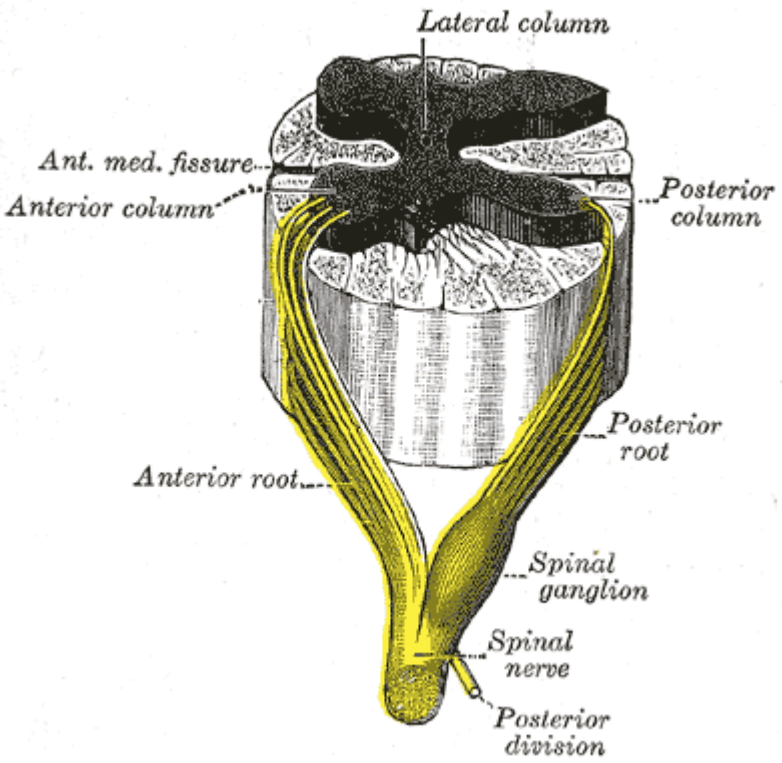
The lateral division of the dorsal root contains lightly myelinated and unmyelinated axons of small diameter. These transmit pain and temperature sensation from the body. These

fibers cross through the anterior white commissure to form the Anterior lateral system in the lateral funiculus.

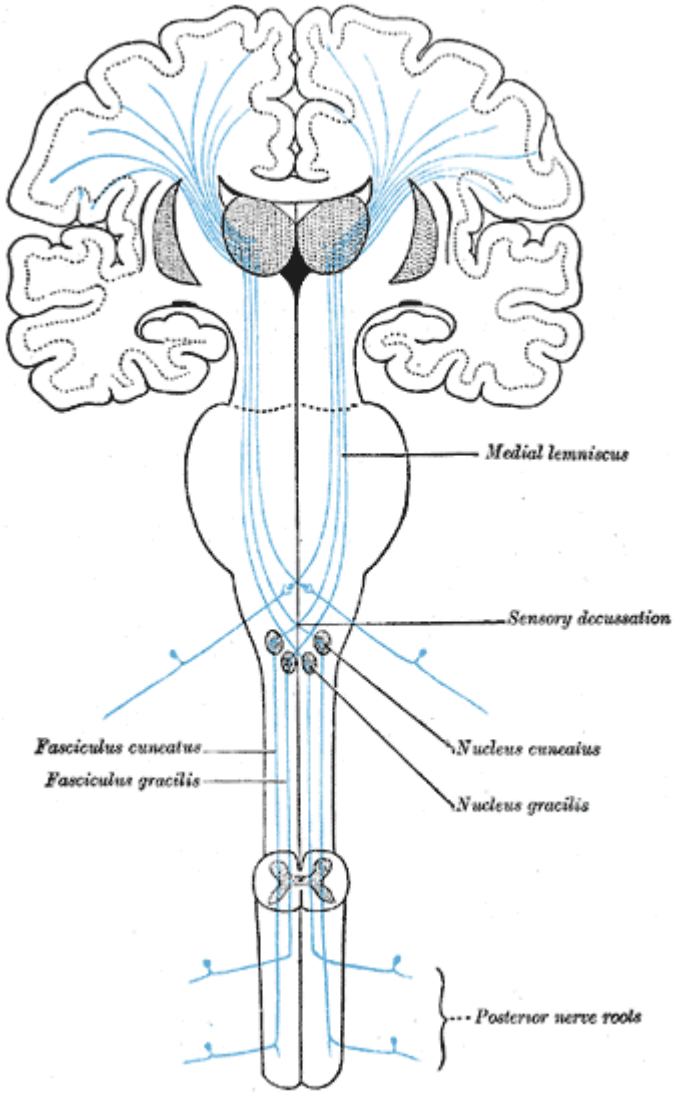
The medial division of the dorsal root contains myelinated axons of larger diameter. These transmit information of discriminative touch, pressure, vibration, and conscious proprioception originating from spinal levels C2 through S5. These fibers are pushed in towards the posterior medial sulcus to form the fasciculus gracilis and the fasciculus cuneatus.



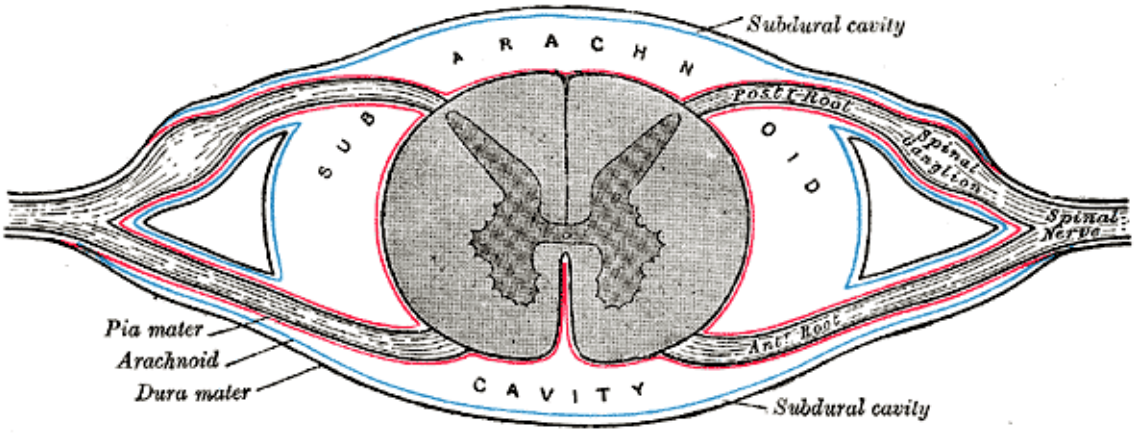
Cervical vertebra



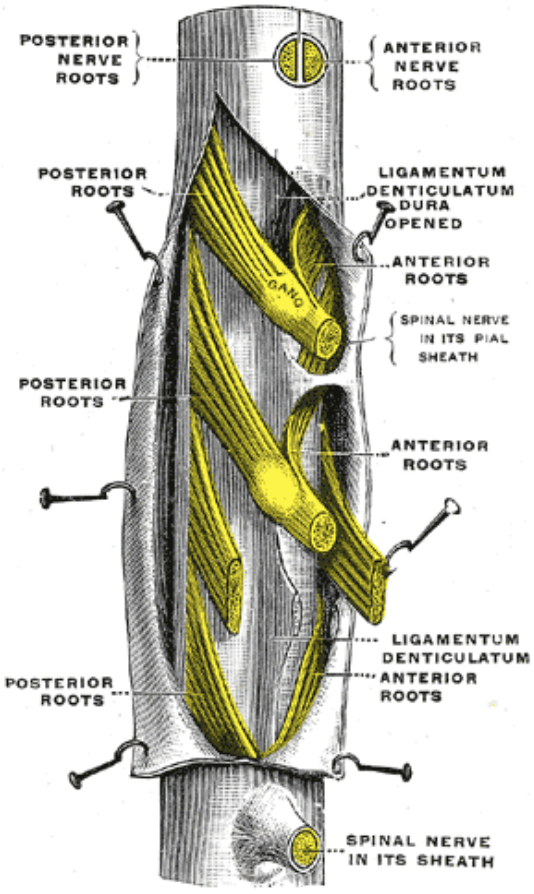
A spinal nerve with its anterior and posterior roots



The sensory tract



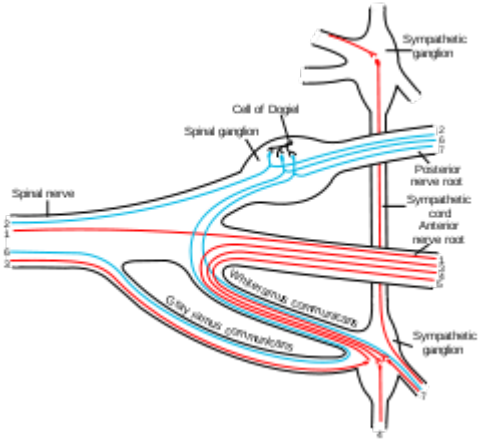
Diagrammatic transverse section of the medulla spinalis and its membranes



A portion of the spinal cord, showing its right lateral surface. The dura is opened and arranged to show the nerve roots.

General somatic efferent fibers

General somatic efferent fibers



Scheme showing structure of a typical spinal nerve.

1. Somatic efferent.

2. Somatic afferent.

3,4,5. Sympathetic efferent.

6,7. Sympathetic afferent.

Gray's *subject #190 849*

The *spinal* **somatic efferent neurons** (**GSE**, '**somatomotor**, or **somatic motor fibers**), arise from motor neuron cell bodies in the ventral horns of the gray matter within the spinal cord. They exit the spinal cord through the ventral roots, carrying motor impulses to skeletal muscle.

Of the somatic efferent neurons, there exist subtypes.

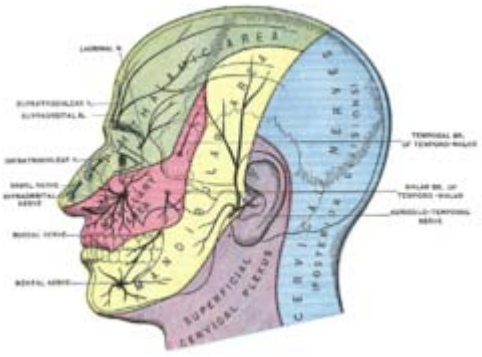
- Alpha motor neurons (α) target extrafusal muscle fibers.
- Gamma motor neurons (γ) target intrafusal muscle fibres

Cranial nerves also supply their own somatic efferent neurons to the extraocular muscles and some of the muscles of the tongue.

Chapter 6

Cervical Plexus and Lumbar Plexus

Cervical plexus

Nerve: Cervical plexus	
	
Dermatome distribution of the trigeminal nerve (Superficial cervical plexus visible in purple, at center bottom.)	
Latin	*plexus cervicalis*
Gray's	*subject #210 925*
From	C1-C4

The **cervical plexus** is a plexus of the ventral rami of the first four cervical spinal nerves which are located from C1 to C5 cervical segment in the neck. They are located laterally to the transverse processes between prevertebral muscles from the medial side and vertebral (m.scalenus, m.levator scapulae, m.splenius cervicis) from lateral side. There is anastomosis with accessory nerve, hypoglossal nerve and sympathetic trunk.

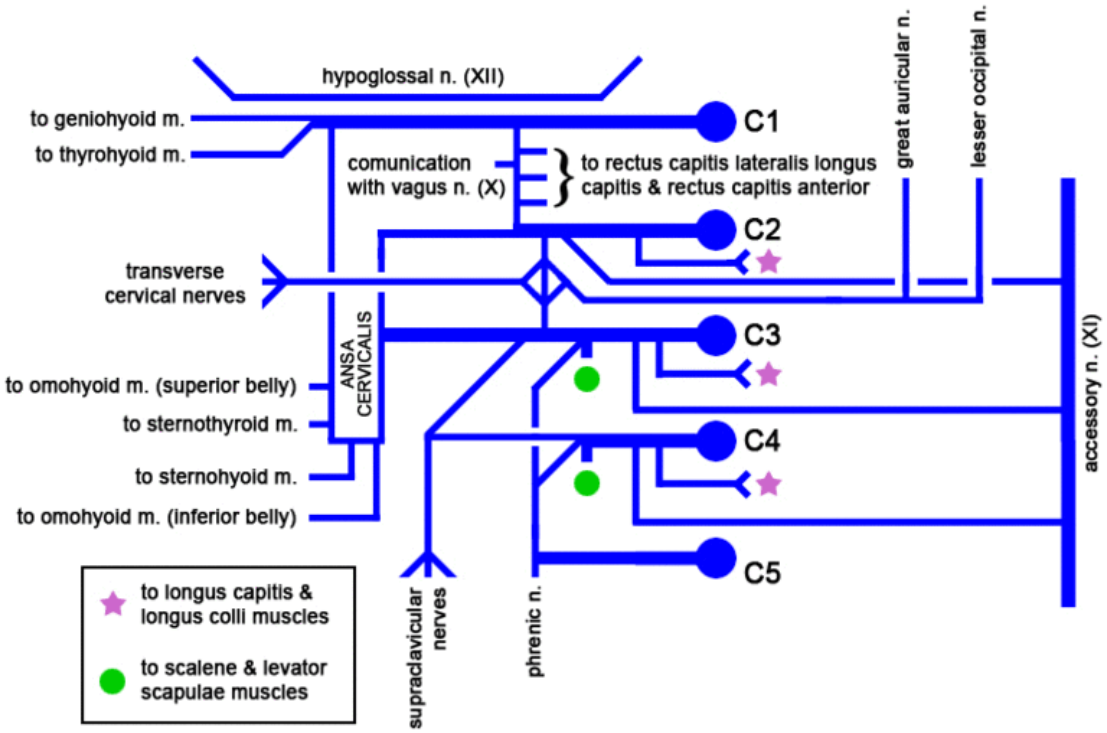
It is located in the neck, deep to sternocleidomastoid. Nerves formed from the cervical plexus innervate the back of the head, as well as some neck muscles. The branches of the cervical plexus emerge from the posterior triangle at the nerve point, a point which lies midway on the posterior border of the Sternocleidomastoid.

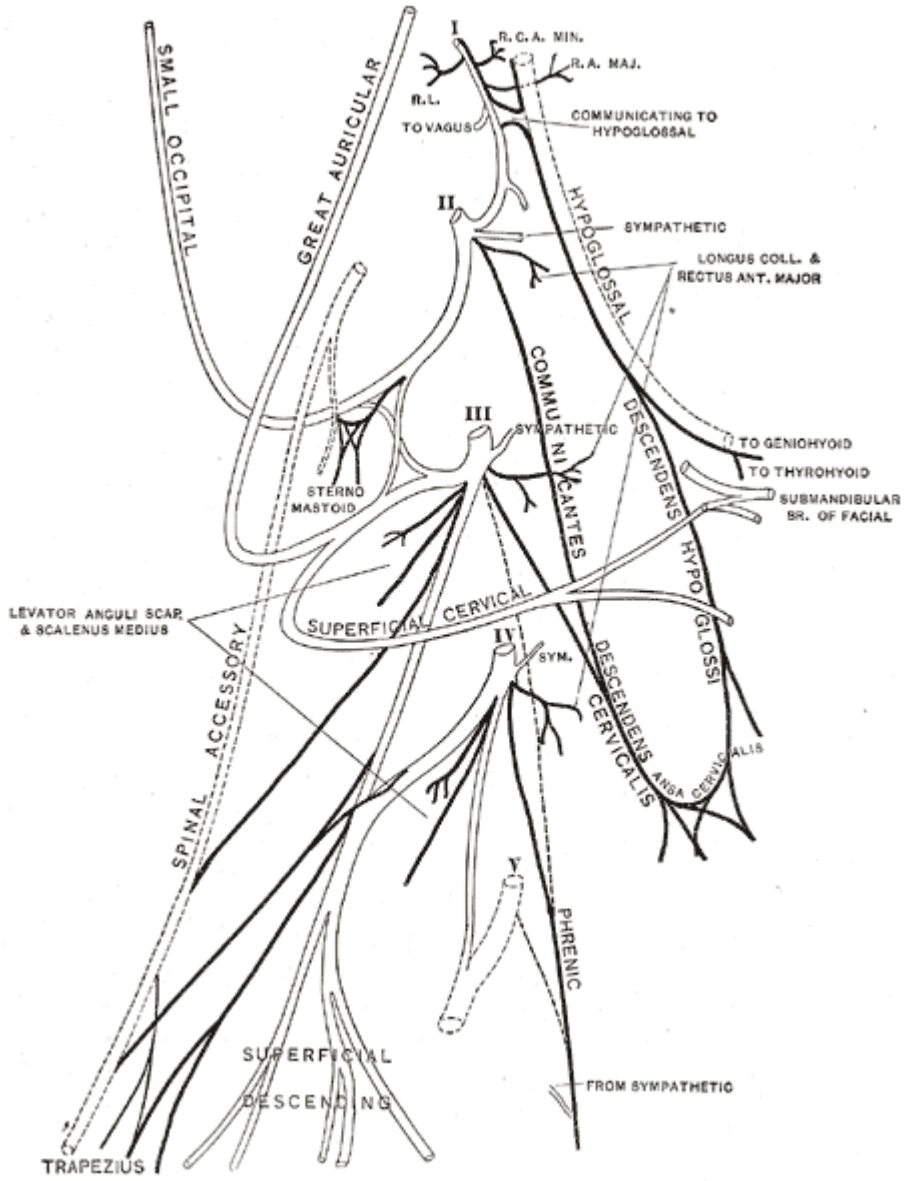
Branches

The cervical plexus has two types of branches: cutaneous and muscular.

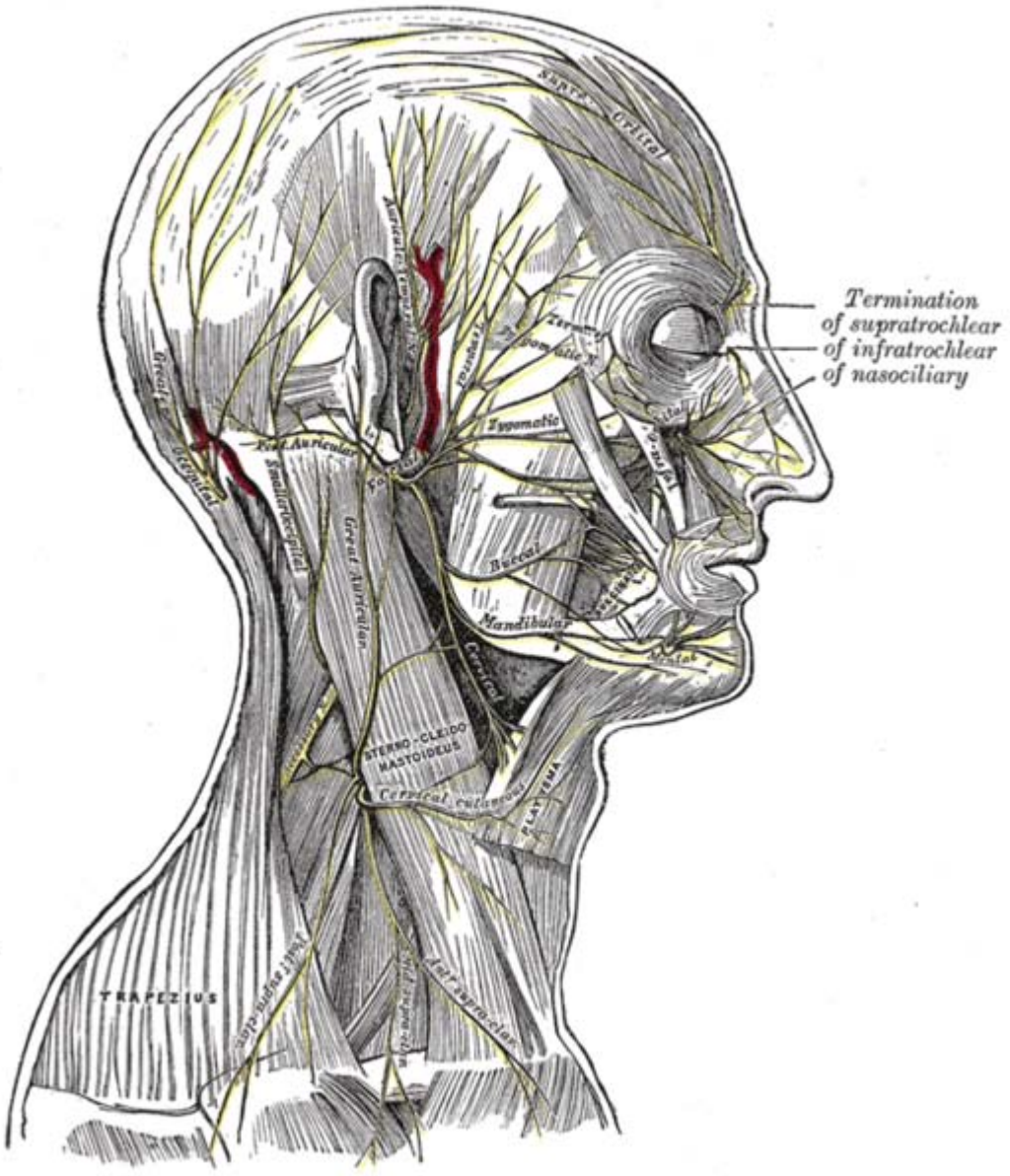
- Cutaneous (4 branches):
  - Lesser occipital nerve - innervates lateral part of occipital region (C2 ONLY)
  - Great auricular nerve - innervates skin near concha auricle and external acoustic meatus (C2&C3)
  - Transverse cervical nerve - innervates anterior region of neck (C2&C3)
  - Supraclavicular nerves - innervate region of suprascapularis, shoulder, and upper thoracic region (C3,C4)
- Muscular
  - Ansa cervicalis (loop formed from C1-C3), etc. (geniohyoid (C1 only), thyrohyoid (C1 only), sternothyroid, sternohyoid, omohyoid)
  - Phrenic (C3-C5 (primarily C4))-innervates diaphragm and the pericardium
  - Segmental branches (C1-C4)- innervates anterior and middle scalenes

Diagram

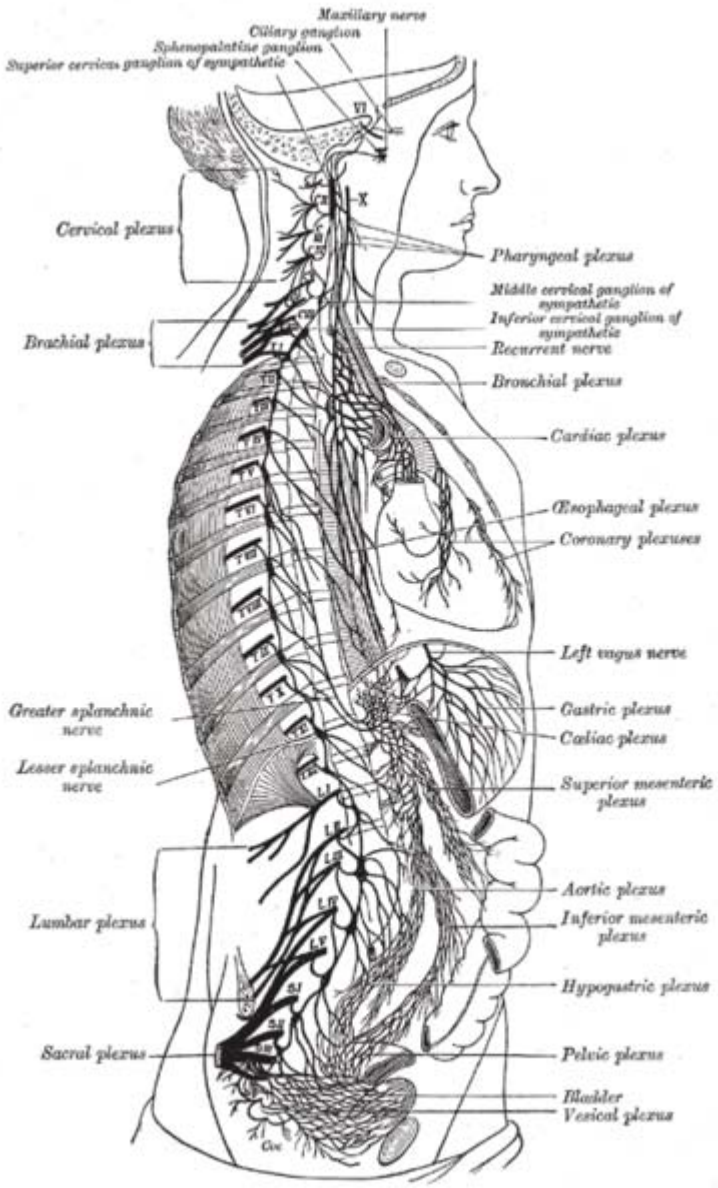




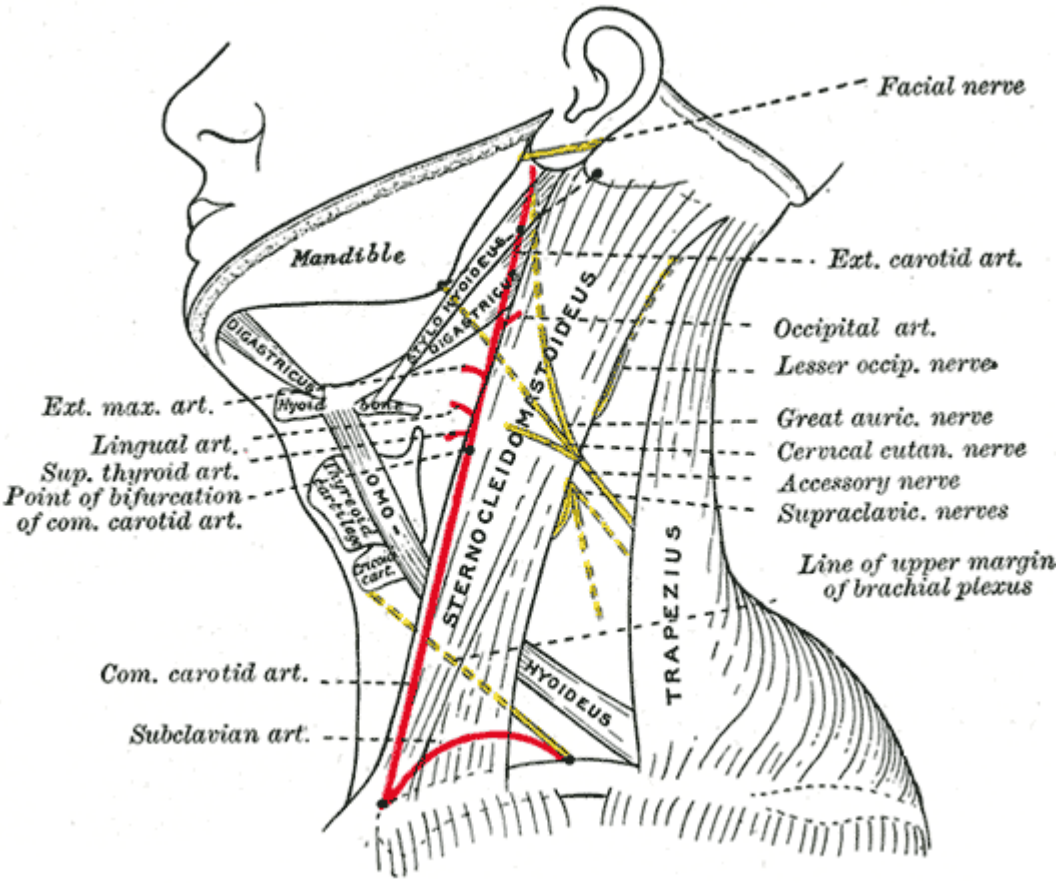
Plan of the cervical plexus



The nerves of the scalp, face, and side of neck



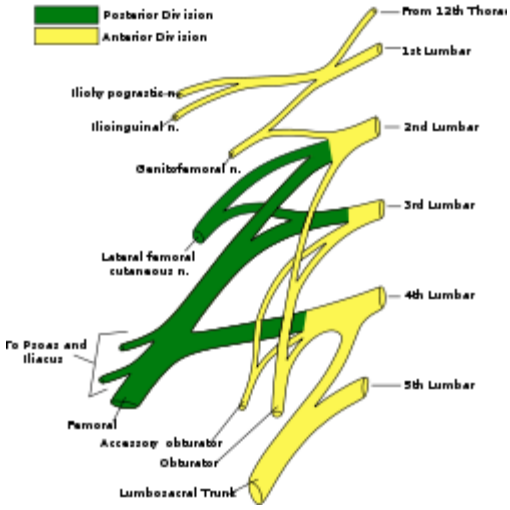
The right sympathetic chain and its connections with the thoracic, abdominal, and pelvic plexuses



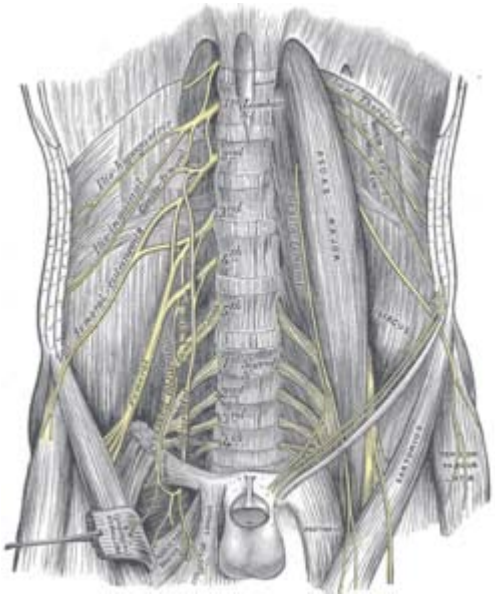
Side of neck, showing chief surface markings

Lumbar plexus

Nerve: Lumbar plexis	
`Latin`	`= plexus lumbalis`



Plan of lumbar plexus.



The lumbar plexus and its branches.

Gray's	*subject #212 949*
From	T12, L1-L4
MeSH	*Lumbosacral+Plexus*

The **lumbar plexus** is a nervous plexus in the lumbar region of the body which forms part of the lumbosacral plexus. It is formed by the ventral divisions of the first four

lumbar nerves (L1-L4) and from contributions of the subcostal nerve (T12), which is the last thoracic nerve. Additionally, the ventral rami of the fourth lumbar nerve pass communicating branches, the lumbosacral trunk, to the sacral plexus. The nerves of the lumbar plexus pass in front of the hip joint and mainly support the anterior part of the thigh.

The plexus is formed lateral to the intervertebral foramina and pass through psoas major. Its smaller motor branches are distributed directly to psoas major, while the larger branches leave the muscle at various sites to run obliquely downward through the pelvic area to leave the pelvis under the inguinal ligament, with the exception of the obturator nerve which exits the pelvis through the obturator foramen.

Branches

The iliohypogastric nerve runs anterior to the psoas major on its proximal lateral border to run laterally and obliquely on the anterior side of quadratus lumborum. Lateral to this muscle, it pierces the transversus abdominis to run above the iliac crest between that muscle and abdominal internal oblique. It gives off several motor branches to these muscles and a sensory branch to the skin of the lateral hip. Its terminal branch then runs parallel to the inguinal ligament to exit the aponeurosis of the abdominal external oblique above the external inguinal ring where it supplies the skin above the inguinal ligament (i.e. the hypogastric region) with the anterior cutaneous branch.

The ilioinguinal nerve closely follows the ilihypogastric nerve on the quadratus lumborum, but then passes below it to run at the level of the iliac crest. It pierces the lateral abdominal wall and runs medially at the level of the inguinal ligament where it supplies motor branches to both transversus abdominis and sensory branches through the external inguinal ring to the skin over the pubic symphysis and the lateral aspect of the labia majora or scrotum.

The genitofemoral nerve pierces psoas major anteriorly below the former two nerves to immediately split into two branches that run downward on the anterior side of the muscle. The lateral femoral branch is purely sensory. It pierces the vascular lacuna near the saphenous hiatus and supplies the skin below the inguinal ligament (i.e. proximal, lateral aspect of femoral triangle). The genital branch differs in males and females. In males it runs in the spermatic cord and in females in the inguinal canal together with the teres uteri ligament. It then sends sensory branches to the scrotal skin in males and the labia majora in females. In males it supplies motor innervation to the cremaster.

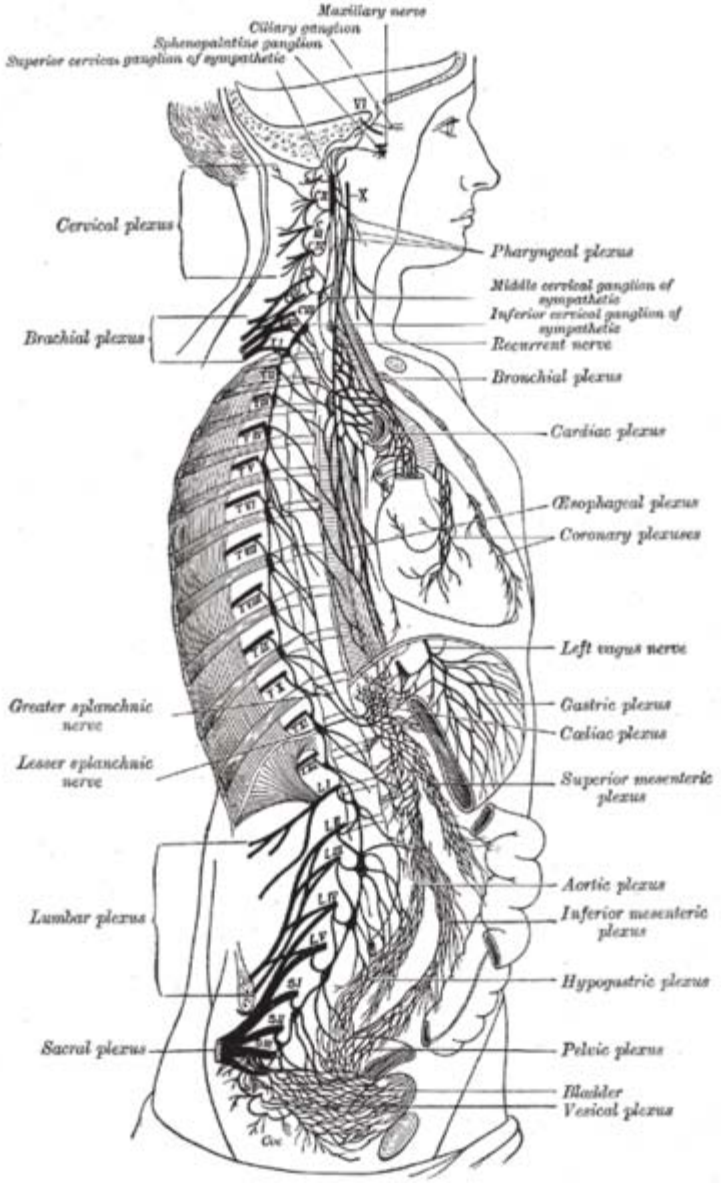
The lateral cutaneous femoral nerve pierces psoas major on its lateral side and runs obliquely downward below the iliac fascia. Medial to the anterior superior iliac spine it leaves the pelvic area through the lateral muscular lacuna. In the thigh it briefly passes under the fascia lata before it breaches the fascia and supplies the skin of the anterior thigh.

The obturator nerve leaves the lumbar plexus and descends behind psoas major on it medial side, then follows the linea terminalis into the lesser pelvis, and finally leaves the pelvic area through the obturator canal. In the thigh, it sends motor branches to obturator externus before dividing into an anterior and a posterior branch, both of which continues distally. These branches are separated by adductor brevis and supply all thigh adductors with motor innervation: pectineus, adductor longus, adductor brevis, adductor magnus, adductor minimus, and gracilis. The anterior branch contributes a terminal, sensory branch which passes along the anterior border of gracilis and supplies the skin on the medial, distal part of the thigh.

The femoral nerve is the largest and longest of the plexus' nerves. It gives motor innervation to iliopsoas, pectineus, sartorius, and quadriceps femoris; and sensory innervation to the anterior thigh, posterior lower leg, and hindfoot. In the pelvic area, it runs in a groove between psoas major and iliacus giving off branches to both muscles, and exits the pelvis through the medial aspect of muscular lacuna. In the thigh it divides into numerous sensory and muscular branches and the saphenous nerve, its long sensory terminal branch which continues down to the foot.

Nerves of the lumbar plexus

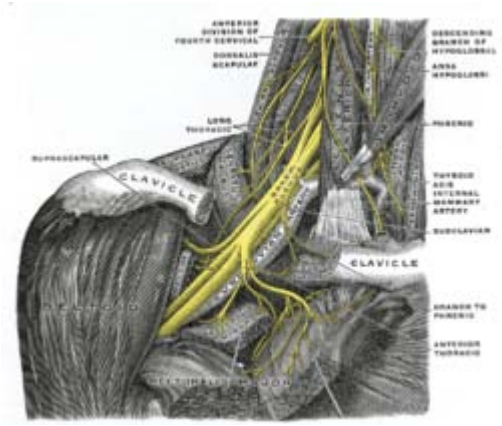
Nerve	Segment	Innervated muscles	Cutaneous branches
Iliohypogastric	T12-L1		• Anterior cutaneous ramus • Lateral cutaneous ramus
Ilioinguinal	L1	• Transversus abdominis • Abdominal internal oblique	• Anterior scrotal nerves in males • Anterior labial nerves in females
Genitofemoral	L1, L2	• Cremaster in males	• Femoral ramus • Genital ramus
Lateral femoral cutaneous	L2, L3		• Lateral femoral cutaneous
Obturator	L2-L4	• Obturator externus • Adductor longus • Adductor brevis • Gracilis • Pectineus • Adductor magnus	• Cutaneous ramus
Femoral	L2-L4	• Iliopsoas • Pectineus • Sartorius • Quadriceps femoris	• Anterior cutaneous branches • Saphenous
Short, direct muscular branches	T12-L4	• Psoas major • Quadratus lumborum • Iliacus • Lumbar intertransverse	



The right sympathetic chain and its connections with the thoracic, abdominal and pelvic plexuses

Chapter 7

Brachial Plexus

Nerve: Brachial plexus	
	
The right brachial plexus with its short branches, viewed from in front.	
Latin	*plexus brachialis*
Gray's	*subject #210 930*
Innervates	Sensory and motor innervation to the upper limb
From	C5, C6, C7, C8, T1
MeSH	*Brachial+plexus*

The **brachial plexus** is an arrangement of nerve fibers, running from the spine, formed by the ventral rami of the lower four cervical and first thoracic nerve roots (C5-T1). It proceeds through the neck, the axilla (armpit region), and into the arm.

Function

The brachial plexus is responsible for cutaneous and muscular innervation of the entire upper limb, with two exceptions: the trapezius muscle innervated by the spinal accessory

nerve (CN XI) and an area of skin near the axilla innervated by the intercostobrachial nerve.

Lesions can lead to severe functional impairment.

Anatomy

Path

The brachial plexus is divided into Roots, Trunks, Divisions, Cords, and Branches. There are five "terminal" branches and numerous other "pre-terminal" or "collateral" branches that leave the plexus at various points along its length.

- The five **roots** are the five anterior rami of the spinal nerves, after they have given off their segmental supply to the muscles of the neck.

- These roots merge to form three **trunks**:
  - "superior" or "upper" (C5-C6)
  - "middle" (C7)
  - "inferior" or "lower" (C8-T1)

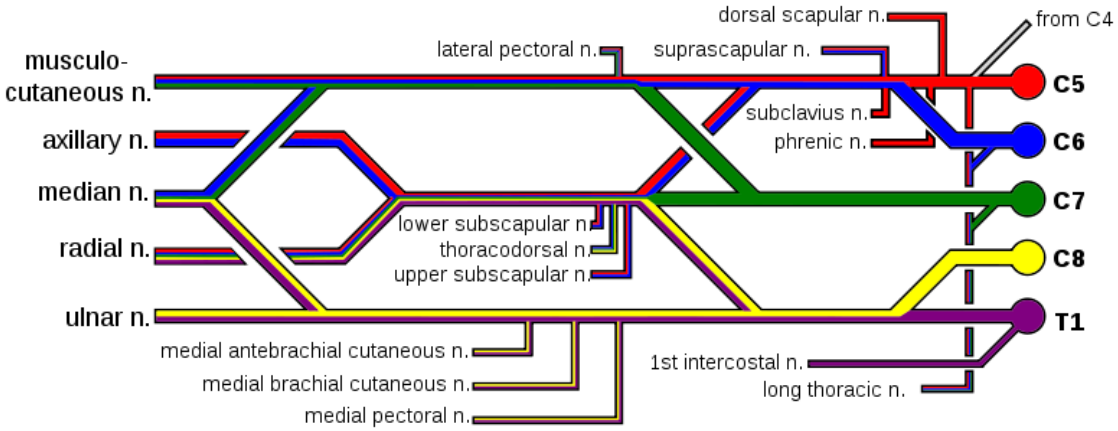
- Each trunk then splits in two, to form six **divisions**:
  - anterior divisions of the upper, middle, and lower trunks
  - posterior divisions of the upper, middle, and lower trunks

- These six divisions will regroup to become the three **cords**. The cords are named by their position with respect to the axillary artery.
  - The *posterior cord* is formed from the three posterior divisions of the trunks (C5-T1)
  - The *lateral cord* is the anterior divisions from the upper and middle trunks (C5-C7)
  - The *medial cord* is simply a continuation of the anterior division of the lower trunk (C8-T1)

- The **branches** are listed below. Most branch from the cords, but a few branch (indicated in italics) directly from earlier structures. The five on the left are considered "terminal branches".

Some mnemonics for remembering the order of the brachial plexus:

- **R**eal **T**exans **D**rink **C**old **B**eer
- **R**ead **T**he **D**arn **C**adaver **B**ook
- **R**eal **T**eachers **D**rink **C**hilled **B**eer
- **R**andy **T**ravis **D**rinks **C**old **B**eer



Diagrammatic representation of the brachial plexus using colour to illustrate the contributions of each nerve root to the branches

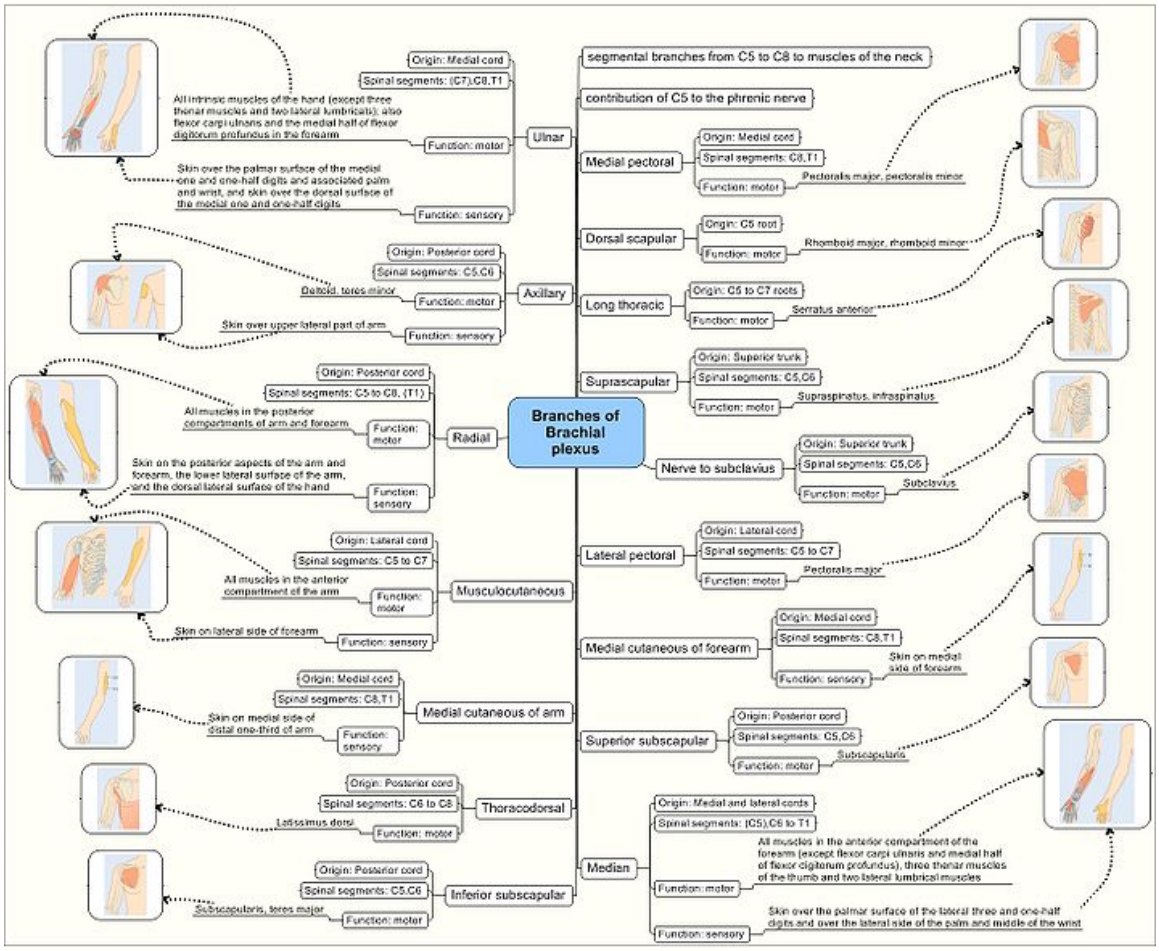
Specific branches

From	Nerve	Roots	Muscles	Cutaneous
roots	dorsal scapular nerve	C5	rhomboid muscles and levator scapulae	-
roots	long thoracic nerve	C5, C6, C7	serratus anterior	-
upper trunk	nerve to the subclavius	C5, C6	subclavius muscle	-
upper trunk	suprascapular nerve	C5, C6	supraspinatus and infraspinatus	-
lateral cord	lateral pectoral nerve	C5, C6, C7	pectoralis major (by communicating with the medial pectoral nerve)	-
lateral cord	musculocutaneous nerve	C5, C6, C7	coracobrachialis, brachialis and biceps brachii	becomes the lateral cutaneous nerve of the forearm
lateral cord	lateral root of the median nerve	C5, C6, C7	fibres to the median nerve	-
posterior cord	upper subscapular nerve	C5, C6	subscapularis (upper part)	-
posterior cord	thoracodorsal nerve (middle subscapular nerve)	C6, C7, C8	latissimus dorsi	-
posterior	lower subscapular	C5,	subscapularis (lower part)	-

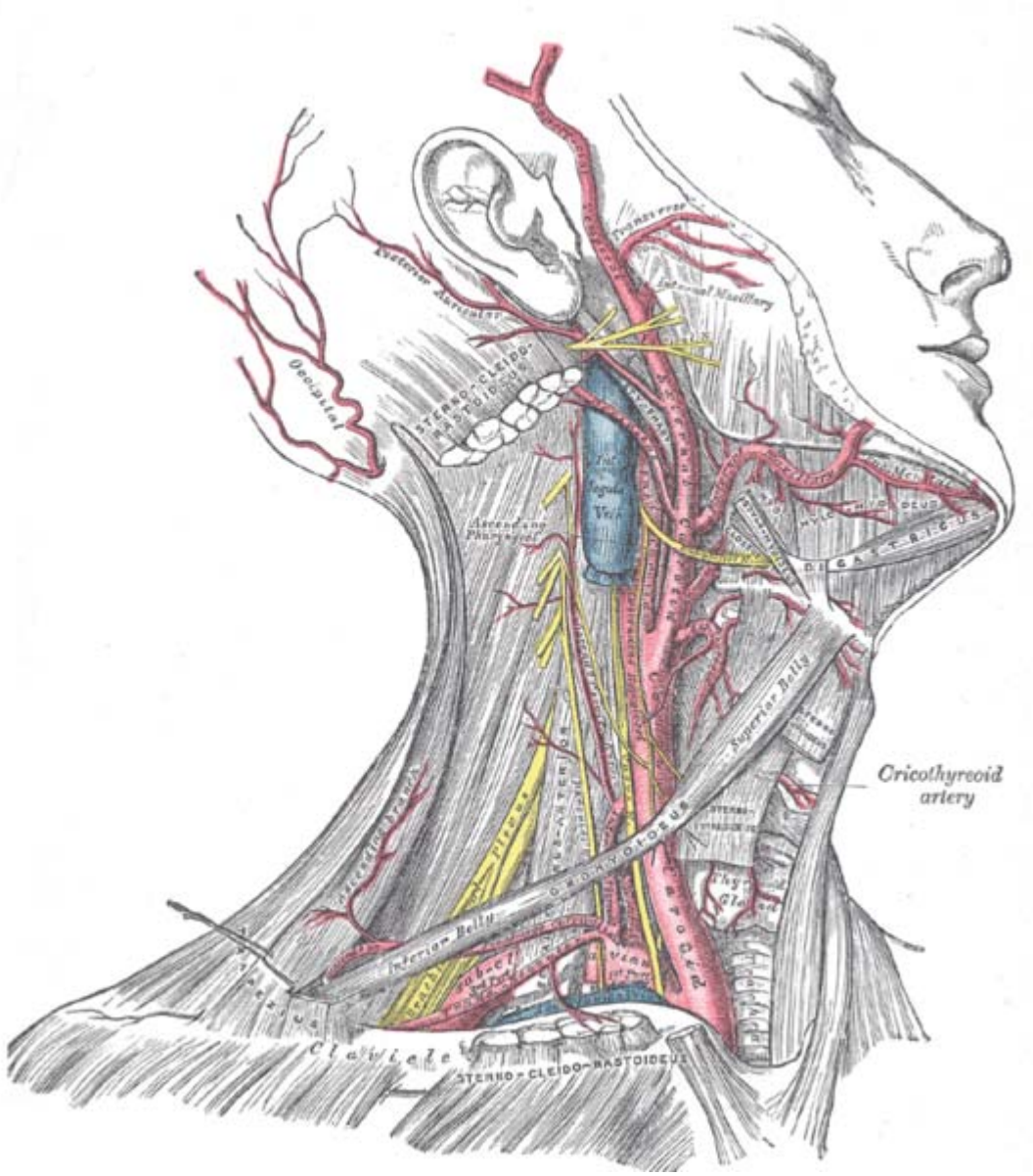
cord	nerve	C6	and teres major	
posterior cord	axillary nerve	C5, C6	anterior branch: deltoid and a small area of overlying skin posterior branch: teres minor and deltoid muscles	posterior branch becomes upper lateral cutaneous nerve of the arm
posterior cord	radial nerve	C5, C6, C7, C8, T1	triceps brachii, supinator, anconeus, the extensor muscles of the forearm, and brachioradialis	skin of the posterior arm as the posterior cutaneous nerve of the arm
medial cord	medial pectoral nerve	C8, T1	pectoralis major and pectoralis minor	-
medial cord	medial root of the median nerve	C8, T1	fibres to the median nerve	portions of hand not served by ulnar or radial
medial cord	medial cutaneous nerve of the arm	C8, T1	-	front and medial skin of the arm
medial cord	medial cutaneous nerve of the forearm	C8, T1	-	medial skin of the forearm
medial cord	ulnar nerve	C8, T1	flexor carpi ulnaris, the medial two bellies of flexor digitorum profundus, the intrinsic hand muscles except the thenar muscles and the two most lateral lumbricals	the skin of the medial side of the hand and medial one and a half fingers on the palmar side and medial two and a half fingers on the dorsal side

Some mnemonics for remembering the branches:

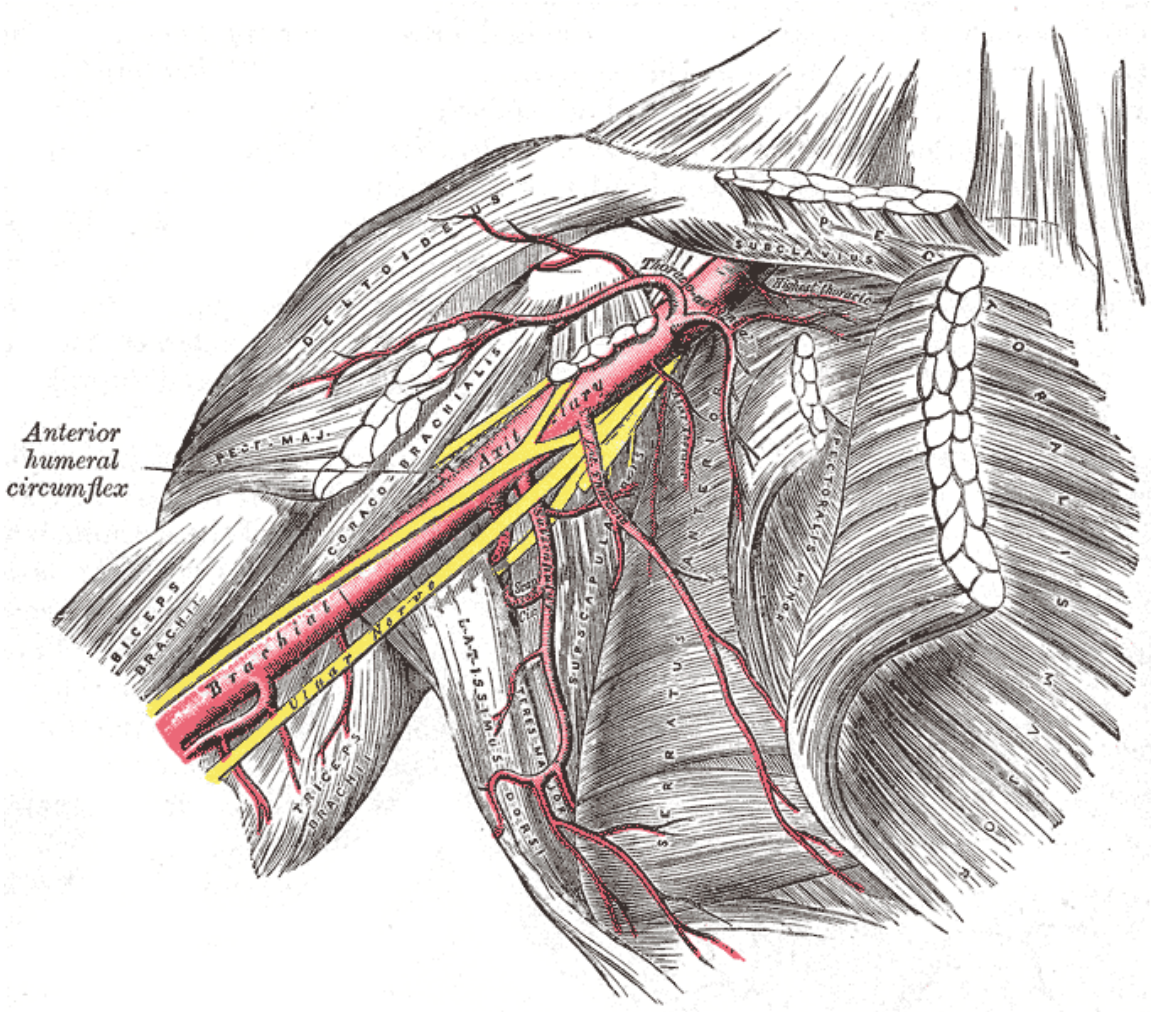
- Posterior cord branches
  - STAR - subscapular (upper and lower), thoracodorsal, axillary, radial
  - ULTRA - upper subscapular, lower subscapular, thoracodorsal, radial, axillary
- Lateral Cord Branches
  - LLM "Lucy Loves Me" - lateral pectoral, lateral root of the median nerve, musculocutaneous
- Medial Cord Branches
  - MMMUM "Most Medical Men Use Morphine" - medial pectoral, medial cutaneous nerve of arm, medial cutaneous nerve of forearm, ulnar, medial root of the median nerve



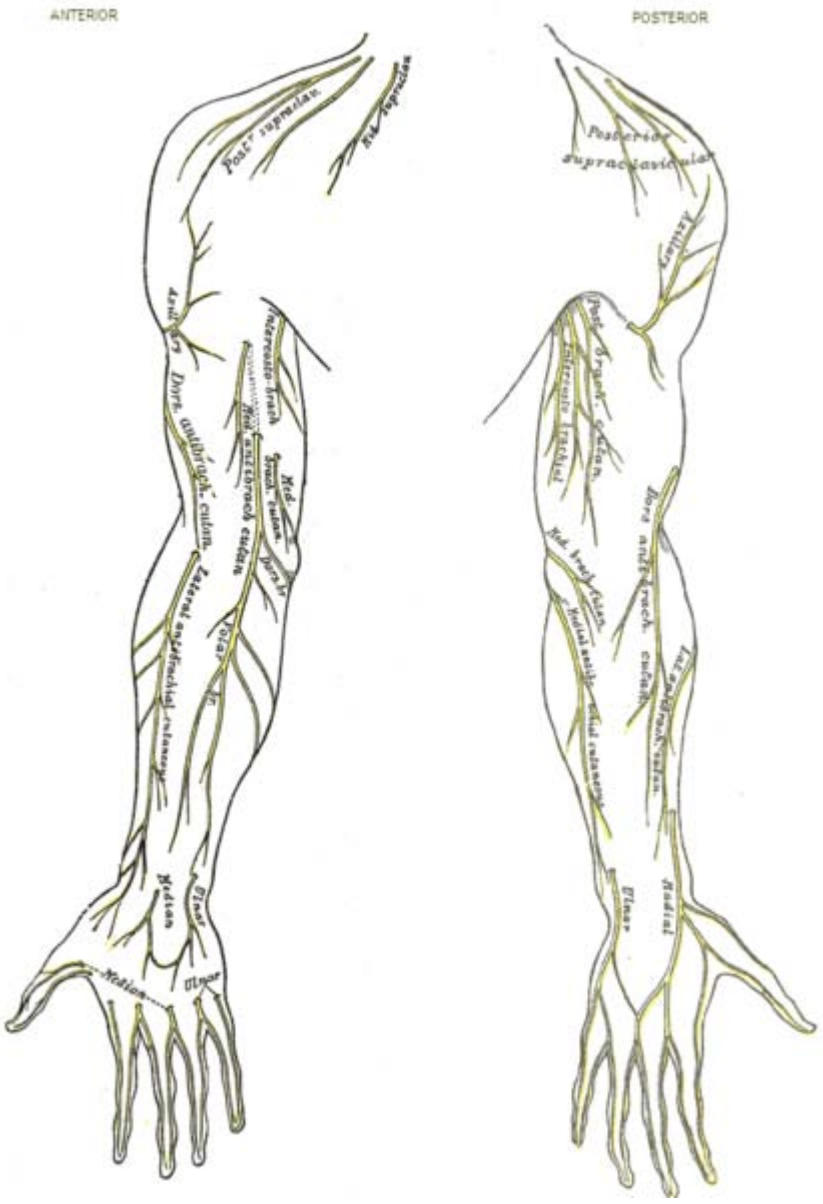
Mind map showing branches of brachial plexus



Superficial dissection of the right side of the neck, showing the carotid and subclavian arteries



The axillary artery and its branches



Cutaneous nerves of right upper extremity

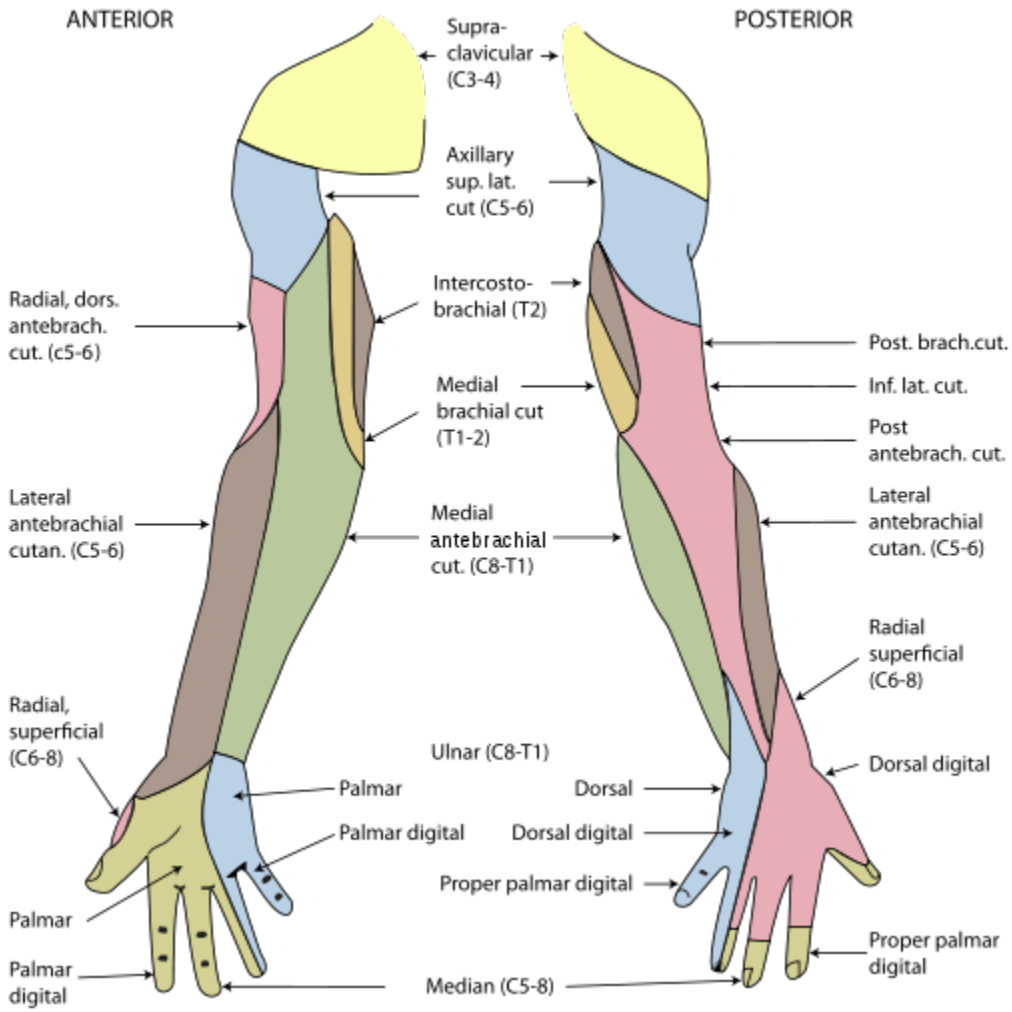
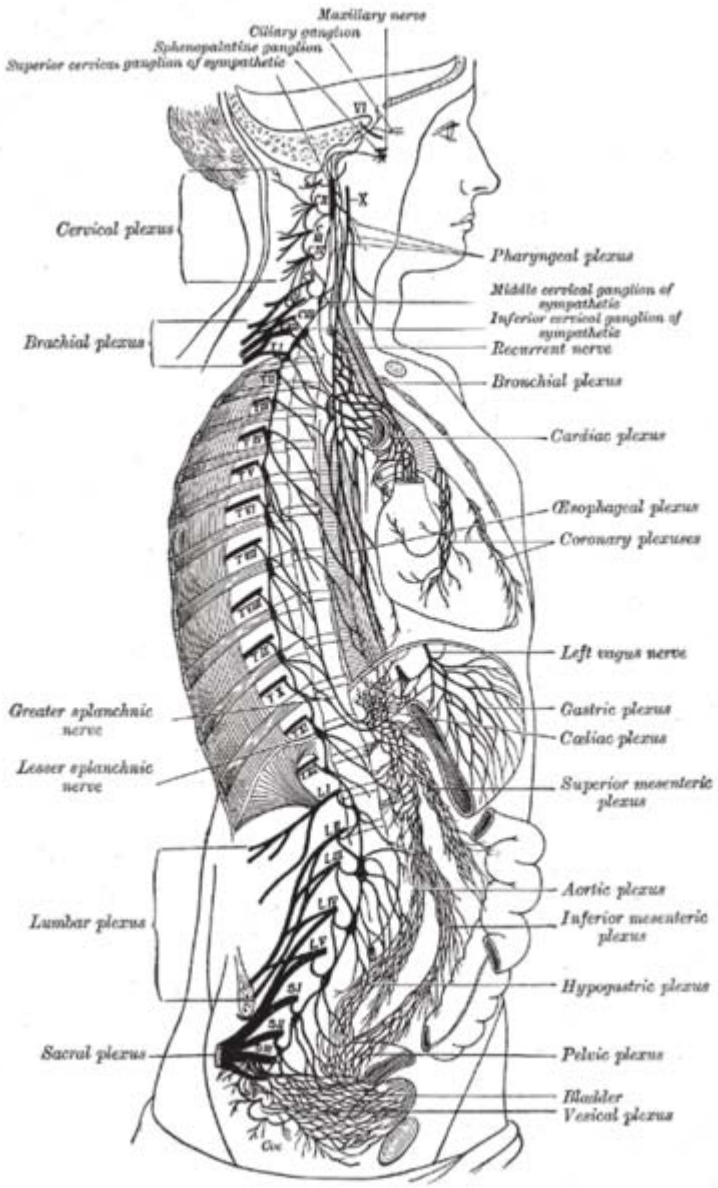
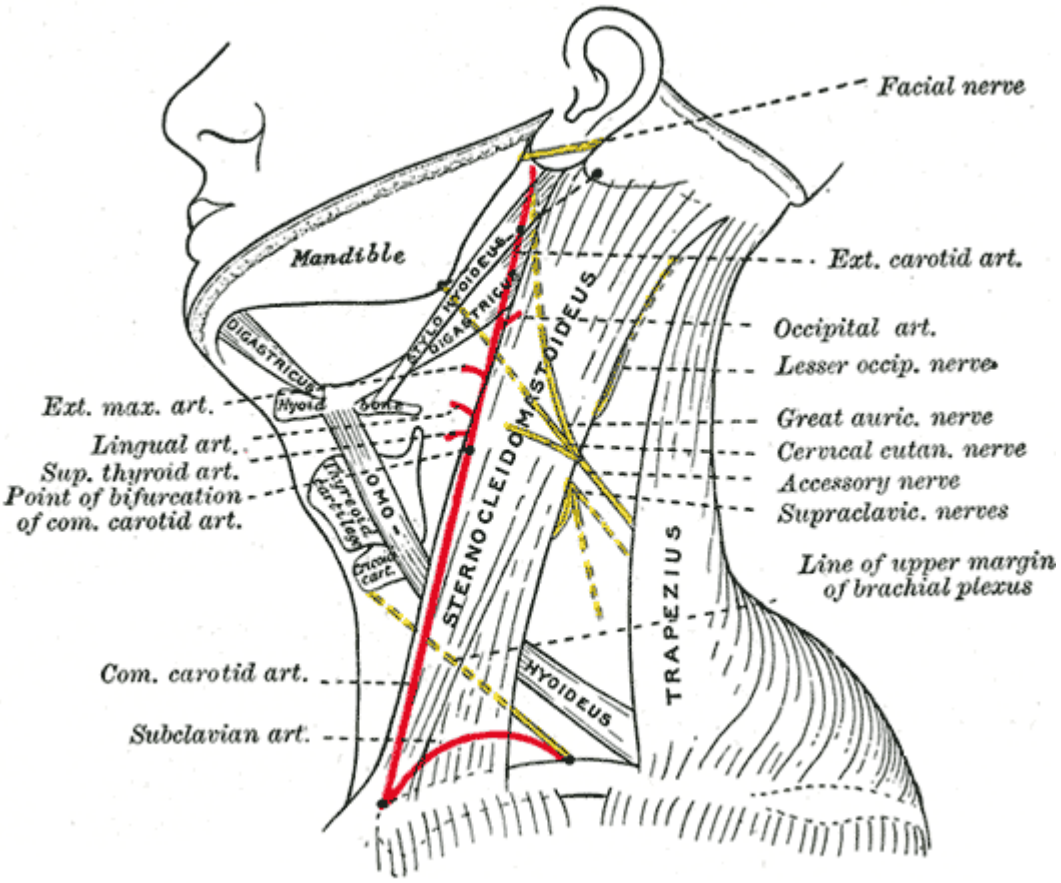


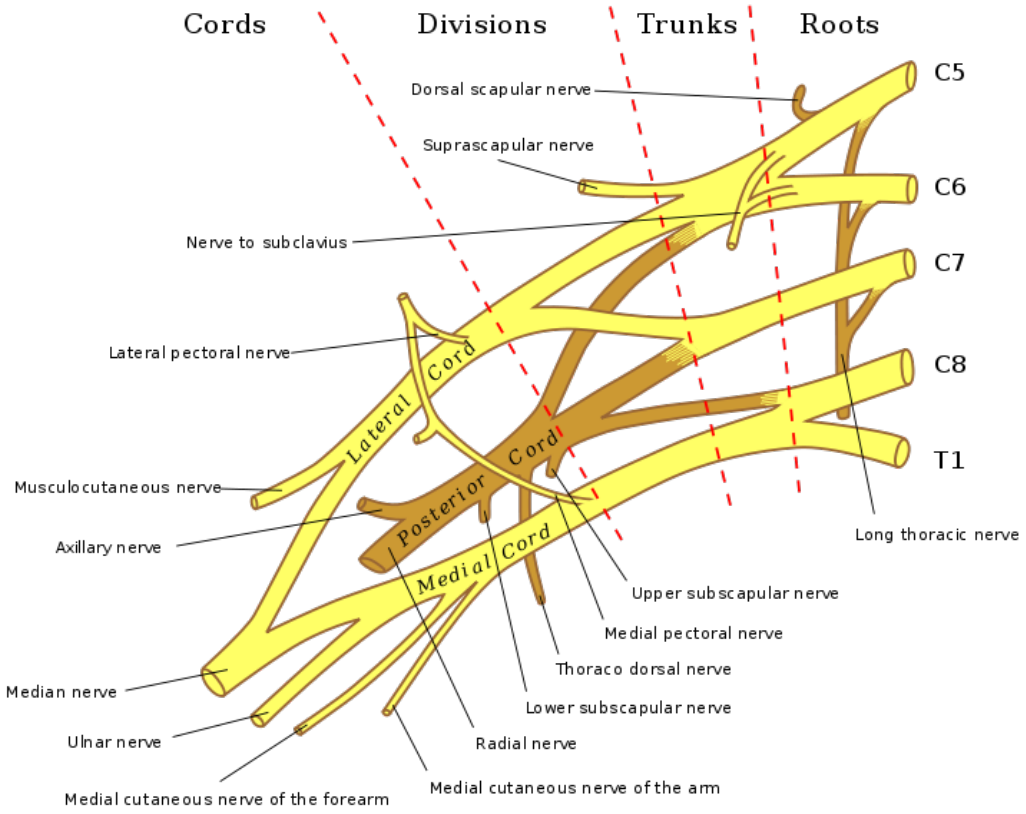
Diagram of segmental distribution of the cutaneous nerves of the right upper extremity



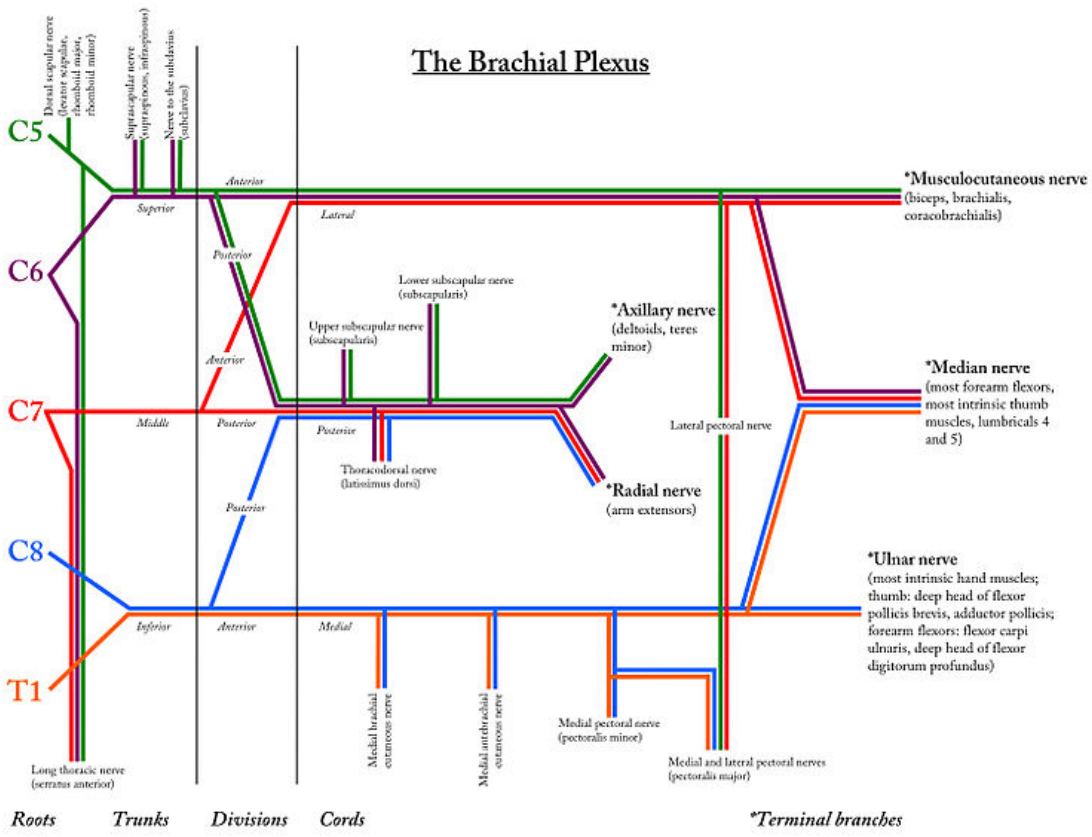
The right sympathetic chain and its connections with the thoracic, abdominal, and pelvic plexuses



Side of neck, showing chief surface markings



Brachial plexus with areas of roots, trunks, divisions and cords marked



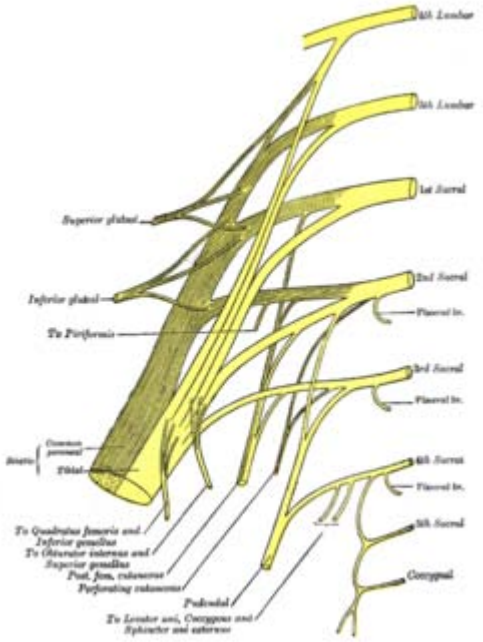
Color-coded diagram of brachial plexus illustrating roots of associated nerves

Chapter 8

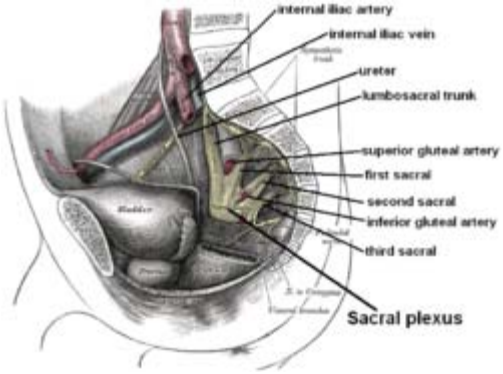
Sacral Plexus and Celiac Plexus

Sacral plexus

Nerve: Sacral plexus



Plan of sacral and pudendal plexuses.



Relations of the sacral plexus. Dissection of side wall of pelvis showing sacral and pudendal plexuses.

Latin	*plexus sacralis*
Gray's	*subject #213 957*
From	L4-L5, S1-S4

In human anatomy, the *sacral plexus* is a nerve plexus which provides motor and sensory nerves for the posterior thigh, most of the lower leg, the entire foot, and part of the pelvis. It is part of the lumbosacral plexus and emerges from the sacral vertebrae (S2-S4).

Composition

The sacral plexus is formed by::

- the lumbosacral trunk
- the anterior division of the first sacral nerve
- portions of the anterior divisions of the second and third sacral nerves

The nerves forming the sacral plexus converge toward the lower part of the greater sciatic foramen, and unite to form a flattened band, from the anterior and posterior surfaces of which several branches arise.

The band itself is continued as the sciatic nerve, which splits on the back of the thigh into the tibial nerve and common fibular nerve; these two nerves sometimes arise separately from the plexus, and in all cases their independence can be shown by dissection.

Often, the sacral plexus and the lumbar plexus are considered to be one large nerve plexus, the lumbosacral plexus. The lumbosacral trunk connects the two plexuses.

Relations

The sacral plexus lies on the back of the pelvis between the piriformis muscle and the pelvic fascia. In front of it are the internal iliac artery, internal iliac vein, the ureter, and the sigmoid colon. The superior gluteal artery and vein run between the lumbosacral trunk and the first sacral nerve, and the inferior gluteal artery and vein between the second and third sacral nerves.

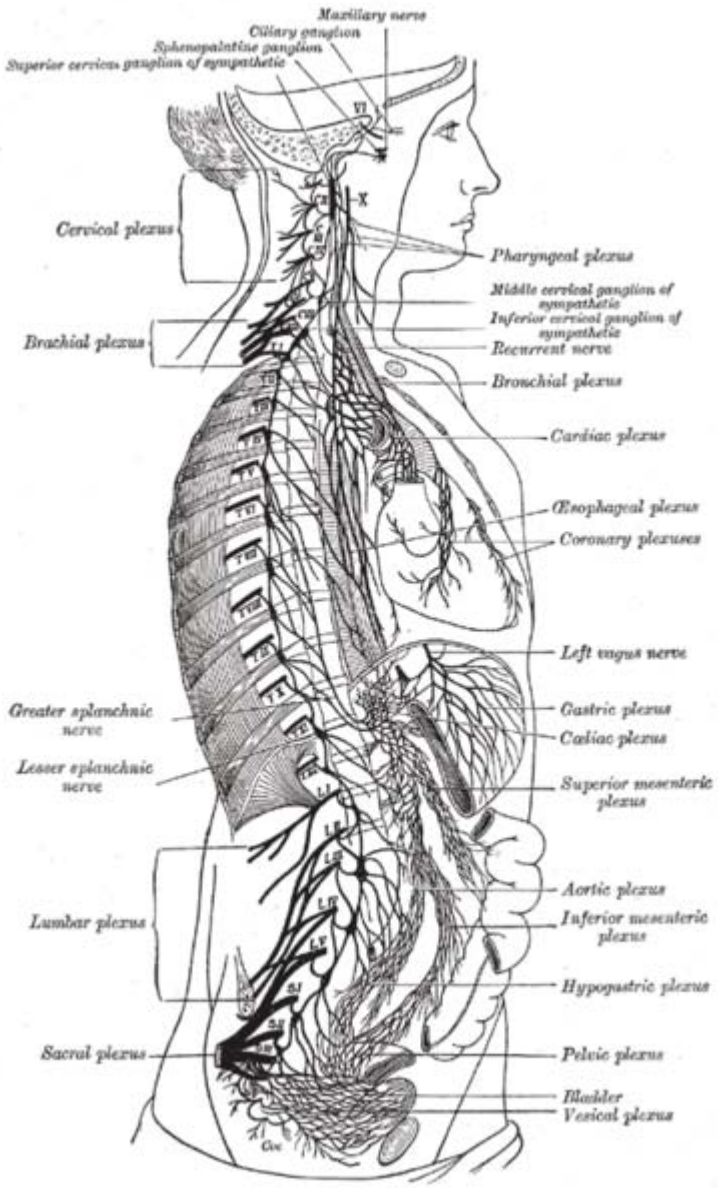
Nerves formed

All the nerves entering the plexus, with the exception of the third sacral, split into ventral and dorsal divisions, and the nerves arising from these are as follows of the table below:

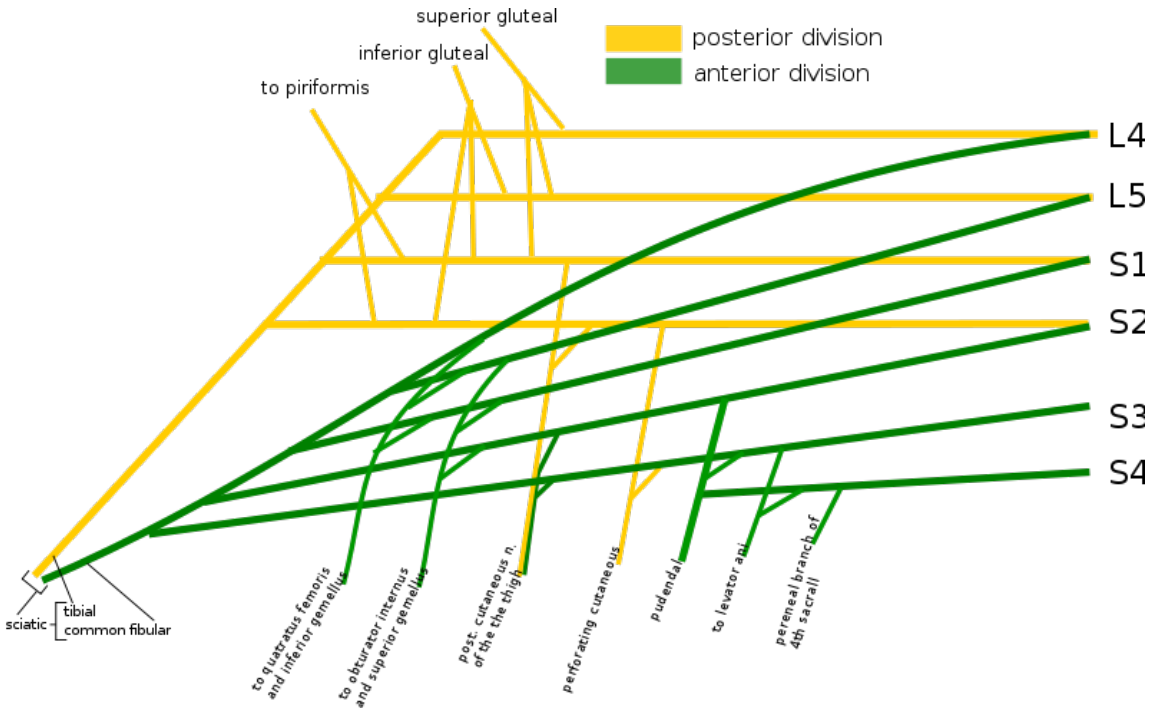
Nerves of the sacral plexus

Nerve	Segment	Innervated muscles	Cutaneous branches
Superior gluteal	L4-S1	Gluteus medius Gluteus minimus Tensor fascia latae	
Inferior gluteal	L5-S2	Gluteus maximus	
			Posterior cutaneous femoral
Posterior cutaneous femoral	S1-S3		• Inferior cluneal nerves • Perineal branches
Direct branches from plexus			
• Piriformis	L5, S2	Piriformis	
• Obturator internus	L5, S1	Obturator internus	
• Quadratus femoris	L4-S1	Quadratus femoris	
		Sciatic	
Sciatic	L4-S3	Semitendinosus (Tib) Semimembranosus (Tib) Biceps femoris • Long head (Tib) • Short head (Fib) Adductor magnus (medial part, Tib)	
Common fibular	L4-S2		Lateral sural cutaneous Communicating fibular
• Superficial fibular		Peroneus longus Peroneus brevis	Medial dorsal cutaneous Intermediate dorsal cutaneous
• Deep fibular		Tibialis anterior Extensor digitorum longus Extensor digitorum brevis Extensor hallucis longus Extensor hallucis brevis Peroneus tertius	Lateral cutaneous nerve of big toe Intermediate dorsal cutaneous
Tibial nerve	L4-S3	Triceps surae Plantaris	Medial sural cutaneous Lateral calcaneal

		Popliteus Tibialis posterior Flexor digitorum longus Flexor hallucis longus	Medial calcaneal Lateral dorsal cutaneous
	• Medial plantar	Abductor hallucis Flexor digitorum brevis Flexor hallucis brevis (medial head) Lumbrical (first and second)	Proper digital plantar
	• Lateral plantar	Flexor hallucis brevis (lateral head) Quadratus plantae Abductor digiti minimi Flexor digiti minimi Opponens digiti minimi Lumbrical (third and fourth) Plantar interossei (first to third) Dorsal interossei (first to fifth) Adductor hallucis	Proper plantar digital
		Pudendal and coccygeal	
Pudendal (Pudendal plexus)	S1-S4	Muscles of the pelvic floor: Levator ani Superficial transverse perineal Deep transverse perineal Bulbospongiosus Ischiocavernosus Shpincter anus externus Urethral sphincter	Inferior rectal Perineal • Posterior scrotal/labial • Dorsal penis/clitoris
Coccygeal (Coccygeal plexus)	S5-Co1	Coccygeus	Anococcygeal Dorsal branches



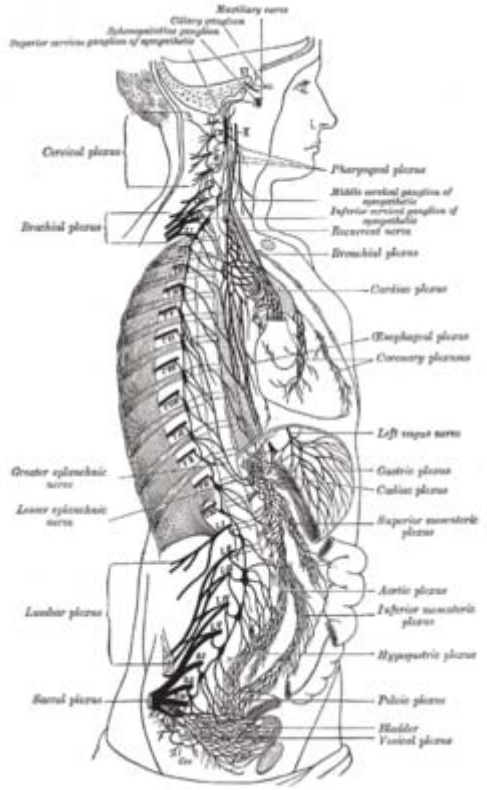
The right sympathetic chain and its connections with the thoracic, abdominal and pelvic plexuses



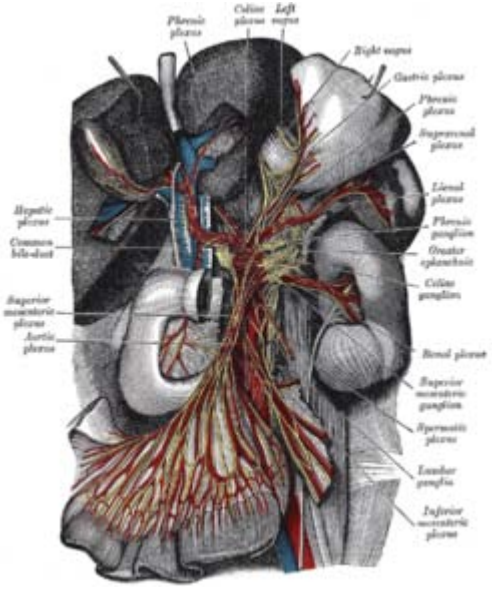
A schematic depiction

Celiac plexus

Nerve: Celiac plexus



The right sympathetic chain and its connections with the thoracic, abdominal, and pelvic plexuses. (Label for celiac plexus at center right.)



The celiac ganglia with the sympathetic plexuses of the abdominal viscera radiating from the ganglia. (Label for celiac plexus at top center.)

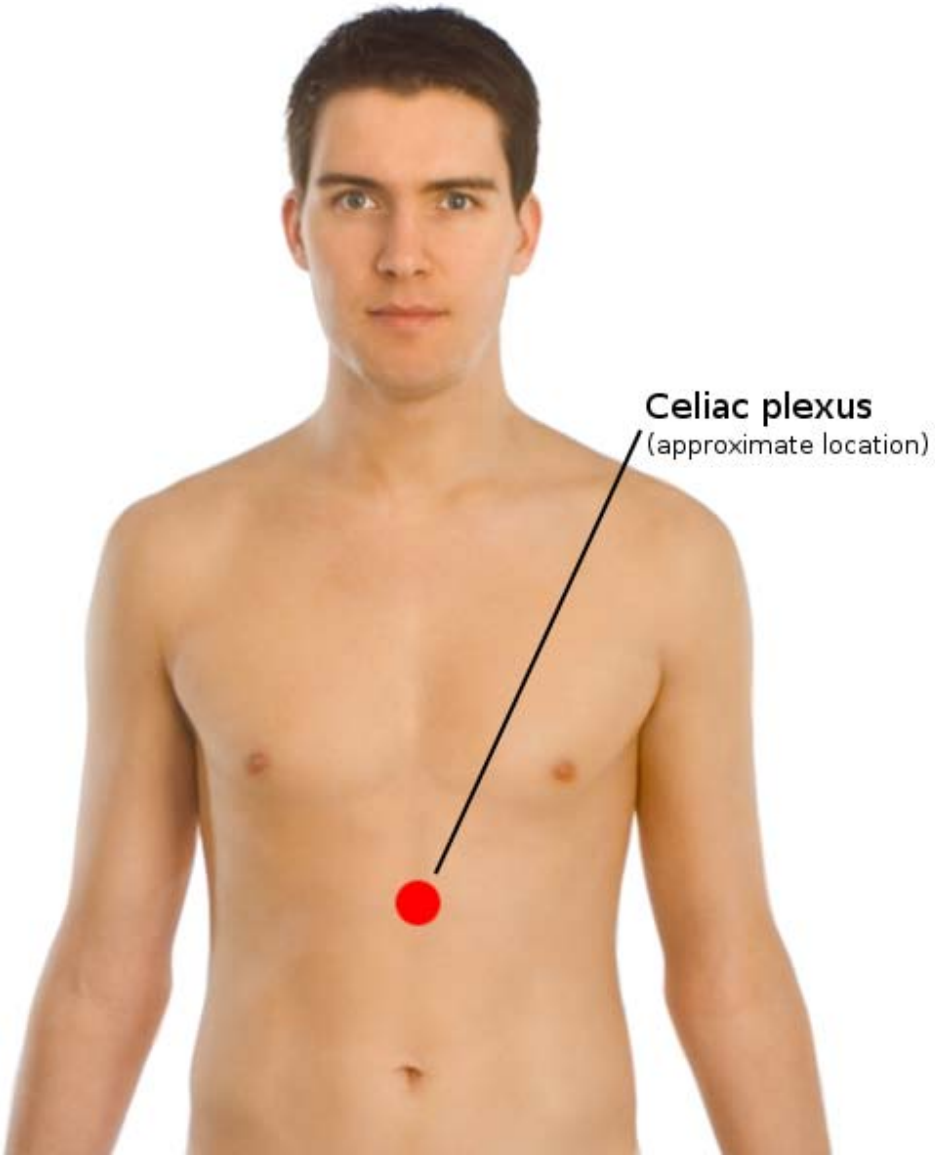
Latin	*plexus coeliacus*
Gray's	*subject #220 985*
From	celiac branches of vagus nerve
MeSH	*Celiac+Plexus*

The **celiac plexus**, also known as the **solar plexus**, is a complex network of nerves (a plexus) located in the abdomen, where the celiac trunk, superior mesenteric artery, and renal arteries branch from the abdominal aorta. It is in back of the stomach and the omental bursa, and in front of the crura of the diaphragm, on the level of the first lumbar vertebra, L1.

The plexus is formed (in part) by the greater and lesser splanchnic nerves of both sides, and also parts of the right vagus nerve.

The celiac plexus proper consists of the celiac ganglia with a network of interconnecting fibers. The aorticorenal ganglia are often considered to be part of the celiac ganglia, and thus, part of the plexus.

Related plexuses



Approximate location of the celiac plexus on the coronal plane

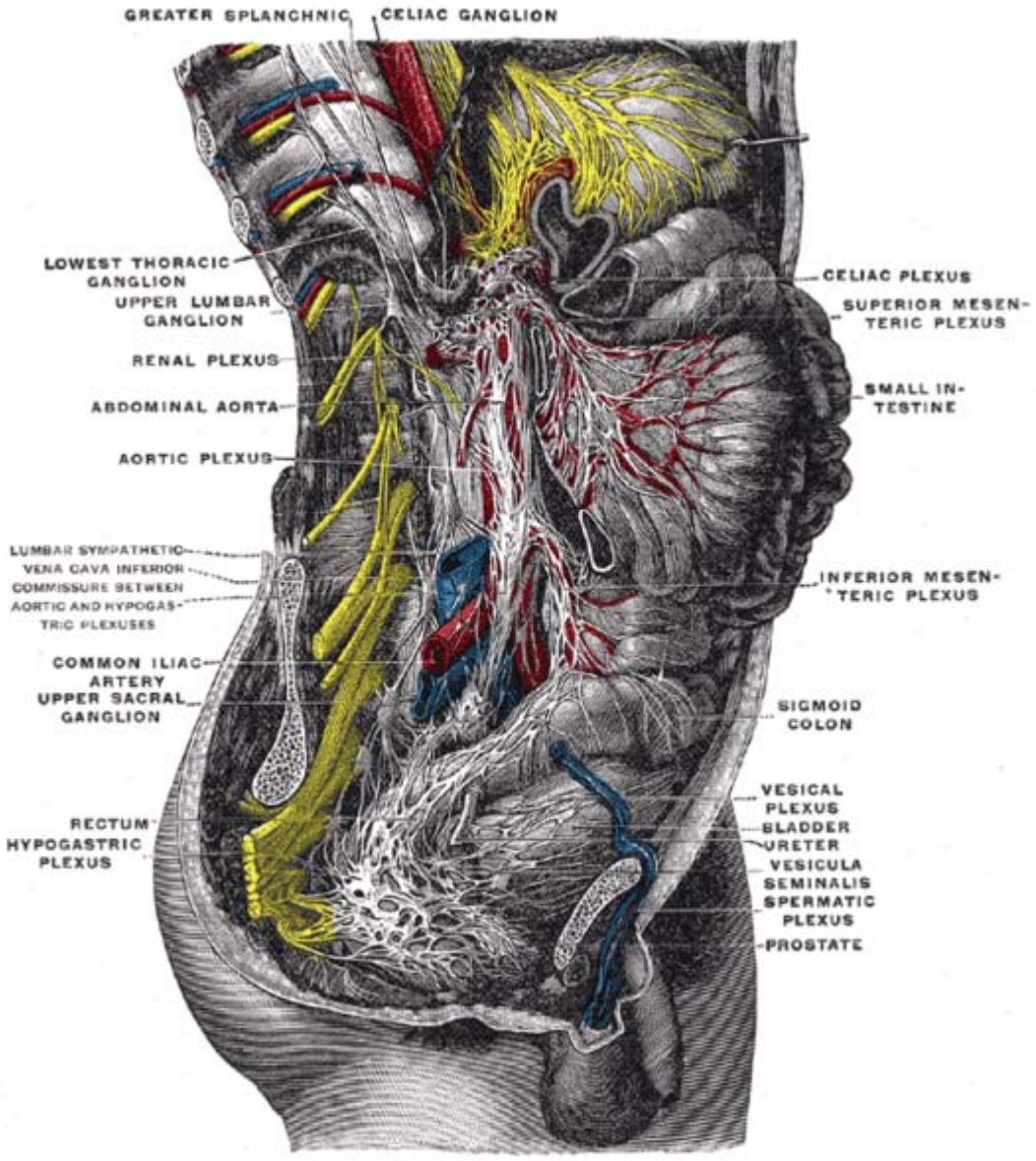
The celiac plexus includes a number of smaller plexuses:

- Hepatic plexus
- Splenic plexus
- Gastric plexuses
- Pancreatic plexus
- Suprarenal plexus

Other plexuses that are derived from the celiac plexus:

- Renal plexus
- Testicular plexus / ovarian plexus
- Superior mesenteric plexus
- Inferior mesenteric plexus

Clinical significance



Lower half of right sympathetic cord

The celiac plexus is often popularly referred to as the solar plexus, generally in the context of a blow to the stomach. In many of these cases, it is not the celiac plexus itself

being referred to, but rather the region where it is located. A blow to the stomach can upset this region. This can cause the diaphragm to spasm, resulting in difficulty in breathing—a sensation commonly known as "getting the wind knocked out of you". A blow to this region can also affect the celiac plexus itself, possibly interfering with the functioning of the viscera, as well as causing great pain.

A celiac plexus block by means of fluoroscopically guided injection is sometimes used to treat intractable pain from cancers such as pancreatic cancer. Frequently celiac plexus block performed by pain management specialists and radiologists is performed via CT guidance. Intractable pain related to chronic pancreatitis is an important indication for celiac plexus ablation.

Chapter 9

Baroreflex and Enteric Nervous System

Baroreflex

The **baroreflex** or **baroreceptor reflex** is one of the body's homeostatic mechanisms for maintaining blood pressure. It provides a negative feedback loop in which an elevated blood pressure reflexively causes heart rate and, thus, blood pressure to decrease; in similar fashion, decreased blood pressure depresses the baroreflex, causing heart rate and, thus, blood pressure to rise.

The system relies on specialized neurons, known as baroreceptors, in the aortic arch, carotid sinuses, and elsewhere to monitor changes in blood pressure and relay them to the brainstem. Subsequent changes in blood pressure are mediated by the autonomic nervous system. Atrial natriuretic peptide forms a parallel negative feedback loop in an endocrinological contrast to the renin-angiotensin system.

Anatomy of the reflex

Baroreceptors include those in the auricles of the heart and vena cavae, but the most sensitive baroreceptors are in the carotid sinuses and aortic arch. The carotid sinus baroreceptors are innervated by the glossopharyngeal nerve (CN IX); the aortic arch baroreceptors are innervated by the vagus nerve (CN X). Baroreceptor activity travels along these nerves, which contact the nucleus of the solitary tract (NTS) in the brainstem.

The NTS sends excitatory fibers (glutamatergic) to the caudal ventrolateral medulla (CVLM), activating the CVLM. The activated CVLM then sends inhibitory fibers (GABAergic) to the rostral ventrolateral medulla (RVLM), thus inhibiting the RVLM. The RVLM is the primary regulator of the sympathetic nervous system, sending excitatory fibers (glutamatergic) to the sympathetic preganglionic neurons located in the intermediolateral nucleus of the spinal cord. Hence, when the baroreceptors are activated (by an increased blood pressure), the NTS activates the CVLM, which in turn inhibits the RVLM, thus inhibiting the sympathetic branch of the autonomic nervous system, leading to a decrease in blood pressure. Likewise, low blood pressure causes an increase in sympathetic tone via "disinhibition" (less inhibition, hence activation) of the RVLM.

The NTS also sends excitatory fibers to the Nucleus ambiguus (vagal nuclei) that regulate the parasympathetic nervous system, aiding in the decrease in sympathetic activity during conditions of elevated blood pressure.

Baroreceptor activation

The baroreceptors are stretch-sensitive mechanoreceptors. When blood pressure rises, the carotid and aortic sinuses are distended, resulting in stretch and, therefore, activation of the baroreceptors. Active baroreceptors fire action potentials ("spikes") more frequently than inactive baroreceptors. The greater the stretch the more rapidly baroreceptors fire action potentials.

These action potentials are relayed to the nucleus of the tractus solitarius (NTS), which uses frequency as a measure of blood pressure. As discussed previously, increased activation of the NTS inhibits the vasomotor center and stimulates the vagal nuclei. The end-result of baroreceptor activation is inhibition of the sympathetic nervous system and activation of the parasympathetic nervous system.

The sympathetic and parasympathetic branches of the autonomic nervous system have opposing effects on blood pressure. Sympathetic activation leads to an elevation of total peripheral resistance and cardiac output via increased contractility of the heart, heart rate, and arterial vasoconstriction, which tends to increase blood pressure. On the converse, parasympathetic activation leads to a decreased cardiac output via decrease in heart rate, resulting in a tendency to decrease blood pressure.

By coupling sympathetic inhibition and parasympathetic activation, the baroreflex maximizes blood pressure reduction. Sympathetic inhibition leads to a drop in peripheral resistance, while parasympathetic activation leads to a depressed heart rate (reflex bradycardia) and contractility. The combined effects will dramatically decrease blood pressure.

In a similar manner, sympathetic activation with parasympathetic inhibition allows the baroreflex to elevate blood pressure.

Set point and tonic activation

The sympathetic neuron fires at different rates, releasing various amounts of Norephinephrine. When the firing rate is high, an increased amount of norephinephrine is released to receptors- causing blood vessels to constrict. When the firing rate is low, a decreased amount of norephinephrine is released to receptors- causing blood vessels to dilate.

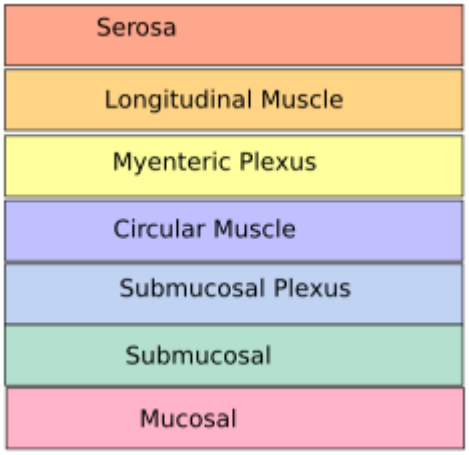
Effect on heart rate variability

The baroreflex may be responsible for a part of the low-frequency component of heart rate variability, the so-called Mayer waves, at 0.1 Hz [Sleight, 1995].

Baroreflex activation therapy for treatment of resistant hypertension

Published feasibility studies have shown that a pacemaker-like device designed to electrically activate the baroreflex, also known as baroreflex activation therapy, significantly lowers blood pressure in patients with treatment-resistant hypertension. One study published on a group of 16 patients reported an average systolic blood pressure reduction of 34 mmHg after three months of treatment and 35 mmHg after 24 months. A drop in systolic blood pressure of at least 20 mmHg was achieved in 12 of 16 (75%) patients at 2 years, and 5 of 16 (31%) achieved a systolic BP of less than 140 mmHg at 2 years. Results published on a separate group of 10 patients from another feasibility trial reported an average systolic blood pressure reduction of 24 mmHg after three months of treatment. Baroreflex activation therapy devices are not currently available outside of clinical research studies.

Enteric nervous system



The enteric nervous system is embedded in the lining of the gastrointestinal system

The **enteric nervous system** (**ENS**) is a subdivision of the autonomic nervous system (ANS), that directly controls the gastrointestinal system.

It is derived from neural crest.

Function

The ENS is capable of autonomous functions such as the coordination of reflexes; although it receives considerable innervation from the autonomic nervous system it can and does operate independently of the brain and the spinal cord. Its study is the focus of neurogastroenterology. The ENS can be damaged by ischemia. Transplantation has been described as a theoretical possibility.

Anatomy

The ENS consists of some one hundred million neurons, one thousandth of the number of neurons in the brain, and considerably more than the number of neurons in the spinal cord. The enteric nervous system is embedded in the lining of the gastrointestinal system.

The neurons of the ENS are collected into two types of ganglia: myenteric (Auerbach's) and submucosal (Meissner's) plexuses. Myenteric plexuses are located between the inner and outer layers of the muscularis externa, while submucosal plexuses are located in the submucosa.

Complexity

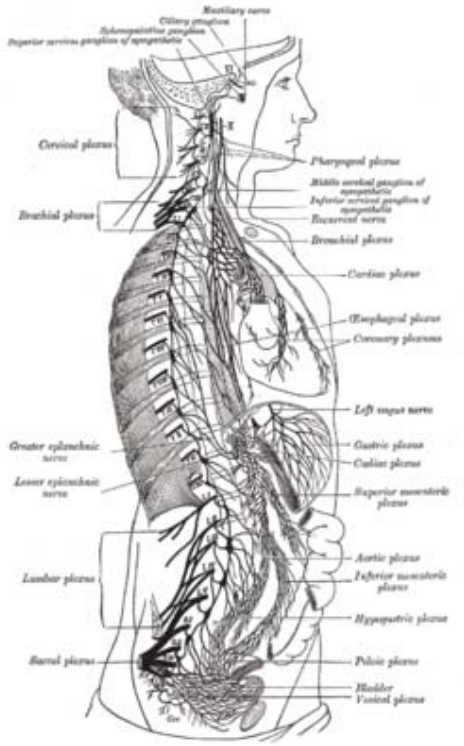
The enteric nervous system has been described as a "second brain". There are several reasons for this. The enteric nervous system can operate autonomously. It normally communicates with the central nervous system (CNS) through the parasympathetic (eg, via the vagus nerve) and sympathetic (eg, via the prevertebral ganglia) nervous systems. However, vertebrate studies show that when the vagus nerve is severed, the enteric nervous system continues to function.

In vertebrates the enteric nervous system includes efferent neurons, afferent neurons, and interneurons, all of which make the enteric nervous system capable of carrying reflexes and acting as an integrating center in the absence of CNS input. The sensory neurons report on mechanical and chemical conditions. Through intestinal muscles, the motor neurons control peristalsis and churning of intestinal contents. Other neurons control the secretion of enzymes. The enteric nervous system also makes use of more than 30 neurotransmitters, most of which are identical to the ones found in CNS, such as acetylcholine, dopamine, and serotonin. The enteric nervous system has the capacity to alter its response depending on such factors as bulk and nutrient composition. In addition, ENS contains support cells which are similar to astroglia of the brain and a diffusion barrier around the capillaries surrounding ganglia which is similar to the blood-brain barrier of cerebral blood vessels.

Chapter 10

Sympathetic Nervous System

Brain: Sympathetic nervous system



The sympathetic nervous system extends from the thoracic to lumbar vertebrae and has connections with the thoracic,cat, and pelvic plexuses.

Latin *Pars sympathica divisionis autonomici systematis nervosi*

The (**ortho-**) **sympathetic nervous system** (**SNS**) is one of the three parts of the autonomic nervous system, along with the enteric and parasympathetic systems. Its general action is to mobilize the body's resources under stress; to induce the fight-or-flight response. It is, however, constantly active at a basal level to maintain homeostasis.

Overview

Alongside the other two components of the autonomic nervous system, the sympathetic nervous system aids in the control of most of the body's internal organs. Stress - as in the flight-or-fight response - and so may be thought to counteract the parasympathetic system, which generally works to promote maintenance of the body at rest. In truth, the functions of both systems are not so straightforward, but this is a useful rule of thumb.

There are two kinds of neurons involved in the transmission of any signal through the sympathetic system; pre- and post- ganglionic. The shorter preganglionic neurons originate from the thoracolumbar region of the spinal cord (levels T1 - L2, specifically) and travel to a ganglion, often one of the paravertebral ganglia, where they synapse with a postganglionic neuron. From there, the long postganglionic neurons extend across most of the body.

At the synapses within the ganglia, preganglionic neurons release acetylcholine, a neurotransmitter that activates nicotinic acetylcholine receptors on postganglionic neurons. In response to this stimulus postganglionic neurons - with two important exceptions - release norepinephrine, which activates adrenergic receptors on the peripheral target tissues. The activation of target tissue receptors causes the effects associated with the sympathetic system.

The two exceptions mentioned above are postganglionic neurons innervating sweat glands—which release acetylcholine for the activation of muscarinic receptors - and the adrenal medulla. The adrenal medulla develops in tandem with the sympathetic nervous system, and acts as a modified sympathetic ganglion: synapses occur between pre- and post- ganglionic neurons within it, but the post ganglionic neurons do not leave the medulla; instead they directly release norepinephrine and epinephrine into the blood.

Function

Organ	Effect
Eye	Dilates pupil
Heart	Increases rate and force of contraction
Lungs	Dilates bronchioles
Digestive tract	Inhibits peristalsis
Kidney	Increases renin secretion
Penis	Promotes ejaculation

The sympathetic nervous system is responsible for up- and down-regulating many homeostatic mechanisms in living organisms. Fibers from the SNS innervate tissues in almost every organ system, providing at least some regulatory function to things as diverse as pupil diameter, gut motility, and urinary output. It is perhaps best known for mediating the neuronal and hormonal stress response commonly known as the *fight-or-*

flight response. This response is also known as *sympatho-adrenal response* of the body, as the preganglionic sympathetic fibers that end in the adrenal medulla (but also all other sympathetic fibers) secrete acetylcholine, which activates the great secretion of adrenaline (epinephrine) and to a lesser extent noradrenaline (norepinephrine) from it. Therefore, this response that acts primarily on the cardiovascular system is mediated directly via impulses transmitted through the sympathetic nervous system and indirectly via catecholamines secreted from the adrenal medulla.

Some evolutionary theorists suggest that the sympathetic nervous system operated in early organisms to maintain survival as the sympathetic nervous system is responsible for priming the body for action. One example of this priming is in the moments before waking, in which sympathetic outflow spontaneously increases in preparation for action.

Organization

Sympathetic nerves originate inside the vertebral column, toward the middle of the spinal cord in the intermediolateral cell column (or lateral horn), beginning at the first thoracic segment of the spinal cord and are thought to extend to the second or third lumbar segments. Because its cells begin in the thoracic and lumbar regions of the spinal cord, the SNS is said to have a *thoracolumbar outflow*. Axons of these nerves leave the spinal cord through the anterior rootlet/root. They pass near the spinal (sensory) ganglion, where they enter the anterior rami of the spinal nerves. However, unlike somatic innervation, they quickly separate out through white rami connectors (so called from the shiny white sheaths of myelin around each axon) that connect to either the paravertebral (which lie near the vertebral column) or prevertebral (which lie near the aortic bifurcation) ganglia extending alongside the spinal column.

To reach target organs and glands, the axons must travel long distances in the body, and, to accomplish this, many axons relay their message to a second cell through synaptic transmission. The ends of the axons link across a space, the synapse, to the dendrites of the second cell. The first cell (the presynaptic cell) sends a neurotransmitter across the synaptic cleft where it activates the second cell (the postsynaptic cell). The message is then carried to the final destination.

Presynaptic nerves' axons terminate in either the paravertebral ganglia or prevertebral ganglia. This can occur through one of four methods:

1. The nerve enters the paravertebral ganglion at the level of its originating spinal nerve, and then ascends to a more superior paravertebral ganglion, where it synapses with the postsynaptic cell.

2. The nerve enters the paravertebral ganglion at the level of its originating spinal nerve and synapses with the postsynaptic cell at that level.

3. The nerve enters the paravertebral ganglion at the level of its originating spinal nerve, and then descends to a more inferior paravertebral ganglion, where it synapses with the postsynaptic cell.

4. The nerve enters the paravertebral ganglion at the level of its originating spinal nerve and then descends to a prevertebral ganglion, where it synapses with the postsynaptic cell.

The postsynaptic cell then goes on to innervate the targeted end effector (ie gland, smooth muscle, etc.). Because paravertebral and prevertebral ganglia are relatively close to the spinal cord, presynaptic neurons are generally much shorter than their postsynaptic counterparts, which must extend throughout the body to reach their destinations.

A notable exception to the routes mentioned above is the sympathetic innervation of the suprarenal (adrenal) glands. In this case, presynaptic neurons pass through paraverterbral ganglia, on through prevertebral ganglia and then synapse directly with suprarenal tissue. This tissue consists of cells that have pseudo-neuron like qualities in that when activated by the presynaptic neuron, they will release their neurotransmitter (epinephrine) directly into the blood stream.

In the SNS and other components of the peripheral nervous system, these synapses are made at sites called ganglia. The cell that sends its fiber is called a preganglionic cell, while the cell whose fiber leaves the ganglion is called a postganglionic cell. As mentioned previously, the preganglionic cells of the SNS are located between the first thoracic segment and third lumbar segments of the spinal cord. Postganglionic cells have their cell bodies in the ganglia and send their axons to target organs or glands.

The ganglia include not just the sympathetic trunks but also the cervical ganglia (superior, middle and inferior), which sends sympathetic nerve fibers to the head and thorax organs, and the celiac and mesenteric ganglia (which send sympathetic fibers to the gut).

Information transmission

Messages travel through the SNS in a bidirectional flow. Efferent messages can trigger changes in different parts of the body simultaneously. For example, the sympathetic nervous system can accelerate heart rate; widen bronchial passages; decrease motility (movement) of the large intestine; constrict blood vessels; increase peristalsis in the esophagus; cause pupillary dilation, piloerection (goose bumps) and perspiration (sweating); and raise blood pressure. Afferent messages carry sensations such as heat, cold, or pain.

The first synapse (in the sympathetic chain) is mediated by nicotinic receptors physiologically activated by acetylcholine, and the target synapse is mediated by adrenergic receptors physiologically activated by either noradrenaline (norepinephrine) or adrenaline (epinephrine). An exception is with sweat glands, which receive sympathetic

innervation but have muscarinic acetylcholine receptors, which are normally characteristic of Parasympathetic nervous system. Another exception is with certain deep muscle blood vessels, which dilate (rather than constrict) with an increase in sympathetic tone. This is because of the presence of more beta2 receptors (rather than alpha1, which are frequently found on other vessels).

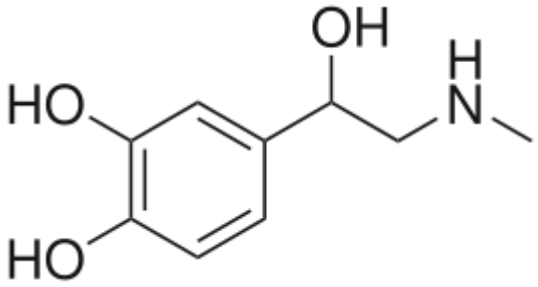
Sympathicotonia

Sympathicotonia is a stimulated condition of the sympathetic nervous system, marked by vascular spasm, elevated blood pressure, and goose bumps.

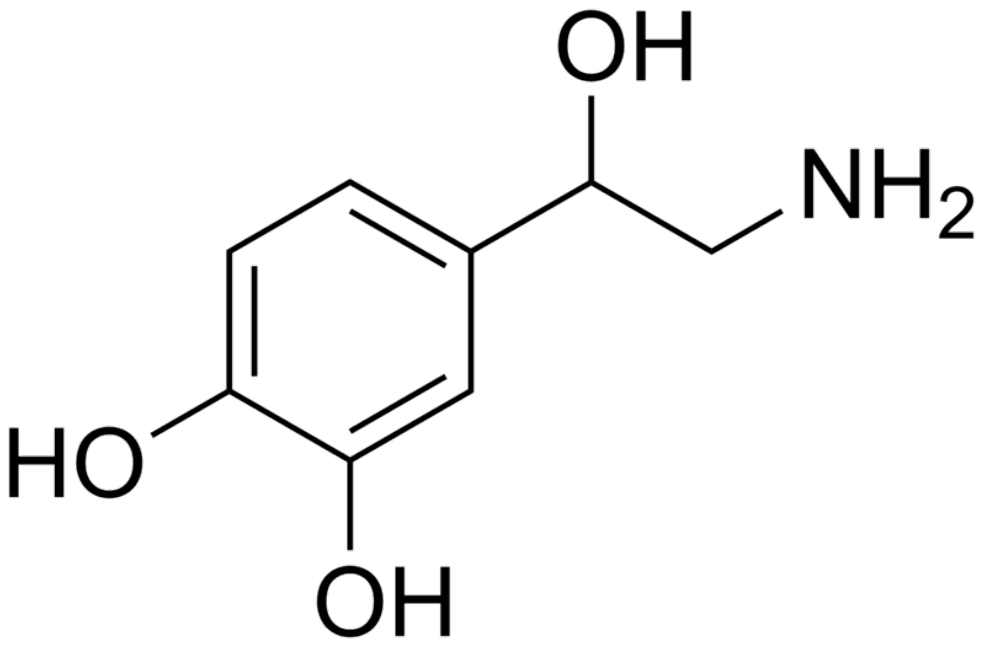
Chapter 11

Chromaffin Cell and Prevertebral Ganglia

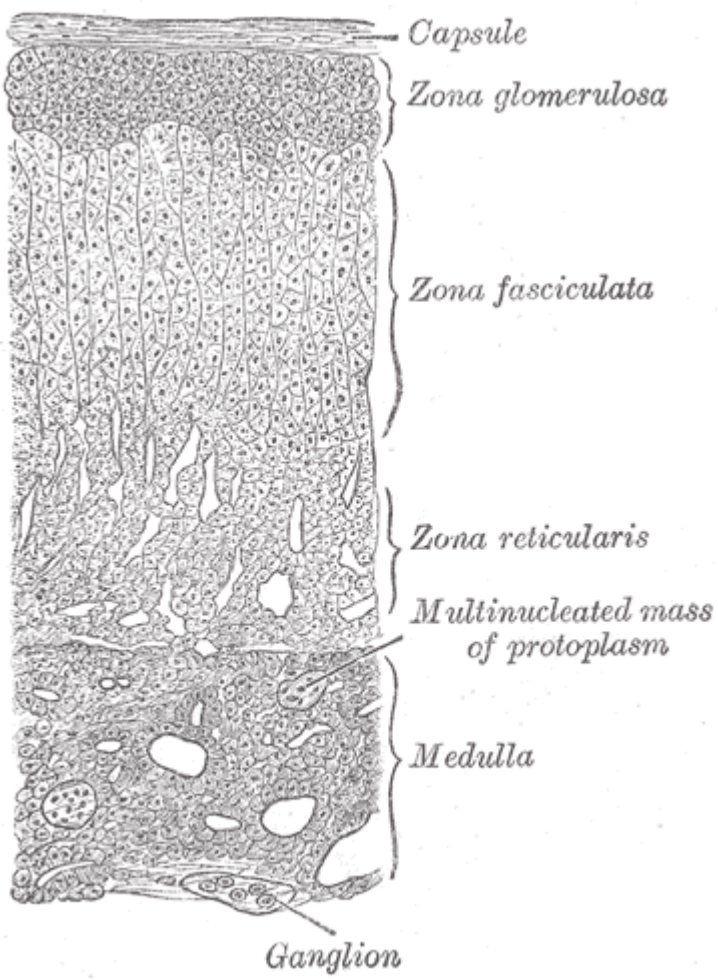
Chromaffin cell



Epinephrine



Norepinephrine



Adrenal gland. (Medulla labeled at bottom right)

Chromaffin cells are neuroendocrine cells found in the medulla of the adrenal gland (suprarenal gland, located above the kidneys) and in other ganglia of the sympathetic nervous system. They are modified post-synaptic sympathetic neurons that receive sympathetic input. Instead of releasing neurotransmitter (catecholamines - ~20% Norepinephrine (Noradrenaline) and ~80% Epinephrine (Adrenaline)) to an adjacent organ or tissue for a specific effect, neurotransmitter is released into systemic circulation for systemic effects on multiple organs. Hence they are called neuroendocrine cells.

In the fifth week of (human) fetal development, neuroblast cells migrate from the neural crest to form the sympathetic chain and preaortic ganglia. The cells migrate a second time to the adrenal medulla. Chromaffin cells also settle near the sympathetic ganglia, vagus nerve, paraganglia, and carotid arteries. In lower concentrations, extra-adrenal chromaffin cells also reside in the bladder wall, prostate, and behind the liver.

Function

Chromaffin cells of the adrenal medulla are innervated by the splanchnic nerve and secrete adrenaline (epinephrine), noradrenaline (norepinephrine), and enkephalin and enkephalin-containing peptides into the blood stream. The secreted adrenaline and noradrenaline play an important role in the fight-or-flight response. The enkephalins and enkephalin-containing peptides are related to, but distinct from endogenous peptides named endorphins (which are secreted from the pituitary); all of these peptides bind to opioid receptors and produce analgesic (and other) responses. The hormones are secreted from granules; this is where the enzyme dopamine β-hydroxylase catalyzes the conversion of dopamine to noradrenaline. Distinct N and E cell forms exist (also Na and A cells in British nomenclature - noradrenaline and adrenaline); the former produce norepinephrine, the latter arise out of N cells through interaction with glucocorticoids, and convert norepinephrine into epinephrine.

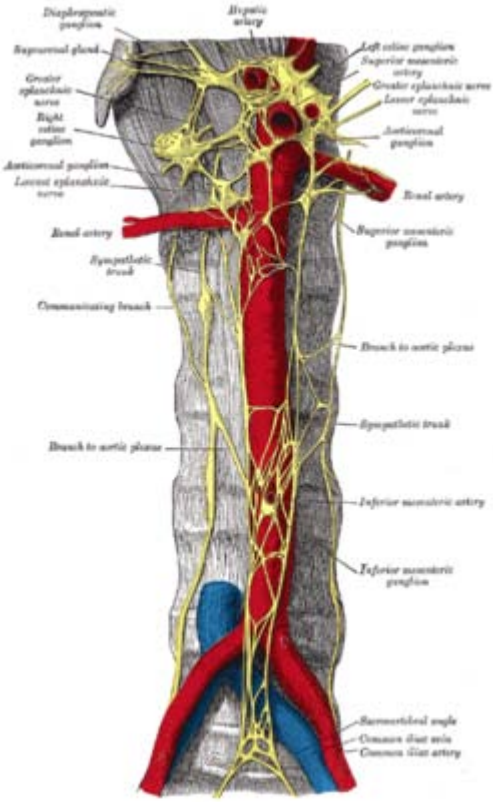
Nomenclature

These cells are so-named because they can be visualized by staining with chromium salts. Chromaffin salts oxidize and polymerize catecholamines to form a brown color, most strongly in the cells secreting noradrenaline.

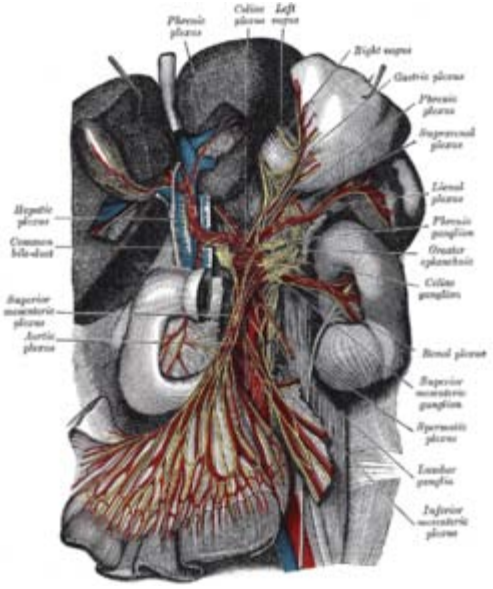
(The enterochromaffin cells are so named because of their histological similarity to chromaffin cells (they also stain yellow when treated with chromium salts), but their function is quite different.)

Prevertebral ganglia

Prevertebral ganglia



Abdominal portion of the sympathetic trunk, with the celiac plexus and hypogastric plexus.



The celiac ganglia with the sympathetic plexuses of the

abdominal viscera radiating from the ganglia.

Gray's *subject #214 977*

Prevertebral ganglia (or **collateral ganglia**, or **preaortic ganglia**) are sympathetic ganglia which lie between the sympathetic chain and the organ of supply.

Function

They are the site of relay of the postganglionic sympathetic fibres that supply abdominal and pelvic viscera.

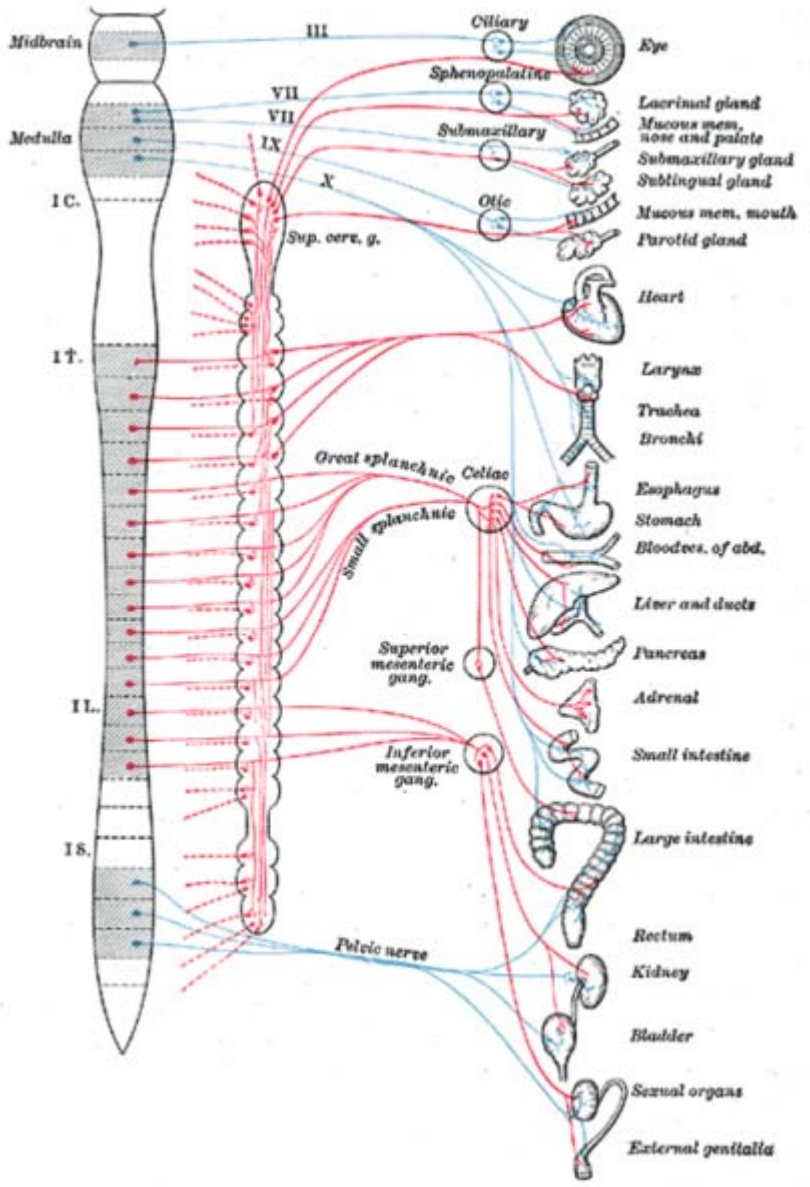
Examples

These include

1. the celiac ganglia (which can include the aorticorenal ganglion),

2. superior mesenteric ganglia, and

3. inferior mesenteric ganglia.

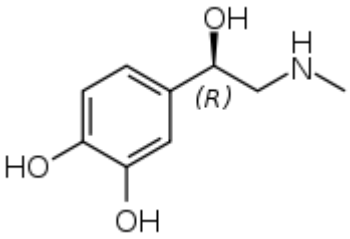


Sympathetic (red) and parasympathetic (blue) nervous system

Chapter 12

Epinephrine

_(R)_-(–)-L-Epinephrine or _(R)_-(–)-L-adrenaline



Systematic (IUPAC) name
_(R)_-4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol
Identifiers
CAS number 51-43-4
ATC code A01AD01 B02BC09 C01CA24 R01AA14 R03AA01 S01EA01
PubChem CID 5816
IUPHAR ligand 509
DrugBank DB00668
ChemSpider 5611 ✓
UNII YKH834O4BH ✓

KEGG	D00095 ✓
ChEMBL	CHEMBL679 ✓
Chemical data	
Formula	$C_9H_{13}NO_3$
Mol. mass	183.204 g/mol
SMILES	eMolecules & PubChem
Pharmacokinetic data	
Bioavailability	Nil (oral)
Metabolism	adrenergic synapse (MAO and COMT)
Half-life	2 minutes
Excretion	Urine
Therapeutic considerations	
Pregnancy cat.	A(AU) C(US)
Legal status	Prescription Only (S4) (AU) POM (UK) ℞-only (US)
Routes	IV, IM, endotracheal, IC

Epinephrine (also known as **adrenaline**) is a hormone and a neurotransmitter. It increases heart rate, constricts blood vessels, dilates air passages and participates in the fight-or-flight response of the sympathetic nervous system. Chemically, epinephrine is a catecholamine, a monoamine produced only by the adrenal glands from the amino acids phenylalanine and tyrosine.

The term *adrenaline* is derived from the Latin roots *ad-* and *renes* and literally means *on the kidney*, in reference to the adrenal gland's anatomic location on the kidney. The Greek roots *epi-* and *nephros* have similar meanings, and give rise to *epinephrine*. The term *epinephrine* is often shortened to **epi** in medical jargon.

Adrenal extracts containing adrenaline were first obtained by Polish physiologist Napoleon Cybulski in 1895. These extracts, which he called "nadnerczyna", contained epinephrine and other catecholamines. Japanese chemist Jokichi Takamine and his assistant Keizo Uenaka independently discovered adrenaline in 1900. In 1901, Takamine successfully isolated and purified the hormone from the adrenal glands of sheep and oxen. Adrenaline was first synthesized in the laboratory by Friedrich Stolz and Henry Drysdale Dakin, independently, in 1904.

Actions in the body

As a hormone, epinephrine acts on nearly all body tissues. Its actions vary by tissue type and tissue expression of adrenergic receptors. For example, epinephrine causes smooth muscle relaxation in the airways, but causes contraction of the smooth muscle that lines most arterioles.

Epinephrine acts by binding to a variety of adrenergic receptors. Adrenaline is a nonselective agonist of all adrenergic receptors, including α_1, α_2, β_1, β_2, and β_3 receptors. Epinephrine's binding to these receptors triggers a number of metabolic changes. Binding to α-adrenergic receptors inhibits insulin secretion by the pancreas, stimulates glycogenolysis in the liver and muscle, and stimulates glycolysis in muscle. β-Adrenergic receptor binding triggers glucagon secretion in the pancreas, increased adrenocorticotropic hormone (ACTH) secretion by the pituitary gland, and increased lipolysis by adipose tissue. Together these effects lead to increased blood glucose and fatty acids, providing substrates for energy production within cells throughout the body.

In addition to these metabolic changes, epinephrine also leads to broad alterations throughout all organ systems.

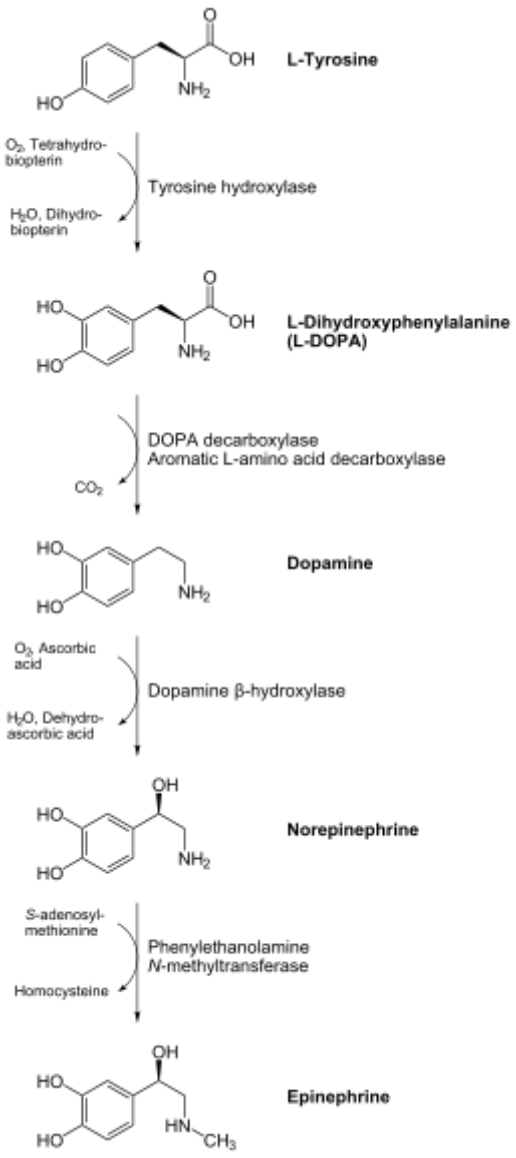
Physiologic responses to epinephrine by organ

Organ	Effects
Heart	Increases heart rate
Lungs	Increases respiratory rate
Nearly all tissues	Vasoconstriction or vasodilation
Liver	Stimulates glycogenolysis
N/A, systemic	Triggers lipolysis
N/A, systemic	Muscles contraction

Biosynthesis and regulation

Adrenaline is synthesized in the medulla of the adrenal gland in an enzymatic pathway that converts the amino acid tyrosine into a series of intermediates and ultimately adrenaline. Tyrosine is first oxidized to L-DOPA, which is subsequently decarboxylated to give dopamine. Oxidation gives norepinephrine, which is methylated to give epinephrine.

Adrenaline is synthesized via methylation of the primary distal amine of noradrenaline by phenylethanolamine N-methyltransferase (PNMT) in the cytosol of adrenergic neurons and cells of the adrenal medulla (so-called chromaffin cells). PNMT is only found in the cytosol of cells of adrenal medullary cells. PNMT uses *S*-adenosylmethionine (SAMe) as a cofactor to donate the methyl group to noradrenaline, creating adrenaline.



The biosynthesis of adrenaline involves a series of enzymatic reactions

For noradrenaline to be acted upon by PNMT in the cytosol, it must first be shipped out of granules of the chromaffin cells. This may occur via the catecholamine-H^+ exchanger VMAT1. VMAT1 is also responsible for transporting newly synthesized adrenaline from the cytosol back into chromaffin granules in preparation for release.

In liver cells, adrenaline binds to the β-Adrenergic receptor which changes conformation and helps Gs, a G protein, exchange GDP to GTP. This trimeric G protein dissociates to Gs alpha and Gs beta/gamma subunits. Gs alpha binds to adenyl cyclase thus converting ATP into Cyclic AMP. Cyclic AMP binds to the regulatory subunit of Protein Kinase A: Protein kinase A phosphorylates Phosphorylase Kinase. Meanwhile, Gs beta/gamma binds to the calcium channel and allows calcium ions to enter the cytoplasm. Calcium

ions bind to calmodulin proteins, a protein present in all eukaryotic cells, which then binds to Phosphorylase Kinase and finishes its activation. Phosphorylase Kinase phosphorylates Glycogen phosphorylase which then phosphorylates glycogen and converts it to glucose-6-phosphate.

Regulation

The major physiologic triggers of adrenaline release center upon stresses such as physical threat, excitement, noise, bright lights, and high ambient temperature. All of these stimuli are processed in the central nervous system.

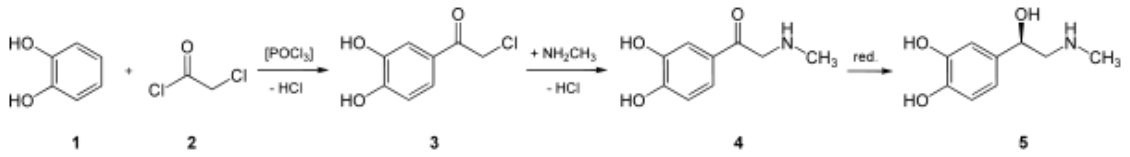
Adrenocorticotropic hormone (ACTH) and the sympathetic nervous system stimulate the synthesis of adrenaline precursors by enhancing the activity of tyrosine hydroxylase and dopamine-β-hydroxylase, two key enzymes involved in catecholamine synthesis. ACTH also stimulates the adrenal cortex to release cortisol, which increases the expression of PNMT in chromaffin cells, enhancing adrenaline synthesis. This is most often done in response to stress. The sympathetic nervous system, acting via splanchnic nerves to the adrenal medulla, stimulates the release of adrenaline. Acetylcholine released by preganglionic sympathetic fibers of these nerves acts on nicotinic acetylcholine receptors, causing cell depolarization and an influx of calcium through voltage-gated calcium channels. Calcium triggers the exocytosis of chromaffin granules and thus the release of adrenaline (and noradrenaline) into the bloodstream.

Adrenaline (as with noradrenaline) does exert negative feedback to down-regulate its own synthesis at the presynaptic alpha-2 adrenergic receptor. Abnormally elevated levels of adrenaline can occur in a variety of conditions, such as surreptitious epinephrine administration, pheochromocytoma, and other tumors of the sympathetic ganglia.

Its action is terminated with re-uptake into nerve terminal endings, some minute dilution, and metabolism by monoamine oxidase and catechol-o-methyl transferase.

Chemical synthesis

Epinephrine may be synthesized by the reaction of catechol with chloroacetyl chloride, followed by the reaction with methylamine to give the ketone, which is reduced to the desired hydroxy compound. The racemic mixture may be separated using tartaric acid.



Formula for the synthesis of adrenaline

For isolation from the adrenal glands tissue of livestock:

- J. Takamine, J. Soc. Chem. Ind., 20, 746 (1901).
- J. B. Aldrich, Am. J. Physiol., 5, 457 (1901).

Synthetic production:

- A. F. Stolz, Chem. Ber., 37, 4149 (1904).
- K. R. Payne, Ind. Chem. Chem. Manuf., 37, 523 (1961).
- H. Loewe, Arzneimittel-Forsch., 4, 583 (1954).
- Farbwerke Meister Lucins & Bruning in Hochst a.M., DE 152814 (1903).
- Farbenwerke Meister Lucins & Bruning in Hochst a.M., DE 157300 (1903).
- Farbenwerke Meister Lucins & Bruning in Hochst a.M., DE 222451 (1908).
- Tullar, B. F. (1948). "The resolution of dl-arterenol". *Journal of the American Chemical Society* **70** (6): 2067. doi:10.1021/ja01186a024. PMID 18863798. edit
- D. Flacher, Z. Physiol. Chem., 58, 189 (1908).

Therapeutic use

Epinephrine ampule, 1 mg (Suprarenin)

Epinephrine is available in a variety of preparations for the management of several medical conditions. Aqueous preparations of adrenaline are obtained by use of hydrochloric acid or tartaric acid, since it undergoes oxidation in the absence of acid medium. Borate salt is used in ophthalmology.

Cardiac arrest

Adrenaline is used as a drug to treat cardiac arrest and other cardiac dysrhythmias resulting in diminished or absent cardiac output. Its actions are to increase peripheral resistance via $\alpha_1$receptor-dependent vasoconstriction and to increase cardiac output via its binding to $\beta_1$receptors. The usual ACLS concentration for injection is Epinephrine 1:10,000.

Shock and anaphylaxis

Due to its vasoconstrictive effects, adrenaline is the drug of choice for treating anaphylaxis. It is also useful in treating sepsis. Allergy patients undergoing immunotherapy may receive an adrenaline rinse before the allergen extract is administered, thus reducing the immune response to the administered allergen. It is also used as a bronchodilator for asthma if specific $\beta_2$agonists are unavailable or ineffective.

Because of various expression of $\alpha_1$or $\beta_2$receptors, depending on the patient, administration of adrenaline may *raise* or *lower* blood pressure, depending whether or not the net increase or decrease in peripheral resistance can balance the positive inotropic and chronotropic effects of adrenaline on the heart, effects which respectively increase the contractility and rate of the heart.

The usual concentration for SQ or IM injection is 1:1,000.

Use in local anesthetics

Epinephrine is added to injectable forms of a number of local anesthetics, such as bupivacaine and lidocaine, as a vasoconstrictor to retard the absorption and therefore prolong the action of the anesthetic agent. Some of the adverse effects of local anesthetic use, such as apprehension, tachycardia and tremor, may be caused by epinephrine.

Autoinjectors

Epinephrine is available in an autoinjector delivery system. EpiPens, Anapens and Twinjects all use epinephrine as their active ingredient. Twinjects contain a second dose of epinephrine in a separate syringe and needle delivery system contained within the body of the autoinjector.

Though both *EpiPen* and *Twinject* are trademark names, common usage of the terms are drifting toward the generic context of any epinephrine autoinjector.

Croup

Racemic epinephrine has historically been used for the treatment of croup. Racemic epinephrine is a 1:1 mixture of the dextrorotatory (D) and levorotatory (L) isomers of epinephrine. The L form is the active component. Racemic epinephrine works by

stimulation of the α-adrenergic receptors in the airway with resultant mucosal vasoconstriction and decreased subglottic edema and by stimulation of the β-adrenergic receptors with resultant relaxation of the bronchial smooth muscle.

Side effects and drug interactions

Adverse reactions to epinephrine include palpitations, tachycardia, arrhythmia, anxiety, headache, tremor, hypertension, and acute pulmonary edema.

Use is contraindicated for patients on non-selective β-blockers because severe hypertension and even cerebral hemorrhage may result. Although commonly believed that administration of epinephrine may cause heart failure by constricting coronary arteries, this is not the case. Coronary arteries only have $\beta_2$receptors, which cause vasodilation in the presence of epinephrine. Even so, administering high-dose epinephrine has not been definitively proven to improve survival or neurologic outcomes in adult victims of cardiac arrest.

Measurement in biological fluids

Epinephrine may be quantitated in blood, plasma or serum as a diagnostic aid, to monitor therapeutic administration or to identify the causative agent in a potential poisoning victim. Endogenous plasma epinephrine concentrations in resting adults are normally less than 10 ng/L, but may increase by 10-fold during exercise and by 50-fold or more during times of stress. Pheochromocytoma patients often have plasma epinephrine levels of 1000-10,000 ng/L. Parenteral administration of epinephrine to acute-care cardiac patients can produce plasma concentrations of 10,000 to 100,000 ng/L.

Use in full contact sports

In contact sports such as boxing, adrenaline chloride, usually a 1:1000 epinephrine solution, is used to stanch bleeding during matches.

Adrenaline junkie

Adrenaline junkie is a term used to describe somebody who appears to be addicted to epinephrine (endogenous) and such a person is sometimes described as getting a "high" from life. The term adrenaline junkie was popularly used in the 1991 movie *Point Break* to describe individuals who enjoyed dangerous activities (such as extreme sports, e.g. BASE jumping) for the adrenaline "rush". Adrenaline junkies appear to favour stressful activities for the release of epinephrine as a stress response. Doing this may result in physical harm because of the potential danger. Whether or not the positive response is caused specifically by epinephrine is difficult to determine, as endorphins are also released during the fight-or-flight response to such activities.

Terminology

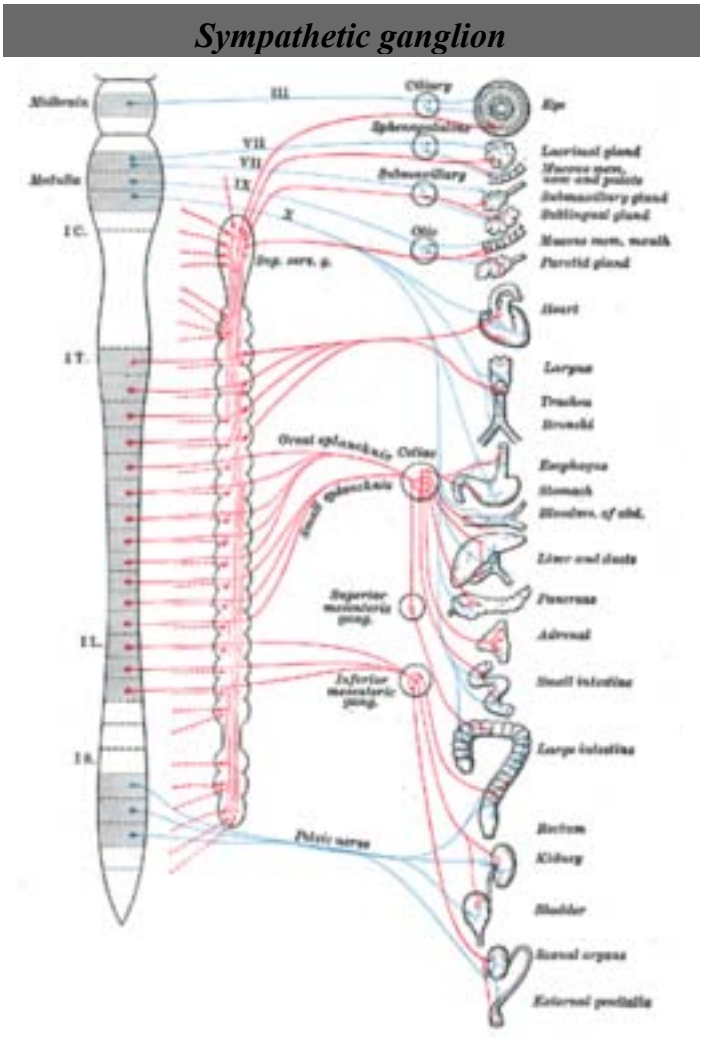
This chemical is widely referred to as *adrenaline* outside of the United States; however, its United States Adopted Name and International Nonproprietary Name is *epinephrine*. *Epinephrine* was chosen because *adrenaline* bore too much similarity to the Parke, Davis & Co trademark *Adrenalin* (without the "e"), which was registered in the United States. The British Approved Name and European Pharmacopoeia term for this chemical is *adrenaline*, and is indeed now one of the few differences between the INN and BAN systems of names.

Amongst American health professionals and scientists, the term epinephrine is used over adrenaline. However, it should be noted that pharmaceuticals that mimic the effects of epinephrine are often called *adrenergics*, and receptors for epinephrine are called adrenergic receptors or adrenoceptors.

Chapter 13

Sympathetic Ganglion and Freezing Behavior

Sympathetic ganglion



Autonomic nervous system innervation, showing the

sympathetic (thoracolumbar) and parasympathetic (craniosacral) systems, in red and blue, respectively

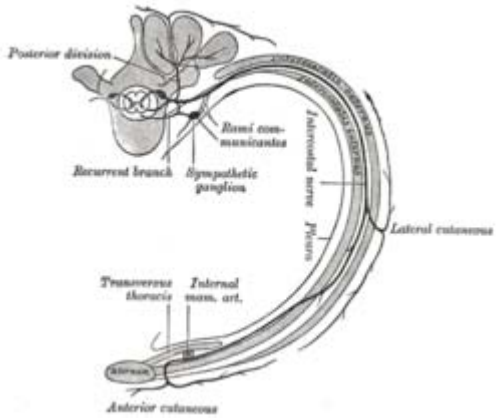


Diagram of the course and branches of a typical intercostal nerve. (Sympathetic ganglion visible at center top.)

Latin *g. sympathicum*

Sympathetic ganglia are the ganglia of the sympathetic nervous system. They deliver information to the body about stress and impending danger, and are responsible for the familiar fight-or-flight response. They contain approximately 20000–30000 nerve cell bodies and are located close to and on either side of the spinal cord in long chains. Sympathetic ganglia are the tissue from which neuroblastoma tumours arise.

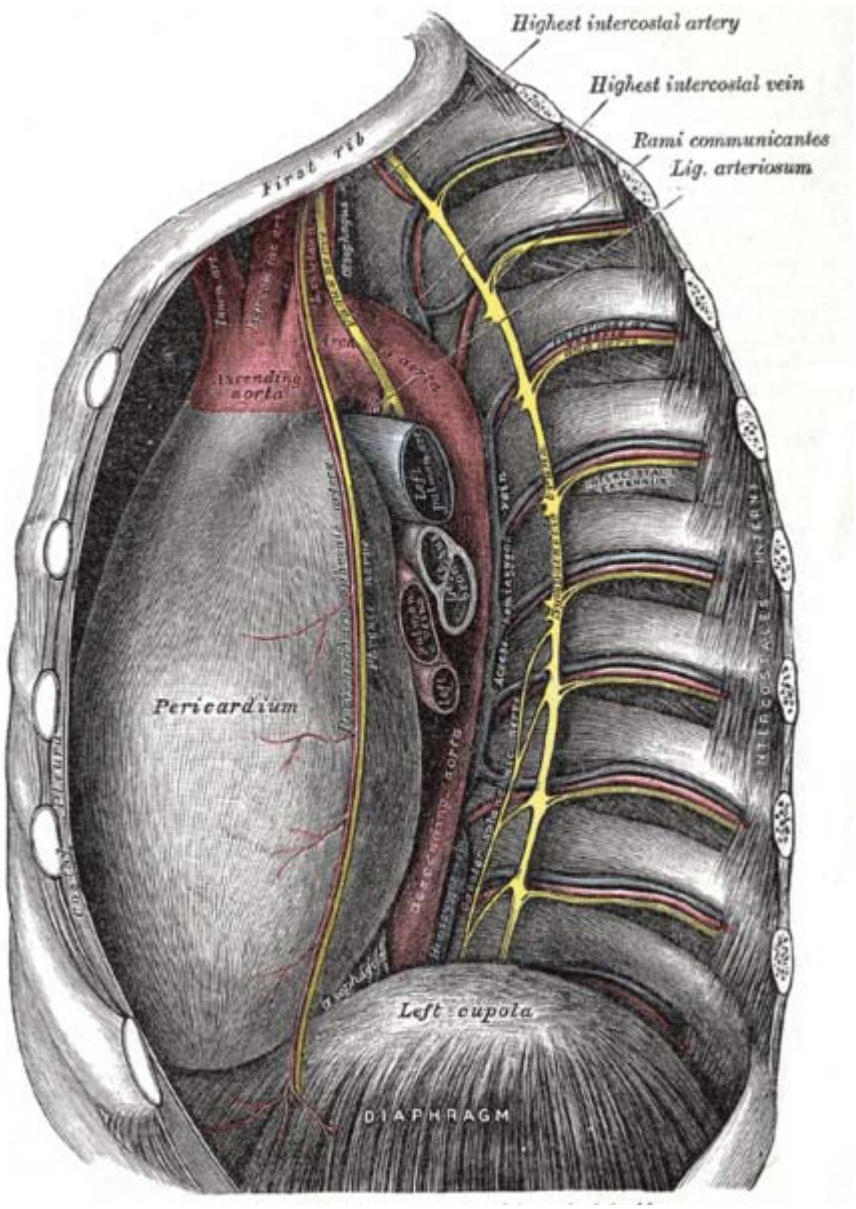
Anatomy

Sympathetic chain ganglia

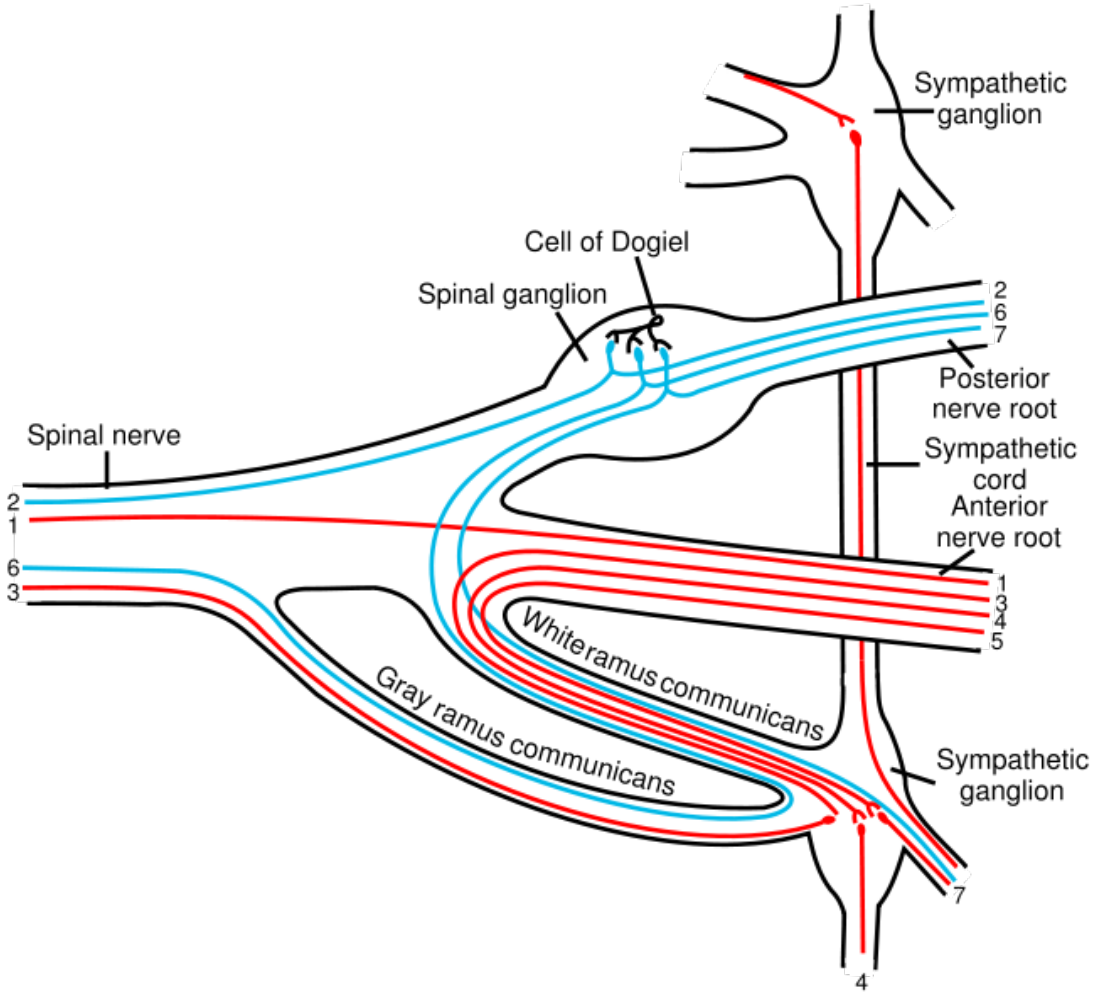
The bilaterally symmetric sympathetic chain ganglia, also called the paravertebral ganglia, are located just ventral and lateral to the spinal cord. The chain extends from the upper neck down to the coccyx, forming the unpaired coccygeal ganglion. Preganglionic nerves from the spinal cord synapse end at one of the chain ganglia and the postganglionic fibre extends to an effector, typically a visceral organ in the thoracic cavity. There are usually 21 or 23 pairs of these ganglia: 3 in the cervical region, 12 in the thoracic region, 4 in the lumbar region, 4 in the sacral region and a single,unpaired ganglion lying in front of the coccyx called the 'Ganglion impar'.

Collateral ganglia

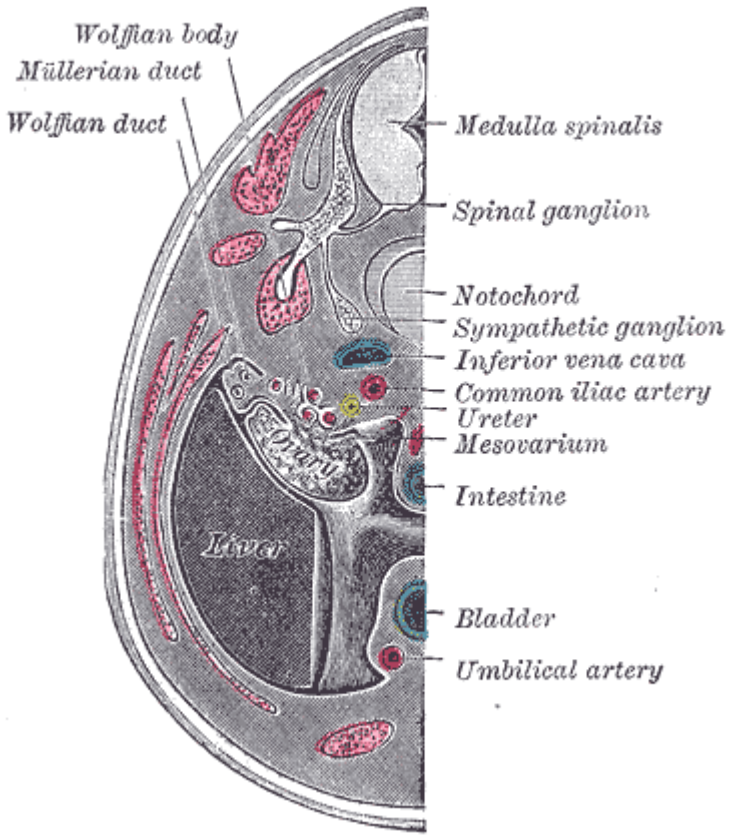
Neurons of the collateral ganglia, also called the prevertebral ganglia, receive input from the splanchnic nerves and innervate organs of the abdominal and pelvic region. These include the celiac ganglia, superior mesenteric ganglia, and inferior mesenteric ganglia.



The thoracic aorta, viewed from the left side



Scheme showing structure of a typical spinal nerve. Note: gray and white rami are mislabeled--the gray ramus contains post ganglionic sympathetic nerves; the white ramus contains preganglionic sympathetic nerves.



Transverse section of human embryo eight and a half to nine weeks old

Freezing behavior

Freezing behavior is the fearful reaction to specific stimuli, most commonly observed by animals. It is caused by the sympathetic nervous system to deal with threats. Studies typically assess a conditioned freezing behavior response to stimuli that typically or innately do not cause fear, such as a tone or shock. Freezing behavior is most easily characterized by changes in blood pressure and lengths of time in crouching position, but it also is known to cause changes such as shortness of breath, increased heart rate, sweating, or choking sensation. However, since it is difficult to measure these sympathetic responses to fear stimuli, studies are typically confined to simple crouching times. A response to stimuli typically is said to be a "fight or flight", but can be shown as rather "fright, fight or flight." In addition, freezing is observed to occur before a fight or flight response.

Physiology

Studies suggest that specific areas of the brain are known to either elicit (or inhibit in the case of lesions) freezing behavior in subjects. The regions include the basolateral amygdala and the hippocampus.

One such study, conducted by Ann E. Power et al., investigated the effects of lesions in the basolateral amygdala. Rats were placed in a chamber containing either real cat hair or fake cat hair. Two groups of rats were tested: rats that had been lesioned in the basolateral amygdala and rats that were the control group (or sham-operated group). All rats at first froze briefly then retreated away from the stimulus upon initial contact. The results showed that the rats that were lesioned in the basolateral amygdala froze much less to the cat hair than the control group of rats. As expected, both groups of rats froze for a significantly less time when presented with the fake cat hair stimulus than when in the presence of the real cat hair. It was also shown that the both control group and the lesioned group made less contacts with the real cat hair than the fake cat hair. These data infer a connection between the basolateral amygdala and freezing behavior.

Another study, conducted by Gisquet-Verrier et al., tested the effects of the hippocampus, in three experiments, on both the freezing behavior and avoidance. The rats were lesioned with ibotenic acid, and were tested against a control group. They first investigated changes from conditioned fear, and results showed that lesions to the hippocampus did not alter freezing behavior and marginally affected avoidance. Next, they tested single conditioning sessions, and it was found that freezing behavior remained unchanged while avoidance was disrupted. Finally, they tested conditioning with a larger stimulus (footshock intensity). It was found that avoidance was unaltered while freezing behavior decreased. Not only did these investigations show that the hippocampus is involved with freezing behavior, but avoidance and freezing behavior do not seem to have similar ways of being quantified when it comes to fear conditioning.

Neurotransmitters

It has been experimentally tested that particular areas of the brain are involved with freezing behavior. As mentioned before, Ann E. Power investigated the effect of basolateral amygdala on freezing behavior. It was also found that muscarinic cholinergic activation plays a role in the behavior. That suggests that neurotransmitters, in general, play a role in freezing behavior. Now let us look at other possible neurotransmitters or chemical treatments that may affect this response. Several investigations show that freezing behavior is influenced by the following:

- Serotonin
- Antipsychotic Drugs
- Methamphetamine
- Inhibitors

Hashimoto et al. investigated the effects of conditioned fear on serotonin and freezing behavior in rats. Through in vivo microdialysis, certain concentrations of extracellular serotonin in the rat brain were able to be measured. It was found that conditioned fear stress increased the levels of the serotonin in the medial prefrontal cortex. This increase was correlated with an increased freezing behavior that was observed. The rats were then given an inhibitor for the extracellular serotonin, which resulted in a reduced freezing behavior. It can be suggested from these results that inhibition of serotonin can decrease freezing behavior and, also, anxiety.

Not only does serotonin influence freezing behavior, but it has been shown that antipsychotic drugs(APDs), such as clozapine, ORG5222, and olanzapine, affect freezing behavior as well. Drugs were administered subcutaneously to rats 30 minutes before footshock stress. It was observed that, 24 hours following the footshock, freezing behavior was present without shocks. This is interesting to note, since there was a sympathetic response to no stimuli at all. This suggests that antipsychotic drugs alter freezing behavior, making the rats more sensitive to fear stimulus, for example.

Methamphetamines have also shown that they could affect freezing behavior. Tsuchiya et al. conducted a study investigating the effect of methamphetamine pretreatment on freezing behavior. Rats were given the drug over a week, ramping up the doses. After that, there was a 5-day period without any drugs administered. The rats were then subjected to conditioned fear stress. Repeated but not single methamphetamine pretreatment resulted in a significantly increased freezing behavior. This evidence suggests that previous exposure to chronic methamphetamine results in an increased sensitivity to subsequent stress than a control group.

Just as neurotransmitters influence freezing behavior, inhibitors, as expected, interrupt neurotransmitters and influence freezing behavior. This study examined the effects of monoamine oxidase inhibitors on freezing behavior. Rats were treated with specific inhibitors that target either monoamine oxidase A or B. The results showed that acute inhibition of both monoamine oxidase A and B reduce axiety or freezing behavior. However, inhibition of monoamine oxidase A or B alone failed to do so.

Hormones

It has been shown that parts of the brain are involved in freezing behavior. It has also been shown that neurotransmitters and similar chemicals influence freezing behavior as well. In a related manner, hormones, progestogens and estrogen, play a role in freezing behavior as well. First, the authors tested the rats in marble burying and conditioned fear when they were in behavioral estrous or diestrous. Female rats in behavioral estrous have elevated levels of these steroid hormones and also elicit more approach and less freezing behavior than diestrous rats. Results showed rats in this behavioral estrous show less impulsive burying and also less freezing behavior than diestrous rats. The authors then administered progesterone and estrogen in ovariectomized rats and tested them in marble burying and conditioned fear. The results for this experiment show administration of progesterone or both estrogen and progesterone decreases impulsive burying. Both

showed a decrease in freezing behavior. The study concludes that "progesterone and/or estrogen may mediate impulsive and/or avoidant behavior." It is interesting to note the changes in freezing behavior in a female's cycle. Therefore, it is typically more appropriate for tests to be done with males only. Freezing behavior is seen to be great impacted by levels of hormones. However, there may be future studies on whether testosterone influences freezing behavior as well.

Chapter 14

Alpha-1 Adrenergic Receptor and Alpha-2 Adrenergic Receptor

Alpha-1 adrenergic receptor

The **alpha-1** (**α_1**) **adrenergic receptor** is a G protein-coupled receptor (GPCR) associated with the G_q heterotrimeric G-protein. It consists of three highly homologous subtypes, including α_{1A}-, α_{1B}-, and α_{1D}-adrenergic. Catecholamines like norepinephrine (noradrenaline) and epinephrine (adrenaline) signal through the α_1-adrenergic receptor in the central and peripheral nervous systems.

Effects

The α_1-adrenergic receptor has several general functions in common with the α_2-adrenergic receptor, but also has specific effects of its own.

General

Common (or still unspecified) effects include:

- Vasoconstriction of arteries to heart (coronary arteries)
- Venoconstriction of veins
- Decrease motility of smooth muscle in gastrointestinal tract

Specific

The primary effect is on smooth muscle, which mainly constrict. However, there are other functions as well.

Smooth muscle

In smooth muscle of blood vessels the principal effect is vasoconstriction. Blood vessels with α_1-adrenergic receptors are present in the skin, the sphincters of gastrointestinal system, kidney (renal artery) and brain. During the fight-or-flight response

vasoconstriction results in the decreased blood flow to these organs. This accounts for the pale appearance of the skin of an individual when frightened.

It also induces contraction of the urinary bladder, although this effect is minor compared to the relaxing effect of β_2-adrenergic receptors. In other words, the overall effect of sympathetic stimuli on the bladder is relaxation, in order to delay micturition during stress.

Other effects are on smooth muscle are contraction in:

- Ureter
- Hairs (arrector pili muscles)
- Uterus (when pregnant)
- Urethral sphincter
- Bronchioles (although minor to the relaxing effect of β_2 receptor on bronchioles)
- Iris dilator muscle
- Seminal tract, resulting in ejaculation

In a few areas the result on smooth muscle is relaxation. These include:

- The rest of the GI tract, except for the sphincters
- Blood vessels of erectile tissue

Neuronal

- Activation of α_1-adrenergic produces anorexia and partially mediates the efficacy of appetite suppressants like phenylpropanolamine and amphetamine in the treatment of obesity.

Other

- Positive inotropic effect on heart muscle ($\alpha_1 << \beta_1$)
- Secretion from salivary gland
- Increase salivary potassium levels
- Glycogenolysis and gluconeogenesis from adipose tissue and liver.
- Secretion from sweat glands
- Na^+ reabsorption from kidney
    - Stimulate proximal tubule NHE3
    - Stimulate proximal tubule basolateral Na-K ATPase
- Activate mitogenic responses and regulate growth and proliferation of many cells

Signaling cascade

α_1-Adrenergic receptors are members of the G protein-coupled receptor superfamily. Upon activation, a heterotrimeric G protein, G_q, activates phospholipase C (PLC), which causes an increase in IP_3 and calcium. This triggers further effects, primarily through the

activation of an enzyme Protein Kinase C. This enzyme, as a kinase, functions by phosphorylation of other enzymes causing their activation, or by phosphorylation of certain channels leading to the increase or decrease of electrolyte transfer in or out of the cell.

Activity during exercise

During exercise these α_1-adrenergic receptors can be selectively blocked by sympathetic nervous activity, allowing the β_2-adrenergic receptors (which mediate vasodilation) to dominate. Note that only the α_1-adrenergic receptors in active muscle will be blocked. Resting muscle will not have its α_1-adrenergic receptors blocked, and hence the overall effect there will be α_1-adrenergic-mediated vasoconstriction.

Ligands

Agonists

- Cirazoline
- Etilefrine
- Metaraminol
- Methoxamine
- Midodrine
- Modafinil
- Naphazoline
- Oxymetazoline
- Phenylephrine (decongestant)
- Synephrine
- Tetrahydrozoline
- Xylometazoline

Antagonists

- Alfuzosin (used in benign prostatic hyperplasia
- Arotinolol
- Carvedilol (used in congestive heart failure; it is a non-selective beta blocker)
- Doxazosin (used in hypertension and benign prostatic hyperplasia)
- Indoramin
- Labetalol (used in hypertension; it is a mixed alpha/beta adrenergic antagonist)
- Moxisylyte
- Phenoxybenzamine
- Phentolamine (used in hypertensive emergencies; it is a nonselective alpha-antagonist)
- Prazosin (used in hypertension)
- Silodosin
- Tamsulosin (used in benign prostatic hyperplasia)
- Terazosin
- Tolazoline
- Trimazosin

Various heterocyclic antidepressants and antipsychotics are α_1-adrenergic receptor antagonists as well. This action is generally undesirable in such agents and mediates side effects like orthostatic hypotension.

Alpha-2 adrenergic receptor

The **alpha-2 (α_2) adrenergic receptor** (or adrenoceptor) is a G protein-coupled receptor (GPCR) associated with the G_i heterotrimeric G-protein. It consists of three highly homologous subtypes, including α_{2A}-, α_{2B}-, and α_{2C}-adrenergic. Some species other than humans express a fourth α_{2D}-adrenergic receptor as well. Catecholamines like norepinephrine (noradrenaline) and epinephrine (adrenaline) signal through the α_2-adrenergic receptor in the central and peripheral nervous systems.

Effects

The α_2-adrenergic receptor binds both norepinephrine released by sympathetic postganglionic fibers and epinephrine (adrenaline) released by the adrenal medulla, binding epinephrine with slightly higher affinity. It has several general functions in common with the α_1-adrenergic receptor, but also has specific effects of its own.

General

Common (or still unspecified) effects include:

- Vasodilation of arteries
- Vasoconstriction of arteries to heart (coronary artery) however the extent of this effect may be limited and may be negated by the vasodilatory effect from β_2 receptors
- Vasoconstriction of veins
- Decrease motility of smooth muscle in gastrointestinal tract
- Contraction of male genitalia during ejaculation

Individual

Individual actions of the α_2 receptor include:

- Mediates synaptic transmission in pre- and postsynaptic nerve terminals
    - Decrease release of acetylcholine
    - Decrease release of norepinephrine
        - Inhibit norepinephrine system in brain
- Inhibition of lipolysis in adipose tissue
- Inhibition of insulin release in pancreas
- Induction of glucagon release from pancreas
- platelet aggregation
- Contraction of sphincters of the gastrointestinal tract
- ↓ Secretion from salivary gland
- Relax gastrointestinal tract(presynaptic effect)
- Decreased aqueous humor fluid production from the ciliary body

Signaling cascade

The alpha subunit of an inhibitory G protein - G_i dissociated from the G protein, and associates with adenyl cyclase (also known as adenylate cyclase or adenylyl cyclase). This causes the inactivation of adenyl cyclase, resulting in a decrease of cAMP produced from ATP. This leads to a decrease of intracellular cAMP. Protein Kinase A is not able to be activated by cAMP, and so phosphorylase kinase cannot be phosphorylated by PKA. Phosphorylase kinase is responsible for the phosphorylation of proteins, and so there is a decrease in the levels of phosphorylated proteins, and the eventual cell response is decreased.

The relaxation of gastrointestinal tract motility is by presynaptic inhibition, where transmitters inhibit further release by homotropic effects.

Ligands

Agonists

- Apraclonidine
- Brimonidine
- Clonidine
- Detomidine
- Dexmedetomidine
- Guanabenz
- Guanfacine
- Lofexidine
- Medetomidine
- Romifidine
- Tizanidine
- Tolonidine
- Xylazine
- Fadolmidine
- Xylometazoline
- Oxymetazoline

Antagonists

- Atipamezole
- Cirazoline
- Efaroxan
- Idazoxan
- Mianserin
- Mirtazapine
- Napitane
- Phenoxybenzamine
- Phentolamine
- Rauwolscine
- Setiptiline
- Tolazoline
- Yohimbine

Agonists

Norepinephrine has higher affinity for the alpha-2 receptor than has epinephrine. Nonselective agonists include clonidine, an antihypertensive. Clonidine is an Alpha 2 Agonist used to reduce blood pressure. It was initially thought to act via presynaptic Alpha 2 receptors, reducing the amount of NE released. However, it binds to imidazoline receptors with a much greater affinity than Alpha 2 receptors. Imidazoline Receptors occur in the Nucleus Tractus Solitarii & Ventrolateral Medulla. Clonidine is now thought to decrease BP via this central mechanism. Other nonselective agonists include dexmedetomidine, lofexidine (another antihypertensive), TDIQ (partial agonist), tizanidine (in spasms, cramping), UK-14,304 and xylazine. Xylazine has veterinary use;

in non-human species this is an immobilizing and anesthetic drug, presumptively also mediated by alpha-2 adrenergic receptors because it is reversed by yohimbine.

α_{2A} selective agonists include guanfacine (an antihypertensive) and octopamine, which is also a β_3 agonist.

(R)-3-Nitrobiphenyline is an α_{2C} selective agonist.

Antagonists

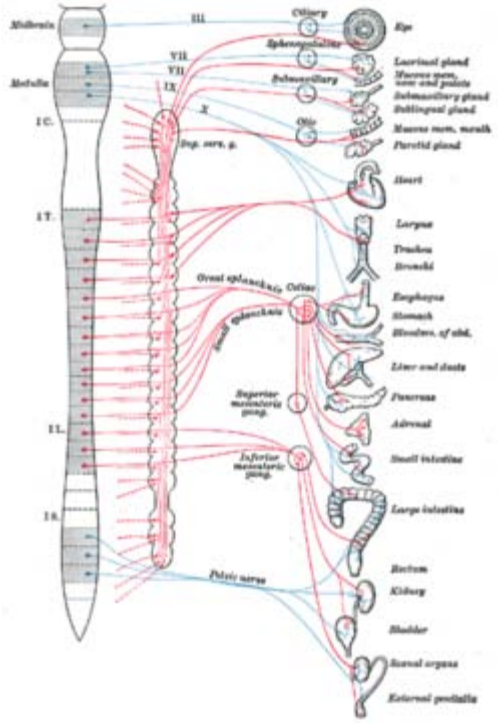
Nonselective alpha blockers include, A-80426, atipamezole, phenoxybenzamine, efaroxan, idazoxan*(experimental), mirtazapine (a tetracyclic antidepressant), mianserin (a tetracyclic antidepressant), SB-269,970 and yohimbine* (a purported aphrodisiac).

α_{2A} selective alpha blockers include BRL-44408 and RX-821,002, while α_{2B} selective alpha blockers include ARC-239 and imiloxan.

Chapter 15

Parasympathetic Nervous System

Brain: Parasympathetic nervous system



Autonomic nervous system innervation, showing the sympathetic and parasympathetic (craniosacral) systems, in red and blue, respectively

Latin *Pars parasympathica divisionis autonomici systematis nervosi*

The **parasympathetic nervous system** (**PSNS**) is one of the two main divisions of the autonomic nervous system (ANS). The ANS is responsible for regulation of internal organs and glands, which occurs unconsciously. The parasympathetic system specifically is responsible for stimulation of activities that occur when the body is at rest, including sexual arousal, salivation, lacrimation (tears), urination, digestion and defecation. Its

action is described as being complementary to that of one of the other main branches of the ANS, the sympathetic nervous system, which is responsible for stimulating activities associated with the fight-or-flight response. Because of this relationship, the action of the parasympathetic nervous system is often described as "rest and digest".

Relation to sympathetic nervous system

Sympathetic and parasympathetic divisions typically function in opposition to each other. This natural opposition is better understood as complementary in nature rather than antagonistic. For an analogy, one may think of the sympathetic division as the accelerator and the parasympathetic division as the brake. The sympathetic division typically functions in actions requiring quick responses. The parasympathetic division functions with actions that do not require immediate reaction. A useful acronym to summarize the functions of the parasympathetic nervous system is SLUDD (salivation, lacrimation, urination, digestion and defecation).

Physical location

The parasympathetic nerves (PSNS) are autonomic (aka "visceral") branches of the peripheral nervous system (PNS). Parasympathetic nerve fibers arise from the central nervous system with the S2, S3, and S4 spinal nerves and from the third, seventh, ninth, and tenth cranial nerves. Because of its location the parasympathetic system is commonly referred to as having "craniosacral outflow", which stands in contrast to the sympathetic nervous system which is said to have "thoracolumbar outflow".

The parasympathetic nerves that arise from the S2, S3, and S4 spinal nerves are commonly referred to as the pelvic splanchnic nerves or the "nervi erigentes".

Pathways

As is true in the sympathetic nervous system, efferent parasympathetic nerve signals are carried from the central nervous system to their targets by a system of two neurons. The first neuron in this pathway is referred to as the preganglionic or presynaptic neuron. Its cell body sits in the central nervous system and its axon usually extends to a ganglion somewhere else in the body where it synapses with the dendrites of the second neuron in the chain. This second neuron is referred to as the postganglionic or postsynaptic neuron.

The axons of presynaptic parasympathetic neurons are usually long: they extend from the CNS into a ganglion that is either very close to or embedded in their target organ. As a result, the postsynaptic parasympathetic nerve fibers are very short.

In the **cranium**, preganglionic PSN (CN III, CN VII, and CN IX) usually arise from specific nuclei in the Central Nervous System (CNS) and synapse at one of four parasympathetic ganglia: ciliary, pterygopalatine, otic, or submandibular. From these four ganglia the PSN complete their journey to target tissues via CN V (trigeminal) branches (ophthalmic nerve CN V_1, maxillary nerve CN V_2, mandibular nerve CN V_3).

The **vagus nerve** (CN X) does not participate in these cranial ganglia as most of its PSN fibers are destined for a broad array of ganglia on or near thoracic vicera (esophagus, trachea, heart, lungs) and abdominal viscera (stomach, pancreas, liver, kidneys). It travels all the way down to the midgut/hindgut junction, which occurs just before the splenic flexure of the transverse colon at a point called "cannon bohm".

The **pelvic splanchnic** efferent preganglionic nerve cell bodies reside in the lateral gray horn of the spinal cord at the S2-S4 spinal levels. Their axons continue away from the CNS to synapse at an autonomic ganglion. The PSN ganglion where these preganglionic neurons synapse will be close to the organ of innervation. This differs from the sympathetic nervous system, where synapses between pre- and post-ganglionic efferent nerves generally occur at ganglia that are farther away from the target organ.

Sensation

The afferent fibers of the autonomic nervous system, which transmit sensory information from the internal organs of the body back to the central nervous system, are not divided into parasympathetic and sympathetic fibers as the efferent fibers are. Instead, autonomic sensory information is conducted by general visceral afferent fibers.

General visceral afferent sensations are mostly unconscious visceral motor reflex sensations from hollow organs and glands that are transmitted to the CNS. While the unconscious reflex arcs normally are undetectable, in certain instances they may send pain sensations to the CNS masked as referred pain. If the peritoneal cavity becomes inflamed or if the bowel is suddenly distended your body will interpret the afferent pain stimulus as somatic in origin. This pain is usually non-localized. The pain is also usually referred to dermatomes that are at the same spinal nerve level as the visceral afferent synapse.

Cranial Nerve Parasympathetic Paths and Control

The oculomotor nerve is responsible for several parasympathetic functions related to the eye. The oculomotor PNS fibers originate in the Edinger-Westphal nucleus in the CNS and travel through the superior orbital fissure to synapse in the ciliary ganglion located just behind the orbit (eye). From the ciliary ganglion the postganglionic PSN fibers leave via short ciliary nerve fibers, a continuation of the nasociliary nerve (a branch of ophthalmic division of the trigeminal nerve, CN V_1). The short ciliary nerves innervate the orbit to control the ciliary muscle (responsible for accommodation) and the sphincter pupillae muscle which is responsible for miosis or constriction of the pupil (in response to light or accommodation).

The parasympathetic aspect of the facial nerve controls secretion of the sublingual and submandibular salivary glands, the lacrimal gland, and the glands associated with the nasal cavity. The preganglionic fibers originate within the CNS in the superior salivatory nucleus and leave as the intermediate nerve (which some consider a separate cranial nerve altogether) to connect with the facial nerve just distal (further out) to it surfacing

the CNS. Just after the facial nerve geniculate ganglion (general sensory ganglion) in the temporal bone, the facial nerve gives off two separate parasympathetic nerves. The first is the greater petrosal nerve and the second is the chorda tympani. The greater petrosal nerve travels through the middle ear and eventually combines with the deep petrosal nerve (sympathetic fibers) to form the nerve of the pterygoid canal. The PSN fibers of the nerve of the pterygoid canal synapse at the pterygopalatine ganglion, which is closely associated with the maxillary division of the trigeminal nerve (CN V_2). The postganglionic PSN fibers leave the pterygopalatine ganglion in several directions. One division leaves on the zygomatic division of CN V_2 and travels on a communicating branch to unite with the lacrimal nerve (branch of the ophthalmic nerve of CN V_1) before synapsing at the lacrimal gland. These PSN to the lacrimal gland control tear production.

A separate group of PSN leaving from the pterygopalatine ganglion are the descending palatine nerves (CN V_2 branch) which include the greater and lesser palatine nerves. The greater palatine PSN synapse on the hard palate and regulate mucus glands located there. The lesser palatine nerve synapses at the soft palate and controls sparse taste receptors and mucus glands. Yet another set of divisions from the pterygopalatine ganglion are the posterior, superior, and inferior lateral nasal nerves; and the nasopalatine nerves (all branches of CN V_2, maxillary division of the trigeminal nerve) that bring PSN to glands of the nasal mucosa. The second PSN branch that leaves the facial nerve is the chorda tympani. This nerve carries secretomotor fibers to the submandibular and sublingual glands. The chorda tympani travels through the middle ear and attaches to the lingual nerve (mandibular division of trigeminal, CN V_3). After joining the lingual nerve the preganglionic fibers synapse at the submandibular ganglion and send postganglionic fibers to the sublingual and submandibular salivary glands.

The glossopharyngeal nerve, CNIX, has parasympathetic fibers that innervate the parotid salivary gland. The preganglionic fibers depart CNIX as the tympanic nerve and continue to the middle ear where they make up a tympanic plexus on the cochlear promontory of the mesotympanum. The tympanic plexus of nerves rejoin and form the lesser petrosal nerve and exit through the foramen ovale to synapse at the otic ganglion. From the otic ganglion postganglionic parasympathetic fibers travel with the auriculotemporal nerve (mandibular branch of trigeminal, CN V_3) to the parotid salivary gland.

The vagus nerve, named from the Latin word *vagus* means literally "Wandering", since the nerve controls such a broad range of target tissues, has PSN that originate in the dorsal nucleus of the vagus nerve and the nucleus ambiguus in the CNS. The vagus nerve is an unusual cranial PSN in that it doesn't join the trigeminal nerve in order to get to its target tissues. Another peculiarity is that the vagus has an autonomic ganglion associated with it at approximately the level of C1 vertebra. The vagus gives no PSN to the cranium. The vagus nerve is hard to track definitively due to its ubiquitous nature in the thorax and abdomen so the major contributions will be discussed. Several PSN nerves come off the vagus nerve as it enters the thorax. One nerve is the recurrent laryngeal nerve, which becomes the inferior laryngeal nerve. From the left vagus nerve the recurrent laryngeal nerve hooks around the aorta to travel back up to the larynx and proximal esophagus while, from the right vagus nerve, the recurrent laryngeal nerve hooks around the right

subclavian artery to travel back up to the same location as its counterpart. These different paths are a direct result of embryological development of the circulatory system. Each recurrent laryngeal nerve supplies the trachea and the esophagus with parasympathetic secretomotor innervation for glands associated with them (and other fibers that are not PSN).

Another nerve that comes off the vagal nerves approximately at the level of entering the thorax are the cardiac nerves. These cardiac nerves go on to form cardiac and pulmonary plexuses around the heart and lungs. As the main vagus nerves continue into the thorax they become intimately linked with the esophagus and sympathetic nerves from the sympathetic trunks to form the esophageal plexus. This is very efficient as the major function of the vagus nerve from there on will be control of the gut smooth muscles and glands. As the esophageal plexus enter the abdomen through the esophageal hiatus anterior and posterior vagal trunks form. The vagal trunks then join with preaortic sympathetic ganglion around the aorta to disperse with the blood vessels and sympathetic nerves throughout the abdomen. The extent of the PSN in the abdomen include the pancreas, kidneys, liver, gall bladder, stomach and gut tube. The vagal contribution of PSN continues down the gut tube until the end of the midgut. The midgut ends 2/3 of the way across the transverse colon near the splenic flexure.

Pelvic Splanchnic Control

The pelvic splanchnic nerves, S2-4, work in tandem to innervate the pelvic viscera. Unlike in the cranium, where one PSN was in charge of one particular tissue or region, for the most part the pelvic splanchnics each contribute fibers to pelvic viscera by first traveling to one or more plexuses before being dispersed to the target tissue. These plexuses are composed of mixed autonomic nerve fibers (PSN and SN) and include the vesical, prostatic, rectal, uterovaginal and inferior hypogastric plexus. The preganglionic neurons in the neurons do not synapse in named ganglion as in the cranium but rather in the walls of the tissues or organs that they innervate. The fiber paths are variable and each individual's autonomic nervous system in the pelvis is unique. The visceral tissues in the pelvis that the PSN control include: urinary bladder, ureters, urinary sphincter, anal sphincter, uterus, prostate, glands, vagina and penis. Unconsciously, the PSN will cause peristaltic movements of the ureters helping to move urine from the kidneys into the bladder and move feces down the intestinal tract and upon necessity, the PSN will assist excreting urine from the bladder or defecation. Stimulation of the PSN will cause the detrusor muscle (urinary bladder wall) to contract and simultaneously relax the internal sphincter urethrae muscle to relax allowing void of urine. Also, PSN stimulation to the internal anal sphincter will relax this muscle and allow defecation. There are other skeletal muscles involved with these processes but the PSN play a huge role in continence.

Another role that the PSN play in the pelvis is in sexual activity. In males, the cavernous nerves from the prostatic plexus stimulate smooth muscle in the fibrous trabeculae of the coiled helicene arteries to relax and allow blood to fill the corpora cavernosum and the corpus spongiosum of the penis, making it rigid to prepare for sexual activity. Upon

emission of ejaculate, the sympathetics participate and cause peristalsis of the ductus deferens and closure of the internal urethral sphincter to prevent semen from entering the bladder. At the same time, parasympathetics cause peristalsis of the urethral muscle, and the pudendal nerve causes contraction of the bulbospongiosus (skeletal muscle is not via PSN), to forcibly emit the semen. During remission the penis becomes flaccid again. In the female, there is erectile tissue analogous to the male yet less substantial that plays a large role in sexual stimulation. The PSN cause release of secretions in the female that decrease friction. Also in the female, the parasympathetics innervate the fallopian tubes which helps peristaltic contractions and movement of the oocyte to the uterus for implantation. The secretions from the female genital tract aids in semen migration. The PSN (and SN to a lesser extent) play a huge role in reproduction.

Clinical Significance

The parasympathetic nervous system promotes digestion and the synthesis of glycogen, and allows for normal function and behavior.

Receptors

The parasympathetic nervous system uses chiefly acetylcholine (ACh) as its neurotransmitter, although other peptides (such as cholecystokinin) may act on the PSNS as a neurotransmitter. The ACh acts on two types of receptors, the muscarinic and nicotinic cholinergic receptors. Most transmissions occur in two stages: When stimulated, the preganglionic nerve releases ACh at the ganglion, which acts on nicotinic receptors of postganglionic neurons. The postganglionic nerve then releases ACh to stimulate the muscarinic receptors of the target organ.

Types of muscarinic receptors

The five main types of muscarinic receptors:

- The M1 muscarinic receptors (*CHRM1*) are located in the neural system.
- The M2 muscarinic receptors (*CHRM2*) are located in the heart, and act to bring the heart back to normal after the actions of the sympathetic nervous system: slowing down the heart rate, reducing contractile forces of the atrial cardiac muscle, and reducing conduction velocity of the sinoatrial node (SA node) and atrioventricular node (AV node). Note, they have a minimal effect on the contractile forces of the ventricular muscle due to sparse innervation of the ventricles from the parasympathetic nervous system.
- The M3 muscarinic receptors (*CHRM3*) are located at many places in the body, such as the endothelial cells of blood vessels, as well as the lungs causing bronchoconstriction. The net effect of uninnervated M3 receptors on blood vessels is vasodilation, as acetylcholine causes endothelial cells to produce nitric oxide, which diffuses to smooth muscle and results in vasodilation. They are also

in the smooth muscles of the gastrointestinal tract (GIT), which help in increasing intestinal motility and dilating sphincters. The M3 receptors are also located in many glands that help to stimulate secretion in salivary glands and other glands of the body. They are also located on the detrusor muscle of the bladder, causing contraction of the bladder.

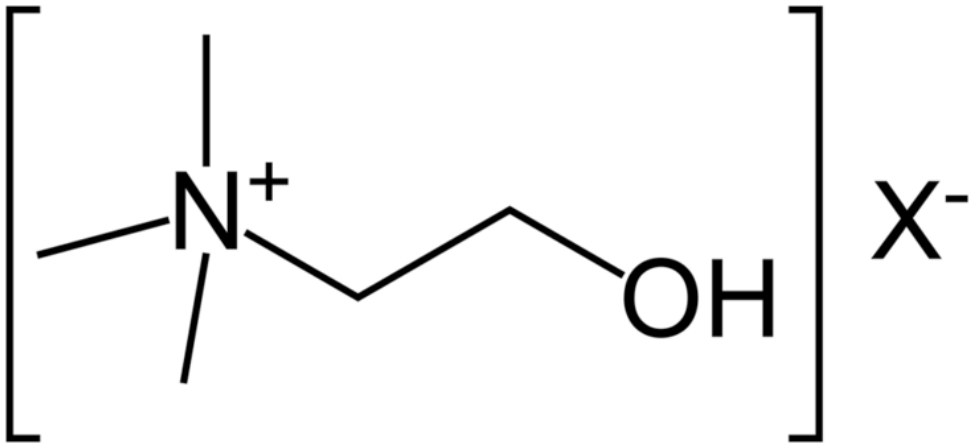
- The M4 muscarinic receptors: Postganglionic cholinergic nerves, possible CNS effects

- The M5 muscarinic receptors: Possible effects on the CNS

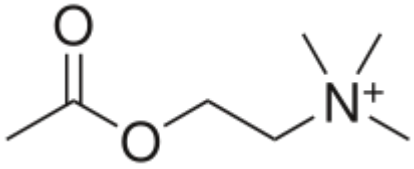
Chapter 16

Cholinergic and Ciliary Ganglion

Cholinergic



The *N*,*N*,*N*-trimethylethanolammonium cation, with an undefined counteranion, X^-



Acetylcholine

The word **choline** generally refers to the various quaternary ammonium salts containing the *N*,*N*,*N*-trimethylethanolammonium cation. Found in most animal tissues, choline is a primary component of acetylcholine, the neurotransmitter, and functions with inositol as a basic constituent of lecithin. It prevents fat deposits in the liver and facilitates the movement of fats into the cells. The richest sources of choline are liver, kidneys, brains, wheat germ, brewer's yeast, and egg yolk. Therefore, **cholinergic** often refers to the neurotransmitter acetylcholine, and is typically used in a neurological perspective. The

parasympathetic nervous system, which uses acetylcholine almost exclusively to send its messages, is said to be almost entirely cholinergic. Neuromuscular junctions, preganglionic neurons of the sympathetic nervous system, the basal forebrain, and brain stem complexes are also cholinergic. In addition, the receptor for the merocrine sweat glands are also cholinergic since acetylcholine is released from post ganglionic sympathetic neurons.

In neuroscience and related fields, the term cholinergic is used in the following related contexts:

- A substance (or ligand) is cholinergic if it is capable of producing, altering, or releasing acetylcholine ("indirect-acting") or mimicking its behaviour at one or more of the body's acetylcholine receptor types ("direct-acting").
- A receptor is cholinergic if it uses acetylcholine as its neurotransmitter.
- A synapse is cholinergic if it uses acetylcholine as its neurotransmitter.

Cholinergic drug

Structure Activity Relationship for Cholinergic Drugs

1. molecule must possess a Nitrogen atom capable of bearing a positive charge, preferably a quarternary ammonium salt.

2. for maximum potency, the size of the alkyl groups substituted on the Nitrogen should not exceed the size of a methyl group.

3. The molecule should have an oxygen atom, preferably an ester-like oxygen capable of participating in a hydrogen bond.

4. There should be a two-carbon unit between the oxygen atom and the nitrogen atom.

A cholinergic drug, also known as a cholinergic agent, cholinergic agonist, or a parasympathomimetic drug, is any drug that functions to enhance the effects mediated by acetylcholine in the central nervous system, the peripheral nervous system, or both. These include acetylcholine's precursors and cofactors, acetylcholine receptor agonists,acetylcholinesterase inhibitors and cholinergic enzymes:

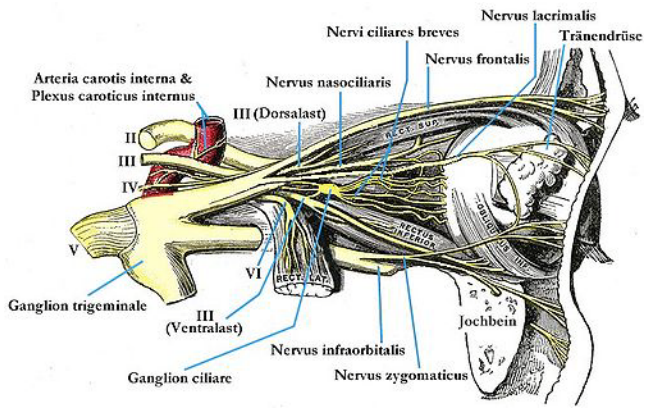
- Acetylcholine receptor agonists
  - Alvameline
  - Muscarine (muscarinic receptors)
  - Nicotine (nicotinic receptors)
  - Pilocarpine (M_3 receptors)
  - Suxamethonium (muscle type receptors)

- Acetylcholine receptor antagonists
  - Scopolamine
  - Dicycloverine
  - Tolterodine
  - Oxybutynin
  - Ipratropium
  - Mamba Toxin (MT_7)
  - Pirenzepine
  - Telenzepine

- Acetylcholinesterase inhibitors (abbreviated AChEIs)
  - Donepezil
  - Galantamine
  - Huperzine A
  - Neostigmine
  - Physostigmine
  - Rivastigmine

Ciliary ganglion

Nerve: Ciliary ganglion



Latin *ganglion ciliare*

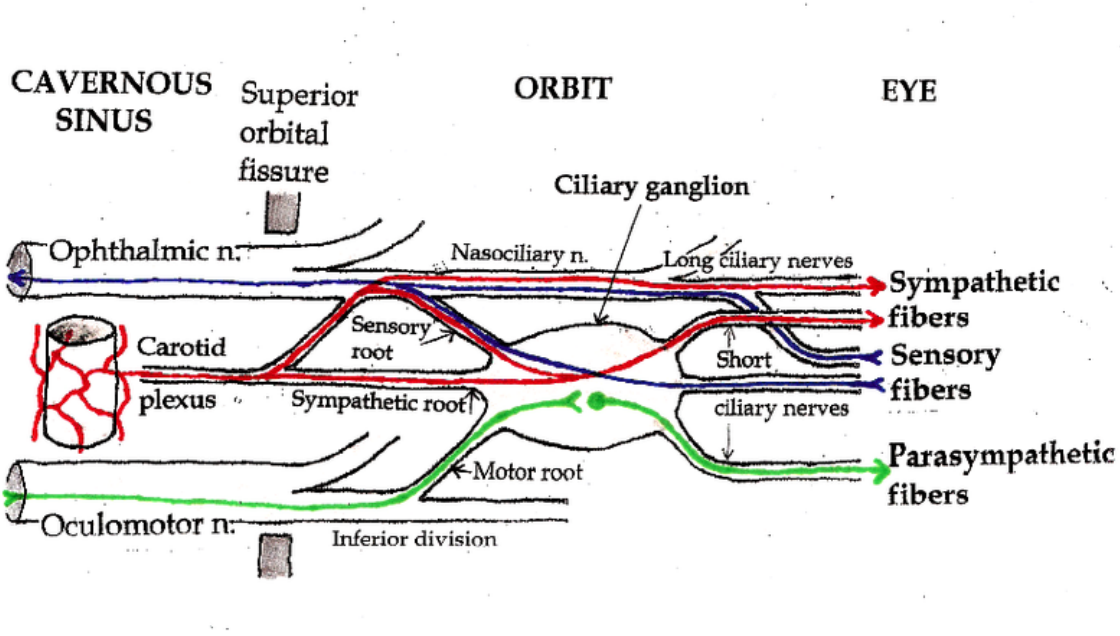
The **ciliary ganglion** is a **parasympathetic** ganglion located in the posterior orbit. It measures 1–2 millimeters in diameter and contains approximately 2,500 neurons. *Preganglionic* axons from the Edinger-Westphal nucleus form synapses with these cells. The *postganglionic* axons run in the short ciliary nerves and innervate two eye muscles:

- the **sphincter pupillae** constricts the pupil, a movement known as Miosis. The opposite, Mydriasis, is the dilation of the pupil.
- the **ciliaris** muscle contracts, releasing tension on the Zonular Fibers, making the lens more convex, also known as accommodation.

Both of these muscles are *involuntary* – they are controlled by the autonomic nervous system.

It is one of four parasympathetic ganglia of the head and neck. (The others are the submandibular ganglion, pterygopalatine ganglion, and otic ganglion).

Anatomy



Pathways in the Ciliary Ganglion. Green = parasympathetic; Red = sympathetic; Blue = sensory

Three types of nerve fibers run through the ciliary ganglion: *parasympathetic fibers*, *sympathetic fibers* and *sensory fibers*. Only parasympathetic fibers form synapses in the ganglion. The other two types of nerve fibers simply pass through. In classical anatomy, the ciliary ganglion is said to have three "roots:"

- a parasympathetic root of ciliary ganglion (or *motor root*)
- a sympathetic root of ciliary ganglion
- a sensory root of ciliary ganglion

Diseases

Adie tonic pupil

Diseases of the ciliary ganglion produce a **tonic pupil**. This is a pupil that does not react to light (it is "fixed") and has an abnormally slow and prolonged response to attempted near vision (accommodation).

When a patient with an Adie pupil attempts to focus on a nearby object, the pupil (which would normally constrict rapidly) constricts slowly. On close inspection, the constricted pupil is not perfectly round. When the patient focuses on a more distant object (say the far side of the room), the pupil (which would normally dilate immediately) remains constricted for several minutes, and then slowly dilates back to the expected size.

Tonic pupils are fairly common – they are seen in roughly 1 out of every 500 people. A patient with anisocoria (one pupil bigger than the other) whose pupil does not react to light (does not constrict when exposed to bright light) most likely has Adie syndrome – idiopathic degeneration of the ciliary ganglion.

Physiology

The strange behavior of tonic pupils was first explained by Irene Loewenfeld in 1979. The ciliary ganglion contain many more nerve fibers directed to the ciliary muscle than nerve fibers directed to the constrictor pupillae – roughly twenty times more. The ciliary muscle is also more massive than the constrictor pupillae, again by a factor of twenty. Based on these observations, Loewenfeld proposed an explanation of the tonic pupil. She noted that pathological destruction of nerve cells in the ciliary ganglion that is found in all cases of Adie pupil. In her own words :

Let's say that in a given fresh Adie's pupil, a random 70% of the cells in the ciliary ganglion stop working; and that, in a couple of months, these neurons re-grow and randomly re-innervate both intraocular sphincters (the ciliary muscle and the iris sphincter). Some parasympathetic light-reaction neurons that were originally destined for the iris sphincter will end up innervating the ciliary muscle. But there will not be enough of them to budge that big muscle, so there will be no detectable accommodation with exposure to light. The other way around, it is a different story. There will be plenty of accommodative neurons re-growing into the iris sphincter, and it won't take very many of them to make a little muscle like the iris sphincter contract. This means that every time the patient accommodates her gaze to a near object, some of the innervation to the ciliary muscle will spill over into the iris and constrict the pupil.

Loewenfeld's theory is now generally accepted. It explains the defining features of a **tonic pupil**:

(1) The pupil does not react to light. The original light-reaction neurons have been destroyed.

(2) Tonic constriction with attempted near vision. Aberrant regeneration of nerve fibers intended for the ciliary muscle causes abnormal, tonic contraction of the pupil with accommodation.
(3) Segmental iris constriction. When carefully examined under magnification, the iris does not constrict uniformly with attempted near vision. Only the re-innervated segments contract, producing a slightly irregular contour to the pupil.
(4) [Denervation supersensitivity]. Like any denervated muscle, the iris becomes supersensitive to its normal neurotransmitter (in this case, acetylcholine). Very weak solutions of cholinergic substances such as pilocarpine (that have no effect on the normal iris) cause the denervated iris to constrict.

Tonic pupils are usually due to *Adie syndrome*, but other diseases can denervate the ciliary ganglion. Peripheral neuropathies (such as diabetic neuropathy) occasionally produce tonic pupils. Herpes zoster virus can attack the ciliary ganglion. Trauma to the orbit can damage the short ciliary nerves. Anything that denervates the ciliary ganglion will produce a tonic pupil due to aberrant nerve regeneration.

Adie syndrome

Adie syndrome is tonic pupil plus absent deep tendon reflexes. Adie syndrome is a fairly common, benign, idiopathic neuropathy that selectively affects the ciliary ganglion and the spinal cord neurons involved in deep tendon reflex arcs. It usually develops in middle age, although it can occur in children. A variant of Adie syndrome, **Ross syndrome**, affects sweating as well.

Early in the course of Adie syndrome (when the cells of the ciliary ganglion have been destroyed, but before regeneration has occurred) the pupil will be fixed and dilated. The *sphincter pupillae* will be paralyzed. There will be no response to accommodation – the *ciliary muscle* is also paralyzed.

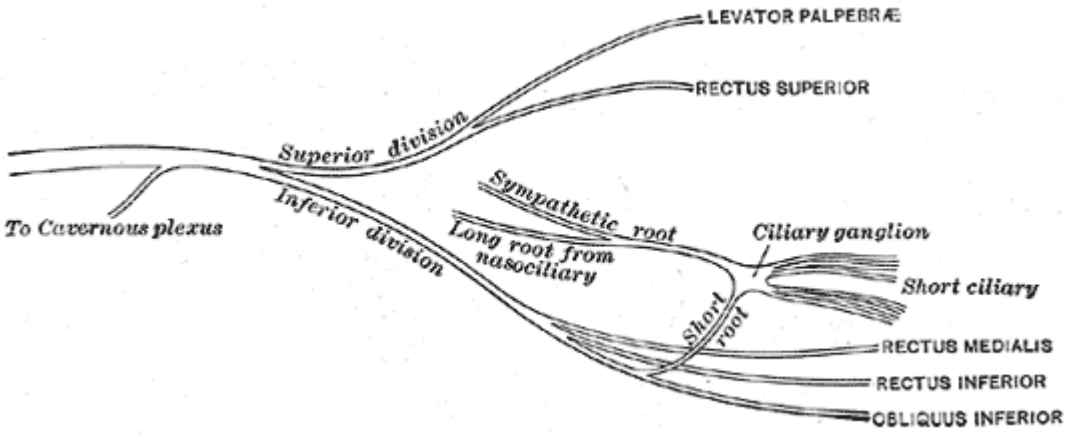
With aberrant nerve regeneration, the pupil will remain fixed, but it will constrict with attempted near vision. The constriction will be abnormal ("tonic").

Late in the course of Adie syndrome, the pupil becomes small (as all pupils do with old age). It will still be "fixed" (it will not constrict to bright light) and it will continue to show abnormal, tonic constriction with attempted near vision.

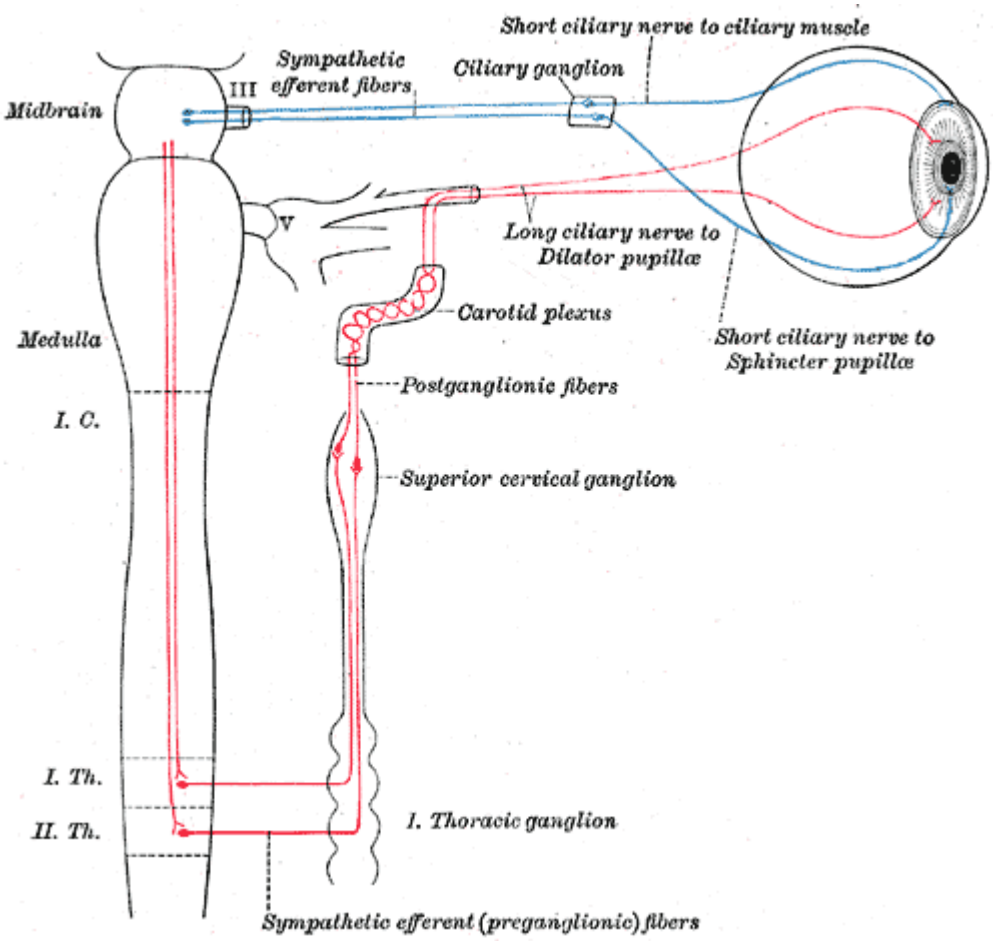
Light-near dissociation

The Adie pupil does not react to light, but it does react to accommodation. This is an example of **"light-near dissociation"**. All other causes of light-near dissociation involve the *brainstem*. They do *not* involve the ciliary ganglion, and they do *not* produce a tonic pupil. Irene Loewenfeld is generally credited for being the first physiologist to make this distinction.

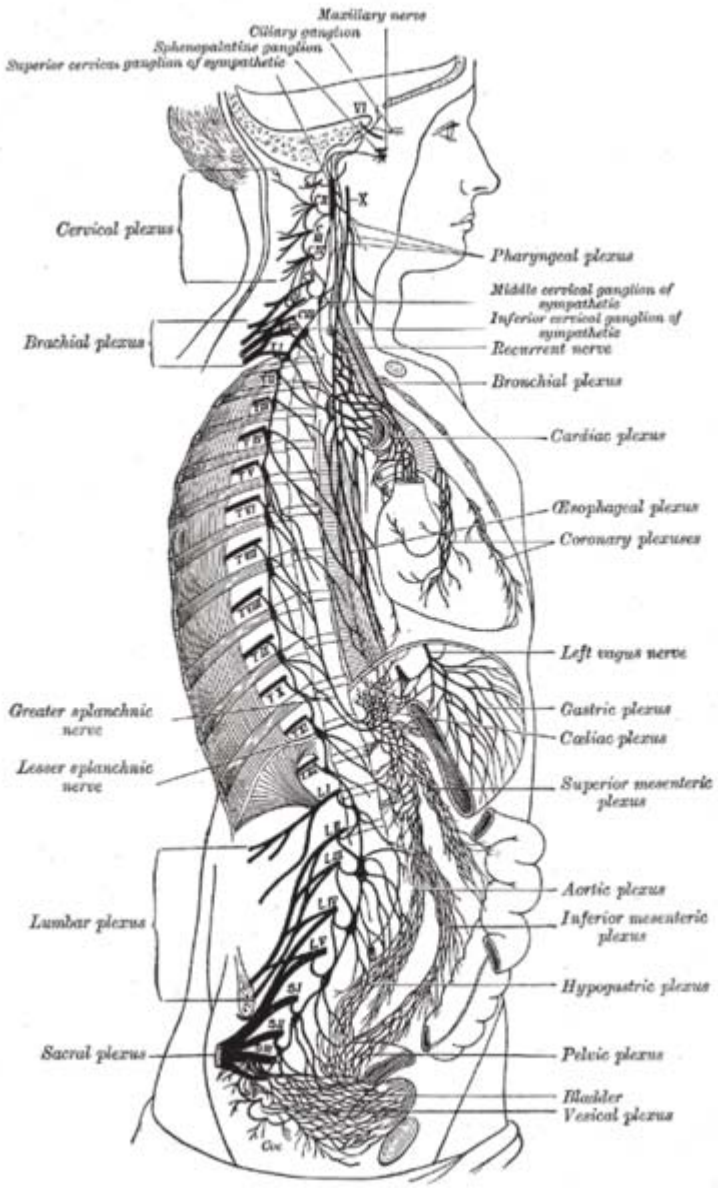
The *brainstem* causes of light-near dissociation include Argyll Robertson pupil and Parinaud syndrome.



Plan of oculomotor nerve



Sympathetic connections of the ciliary and superior cervical ganglia



The right sympathetic chain and its connections with the thoracic, abdominal and pelvic plexuses

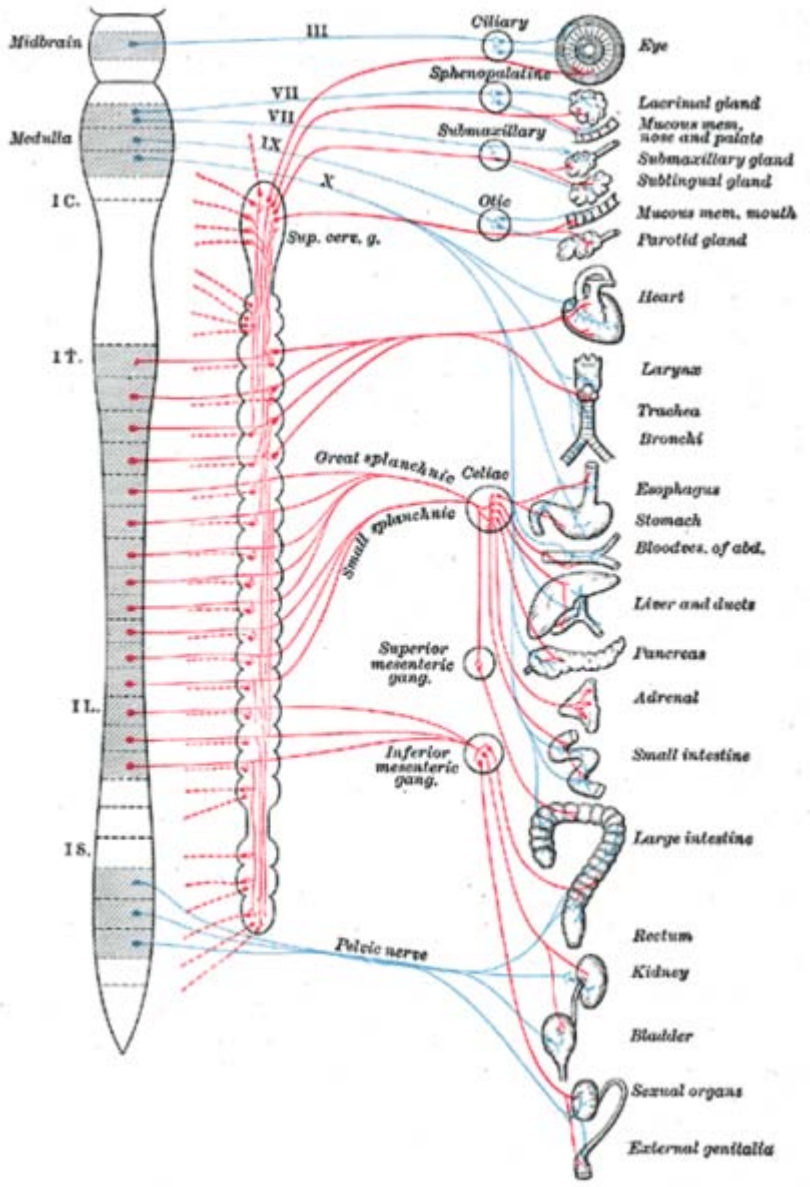


Diagram of efferent sympathetic nervous system