Chapter 2
Neurocytology: Cells of the CNS

Abstract There are two major cell types that form the nervous system: supporting cells and conducting cells. The supporting cells of the peripheral nervous system consist of Schwann cells, fibroblasts, and satellite cells, while the supporting cells in the CNS consist of the glia; the lining cells of the ventricles, the ependymal; the meningeal coverings of the brain; the circulating blood cells; and the endothelial lining cells of the blood vessels. The conducting cells, or neurons, form the circuitry within the brain and spinal cord, and their axons can be as short as a few microns or as long as 1 m. The supporting cells are constantly being replaced, but the majority of conducting cells/neurons, once formed, remain throughout our life.

Keywords Neuron • Dendrites • Soma • Synapse • Dendritic spines • Astrocyte • Oligodendrocyte • Blood–brain barrier • Transport

2.1 The Neuron

The basic functional unit of the nervous system is the *neuron*. The neuron doctrine (postulated by Waldeyer in 1891) described the neuron as having one axon, which is efferent, and one or more dendrites, which are afferent. It was also noted that nerve cells are contiguous, not continuous, and all other elements of the nervous system are there to feed, protect, and support the neurons. Neurons consist of a cell body, dendrites, and axon that terminate as a synapse. The axon is usually covered by the insulator myelin (Table 2.1).

Although muscle cells can also conduct electric impulses, only neurons, when arranged in networks and provided with adequate informational input, can respond in many ways to a stimulus. Probably the neuron's most important feature is that each is unique. If one is damaged or destroyed, no other nerve cell can provide a precise or complete replacement. Fortunately, the nervous system was designed with considerable redundancy; consequently, it takes a significant injury to incapacitate the individual (*as in Alzheimer's or Parkinson's disease*).

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Table 2.1 Parts of a neuron

Region	Contents
Soma majority of inhibitory synapses are found on its surface	The neuron's trophic center, containing the nucleus, nucleolus, and many organelles
Dendrite	Continuation of the soma, has many branches forming large surface area, contains neurotubules and majority of synapses on its surface Type I neurons have dendritic spines
Axon myelin: an insulator, covers axon	Conducts action potentials to other neurons via the synapse. Length: few millimeters to a meter
Synapse	Site where an axon connects to the dendrites, soma, or axon of another neuron Consists of perisynaptic part containing neurotransmitters, postsynaptic portion with membrane receptors separated by a narrow cleft

2.1.1 Dendrites

The dendritic zone receives input from many different sources (Fig. 2.1). The action potential originates at the site of origin of the axon and is transmitted down the axon in an all-or-nothing fashion to the synapse, where the impulse is transmitted to the dendritic zone of the next neuron on the chain.

Dendrites have numerous processes that increase the neuron's receptive area. The majority of synapses on a nerve cell are located on the dendrite surface. With the electron microscope, the largest dendrites can be identified by the presence of parallel rows of neurotubules, which provide highways for the transport of the action potential. The dendrites in many neurons are also studded with small membrane extensions, the dendritic spines.

2.1.2 Soma

The soma (perikaryon or cell body) of the neuron varies greatly in form and size. Unipolar cells have circular cell bodies; bipolar cells have ovoid cell bodies; multipolar cells have polygonal cell bodies. The soma is the trophic center for each neuron.

2.1.3 Golgi Type I and II Neurons

Neurons can also be grouped by axon length: Those with long axons are called Golgi type I (or pyramidal) cells; those with short axons are called Golgi type II (or satellite) cells (Gray 1959). The Golgi type I cell (Fig. 2.2) has an apical and basal dendrite, each of which has secondary, tertiary, and quaternary branches, with smaller

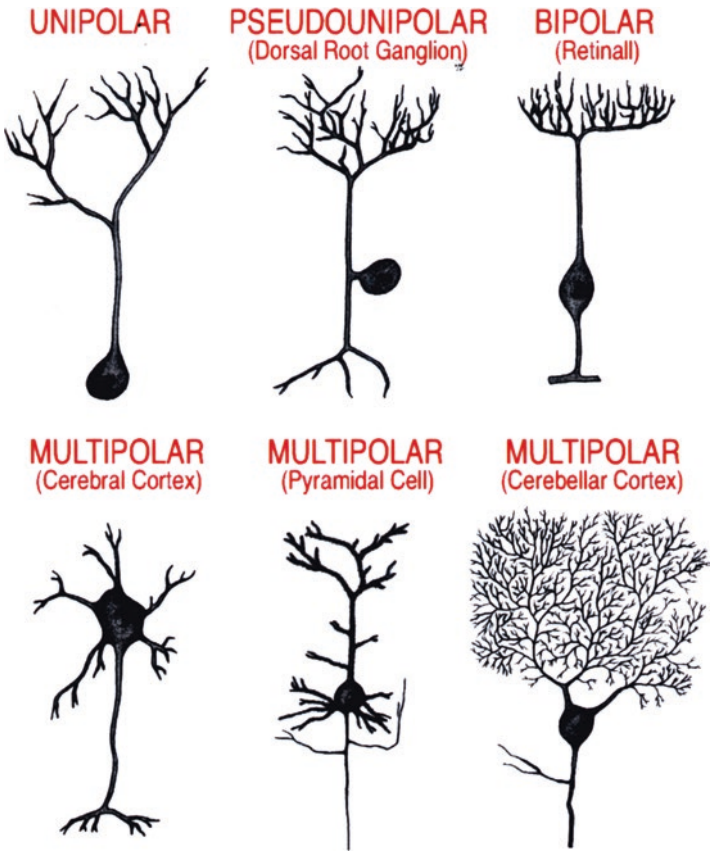


Fig. 2.1 Examples of neurons found within the brain

branches arising from each of these branches that extend into all planes. They form the basic long circuitry within the central nervous system. The axons of pyramidal neurons run long distances within the cortex, but they may also exit from the cortex.

2.1.4 Dendritic Spines (Fig. 2.2)

Throughout much of the central nervous system, spines are found on the dendrites. In the early studies on the brain, these dendritic processes were initially thought to be an artifact of the Golgi silver neuronal stain, but with electron micrographic analysis of the brains, they have been noted to be a dynamic addition to the surface area of many neurons, and a modification of their numbers and types has been shown to produce mental retardation, Alzheimer's disease, and schizophrenia (Fig. 2.3). In the cerebral cortex, there are two basic types of neurons and a cell with a long axon, type I, and a cell with a short axon, type II.

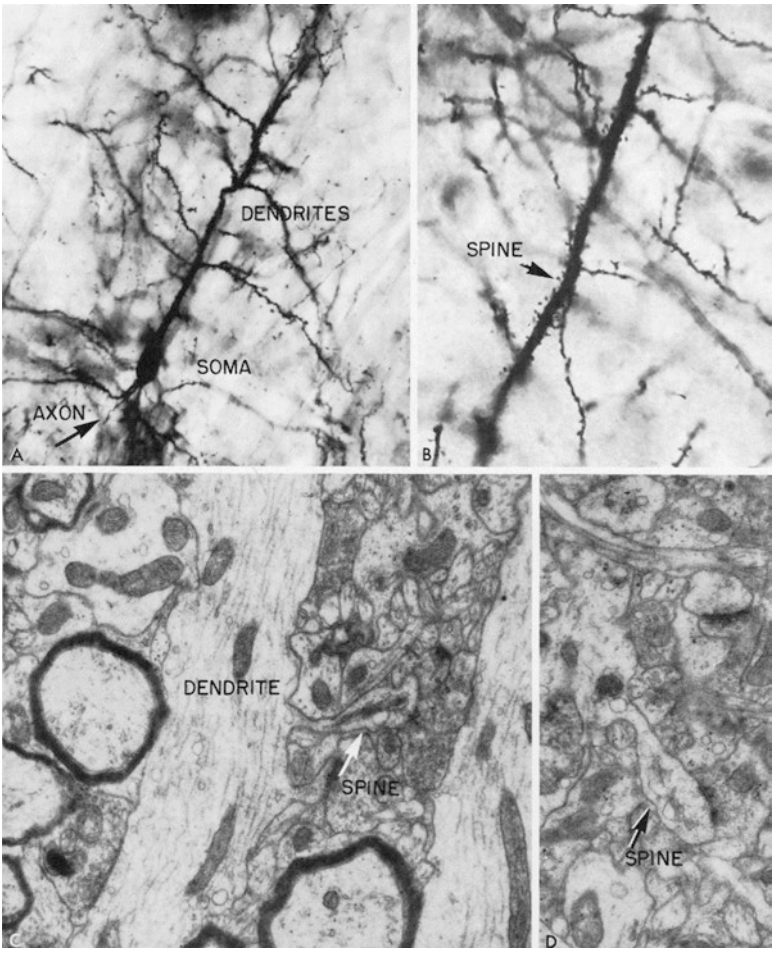


Fig. 2.2 Golgi type I cells (neurons with long axons) in the motor cortex of a rat. (**a**) shows entire cell soma, axon, and dendrite ×150 and (**b**) dendritic spines, ×1100 ((**a**) and (**b**)—Golgi rapid stain), (**c**) and (**d**) are electron micrographs of dendritic spines with excitatory synapses, ×30,000

Golgi type I cell. In the cerebral cortex, spines are numerous on the Golgi type I pyramidal neuron (Fig. 2.2, 2.7), a neuron with long axons, and their axons form many of the long tracts within the CNS. The transmitter in type I cells is glutamate.

The Golgi type II cell. The Golgi type II cells (Fig. 2.3) have few if any dendritic spines, and the axon usually extends only a short distance within the cerebral cortex (0.3–5 mm).

Spines are absent from the initial segment of the apical and basal dendrite of pyramidal neurons, but they become numerous farther along the dendritic branches. Dendritic spines are bulbous, with a neck approximately 1–3 μm in diameter

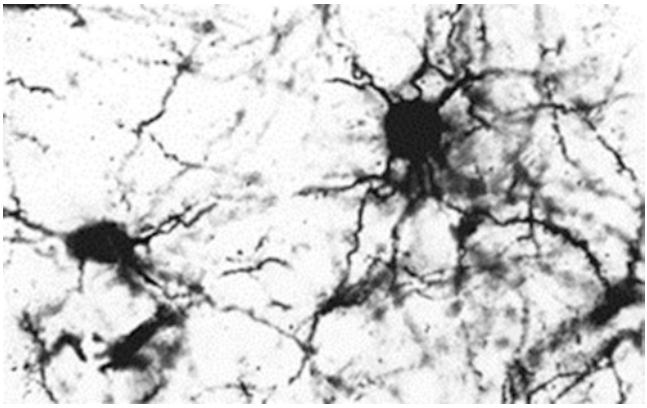


Fig. 2.3 Golgi type II cells (neurons with short axons) in the motor cortex of the rat (Golgi-Cox stain, ×450).

connecting to the dendrite (Fig. 2.2). Many spines are found on dendrites, and these spines contain a spine apparatus which functions like a capacitor, charging and then discharging when its current load is exceeded. Immediately behind the postsynaptic membrane is an elaborate complex of interlinked proteins called the postsynaptic density (PSD), in which adhesion molecules, receptors, and their associated signaling proteins are highly concentrated (Fig. 2.1).

Dendritic spines are actin-rich protrusions from neuronal dendrites that form the postsynaptic part of most excitatory synapses. They provide compartments that locally control the signaling mechanisms at individual synapses. Many axon terminals are located on the spines. Their importance stems from the fact that they greatly expand the dendrite's receptive synaptic surface and are major sites of information processing and storage in the brain. Changes in the shape and size of dendritic spines are correlated with the strength of excitatory synaptic connections and heavily depend on remodeling of its underlying actin cytoskeleton (Hotulainen and Hoogenraad 2010). Spine structure is regulated by molecular mechanisms that include the extrinsic factors (such as perisynaptic astroglia) and the intrinsic factors (such as organelles) that are required to build and maintain synapses. Specific mechanisms of actin regulation are also integral to the formation, maturation, and plasticity of dendritic spines and to learning and memory. Hippocampal spines show structural plasticity which may form the basis for the physiological changes in synaptic transmission that underlie learning and memory.

Cytoplasm and Organelles (Fig. 2.4)

The basic eukaryotic cell contains the following:

1. Plasma membrane
2. Glycocalyx (components external to the plasma membrane)
3. Cytoplasm (semifluid)
4. Cytoskeleton—microfilaments and microtubules that suspend organelles, give shape, and allow motion

Plasma Membrane
A lipid/protein/carbohydrate complex, providing a barrier and containing transport and signaling systems.

Nucleus
Double membrane surrounding the chromosomes and the nucleolus. Pores allow specific communication with the cytoplasm. The nucleolus is a site for synthesis of RNA making up the ribosome.

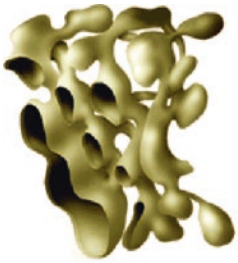
Mitochondria
Surrounded by a double membrane with a series of folds called cristae. Functions in energy production through metabolism. Contains its own DNA, and is believed to have originated as a captured bacterium.

-seen in plants Chloroplasts (plastids)
Surrounded by a double membrane, containing stacked thylakoid membranes. Responsible for photosynthesis, the trapping of light energy for the synthesis of sugars. Contains DNA, and like mitochondria is believed to have originated as a captured bacterium.

Rough endoplasmic reticulum (RER)
A network of interconnected membranes forming channels within the cell. Covered with ribosomes (causing the "rough" appearance) which are in the process of synthesizing proteins for secretion or localization in membranes.

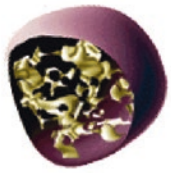
Ribosomes
Protein and RNA complex responsible for protein synthesis.

Fig. 2.4 Characteristic biomembranes and organelles in the presence of membrane-enclosed subcellular organelles of eukaryotic cells



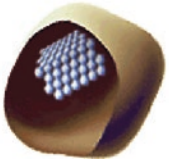
Smooth endoplasmic reticulum (SER)
A network of interconnected membranes forming channels within the cell. A site for synthesis and metabolism of lipids. Also contains enzymes for detoxifying chemicals including drugs and pesticides.

Golgi apparatus
A series of stacked membranes. Vesicles (small membrane surrounded bags) carry materials from the RER to the Golgi apparatus. Vesicles move between the stacks while the proteins are "processed" to a mature form. Vesicles then carry newly formed membrane and secreted proteins to their final destinations including secretion or membrane localization.



Lysosymes
A membrane bound organelle that is responsible for degrading proteins and membranes in the cell, and also helps degrade materials ingested by the cell.

Vacuoles
Membrane surrounded "bags" that contain water and storage materials in plants.



Peroxisomes or Microbodies
Produce and degrade hydrogen peroxide, a toxic compound that can be produced during metabolism.

Cell wall
Plants have a rigid cell wall in addition to their cell membranes.

Fig. 2.4 (continued)

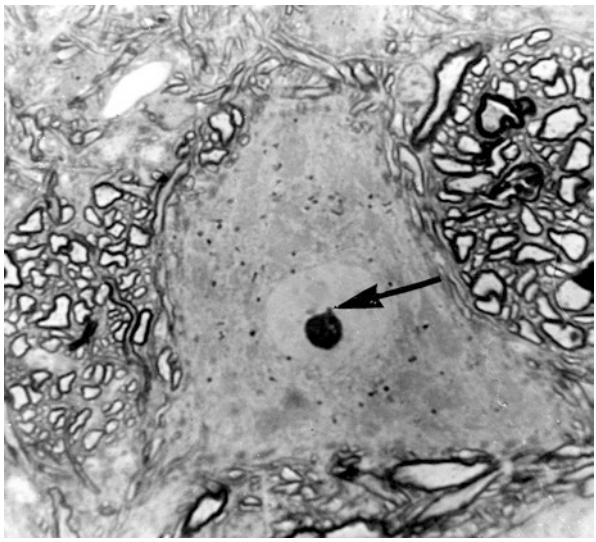


Fig. 2.5 Ventral horn cell of a female squirrel monkey. Note the nucleus, nucleolus, and the accessory body of Barr (*arrow*). 1 μm epoxy section ×1400

Table 2.2 Rate of axonal transport of cellular structures (data from Graftstein and Forman; Mcquarrie; Wujek and Lasek)

Transport rate (mm/day)	Cellular structure
Fast 300 ↔ 400	Vesicles, smooth endoplasmic reticulum, and granules
Intermediate 50 ↔ 15	– Mitochondria – Filament proteins
Slow 3 ↔ 4 Slow 0.3 ↔ 1	– Actin, fodrin, enolase, component CPK, calmodulin, B and clathrin – Neurofilament protein, component tubulin, and MAPS

These structures are seen in most cells and in all neurons and glial cell types and permit each neuron to function (Table 2.2). In these eukaryotic cells, the organelles tend to be compartmentalized and include the nucleus, polyribosomes, rough endoplasmic reticulum, smooth endoplasmic reticulum, mitochondria, and inclusions (Fig. 2.11). Most neuronal cytoplasm is formed in the organelles of the soma and flows into the other processes. Newly synthesized macromolecules are transported to other parts of the nerve cell, either in membrane-bound vesicles or as protein particles. As long as the soma with a majority of its organelles is intact, the nerve cell can live. Thus, it is the *trophic center* of the neuron. Separation of a process from the soma produces death of that process. (Springer Images 2014)

2.1.5 Nucleus

2.1.5.1 Rough Endoplasmic Reticulum: Nissl Body (Figs. 2.6 and 2.7)

The rough endoplasmic reticulum or Nissl substance, which turns amino acids into proteins, is the chromodial substance found in light micrographs. It can be demonstrated by using a light microscope and basic dyes, such as methylene blue, cresyl violet, and toluidine blue. The appearance and amount vary from cell to cell. With electron microscopy, cisterns containing parallel rows of interconnecting rough endoplasmic reticulum are revealed (Fig. 2.14). Ribosomes (clusters of ribosomal RNA) are attached to the outer surfaces of the membranes and consist of a large and a small RNA–protein subunit. The Nissl substance is most concentrated in the soma and adjacent parts of the dendrite (Fig. 2.6). It is, however, also found throughout the dendrite (Fig. 2.8B) and even in the axon hillock.

2.1.5.2 Mitochondria (Figs. 2.8 and 2.12)

These organelles, found throughout the neuron, are the third largest organelles after the nucleus and endoplasmic reticulum and supply the energy for many activities in the eukaryotic cell. They are rod shaped and vary from 0.35 to 10 μm in length and

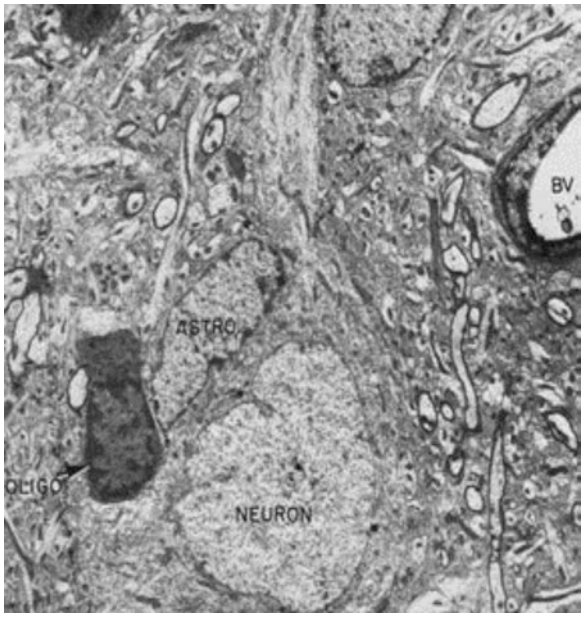


Fig. 2.6 Electron micrograph showing a Type I pyramidal neuron with its adjoining astrocyte and oligodendrocyte. ×13500

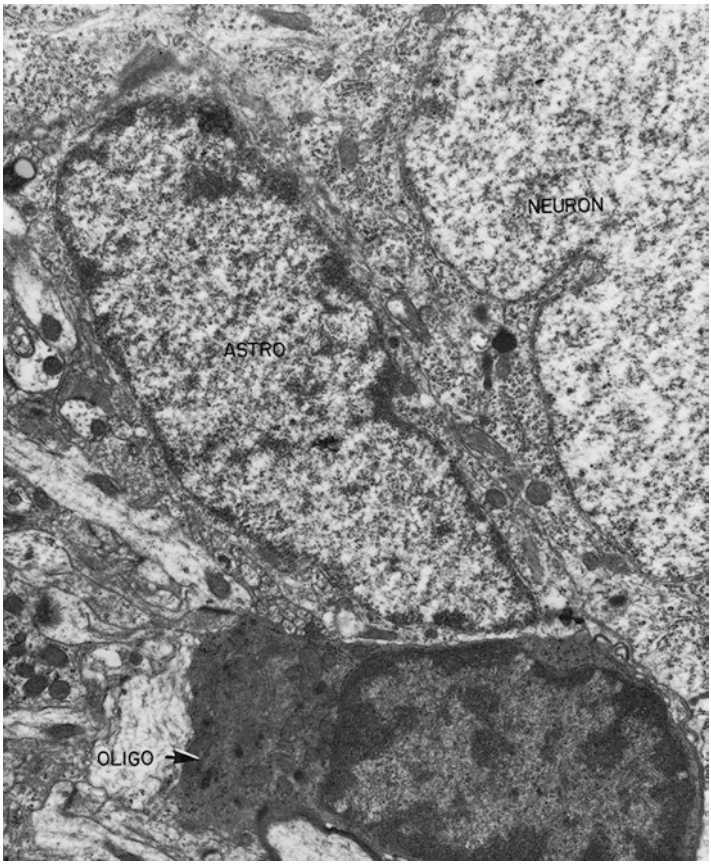


Fig. 2.7 Electron micrograph of the cerebral cortex showing the principal cell types in the central nervous system: neuron, astrocyte (astro), oligodendrocyte (oligo), and a blood vessel (BV) × 13500

0.35 to 0.5 μm in diameter. The wall of a mitochondrion consists of two layers—an outer and inner membrane. The outer membrane contains pores that render the membrane soluble to proteins with molecular weights of up to 10,000. The inner membrane is less permeable and has folds called cristae that project into the center of the mitochondrial matrix. The interior of the mitochondrion is filled with a fluid denser than cytoplasm. On the inner membrane, enzymes are found that provide much of the energy required for the nerve cell. These respiratory enzymes (flavoproteins and cytochromes) catalyze the addition of a phosphate group to adenosine diphosphate (ADP), forming ATP. In the cytoplasm, ADP provides the energy required for cellular metabolic functions. Cations and mitochondrial DNA (mtDNA) have been demonstrated in the mitochondrial matrix. Mitochondrial DNA is derived from the mother.

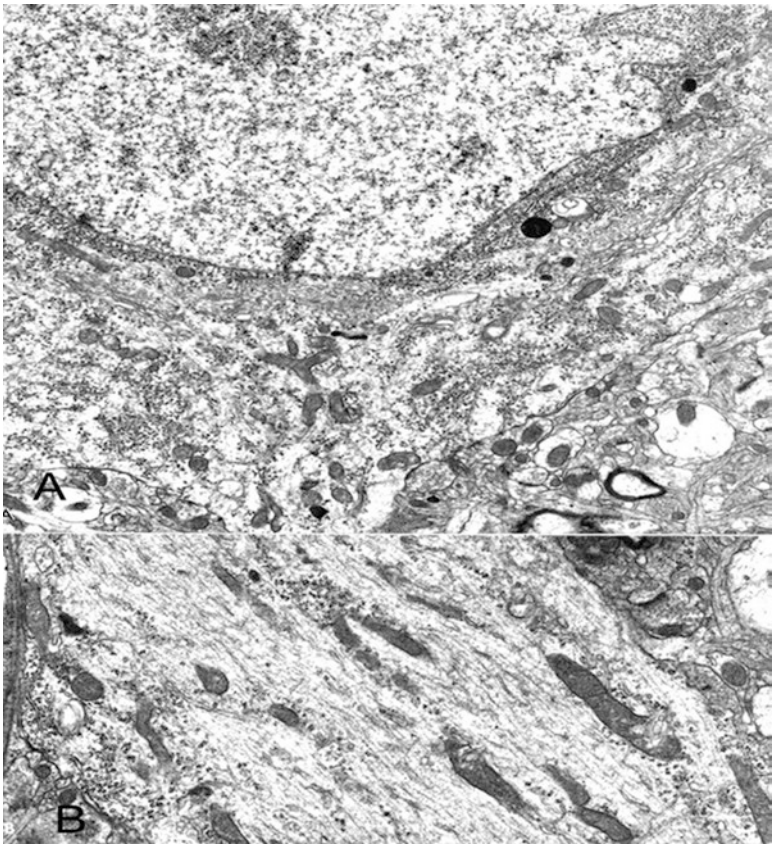


Fig. 2.8 Electron micrographs of a pyramidal neuron in the rat cerebral cortex, (**a**) soma and nucleus, and (**b**) dendrite. Note the large amount of Nissl substance in the soma. The dendrites have less Nissl substance and many microtubules. ×33,000

In the mitochondria is a DNA from one's mother, and an intriguing study links this mitochondrial DNA to a common human female ancestor, Lucy (of the species *Australopithecus afarensis*, who lived in Southern Africa over 3,000,000 years ago, Johanson and Wong 2009, Tatersall 2009). In the cytoplasm, enzymes are found that break down glucose into pyruvic and acetoacetic acid. These substances are taken into the mitochondrial matrix and participate in the Krebs citric acid cycle, which allows the mitochondria to metabolize amino acids and fatty acids.

2.1.5.3 Neurosecretory Granules

Neurons in the supraoptic and paraventricular nuclei of the hypothalamus form neurosecretory material (Bodian 1963, 1966; Palay 1957; Scharrer 1966). The axons of these cells form the hypothalamic–hypophyseal tract, which runs through the median

eminence, down the infundibular stalk to the neurohypophysis (pars nervosa), where the axons end in close proximity to the endothelial cells. The secretory granules are 130–150 millimicrons in diameter and are found in the tract (see Fig. 9.4).

2.1.6 Neuronal Cytoskeleton

In silver-stained sections examined in a light microscope, a neurofibrillary network can be seen in the neurons (Fig. 2.10). Electron micrographs can distinguish microtubules, 3–30 μm in diameter, and neurofilaments, 1 nm in diameter. It appears that fixation produces clumping of the tubules and filaments into the fibrillar network seen in light micrographs.

Neurons in common with other eukaryotic cells contain a cytoskeleton that maintains its shape. This cytoskeleton consists of at least three types of fibers:

1. Microtubules 30 nm in diameter
2. Microfilaments 7 nm in diameter
3. Intermediate filaments 10 nm in diameter

If the plasma membrane and organelle membrane are removed, the cytoskeleton is seen to consist of actin microfilaments, tubulin-containing microtubules, and crisscrossing intermediate filaments. Neurotubules (microtubules) predominate in dendrites and in the axon hillock, whereas microfilaments are sparse in dendrites and most numerous in axons (Fig. 2.12). Microtubules and intermediate filaments are found throughout the axon. Microfilaments form much of the cytoskeleton of the entire neuron.

Neurofibrillary tangles are bundles of abnormal filaments within a neuron (Fig. 2.10b).

2.1.7 Microtubules and Axoplasmic Flow

In the classic experiment of Weiss and Hiscoe (1948), they placed a ligature on a peripheral nerve, and this produced a swelling proximal to the tie, demonstrating that material flows from the soma, or trophic center, into the axon and ultimately to the axon terminal. The development of techniques that follow this axoplasmic flow has revolutionized the study of circuitry within the central nervous system. The ability to map this circuitry accurately has given all neuroscientists a better understanding of the integrative mechanisms in the brain. With the protein-manufacturing apparatus present only in the soma, and to a lesser degree in the dendrites, a mechanism must exist to transport proteins and other molecules from the soma, down the axon, and into the presynaptic side.

Axoplasmic transport is an active process responsible for movement of organelles (mitochondria), lipids, proteins, synaptic vesicles, and other parts of the cell mem-

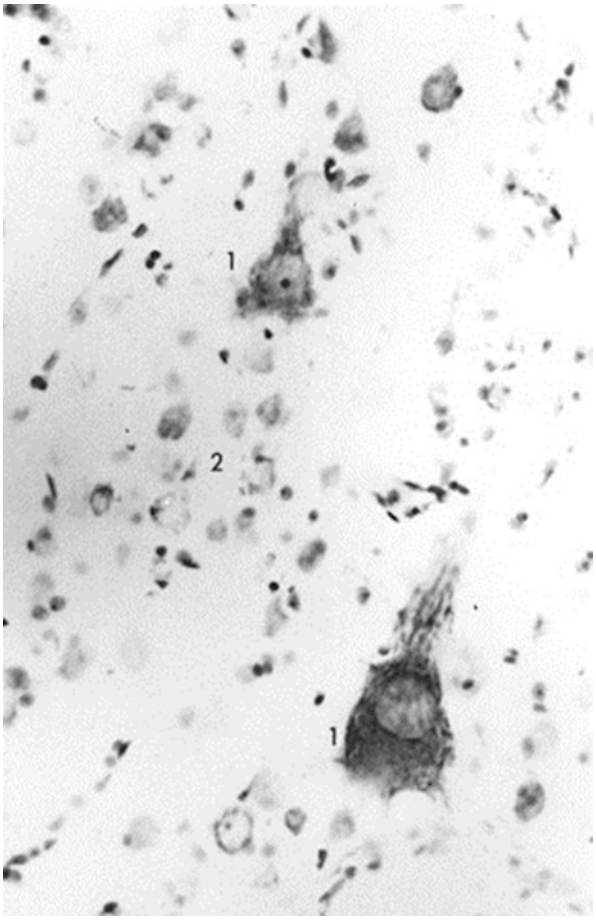


Fig. 2.9 The Nissl body/rough endoplasmic reticulum in the pyramidal neurons #1 in layer 5 in the leg region of the motor cortex of a chimpanzee. The larger pyramidal cell is a giant cell of Betz; note the astrocyte located next to its apical dendrite. The cell stained in #2 is an astrocyte. Thionin stain, ×205

branes to and from the soma down the axon to the synapses and back up to the soma. Microtubules provide the structural basis for this transport and axoplasmic flow, and they contain the protein motors kinesins and dyneins which are the molecular basis of this transport with the catalyzing of ATP to ADP providing the energy for this active transport. This mechanism of transport is not diffusion but rather retrograde axonal transport associated with the microtubule network that exists throughout the nerve cell. The rate of flow varies depending upon the product being transported and ranges from more than 300 mm/day to less than 1 mm a day. The main direction of the flow is *anterograde*, from the cell body into the axon and synapse. There is also a very active *retrograde* flow from the synaptic region back to the cell body that is a source for recycling many of the substances found at the synaptic ending.

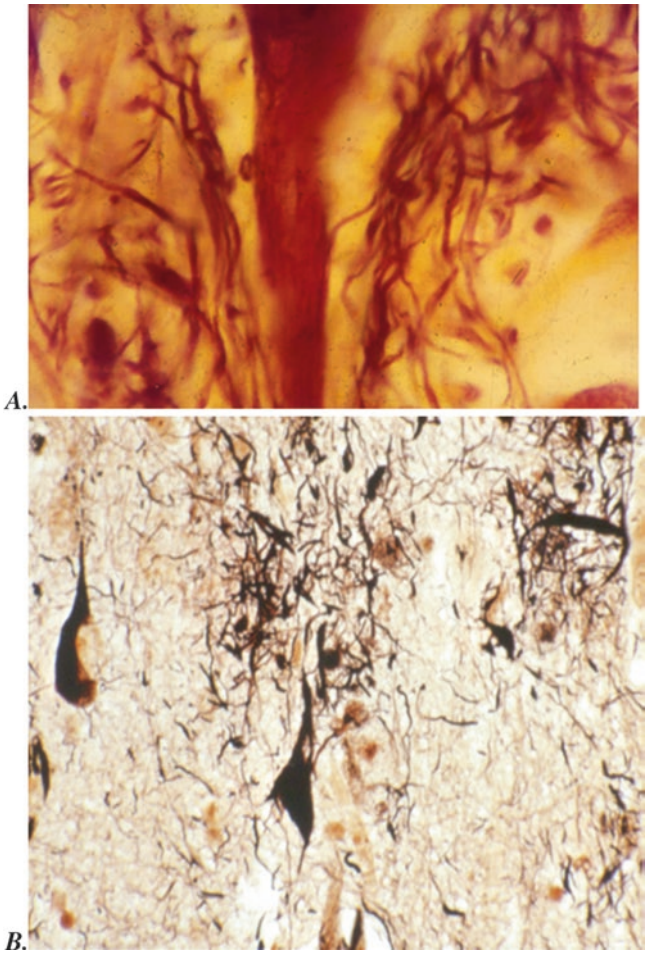


Fig. 2.10 (**a**) Cytoskeleton of the CNS as shown in a neurofibrillary stain (Bielschowsky) of a ventral horn cell in the cat spinal cord, showing neurofibrillary network in axons, soma, and dendrites (from SJ). (**b**) Neurofibrillary tangles in pyramidal cells in the hippocampus of an 87-year-old female with progressive dementia. Bielschowsky silver stain (Courtesy of Dr. Tom Smith, Dept. of Pathology, U Mass Medical School)

The particles that move the fastest as noted in Table 2.2 consist of small vesicles of the secretory and synaptic vesicles, and the slowest group is the cytoskeletal components. Mitochondria are transported down from the cell body at an intermediate rate. The retrograde flow from the synaptic telodendria back into the soma returns any excess of material for degradation or reprocessing. The retrograde flow permits any excess proteins or amino acids to be recycled. It also permits products synthesized or released at the axonal cleft to be absorbed and then transported back to the cell.

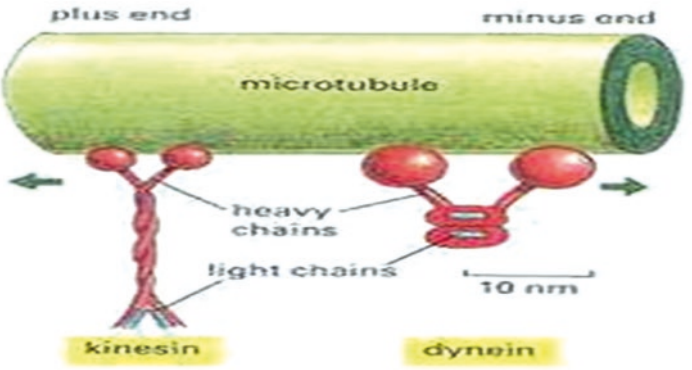


Fig. 2.11 Protein motors kinesin and dyneins. From Springer Images 2015

Microtubules (Fig. 2.8) help to transport membrane-bound vesicles, protein, and other macromolecules. This orthograde transport, or anterograde axonal transport, is the means whereby these molecules formed in the soma/trophic center are transported down the axon into the axonal telodendria. The individual microtubules in the nervous system are 10–35 nm in length and together form the cytoskeleton. The intermediate filaments are associated with the microtubules. The wall of the microtubule consists of a helical array of repeating tubulin subunits containing the A and B tubulin molecule. The microtubule wall consists of globular subunits 4–5 nm in diameter; the subunits are arranged in 13 protofilaments that encircle and run parallel to the long axis of the tubule, and they are hollow tubes. Each microtubule also has a defined polarity.

Protein motors—kinesins and dyneins (Fig. 2.11). These microtubules form tracks which are associated with protein motors, kinesins and dynein. The kinesin motors are involved in anterograde transport, while the dyneins are motors that move toward the negative end in retrograde transport through the microtubule. Their movement is powered by catalyzing the hydrolysis of ATP (ATPase) to ADP. This dephosphorization releases the energy which is the mechanism of transport in the central nervous system.

2.1.8 Neurofibrillary Tangles

2.1.8.1 Axon and Axon Origin (Axon Hillock) (Fig. 2.10a)

The axon originates at the hillock and is a slender process that usually arises from a cone-shaped region on the perikaryon (Fig. 2.12). This region includes filaments, stacks of tubules, and polyribosomes (Fig. 2.12b). The initial segment of the axon, arising from the axon hillock, is covered by a dense material that functions as an insulator membrane at the hillock that is covered by an electron-dense material.

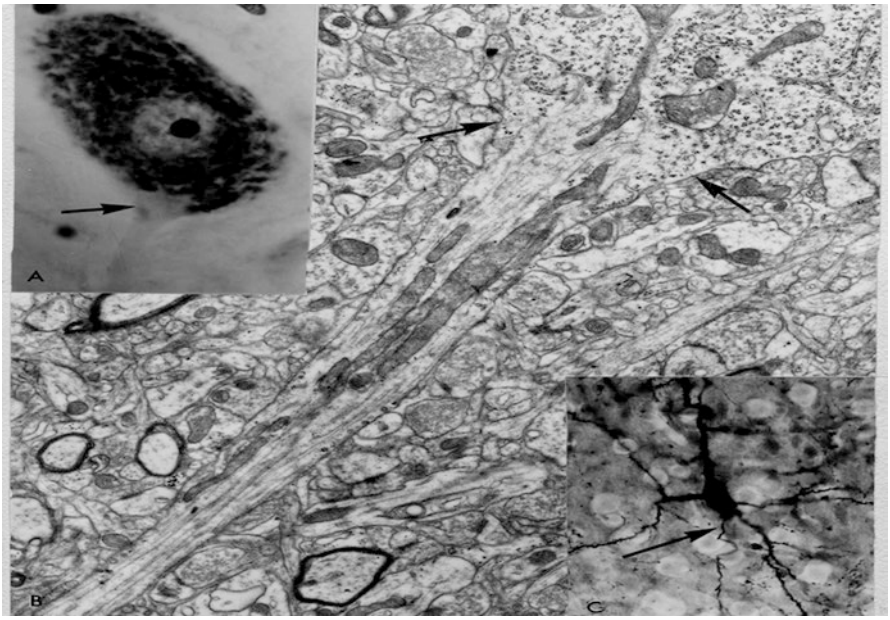


Fig. 2.12 Appearance of the axon hillock, axon origin. (**a**) In a Nissl stain, ×400; (**b**) in an electron micrograph, ×15,000; and (**c**) in a Golgi rapid stain, ×350

2.1.8.2 Myelin Sheath: The Insulator in an Aqueous Media (Fig. 2.14)

The myelin membrane like all membranes contains phospholipid bi-layers (Fig. 2.14). In the central nervous system, myelin includes the following proteins:

Proteolipid protein (51%)
Myelin basic protein (44%)
Myelin-associated glycoprotein (1%)
3,3-Cyclic nucleotide (4%)

The oligodendrocytic process forms the myelin sheaths by wrapping around the axon. The space between the axonal plasma membrane and the forming myelin is reduced until most of the exoplasmic and cytoplasmic space is finally forced out. The result is a compact stack of membranes. The myelin sheath is from 3 to 100 membranes thick and acts as an insulator by preventing the transfer of ions from the axonal cytoplasm into the extracellular space.

Myelin sheaths are in contact with the axon. In light microscopy, they appear as discontinuous tubes 0.5–3 mm in length, interrupted at the node of Ranvier (Fig. 2.13).

The axon is devoid of myelin at the site of origin (the nodes) and at the axonal telodendria. At the site of origin, the axon is covered by an electron-dense membrane, and at the site of the synaptic telodendria, the various axonal endings are

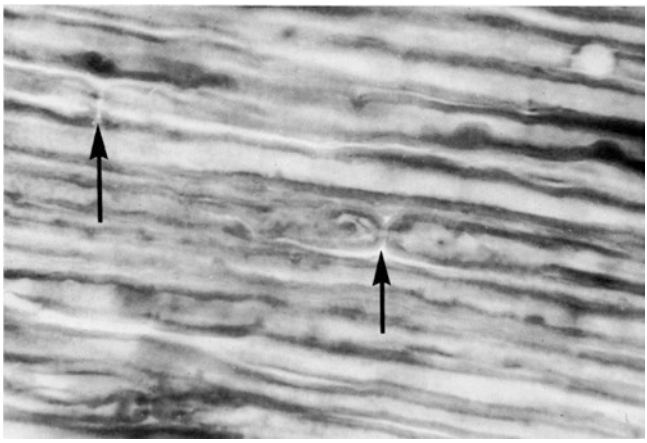


Fig. 2.13 Node of Ranvier. Longitudinal section of a peripheral nerve fixed in osmium, demonstrating nodes of Ranvier (*arrows*) (×1000)

isolated from one another by astrocytic processes. In electron micrographs, each myelin lamella actually consists of two unit membranes with the entire lamella being 130–180 Å thick (Fig. 2.14). Myelin is thus seen to consist of a series of light and dark lines. The dark line, called the major dense line (MDL), represents the apposition of the inner surface of the unit membranes. The less-dense line, called the interperiod line (IPL), represents the approximation of the outer surfaces of adjacent myelin membranes. Only at the node of Ranvier is the axonal plasma membrane in communication with the extracellular space. The influx of Na^+ at each node causes the action potential to move rapidly down the axon by jumping from node to node—saltatory conduction.

2.1.8.3 Myelination: Schwann Cell in PNS and Oligodendrocyte in CNS

The process of covering a naked axon with myelin is myelination. An axon starts with just a covering formed by the plasma membrane of either the *Schwann cell* or the *oligodendrocyte*. More and more layers are added until myelination is complete. The myelin is laid down by the processes of either the Schwan cell in the PNS or oligodendrocyte in the CNS twisting around the axon (Geren 1956; Robertson 1955) (Fig. 2.14).

The *sequence of myelination* has been studied centrally in great detail (Jacobson 1963); it begins in the spinal cord, moves into the brain stem, and finally ends up with the diencephalon and cerebrum last. A delay in myelination will produce developmental delays and may be a consequence of many factors, including genetic and nutritional ones (e.g., alcoholism—fetal alcohol syndrome), and is usually very harmful to the fetus. Breakdown of the myelin in a disease, e.g., multiple sclerosis,

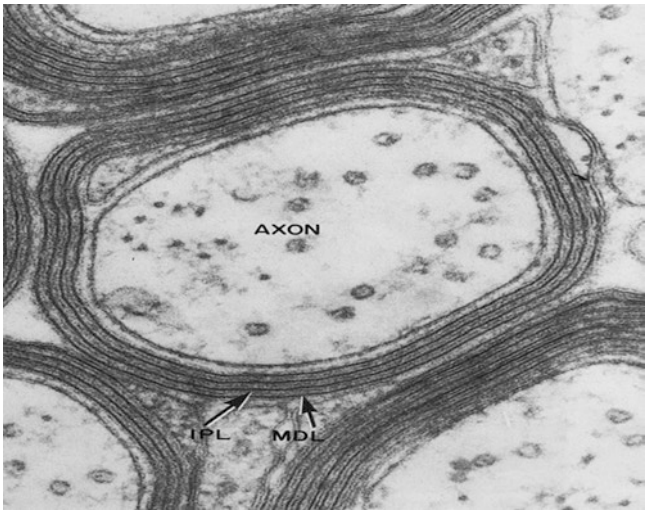


Fig. 2.14 Myelin sheath from the optic nerve of a mouse demonstrating repeated units ohte myelin sheath consisitng of *light* an *dark lines*. The *dark line* is called the major dense line (MDL) represents the oppositon of the inner unit membranes. The less dense line called the interperiod line, IPL, represents the a approximstion of the outer surface of adjacent myelin membranes (×67,000) (Courtesy of Alan Peters, Department of Anatomy, Boston University School of Medicine)

Table 2.3 Location and functions of neurotransmitters

Agent	Location	Function
L-Glutamine	Excitatory neurons	Excitation
GABA	Inhibitory neurons	Inhibition (fast/slow)
Acetylcholine	Motor neurons, basal forebrain, midbrain, and pontine tegmentum	Excitation and modulation
Monoamines – Norepinephrine – Serotonin – Histamine	Brainstem, hypothalamus – Locus ceruleus – Raphe nuclei – Hypothalamus	Modulation
Neuropeptides	Limbic system, hypothalamus, autonomics, and pain pathways	Modulation

produces major functional deficits where they can affect the basic function of the cell—the signaling process. Fast axonal transport is associated with the microtubules. The slower components including membrane-associated proteins (MAPS) are transported inside the microtubules, but the mitochondria actually descend in the axonal cytoplasm (Table 2.3).

2.1.8.4 Central Nervous System Pathways

The axons in the peripheral nervous system are organized into nerves, while in the central nervous system, the axons run in groups called tracts with each axon enwrapped in myelin, and groups of axons are bundled together by the processes of fibrous astrocytes. The axons vary in diameter (5–33 μm) and in length (0.5 mm–1 m), but these axons cannot be separated into functional categories based on axonal diameter. These many pathways (e.g., corticospinal, spinothalamic) will be discussed within each level of the central nervous system.

2.2 Synapse

Synapses can be seen at the light microscopic level (Fig. 2.13); however, to identify all the components of synapses, the electron microscope must be used. At the electron microscopic level, the synapse consists of the axonal ending, which forms the presynaptic side, and the dendritic zone, which forms the postsynaptic side (Fig. 2.14). Collectively, the pre- and postsynaptic sides and the intervening synaptic cleft are called the synapse.

2.2.1 Synaptic Structure

The electron microscope has permitted one to reveal many new details in synaptic structure (Bodian 1970; Colonnier 1969; Gray 1959; Palay 1967).

At the synapse, the electrical impulse from one cell is transmitted to another. Synapses vary in size from the large endings on motor neurons (1–3 μm) to smaller synapses on the granule and stellate cells of the cortex and cerebellum (less than 0.5 μm). Synapses primarily occur between the axon of one cell and the dendrite of another cell. Synapses are usually located on the dendritic spins but are also seen on the soma and rarely between axons. At the synapse, the axon arborizes and forms several synaptic bulbs that are attached to the plasma membrane of the opposing neuron by intersynaptic filaments (Fig. 2.13).

2.2.2 Synaptic Types

The synapses can be seen at the light microscopic level (Fig. 2.15), but they are best seen with the electron micrograph. where one sees two basic types of synapses, electrical and chemical, and they differ in location and appearance.

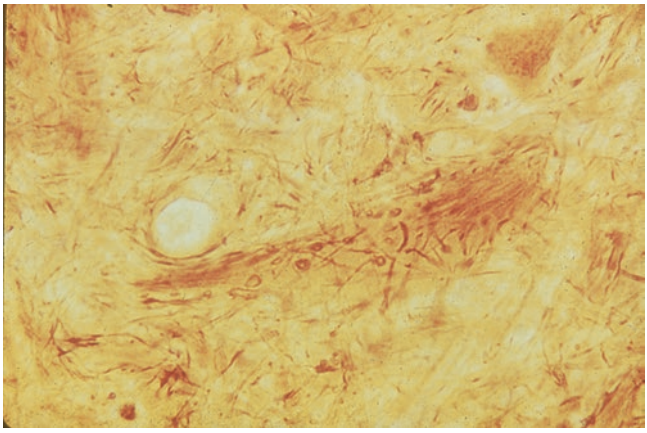


Fig. 2.15 Silver stain of a 1 micron plastic embedded section demonstrating boutons on neruons in the reticular formation. ×1400

Electrical synapses are connected by membrane bridges, gap junction connections, which permit the electric impulse to pass directly from one cell to the other. Electric synapses have almost no delay and little chance of misfiring. These synapses are seen in many fish.

Chemical synapses have a presynaptic side, containing vesicles and a gap, and the postsynaptic side with membrane receptors. The neurotransmitter released by the action potential is exocytosed and diffuses across the synaptic cleft and binds to the specific receptor on the postsynaptic membrane. Most of the synapses seen in the mammalian central nervous system are chemical.

2.2.3 Synaptic Transmission

Synaptic transmission in the mammalian central nervous system is primarily a chemical and not an electrically mediated phenomenon, based on the presence of:

1. A 30–40 nm cleft
2. Synaptic vesicles
3. Appreciable synaptic delay due to absorbance of the chemical onto the postsynaptic receptor site. In contrast electrical synapses have cytoplasmic bridges that interconnect the pre- and postsynaptic membranes resulting in a minimal synaptic delay as transmission is ionic rather than by release of chemical from a vesicle.

2.2.4 Neurotransmitters (Table 2.3)

Excitatory neurotransmitters include glutamate and acetylcholine. *Inhibitory neurotransmitters* include GABA, histamine, neurotensin, and angiotensin. Many other compounds have been identified as neurotransmitters. These substances are found in synaptic vesicles on the presynaptic side. Introduction of the compound into the synaptic cleft produces the same change in the resting membrane potential as stimulation of the presynaptic axon; the compound is rapidly degraded, and the membrane potential returns to the resting state. The neurotransmitters are either amino acids or small neuropeptides. The classic neurotransmitters in the central nervous system include acetylcholine, epinephrine, norepinephrine, serotonin, glycine, glutamate, dopamine, and GABA. Acetylcholine is the best documented transmitter in the peripheral nervous system and has been isolated in synaptic vesicles in the central nervous system. Acetylcholine esterase has been found throughout the central and peripheral nervous systems and at postganglionic sympathetic endings.

2.2.5 Modulators of Neurotransmission

At certain synaptic sites, the following compounds may also function as modulator (usually a slower transmitter) form of neurotransmission: adenosine, histamine, octopamine, B-alanine, ATP, and taurine. Many of the neuropeptides, such as substance P, vasoactive peptide, peptide Y, and somatostatin, are also active in neurotransmission or neuromodulation. Catecholamines and 5-hydroxytryptamine are transmitters linked to synaptic transmission in the central nervous system. Noradrenaline is a transmitter at the preganglionic synapses. Many steroids and hormones have also been linked to synaptic transmission. It is still uncertain whether these compounds play a direct role in nervous transmission or if they are just related by their importance to the ongoing functions of the entire nervous system (Table 2.3).

2.2.6 Synaptic Vesicles (Fig. 2.16) (Table 2.4)

The synaptic vesicles differ in size and shape and may be agranular, spherical, flattened, or round with a dense core. The spheroidal vesicles retain their shape regardless of any manipulation. The four basic categories of synaptic vesicles are given in Table 2.4.

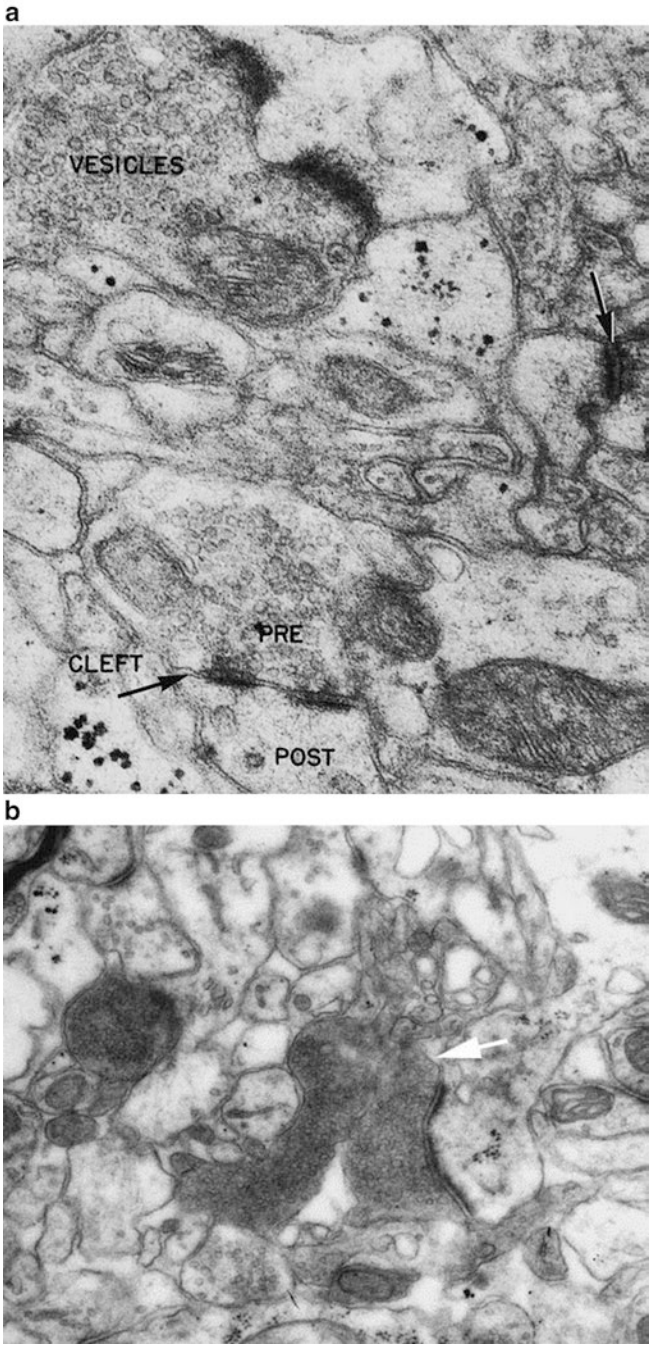


Fig. 2.16 (**a**) Normal appearance of excitatory synapses in the sensory cortex of the rat demonstrating agranular synaptic vesicles (300–400 Å) in the presynaptic axonal side. Note the electron-dense synaptic membranes and the intersynaptic filaments in the synaptic cleft. Electron micrograph (×65,000). (**b**) Appearance of degenerating excitatory synapses in the sensory cortex of the brain after removal of the contralateral region demonstrating increased density of presynaptic side with edematous parenchyma and the clumping of the synaptic vesicle and the fibrillary appearance of the degenerating axonal endings

Table 2.4 Categories of synaptic vesicles

Type and diameter in nm	Location
Spheroidal or flattened (30–40 nm)—inhibitory synapses	At neuromuscular junction and throughout clear center. Most common type in central nervous system
Spheroidal with 38 nm 40–80 nm electron-dense granule—excitatory	Autonomic endings in the intestines, vas deferens, and pineal body; contains catecholamines
Spheroidal with a droplet (50 nm 80–90 nm); catecholamines present in vesicles—excitatory	Found at preganglionic sympathetic synapses, neuromuscular junctions in smooth muscle, and in parts of the hypothalamus, basal nuclei, brain stem, and cerebellum
Spheroidal with a large droplet that nearly fills the vesicle (Fig. 3.15) (130–300 nm). Vesicles contain vasopressin and oxytocin—excitatory	Characteristic of nerve endings in the hypothalamus, also found in the soma, axons, and presynaptic endings of nerve cells of the hypothalamic–hypophyseal tract

2.2.6.1 Excitatory Synapses

Excitatory synapses depolarize the membrane potential and make it more positive, and they appear asymmetrical, having a prominent postsynaptic bush with presynaptic vesicles (Figs. 2.15 and 2.16). This type of synapse is most commonly seen on dendrites. Glutamate has been identified in excitatory synapses. At the excitatory synapse, there is a change in permeability that leads to depolarization of the postsynaptic membrane and which can lead to the generation of an action potential.

2.2.6.2 Inhibitory Synapses

Inhibitory synapses hyperpolarize the membrane potential and make it more negative. They are symmetrical with thickened membranes on the pre- and postsynaptic side and vesicles only on the presynaptic side. GABA has been identified in the inhibitory synapses. At an inhibitory synapse, the neurotransmitter binds to the receptor membrane, which changes the permeability and tends to block the formation of the action potential. Synapses on the soma are symmetrical, and they are considered inhibitory.

2.2.6.3 Synaptic Architecture (Fig. 2.17)

Dendritic spines. Dendritic spines are small membranous protrusions that contain the postsynaptic machinery, including the glutamate receptors, the actin cytoskeleton, and a wide variety of membrane-bound organelles, such as smooth endoplasmic reticulum, mitochondria, and endosomes.

In addition, dendritic spines in the hippocampus can be affected by stress (Yuncai Chen, Céline M. Dubé, Courtney J. Rice, and Tallie Z. Baram, 2010) with a resultant dendritic regression and loss of dendritic spines in hippocampal neurons that is

accompanied by deficits in synaptic plasticity and memory. However, the responsible mechanisms remain unresolved. In this study, they found that within hours of the onset of stress, the density of dendritic spines declined in vulnerable dendritic domains. This rapid, stress-induced spine loss was abolished by blocking the receptor ($CRFR_1$) of corticotrophin-releasing hormone (CRH), a hippocampal neuropeptide released during stress. Exposure to CRH provoked spine loss and dendritic regression in hippocampal organotypic cultures, and selective blockade of the $CRFR_1$ receptor had the opposite effect. In this study in addition, time-lapse imaging revealed that CRH reduced spine density by altering dendritic spine dynamics, and this mechanism involved destabilization of spine F-actin. Knockout mice lacking the $CRFR_1$ receptor had augmented spine density. These findings support a mechanistic role for CRH–$CRFR_1$ signaling in stress-evoked spine loss and dendritic remodeling.

A study on the number of dendritic spines in the prefrontal cortex of schizophrenic patients demonstrated some reduction in the number of spines suggesting some pruning of spines in these patients. In addition, this study has shown that the molecular basis of these changes was reflected in a reduction of the Cdc42 and Duo mRNA which are important in spine maintenance and development (Hill, Hashimoto, Lewis 2006).

2.2.7 Effectors and Receptors

1. **Effectors**. The motor nerves (vasomotor), muscles in hair follicles (pilomotor), and sweat glands (sudomotor).
2. **Receptors** (Table 2.5)
   (a) Cutaneous sensory. A stereogram of the skin is shown in Fig. 1.3. Table 2.5 lists the mechanoreceptors in the body's sensory endings. Sensory endings, found throughout the body, subserves pain touch, temperature, vibration, pressure, heat, and cold in the skin, muscles, and viscera as well as the specialized somatic and visceral sensations of taste, smell, vision, audition, and balance.
   (b) Visceral sensory. These receptors are similar to somatic sensory receptors associated with the somatic nervous system, except that they are located in the viscera and their accessory organs.

2.3 Supporting Cells of the Central Nervous System

The central nervous system has billions of neurons, but the number of supporting cells exceeds them by a factor of 5 or 6. Supporting cells form a structural matrix, an internal milieu, and play a vital role in transporting gases, water, electrolytes, and

Table 2.5 Mechanoreceptor

Modality	Receptor
Sound	Cochlea in inner ear/petrous portion of temporal bone transforms mechanical into neural impulses
Light touch and vibration	Encapsulated endings—Meissner's and Pacinian corpuscles
Proprioception: Encapsulated sensory endings	Muscle spindles and Golgi tendon organs in joints Meissner's and Pacinian corpuscles, Merkel's tactile disks
Pain and temperature	Free nerve endings, end bulbs of Krausse and Golgi-Mason

metabolites from blood vessels to the neural parenchyma and in removing waste products from the neuron. In contrast to the neuron, the supporting cells in the adult central nervous system normally undergo mitotic division.

The supporting cells are divided into macroglia and microglia:

Macroglia include astrocytes, oligodendrocytes, and ependyma and are the supporting cells or neuroglia (nerve glue) of the central nervous system (Fig. 2.7).

Microglia include the mesodermal microglia cells (of Hortega), perivascular cells, and any white blood cells found within the parenchyma of the central nervous system.

Schwann cells, **satellite cells**, **and fibroblasts** are supporting cells of the peripheral nervous system. Functions of the different supporting cells in the nervous system are summarized in Table 2.6.

2.3.1 Astrocytes (Figs. 2.6 and 2.14; Table 2.7)

Astrocytes are of two types: fibrous (most common in white matter) or protoplasmic (most common in gray matter).

Astrocytes are now thought to be involved in almost all aspects of brain function as they form much of the *internal milieu* of the brain. Astrocytes generate signals that are chemical rather than electrical. Astrocytes are star-shaped glia that hold neurons in place, get nutrients from them, and digest parts of dead neurons. But because astrocytes cannot generate action potentials, they haven't received a lot of attention, until recently. It has been discovered that astrocytes can indeed communicate with neurons and modify the signals they send or receive. That means astrocytes are much more involved than we thought in the processing of information and in the signaling that occurs at the synapse.

Glymphatic channels. The processes of the astrocytes form periarterial channels for the passage of macromolecules in the brain propelled by the arterial blood flow. The waste products in the brain are transported into the perivenous channels which permit the elimination of macromolecules via the perivenous channels into the subarachnoid space and then into venous sinuses via the arachnoid granulations (Nedergaard and Goldman, Scientific American, 2016, vol. 314, pp. 46–49).

Table 2.6 Functions of CNS supporting cells

Cell type	Functions
Astrocytes: – Fibrous type (white matter) – Protoplasmic type (gray matter)	Major supporting cells in the brain—forming microenvironment for neurons and aid them by transporting in and out necessary compounds – Act as phagocyte and enwrap axons contain many filaments – Isolate synapses, enwrap blood vessels, and form membranes on the brain's inner and outer surface – Forms glymphatic channels
Oligodendrocytes	Form and maintain myelin and are very important in conduction of the action potential
Ependyma cells	Ciliated lining cells of the ventricular system
Endothelial cells	Lining cells of blood vessels in the brain that form blood–brain barrier
Microglia (pericytes)	Supporting cells and multipotential cells found in the basement membrane of blood vessels and within brain parenchyma Have phagocytic functions with injury to the CNS Appear to be involved in maintaining or eliminating/pruning dendritic spines Can become neurons ??
Mononuclear cells	White cells from the circulation that readily enter and stay in the brain (lymphocytes, monocytes, and macrophages) and function as sentinels for the immune system

Table 2.7 Role of astrocytes in the central nervous system

1.	Forms a complete membrane on the external surface of the brain called the external glial limiting membrane, which enwraps all entering blood vessels
2.	Forms the inner glial membrane which fuses with the ependymal processes
3.	Isolates neuronal processes
4.	Forms the skeleton of the central nervous system
5.	Tends to segregate synapses and release or absorb transmitters
6.	Helps form the blood–brain barrier by enwrapping brain capillaries
7.	Forms the vessels of the glymphatic system (Jessen et al. 2015)
8.	Releases and absorbs gliotransmitters
9.	If the brain is damaged by infarction, for example, astrocytes proliferate and form scars—the scar will interfere with any successful axonal regeneration

Gliotransmitters (Table 2.8). Gliotransmitters were first identified in 1994, and in order to be included in this category, (1) they must be synthesized and or stored in astrocytes, (2) released triggered by physiological actions, (3) activated rapidly in neighboring cells, and (4) have a role in physiological processes.

2.3.2 *Oligodendrocytes (Fig. 2.9)*

In light micrographs, the oligodendrocyte has a small darkly stained nucleus surrounded by a thin ring of cytoplasm (Figs. 2.14 and 2.15). In electron micrographs, oligodendrocytes are dense cells with many microtubules and few neurofilaments (Fig. 2.6). Dense clumps of rough endoplasmic reticulum and clusters of polyribosomes are seen in the cytoplasm, which is denser but scantier than that in neurons. The nucleus tends to be located toward one pole of the cell; the nuclear chromatin tends to be heavily clumped. In electron micrographs, oligodendrocytes can be distinguished from astrocytes because they have a darker cytoplasm and nucleus, few if any filaments, and more heavily condensed chromatin (Fig. 2.6). The role of the oligodendrocyte is to form and maintain myelin (although they may also be responsible for breaking down myelin in multiple sclerosis). Oligodendrocytes are usually seen in close proximity to astrocytes and neurons, and all three cell types are important in forming and maintaining myelin.

2.3.3 *Endothelial Cells*

Endothelial cells form the lining of the capillaries in the central nervous system (Fig. 2.17). They are of mesodermal origin and bound together by tight junctions. Their tight junctions and pinocytosis provide the basis of the blood–brain barrier (see below).

2.3.4 *Mononuclear Cells: Monocytes and Microglia*

2.3.4.1 Mononuclear Cells/Mesodermal in Origin

Mononuclear cells—lymphocytes, monocytes, and histiocytes—are found in the central nervous system, where they act as phagocytes, breaking down myelin and neurons. Myelin destruction always triggers intense macrophage reaction within 48 h, followed by infiltration of monocytes first and then lymphocytes. Note that astrocytes have also been shown to engulf degenerating myelin sheaths, axonal processes, and degenerating synapses.

An Immunologically Privileged Site-NO

The central nervous system was once considered an immunologically privileged site because:

(a) It was thought that there was no specific lymph drainage from the central nervous system to alert the immune system of infection—not true.
(b) Neurons and glia do not express the major histocompatibility complex.

Table 2.8 Chemical gliotransmitters

Gliotransmitter	Cellular storage site	Release mechanism	Release stimulants and modulators	Site of action (receptor)	Cell targets and effects
Glutamate	SLMV, cytosol	Ca^{2+}-dependent exocytosis	Glutamate, GABA, ATP, PG, TNF-alpha, SDF1alpha	mGluR, AMPAR, kainite, NMDAR	Astrocyte, neurons, mostly stimulators
ATP	?DCG	Ca^{2+}-dependent exocytosis (activation of channels and/or transporters)	ATP, glutamate, dopamine, LPA, thrombin	P2X, P2Y	Astrocytes, microglia, neurons, blood vessel cells (mostly stimulators)
Adenosine	Cytosol	Ectonucleotidase-mediated ATP dephosphorylation (activation of channels and/or transporters)	ATP, glutamate, dopamine, LPA, thrombin	A1, A2	Neurons mostly inhibitors
D-Serine	?SLMV	Ca^{2+}-dependent exocytosis	Glutamate	NMDAR (glycine site)	Neurons (stimulators)
Eicosanoids (PG, HETE)	Not known to be stored	Ca^{2+}-dependent synthesis followed by rapid release	Glutamate, TNF-alpha, SDF1alpha, noradrenaline	Eicosanoid receptors	Astrocytes, microglia, neuron, blood vessel cells (mostly stimulators)
Cytokines TNF-alpha	Cell surface	Ca^{2+}-dependent TACE-mediated surface proteolysis	SDF1alpha	TNF-alpha receptors	Astrocytes, neurons (stimulators)
Proteins and peptides	DCG	Ca^{2+}-dependent exocytosis	Ach (for AchBP)	Ach binding, ANP, and other peptide receptors	Neurons (AchBP, inhibitors)
Taurine and homocysteic acid?					

Key: Activation of channels and/or transporters, Ach, acetylcholine
AchBP acetylcholine-binding protein, *ANP* atrial natriuretic peptide, *PAR* alpha amino 3-hydorxy 5 methyl-4-isoxaazole propionic acid glutamate receptor, *DCG* dense-core granules, *HETE* 20-frioxyeicosaltetraaenoicacid, *LPA* lysophosphatidic acid, *mGlur* metabotropic glutamate receptor, *NMDAR* *n*-methyl-dapartine glutamate receptor, *P2X,P2Y* purinergic 2X and 2Y receptors, *PG* prostaglandin, *SDF1alpha* stromal-derived factor-1alpha, *SLMV* synaptic-like microvesicle, *TACE* TNF-alpha-converting enzyme, *TNF* tumor necrosis factor alpha
Eicosanoid receptors are the physiologically active substances derived from arachidonic acid, including the prostaglandins (PG), thromboxanes (TX), leukotrienes (LT), and lipoxins (LX). The PGs and TXs are collectively identified as prostanoids
Adapted from Volterra and Meldolesi (2005). Astrocytes, from brain glue to communication elements. *Nature Review Neuroscience* 5: 626–640

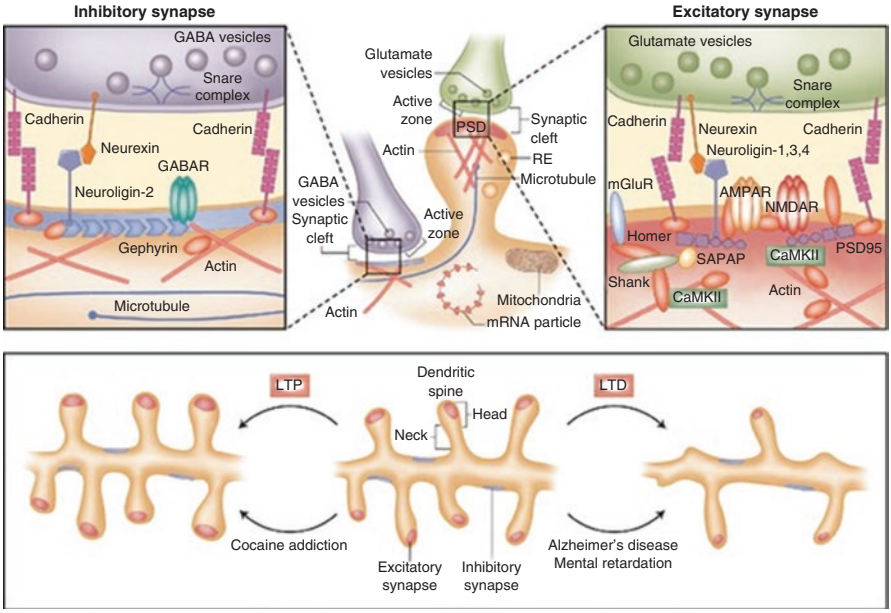


Fig. 2.17 Molecular architecture of inhibitory and excitatory synapses. Molecular architecture of inhibitory and excitatory synapses. *Top panels* show excitatory and inhibitory synapses. Excitatory synapses target on mature mushroom-shaped spines containing a prominent postsynaptic density (PSD), and inhibitory synapses are present along the dendritic shaft lacking postsynaptic thickening. Various organelles support the synapse; mitochondria provide energy, polyribosomes and RNA particles allow local protein synthesis, recycling endosomes (REs) transport internalized synaptic receptors back to the plasma membrane, and the cytoskeleton regulates spine dynamics. The abundant actin cytoskeleton is connected to the PSD and is the primary determinant of spine shape and motility. Transient invasion of dynamic microtubule into dendritic spines can regulate the formation of spine head protrusions and rapid spine growth. Excitatory and inhibitory synapses contain a unique set of channels, scaffolding proteins, and other postsynaptic molecules. The microanatomy of the inhibitory and excitatory synapses and their organization of proteins and protein–protein interactions are depicted in the *left* and *right panels*, respectively. Major families of postsynaptic proteins are shown, including scaffolding proteins, adhesion molecules, and receptors. *Lower panel* shows major morphologic events occurring in dendritic spines upon long-term potentiation (LTP, *left*) or long-term depression (LTD, *right*). In Alzheimer's disease and mental retardation, signaling cascades are triggered similar to LTD, leading to thinner, immature spines. In contrast, cocaine addiction shows similarities to LTP, resulting in bigger, mushroom-shaped, mature spines. The molecular and morphologic changes in the synapse are hallmarks of the disease pathology and are responsible for the cognitive alterations in neuropsychiatric diseases. *Abbreviations*: *CamKII* Ca^{2+}/calmodulin-dependent kinase II, *AMPAR* amino-3-hydroxy-5-methyl-4-isoazolepropionate receptor, *GABA* γ-aminobutyric acid, *GABAR* GABA receptor, *NMDAR* *N*-methyl-D-aspartate receptor, *mGluR* metabotropic glutamate receptor, *SAPAP* synapse-associated protein 90/PSD-95-associated protein (From Spronsen, Myrrhe; Hoogenraad, Casper, 2010)

(c) The major cell for stimulating the immune response (leukocyte dendritic cells) is not normally present in the disease-free nervous system.

It is now known that immune cells regularly enter the brain through the capillaries and that macrophages infected with human immunodeficiency virus (HIV), for example, can infect the brain directly, the so-called Trojan Horse phenomenon (Haase 1986; Price et al. 1988; Orenstein 2007).

Intracerebral vascular system. Recent studies have shown a lymphatic vascular system in the meninges of the brain (Louveau et al. 2015) and (Aspelund 2015) which is an alternative way for T-cells to enter the brain and provide immune responses which have a key role in fighting disease within the brain. In addition, there is a regular immune surveillance of the central nervous system, which is sufficient to control many viral infections (Sedgwick and Dorries 1991).

Microglial cells. Microglial cells originate from monocytes that enter the brain (Fig. 2.18; Table 2.9). *Neurons, astrocytes, and oligodendrocytes are ectodermal in origin, but microglial cells are mesodermal in origin*. The ovoid microglia cells are the smallest of the supporting cells and are divided into two categories: (**a**) perivascular cells and (**b**) the resting microglial cells in the brain parenchyma.

Pericytes are found in relation to capillaries but external to the endothelial cells and enwrapped in the basal lamina. In electron micrographs, they are not as electron dense as oligodendrocytes and lack the neurofilaments of the astrocyte and the tubules of the oligodendrocyte. The cytoplasm is denser than that of astrocytes and contains fat droplets and laminar dense bodies. The granular endoplasmic reticulum consists of long stringy cisterns.

Microglia are considered multipotent cells because with the proper stimulus, they can become macrophages. The pericyte contains actin, and this cell may well be important in controlling the channels entering the endothelial cells (Herman and Jacobson 1988).

The gut microbiome and the brain. There has been much recent interest in the relationship between the bacteria which live in the human gut, gut microbiota, and their communication with the brain and how it influences the functions in the brain and our well-being. This interaction between the CNS and the enteric nervous system/the brain in the gut (Chap. 9) is found throughout the GI system and can be self-functional or is bidirectional. The vagus nerve appears to be the key to the functions in the enteric nervous system and forms the major interface between the CNS and enteric systems, and also it affects the endocrine and immune system by modulating neurotransmitters (Gershon 1999). In addition, there is great variability in the types of flora that inhabits our GI system, and it is well known that they can become unhealthy and that may contribute to metabolic, autoimmune, and brain disorders including diabetes, seizure disorders, MS, and even Alzheimer's disease. Ongoing studies should better elucidate the actual role of our microbiome in relationship to our neural function and overall health.

Giant cells. Activated microglial cells can also evolve into giant multinucleated cells by the fusion of reactive cells. They are seen in viral infections and are consid-

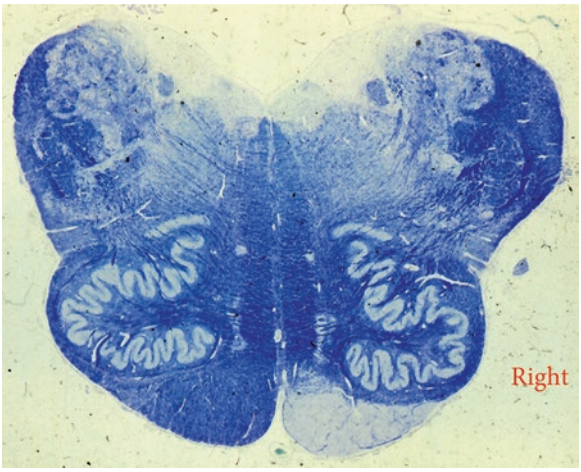


Fig. 2.18 Wallerian degeneration in the right medullary pyramid in a human several years after an infarct in the right motor–sensory strip—note that the absence of myelin is on the *right side* as this is ipsilateral to the lesion and above the decussation of the corticospinal tract. *Left side* is normal, Weigert myelin stain, ×90

Table 2.9 Microglial cells

Cell type	Function
Monocytes	Enter the brain during early development and is the stem cell of microglia
Pericytes	Found inside the brain in the (perivascular cell) basement membrane of the blood vessel and can act as a macrophage
Amoeboid microglia	Transitional form leads to resting microglia
Resting microglia	Downregulated from amoeboid (ramified) microglia, probably the sentinels in the brain that raise the alarm for invasive diseases
Activated microglia	Upregulated resting cell changes into partially activated macrophage with MHC class I
Reactive microglia	Fully activated macrophage with MHC class II and phagocytic properties and may become giant cells

ered the hallmark of AIDS dementia. These cells form by fusion of reactive cells, multinucleated cells associated with viral brain infections and Creutzfeldt–Jakob disease, hallmark of AIDS dementia. Reactive microglial cell is a fully active macrophage containing class II MHC and phagocytic activity. These cells are very active during all major disease states in the brain. Also called gitter cells, giant multinucleated cells are often found in patients with Creutzfeldt–Jakob disease, a transmissible spongiform degeneration (Fig. 2.19) and a disease caused by proteinaceous infectious particles or prions (Baker and Ridley 2001; Litzman 2001; Baker 2001). Compare the normal-appearing synapse in this case of Creutzfeldt–Jakob disease to that of the normal-appearing synapses and degenerating axons seen after an experimental lesion (Fig. 2.16a, b).

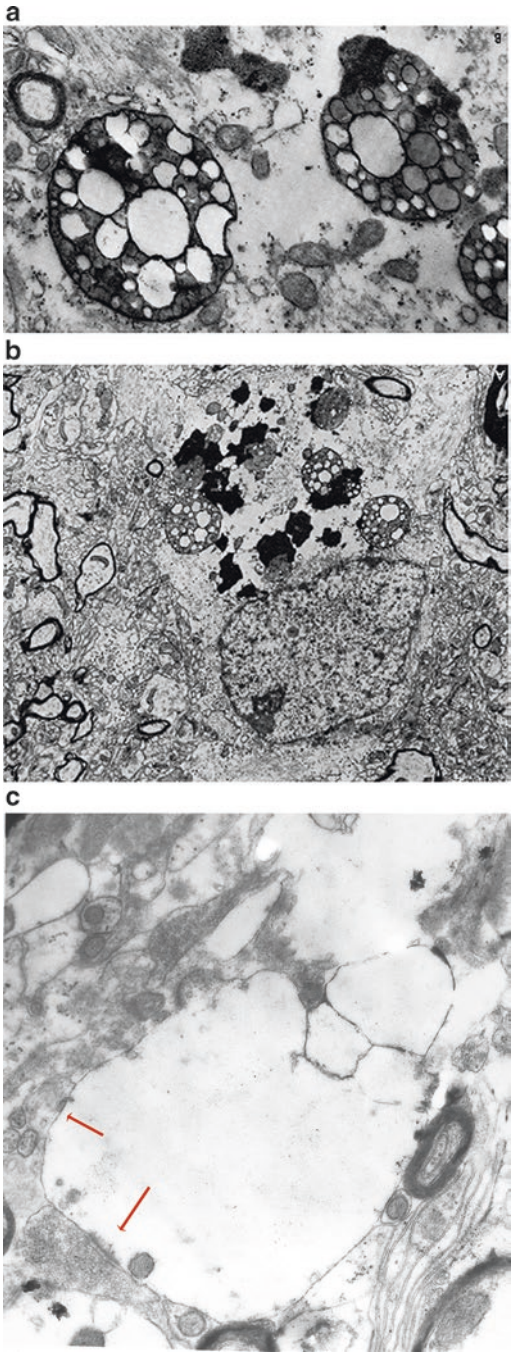


Fig. 2.19 Electron micrograph of a biopsy from the cortex of a 65-year-old male patient with Creutzfeldt–Jakob disease. (**a**, **b**) Reactive astrocytes, gitter cell, in the cerebral cortex. Note the prominent digestion vacuoles (**b**) at higher power. (**c**) Note the presence of intact synapse on the surface of the degenerating neurons in this case of spongiform neuronal degeneration ((**a**) ×8000; (**b**, **c**), ×35,000)

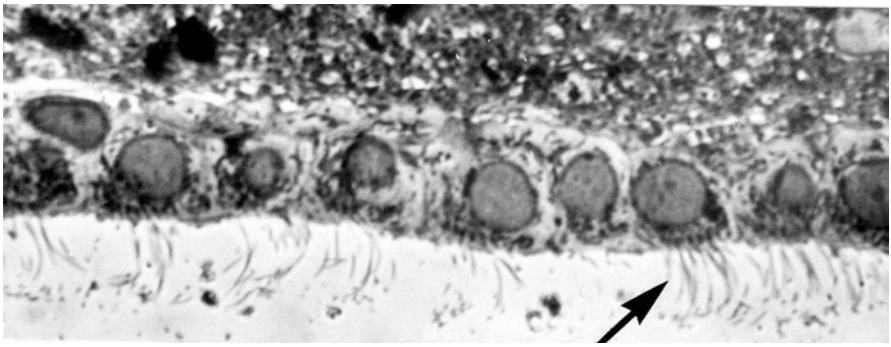


Fig. 2.20 Ependymal lining cell in the third ventricle of a rat. Note the prominent cilia extending into the ventricle (*arrows*) in this 1 μm plastic section

2.3.5 Ependymal Cells (Fig. 2.20)

Ependymal cells line all parts of the ventricular system (lateral ventricles, third ventricle, cerebral aqueduct, fourth ventricle, and spinal canal). They are cuboidal, ciliated, and contain filaments and other organelles. The processes of these cells extend in the central nervous system and fuse with astrocytic processes to form the inner limiting glial membrane. Highly modified ependymal cells are found attached to the blood vessels in the roof of the body of the lateral ventricles, the inferior horn of the lateral ventricles, and the third and fourth ventricles. There they form the choroid plexus, which secretes much of the cerebrospinal fluid (Fig. 2.21). Ependymal cells originate from the germinal cells lining the embryonic ventricle, but they soon stop differentiating and stay at the lumen on the developing ventricles.

2.3.6 Supporting Cells in the Peripheral Nervous System

Satellite cells. Satellite cells, which are found only in the peripheral nervous system among sensory and sympathetic ganglia, originate from neural crest cells. Many satellite cells envelop a ganglion cell. Functionally, they are similar to the astrocytes, although they look more like oligodendrocytes.

Schwann cells. Schwann cells are ectodermal in origin (neural crest) in the peripheral nervous system and function like oligodendrocytes, forming the myelin and neurilemmal sheath. In addition, the unmyelinated axons are embedded in their cytoplasm. Schwann cell cytoplasm stops before the nodes of Ranvier (Fig. 2.12), leaving spaces between the node and Schwann cells. In an injured nerve, Schwann cells can form tubes that penetrate the scar and permit regeneration of the peripheral axons. Nerve growth factor is important to the proliferation of the Schwann cells.

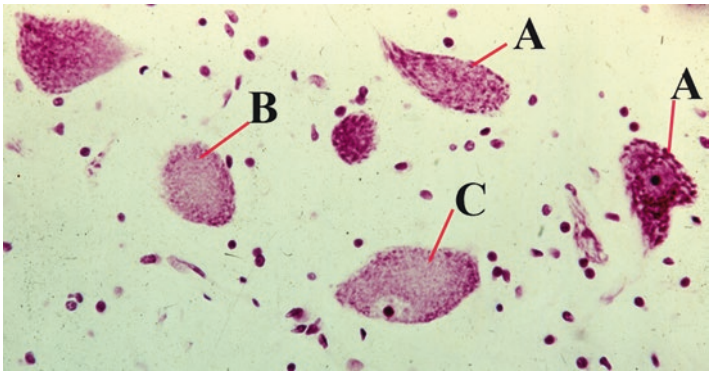


Fig. 2.21 Ventral horn cells in the human lumbar spinal cord after injury to the femoral nerve. (**a**) Normal ventral horn cell. (**b**) Chromatolytic neurons, showing a peripheral ring of Nissl substance (peripheral chromatolysis). (**c**) Chromatolytic neuron with eccentric nucleus and some dissolution of the cytoplasmic Nissl substance. Thionin Nissl stain, ×400)

Neural crest cells. These cells originate embryological as neuroectodermal cells on either side of the dorsal crest of the developing neural tube but soon drop dorsolateral to the evolving spinal cord area. Neural crest cells migrate out to form the following: dorsal root ganglion cells, cranial nerve ganglia, satellite cells, autonomic ganglion cells, Schwann cells of the peripheral nervous system, chromaffin cells of the adrenal medulla, calcitonin-secreting cells and carotid body type I cells, pigment cells of the integument, and pharyngeal arch cartilages. In the connective tissues, they form the following: corneal endothelium and stroma; tooth papillae; dermis; smooth muscle; adipose tissue of the skin of the head and neck; connective tissue of the salivary, lacrimal, thymus, thyroid, and pituitary glands; connective tissue of salivary, lachrymal, thymus, thyroid, and pituitary glands; connective tissue, and smooth muscle of aortic arch origin.

2.4 Response of the Nervous System to Injury

2.4.1 Degeneration

Neuronal death or atrophy may result from trauma, circulatory insufficiency (strokes), tumors, infections, metabolic insufficiency, developmental defects, and degenerative and heredodegenerative diseases.

1. **Retrograde changes in the cell body** (Fig. 2.21). Section of the axon or direct injury to the dendrites or cell body produces the following series of responses in the soma:

   (a) **Swelling** of nucleus, nucleolus, and cytoplasm. The nucleus is displaced from the center of the cell body and may even lie adjacent to the plasma

membrane of the neuron. The nucleus becomes eccentric as a direct response to injury of the axon or dendrite. Nissl substance appears to dissolve.

(b) **Chromatolysis of RNA**. The responses of neuronal soma to injury (chromatolysis) can be summarized in three steps.

(c) Synaptic degeneration is noted after interruption of the axoplasmic flow with a resultant increase in density in the synaptic ending prior to actual phagocytosis (Fig. 2.19). In a biopsy from a case of Creutzfeldt–Jakob disease, we have reported neuronal degeneration with intact-appearing synaptic endings still seen on these swollen neurons (Fig. 2.19c).

- **Dissolution** of the Nissl substance (ribosomal RNA), called *chromatolysis* (Fig. 2.19), allows the protein-manufacturing processes to be mobilized to help the neuron survive the injury. Slow dissolution of Nissl substance starts centrally in damaged neurons and proceeds peripherally, until only the most peripherally placed Nissl substance is left intact (which is probably essential to the protein metabolism to keep the surviving parts of the neuron alive and functional).
- **Proliferation** of metabolic processes in the nucleus including mRNA occurs. Endoplasmic reticulum and mitochondria start manufacturing membranes and increasing the energy available in the cell. The organelles in the cell actually swell. The mRNA then begins the manufacturing of membrane that is transported down the intact tubules into the growing axonal ending (growth cone). All other organelles in the cell body and dendrites also respond to the injury. The mitochondria swell, and the smooth endoplasmic reticulum proliferates to help in the formation of new plasma membrane and new myelin. These responses represent the increased energy requirements of the nerve cell and the need to form plasma membrane during the regenerative process.
- **Recovery**. If the cell survives the injury, all organelles return to normal: The nucleus returns to the center of the cell body, and the process in the nerve cell returns to its pretraumatic size. If the injury is too extensive, the neuron atrophies or dies. If seriously injured, the cell becomes atrophic or may be phagocytized.

2. **Atrophic change**. In atrophic change, the nerve cell is too severely damaged to repair itself. Consequently, the cell body shrinks and becomes smaller. This response is similar to the response of a nerve cell to insufficient blood supply, which produces an ischemic neuron. If necrosis occurs, the neuron cannot survive. The Nissl substance begins to disperse, and after 7 days, the nucleus becomes dark and the cytoplasm eosinophilic. Within a few days, these cells are phagocytized.
3. **Wallerian degeneration**. When an axon is sectioned, the distal part that is separated from the trophic center (cell body) degenerates, a process called Wallerian, or anterograde, degeneration (Figs. 2.22 and 2.23). At the same time, the cell body undergoes a process called axonal, or retrograde, degeneration. If the cell body remains intact, the proximal portion begins to regenerate. The distal stump is usually viable for a few days, but its degeneration begins within 13 h of injury. The axon starts to degenerate before the myelin sheath. In 4–7

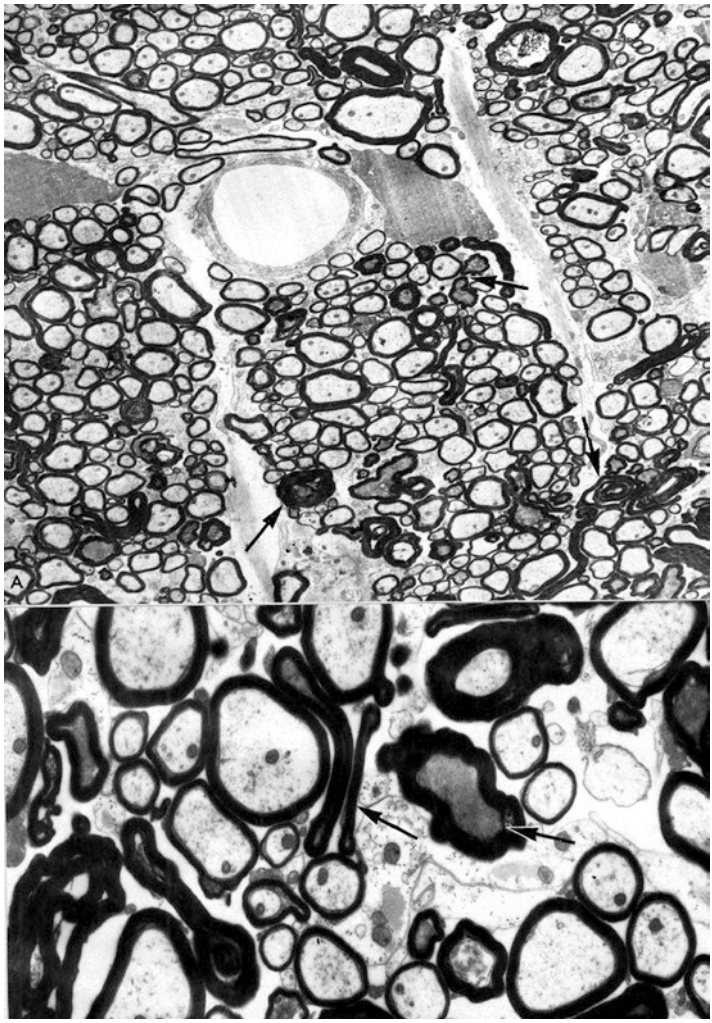


Fig. 2.22 Degenerating axons in the medullary pyramidal tract of a rat 15 days after removal of the motor cortex. (**a**) *Arrows* point out some degenerating axons, ×8000. (**b**) Showing details of degenerating axons. Note the collapsed axons and dense axoplasm and also the many axons unaffected by the lesion, ×20,000

days, the axon appears beaded and is beginning to be phagocytized by macrophages, which enter from the circulatory system. Fragments of degenerating axons and myelin are broken down in digestion chambers (Fig. 2.19), and it may take several months before all of the fragments are ingested. In the proximal portion, degenerative changes are noted back to the first unaffected node. As the myelin degenerates, it is broken up into smaller pieces that can be ingested more easily.

2.5 Regeneration

2.5.1 Peripheral Nerve Regeneration

Within a few days after section, the proximal part (attached to a functional neuronal soma) of the nerve starts regrowing. Nerve growth factor is produced after injury to the axon, and it promotes the axonal sprouting. If the wound is clean, e.g., a stab sound, sewing the nerve ends together can dramatically increase the rate of recovery in the affected limb. The regenerating nerves may cross the scar within several weeks. The crossing is helped by the Schwann cells and fibroblasts, which proliferate from the proximal end of the nerve. The Schwann cells form new basement membrane and provide tubes through which the regenerating axons can grow.

In certain peripheral nervous system diseases, only segmental degeneration occurs. One example is diphtheria: The myelin sheath degenerates but the axon remains intact. Phagocytes break down the myelin, and Schwann cells rapidly reform myelin. The rate of movement of the slow component of axoplasmic flow probably accounts for the rate of axonal regrowth, which is limited to about 1 mm a day. Slow components of the axoplasmic flow (-Scb) carry actin, fodrin, calmodulin, *Clathrina*, and glycolytic enzymes that form the network of microtubules, intermediate filaments, and the axolemma, which limit the rate of daily axonal regeneration, although functional recovery may be a little faster (McQuarrie and Grafstein 1983; Wujek and Lasek 1983; Kandel et al. 2000, 2009).

Motor fiber may also reinnervate the wrong motor end plate, as when a flexor axon innervates an extensor. In such a case, the patient has to relearn how to use the muscle. The muscle that is denervated assists the regenerating axons by expressing molecules that influence the regenerating axons. Some of the molecules are concentrated in the synaptic basal lamina of the muscle. Other molecules are upregulated following denervation and help in attracting and reestablishing the synapse in the muscle. These upregulated molecules include growth factors (IGF-3 and FGF-5), acetylcholinesterase (AChE), agrin, laminin, s-laminin, fibronectin, collagen, and the adhesion molecules N-CAM and N-cadherin (Hall and Sanes 1993; Horner and Gage 2000, 2016). Successful nerve regeneration also depends on an adequate blood supply. For example, in a large gunshot wound, nerves attempt to regenerate but may not succeed.

The following is a summary of the sequence of regeneration in the peripheral nervous system:

1. Peripheral nerve is interrupted.
2. The axon dies back to the first unaffected node of Ranvier, with the myelin and distal axon beginning to degenerate within 3–4 h.
3. At the site of injury, the axon and myelin degenerate to form a scar. Phagocytosis begins within 48 h.
4. Axons separated from the cell body degenerate. With an adequate blood supply, the portion of the axon still connected to the intact cell body begins regenerating by sprouting.

5. Within 72 h, Schwann cells begin to proliferate and form basement membranes and hollow tubes. Nerve growth factor is also formed and released that stimulates sprouting.
6. From each of the severed axons, sprouts attempt to penetrate the scar. After one sprout successfully grows through the scar, the other sprouts die. Nerves take a month or more to grow through the scar.
7. Once an axon penetrates the scar, it grows at 1 mm/day; about one-third of the severed axons actually reinnervate the muscle and skin.

2.5.2 Regeneration in the Central Nervous System

After an injury, axons in the central nervous system regenerate, but there seems to be no equivalent to the Schwann cell because oligodendrocytes and astrocytes do not form tubes to penetrate the scar. Instead, they form a scar that is nearly impenetrable. Even if the axons penetrate the scar, they have no means of reaching the neuron to which they were originally connected. Horner and Gage (2000) have reviewed the question of how to regenerate the damaged central nervous system in the brain that is inherently very plastic. They have noted that it is not the failure of neuronal regeneration, but it is rather a feature of the damaged environment; and it is now possible to reintroduce the factors present in the developing nervous system that produced this wonderful organ. The gene responsible for needed growth factors is probably missing or inactivated in adult tissue. Recently a brain-derived neurotrophic factor has been identified, which may eventually help in finding a way to guide the axon, and also the identification of a potent inhibitor of neurite outgrowth associated with myelin, NoGo-A. Developmentally NoGo is important in migration and neurite growth, while in the adult, it has negative functions in recovery from injuries. Efforts are focused to develop agents to counteract its effects (Schwab 2012). Animal studies have shown that neurons have considerable plasticity. That is, if some axons in a region die off, bordering unaffected axons will sprout and form new synapses over many months, filling in where the synapses were and resulting in major functional reorganization. This reorganization may eventually produce some recovery of function.

Bypassing the scar. To bypass the obstacles produced by the scar, it has been shown in experiments with rodents that scaffolds made from silk fibroin (Liu 2016) or carbon nanotubes (Ahn et al. 2015) can be placed between regions in the brain with resultant successful axonal regeneration into damaged regions. Studies using scaffolding are currently being undertaken in humans with lesions in the spinal cord.

2.5.3 Neurogenesis in the Adult Brain Stem

Functional neurogenesis occurs throughout life in the adult brain in dentate gyrus of the hippocampus, from the subventricular zone of the lateral ventricle and olfactory bulbs. Gage and colleagues have shown that these immature neurons can be

encouraged to mature and even become functional by environmental enrichment and exercise (Gage 2000, 2002; Nokia et al. 2016).

Stem cells. A source of replacement for damaged neurons? In addition to these immature cells in the dentate gyrus and olfactory bulbs, in the adult brain, neuronal stem cells have been identified in the many regions of the brain and spinal cord. It may be possible under the right conditions to also activate these cells and help to reverse the effects of lesions in the CNS (Kornack and Rackic 1999). After the implantation of immature neurons (neuroblasts) in regions affected by certain diseases (e.g., the corpus striatum of patients with Parkinson's disease), there has been some recovery (Sladek and Gash 1984; Gage et al. 1991). In Parkinsonian patients, the age of the individual receiving the transported cells seems to affect the outcome with younger patients (less than 50 years of age) more likely to show some improvement.

2.5.4 Nerve Growth Factors (NGF)

The first nerve growth factor was isolated by Levi-Montalcini and Angeletti in Levi-Montalcini and Angeletti 1968—Nobel Prize in 1986 shared with S Cohen—but only recently have biotechnology techniques been able to produce these factors in large quantities. NGF is now being tested to help in many diseases by improving the nasal delivery method and gene delivery, and recently its role in immune system regulation has been identified.

Attempts have been made to help regeneration in the central nervous system, for instance, by physically placing Teflon tubes on Schwann cells through the scarred portion of the spinal cord in the hope that the nerves would follow these channels. However, even though nerves do grow down these channels, no functional recovery occurs.

Many factors that promote neuronal survival and axon outgrowth (e.g., brain-derived neurotrophic factor, BDNF) have been identified, and the focus is now on getting these cells to produce axons to grow into the injured areas and then to grow through into the uninjured area. With the identification of neurotrophic factor (netrins 1 and 3) that produces axonal growth (Serafini et al. 1994) and with the studies of programmed cell death, we are beginning to identify genes that may be responsible for premature neuron death (Oppenheim 1991); we are now entering an era of brain research that offers great promise to help patients with neurodegenerative diseases: Huntington's, Parkinson's, and Alzheimer's.

2.5.5 Glial Response to Injury

Neuronal death triggers an influx of phagocytic cells by releasing factors which attract white cells from the blood stream, and the indwelling microglia proliferate and break down the dying neurons.

Necrosis. In organs with numerous fibroblasts, necrotic areas are soon filled with proliferating fibroblasts, but in the central nervous system, there are few fibroblasts, and the astrocytes do not proliferate in sufficient numbers. Within a few days of an ischemic attack with infarction, neutrophils are seen at the site of injury. Shortly thereafter, microglial cells and histiocytes are seen in the region of the dying cells. Since the blood–brain barrier is usually compromised, monocytes may now migrate into the parenchyma of the central nervous system in greater numbers and assist in phagocytosis. The time it takes for the complete removal of injured cells depends on the size of the lesion. Large infarcts may take several years before phagocytosis is complete. If the lesion is huge, such as a large infarct in the precentral gyrus, a cavity lined by astrocytic scar will form. In small lesions, the neurons are phagocytized glia proliferate, a process called replacement gliosis.

2.6 Blood–Brain Barrier

2.6.1 Blood–Brain Barrier (Fig. 2.24)

Endothelial cells form this barrier in the central nervous system. The endothelial cells line the capillaries, and the choroid plexuses are joined together by tight junctions, zonula occludens. The capillaries are not perforated, and the endothelial cells show very little pinocytosis or receptor-mediated endocytosis (Brightman 1989; Pardridge 2006). This endothelial lining is called the blood–brain barrier because it is very selective to certain large molecules and dyes and limits the entry of other substances, including amino acids, water, glucose, and electrolytes into the brain parenchyma. This interface between the brain and blood system can be modulated and even opened by many inflammatory mediators (bradykinin, histamine, serotonin, arachidonic acid), some of which can affect the tight junctions and also affect the neuron and adjoining glia, pericytes, smooth muscles, and cells. Factors which modulate the BBB have also been used to treat disease within the brains including cancers and infections.

In the peripheral nervous system, the endothelial cells are fenestrated and very active in *pinocytosis*. Fluid-phase endocytosis in the peripheral nervous system is relatively nonspecific; the endothelial cells engulf molecules and then internalize them by vesicular endocytosis. In receptor-mediated endocytosis, which is found in the central nervous system, a ligand first binds to a membrane receptor on one side of the cell. After binding to the ligand, the complex is internalized into a vesicle and transported across the cell, and the ligand is usually released.

All vascular branches within the central nervous system are surrounded by a thin covering formed by astrocytic processes (Fig. 2.23). However, the astrocytic processes do not fuse with the endothelial lining of the blood vessel or with the processes of other cells, so they have minimal effect on limiting the entry of solutes into the brain parenchyma. Thus, the extracellular space can be entered once the materials pass through the endothelium.

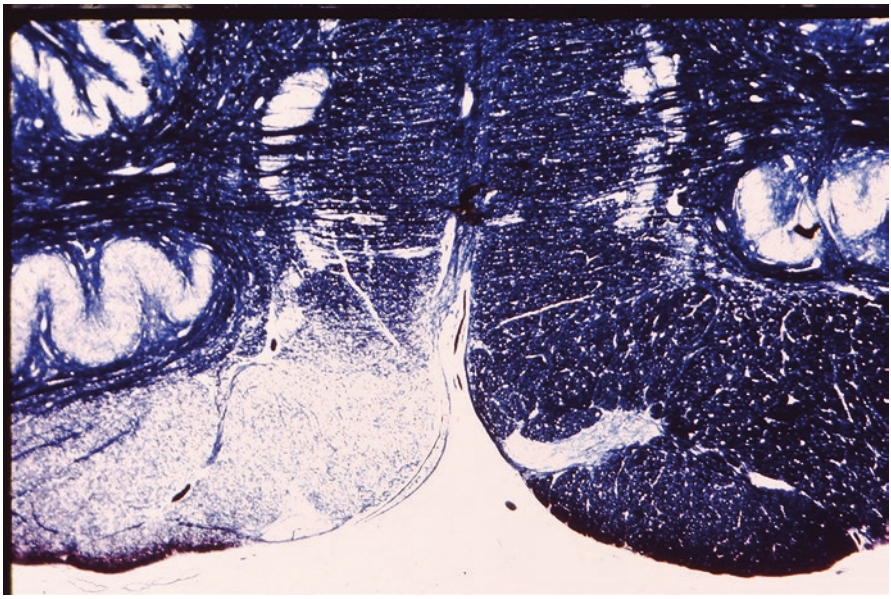


Fig. 2.23 Wallerian degeneration in the left medullary pyramid in a human several years after an infarct in the left motor–sensory strip—note that the absence of myelin is on the *left side* and this is above the decussation of the corticospinal tract. *Right side* is normal, Weigert myelin stain, ×90

The intravenous perfusion of various dye compounds (trypan blue, Evans blue) or stress has been shown to open the blood–brain barrier by activating the hypothalamic–hypophyseal–adrenal axis and release CRH (Esposito et al. 2001). Acute lesions of the central nervous system including those caused by infections usually increase the permeability of the barrier and alter the concentrations of water, electrolytes, and protein. In some viral diseases, for example, infected leukocytes (macrophages) more easily penetrate directly into the brain by passing between the normally tight junctions in the endothelial cells. This is one way HIV enters the brain from the blood. Also, central nervous system tumors produce growth factors that cause blood vessels to sprout. These new capillaries have immature tight junctions that are also quite leaky and have been studied with some success as a way to deliver chemotherapeutic agents specifically to the tumor.

2.6.2 Extracellular Space

Between the cells in the central nervous system is the extracellular space, measuring between 30 and 40 nm and filled with cerebrospinal fluid (CSF) and other solutes. The CSF is formed primarily by the choroid plexus in the lateral ventricle,

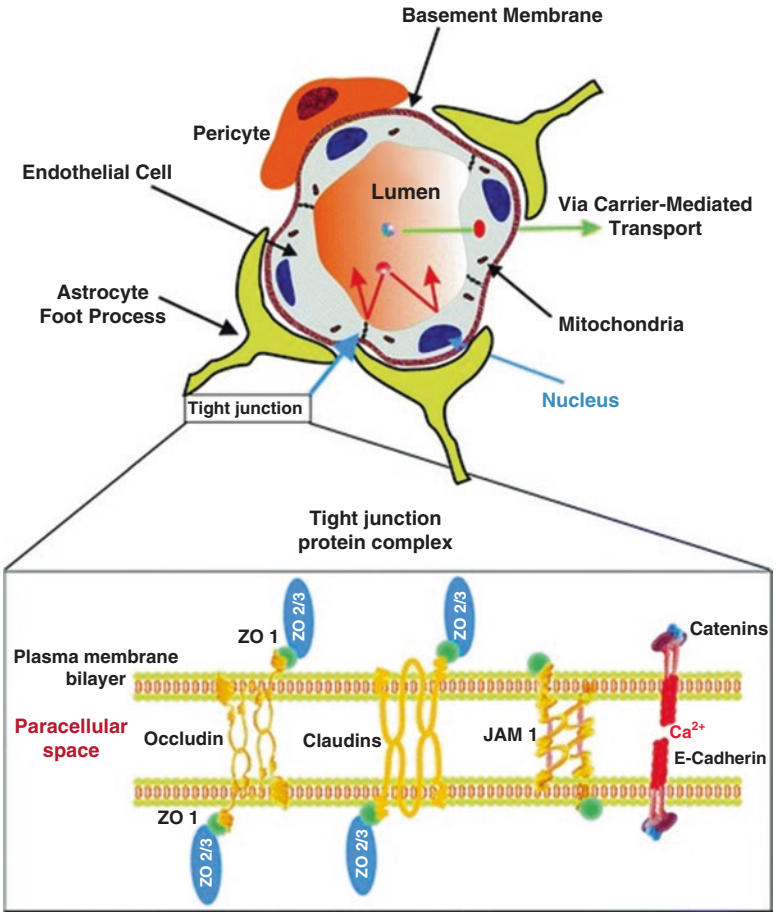


Fig. 2.24 Schematic representation of a brain microvasculature. The blood–brain barrier is created by the tight apposition of contiguous endothelial cells. Note the endothelial cells lining the blood vessels are in close contact with a variety of accessory cells such as astrocytes and pericytes which modulate the expression of BBB characteristics. Tight junctions between contiguous endothelial cells prevent the passage of large molecules and pathogens between the blood and the brain. Tight junctions consist of rows of transmembrane proteins (major types are claudins, occludins, and junctional adhesion molecules) anchored in the membranes of two adjacent endothelial cells, while the intracellular portion is anchored to cytoskeletal proteins (e.g., actin) through scaffold protein such as ZO-1. From Cucullo, Luca, **Book:** *Mammalian Brain Development*

third ventricle, and fourth ventricle (Fig. 2.24). The amount of extracellular space in the brain is still a matter of controversy. Chemicals (gliotransmitters; see Table 2.7) can readily pass from the glia cells to the extracellular space and affect the neurons. Solutes from the blood plasma also readily enter through the endothelial lining into the extracellular space, and the solutes present in this space (whether deleterious or not) affect the functions of the central nervous system. A

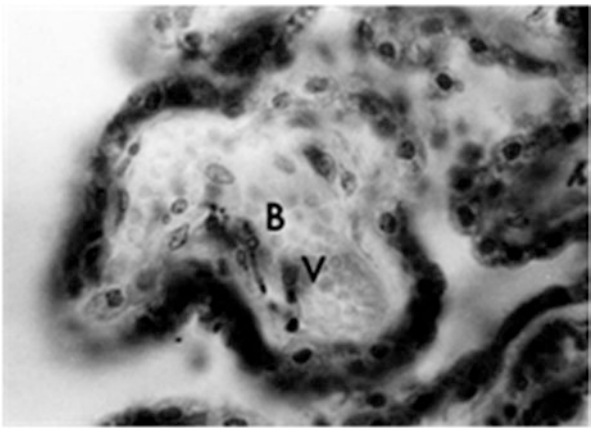


Fig. 2.25 Site of cerebrospinal fluid production (CSF): the choroid plexus in the fourth ventricle. Note the blood vessel (BV) in the center and the cuboidal epithelial cells (*arrow*) that form the CSF on the outside of the vessel (×300)

small portion of the cerebrospinal fluid appears to be formed by the diffusion of extracellular fluid. Cerebrospinal fluid may also be reabsorbed after temporary storage in the extracellular space. Fat-soluble compounds that readily pass through the blood–brain barrier can enter the extracellular space and may be useful in resolving infections in the central nervous system or in improving the function of certain brain cells.

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