Box 7–3 Defects in Myelin Proteins Disrupt Conduction of Nerve Signals (continued)

In the peripheral nervous system, MAG is expressed by Schwann cells early during production of myelin and eventually becomes a component of mature (compact) myelin. Its early expression, subcellular location, and structural similarity to other surface recognition proteins suggest that it is an adhesion molecule important for the initiation of the myelination process. Two isoforms of MAG are produced from a single gene through alternative RNA splicing.

The major protein in mature peripheral myelin, *myelin protein zero* (MPZ or P_0), spans the plasmalemma of the Schwann cell. It has a basic intracellular domain and, like MAG, is a member of the immunoglobulin superfamily. The glycosylated extracellular part of the protein, which contains the immunoglobulin domain, functions as a homophilic adhesion protein during myelin-ensheathing by interacting with identical domains on the surface of the apposed membrane. Genetically engineered mice in which the function of P_0 has been eliminated have poor motor coordination, tremors, and occasional convulsions.

Observation of *trembler* mouse mutants led to the identification of *peripheral myelin protein 22* (PMP22). This Schwann cell protein spans the membrane four times and is normally present in compact myelin. PMP22 is altered by a single amino acid in the mutants. A similar protein is found in humans, encoded by a gene on chromosome 17.

Mutations of the *PMP22* gene on chromosome 17 produce several hereditary peripheral neuropathies, while a duplication of this gene causes one form of *Charcot-Marie-Tooth disease* (Figure 7–18). This disease is the most common inherited peripheral neuropathy and is characterized by progressive muscle weakness, greatly decreased conduction in peripheral nerves, and cycles of demyelination and remyelination. Because both duplicated genes are active, the disease results from *increased* production of PMP22 (a two- to threefold increase in gene dosage). Mutations in a number of genes expressed by Schwann cells can produce inherited peripheral neuropathies.

In the central nervous system, more than half of the protein in myelin is the proteolipid protein (PLP), which has five membrane-spanning domains. Proteolipids differ from lipoproteins in that they are insoluble in water. Proteolipids are soluble only in organic solvents because they contain long chains of fatty acids that are covalently linked to amino acid residues throughout the proteolipid molecule. In contrast, lipoproteins are noncovalent complexes of proteins with lipids and often serve as soluble carriers of the lipid moiety in the blood.

Many mutations of PLP are known in humans as well as in other mammals, eg, the *jimpy* mouse. One example is Pelizaeus-Merzbacher disease, a heterogeneous X-linked disease in humans. Almost all PLP mutations occur in a membrane-spanning domain of the molecule. Mutant animals have reduced amounts of (mutated) PLP, hypomyelination, and degeneration and death of oligodendrocytes. These observations suggest that PLP is involved in the compaction of myelin.

A

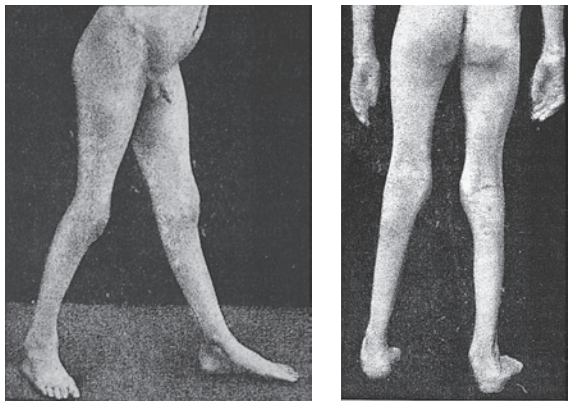
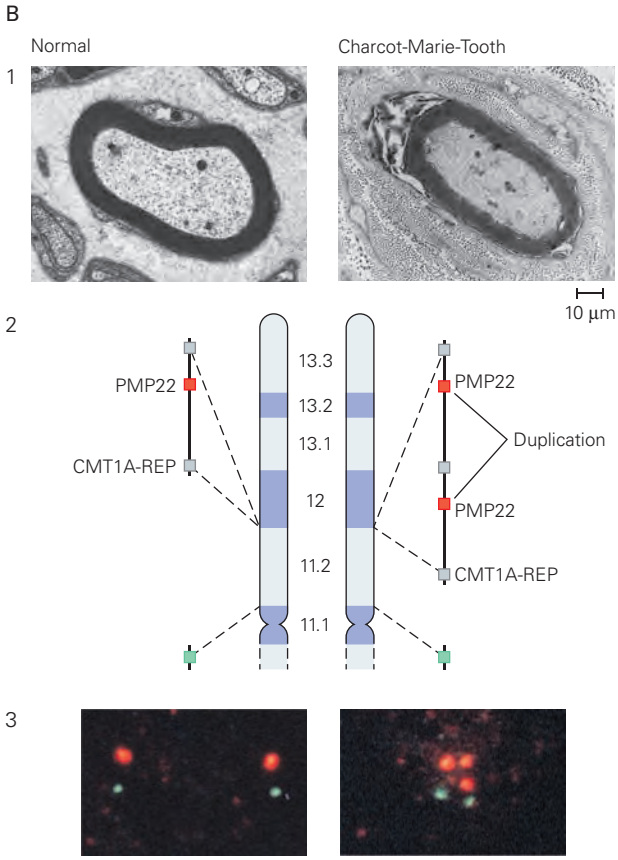


Figure 7–18 Charcot-Marie-Tooth disease (type 1A) results from increased production of peripheral myelin protein 22.

A. A patient with Charcot-Marie-Tooth disease shows impaired gait and deformities. (Reproduced, with permission, from Charcot's original description of the disease, Charcot and Marie 1886.)



B. The disordered myelination in Charcot-Marie-Tooth disease (type 1A) results from increased production of peripheral myelin protein 22 (PMP22).

1. Sural nerve biopsies from a normal individual (reproduced, with permission, from A.P. Hays) and from a patient with Charcot-Marie-Tooth disease (reproduced, with permission, from Lupski and Garcia 1992). In the patient's biopsy, the myelin sheath is slightly thinner than normal and is surrounded by concentric rings of Schwann cell processes. These changes are typical of the recurrent demyelination and remyelination seen in this disorder.

2. The increase in PMP22 is caused by a duplication of a normal 1.5-Mb region of the DNA on the short arm of chromosome 17 at 17p11.2-p12. The *PMP22* gene is flanked by two similar repeat sequences (CMT1A-REP), as shown in the normal chromosome 17 on the *left*. Normal individuals have two normal chromosomes. In patients with the disease (*right*), the duplication results in two functioning *PMP22* genes, each flanked by a repeat sequence. The normal and duplicated regions are shown in the expanded diagrams indicated by the **dashed lines**. (The repeats are thought to have given rise to the original duplication, which was then inherited. The presence of two similar flanking sequences with homology to a transposable element is believed to increase the frequency of unequal crossing over in this region of chromosome 17 because the repeats enhance the probability of mispairing of the two parental chromosomes in a fertilized egg.)

3. Although a large duplication (3 Mb) cannot be detected in routine examination of chromosomes in the light microscope, evidence for the duplication can be obtained using fluorescence in situ hybridization. The *PMP22* gene is detected with an oligonucleotide probe tagged with the dye Texas Red. An oligonucleotide probe that hybridizes with DNA from region 11.2 (indicated by the green segment close to the centromere) is used for in situ hybridization on the same sample. A nucleus from a normal individual (*left*) shows a pair of chromosomes, each with one red site (*PMP22* gene) for each green site. A nucleus from a patient with the disease (*right*) has one extra red site, indicating that one chromosome has one *PMP22* gene and the other has two *PMP22* genes. (Adapted, with permission, from Lupski et al. 1991.)

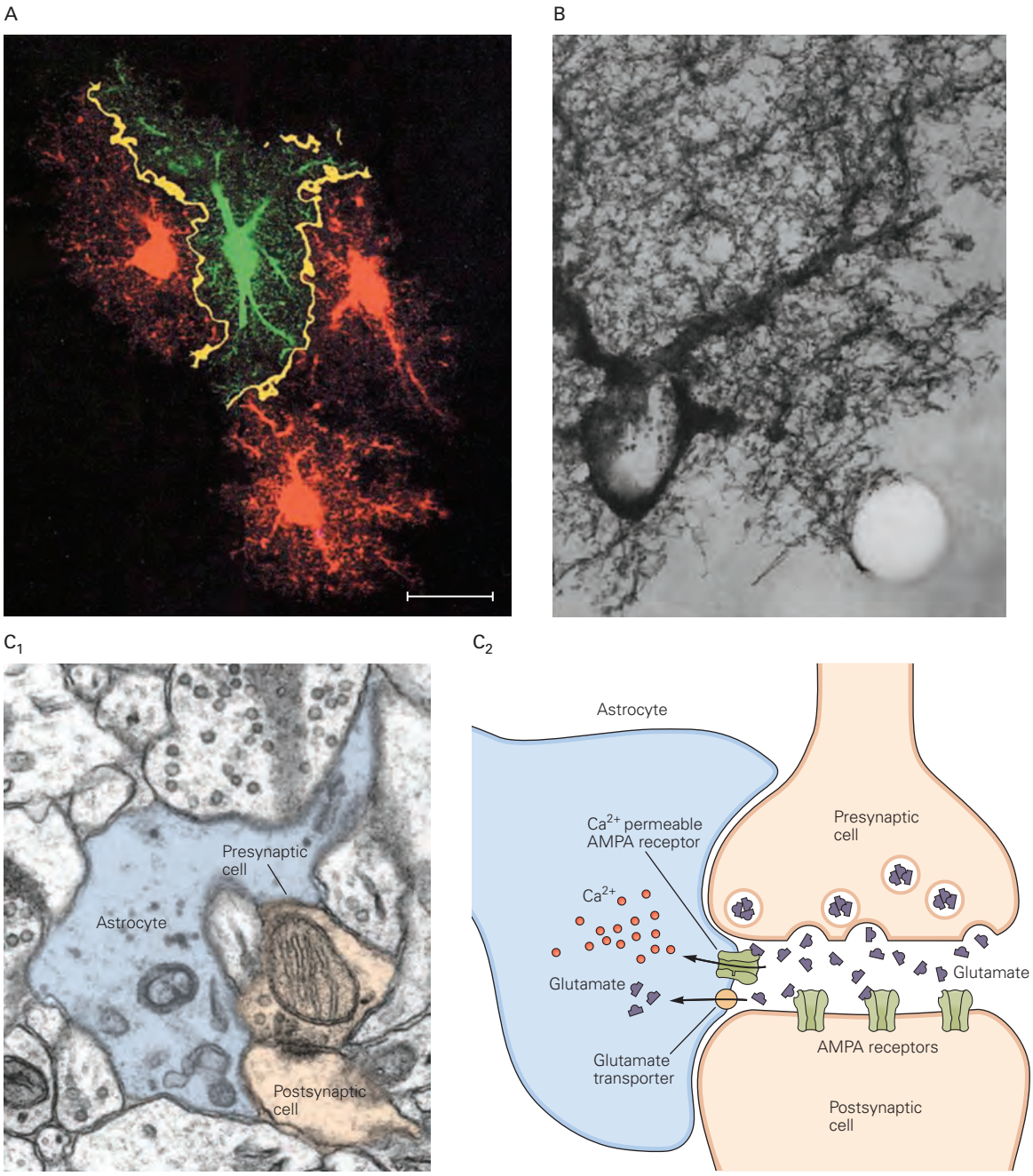


Figure 7–19 Astrocyte processes are intimately associated with synapses.

A. Astrocytes occupy discrete volumes. The central astrocyte (**green**) is shown to occupy a volume distinct from its three neighbors (**red**), with only a small overlap (**yellow**) at the ends of their processes, which are interconnected by gap junctions Bar = 20 µm. (Reproduced, with permission, from Bushong et al. 2002. Copyright © 2002 Society for Neuroscience.)

B. This high-voltage electron micrograph shows several thick processes emanating from the cell body of an astrocyte and branching into extraordinarily fine processes. The typical envelopment of a blood vessel is shown at lower right. (Reproduced, with permission, from Hama et al. 1994. Copyright © 1994 Wiley.)

C. The processes of astrocytes are intimately associated with both presynaptic and postsynaptic elements. **1.** The close association between astrocyte processes and synapses is seen in this electron micrograph of hippocampal cells. (Reproduced, with permission, from Ventura and Harris 1999. Copyright © 1999 Society for Neuroscience.) **2.** Glutamate released from the presynaptic neuron activates not only receptors on the postsynaptic neuron but also AMPA-type (α-amino-3-hydroxy-5-methylisoxazole-4-propionate) receptors on astrocytes. Astrocytes remove glutamate from the synaptic cleft by uptake through high-affinity transporters. (Adapted from Gallo and Chittajallu 2001.)

nearby neuronal activity by triggering the release of nutrients and regulating blood flow. An increase in Ca^{2+} in astrocytes leads to the secretion of signals that enhance synaptic function and even behavior. Thus astrocyte–neuron signaling contributes to normal neural circuit functioning.

Astrocytes also are important for the development of synapses. Their appearance at synapses in the postnatal brain coincides with periods of synaptogenesis and synapse maturation. Astrocytes prepare the surface of the neuron for synapse formation and stabilize newly formed synapses. For example, astrocytes secrete several synaptogenic factors, including thrombospondins, hevin, and glycipans, that promote the formation of new synapses. Astrocytes can also help remodel and eliminate excess synapses during development by phagocytosis (Chapter 48). In the adult CNS, astrocytes continue to phagocytose synapses, and as this phagocytosis is dependent on neuronal activity, it is possible that this remodeling of synapses contributes to learning and memory. In pathological states, such as chromatolysis produced by axonal damage, astrocytes and presynaptic terminals temporarily retract from the damaged postsynaptic cell bodies. Astrocytes release neurotrophic and gliotrophic factors that promote the development and survival of neurons and oligodendrocytes. They also protect other cells from the effects of oxidative stress. For example, the glutathione peroxidase in astrocytes detoxifies toxic oxygen free radicals released during hypoxia, inflammation, and neuronal degeneration.

Finally, astrocytes ensheathe small arterioles and capillaries throughout the brain, forming contacts between the ends of astrocyte processes and the basal lamina around endothelial cells. The CNS is sequestered from the general circulation so that macromolecules in the blood do not passively enter the brain and spinal cord (the *blood–brain barrier*). The barrier is largely the result of tight junctions between endothelial cells and cerebral capillaries, a feature not shared by capillaries in other parts of the body. Nevertheless, endothelial cells have a number of transport properties that allow some molecules to pass through them into the nervous system. Because of the intimate contacts of astrocytes and blood vessels, the transported molecules, such as glucose, can be taken up by astrocyte end-feet.

Following brain injury and disease, astrocytes undergo a dramatic transformation called *reactive astrocytosis*, which involves changes in gene expression, morphology, and signaling. The functions of reactive astrocytes are complex and poorly understood, as they both hinder and support CNS recovery. Recent studies have found evidence for at least two kinds of reactive astrocytes; one type helps to promote repair and recovery, whereas another is harmful, actively contributing to the death of neurons after acute CNS injury; however there are likely other subtypes. These neurotoxic reactive astrocytes are prominent in patients with Alzheimer disease and other neurodegenerative diseases and thus are an attractive target for new therapies. An interesting question is why the brain ever generates a neurotoxic reactive astrocyte. Quite possibly, removal of injured or sick neurons allows synapses to reorganize to help preserve neural circuit function. In addition, removal of virally infected neurons could help limit the spread of viral infections.

Microglia Have Diverse Functions in Health and Disease

Microglia compose about 10% of glia in the CNS and exist in multiple morphological states in the healthy and damaged brain. Despite being described by Rio Hortega over 100 years ago, the functions of microglia are poorly understood compared to other cell types. Unlike neurons, astrocytes, and oligodendrocytes, microglia do not belong to the neuroectodermal lineage. Long thought to derive from the bone marrow, recent fate mapping studies reveal that microglia are in fact derived from myeloid progenitors in the yolk sac.

Microglia colonize brain very early in embryonic development and reside in all regions of the brain throughout life (Figure 7–20). During development, microglia help sculpt developing neural circuits by engulfing pre- and postsynaptic structures (Figure 7–21), and emerging evidence suggests microglia may modulate other aspects of brain development and brain homeostasis. Recent in vivo imaging studies have revealed dynamic interactions between microglia and neurons. In the healthy adult cerebral cortex, microglia processes continuously survey their surrounding extracellular environment and contact neurons and synapses, but the functional significance of this activity remains unknown.

Following injury and disease, microglia undergo a dramatic increase in the motility of their processes and changes in morphology and gene expression and can be rapidly recruited to sites of damage where they can have beneficial roles. For example, they serve to bring lymphocytes, neutrophils, and monocytes into the CNS and expand the lymphocyte population, important immunological activities in infection, stroke, and immunologic demyelinating disease. They also protect the brain by phagocytosing debris as well as unwanted

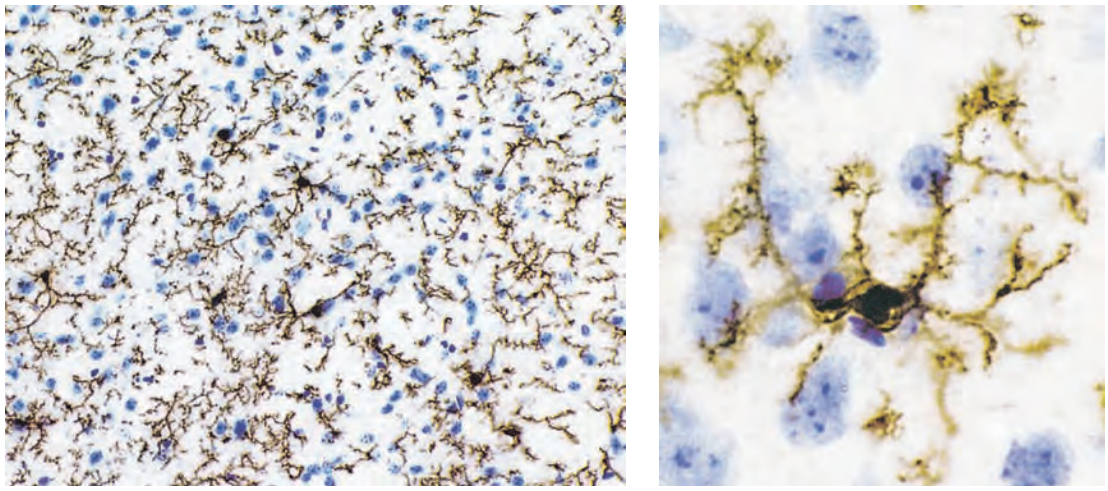


Figure 7–20 Large numbers of microglia reside in the mammalian central nervous system. The micrograph on the *left* shows microglia (in **brown,** immunocytochemistry) in the cerebral cortex of an adult mouse. The **blue** blobs are the nuclei of nonmicroglial cells. The microglial cells have fine, lacy processes, as shown in the higher magnification micrograph on the *right*. (Reproduced, with permission, from Berry et al. 2002.)

and dying cells and toxic proteins, actions that are critical for preventing further damage and maintaining brain homeostasis. Although critical for the immune response to infection or trauma, microglia also contribute to pathological neuroinflammation by releasing cytokines and neurotoxic proteins and by inducing neurotoxic reactive astrocytes. They also contribute to synapse loss and dysfunction in models of Alzheimer disease and neurodegenerative disease.

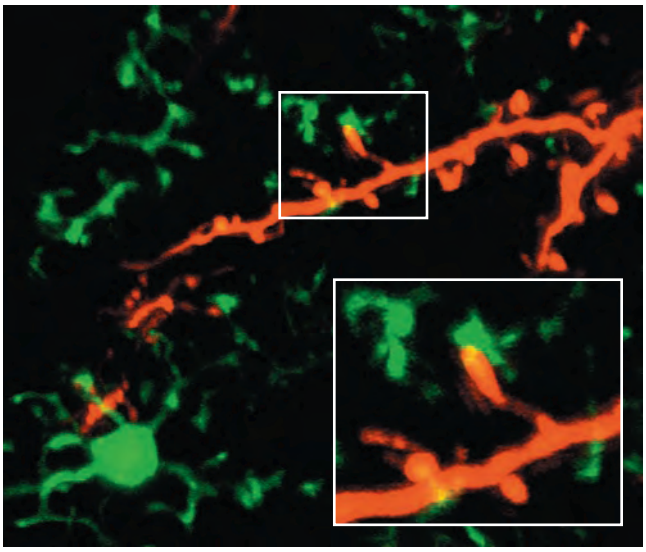


Figure 7–21 Microglia interact with and sculpt synaptic elements in the healthy brain. Two-photon imaging in the olfactory bulb of adult mice shows microglial processes expressing a fractalkine receptor–GFP fusion (CX3CR1-GFP) (**green**) connecting to tdTomato-labeled neurons (**red**). (Reproduced, with permission, from Hong and Stevens 2016.)

Choroid Plexus and Ependymal Cells Produce Cerebrospinal Fluid

The function of neurons and glia is tightly regulated by the extracellular environment of the CNS. *Interstitial fluid* (ISF) fills spaces between neurons and glia in the parenchyma. *Cerebrospinal fluid* (CSF) bathes the brain's ventricles, the subarachnoid space of the brain and spinal cord, and the major cisterns of the CNS. The ISF and CSF deliver nutrients to cells in the CNS, maintain ion homeostasis, and serve as a removal system for metabolic waste products. In conjunction with the meningeal layers that surround the brain and spinal cord, the CSF provides a cushion that protects CNS tissues from mechanical damage. The fluid environment of the CNS is maintained by endothelial cells of the blood–brain barrier and choroid plexus epithelial cells of the blood–CSF barrier. These barriers not only serve to regulate the extracellular environment of the brain and spinal cord but also relay critical information between the CNS and the periphery.

The cells of the *choroid plexus* and the *ependymal layer* contribute to CSF production, composition, and dynamics. The choroid plexuses appear as epithelial invaginations soon after neural tube closure where the lateral, third, and fourth ventricles will eventually

form. Through embryonic development, the choroid plexuses mature, each forming a ciliated cuboidal epithelial layer that encapsulates a stromal and immune cell network and an extensive capillary bed. The ependyma is a single layer of ciliated cuboidal cells, a type of glia cell that lines the ventricles of the brain. At several places in the lateral and fourth ventricles, specialized ependymal cells form the epithelial layer that surrounds the choroid plexus (Figure 7–22B).

The choroid plexus produces most of the CSF that bathes the brain. Loose junctions between ependymal cells provide access for CSF to the brain's interstitial space. Ciliary motion in the ependymal cells helps to move CSF through the ventricular system (Figure 7–22A), facilitating long-range delivery of molecules to other cells in the CNS and transport of waste from the CNS to the periphery.

The choroid plexus transports fluid and solutes from the serum into the CNS to generate CSF. The fenestrated capillaries that traverse the choroid plexus allow free passage of water and small molecules from the blood into the stromal space of the choroid plexus. The choroid plexus epithelial cells, however, form tight junctions, preventing further unregulated movement of these molecules into the brain. Instead, import of water, ions, metabolites, and protein mediators that compose the CSF is tightly regulated by transporters and channels in the choroid plexus epithelium. Active transport mechanisms in the epithelium are bidirectional, additionally mediating the flux of molecules from the CSF back into the peripheral circulation.

The choroid plexus epithelial cells also synthesize and secrete many proteins into the CSF. In the healthy

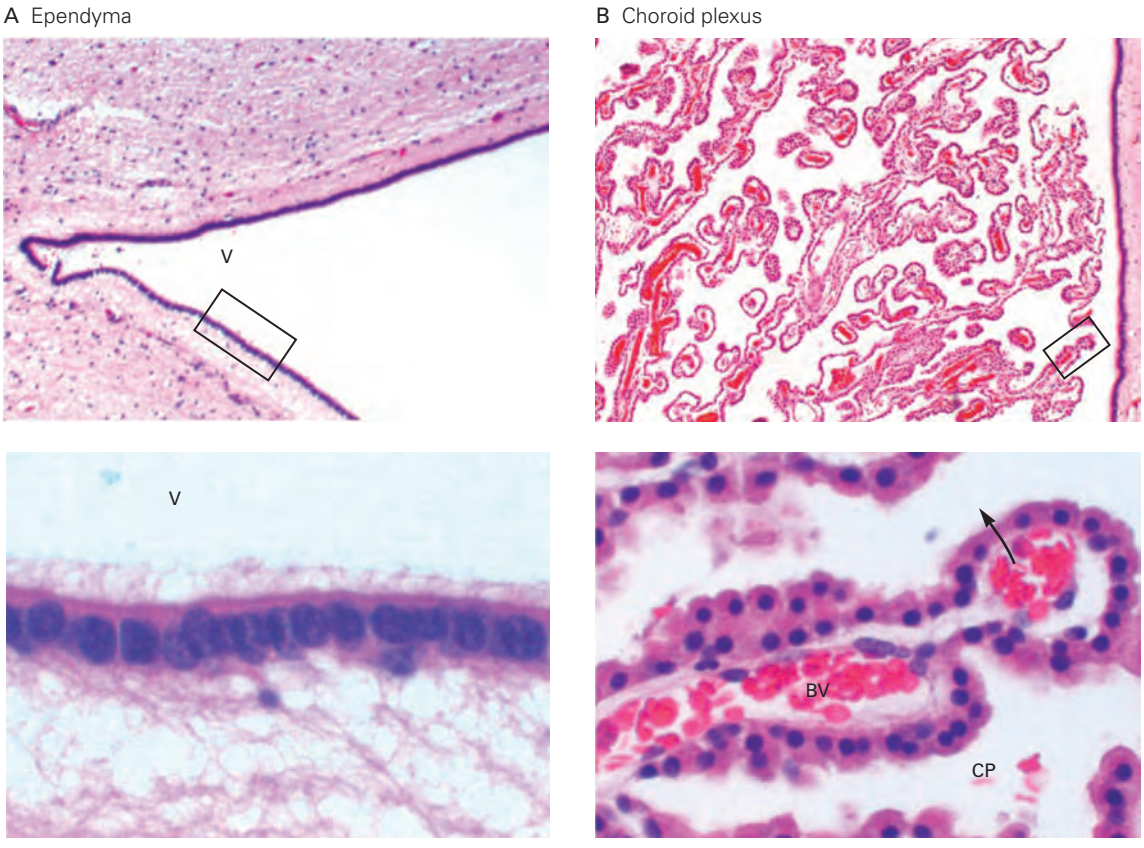


Figure 7–22 Ependyma and choroid plexus.

A. The ependyma is a single layer of ciliated, cuboidal cells lining the cerebral ventricles (**V**). The lower image, a high magnification of the ependymal lining (rectangle in upper image), shows the cilia on the ventricular side of the ependymal cells.

B. The choroid plexus is continuous with the ependyma but projects into the ventricles, where it covers thin blood vessels and forms a highly branched papillary structure. This is the site of cerebrospinal fluid formation. High magnification (lower image) shows the blood vessel core (**BV**) and overlying choroid plexus (**CP**). The arrow denotes the direction of fluid flow from capillary into ventricle during the formation of cerebrospinal fluid.

embryonic and postnatal brain, these proteins modulate development of neural stem cells and may regulate processes such as cortical plasticity. The choroid plexus epithelial cell secretome can also be altered by inflammatory signals from the periphery or from within the brain, with consequences for neuronal function during infection and in aging. Functional roles for other choroid plexus–derived factors in the healthy and diseased brain—including microRNAs, long noncoding RNAs, and extracellular vesicles—are beginning to emerge, further underlining the important contribution of this structure to brain development and homeostasis.

Highlights

1. The morphology of neurons is elegantly suited to receive, conduct, and transmit information in the brain. Dendrites provide a highly branched, elongated surface for receiving signals. Axons conduct electrical impulses rapidly over long distances to their synaptic terminals, which release neurotransmitters onto target cells.
2. Although all neurons conform to the same basic cellular architecture, different subtypes of neurons vary widely in their specific morphological features, functional properties, and molecular identities.
3. Neurons in different locations differ in the complexity of their dendritic trees, extent of axon branching, and the number of synaptic terminals that they form and receive. The functional significance of these morphological differences is plainly evident. For example, motor neurons must have a more complex dendritic tree than sensory neurons, as even simple reflex activity requires integration of many excitatory and inhibitory inputs. Different types of neurons use different neurotransmitters, ion channels, and neurotransmitter receptors. Together, these biochemical, morphological, and electrophysiological differences contribute to the great complexity of information processing in the brain.
4. Neurons are among the most highly polarized cells in our body. The considerable size and complexity of their dendritic and axonal compartments represent significant cell biological challenges for these cells, including transport of various organelles, proteins, and mRNA over long distances (up to a meter for some axons). Most neuronal proteins are synthesized in the cell body, but some synthesis occurs in dendrites and axons. The newly synthesized proteins are folded with the assistance of chaperones, and their final structure is often modified by permanent or reversible posttranslational modifications. The final destination of a protein in the neuron depends on signals encoded in its amino acid sequence.
5. Transport of proteins and mRNA occurs with great specificity and results in the vectorial transport of selected membrane components. The cytoskeleton provides an important framework for the transport of organelles to different intracellular locations in addition to controlling axonal and dendritic morphology.
6. All these fundamental cell biological processes are profoundly modifiable by neuronal activity, which produces the dramatic changes in cell structure and function by which neural circuits adapt to experience (learning).
7. The nervous system also contains several types of glial cells. Oligodendrocytes and Schwann cells produce the myelin insulation that enables axons to conduct electrical signals rapidly. Astrocytes and nonmyelinating Schwann cells ensheathe other parts of the neuron, particularly synapses. Astrocytes control extracellular ion and neurotransmitter concentrations and actively participate in the formation and function of synapses. Microglia resident immune cells and phagocytes dynamically interact with neurons and glial cells and have diverse roles in health and disease.
8. The cells of the choroid plexus and the ependymal layer contribute to CSF production, composition, and dynamics.
9. New advances in genomics and single-cell RNA sequencing are beginning to define the immense diversity of cell types, not only among neurons but also among glial cells.
10. Recent progress in genetics, cell biology, and in vivo microscopy (two-photon microscopy, light-sheet microscopy) is providing new insights into the unique mechanisms by which neurons establish and maintain their polarity throughout an individual's life span.
11. These new insights provide important clues into the cell biological steps, including for example defects in axon transport, that trigger neurodegenerative diseases such as Huntington, Parkinson, and Alzheimer disease.

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