Addictive drugs share the property of increasing dopamine release in the nucleus accumbens (Chap. 465e). Amphetamine increases intracellular release of dopamine from vesicles and reverses transport of dopamine through the dopamine transporters. Patients prone to addiction show increased activation of the nucleus accumbens following administration of amphetamine. Cocaine binds to dopamine transporters and inhibits dopamine reuptake. Ethanol inhibits inhibitory neurons in the VTA, leading to increased dopamine release in the nucleus accumbens. Opioids also disinhibit these dopaminergic neurons by binding to μ receptors expressed by γ-aminobutyric acid (GABA)–containing interneurons in the VTA. Nicotine increases dopamine release by activating nicotinic acetylcholine receptors on cell bodies and nerve terminals of dopaminergic VTA neurons. Tetrahydrocannabinol, the active ingredient of cannabis, also increases dopamine levels in the nucleus accumbens. Blockade of dopamine in the nucleus accumbens can terminate the rewarding effects of addictive drugs.

Not all cell-to-cell communication in the nervous system occurs via neurotransmission. Gap junctions provide for direct neuron-neuron electrical conduction and also create openings for the diffusion of ions and metabolites between cells. In addition to neurons, gap junctions are also widespread in glia, creating a syncytium that protects neurons by removing glutamate and potassium from the extracellular environment. Gap junctions consist of membrane-spanning proteins, termed *connexins*, that pair across adjacent cells. Mechanisms that involve gap junctions have been related to a variety of neurologic disorders. Mutations in connexin 32, a gap junction protein expressed by Schwann cells, are responsible for the X-linked form of Charcot-Marie-Tooth (CMT) disease (Chap. 459). Mutations in either of two gap junction proteins expressed in the inner ear—connexin 26 and connexin 31—result in autosomal dominant progressive hearing loss (Chap. 43). Glial calcium waves mediated through gap junctions also appear to explain the phenomenon of spreading depression associated with migraine auras and the march of epileptic discharges. Spreading depression is a neural response that follows a variety of different stimuli and is characterized by a circumferentially expanding negative potential that propagates at a characteristic speed of 20 m/s and is associated with an increase in extracellular potassium.

SIGNALING PATHWAYS AND GENE TRANSCRIPTION

The fundamental issue of how memory, learning, and thinking are encoded in the nervous system is likely to be clarified by identifying the signaling pathways involved in neuronal differentiation, axon guidance, and synapse formation, and by understanding how these pathways are modulated by experience. Many families of transcription factors, each comprising multiple individual components, are expressed in the nervous system. Elucidation of these signaling pathways has already begun to provide insights into the cause of a variety of neurologic disorders, including inherited disorders of cognition such as X-linked mental retardation. This problem affects ~1 in 500 males, and linkage studies in different families suggest that as many as 60 different X-chromosome-encoded genes may be responsible. The formation of RNA-DNA duplexes that block transcription has also been observed with the CGG repeat expansions that occur in fragile X gene-associated mental retardation. Rett's syndrome, a common cause of (dominant) X-linked progressive mental retardation in females, is due to a mutation in a gene (*MECP2*) encoding a DNA-binding protein involved in transcriptional repression. Because the X chromosome comprises only ~3% of germline DNA, then by extrapolation, the number of genes that potentially contribute to clinical disorders affecting intelligence in humans must be potentially very large. As discussed below, there is increasing evidence that abnormal gene transcription may play a role in neurodegenerative diseases, such as Huntington's disease, in which proteins with polyglutamine expansions bind to and sequester transcription factors. A critical transcription factor for neuronal survival is CREB (cyclic adenosine monophosphate responsive element-binding) protein, which also plays an important role in memory in the hippocampus. The regulatory gene repressor element 1-silencing transcription factor (REST) coordinates the expression of neuroprotective stress genes during normal aging. It turns off genes involved in cell death and pathology and boosts protective factors. High levels of REST are associated with normal cognition even in the presence of both amyloid plaques and neurofibrillary tangles. Although REST increases with normal aging, it fails to increase in the nucleus in patients with Alzheimer's disease and is found clumped with amyloid in autophagosomes.

MYELIN AND NEUROINFLAMMATION

Myelin is the multilayered insulating substance that surrounds axons and speeds impulse conduction by permitting action potentials to jump between naked regions of axons (nodes of Ranvier) and across myelinated segments. Molecular interactions between the myelin membrane and axon are required to maintain the stability, function, and normal life span of both structures. A single oligodendrocyte usually ensheaths multiple axons in the central nervous system (CNS), whereas in the peripheral nervous system (PNS), each Schwann cell typically myelinates a single axon. Myelin is a lipid-rich material formed by a spiraling process of the membrane of the myelinating cell around the axon, creating multiple membrane bilayers that are tightly apposed (compact myelin) by charged protein interactions. Several inhibitors of axon growth are expressed on the innermost (periaxonal) lamellae of the myelin membrane (see "Stem Cells and Transplantation," below). A number of clinically important neurologic disorders are caused by inherited mutations in myelin proteins of the CNS or PNS (Fig. 444e-1). Constituents of myelin also have a

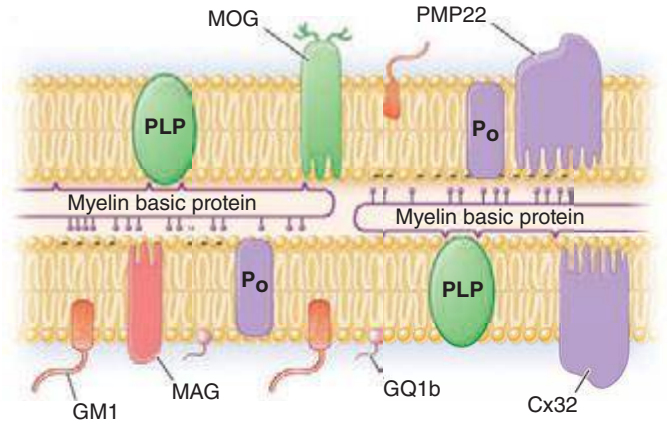

FIGURE 444e-1 The molecular architecture of the myelin sheath illustrating the most important disease-related proteins. The illustration represents a composite of central nervous system (CNS) and peripheral nervous system (PNS) myelin. Proteins restricted to CNS myelin are shown in *green*, proteins of PNS myelin are *lavender*, and proteins present in both CNS and PNS are *red*. In the CNS, the X-linked allelic disorders, Pelizaeus-Merzbacher disease and one variant of familial spastic paraplegia, are caused by mutations in the gene for proteolipid protein (PLP) that normally promotes extracellular compaction between adjacent myelin lamellae. The homologue of PLP in the PNS is the P_0 protein, mutations in which cause the neuropathy Charcot-Marie-Tooth disease (CMT) type 1B. The most common form of CMT is the 1A subtype caused by a duplication of the *PMP22* gene; deletions in *PMP22* are responsible for another inherited neuropathy termed *hereditary liability to pressure palsies* (Chap. 459).

In multiple sclerosis (MS), myelin basic protein (MBP) and the quantitatively minor CNS protein, myelin oligodendrocyte glycoprotein (MOG), are likely T cell and B cell antigens, respectively (Chap. 458). The location of MOG at the outermost lamella of the CNS myelin membrane may facilitate its targeting by autoantibodies. In the PNS, autoantibodies against myelin gangliosides are implicated in a variety of disorders, including GQ1b in the Fisher variant of Guillain-Barré syndrome, GM1 in multifocal motor neuropathy, and sulfatide constituents of myelin-associated glycoprotein (MAG) in peripheral neuropathies associated with monoclonal gammopathies (Chap. 460).