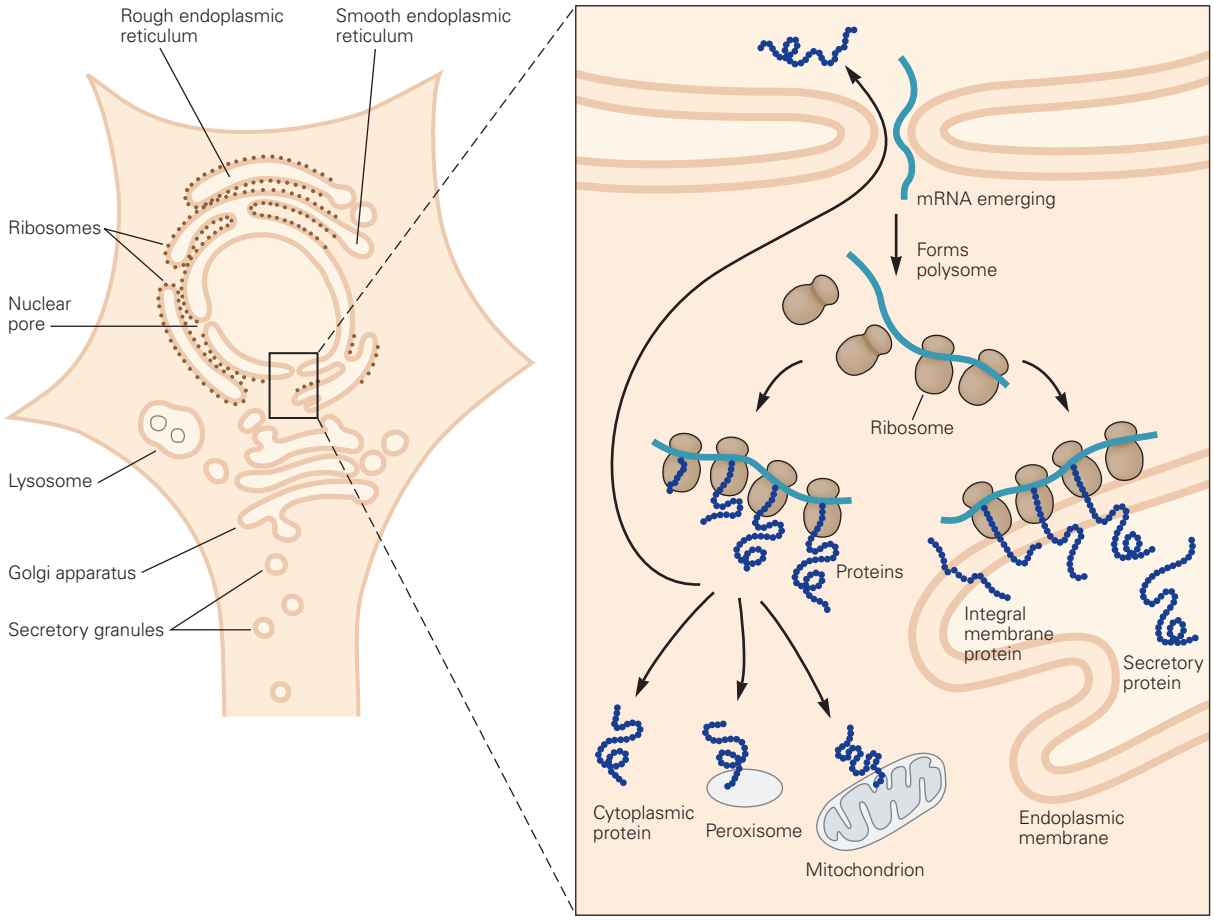
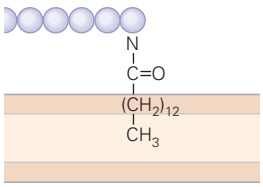


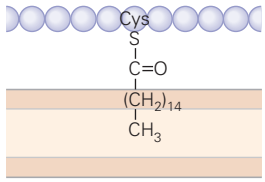
Figure 7–13 Protein synthesis in the endoplasmic reticulum. Free and membrane-bound polysomes translate mRNA that encodes proteins with a variety of destinations. Messenger RNA, transcribed from genomic DNA in the neuron's nucleus, emerges into the cytoplasm through nuclear pores to form polyribosomes (see enlargement). The polypeptides that become secretory and membrane proteins are translocated across the membrane of the rough endoplasmic reticulum.

in the reducing environment of the cytosol. Disulfide linkages are crucial to the tertiary structure of these proteins.

Proteins may be modified by cytosolic enzymes either during synthesis (cotranslational modification) or afterward (posttranslational modification). One example is *N*-acylation, the transfer of an acyl group to the N-terminus of the growing polypeptide chain. Acylation by a 14-carbon fatty acid myristoyl group permits the protein to anchor in membranes through the lipid chain.



Other fatty acids can be conjugated to the sulfhydryl group of cysteine, producing a thioacylation:

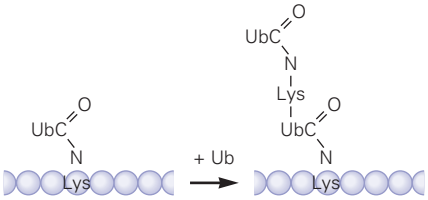


Isoprenylation is another posttranslational modification important for anchoring proteins to the cytosolic side of membranes. It occurs shortly after synthesis of the protein is completed and involves a series of enzymatic steps that result in thioacylation by one of two long-chain hydrophobic polyisoprenyl moieties (farnesyl, with 15 carbons, or geranyl-geranyl, with 20) of the sulfhydryl group of a cysteine at the C-terminus of proteins.

Some posttranslational modifications are readily reversible and thus used to regulate the function of a protein transiently. The most common of these modifications is the phosphorylation at the hydroxyl group in serine, threonine, or tyrosine residues by protein kinases. Dephosphorylation is catalyzed by protein phosphatases. (These reactions are discussed in Chapter 14.) As with all posttranslational modifications, the sites to be phosphorylated are determined by particular sequences of amino acids around the residue to be modified. Phosphorylation can alter physiological processes in a reversible fashion. For example, protein phosphorylation–dephosphorylation reactions regulate the kinetics of ion channels, the activity of transcription factors, and the assembly of the cytoskeleton.

Still another important posttranslational modification is the addition of *ubiquitin*, a highly conserved protein with 76 amino acids, to the ∈-amino group of specific lysine residues in the protein molecule. Ubiquitination, which regulates protein degradation, is mediated by three enzymes. E1 is an activating enzyme that uses the energy of ATP. The activated ubiquitin is next transferred to a conjugase, E2, which then transfers the activated moiety to a ligase, E3. The E3, alone or together with E2, transfers the ubiquitinyl group to the lysine residue in a protein. Specificity arises because a given protein molecule can only be ubiquinated by a specific E3 or combination of E3 and E2. Some E3s also require special cofactors—ubiquitination occurs only in the presence of E3 and a cofactor protein.

Monoubiquitination tags a protein for degradation in the endosomal–lysosomal system. This is especially important in endocytosis and recycling of surface receptors. Ubiquitinyl monomers are successively linked to the ∈-amino group of a lysine residue in the previously added ubiquitin moiety. Addition of more than five ubiquitins to the multiubiquitin chain tags the protein for degradation by the proteasome, a large complex containing multifunctional protease subunits that cleave proteins into short peptides.



The ATP–ubiquitin–proteasome pathway is a mechanism for the selective and regulated proteolysis of proteins that operates in the cytosol of all regions of the neuron—dendrites, cell body, axon, and terminals. Until recently, this process was thought to be primarily directed to poorly folded, denatured, or aged and damaged proteins. We now know that ubiquitin-mediated proteolysis can be regulated by neuronal activity and plays specific roles in many neuronal processes, including synaptogenesis and long-term memory storage.

Another important protein modification is glycosylation, which occurs on amino groups of asparagine residues (N-linked glycosylation) and results in the addition en bloc of complex polysaccharide chains. These chains are then trimmed within the endoplasmic reticulum by a series of reactions controlled by chaperones, including heat shock proteins, calnexin, and calreticulin. Because of the great chemical specificities of oligosaccharide moieties, these modifications can have important implications for cell function. For example, cell-to-cell interactions that occur during development rely on molecular recognition between glycoproteins on the surfaces of the two interacting cells. Also, because a given protein can have somewhat different oligosaccharide chains, glycosylation can diversify the function of a protein. It can increase the hydrophilicity of the protein (useful for secretory proteins), fine-tune its ability to bind macromolecular partners, and delay its degradation.

An interesting posttranslational modification of mRNA is RNA interference (RNAi), the targeted destruction of double-stranded RNAs. This mechanism, which is believed to have arisen to protect cells against viruses and other rogue fragments of nucleic acids, shuts down the synthesis of any targeted protein. Double-stranded RNAs are taken up by an enzyme complex that cleaves the molecule into oligomers. The RNA sequences are retained by the complex. As a result, any homologous hybridizing RNA strands, either double- or single-stranded, will be destroyed. The process is regenerative: The complex retains a hybridizing fragment and goes on to destroy another RNA molecule until none remain in the cell. Although the physiological role of RNAi in normal cells is unclear, transfection or injection of RNAi into cells is of great research and clinical importance (Chapter 2).

Secretory Proteins Are Modified in the Golgi Complex

Proteins from the endoplasmic reticulum are carried in transport vesicles to the Golgi complex where they are modified and then moved to synaptic terminals and other parts of the plasma membrane. The Golgi complex appears as a grouping of membranous sacks aligned with one another in long ribbons.

The mechanism by which vesicles are transported between stations of the secretory and endocytic

pathways has been remarkably conserved from simple unicellular prokaryotes (yeast) to neurons and glia of multicellular organisms. Transport vesicles develop from membrane, beginning with the assembly of proteins that form *coats*, or coat proteins, at selected patches of the cytosolic surface of the membrane. A coat has two functions. It forms rigid cage-like structures that produce evagination of the membrane into a bud shape, and it selects the protein cargo to be incorporated into the vesicles.

There are several types of coats. *Clathrin coats* assist in evaginating Golgi complex membrane and plasmalemma during endocytosis. Two other coats, COPI and COPII, cover transport vesicles that shuttle between the endoplasmic reticulum and the Golgi complex. Coats usually are rapidly dissolved once free vesicles have formed. The fusion of vesicles with the target membrane is mediated by a cascade of molecular interactions, the most important of which is the reciprocal recognition of small proteins on the cytosolic surfaces of the two interacting membranes: vesicular soluble *N*-ethylmaleimide–sensitive factor attachment protein receptors (v-SNAREs) and t-SNAREs (target-membrane SNAREs). The role of SNARE proteins in neurotransmitter release through synaptic vesicle fusion with the plasma membrane is discussed in Chapter 15.

Vesicles from the endoplasmic reticulum arrive at the *cis* side of the Golgi complex (the aspect facing the nucleus) and fuse with its membranes to deliver their contents into the Golgi complex. These proteins travel from one Golgi compartment (cisterna) to the next, from the *cis* to the *trans* side, undergoing a series of enzymatic reactions. Each Golgi cisterna or set of cisternae is specialized for a particular type of reaction. Several types of protein modifications, some of which begin in the endoplasmic reticulum, occur within the Golgi complex proper or within the transport station adjacent to its *trans* side, the *trans-Golgi network* (the aspect of the complex typically facing away from the nucleus toward the axon hillock). These modifications include the addition of N-linked oligosaccharides, O-linked (on the hydroxyl groups of serine and threonine) glycosylation, phosphorylation, and sulfation.

Both soluble and membrane-bound proteins that travel through the Golgi complex emerge from the trans-Golgi network in a variety of vesicles that have different molecular compositions and destinations. Proteins transported from the trans-Golgi network include secretory products as well as newly synthesized components for the plasmalemma, endosomes, and other membranous organelles (see Figure 7–2). One class of vesicles carries newly synthesized plasmalemmal proteins and proteins that are continuously secreted (*constitutive secretion*). These vesicles fuse with the plasma membrane in an unregulated fashion. An important type of these vesicles delivers lysosomal enzymes to late endosomes.

Still other classes of vesicles carry secretory proteins that are released by an extracellular stimulus (*regulated secretion*). One type stores secretory products, primarily neuroactive peptides, in high concentrations. Called *large dense-core vesicles* because of their electron-dense (osmophilic) appearance in the electron microscope, these vesicles are similar in function and biogenesis to peptide-containing granules of endocrine cells. Large dense-core vesicles are targeted primarily to axons but can be seen in all regions of the neuron. They accumulate in the cytoplasm just beneath the plasma membrane and are highly concentrated at axon terminals, where their contents are released through Ca^{2+}-regulated exocytosis.

Recent work has demonstrated that *small synaptic vesicles*—the electron-lucent vesicles responsible for the rapid release of neurotransmitter at axon terminals—are actively transported toward the synaptic terminals as individual cargoes. It is thought that protein components of small synaptic vesicles originate from large precursor vesicles from the trans-Golgi network. These synaptic vesicles already incorporate most of the proteins that enable their fusion at the presynaptic active zone. The neurotransmitter molecules stored in these synaptic vesicles are released by exocytosis regulated by Ca^{2+} influx through channels close to the release site. The vesicles can then undergo cycles of recycling/exocytosis as described in Chapter 15. Importantly, these vesicles are refilled through specialized transporters called vesicular transporters that are specific for each neurotransmitter (eg, glutamate, γ-aminobutyric acid [GABA], acetylcholine).

Surface Membrane and Extracellular Substances Are Recycled in the Cell

Vesicular traffic toward the cell surface is continuously balanced by *endocytic traffic* from the plasma membrane to internal organelles. This traffic is essential for maintaining the area of the membrane in a steady state. It can alter the activity of many important regulatory molecules on the cell surface (eg, by removing receptors and adhesion molecules). It also removes nutrients and molecules, such as expendable receptor ligands and damaged membrane proteins, to the degradative compartments of the cells. Finally, it serves to recycle synaptic vesicles at nerve terminals (Chapter 15).

A significant fraction of endocytic traffic is carried in clathrin-coated vesicles. The clathrin coat interacts selectively through transmembrane receptors with extracellular molecules that are to be taken up into the cell. For this reason, clathrin-mediated uptake is often referred to as *receptor-mediated endocytosis.* The vesicles eventually shed their clathrin coats and fuse with the early endosomes, in which proteins to be recycled to the cell surface are separated from those destined for other intracellular organelles. Patches of the plasmalemma can also be recycled through larger, uncoated vacuoles that also fuse with early endosomes (*bulk endocytosis*).

Glial Cells Play Diverse Roles in Neural Function

Ramón y Cajal recognized the close association of glia with neurons and synapses in the brain (Figure 7–14). Although their function was at that time a mystery, he predicted that glia must do more than hold neurons together. Indeed, it is now clear that glial cells are critical players in brain development, function, and disease.

Glia Form the Insulating Sheaths for Axons

A major function of oligodendrocytes and Schwann cells is to provide the insulating material that allows rapid conduction of electrical signals along the axon. These cells produce thin sheets of myelin that wrap concentrically, many times, around the axon. CNS myelin, produced by oligodendrocytes, is similar, but not identical, to peripheral nervous system myelin, produced by Schwann cells.

Both types of glia produce myelin only for segments of axons. This is because the axon is not continuously wrapped in myelin, a feature that facilitates propagation of action potentials (Chapter 9). One Schwann cell produces a single myelin sheath for one segment of one axon, whereas one oligodendrocyte produces myelin sheaths for segments of as many as 30 axons (Figures 7–1 and 7–15).

The number of layers of myelin on an axon is proportional to the diameter of the axon—larger axons have thicker sheaths. Axons with very small diameters are not myelinated; nonmyelinated axons conduct action potentials much more slowly than do myelinated axons because of their smaller diameter and lack of myelin insulation (Chapter 9).

The regular lamellar structure and biochemical composition of the sheath are consequences of how

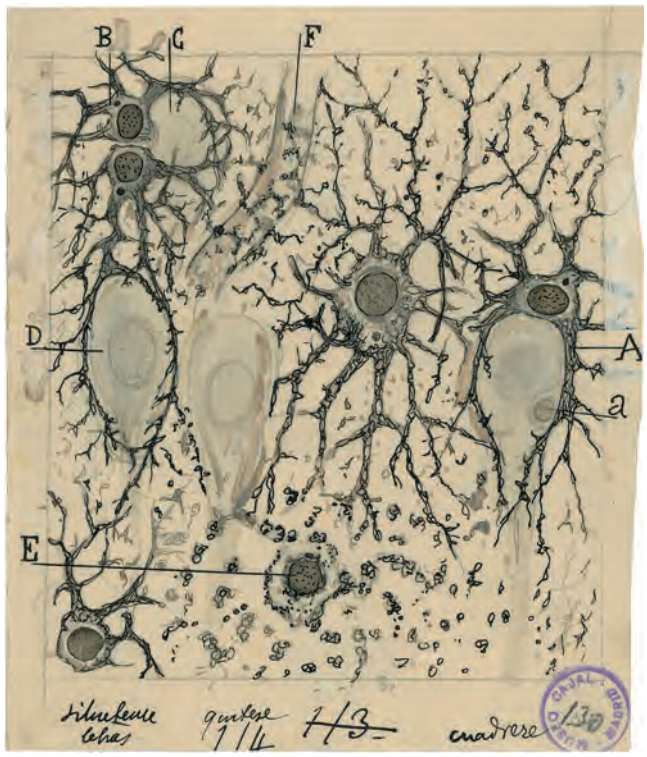


Figure 7–14 Astrocytes interact with neurons and synapses in the brain. This drawing by Ramón y Cajal (based on tissue stained with the sublimated gold chloride method) shows astrocytes of the pyramidal layer and stratum radiatum of Ammon's horn in the human brain. (**A**) A large astrocyte ensheathes a pyramidal neuron. (**B**) Twin astrocytes form a nest around a nerve cell body (**C**). One of the astrocytes sends two branches to form another nest (**D**). (**E**) A cell shows signs of autolysis. (**F**) Capillary vessel. (Reproduced, with permission, from the Instituto Cajal, Madrid, Spain.)

myelin is formed from the glial plasma membrane. In the development of the peripheral nervous system, before myelination takes place, the axon lies within a trough formed by Schwann cells. Schwann cells line up along the axon at regular intervals that become the myelinated segments of axon. The external membrane of each Schwann cell surrounds the axon to form a double membrane structure called the *mesaxon*, which elongates and spirals around the axon in concentric layers (Figure 7–15C). As the axon is ensheathed, the cytoplasm of the Schwann cell is squeezed out to form a compact lamellar structure.

The regularly spaced segments of myelin sheath are separated by unmyelinated gaps, called *nodes of Ranvier*, where the plasma membrane of the axon is exposed to the extracellular space for approximately 1 µm (Figure 7–16). This arrangement greatly increases the speed at which nerve impulses are conducted

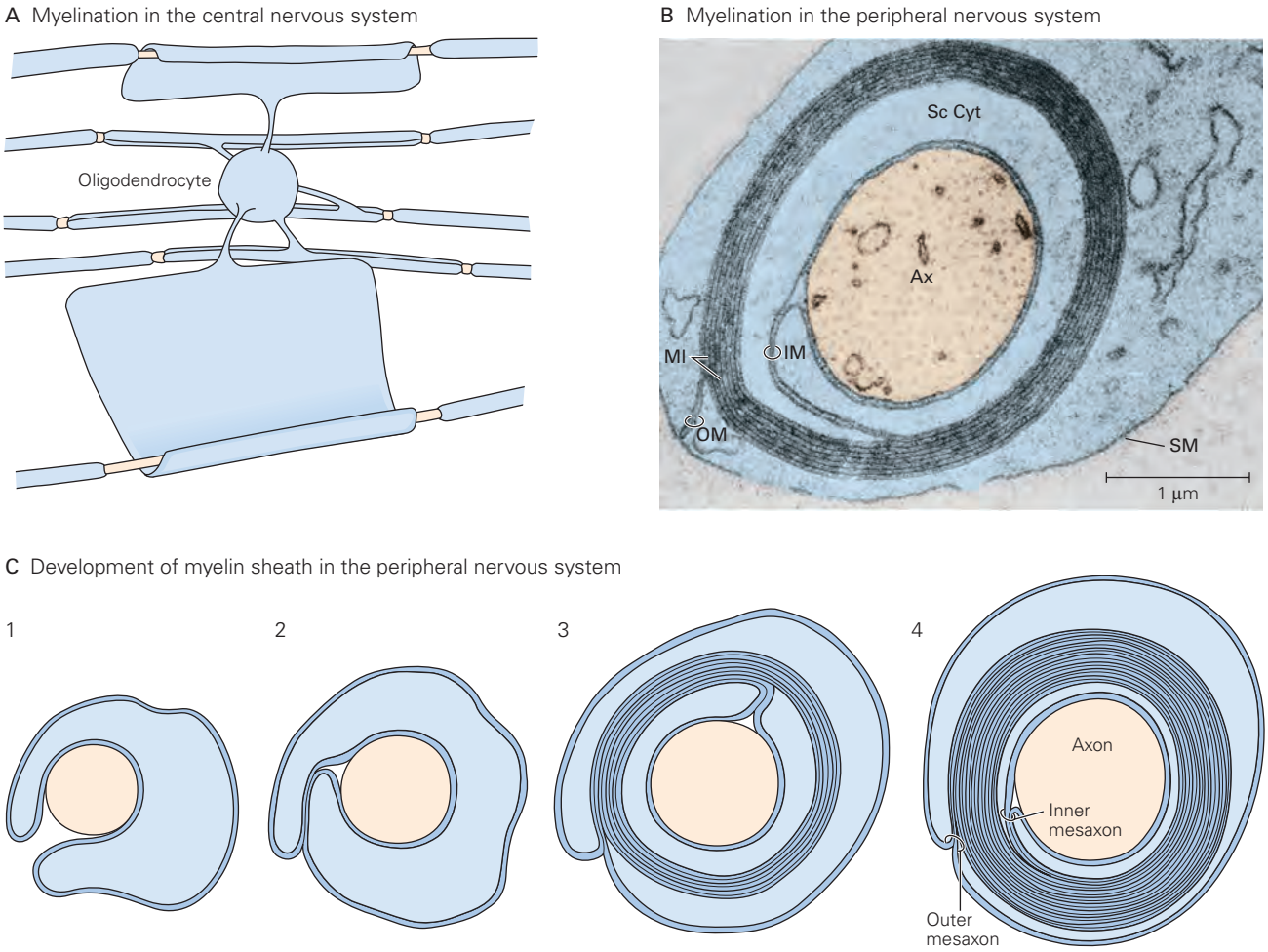


Figure 7–15 Glial cells produce the myelin that insulates the axons of central and peripheral neurons.

A. Axons in the central nervous system are wrapped in several layers of myelin produced by oligodendrocytes. Each oligodendrocyte can myelinate many axons. (Adapted from Raine 1984.)

B. This electron micrograph of a transverse section through an axon (**Ax**) in the sciatic nerve of a mouse shows the origin of a sheet of myelin (**MI**) at a structure called the inner mesaxon (**IM**). The myelin arises from the surface membrane (**SM**) of a Schwann cell, which is continuous with the outer mesaxon (**OM**). In this image, the Schwann cell cytoplasm (**Sc Cyt**) still surrounds the axon; eventually it is squeezed out and the myelin layers become compact, as shown in part **C**. (Reproduced, with permission, from Dyck et al. 1984.)

C. A peripheral nerve fiber is myelinated by a Schwann cell in several stages. In stage 1, the Schwann cell surrounds the axon. In stage 2, the outer aspects of the plasma membrane have become tightly apposed in one area. This membrane fusion reflects early myelin membrane formation. In stage 3, several layers of myelin have formed because of continued rotation of the Schwann cell cytoplasm around the axon. In stage 4, a mature myelin sheath has formed; much of the Schwann cell cytoplasm has been squeezed out of the innermost loop. (Adapted, with permission, from Williams et al. 1989.)

(up to 100 m/s in humans) because the signal jumps from one node to the next, a mechanism called *saltatory conduction* (Chapter 9). Nodes are easily excited because the density of Na^+ channels, which generate the action potential, is approximately 50 times greater in the axon membrane at the nodes than in myelin-sheathed regions of membrane. Cell adhesion molecules around nodes keep the myelin boundaries stable.

In the human femoral nerve, the primary sensory axon is approximately 0.5 m long and the internodal distance is 1 to 1.5 mm; thus, approximately 300 to 500 nodes of Ranvier occur along a primary afferent fiber between the thigh muscle and the cell body in the

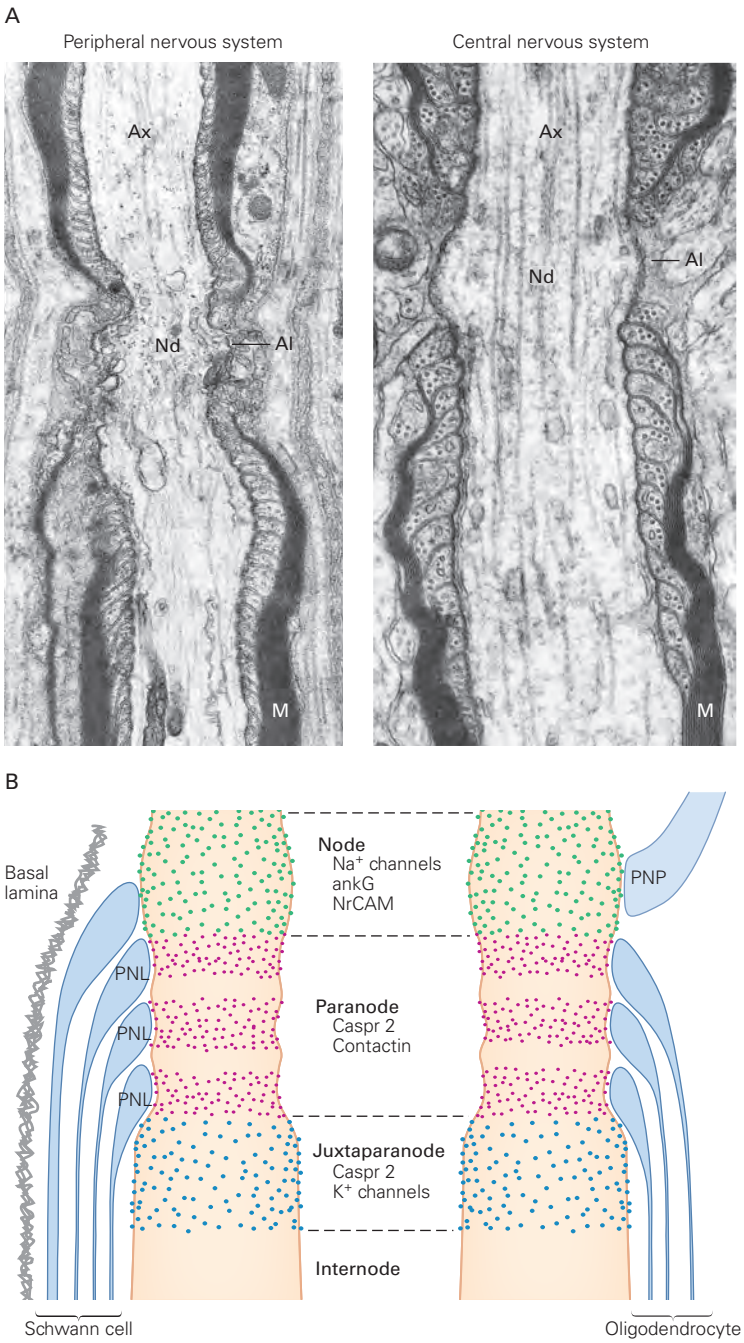


Figure 7–16 The myelin sheath of axons has regular gaps called the *nodes of Ranvier.*

A. Electron micrographs show the region of nodes in axons from the peripheral nervous system and spinal cord. The axon (**Ax**) runs vertically in both micrographs. The layers of myelin (**M**) are absent at the nodes (**Nd**), where the axon's membrane (axolemma, **Al**) is exposed. (Reproduced, with permission, from Peters et al. 1991.)

B. Regions on both sides of a node of Ranvier are rich in stable contacts between myelinating cells and the axon, to ensure that the nodes do not move or change in size and to restrict the localization of K^+ and Na^+ channels in the axon. Potassium-permeable channels and the adhesion protein Caspr2 are concentrated in the juxtaparanode. Paranodal loops (**PNL**) of Schwann cell or oligodendrocyte cytoplasm form a series of stable junctions with the axon. The paranode region is rich with adhesion proteins such as Caspr2, contactin, and neurofascin (NF155). At the nodes in central axons, perinodal astroglial processes (**PNP**) contact the axonal membrane, which is enormously enriched with Na^+ channels. This localization of Na^+ permeability is a major basis for the saltatory conduction in myelinated axons. The membrane-cytoskeletal linker ankyrin G (**ankG**) and the cell adhesion molecules NrCAM and NF186 are also concentrated at the nodes. (Reproduced, with permission, from Peles and Salzer 2000. Copyright © 2000 Elsevier.)

dorsal root ganglion. Because each internodal segment is formed by a single Schwann cell, as many as 500 Schwann cells participate in the myelination of each peripheral sensory axon.

Myelin has bimolecular layers of lipid interspersed between protein layers. Its composition is similar to that of the plasmalemma, consisting of 70% lipid and 30% protein with high concentrations of cholesterol and phospholipid. In the CNS, myelin has two major proteins: myelin basic protein, a small, positively charged protein that is situated on the cytoplasmic surface of compact myelin, and proteolipid protein, a hydrophobic integral membrane protein. Presumably, both provide structural stability for the sheath.

Both have also been implicated as important autoantigens against which the immune system can react to produce the demyelinating disease multiple sclerosis. In the peripheral nervous system, myelin contains a major protein, P_0, as well as the hydrophobic protein PMP22. Autoimmune reactions to these proteins produce a demyelinating peripheral neuropathy, the *Guillain-Barré syndrome*. Mutations in myelin protein genes also cause a variety of demyelinating diseases in both peripheral and central axons (Box 7–3). Demyelination slows down, or even stops, conduction of the action potential in an affected axon, because it allows electrical current to leak out of the axonal membrane. Demyelinating diseases thus have devastating effects on neuronal circuits in the central and peripheral nervous systems (Chapter 57).

Astrocytes Support Synaptic Signaling

Astrocytes are found in all areas of the brain; indeed, they constitute nearly half the number of brain cells. They play important roles in nourishing neurons and in regulating the concentrations of ions and neurotransmitters in the extracellular space. But astrocytes and neurons also communicate with each other to modulate synaptic signaling in ways that are still poorly understood. Astrocytes are generally divided into two main classes, which are distinguished by morphology, location, and function. *Protoplasmic astrocytes* are found in gray matter, and their processes are closely associated with synapses as well as blood vessels. *Fibrillary (or fibrous) astrocytes* in white matter contact axons and nodes of Ranvier. In addition, specialized astrocytes include Bergmann glia in the cerebellum and Müller glia in the retina.

Astrocytes have large numbers of thin processes that enfold all the blood vessels of the brain and ensheathe synapses or groups of synapses. By their intimate physical association with synapses, often closer than 1 μm, astrocytes are positioned to regulate extracellular concentrations of ions, neurotransmitters, and other molecules (Figure 7–19). In fact, astrocytes express many of the same voltage-gated ion channels and neurotransmitter receptors that neurons do and are thus well equipped to receive and transmit signals that could affect neuronal excitability and synaptic function.

How do astrocytes regulate axonal conduction and synaptic activity? The first recognized physiological role was that of K^+ buffering. When neurons fire action potentials, they release K^+ ions into the extracellular space. Because astrocytes have high concentrations of K^+ channels in their membranes, they can act as *spatial buffers*: They take up K^+ at sites of neuronal activity, mainly synapses, and release it at distant contacts with blood vessels. Astrocytes can also accumulate K^+ locally within their cytoplasmic processes along with Cl^- ions and water. Unfortunately, accumulation of ions and water in astrocytes can contribute to severe brain swelling after head injury.

Astrocytes also regulate neurotransmitter concentrations in the brain. For example, high-affinity transporters located in the astrocyte's plasma membrane rapidly clear the neurotransmitter glutamate from the synaptic cleft (Figure 7–19C). Once within the glial cell, glutamate is converted to glutamine by the enzyme glutamine synthetase. Glutamine is then transferred to neurons, where it serves as an immediate precursor of glutamate (Chapter 16). Interference with these uptake mechanisms results in high concentrations of extracellular glutamate that can lead to the death of neurons, a process termed excitotoxicity. Astrocytes also degrade dopamine, norepinephrine, epinephrine, and serotonin.

Astrocytes sense when neurons are active because they are depolarized by the K^+ released by neurons and have neurotransmitter receptors similar to those of neurons. For example, Bergmann glia in the cerebellum express glutamate receptors. Thus, the glutamate released at cerebellar synapses affects not only postsynaptic neurons but also astrocytes near the synapse. The binding of these ligands to glial receptors increases the intracellular free Ca^{2+} concentration, which has several important consequences. The processes of one astrocyte connect to those of neighboring astrocytes through intercellular aqueous channels called gap junctions (Chapter 11), allowing transfer of ions and small molecules between many cells. An increase in free Ca^{2+} within one astrocyte increases Ca^{2+} concentrations in adjacent astrocytes. This spread of Ca^{2+} through the astrocyte network occurs over hundreds of micrometers. It is likely that this Ca^{2+} wave modulates

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

Because in myelinated axons normal conduction of the nerve impulse depends on the insulating properties of the myelin sheath, defective myelin can result in severe disturbances of motor and sensory function.

Many diseases that affect myelin, including some animal models of demyelinating disease, have a genetic basis. The *shiverer* (or *shi*) mutant mice have tremors and frequent convulsions and tend to die young. In these mice, the myelination of axons in the central nervous system is greatly deficient and the myelination that does occur is abnormal.

The mutation that causes this disease is a deletion of five of the six exons of the gene for myelin basic protein, which in the mouse is located on chromosome 18. The mutation is recessive; a mouse develops the disease only if it has inherited the defective gene from both parents. *Shiverer* mice that inherit both defective genes have only approximately 10% of the myelin basic protein (MBP) found in normal mice (Figure 7–17A).

When the wild-type gene is injected into fertilized eggs of the *shiverer* mutant with the aim of rescuing the mutant, the resulting transgenic mice express the wild-type gene but produce only 20% of the normal amounts of MBP. Nevertheless, myelination of central neurons in the transgenic mice is much improved. Although they still have occasional tremors, the transgenic mice do not have convulsions and have a normal life span (Figure 7–17B).

In both the central and peripheral nervous systems, myelin contains a protein termed *myelin-associated glycoprotein* (MAG). MAG belongs to the immunoglobulin superfamily that includes several important cell surface proteins thought to be involved in cell-to-cell recognition, eg, the major histocompatibility complex of antigens, T-cell surface antigens, and the neural cell adhesion molecule (NCAM).

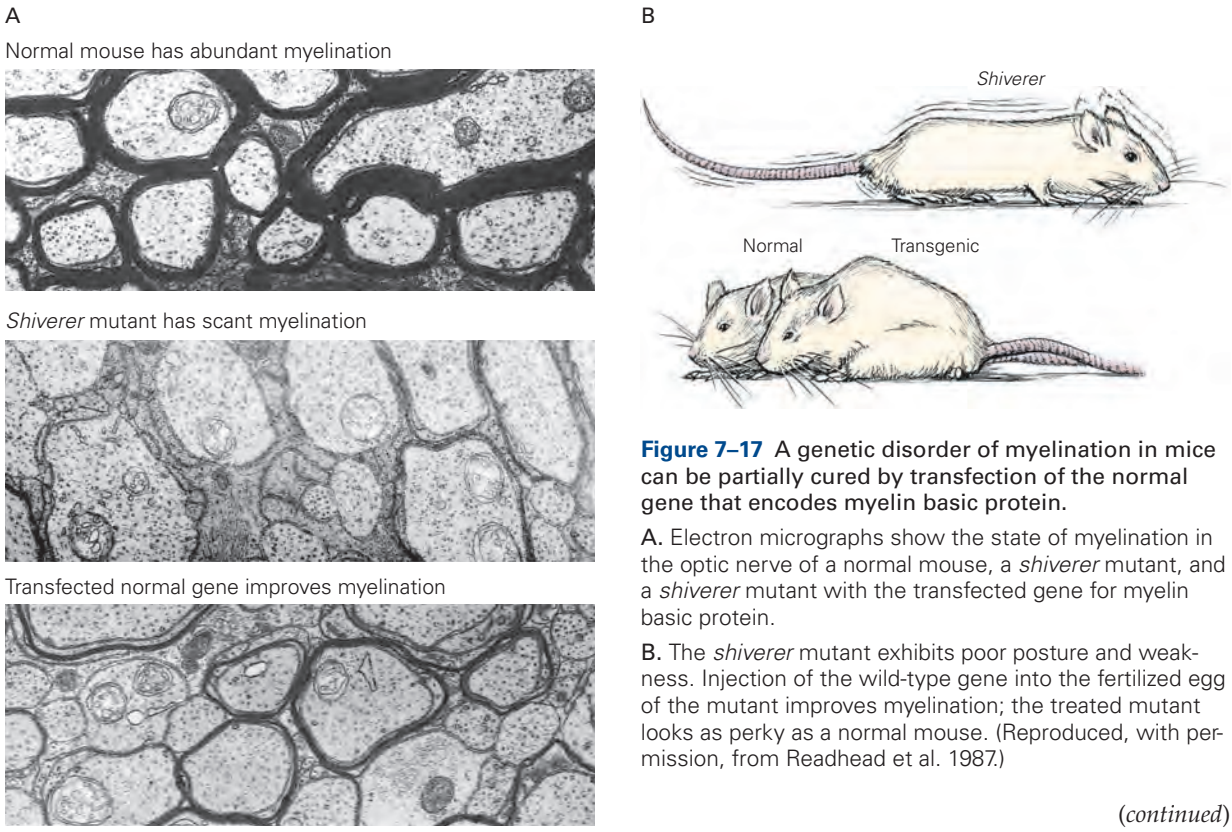


Figure 7–17 A genetic disorder of myelination in mice can be partially cured by transfection of the normal gene that encodes myelin basic protein.

A. Electron micrographs show the state of myelination in the optic nerve of a normal mouse, a *shiverer* mutant, and a *shiverer* mutant with the transfected gene for myelin basic protein.

B. The *shiverer* mutant exhibits poor posture and weakness. Injection of the wild-type gene into the fertilized egg of the mutant improves myelination; the treated mutant looks as perky as a normal mouse. (Reproduced, with permission, from Readhead et al. 1987.)

(*continued*)

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

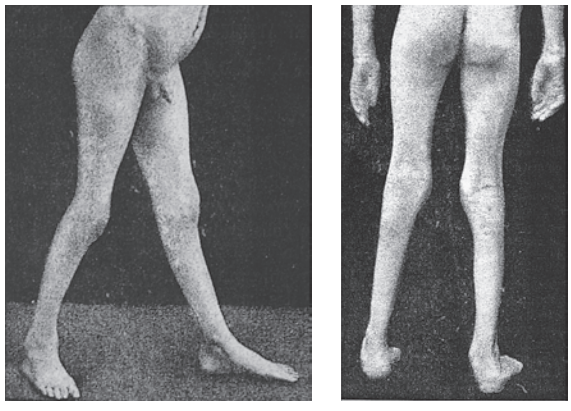


Figure 7–18 Charcot-Marie-Tooth disease (type 1A) results from increased production of peripheral myelin protein 22.

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.)