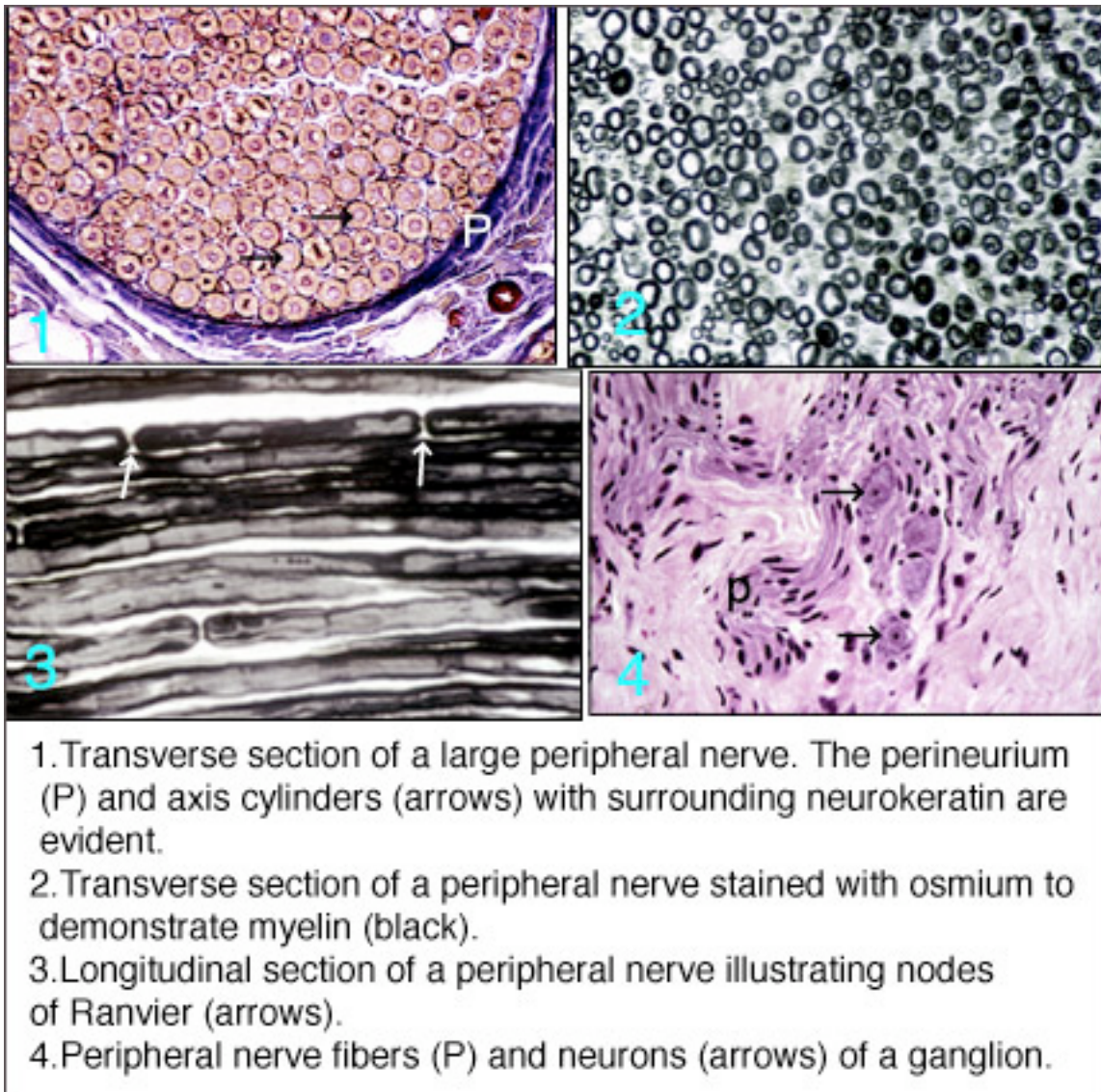


Nerve Tissue



1. Transverse section of a large peripheral nerve. The perineurium (P) and axis cylinders (arrows) with surrounding neurokeratin are evident.
2. Transverse section of a peripheral nerve stained with osmium to demonstrate myelin (black).
3. Longitudinal section of a peripheral nerve illustrating nodes of Ranvier (arrows).
4. Peripheral nerve fibers (P) and neurons (arrows) of a ganglion.

Nervous tissue, one of the four basic tissues, consists of nerve cells (neurons) and supporting cells (neuroglia). Nerve cells are highly specialized to react to stimuli and conduct the excitation from one region of the body to another. Thus, the nervous system is characterized by both irritability and conductivity, properties that are essential to the functions of nervous tissue - to provide communication and to coordinate body activities.

The nervous tissue of the brain and spinal cord makes up the central nervous system; all other nervous tissue constitutes the peripheral nervous system. Nervous tissue specialized to perceive an external stimulus is called a receptor, from which sensory stimuli are carried by the peripheral nervous system to the central nervous system, which acts as an integration and communications center. Other neurons, the effectors, conduct nerve impulses from the central nervous system to other tissues, where they elicit an effect.

The specialized contacts between neurons are called synapses; the impulses are transferred between nerve cells by electrical couplings or chemical transmitters. Some neurons of the brain secrete substances (hormones) directly into the bloodstream, and therefore, the brain

may be considered a neuroendocrine organ. Neurons also can stimulate or inhibit other neurons they contact.

Neurons

The nerve cell, or neuron, is the structural and functional unit of nervous tissue. Usually large and complex in shape, it consists of a cell body, the perikaryon, and several cytoplasmic processes. Dendrites are processes that conduct impulses to the perikaryon and usually are multiple. The single process that carries the impulse from the perikaryon is the axon.

The perikarya of different types of neurons vary markedly in size (4 to 140 μm) and shape and usually contain a large, central, spherical nucleus with a prominent nucleolus. The cytoplasm is rich in organelles and may contain a variety of inclusions. Bundles of neurofibrils form an anastomosing network around the nucleus and extend into the dendrites and axon. Neurofibrils must be stained selectively to be seen with the light microscope. Ultrastructurally, neurofibrils consist of aggregates of slender neurofilaments, 10 nm in diameter, and microtubules that, although called neurotubules, appear to be identical to microtubules found in other cells. Neurofilaments act as an internal scaffold for the perikaryon and its processes and function to maintain the shape of neurons. Specialized membrane proteins anchor the neurofilaments to the plasmalemma. The perikarya of most neurons contain characteristic chromophilic (Nissl) substance, which, when stained with dyes such as cresyl violet or toluidine blue, appears as basophilic masses within the cytoplasm of the perikaryon and dendrites. It is absent from the axon and axon hillock, the region of the perikaryon from which the axon originates. In electron micrographs, Nissl substance is seen to consist of several parallel cisternae of granular endoplasmic reticulum. Small slender or oval mitochondria are scattered throughout the cytoplasm of neurons and contain lamellar and tubular cristae. Well-developed Golgi complexes have a perinuclear position in the cell. Although centrioles are seen occasionally, neurons in the adult usually do not divide. Inclusions also may be found in the perikarya. Dark brown granules of melanin pigment occur in neurons from specific regions of the brain, such as the substantia nigra, locus ceruleus, and dorsal motor nucleus of the vagus nerve, and in spinal and sympathetic ganglia. More common inclusions are lipofuscin granules, which increase with age and are the by-products of normal lysosomal activity. Lysosomes are abundant in most neurons due to the high turnover of plasmalemma and other cellular components. The lipid droplets seen in many neurons represent storage material or may occur as the result of pathologic metabolism.

Nerve Processes

Nerve processes are cytoplasmic extensions of the perikaryon and occur as dendrites and axons. Each neuron usually has several dendrites that extend from the perikaryon, dividing repeatedly to form branch-like extensions. Although tremendously diverse in the number, size, and shape of dendrites, each variety of neuron has a similar branching pattern. The dendritic cytoplasm contains elongate mitochondria, Nissl substance, scattered neurofilaments, and parallel-running microtubules. The cell membrane of most dendrites forms numerous minute projections called dendritic spines or gemmules that serve as areas for synaptic contact between neurons; an important function of dendrites is to receive impulses from other neurons. Dendrites provide most of the surface area for receptive synaptic contact between neurons, although in some neurons the perikaryon and initial segment of the axon also may act as receptor areas. The number of synaptic points on the dendritic tree varies with the type of

neuron but may be in the hundreds of thousands. Dendrites play an important role in integrating the many incoming impulses.

A neuron has only one axon, which conducts impulses away from the parent neuron to other functionally related neurons or effector organs. The axon arises from the axon hillock, an elevation on the surface of the perikaryon that lacks Nissl substance. Occasionally, axons may arise from the base of a major dendrite. Axons usually are much longer and more slender than dendrites and may or may not give rise to side branches called collaterals, which, unlike dendritic branches, usually leave the parent axon at right angles. Axons also differ in that the diameter is constant throughout most of the length and the external surface generally is smooth. Axons end in several branches called telodendria, which vary in number and shape and may form a network or basket-like arrangement around postsynaptic neurons.

The cytoplasm of the axon, the axoplasm, contains numerous neurofilaments, neurotubules, elongate profiles of smooth endoplasmic reticulum, and long, slender mitochondria. Since axoplasm does not contain Nissl substance, protein synthesis does not occur in the axon. Protein metabolized by the axon during nerve transmission is replaced by that synthesized in cisternae of granular endoplasmic reticulum in the Nissl substance of the perikaryon. Neurotubules function to transport the new protein as well as other materials within the axon.

Antegrade transport involves movement of material from the perikaryon to axon terminals and may be slow or fast. Fast transport (410 mm/day) involves transfer of membranous organelles, neurosecretory vesicles, calcium, sugars, amino acids, and nucleotides: Slow transport (1-6 mm/day) includes movement of proteins, metabolic enzymes, and elements of the cytoskeleton. Fast antegrade transport is mediated by kinesin, a microtubule associated protein (MAP), which has ATPase activity. One end of the kinesin molecule attaches to a transport vesicle or organelle. The remaining end undergoes cyclic interaction with the microtubule wall, resulting in movement toward the axon terminal. Retrograde transport is the transfer of exhausted organelles, proteins, small molecules, and recycled membrane from the axonal endings to the perikaryon and provides a route by which some toxins (tetanus) and viruses (herpes, polio, rabies) can invade the central nervous system. Retrograde rapid transport occurs at a rate of about 310 mm/day and depends on another microtubule-associated protein called dynein, which also has ATPase activity. Dendritic transport also occurs but is less well understood. Axons transmit responses as electrical impulses called action potentials, which begin in the region of the axon hillock and the initial segment of the axon. An impulse behaves in an "all or none" fashion. Only when the threshold of activity is reached is the action potential transmitted along the axon to its terminations, which synapse with adjacent neurons or end on effector cells. An axon always induces a positive activity - for example, causing muscle cells to contract or stimulating epithelial cells to secrete. Impulses directed to another neuron may be excitatory or inhibitory.

Distribution of Neurons

The central nervous system is divided into gray matter and white matter, reflecting the concentration of perikarya. Gray matter contains the perikarya of neurons and their closely related processes, whereas white matter is composed chiefly of bundles or masses of axons and their surrounding sheaths. In the spinal cord, gray matter has a central location surrounded by white matter; in the cerebral and cerebellar cortices, gray matter is at the periphery and covers the white matter. Aggregates of perikarya occur within the gray matter of the central nervous system and act as distinct functional units called nuclei. Similar aggregates or individual neurons located outside the central nervous system are called ganglia.

Types of Neurons

Neurons may be divided into types according to their location, number of dendrites, and length and position of axons. In humans, most neurons lie within the gray matter of the central nervous system. Some neurons have numerous, well-developed dendrites and very long axons that leave the gray matter to enter the white matter of the central nervous system and ascend or descend in the major fiber tracts of the brain or spinal cord or leave the central nervous system and contribute to the formation of peripheral nerves. Neurons of this type conduct impulses over long distances and are called Golgi type I neurons. Other neurons whose axons are short and do not leave the region of the perikaryon are called Golgi type II neurons. These are especially numerous in the cerebellar and cerebral cortices and retina of the eye. They vary greatly in size and shape and have several branching dendrites. Golgi type II neurons primarily serve as association neurons - that is, they collect nerve impulses and disseminate them to surrounding neurons.

Individual neurons also can be classified by their number of dendrites. Unipolar neurons lack dendrites and have only a single process, the axon. Although common in the developing nervous system, they are rare in adults. Bipolar neurons have a single dendrite and an axon, usually located at opposite poles of the perikaryon. They are found in the retina, olfactory epithelium, and cochlear and vestibular ganglia. Neurons of all craniospinal ganglia originate as bipolar neurons in the embryo, but during development, the dendrite and axon migrate to a common site in the cell body, where they unite to form a single process. In the adult, this type of neuron is said to be pseudounipolar. The combined process, often called a dendraxon, may run for a short distance and then divide into two processes, one of which serves as a dendrite and receives stimuli from peripheral regions of the body and the other acts as an axon and enters the gray matter of the central nervous system to synapse with other neurons. Although the process directed toward the periphery acts as a dendrite, it is unusual because, morphologically, it resembles an axon. This functional dendrite is smooth and unbranched and usually receives nervous input from a receptor organ. Multipolar neurons are the most common type. They vary considerably in size and shape and are characterized by multiple dendrites. Internuncial and motor neurons are of this type. Of these, the internuncial neuron is the most numerous.

Ganglia

Ganglia are classified as cranial, spinal, and autonomic. Macroscopically, cranial and spinal ganglia appear as globular swellings on the sensory roots of their respective nerves. Each ganglion is enveloped by a connective tissue capsule and may contain perikarya of only a few neurons or as many as 55,000. A delicate network of collagenous and reticular fibers, accompanied by small blood vessels, extends between individual neurons and together with bundles of nerve processes often separates the perikarya into groups. Two distinct capsules surround the perikarya. The inner capsule is made up of a single layer of low cuboidal supporting cells called satellite cells. The outer capsule lies immediately outside the basal lamina of the satellite cells and consists of a delicate vascular connective tissue.

Cranial and spinal ganglia are sensory ganglia and contain pseudounipolar neurons. The perikarya appear spherical or pear-shaped and are 15 to 100 μm in diameter. They often show a large, central nucleus and a distinct nucleolus. The dendraxon of the pseudounipolar neuron may become convoluted to form a glomerulus. This nerve process then divides: One branch, a

functional dendrite, passes to a receptor organ; the other, a functional axon, passes into the central nervous system. The perikarya of these pseudounipolar neurons do not receive synapses from other neurons.

Autonomic ganglia consist of collections of perikarya of visceral efferent motor neurons and are located in swellings along the sympathetic chain or in the walls of organs supplied by the autonomic nervous system. They generally have a connective tissue capsule. The neurons usually are multipolar and assume various sizes and shapes. Perikarya range from 15 to 60 μm in diameter; the nucleus is large, round, and often eccentrically placed in the cell; and binucleate cells are not uncommon. Lipofuscin granules are more frequent in neurons of autonomic ganglia than in craniospinal ganglia. The ganglia of larger sympathetic chains are encapsulated by satellite cells, but a capsule may be absent around ganglia in the walls of the viscera. Unlike craniospinal ganglia, neurons of autonomic ganglia receive numerous synapses and are influenced by other neurons.

Nerve Fibers

A nerve fiber consists of an axon (axis cylinder) and a surrounding sheath of cells. Large nerve fibers are enclosed by a lipoprotein material called myelin; smaller nerve fibers may or may not be surrounded by myelin. Thus, nerve fibers may be classified as myelinated or unmyelinated. Axons of peripheral nerves are enclosed by a sheath of flattened cells called Schwann cells. These cells are thin, attenuated cells with flattened, elongate nuclei located near the center of the cells. Their cytoplasm contains a small Golgi complex, a few scattered profiles of granular endoplasmic reticulum, scattered mitochondria, microtubules, microfilaments, and at times, numerous lysosomes. A continuous external (basal) lamina covers successive Schwann cells and the axonal surfaces of the nodes. The integrity of the external lamina is vital to regenerating axons and Schwann cells after injury. Schwann cells invest nerve fibers from near their beginnings almost to their terminations. The resulting neurilemma (sheath of Schwann) is continuous with the capsule of satellite cells that surrounds the perikarya of neurons in craniospinal ganglia. Schwann cells produce and maintain the myelin on nerve fibers of the peripheral nervous system. The neurilemmal and myelin sheaths are interrupted by small gaps at regular intervals along the extent of the nerve fiber. These interruptions represent regions of discontinuity between individual Schwann cells and are called nodes of Ranvier. The neurilemmal and myelin sheaths are made up of a series of small individual segments, each of which consists of the region between two consecutive nodes of Ranvier and makes up one internode or internodal segment. An internode represents the area occupied by a single Schwann cell and its myelin and is about 1 to 2 mm in length. Myelin is not a secretory product of Schwann cells but a mass of lipoprotein and glycolipid that includes galactocerebroside, which is abundant in myelin. Myelin results from a successive layering of the Schwann cell plasmalemma as it wraps around the axon. The wraps of cell membrane that form myelin are tightly bound together by specialized proteins. Myelin may appear homogeneous, but after some methods of preparation, it may be represented by a network of residual protein called neurokeratin.

Ultrastructurally, myelin appears as a series of regular, repeating light and dark lines. The dark lines, called major dense lines, result from apposition of the inner surfaces of the Schwann cell plasmalemma. The cytoplasmic surfaces are united by a protein called myelin basic protein (MBP). Po protein is associated with myelin basic protein to form the major dense line. Po protein constitutes about 50% of the protein in peripheral nervous system myelin and aids in holding the myelin together. The less dense intraperiod lines represent the fusion of the outer

surfaces of the Schwann cell plasmalemma and lie between the repeating major dense lines. The outer surfaces of the Schwann cell plasmalemma are united by an adhesion molecule called proteolipid protein (PLP). Oblique discontinuities often are observed in the myelin of peripheral nerves and form the Schmidt-Lantermann incisures or clefts. The clefts represent local separations of the myelin lamellae.

Unmyelinated fibers (axons) also are surrounded by Schwann cells. In electron micrographs, 15 or more unmyelinated axons often are found in recesses in the plasmalemma of a single Schwann cell. The cell membrane of the Schwann cell closely surrounds each axon and is intimately associated with it. As the cell membrane of the Schwann cell encircles the axon, it courses back to come in contact with itself. This point of contact is called the mesaxon. In myelinated nerves, the primary infoldings of the Schwann cell membrane at the axon-myelin junction is called the internal mesaxon. The junction between the superficial lamellae of the myelin sheath and the Schwann cell plasmalemma is the external mesaxon.

The speed with which an impulse is transmitted along a nerve fiber is proportional to the diameter of the fiber. The diameter of heavily myelinated nerve fibers is much greater than that of unmyelinated fibers, and therefore, conduction is faster in myelinated fibers. Nerve fibers in peripheral nerves can be classified according to the diameter and speed of conduction. Type A nerve fibers are large, myelinated motor and sensory fibers, 3 to 20 μm in diameter that conduct impulses at 15 to 120 m/second. More finely myelinated fibers with diameters up to 3 μm that conduct impulses at 3 to 15 m/second are type B fibers. They represent many of the visceral sensory fibers. Type C fibers are small, unmyelinated nerve fibers that conduct impulses at 0.5 to 2.0 m/second.

The first event in development of an action potential along a nerve fiber is a sudden increase in permeability to sodium ion, resulting in depolarization of the axon and development of a negative charge along the axon surface. The local current created between the depolarized and resting surface membranes causes an increased permeability of the membrane to sodium ion. A cycle of membrane activation is established that results in the transmission of the depolarization process (a nerve impulse) along the nerve fiber. Once depolarization occurs, it will pass along the entire cell membrane of the axon. The nerve impulse lasts for only a short time, and repolarization is brought about by a sodium pump mechanism in the cell membrane of the axon. The generation of a nerve impulse is an "all or nothing" phenomenon. In the faster-conducting myelinated nerves, impulses travel from node to node; this method of impulse conduction is called saltatory conduction. The node of Ranvier is the only segment of the axon not invested by the myelin sheath and is exposed to the extracellular fluid. It is at this location that action potentials are generated due to a high concentration of ion channels. Because depolarization occurs only at the nodes of Ranvier, nerve impulses jump from node to node across the intervening internodal segment. The axon at each node is slightly thicker than that associated with internodal segments, and the plasmalemma of the node region contains most of the sodium voltage-gated channel proteins held in place at this location by the link protein ankyrin, which attaches them to the cytoskeleton. This explains, in part, the higher velocity of nerve transmission in myelinated nerve fibers.

Peripheral Nerves

Peripheral nerves consist of several nerve fibers united by surrounding connective tissue. They are mixed nerves consisting of sensory (afferent) and motor (efferent) nerve fibers that may be myelinated or unmyelinated. The sheath of connective tissue surrounding a peripheral nerve makes up the epineurium and unites several bundles of nerve fibers into a single unit, a

peripheral nerve. The epineurium consists of fibroblasts, longitudinally arranged collagen fibers, and scattered fat cells. Each bundle or fascicle of nerve fibers is enclosed by concentric layers of flattened, fibroblast-like cells that form a dense sheath called the perineurium. The perineurium is limited externally and internally by a basal lamina. Tight junctions occur between cells, and the tightly adherent cells form a perineurial compartment for individual fascicles. Delicate collagenous fibers, reticular fibers, fibroblasts, and macrophages lie between individual nerve fibers within each fascicle and constitute the endoneurium. Small blood vessels are found primarily in the epineurium, but in thicker regions of the endoneurium they may occur as delicate capillary networks. The perineurium and epineurium of peripheral nerves become continuous with the meninges of the central nervous system.

Peripheral Nerve Endings

Nerve endings increase the surface contact area between nervous and non-nervous structures and allow stimuli to be transmitted from nerve endings to muscles, causing them to contract, or to epithelial cells, causing them to secrete. When stimulated, dendrites at the periphery generate impulses that are transferred along the nerve fiber to sensory ganglia and ultimately to the central nervous system. Peripheral efferent (motor) nerve fibers can be divided into somatic and visceral efferent groups. Somatic efferent fibers end in skeletal muscle as small, oval expansions called motor end plates. The skeletal muscle cells supplied by a single motor neuron constitute a motor unit. Muscles with a large number of motor units can make more precise movements than those with fewer units for the same number of muscle cells. Visceral efferent nerve fibers stimulate smooth muscle, cardiac muscle, and glandular epithelium. Visceral motor endings of smooth muscle terminate as two or more swellings that pass between individual muscle cells. In cardiac muscle, numerous thin nerve fibers end near the surface of individual muscle cells but form no specialized contacts with them. Endings in glands are from unmyelinated nerves and form elaborate, delicate nets along the external surface of the basal lamina of the gland cells: fine branches penetrate the basal lamina and pass between individual epithelial cells.

Terminal peripheral nerve fibers that are excitable to stimuli are receptors and can transform chemical and physical stimuli into nerve impulses. Receptors vary in morphology, may be quite complex, and often are grouped into free (naked), diffuse, and encapsulated nerve endings.

Free (naked) nerve endings arise from myelinated and unmyelinated fibers of relatively small diameter. They are widely distributed and, although most numerous in the skin, are present in the connective tissue of visceral organs, in deep fascia, in muscles, and in mucous membranes. As myelinated fibers near their terminations, they lose their myelin and form unmyelinated terminal arborizations. Unmyelinated nerve fibers end in numerous fibrils that terminate as small, knob-like thickenings. Many naked nerve endings act as pain receptors. A diffuse type of naked receptor encircles the base of hair follicles to form peritrichal nerve endings that are sensitive to hair movement. In addition to the naked interepithelial nerve endings that terminate among epithelial cells, there are some endings that form concave neurofibrillar discs applied to a single modified epithelial cell of stratified squamous epithelium. These more specialized nerve endings are called the tactile discs of Merkel.

In encapsulated nerve endings, the terminals are enclosed in a capsule of connective tissue. They vary considerably in size, shape, location, and type of stimuli perceived. As the nerve fibers near their respective capsules, they generally lose their myelin and neurilemmal sheaths and enter the capsule as naked nerve endings.

Synapse

The site where impulses are transmitted from one neuron to another is called a synapse and may occur between axon and dendrite (axodendritic), axon and cell body (axosomatic), axon and axon (axoaxonic), dendrite and dendrite (dendrodendritic), dendrite and perikaryon (somatodendritic), or cell bodies of adjacent neurons (somatosomatic). The number of synapses associated with a single neuron varies according to the type of neuron. Small Golgi type II neurons (granule cells of the cerebellum) may have only a few synaptic points, whereas other neurons, such as Golgi type I (Purkinje cells of the cerebellum), may have several hundred thousand. Physiologically, excitatory and inhibitory synapses occur.

Synaptic endings of axons usually occur as small swellings at the tips of axon branches and are called terminal boutons. The axon may end in thin branches that surround the perikaryon or dendrites of another neuron; these endings are called calyces (basket endings). Synaptic contacts also may occur at intervals along the terminal segment of an axon, forming boutons en passage. Synaptic endings vary considerably in form from one type of neuron to another but generally show some common features. Each neuron is a distinct cellular unit, and there is no cytoplasmic continuity between cells. In some ways, synaptic points resemble desmosomes and may aid in maintaining contact between nerve cells. Ultrastructurally, the presynaptic area (terminal bouton) contains clusters of mitochondria and numerous membrane-bound vesicles with diameters of 40 to 60 nm. These synaptic vesicles contain neurotransmitter substances such as dopamine, norepinephrine, acetylcholine, serotonin, amino acids, and a number of peptides. Acetylcholine is the transmitter substance found most commonly in the electron-lucent synaptic vesicles of the central nervous system and motor end plates. Synaptic vesicles of most sympathetic postganglionic axons are characterized by electron-dense cores and contain catecholamines. The vesicles congregate near the presynaptic membrane, a slightly thickened area of the axon plasmalemma at the synaptic contact. Pre- and post-synaptic membranes are separated by a narrow space, 20 to 30 nm wide, called the synaptic cleft, which may contain fine filaments and glycosaminoglycans. The postsynaptic membrane shows increased electron density and is slightly thickened, and its internal surface is associated with a network of dense filamentous material called the subsynaptic web. The cytoplasm of the postsynaptic region lacks synaptic vesicles and shows fewer mitochondria than are found in the presynaptic area. The postsynaptic plasmalemma contains several special transmembrane proteins and receptors involved in neurotransmission. As an action potential reaches the presynaptic area of an axon, the synaptic vesicles fuse at sites along the presynaptic membrane and release transmitter substance into the synaptic cleft. The transmitter substance released interacts with receptors in the postsynaptic membrane, causing an immediate increase in the permeability of the post-neuronal cell membrane to sodium ion, thus changing the resting membrane potential. If the potential of the postsynaptic membrane rises above a certain level, the threshold of excitation, an action potential is transmitted by the postsynaptic neuron. The first parts of the postsynaptic neuron to initiate an action potential are the axon hillock and initial segment of the axon. The initial segment of an axon is a few microns long and lacks a myelin sheath. In most neurons, the cell membrane of this region has a lower threshold of excitation than does that of the perikaryon or dendrites. If transmitter substances decrease the permeability of the postsynaptic membrane, the threshold of excitation rises and the net effect is inhibitory. As a wave of depolarization reaches the presynaptic membrane, increased levels of calcium ion result, triggering a release by exocytosis of transmitter substance into the synaptic cleft. The transmitter released interacts with receptors within the postsynaptic membrane to elicit one of three possible effects (depolarization,

hyperpolarization, neuromodulation) in the target neuron. If the transmitter substance (acetylcholine, glutamate) binds to specific ion-channel receptor proteins, the ion-channel receptor proteins in the postsynaptic membrane open that allows entry of positively charged ions (sodium, potassium, calcium) resulting in depolarization and excitation of the target neuron. If, on the other hand, the transmitter substance released is gamma-amino butyric acid (GABA), or glycine, which binds to ion-channel receptor proteins that allow entry of negatively charged ions (primarily chloride ion) into the cell, and then hyperpolarization occurs, resulting in inhibition. In some instances transmitters (opioid proteins, dopamine, small neuropeptides, epinephrine, and norepinephrine) bind to G-protein-linked receptors and not intrinsic ion channels. These receptors stimulate second-messenger molecule systems that through a cascade of intracellular events modify the sensitivity or modulate the target neuron to depolarization.

Two groups of synaptic vesicle are thought to exist within the axon terminal: a small group that is released with the arrival of an action potential and a larger reserve group that is linked to the cytoskeleton by actin filaments. Synaptic vesicles of the reserve group move to a releasable group as needed. Synapsin I, a phosphoprotein associated with the cytoplasmic surface of synaptic vesicles, links actin to the vesicle surface, which results in the accumulation of reserve vesicles. Phosphorylation of synapsin I, due to the influx of calcium ion triggered by the action potential, disassociates this link, allowing these vesicles to join the releasable group. An additional phosphoprotein, synapsin II, is thought to mediate the interaction of synaptic vesicles with the cytoskeleton. At rest a calcium-sensitive trigger protein (synaptotagmin) blocks membrane fusion and exocytosis. When an action potential reaches the terminal bouton, voltage-gated calcium ion channels open. The subsequent increase in calcium ion concentration releases a trigger protein, allowing membrane fusion and exocytosis to occur. The membrane of the synaptic vesicle contains synaptobrevin an anchoring protein that unites the vesicle to docking proteins in the presynaptic membrane. The presynaptic membrane contains proteins that promote membrane fusion with the synaptic vesicle and allows exocytosis to occur. Following vesicle fusion with the presynaptic membrane and release of transmitter, equal amounts of cell membrane are taken up by the formation of clathrin-coated vesicles via endocytosis. These vesicles may fuse with cisternae of endoplasmic reticulum containing transmitter substances. New vesicles form by budding from these cisternae to return to the pool of reserve synaptic vesicles.

Acetylcholine released from the axon terminal is rapidly hydrolyzed by acetylcholine esterase into acetate and choline in the synaptic cleft. Choline is then transported back through the presynaptic membrane by a choline transporter, converted to acetylcholine by the enzyme choline acetyltransferase, and repackaged into newly formed synaptic vesicles. Inhibitory transmitters such as GABA, on the other hand, are taken up by specific GABA transporters located in the plasma membrane of surrounding astrocyte processes. In the astrocyte cytoplasm GABA is broken down to glutamine, which reenters the nerve terminal. Here, glutamine is enzymatically converted back into GABA and packaged into synaptic vesicles.

Neuropeptides, unlike many of the other transmitters, must be synthesized in the perikaryon and transported to the axon terminal. Electrical coupling is another means of transferring impulses in some types of synapses and occurs at gap junctions. Gap junctions act as ion channels.

Neuroglia

Neurons form a relatively small proportion of the cells in the central nervous system. Most of the cells are non-neuronal supporting cells called neuroglia.

Depending on the location in the central nervous system, neuroglia may outnumber neurons by as much as 50:1. Together, neuroglia account for about 50% of the weight of the brain and outnumber neurons about ten to one. It is estimated that about 1,000 billion glia occur in the CNS as compared to about 100 billion neurons. Neuroglia generally are smaller than neurons and in light microscopic preparations can be identified by their small, round nuclei, which are scattered among neurons and their processes. Neuroglia includes ependymal cells, astrocytes, oligodendrocytes, and microglia. Astrocytes and oligodendrocytes often are collectively referred to as macroglia.

Morphologically, astrocytes are divided into protoplasmic and fibrous types. Protoplasmic astrocytes are found mainly in the gray matter and are characterized by numerous, thick-branched processes. Fibrous astrocytes occur mainly in white matter and are distinguished by long, thin, generally unbranched processes. The two forms of astrocyte may represent a single type that varies in morphology according to its location and metabolic state. In electron micrographs, astrocytes usually show an electron-lucent, largely organelle-free cytoplasm and euchromatic nuclei. The cytoplasm of the cell body and its processes contains bundles of intermediate filaments called glial filaments, consisting of glial fibrillary acid protein (GFAP). These filaments are particularly abundant in protoplasmic astrocytes. Astrocytes provide a framework of support for the neurons and contribute to their nutrition and metabolic activity. The astrocyte processes vary considerably in appearance. Some are thick and long; others are thin and sheetlike. The processes often expand to form end feet (foot processes) that are aligned along the internal surface of the pia mater and around the walls of blood vessels. The largest concentration of end feet occurs beneath the pial surface, where they surround the brain and spinal cord to form a membrane-like structure called the glia limitans. Smaller neuroglial cells with fewer processes and more deeply stained nuclei are oligodendrocytes, of which there are two types. Interfascicular oligodendrocytes occur mainly in the fiber tracts that form the white matter of the brain and spinal cord. Perineuronal satellite oligodendrocytes are restricted to the gray matter and are closely associated with the cell bodies of neurons. The cytoplasm of both types of oligodendrocytes contains free ribosomes, short cisternae of granular endoplasmic reticulum, an extensive Golgi complex, and numerous mitochondria. Large numbers of microtubules form parallel arrays that run throughout the cytoplasm of the cell body and into its processes.

Schwann cells are not present in the central nervous system; oligodendrocytes serve as the myelin-forming cells for this region. Myelinated nerve fibers of the central nervous system have nodes of Ranvier, but unlike peripheral myelinated fibers, they do not show incisures. Nodes in the central nervous system are bare, while those of the peripheral nervous system are partly covered by extensions of cytoplasm from adjacent Schwann cells into the paranodal area. The myelin sheath begins just beyond the initial segment of the axon, a few microns from the axon hillock, and ensheathes the rest of the axon to near its end. Each internodal segment of a nerve fiber in the central nervous system is formed by a single cytoplasmic process from a nearby oligodendrocyte, which wraps around the axon. Unlike Schwann cells of the peripheral nervous system, a single oligodendrocyte provides the internodal segments of the myelin sheath for several separate, but adjacent axons.

In some regions, as in the optic nerve, a single oligodendrocyte may be responsible for the internodal segments on 40 to 50 axons. In the CNS, like the PNS, special adhesion molecules

(proteolipid protein) link the external surfaces of oligodendrocyte plasmalemma together. The cytoplasmic surfaces of the plasmalemma are united by myelin basic protein.

Because perineuronal satellite oligodendrocytes lie close to the perikarya of neurons, it has been proposed that oligodendrocytes influence the metabolism and nutrition of neurons. In addition, glia appear to be involved in calcium homeostasis and in the recycling of certain types of neurotransmitters.

In the central nervous system, perineuronal satellite and interfascicular oligodendrocytes have the same relationship to perikarya and their axons as that which exists between satellite cells and Schwann cells of peripheral nerve fibers. Schwann cells and satellite cells could be considered as neuroglial elements of the peripheral nervous system.

Small cells called microglia also are present in the central nervous system. Microglia have extensive ramifying processes, a characteristic phenotype that suggests they may be dendritic antigen-presenting cells. They also express class II MHC molecules. In areas of damage or disease, they are thought to proliferate and become phagocytic and are supplemented by monocytes from the blood that transform into additional macrophages. As material is phagocytosed, the cells enlarge and then are called Gitterzellen, or compound granular corpuscles. Monocytes appear to be the precursors of microglial cells, which thus are part of the mononuclear system of phagocytes with ultimate derivation from the bone marrow.

Motor Nerve Endings

Each skeletal muscle is supplied by one or more nerves that contain both motor and sensory fibers. A motor neuron and the muscle fibers supplied by it make up a motor unit. The size of the motor unit is determined by the number of muscle fibers served by a single nerve fiber and varies between muscles. Small motor units occur where precise control of muscle activity is required; large units are found in muscles used for coarser activities. In the extraocular muscles of the eye, every muscle fiber is supplied by a nerve (forming small motor units), whereas in the major muscles of the limb, a single nerve fiber may supply 1,500 to 2,000 muscle fibers - a large motor unit. All the muscle fibers contained in one motor unit appear to be of the same histochemical type; thus, there are type I and type II motor units. Branches of a motor nerve end on the muscle fiber at a specialized region called the motor end plate or myoneural junction. The junction appears as a slightly elevated plaque on the muscle fiber associated with an accumulation of nuclei. As the nerve approaches the end-plate it loses its myelin sheath and ends in a number of bulbous expansions, the outer surfaces of which are covered by a continuation of the Schwann's cells. The nerve endings lie in shallow recesses, the synaptic troughs (primary synaptic clefts), on the surface of the muscle fiber. The sarcolemma that lines these clefts invaginates to form numerous secondary synaptic clefts or junctional folds. Although the nerve and muscle fibers are intimately related at the junctions, their cell membranes remain separated by a glycoprotein layer derived from fusion of the external laminae of the muscle fiber, nerve fiber, and Schwann's cells. This layer extends along the primary synaptic cleft and dips into each secondary cleft. Numerous large, vesicular nuclei and abundant mitochondria, ribosomes, and granular endoplasmic reticulum are present in the sarcoplasm that underlies the nerve terminal. The nerve terminals contain many mitochondria and a large number of synaptic vesicles that contain acetylcholine, a neurotransmitter agent. A nerve impulse results in depolarization of the axon terminal, which permits an influx of calcium ions. This event triggers the release of acetylcholine into the synaptic cleft. The synaptic vesicles release acetylcholine by exocytosis at specific sites in the presynaptic membrane called active zones. Acetylcholine receptors (nicotinic acetylcholine receptors) are present in

the sarcolemma on the outer edges of the secondary clefts, while acetylcholinesterase is located along the inner surface deep within the secondary clefts and in the external lamina of this area. The acetylcholine receptors contain ion channels made up of a complex of five similar subunits which when bound to acetylcholine undergo a conformational change opening the channel and permitting the entry of sodium ions. This influx results in a depolarization of the sarcolemma, and the action potential created travels over the sarcolemma to the T-tubule system and initiates contraction. This postsynaptic receptor site can be blocked or interfered with by a variety of factors. For example, curare (a plant toxin) can selectively bind to the nicotinic acetylcholine receptor proteins within the postsynaptic muscle plasmalemma effectively blocking and preventing muscle contraction. An autoimmune disease such as myasthenia gravis is characterized by circulating antibodies that develop against the nicotinic acetylcholine receptor proteins and interfere with normal muscle activity.

Sensory Nerve Endings

Skeletal muscle contains many sensory endings, some of which are simple spiral terminations of nonmyelinated nerves that wrap about the muscle fibers and others that are highly organized structures called muscle spindles or neuromuscular spindles. Each muscle spindle consists of an elongated, ovoid connective tissue capsule that encloses a few thin, modified skeletal muscle fibers associated with sensory and motor nerves. The modified muscle fibers traverse the capsule from end to end and form the intrafusal fibers to distinguish them from the ordinary muscle fibers (extrafusal fibers) outside the capsule. Two distinct types of intrafusal fibers are present. Both are striated over most of their lengths, but midway along the fibers the striations are replaced by aggregates of nuclei. One type of intrafusal fiber is larger, and its nonstriated region is occupied by a cluster of nuclei that produces a slight expansion of the fibers in this region; these form the nuclear bag fibers. The second type of fiber is thinner, and the nuclei in the central region form a single row, hence their name, nuclear chain fiber. Nuclear bag fibers extend beyond the capsule to attach to the endomysium of nearby extrafusal fibers. Nuclear chain fibers are the more numerous and shorter. They attach to the capsule at the poles of the spindle or to the sheaths of nuclear bag fibers. Since the central areas of the intrafusal fibers lack myofibrils, these regions are noncontractile.

Each spindle receives a single, thick sensory nerve fiber that gives off several nonmyelinated branches that end in a complex system of rings and spirals at the central regions of the intrafusal fibers. These annulospiral endings run beneath the external lamina in grooves in the sarcolemma. Flower spray endings are cluster- or spray-like terminations of smaller sensory nerves that occur mainly on nuclear chain fibers. Intrafusal fibers also receive small motor nerve fibers that end either as motor end plates or as long, diffuse trail endings that ramify over the intrafusal fibers, making several contacts with them.

Muscle spindles serve as stretch receptors and are found mainly in slow-contracting extensor muscles involved in maintaining posture. They are present also in muscles used for fine movements. Stimulation by motor nerves maintains tension on the intrafusal fibers, resulting in a stretching of their nonstriated segments. The degree of stretch is sufficient to maintain the sensory nerve endings in this region in a state of excitation that is close to their thresholds. When a whole muscle is stretched, it causes increased tension on the intrafusal fibers and stretching of their nonstriated regions, resulting in the discharge of impulses by the sensory nerve. When the muscle contracts, tension on the spindle is reduced and sensory nerve endings cease firing. The frequency of the discharges by the nerve endings is proportional to

the tension on the intrafusal fibers; together with the number of active spindles, a degree of muscle contraction appropriate to the stimulus is ensured.

Tendon organs are encapsulated sensory receptors found at tendon-muscle junctions. The organ consists of a capsule of dense irregular connective tissue traversed by specialized collagen bundles that are continuous with collagen fibers outside the capsule. A single large sensory nerve pierces the capsule and gives rise to several nonmyelinated branches whose terminations entwine among the collagen bundles. The tendon organ senses stresses produced by muscle contractions, preventing them from becoming excessive.

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