

Nerve Tissue

The human nervous system, by far the most complex system in the human body, is formed by a network of more than 100 million nerve cells (**neurons**), assisted by many more glial cells. Each neuron has, on average, at least 1000 interconnections with other neurons, forming a very complex system for communication.

Nerve tissue is distributed throughout the body as an integrated communications network. Anatomically, the nervous system is divided into the **central nervous system**, consisting of the brain and the spinal cord, and the **peripheral nervous system**, composed of nerve fibers and small aggregates of nerve cells called **nerve ganglia**.

Structurally, nerve tissue consists of two cell types: **nerve cells**, or **neurons**, which usually show numerous long processes, and several types of **glial cells**, which have short processes, support and protect neurons, and participate in neural activity, neural nutrition, and the defense processes of the central nervous system.

The nervous system generates two great classes of functions: stabilization of the intrinsic conditions (eg, blood pressure, O₂ and CO₂ content, pH, blood glucose levels, and hormone levels) of the organism within normal ranges and behavioral patterns (eg, feeding, reproduction, defense, interaction with other living creatures).

Neurons

Nerve cells, or neurons, are responsible for the reception, transmission, and processing of stimuli; the triggering of certain cell activities; and the release of neurotransmitters and other informational molecules. Most neurons consist of three parts 1- the **dendrites**, which are multiple elongated processes specialized in receiving stimuli from the environment, sensory epithelial cells, or other neurons; 2- the **cell body**, or **perikaryon**, which is the trophic center for the whole nerve cell and is also receptive to stimuli; and the 3- **axon**, which is a single process specialized in generating or conducting nerve impulses to other cells (nerve, muscle, and gland cells). Axons may also receive information from other neurons; this information mainly modifies the transmission of action potentials to other neurons. The distal portion of the axon is usually branched and constitutes the **terminal arborization**. Each branch of this arborization terminates on the next cell in dilatations called **end bulbs (boutons)**, which interact with other neurons or nonnerve cells, forming structures called **synapses**. Synapses transmit information to the next cell in the circuit.

Neurons and their processes are extremely variable in size and shape. Cell bodies can be spherical, ovoid, or angular; some are very large, measuring up to 150µm in diameter, large enough to be visible to the naked eye. Other nerve cells are among the smallest cells in the body; for example, the cell bodies of granule cells of the cerebellum are only 5 µm in diameter.

Based on the size and shape of their processes, most neurons can be placed in one of the following categories: **multipolar neurons**, which have more than two cell processes, one process being the axon and the others dendrites; **bipolar neurons**, with one dendrite and one axon; and **pseudounipolar neurons**, which have a single process that is close to the perikaryon and divides into two branches. The process then forms a T shape, with one branch extending to a peripheral ending and the other toward the central nervous system. In pseudounipolar neurons, stimuli that



are picked up by the dendrites travel directly to the axon terminal without passing through the perikaryon.

Most neurons of the body are multipolar. Bipolar neurons are found in the cochlear and vestibular ganglia as well as in the retina and the olfactory mucosa. Pseudounipolar neurons are found in the spinal ganglia (the sensory ganglia located in the dorsal roots of the spinal nerves). They are also found in most cranial ganglia.

Neurons can also be classified according to their functional roles. **Motor (efferent) neurons** control effector organs such as muscle fibers and exocrine and endocrine glands. **Sensory (afferent) neurons** are involved in the reception of sensory stimuli from the environment and from within the body. **Interneurons** establish relationships among other neurons, forming complex functional networks or circuits (as in the retina).

In the central nervous system, nerve cell bodies are present only in the gray matter. White matter contains neuronal processes but no nerve cell bodies. In the peripheral nervous system, cell bodies are found in ganglia and in some sensory regions (eg, olfactory mucosa).

Cell Body

The cell body, also called **perikaryon**, is the part of the neuron that contains the nucleus and surrounding cytoplasm, exclusive of the cell processes. It is primarily a trophic center, although it also has receptive capabilities. The perikaryon of most neurons receives a great number of nerve endings that convey excitatory or inhibitory stimuli generated in other nerve cells. Most nerve cells have a spherical, unusually large, euchromatic (pale-staining) nucleus with a prominent nucleolus. Binuclear nerve cells are seen in sympathetic and sensory ganglia. The chromatin is finely dispersed, reflecting the intense synthetic activity of these cells.

The cell body contains a highly developed rough endoplasmic reticulum organized into aggregates of parallel cisternae. In the cytoplasm between the cisternae are numerous polyribosomes, suggesting that these cells synthesize both structural proteins and proteins for transport. When appropriate stains are used, rough endoplasmic reticulum and free ribosomes appear under the light microscope as basophilic granular areas called **Nissl bodies**. The number of Nissl bodies varies according to neuronal type and functional state. They are particularly abundant in large nerve cells such as motor neurons. The **Golgi complex** is located only in the cell body and consists of multiple parallel arrays of smooth cisternae arranged around the periphery of the nucleus. Mitochondria are especially abundant in the axon terminals. They are scattered throughout the cytoplasm of the cell body. **Neurofilaments** (intermediate filaments with a diameter of 10 nm) are abundant in perikaryons and cell processes. Neurofilaments bundle together as a result of the action of certain fixatives. When impregnated with silver, they form **neurofibrils** that are visible with the light microscope. The neurons also contain microtubules that are identical to those found in many other cells. Nerve cells occasionally contain inclusions of pigments, such as **lipofuscin**, which is a residue of undigested material by lysosomes.



Dendrites

Dendrites (Gr. *dendron*, tree) are usually short and divide like the branches of a tree. They receive many synapses and are the principal signal reception and processing sites on neurons. Most nerve cells have numerous dendrites, which considerably increase the receptive area of the cell. The arborization of dendrites allows one neuron to receive and integrate a great number of axon terminals from other nerve cells. It has been estimated that up to 200,000 axonal terminations establish functional contact with the dendrites of a Purkinje cell of the cerebellum. That number may be even higher in other nerve cells. Bipolar neurons, with only one dendrite, are uncommon and are found only in special sites. Unlike axons, which maintain a constant diameter from one end to the other, dendrites become thinner as they subdivide into branches. The cytoplasmic composition of the dendrite base, close to the neuron body, is similar to that of the perikaryon but is devoid of Golgi complexes. Most synapses impinging on neurons are located in **dendrite spines**. Dendrite spines are the first processing locale for synaptic signals arriving on a neuron. The processing apparatus is contained in a complex of proteins attached to the cytosolic surface of the postsynaptic membrane, which is visible under the electron microscope and received the name postsynaptic membrane long before its function was disclosed. Dendritic spines participate in the plastic changes that underlie adaptation, learning, and memory. They are dynamic structures with a morphological plasticity based on the cytoskeletal protein actin, which is related to the development of the synapses and their functional adaptation in adults.

Axons

Most neurons have only one axon; a very few have no axon at all. An axon is a cylindrical process that varies in length and diameter according to the type of neuron. Although some neurons have short axons, axons are usually very long processes. For example, axons of the motor cells of the spinal cord that innervate the foot muscles may be up to 100 cm (about 40 inches) in length. All axons originate from a short pyramid-shaped region, the **axon hillock**, that usually arises from the perikaryon. The plasma membrane of the axon is called the **axolemma**; its contents are known as **axoplasm**.

In neurons that give rise to a myelinated axon, the portion of the axon between the axon hillock and the point at which myelination begins is called the **initial segment**. This is the site at which various excitatory and inhibitory stimuli impinging on the neuron are algebraically summed, resulting in the decision to propagate or not to propagate an action potential, or nerve impulse. It is known that several types of ion channels are localized in the initial segment and that these channels are important in generating the change in electrical potential that constitutes the action potential. **In contrast to dendrites**, axons have a constant diameter and do not branch profusely. Occasionally, the axon, shortly after its departure from the cell body, gives rise to a branch that returns to the area of the nerve cell body. All axon branches are known as **collateral branches**. Axonal cytoplasm (axoplasm) possesses mitochondria, microtubules, neurofilaments, and some cisternae of smooth endoplasmic reticulum. The absence of polyribosomes and rough endoplasmic reticulum emphasizes the dependence of the axon on the perikaryon for its maintenance. If an axon is severed, its peripheral parts degenerate and die. There is a lively bidirectional transport of small and large molecules along the axon. Macromolecules and organelles that are synthesized in the cell body are transported continuously by an **anterograde flow** along the axon to its terminals. Anterograde flow occurs at three distinct speeds. A slow stream (a few millimeters per day) transports proteins and actin filaments. A flow of intermediate speed transports mitochondria, and

a fast stream (100 times more rapid) transports the substances contained in vesicles that are needed at the axon terminal during neurotransmission.

Glial Cells & Neuronal Activity

Glial cells are 10 times more abundant in the mammalian brain than neurons; they surround both cell bodies and their axonal and dendritic processes that occupy the interneuronal spaces. Nerve tissue has only a very small amount of extracellular matrix, and glial cells

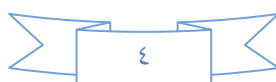
Glial Cell Type	Origin	Location	Main Functions
Oligodendrocyte	Neural tube	Central nervous system	Myelin production, electric insulation
Schwann cell	Neural tube	Peripheral nerves	Myelin production, electric insulation
Astrocyte	Neural tube	Central nervous system	Structural support, repair processes
			Blood brain barrier, metabolic exchanges
Ependymal cell	Neural tube	Central nervous system	Lining cavities of central nervous system
Microglia	Bone marrow	Central nervous system	Macrophagic activity

Oligodendrocytes

Oligodendrocytes (Gr. *oligos*, small, + *dendron* + *kytos*, cell) produce the myelin sheath that provides the electrical insulation of neurons in the central nervous system. These cells have processes that wrap around axons, producing a myelin sheath.

Schwann Cells

Schwann cells have the same function as oligodendrocytes but are located around axons in the peripheral nervous system. One Schwann cell forms myelin



around a segment of one axon, in contrast to the ability of oligodendrocytes to branch and serve more than one neuron and its processes.

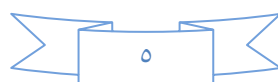
Astrocytes

Astrocytes (Gr. *astron*, star, + *kytos*) are star-shaped cells with multiple radiating processes. These cells have bundles of intermediate filaments made of **glial fibrillary acid protein** that reinforce their structure. Astrocytes bind neurons to capillaries and to the pia mater (a thin connective tissue that covers the central nervous system). Astrocytes with few long processes are called **fibrous astrocytes** and are located in the white matter; **protoplasmic astrocytes**, with many short-branched processes, are found in the gray matter. Astrocytes are by far the most numerous glial cells and exhibit an exceptional morphological and functional diversity.

In addition to their supporting function, astrocytes participate in controlling the ionic and chemical environment of neurons. Some astrocytes develop processes with expanded **end feet** that are linked to endothelial cells. It is believed that through the end feet, astrocytes transfer molecules and ions from the blood to the neurons. Expanded processes are also present at the external surface of the central nervous system, where they make a continuous layer. Furthermore, when the central nervous system is damaged, astrocytes proliferate to form cellular scar tissue. Astrocytes also play a role in regulating the numerous functions of the central nervous system. Astrocytes *in vitro* exhibit adrenergic receptors, amino acid receptors and peptide receptors (including natriuretic peptide, angiotensin II, endothelins, vasoactive intestinal peptide, and thyrotropin-releasing hormone). The presence of these and other receptors on astrocytes enables them to respond to several stimuli.

Astrocytes can influence neuronal survival and activity through their ability to regulate constituents of the extracellular environment, absorb local excess of neurotransmitters, and release metabolic and neuroactive molecules.

Finally, astrocytes are in direct communication with one another via gap junctions, forming a network through which information can flow from one point to another, reaching distant sites. For example, by means of gap junctions and the release of various cytokines, astrocytes can interact with oligodendrocytes to influence myelin turnover in both normal and abnormal conditions.



Ependymal Cells

Ependymal cells are low columnar epithelial cells lining the ventricles of the brain and central canal of the spinal cord. In some locations, ependymal cells are ciliated, which facilitates the movement of cerebrospinal fluid.

Microglia

Microglia (Gr. *micros*, small, + *glia*) are small elongated cells with short irregular processes. They can be recognized in routine hematoxylin and eosin (H&E) preparations by their dense elongated nuclei, which contrast with the spherical nuclei of other glial cells. Microglia, phagocytic cells that represent the mononuclear phagocytic system in nerve tissue, are derived from precursor cells in the bone marrow. They are involved with inflammation and repair in the adult central nervous system, and they produce and release neutral proteases and oxidative radicals. When activated, microglia retract their processes and assume the morphological characteristics of macrophages, becoming phagocytic and acting as antigen-presenting cells. Microglia secrete a number of immunoregulatory cytokines and dispose of unwanted cellular debris caused by central nervous system lesions.

Nerves

In the peripheral nervous system, the nerve fibers are grouped in bundles to form the nerves. Except for a few very thin nerves made up of unmyelinated fibers, nerves have a whitish, homogeneous, glistening appearance because of their myelin and collagen content.

Nerves have an external fibrous coat of dense connective tissue called **epineurium**, which also fills the space between the bundles of nerve fibers. Each bundle is surrounded by the **perineurium**, a sleeve formed by layers of flattened epitheliumlike cells. The cells of each layer of the perineurial sleeve are joined at their edges by tight junctions, an arrangement that makes the perineurium a barrier to the passage of most macromolecules and has the important function of protecting the nerve fibers from aggression. Within the perineurial sheath run the Schwann cell-sheathed axons and their enveloping connective tissue, the **endoneurium**. The endoneurium consists of a thin layer of reticular fibers, produced by Schwann cells. The nerves establish communication between brain and spinal cord centers and the sense organs and effectors (muscles, glands, etc). They possess afferent and efferent fibers to and from the central nervous system. **Afferent** fibers carry the information

obtained from the interior of the body and the environment to the central nervous system. **Efferent** fibers carry impulses from the central nervous system to the effector organs commanded by these centers. Nerves possessing only sensory fibers are called **sensory nerves**; those composed only of fibers carrying impulses to the effectors are called **motor nerves**. Most nerves have both sensory and motor fibers and are called **mixed nerves**; these nerves have both myelinated and unmyelinated axons.

Myelinated Fibers

In myelinated fibers of the peripheral nervous system, the plasmalemma of the covering Schwann cell winds and wraps around the axon. The layers of membranes of the sheath cell unite and form **myelin**, a whitish lipoprotein complex whose lipid component can be partly removed by standard histological procedures.

Myelin consists of many layers of modified cell membranes. These membranes have a higher proportion of lipids than do other cell membranes. The myelin sheath shows gaps along its path called the **nodes of Ranvier**; these represent the spaces between adjacent Schwann cells along the length of the axon. Interdigitating processes of Schwann cells partially cover the node. The distance between two nodes is called an **internode** and consists of one Schwann cell. The length of the internode varies between 1 and 2 mm.

There are no Schwann cells in the central nervous system; there, the processes of the oligodendrocytes form the myelin sheath. Oligodendrocytes differ from Schwann cells in that different branches of one cell can envelop segments of several axons.

Unmyelinated Fibers

In both the central and peripheral nervous systems, not all axons are sheathed in myelin. In the peripheral system, all unmyelinated axons are enveloped within simple clefts of the Schwann cells. Unlike their association with individual myelinated axons, each Schwann cell can sheathe many unmyelinated axons. Unmyelinated nerve fibers do not have nodes of Ranvier, because abutting Schwann cells are united to form a continuous sheath.

The central nervous system is rich in unmyelinated axons; unlike those in the peripheral system, these axons are not sheathed. In the brain and spinal cord, unmyelinated axonal processes run free among the other neuronal and glial processes.

