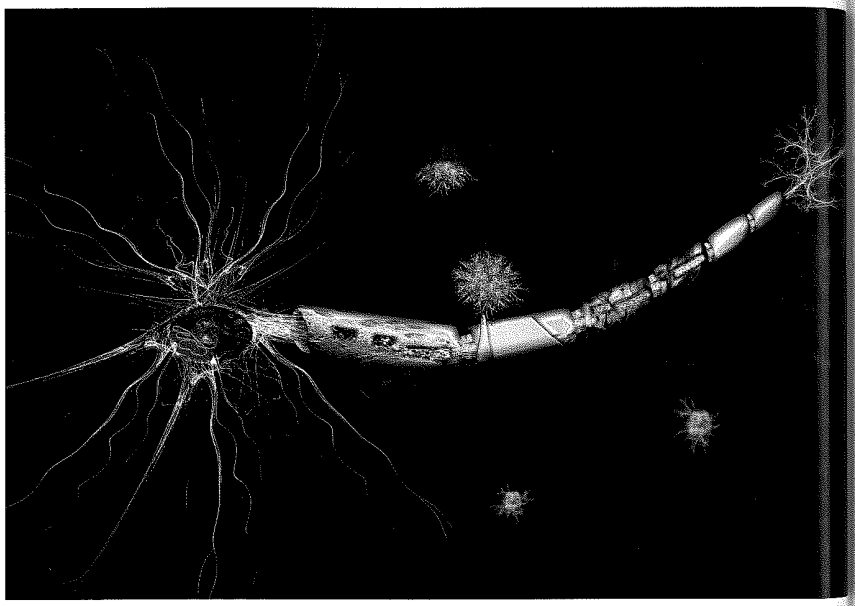
CHAPTER 2



The myelin sheath of a neuron damaged by MS is being repaired by an oligodendrocyte. (Carol Werner/Medical Images.)

Structure and Function of the Nervous System

MICHELLE WAS A FIRST-SEMESTER SENIOR ENGLISH MAJOR when she first noticed that she was unusually fatigued and often felt dizzy and weak, barely able to lift her legs to climb stairs. She said it felt as though she were walking through oatmeal. As the semester wore on, Michelle found she had increasing trouble reading her assignments because of blurred vision and a sense that the words were moving on the page. Although these symptoms disappeared temporarily, they recurred with greater intensity just a few weeks later. When she realized she was almost too weak to walk and began slurring her speech, she made an appointment to see her hometown doctor. After a series of tests, Michelle's doctor told her she had multiple sclerosis (MS)—a progressive, degenerative autoimmune disease in which the immune system attacks the nerve cells in the brain and spinal cord, producing sensory and motor deficits. The doctor tried to reassure her. He said that MS is a disease that is characterized by remissions (absence of symptoms) and relapses and that some people go years before experiencing another episode. During remission, many people lead perfectly normal lives. However, it is a disease that can be treated but not cured. Fortunately, there are disease-modifying drugs that reduce the relapse rate and subsequently slow the progression of MS. This chapter describes nervous system structure and function. By the end of the chapter, you should have a good idea of what causes MS and of why Michelle experienced the particular symptoms she did.

As we already know, psychopharmacology is the study of how drugs affect emotion, memory, thinking, and behavior. Drugs can produce these widespread effects because they modify the function of the human brain, most often by altering the chemical nature of the nervous system. To gain an understanding of drug action, we first need to know a bit about individual nerve cell structure and electrochemical function. Second, we need to have an essential understanding of how these individual cells form the complex circuits that represent the anatomical basis for behavior. We hope that for most readers, Chapter 2 will be a review of (1) the structure of nerve cells, (2) electrochemical properties of neurons, and (3) anatomy

of the nervous system, as we put the individual neurons together into functional units. Chapter 3 follows up with greater detail on the chemical nature of nerve cell function. ■

Cells of the Nervous System

All tissues in the body are composed of cells, and the special characteristics of different types of cells determine the structures and functions of the tissues and the organs. Understanding how those cells became specialized (differentiated) is of tremendous importance to basic science as well as clinical research. **BOX 2.1** describes embryonic stem cells and their potential in research and therapeutics. Embryonic stem cells destined to form the nervous system become two primary types of cells: nerve cells called **neurons** and supporting cells called **glial cells** that provide metabolic support, protection, and insulation for neurons (see the section on glial cells later in the chapter). The principal function of neurons is to transmit information in the form of electrical signaling over long distances. **Sensory neurons**, which are sensitive to environmental stimuli, convert physical stimuli in the world around us and in our internal environment into an electrical signal and transmit that information to circuits of **interneurons**, which are nerve cells within the brain and spinal cord. Interneurons form complex interacting neural circuits and are responsible for conscious sensations, recognition, memory, decision making, and cognition. In turn, **motor neurons** direct a biobehavioral response appropriate for the situation. Although these neurons have common features, their structural arrangements and sizes vary according to their specific functions. **FIGURE 2.1** provides some examples of the many possible shapes of neurons that were first described by the nineteenth-century histological studies of the Spanish neuroanatomist Ramón y Cajal. For much of the twentieth century, neuroscientists relied on the same set of techniques developed by early neuroanatomists to describe and categorize the diversity of cell types in the nervous system.

Histological methods that prepare tissue for microscopic study involve preparing very thin slices of the brain after it has been perfused with a salt solution to remove the blood, and treating the tissue with fixative that kills potentially damaging microorganisms, stops enzymatic damage, and hardens normally soft tissue. After slicing, one of several types of stain is applied to make fine cellular details visible. The Golgi technique, developed in 1873 by the Italian scientist Camillo Golgi, stains only a few cells in their entirety for detailed visualization of individual neurons (see Figure 2.1); others selectively stain myelin to view bundles of axons. Still others selectively stain cell bodies or degenerating axons that identify damaged cells. After the tissue is stained, slices are examined with light or electron microscopy. Although variations on this basic technique are still frequently used, from the late 1970s onward, remarkable new technologies (see Chapter 4) in cell biology and molecular biology provided investigators with many additional tools with which to identify minute differences in the structural features of neurons, trace their multiple connections, and evaluate physiological responses.

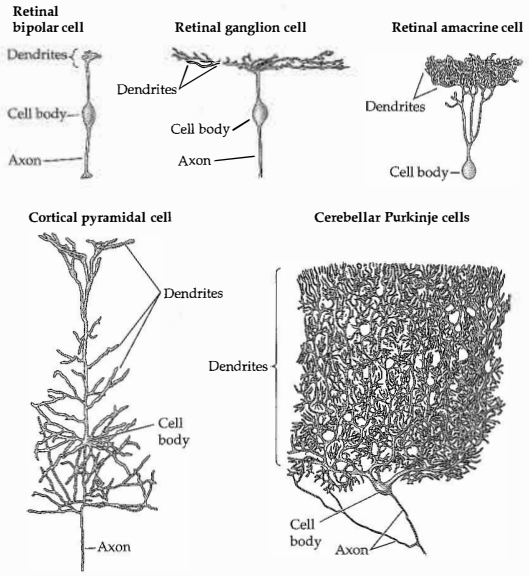


FIGURE 2.1 Varied shapes of neurons These drawings are from actual nerve cells stained by the Golgi technique. Neurons are drawn to different scales to show their varied structures.

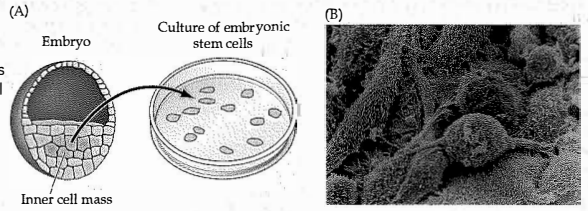
Neurons have three major external features

Although neurons come in a variety of shapes and sizes and utilize various neurochemicals, they have several

BOX 2.1 The Cutting Edge

Embryonic Stem Cells

Stem cells are undifferentiated (i.e., unspecialized) cells that have the ability to proliferate; that is, they replicate themselves over long periods of time by cell division. A second distinguishing feature is that although they are unspecialized, stem cells have the capacity to become any specific tissue or organ cell type, such as red blood cell, muscle, or neuron, each with its unique structure and functions. This is possible because all cells of the body have identical genetic material, but some genes are activated and others are silenced to produce a cell type with all the appropriate proteins to perform its specialized functions. Hence in a nerve cell, particular genes are silenced, and in a heart cell, other genes are silenced. Embryonic stem cells are derived primarily from a portion of very early-stage embryos that would normally become the three germ layers that ultimately develop into all the different tissues of the body. The cells are maintained in a laboratory cell culture dish and multiply, potentially yielding millions of embryonic stem cells (see **Figure**). If after 6 months, the cells have not differentiated into specific tissue cells, they are considered pluripotent, having more than one potential outcome. Scientists attempt to control differentiation to a specific cell type by changing the chemicals in the culture dish or by inserting specific genes into the cells to provide direction.



Culture of embryonic stem cells (A) Embryonic stem cells are cultured from the inner cell mass of an early-stage embryo. (B) Scanning electron micrograph of cultured embryonic stem cells. (© Dr. Yorgos Nikas/Science Source.)

There are several potential benefits from stem cell research. First, in the laboratory, the differentiated cells can be used to develop model systems to improve our understanding of how an organism develops from a single cell. Knowing something about what genes and molecular controls direct normal differentiation may provide important clues about the nature of disease-causing aberrations and the causes of cancer and birth defects, both of which are due to abnormal cell differentiation and cell division. This understanding can lead to new strategies for treatment. Second, drug development can be more efficient if multiple cell lines are used to screen new drugs for potential toxic effects on various cell types from multiple organs. Such preliminary testing would also reduce harm to animals or humans. Third, the most publicized potential application of stem cell research is the use of stem cells for cell transplantation therapies for degenerative diseases or diseased organs. Promising results from initial research with stem cells involved animal models of Parkinson's disease, which showed that administered stem cells migrate to the damaged area of the brain and replace lost dopamine neurons, producing significant improvement in motor function. Others used the cells to replace lost oligodendroglial cells that provide myelin in a rat model of human demyelinating disease (Brüstle et al., 1999). Stem cells can also be directed to form specific classes of CNS neurons. For example, by providing appropriate inductive signals and transcription factors, stem cells can be directed to become motor neurons. These cells replicate in the spinal cord, extend axons, and form synapses with target muscle (Wichterle et al., 2002).

Successes with rat models have encouraged early trials in human patients. Efforts have been made to replace inactive pancreatic β-cells in individuals with type 1 diabetes to restore normal levels of insulin. Additional trials have been initiated to evaluate stem cell use in Parkinson's disease, amyotrophic lateral sclerosis (ALS), macular degeneration, and severe burns. The first trials to treat patients with paraplegia after injury to the thoracic region of the spinal cord are under way. The list of neurodegenerative disorders that might someday be tackled by stem cell transplantation is long and includes Alzheimer's disease, ALS, stroke, brain trauma and tumors, MS, Tay-Sachs disease, Duchenne muscular dystrophy, and many others. Evidence also suggests that there is reduced proliferation of brain stem cells in patients with schizophrenia, depression, and bipolar disorder, which may someday be corrected by stem cell transplantation.

(Continued)

BOX 2.1 The Cutting Edge (continued)

The potential for this type of treatment is enormous, but whether results in humans will resemble those of the animal research must still be determined. Among the hurdles remaining is the need to increase basic research into the cellular events that lead to differentiation of pluripotent stem cells into the specific types of cells needed. In addition, steps may be needed to modify the stem cells to avoid immune rejection of the tissue. Finally, methods of delivery of the cells into the appropriate part of the body will need to be developed for each type of cell therapy. Clearly, treatment of brain disorders is particularly challenging.

A second approach to cell therapy is to use adult stem cells, which are found in many tissues, including brain, blood, skin, and heart. These cells normally function to repair the damaged tissue of the organ in which they reside and so are not pluripotent but are limited in differentiation to cell types within that organ. For instance, cardiac progenitor cells normally repair heart muscle, although at too slow a rate to help someone with significant damage, such as after a heart attack. There is some limited evidence for transdifferentiation of adult cells, which means that certain stem cell types can differentiate into cell types characteristic of tissues other than that of their origin. However, transdifferentiation is somewhat controversial among researchers, and it is not clear whether it occurs in humans. Hence in general, adult stem cells are considered much more limited in their therapeutic potential than those derived from embryos. A second limitation with adult stem cells is that each tissue has only a small number of stem cells, so isolating them is difficult. Furthermore, once they are removed from the body, their ability to divide is limited, so it is more difficult to make the large quantities needed for transplantation. The number of adult cells further decreases with age, and the older cells may have more DNA damage, which may explain their shorter life span compared with pluripotent stem cells. One potential advantage of using adult stem cells is that there might be less risk of immune rejection, because the patient's cells would be isolated, multiplied in cell culture, and then readministered to that same patient.

Psychopharmacology is particularly interested in neural stem cells that are found in only two brain areas: the subventricular zone that lines the lateral ventricles and the hippocampal dentate gyrus. These cells support neurogenesis—the birth of new nerve cells throughout the life span—but also differentiate into oligodendroglia and astrocytes. The importance of neurogenesis in the hippocampus has become an important focus of research into the mechanism of action of antidepressants—a topic that will be discussed further in Chapter 18.

In an effort to overcome the ethical and political hurdles imposed on embryonic stem cell research that have restricted government funding, scientists have developed *induced* pluripotent stem cells (IPS cells). IPS cells are created by genetically reprogramming mature cells to develop the characteristics of the embryonic stem cell, essentially reversing the cell's differentiated fate. These cells have the cell markers of embryonic cells, reproduce in cell culture, and can develop into a wide variety of cells. Further, they avoid the controversial use of human embryos. IPS cells have been useful in drug development and testing and basic research, and a few small studies have been performed in human patients who were undergoing heart surgery. Stem cells injected into the blood or directly into the injured heart seemed to help heart function. However, these studies, although encouraging, are very preliminary. Another advantage of IPS cells is that they would be a match to the cell donor, so they should not be rejected by the immune system. However, a significant downside is that genetic reprogramming requires the use of viral vectors to get the genetic material into the adult cells. Since the use of the retrovirus may produce cancers, alternative nonviral techniques must be developed. Furthermore, more careful evaluation and comparison of IPS cells with embryonic stem cells and adult stem cells are needed to promote understanding of how they differentiate and to evaluate the potential for causing genetic errors or cancer. Unfortunately, some research suggests that IPS cells are less efficient at proliferation than embryonic stem cells, have higher rates of cell death, and prematurely lose their ability to divide (Feng et al., 2010). It is clear that much more research is needed before these cells will be useful therapeutically. A good source of further information is the NIH website Stem Cell Information (NIH, n.d.).

principal external features in common (**FIGURE 2.2**). These features include (1) the **soma**, or cell body, which contains the nucleus and other organelles that maintain cell metabolic function; (2) the **dendrites**, which are treelike projections from the soma that receive information from other cells; and (3) the **axon**, the single tubular extension that conducts the electrical signal from the cell body to the terminal buttons on the axon terminals. Like all other cells, neurons are enclosed by a semipermeable membrane and are filled with a

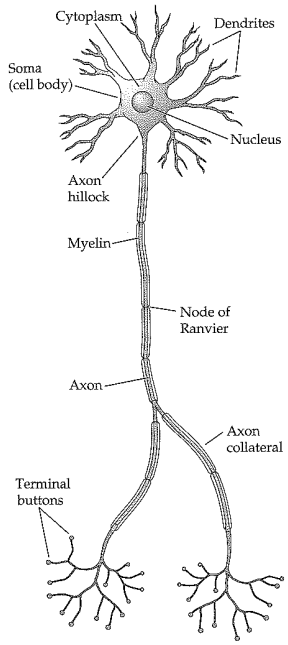


FIGURE 2.2 Principal parts of neurons Despite differences in size and shape, most neurons have numerous features in common.

salty, gelatinous fluid—the **cytoplasm**. Neurons are also surrounded by salty fluid (**extracellular fluid**), from which they take oxygen, nutrients, and drugs, and into which they secrete metabolic waste products that ultimately reach the blood and then are filtered out by the kidneys (see Chapter 1). Like other cells, neurons have **mitochondria**, which are responsible for generating energy from glucose in the form of adenosine triphosphate (ATP). Mitochondria are found throughout the cell, but particularly where energy needs are great. Since neurons use large quantities of ATP, mitochondrial function is critical for survival, and ATP is synthesized continually to support neuron function. The assumption that the rate of synthesis of ATP reflects neuron activity is an underlying premise of several neurobiological techniques that give us the opportunity to visualize the functioning of brain cells (see Chapter 4 for a discussion of positron emission tomography [PET] and functional magnetic resonance imaging [fMRI]).

DENDRITES The general pattern of neuron function involves the dendrites and soma receiving information from other cells across the gap between them, called the **synapse**. On the dendrites of a single neuron, as well as on the soma, there may be thousands of receptors that respond to neurochemicals released by other neurons. Depending on the changes produced in the receiving cell, the overall effect may be either excitatory or inhibitory. Hence each neuron receives and integrates a vast amount of information from many cells; this function is called **convergence**. The integrated information in turn can be transmitted to a few neurons or to thousands of other neurons; this process is known as **divergence**. If we look a bit more carefully using higher magnification, we see that dendrites are usually covered with short **dendritic spines** (**FIGURE 2.3**)

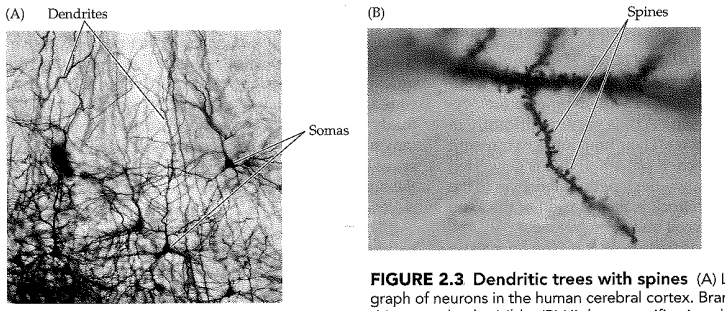


FIGURE 2.3 Dendritic trees with spines (A) Light micrograph of neurons in the human cerebral cortex. Branching dendrites are clearly visible. (B) Higher magnification shows multiple spines all along the dendrite. (A, courtesy of A.-S. LaMantia and D. Purves; B, Mathilde Renard/Medical Images.)

that dramatically increase the receiving surface area. The complex architecture of the dendritic tree reflects the complexity of synaptic connections with other neurons and determines brain function. Dendrites and their spines exhibit the special feature of being constantly modified and can change shape rapidly in response to changes in synaptic transmission (Fischer et al., 1998). Long-lasting changes in synaptic activity change the size and number as well as the shape of dendritic spines from thin to mushroom shaped; this apparently serves as the basis for more efficient signaling. These changes occur throughout life and permit us to continue to learn new associations as we interact with our environment.

Evidence suggesting the importance of dendritic spines to learning comes from studies of human patients and animal models of mental impairment. Individuals with intellectual disabilities have dendritic spines that are unusually small and immature looking; this may result from either a failure of maturation of small spines into larger spines or an inability to maintain spine structure. It is impossible to retain knowledge acquired during development without the large spines, and that failure manifests as intellectual deficiencies. In contrast, individuals with schizophrenia who experience a profound thought disorder have dendritic spines of a normal *size* but reduced spine *density*, particularly in the prefrontal cortex. Although their intelligence is in the normal range, cognitive and negative symptoms of the disorder include poor working memory, lack of attention, poor episodic memory, and low motivation—all of which may be explained by poor connectivity between neurons. Further investigation into the cellular mechanisms of dendritic spine size and density may provide the means to visualize and modify spine dynamics and perhaps may lead to new ways to diagnose and treat brain disorders. For further details on dendritic spine dynamics, the reader is directed to a review by Kasai and colleagues (2010).

AXONS AND TERMINAL BUTTONS The single long extension from the soma is the axon. Axons are tubular in structure and are filled with axoplasm (i.e., cytoplasm within the axon). Axons vary significantly in both length and diameter. Their function is to transmit the electrical signal (action potential) that is generated at the **axon hillock** down the length of the axon to the terminals. The axon hillock is that portion of the axon that is adjacent to the cell body.

Although there is usually only one axon for a given neuron, axons split or bifurcate into numerous branches called **axon collaterals**, providing the capacity to influence many more cells. At the ends of the axons are small enlargements called **terminal buttons**, which are located near the dendrites or somas of other cells.

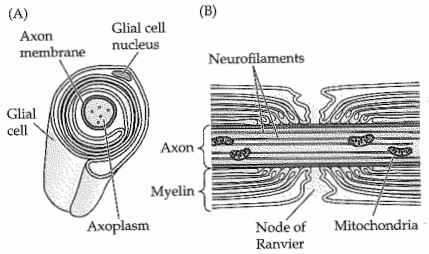


FIGURE 2.4 Myelin sheath (A) Cross section of an axon with multiple layers of glial cell wraps forming the myelin sheath. (B) Longitudinal drawing of a myelinated axon at a node of Ranvier.

Terminal buttons are also called *boutons* or *axon terminals*. Terminal buttons contain small packets (**synaptic vesicles**) of neurochemicals (called **neurotransmitters**) that provide the capacity for chemical transmission of information across the synapse to adjacent cells or to the target organ. Neurons are frequently named according to the neurotransmitter that they synthesize and release. Hence cells that release dopamine are dopaminergic neurons, those that release serotonin are serotonergic, and so forth.

Most axons are wrapped with a fatty insulating coating, called **myelin**, created by concentric layers of glial cells (**FIGURE 2.4A**). There are two types of glial cells that form the myelin sheath: Schwann cells, which myelinate peripheral nerves that serve muscles, organs, and glands; and oligodendroglia, which myelinate nerves within the brain and spinal cord. The myelin sheath provided by both types of glial cells is not continuous along the axon but has breaks in it where the axon is bare to the extracellular fluid. These bare spots, called **nodes of Ranvier** (**FIGURE 2.4B**), are the sites at which the action potential is regenerated during conduction of the electrical signal along the length of the axon. The myelin sheath increases the speed of conduction along the axon; in fact, the thicker the myelin, the quicker the conduction. While a small number of neurons are unmyelinated and conduct slowly, others are thinly wrapped, and some rapidly conducting neurons may have a hundred or more wraps. Myelination also saves energy by reducing the effort required to restore the neuron to its resting state after transmission of the electrical signal.

The best example of the importance of myelin to neuron function comes from multiple sclerosis (MS), the disease that was introduced in the opening vignette. MS is an autoimmune disease in which the immune system attacks a protein in the myelin produced by oligodendrocytes (but not Schwann cells), so the myelin loss is confined to the brain, spinal cord, and optic

nerves. The particular symptoms experienced depend on which neurons have lost their myelin sheath, and they vary greatly from person to person and even within the same person over time. Among the most common symptoms are fatigue; numbness; poor coordination and balance; vision problems; bladder, bowel, and sexual dysfunction; cognitive problems; and depression. There are many more less-common symptoms, as well as what are called secondary symptoms because they result from the primary conditions. For example, the motor symptoms may lead to inactivity that in turn may cause muscle weakness and bone loss. Although myelin can be repaired by oliogodendroglia the repair is slow and not very effective in MS. However researchers are hopeful that new drugs will be developed that reverse nerve damage by facilitating remyelination to improve symptoms (for example, see Dombrowski et al., 2017). Currently available pharmacotherapies and greater detail on MS is provided in Chapter 20. See Recommended Readings on the Companion Website to access *What Is Multiple Sclerosis*, a brief animation of the causes of MS. The impact of having MS is described in one of many available YouTube video clips as well.

SOMA The cell body is responsible for the metabolic care of the neuron. Among its important functions is the synthesis of proteins that are needed throughout the cell for growth and maintenance. These proteins include such things as enzymes, receptors, and components of the cell membrane. Within the nucleus are pairs of chromosomes that we inherited from our parents. **Chromosomes** are long strands of deoxyribonucleic acid (DNA), and **genes** are small portions of chromosomes that code for the manufacture of a specific protein molecule. Hence the **coding region** of a gene provides the "recipe" for a specific protein such as a receptor or an enzyme. Although every cell in the body contains the full genetic library of information, each cell type manufactures only those proteins needed for its specific function. Hence liver cells manufacture enzymes to metabolize toxins, and neurons manufacture enzymes needed to synthesize neurotransmitters and carry out functions necessary for neural transmission. In addition, which specific genes are activated is determined in part by our day-to-day experience. Neurobiologists are finding that experiences such as prolonged stress and chronic drug use may turn on or turn off the production of particular proteins by modifying transcription factors. **Transcription factors** are nuclear proteins that direct protein production. Transcription factors such as CREB bind to the **promoter region** of the gene adjacent to the coding region, modifying its rate of transcription.

Transcription occurs in the nucleus, where messenger RNA (mRNA) makes a complementary copy of the active gene. After moving from the nucleus to the

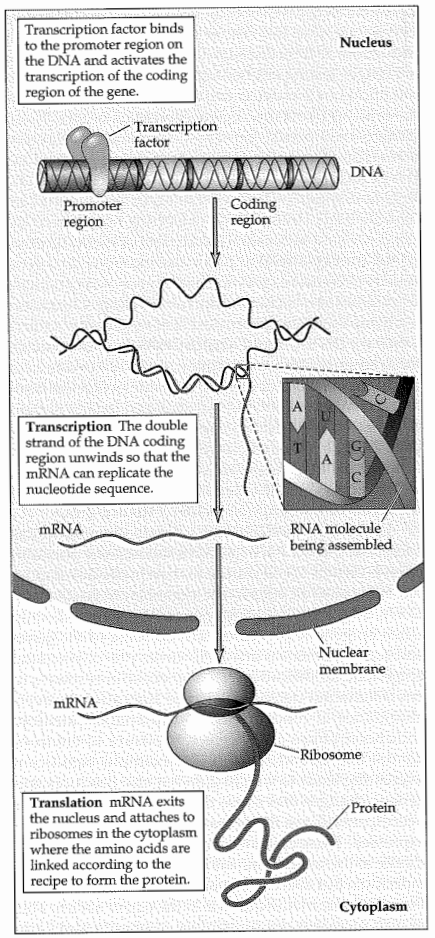


FIGURE 2.5 Stages of protein synthesis Activation of a gene by a transcription factor initiates the formation of mRNA within the nucleus, followed by translation into a protein on the ribosomes in the cytoplasm.

cytoplasm, mRNA attaches to organelles called **ribosomes**, which decode the recipe and link the appropriate amino acids together to form the protein. This process is called **translation**. Some of the basic steps in protein synthesis are shown in **FIGURE 2.5**.

EPIGENETICS We already said that environmental events can alter the rate of gene expression through induction of transcription factors. In addition, there are longer-lasting environmentally induced epigenetic modifications that determine which genes will be turned on or off and how much gene expression occurs. These changes may persist through the lifetime of the organism and may even be passed on to future generations if modifications are present in the germ cell line (i.e., eggs and sperm). These events occur despite the fact that the basic structure of the DNA is not altered. Instead, the simple covalent attachment of methyl groups (**DNA methylation**) to particular locations on a gene usually decreases expression of that gene. A second type of modification is **chromatin remodeling**. Chromatin is a complex of small spherical histone proteins around which the DNA wraps (**FIGURE 2.6A**). Environmentally induced acetylation, methylation, or phosphorylation of the lysine residues of histone tails can loosen the chromatin structure, allowing transcription factors to bind to the DNA and activate expression of the gene (**FIGURE 2.6B**). In other cases, chemical modification of the histone tails makes the chromatin more tightly packed, which represses gene expression by physically limiting the access of transcription factors (**FIGURE 2.6C**).

Epigenetic modification of gene expression has been understood since the 1970s because the phenomenon is central to cell differentiation in the developing fetus. Because all cells in the organism have identical DNA, they differentiate into organ-specific cells only when epigenetic processes turn on some of the genes and turn off others in utero. However, pre- or postnatal epigenetic modification can also occur in response to environmental demands such as starvation or overabundance of food, stress, poor prenatal nutrition, childhood abuse and neglect, exposure to environmental toxins, and so forth. For example, significant overeating leads to weight gain but also produces epigenetic changes that cause the genes for obesity to be overexpressed and the genes for longevity to be underexpressed. These epigenetic modifications not only contribute to the weight gain and shortened life span of the individual but also can be passed on to offspring when the epigenetic modification is in the egg or sperm. This in turn increases the probability of obesity and early mortality in the offspring (Kaati et al., 2007). For more detail see Transgenerational Epigenetic Transmission below. A brief video, *The Epigenome at a Glance*, from the University of Utah is available online (Genetic Science Learning Center, 2013, July 15). For additional online materials and interactive activities, go to the parent site: Learn.genetics.utah.edu/content/epigenetics/.

TRANSGENERATIONAL EPIGENETIC TRANSMISSION The concept that parents' environmental exposure can influence their offspring's behavior, metabolism, or disease status is an intriguing concept, although the mechanism of transfer is not well understood. It is clear that maternal experiences during pregnancy are capable of affecting fetal development, since the uterus is the fetus's initial environment. However, recent evidence suggests that environmental events occurring *before* conception can also impact the health and behavior of the offspring. Many studies have shown that the offspring of extremely stressed parents have greater risk for mental and physical difficulties even when parental trauma predated conception. This would suggest that the trauma can cause epigenetic modifications to the genome and be passed on via gametes (eggs and sperm). More recently it has been shown that the mother's experiences are not the only influence on the phenotype of the offspring. The father's environment can also pass on epigenetic markers on sperm or in seminal fluid (see Bowers and Yehuda, 2016). Since experiments on humans would not be ethical, it is easier to study the mechanisms of transgenerational epigenetic transmission in male rodents because they do not participate in raising the young. In contrast, interpretation of data in female rats must consider multiple factors, including maternal influence on intrauterine fetal development, nurturing behaviors with the young, and lactation (Rando, 2012). In numerous rodent studies young male animals were provided with a normal diet or one that lacked protein or contained excess fat. When they reached adulthood, they were mated with females that had always had a normal diet. When the offspring of the pair were evaluated, they found that the abnormal diets of the fathers altered metabolic factors such as glucose control (in humans, associated with diabetes) and cholesterol metabolism (in humans, associated with heart disease) as well as blood pressure and other cardiovascular irregularities (Rando, 2015).

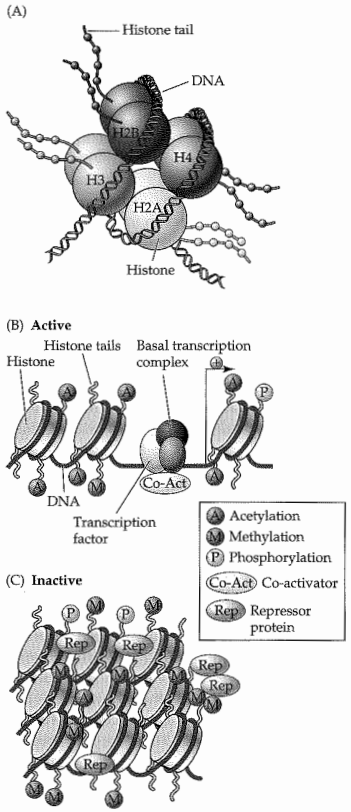


FIGURE 2.6 Epigenetic regulation of gene transcription (A) Chromatin is a complex of DNA, histone proteins, and nonhistone proteins (not shown). (B) When histone tails are acetylated, charges open up the chromatin, creating an active state that allows transcription factors to bind to the promoter region of a gene to enhance transcription. (C) The inactive state of chromatin is caused by methylation of histone tails, which pulls the chromatin tighter and prevents the binding of transcription factors, reducing transcription of the gene. (A, after Levenson and Sweatt, 2005 and Tsankova et al., 2007; B,C after Tsankova et al., 2007.)

Transgenerational inheritance goes well beyond dietary modification. Dias and Ressler (2014) used male mice and conditioned them with foot shock, which produced a distinct startle response, when one odor (acetophenone) or another (propanol) was presented. These odors were chosen because they activate different receptors in the olfactory system. After the association was established, the males were mated with healthy female mice. The male offspring resulting from the mating were tested for their behavioral sensitivity to the odors. Dias and Ressler found that the young unconditioned animals showed greater sensitivity to the odor their parents had been conditioned to, compared with control mice. Further, the offspring whose fathers associated acetophenone with foot shock were not more sensitive to propanol and vice versa. Hence mice who had never experienced the odor before testing responded differentially to the odors, based on the earlier paternal painful experience associated with a particular odor. This may represent an evolutionarily adaptive way to pass on information about potentially harmful environmental stimuli to future generations. Expanding on their results, the researchers found that the neuroanatomical pathway associated with the acetophenone olfactory receptor (Olfr151) was enhanced in the acetophenone-sensitive offspring compared with the other mice. Further, those same offspring and their fathers showed DNA hypomethylation (an epigenetic marker described above).

Epigenetic mechanisms became a major focus of research when it became clear that epigenetic differences caused by environmental factors could potentially explain a lot of previously unanswered questions. For instance, it may explain why monozygotic twins who have identical genes do not necessarily develop the same disorders, such as schizophrenia or bipolar disorder, cancer, or diabetes. Apparently, despite the identical genes, environmental events have caused those genes to be expressed in different patterns in the two individuals. Epigenetic events may also help to explain the persistence of the drug-taking behavior characteristic of addiction (see Chapter 9). Drugs of abuse cause neuroadaptive changes that are very long lasting and that persist, despite years of abstinence. These changes in structural and behavioral plasticity are associated with increased activation of specific transcription factors. However, these transcription factors return to baseline levels after several months of abstinence, so they are not likely to maintain drug dependence over prolonged periods. One explanation may be that drugs of abuse enhance histone acetylation of multiple genes, which would produce much more persistent changes in gene expression. The potential for clinical use of epigenetic manipulations in drug treatment programs is suggested by a study showing that inhibition of an enzyme that removes acetyl groups from histone, which increased acetylation in nucleus accumbens, reduced drug-seeking behavior in laboratory animals and also reduced the probability of relapse when the mice were re-exposed to cocaine (Malvaez et al., 2010).

An additional potentially significant role for epigenetic mechanisms may help to explain the etiology of many complex disorders, such as anxiety and depression, that have not shown a strong genetic link despite the newest sophisticated molecular genetic techniques. For these and other psychiatric disorders, the genetic polymorphisms identified so far contribute only about 1% of the risk for developing the disease. Hence the environment along with epigenetic mechanisms may have a greater part in initiating the disorder. Epigenetic changes may also help to explain why some disorders, such as autism and many neurological disorders, appear to run in families and yet have no classic genetic transmission (Sweatt, 2013). Finally, epigenetic mechanisms may also help us understand the link between early life events such as abuse or neglect and the increased occurrence of clinical depression (see Chapter 18) and anxiety disorders (see Chapter 17) later in life.

The ultimate goal for neuropharmacology is to develop drugs that can be used to manipulate epigenetic

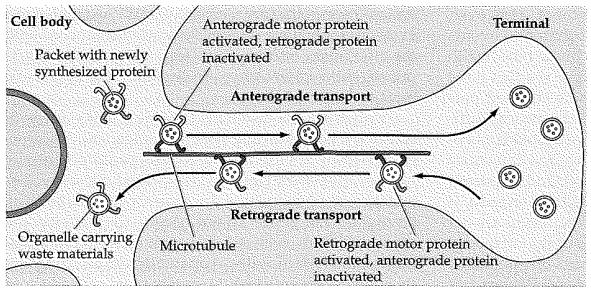


FIGURE 2.7 Axoplasmic transport The movement of newly synthesized proteins from the soma to the axon terminals (anterograde) is powered along the microtubules by a motor protein called kinesin. Old proteins are carried from the terminals to the soma (retrograde) by the motor protein dynein.

factors, for example, to deacetylate histone or increase methylation of DNA to treat psychiatric disorders that have genetic components, such as autism, schizophrenia, depression, Alzheimer's disease, and others. In essence, the drug could be used to enhance gene expression that may have been suppressed by the disorder or turn off expression of genes that are associated with the development of symptoms.

AXOPLASMIC TRANSPORT Having said that proteins are synthesized within the soma and knowing that proteins are needed throughout the neuron, we must consider how these proteins are moved to the required destination. The process is called **axoplasmic transport**, and it depends on structures of the cytoskeleton. The **cytoskeleton**, as the name suggests, is a matrix composed of tubular structures, which include microtubules and neurofilaments that form a mesh-like mass that provides shape for the cell. In addition, the microtubules, which run longitudinally down the axon, provide a stationary track along which small packets of newly synthesized protein are carried by specialized motor proteins (**FIGURE 2.7**). Movement of materials occurs in both directions. Newly synthesized proteins are packaged in the soma and transported in an anterograde direction toward the axon terminals. At the terminals, the contents are released, and retrograde axonal transport carries waste materials from the axon terminals back to the soma for recycling.

Abnormalities of the cytoskeleton constitute one of several pathological features of the brain in people with Alzheimer's disease—the neurofibrillary tangles. These tangles are made up of long, paired, spiral neurofilaments braided together. The neurofilament proteins, called tau, are normally important in keeping the microtubules running parallel and longitudinally directed down the axon. Tau normally has phosphate molecules attached to it, but in Alzheimer's disease a large number of additional phosphate groups attach. This hyperphosphorylation causes tau to separate from the microtubules, and tau becomes twisted together to form tangles and accumulates as a mass in the soma. The microtubules disintegrate destroying the material transport system, and the axons shrivel up so neurons can no longer communicate with each other. The number of such tangles is directly related to the extent of cognitive impairment, which demonstrates clearly the importance of the cytoskeleton to brain function. Alzheimer's disease is discussed in detail in Chapter 20.

Characteristics of the cell membrane are critical for neuron function

One of the more important characteristics of neurons is the cell membrane. In Chapter 1 we learned that the neuronal membrane is essentially a phospholipid bilayer that prevents most materials from freely passing (see Figure 1.5), unless they are lipid soluble. In addition to phospholipids, membranes have proteins inserted into the bilayer. Many of these proteins are **receptors**—large molecules that are the initial sites of action of neurotransmitters, hormones, and drugs. Details of these receptors and their functions are described in Chapter 3. Other important proteins associated with the membrane are enzymes that catalyze biochemical reactions in the cell. A third important group of proteins consists of ion channels and transporters. Because the membrane is not readily permeable to charged molecules, special devices are needed to move molecules such as amino acids, glucose, and metabolic products across the membrane. Movement of these materials is achieved by transporter proteins, which are described further in Chapter 3. In addition, charged particles (ions), such as potassium (K^+), sodium (Na^+), chloride (Cl^-), and calcium (Ca^{2+}), that are needed for neuron function can be moved through the membrane only via ion channels. These channels are protein molecules that penetrate through the cell membrane and have a water-filled pore through which ions can pass.

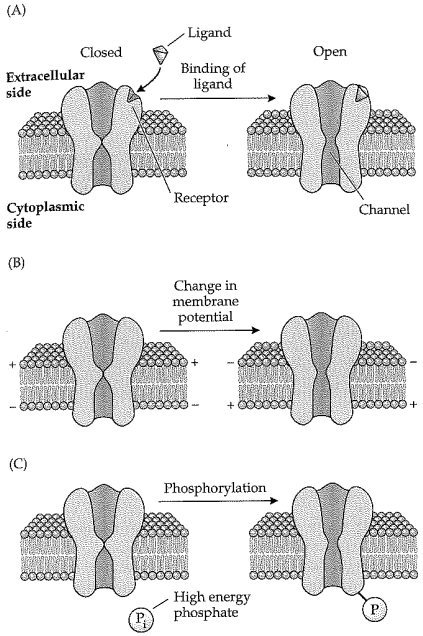


FIGURE 2.8 Ion channels (A) When a ligand (neurotransmitter, hormone, or drug) binds to a receptor on the channel, the ligand-gated channel protein changes shape and opens the gate, allowing passage of a specific ion. (B) A voltage-gated channel is opened when the electrical potential across the membrane near the channel is altered. (C) Modification of a channel by a second messenger, which produces intracellular phosphorylation (addition of a phosphate group) and regulates the state of the channel. (After Siegelbaum and Koester, 2000.)

Ion channels have several important characteristics. First, they are relatively specific for particular ions, although some allow more than one type of ion to pass through. Second, most channels are not normally open to allow free passage of the ions, but are in a closed configuration that can be opened momentarily by specific stimuli. These channels are referred to as **gated channels**. Two types of channels of immediate interest to us are **ligand-gated channels** and **voltage-gated channels**. Looking at the ligand-gated channel in **FIGURE 2.8A**, you can see that when a drug, hormone, or neurotransmitter binds to a receptor that recognizes the ligand, the channel protein changes shape and opens the gate, allowing flow of a specific ion either into or out of the cell. The direction in which an ion moves is determined by its relative concentration; it always travels from high to low concentration. Hence, given an open gate, Na^+, Cl^-, and Ca^{2+} will move into the cell, while K^+ moves out (see details on local potentials in the next section). A second type of channel, which will be of importance later in this chapter, is the type that is opened by voltage differences across the membrane. These voltage-gated channels are opened not by ligands, but by the application of a small electrical charge to the membrane surrounding the channel (**FIGURE 2.8B**). Other channels are modified by second messengers (**FIGURE 2.8C**), but discussion of these will have to wait until Chapter 3. Regardless of the stimulus opening the channel, it opens only briefly and then closes again, limiting the total amount of ion flux.

Glial cells provide vital support for neurons

Glial cells have a significant role in neuron function because they provide physical support to neurons, maintain the chemical environment of neurons, and provide immunological function. The four principal types include oligodendroglia, Schwann cells, astrocytes, and microglia. **Schwann cells** and **oligodendroglia**, described earlier, produce the myelin sheath on neuronal axons of the peripheral nervous system (PNS) and the central nervous system (CNS), respectively. Schwann cells and oligodendroglia differ in several ways in addition to their location in the nervous system. Schwann cells (**FIGURE 2.9A**) are dedicated

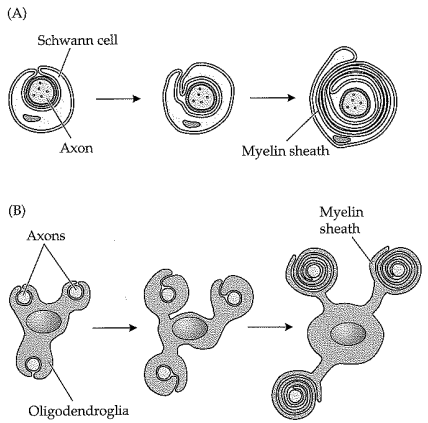
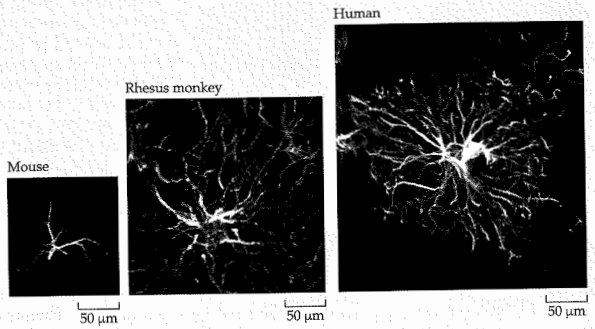


FIGURE 2.9 Glial cells forming myelin (A) Schwann cells in the PNS dedicate themselves to a single axon and wrap many times to form the myelin for one segment. (B) Each oligodendroglia in the CNS sends out multiple sheetlike arms that wrap around segments of multiple nearby axons to form the myelin sheath.

BOX 2.2 Of Special Interest

Astrocytes

Although astrocytes were previously believed to act merely as a "brain glue" by providing support for the all-important neurons, in the last 30 years many new vital functions have been identified for these cells. Their importance to nervous system function is suggested by the fact that the ratio of astroglia to neurons increases with the complexity of brain function. In worms, there is one astrocyte for every six neurons (1:6), the ratio in rodent cortex is 1:3, and in human cortex there are slightly more astrocytes than neurons (1.4:1) (Sofroniew and Vinters, 2010). Not only does the ratio of astrocytes to neurons change, but the astrocyte domain (soma plus processes) increases with increasing complexity of brain function (see **Figure**).



Astrocytes in cortex of an adult mouse, a rhesus monkey, and a human Although all show a bushy morphology, the size of the astrocyte increases with increasing complexity of brain function. (From Kimelberg and Nedergaard, 2010.)

Much of the research has been focused on how the glial cells respond to tissue damage, because they are potentially novel therapeutic targets for many diseases of the nervous system that involve gliosis (activation and accumulation of glial cells in response to CNS injury). These diseases include Alzheimer's disease, neuropathic pain, multiple sclerosis, Parkinson's disease, seizure disorders, migraine, and many others. The response to CNS injury begins with the arrival of microglia, which provide a rapid response to inflammatory signals caused by brain damage. The arrival of microglia initiates the action of astrocytes, called astrogliosis. Gliosis, a reactive change in glial cells following CNS damage, is characterized by an increase in filaments of the cytoskeleton, leading to cell enlargement and buildup of scar tissue. Depending on the nature and extent of damage, astroglia can have either beneficial or detrimental effects. For instance, in some cases they release anti-inflammatory molecules, but in other circumstances they may release pro-inflammatory neurotoxic substances. These neurotoxic substances may contribute further to inflammatory disorders such as multiple sclerosis. Additionally, while astroglia protect against programmed cell death, in other cases the astroglial scar tissue prevents the regeneration of axons. Although the scar tissue may impair recovery, in other cases it may prevent the spreading of an infectious agent to healthy brain tissue by creating a physical barrier (see Sofroniew and Vinters, 2010).

Astroglia do not have electrical excitability, as neurons do, but are capable of communicating with nearby cells (both neurons and other glia) by altering their intracellular calcium concentration. Neurons can signal to the astrocytes by releasing neurotransmitters, including glutamate, GABA (γ-aminobutyric acid), acetylcholine, and norepinephrine. The astrocytes can reciprocally influence the function of neighboring neurons, so there is a coordinated network of glial–neuron activity.

Furthermore, astroglia also have proteins in their membranes, called transporters, that remove certain neurotransmitters from the synapse, hence terminating their synaptic action. This function is especially important for the amino acid neurotransmitter glutamate. Uptake of glutamate by astrocytes has several functions. After glutamate is taken up, the astrocyte converts it to glutamine. Glutamine can be transported back into neurons, where it can be converted back into glutamate for neurotransmission (Boison et al., 2010). The uptake of glutamate by astrocytes is also important when synaptic glutamate levels are high for prolonged periods, because glutamate can have damaging effects (excitotoxicity) on neurons (see Chapter 8). Impaired uptake of glutamate by astrocytes has been implicated in some neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), and also disorders associated with severe energy failure, such as severe head trauma or status epilepticus, which is characterized by prolonged, uncontrolled seizures. Multiple studies have shown

BOX 2.2 Of Special Interest *(continued)*

structural and physiological abnormalities in astrocytes in epileptic tissue such as in the hippocampus. Others have found that animals that have been genetically modified to prevent glutamate uptake have been highly susceptible to excitotoxicity and many have developed epileptic seizures (see Boison et al., 2010). Failure of astroglia function not only prevents glutamate uptake but also impairs the ability to remove excess synaptic K^+ and maintain the appropriate salt–water balance and extracellular pH.

In addition to the significant role of astrocytes in responding to tissue damage, modulating synaptic function, and maintaining the extracellular fluid, astrocytes also surround all the blood vessels in the brain (see Figure 1.8) and so in that way play a large role in regulating CNS blood flow. They respond to the neurotransmitters released by adjacent neurons by increasing their intracellular Ca^{2+}. This in turn causes the release of vasoactive chemicals, such as prostaglandins, that produce vasodilation. They regulate the amount of blood flow in a given brain region based on the level of synaptic activity of hundreds of neurons. In this way astroglia can coordinate the availability of oxygen and glucose in the blood with the amount of neural activity. As you will see in Chapter 4, that principle is the basis for fMRI, which scans the brain for increased blood flow and oxygenation to identify those areas that are most metabolically active. Although it is unclear what the precise chemical mediators between the astrocytes and blood vessels are, much more research is ongoing (Howarth, 2014).

Additionally, because astrocytes bridge the gap between blood vessels and neurons, they are able to take up glucose from the blood and store it in the form of glycogen. During times when blood glucose is low and/or neurons show enhanced electrical activity, the astrocytes convert glycogen to lactate and transfer it to neurons to provide energy to the cells. Several excellent reviews on astrocyte function and their role in CNS disorders and brain pathology are available (Kimelberg and Nedergaard, 2010; Sofroniew and Vinters, 2010).

to a single neuron, and these PNS axons, when damaged, are prompted to regenerate axons because of the Schwann cell response. First, the Schwann cells release growth factors, and second, they provide a pathway for regrowth of the axon toward the target tissue. Oligodendroglia, (**FIGURE 2.9B**) in contrast, send out multiple paddle-shaped "arms," which wrap many different axons to produce segments of the myelin sheath. In addition, they do not provide nerve growth factors when an axon is damaged, nor do they provide a path for growth.

Two other significant types of glial cells are the astrocytes and microglia. **Astrocytes** are large, star-shaped cells that have numerous extensions. They intertwine with neurons and provide structural support; in addition, they help to maintain the ionic environment around neurons and modulate the chemical environment as well by taking up excess neurochemicals that might otherwise damage cells. Because astrocytes have a close relationship with both blood vessels and neurons, it is likely that they may aid the movement of necessary materials from the blood to nerve cells. Greater detail on astrocyte function is provided in **BOX 2.2**. **Microglia** are far smaller than astrocytes and act as scavengers that collect at sites of neuron damage to remove dying cells. In addition to their phagocytotic function, microglia are the primary source of immune response in the CNS and are responsible for the inflammation reaction that occurs after brain damage. Chapter 19 describes their potential role in the etiology of schizophrenia. **TABLE 2.1** summarizes the functions of glial cells.

TABLE 2.1 Functions of Glial Cells

Cell	Function
Astrocytes	Provide structural support
	Maintain ionic and chemical environment
	Store nutrients to provide energy for neurons
	Perform gliosis
	Regulate CNS blood flow
	Coordinate reciprocal glia–neuron activity
Microglia	Perform phagocytosis
	Provide immune system function
Schwann cells	Form myelin sheath on a single axon in the PNS
	Release growth factors following neuron damage
	Provide a channel to guide axons to targets
Oligodendroglia	Form myelin sheath on multiple axons in the CNS
	Inhibit regrowth of axons following neuron damage

Section Summary

- Neurons are surrounded by a cell membrane and are filled with cytoplasm and the organelles needed for optimal functioning.
- Among the most important organelles are the mitochondria, which provide energy for the metabolic work of the cell.
- The principal external features of a neuron are the soma, treelike dendrites, and a single axon extending from the soma that carries the electrical signal all the way to the axon terminals.
- Axon terminals contain synaptic vesicles filled with neurotransmitter molecules that are released into the synapse between cells when the action potential arrives.
- The dendrites of a neuron are covered with minute spines that increase the receiving surface area of the cell. These spines are reduced in size in individuals with intellectual impairment and reduced in number in those with schizophrenia.
- Thousands of receptors that respond to neurotransmitters released by other neurons are found on the dendrites, dendritic spines, and soma of the cell.
- The axon hillock is located at the juncture of soma and axon and is responsible for summation (or integration) of the multiple signals required to generate an action potential.
- Conduction of the action potential along the axon is enhanced by the insulating property of the myelin created by nearby glial cells.
- The nucleus of the cell is located within the soma, and protein synthesis occurs there. Transcription of the genetic code for a specific protein by mRNA occurs within the nucleus, and translation of the "recipe," carried by the mRNA, occurs on the ribosomes in the cytoplasm. Ribosomes link together appropriate amino acids to create the protein.
- Changes in synaptic activity increase or decrease the production of particular proteins by activating transcription factors in the nucleus.
- Epigenetics is the study of how environmental demands such as diet, environmental toxins, stress, prenatal nutrition, and many others turn on or turn off the expression of specific genes. Although epigenetic markers do not modify DNA, they can last a lifetime and may be transmitted to future generations. Two common markers are DNA methylation and chromatin remodeling.
- Future drug development will target epigenetic factors to treat psychiatric disorders that have genetic components by turning on protective genes or turning off genes associated with symptom development.
- Newly manufactured proteins are packaged into vesicles in the soma and are moved by motor proteins that slide along the neuron's microtubules (part of the cytoskeleton) to the terminals (anterograde transport). Protein waste and cell debris are transported from the terminals back to the soma (retrograde transport) for recycling.
- The cell membrane is a phospholipid bilayer that prevents most materials from passing through, unless the material is lipid soluble. Special transporters carry other essential materials, such as glucose, amino acids, and neurotransmitters into the cell. Ion channels allow ions such as Na^+, K^+, Cl^-, and Ca^{2+} to move across the membrane. Other proteins associated with the membrane include receptors and enzymes.
- Four types of glial cells are found in the nervous system. Schwann cells and oligodendroglia produce the myelin sheath on peripheral and central nervous system neurons, respectively. Astrocytes regulate the extracellular environment of the neurons, regulate CNS blood flow, and provide physical support and nutritional assistance. Microglia act as phagocytes to remove cellular debris and provide immune function.

Electrical Transmission within a Neuron

The transmission of information within a single neuron is an electrical process and depends on the semipermeable nature of the cell membrane. When the normal resting electrical charge of a neuron is disturbed sufficiently by incoming signals from other cells, a threshold is reached that initiates the electrical signal (action potential) that conveys the message along the entire length of the axon to the axon terminals. This section of the chapter looks at each of the stages: resting membrane potential, local potentials, threshold, and action potential.

Ion distribution is responsible for the cell's resting potential

All neurons have a difference in electrical charge inside the cell compared with outside the cell, called the **resting membrane potential**. This can be measured by placing one electrode on the exterior of the cell in the extracellular fluid and a second, much finer microelectrode into the intracellular fluid inside the cell (**FIGURE 2.10**). The inside of the neuron is more negative than the outside, and a voltmeter would tell us that the difference is approximately –70 millivolts (mV), making the neuron **polarized** in its resting state.

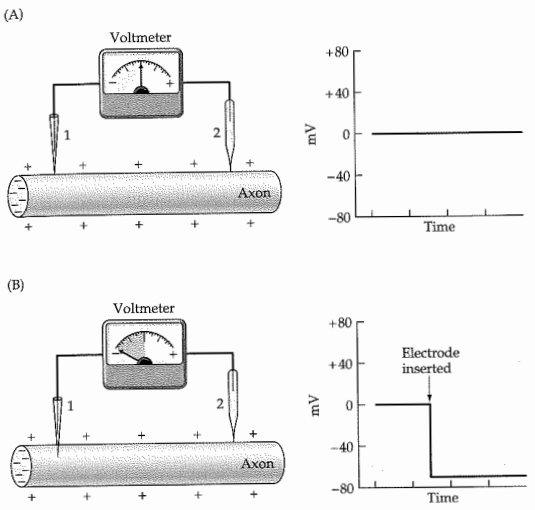


FIGURE 2.10 Membrane potential recording from a squid axon
(A) When both electrodes are applied to the outside of the membrane, no difference in potential is recorded. (B) When the microelectrode is inserted into the axoplasm, a voltage difference between inside and outside is recorded. The graph shows the voltage change when one electrode penetrates the cell.

Selective permeability of the membrane and uneven distribution of ions inside and outside the cell are responsible for the membrane potential. This means that when the cell is at rest, there are more negatively charged particles (ions) inside the cell and more positively charged ions outside the cell. **FIGURE 2.11** shows the relative concentration of different ions on either side of the membrane. Inside we find many large, negatively charged molecules, such as proteins and amino acids, which cannot leave the cell. Potassium is also in much higher concentration (perhaps 20 times higher) inside the cell than outside. In contrast, Na^+ and Cl^- are present in greater concentration outside the cell than inside.

Several forces are responsible for this ion distribution and membrane potential. The concentration gradient and electrostatic pressure for the K^+ ion are particularly important; K^+ moves more freely through the membrane than other ions because some of its channels are not gated at the resting potential. Recall that ions move through relatively specific channels and that most are gated, meaning that they are normally held closed until opened by a stimulus. Since the inside of the cell normally has numerous large, negatively charged materials that do not move through the membrane, the positively charged K^+ ion is pulled into the cell because it is attracted to the internal negative charge, that is, by **electrostatic pressure** (see Figure 2.11). However, as the concentration of K^+ inside rises, K^+ responds to the concentration gradient

	● Na^+	● K^+	● Cl^-	○ Ca^{2+}	● Protein
Concentration outside cell	440	20	560	10	Few
Concentration inside cell	50	400	40–150	0.0001	Many

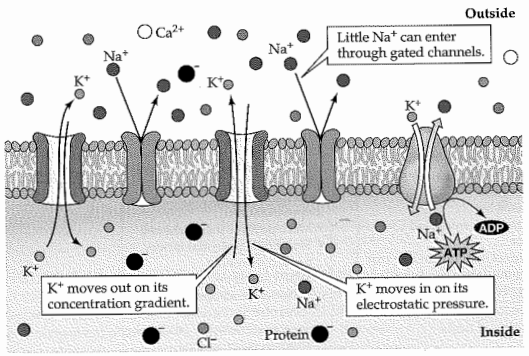


FIGURE 2.11 Distribution of ions inside and outside a neuron at resting potential Na^+ and Cl^- are more concentrated outside the cell and cannot move in freely through their gated channels. Some K^+ channels are not gated, allowing the concentration of the ion to force K^+ outward while electrostatically it is pulled in. At –70 mV, equilibrium between the two forces is reached. The Na^+–K^+ pump helps to maintain the ion distribution. It requires significant energy (ATP) to move ions against their concentration gradients.

by moving out of the cell. The concentration gradient is a force that equalizes the amount or concentration of material across a biological barrier. When the two forces on K^+ (inward electrostatic pressure and outward concentration gradient) are balanced at what is called the **equilibrium potential for potassium**, the membrane potential is still more negative inside (–70 mV). In addition, because small amounts of Na^+ leak into the cell, an energy-dependent pump contributes to the resting potential by exchanging Na^+ for K^+ across the membrane. For every three ions of Na^+ pumped out by this **Na^+–K^+ pump**, two K^+ ions are pumped in, keeping the inside of the cell negative.

In summary, all cells are polarized at rest, having a difference in charge across their membranes. The potential is due to the uneven distribution of ions across the membrane, which occurs because ions move through relatively specific channels that normally are not open. K^+ has greater ability to move freely through ungated channels. Although all cells are polarized, what makes neurons different is that rapid changes in the membrane potential provide the means for neurons to conduct information; this, in turn, influences hundreds of other cells in the nervous system. The rapid change in membrane potential that is propagated down the length of the axon is called the **action potential**. For a cell to generate an action potential, the membrane potential must be changed from resting (–70 mV) to the **threshold** for firing (–50 mV). At –50 mV, voltage-gated Na^+ channels open, generating a rapid change in membrane potential. Before we look closely at the action potential, let's see what happens to a neuron to cause the membrane potential to change from resting to threshold.

Local potentials are small, transient changes in membrane potential

Although the membrane potential at rest is –70 mV, various types of stimuli that disturb the membrane can open ion channels momentarily, causing small, local changes in ion distribution and hence electrical potential differences called **local potentials**. To visualize the small changes in membrane potential, we attach our electrodes to an amplifier and to a computer that measures and records the changing voltage over time (**FIGURE 2.12**). For instance, applying a small, positive electrical current or momentarily opening gated Na^+

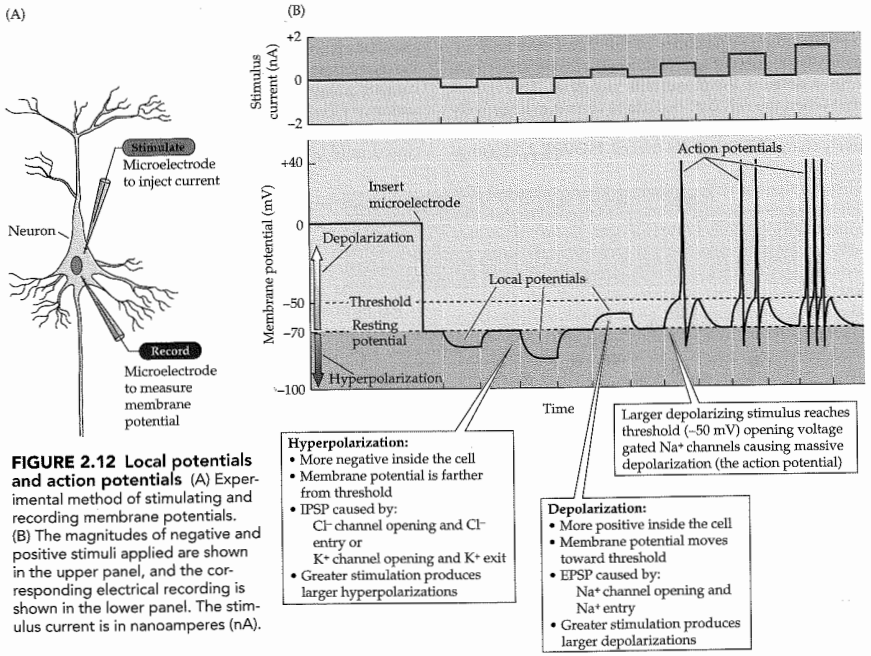


FIGURE 2.12 Local potentials and action potentials (A) Experimental method of stimulating and recording membrane potentials. (B) The magnitudes of negative and positive stimuli applied are shown in the upper panel, and the corresponding electrical recording is shown in the lower panel. The stimulus current is in nanoamperes (nA).

channels allows a relatively small number of Na^+ ions to enter the cell. These ions enter because Na^+ is more concentrated outside than inside, so the concentration gradient drives the ions in. The oscilloscope shows that positively charged ions make the inside of the cell slightly more positive in a small, localized area of the membrane, bringing the membrane potential a tiny bit closer to the threshold for firing. This change is called a local **depolarization** and is excitatory. Other stimuli may open Cl^- channels, which allow Cl^- into the cell because the ion's concentration is greater on the outside of the cell. The local increase in the negatively charged ion makes the cell slightly more negative inside and brings the resting potential farther away from threshold. This **hyperpolarization** of the membrane is inhibitory. Finally, if gated K^+ channels are opened by a stimulus, K^+ is driven outward locally on the basis of its concentration gradient. Because positively charged ions leave the cell, it becomes just slightly more negative inside, making the membrane potential farther from threshold and causing local hyperpolarization. These local potentials are of significance to psychopharmacology because when drugs or neurotransmitters bind to particular receptors in the nervous system, they may momentarily open specific ion channels (see Figure 2.8), causing an excitatory or inhibitory effect. Because neurotransmitters act on the postsynaptic membrane, the effects are called **excitatory postsynaptic potentials (EPSPs)** or **inhibitory postsynaptic potentials (IPSPs)**.

These local potentials (hyperpolarizations and depolarizations), generated on the dendrites and cell body, have several significant characteristics. First, they are graded, meaning that the larger the stimulus, the greater is the magnitude of hyperpolarization or depolarization. Also, as soon as the stimulus stops, the ion channels close and the membrane potential returns to resting levels. These local potentials decay rapidly as they passively travel along the cell membrane. Finally, local potentials show summation, sometimes called **integration**, meaning that several small depolarizations can add up to larger changes in membrane potential, as several hyperpolarizations can produce larger inhibitory changes. When hyperpolarizations and depolarizations occur at the same time, they cancel each other out. The receptor areas of a neuron involved in local potential generation receive information from thousands of synaptic connections from other neurons that at any given instant produce IPSPs or EPSPs (as well as other biochemical changes to be described in Chapter 3). Integration of EPSPs and IPSPs occurs in the axon hillock (**FIGURE 2.13**) and is responsible for generation of the action potential if the threshold for activation is reached.

Sufficient depolarization at the axon hillock opens voltage-gated Na^+ channels, producing an action potential

The summation of local potentials at the axon hillock is responsible for generation of the action potential. The

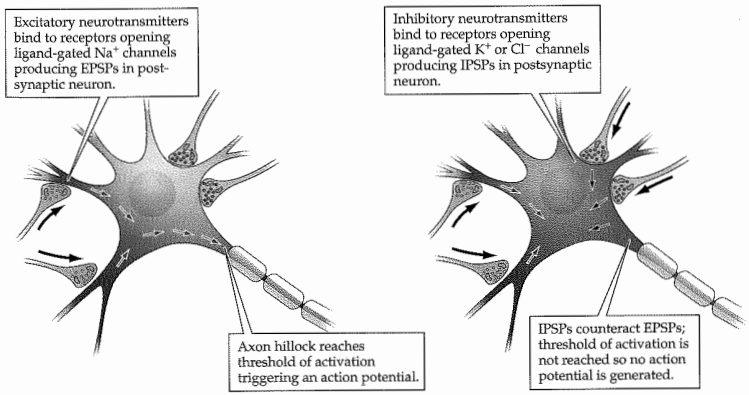


FIGURE 2.13 Summation of local potentials Many inhibitory and excitatory synapses influence each neuron, causing local electrical potentials (IPSPs and EPSPs) as well as biochemical changes. At each instant in time, the electrical potentials summate and may reach the threshold for firing. Integration of electrical events occurs at the axon hillock, where the action potential is first generated. The action potential is then conducted along the axon to the axon terminals.

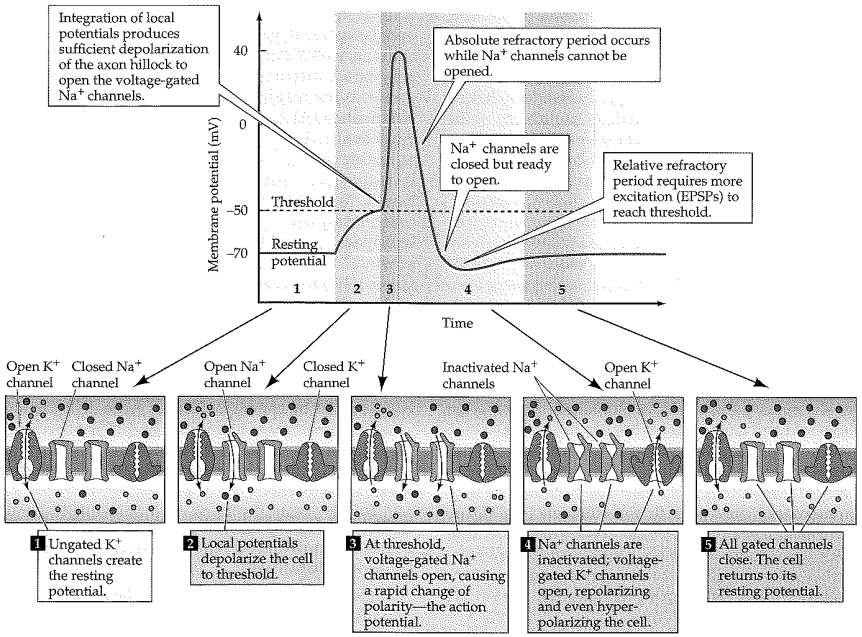


FIGURE 2.14 Stages of the action potential
Opening and closing of Na^+ and K^+ channels are responsible for the characteristic shape of the action potential.

–50 mV membrane potential (threshold) is responsible for opening large numbers of Na^+ channels that are voltage gated, that is, the change in voltage across the membrane near these channels is responsible for opening them (**FIGURE 2.14**). Because Na^+ is much more concentrated outside the cell, its concentration gradient moves it inward; in addition, since the cell at threshold is still negative inside, Na^+ is driven in by the electrostatic pressure. These two forces move large numbers of Na^+ ions into the cell very quickly, causing the rapid change in membrane potential from –50 mV to +40 mV (called *the rising phase of the action potential*) before the Na^+ channels close and remain closed for a fixed period of time while they reset. The time during which the Na^+ channels are closed and cannot be opened, regardless of the amount of excitation, prevents the occurrence of another action potential and is called the **absolute refractory period**. The closing of Na^+ channels explains why the maximum number of action potentials that can occur is about 1200 impulses per second. The action potential is a rapid change in membrane potential that lasts only about 1 millisecond. When the membrane potential approaches resting levels, the Na^+ channels are reset and ready to open.

Meanwhile, during the rising phase, the changing membrane potential due to Na^+ entry causes voltage-gated K^+ channels to open, and K^+ moves out of the cell. K^+ channels remain open after Na^+ channels have closed, causing the membrane potential to return to resting levels. The membrane potential actually overshoots the resting potential, so the membrane remains hyperpolarized for a short time until the excess K^+ diffuses away or is exchanged for Na^+ by the Na^+–K^+ pump. Because the membrane is more polarized than normal, it is more difficult to generate an action potential. The brief hyperpolarizing phase is called the **relative refractory period** because it takes more excitation to first reach resting potential and further depolarization to reach threshold. The relative refractory period explains why the intensity of stimulation determines rate of firing. Low levels

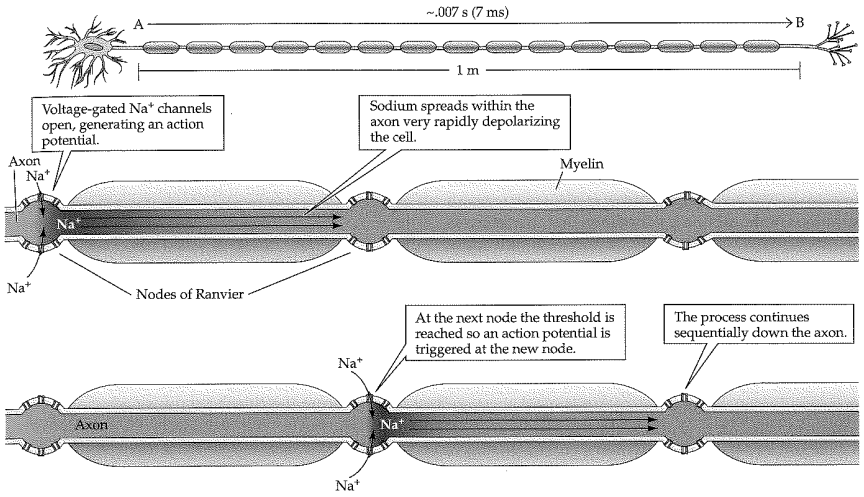


FIGURE 2.15 Conduction along myelinated axons
The generation of the action potential at one node spreads depolarization along the axon, which in turn changes the membrane potential to threshold and opens voltage-gated Na^+ channels at the next node of Ranvier.

of excitation cannot overcome the relative refractory period, but with increasing excitation, the neuron will fire again as soon as the absolute refractory period has ended.

If the threshold is reached, an action potential occurs (first at the hillock). Its size is unrelated to the amount of stimulation; hence it is considered *all-or-none*. Reaching the threshold will generate the action potential, but more excitatory events (EPSPs) will not make it larger; fewer excitatory events will not generate an action potential at all. The action potential moves along the axon because positively charged Na^+ ions spread passively to nearby regions of the axon, which changes the membrane potential to threshold and causes the opening of other voltage-gated Na^+ channels (**FIGURE 2.15**). The regeneration process of the action potential continues sequentially along the entire axon and does not decrease in size; hence it is called *nondecremental* (i.e., it does not decay). In myelinated axons, the speed of conduction is as much as 15 times quicker than in nonmyelinated axons because regeneration of the action potential occurs only at the nodes of Ranvier. This characteristic makes the conduction seem to jump along the axon, so it is called **saltatory conduction**. In addition, myelinated axons use less energy because the Na^+–K^+ pump, which uses large amounts of ATP, has to work only at the nodes rather than all along the axon. Now that we understand normal neuron firing, it is worth a look at **Web Box 2.1**, which describes abnormal firing during epileptic seizures. The reader may also find the animations of electrophysiological processes on the Companion Website to be helpful. **TABLE 2.2** lists characteristics specific to local and action potentials.

Drugs and poisons alter axon conduction

As we will learn, most drugs act at synapses to modify chemical transmission. However, a few alter action potential conductance along the axon. Drugs that act as local anesthetics, such as procaine (Novocaine), lidocaine

TABLE 2.2 Characteristics of Local Potentials and Action Potentials

Local potentials	Action potentials
Graded	All-or-none
Decremental	Nondecremental
Spatial and temporal summation	Intensity of stimulus coded by rate of firing
Produced by opening of ligand-gated channels	Produced by opening of voltage-gated channels
Depolarization or hyperpolarization	Depolarization

(Xylocaine), and benzocaine (found in Anbesol), impair axonal conduction by blocking voltage-gated Na^+ channels. It should be apparent that if voltage-gated Na^+ channels cannot open, an action potential cannot occur, and transmission of the pain signal cannot reach the brain. Hence the individual is not aware of the damaging stimulus. Several antiepileptic drugs also block voltage-gated Na^+ channels but in a more subtle manner. One such drug is phenytoin (Dilantin), which apparently reduces Na^+ conduction during rapid, repeated, and sustained neuronal firing, a condition that characterizes seizure activity. This selectivity can occur because rather than blocking the channel, phenytoin selectively binds to closed Na^+ channels. Since it takes time for the drug to unbind, its presence prolongs the refractory state of the channel, slowing down the firing rate.

Neurotoxins that bind to Na^+ channels have much more striking effects. One of these is saxitoxin, which is a poison that blocks voltage-gated Na^+ channels throughout the nervous system when it is ingested. Saxitoxin is found in shellfish exposed to "red tide," a common event along the nation's coastlines that is caused by large concentrations of microscopic red dinoflagellates of the species *Gonyaulax*, a marine plankton that produces the neurotoxin. Oral ingestion circulates the toxin throughout the body and causes conduction failure and subsequent death due to suffocation. It is a hazard not only for humans, but also for fish, birds, and animals such as manatees. A second toxin, tetrodotoxin, is also found in several types of fish, including the Japanese puffer fish, which is considered one of the most poisonous vertebrates in the world. However, it is considered a delicacy in Japan, where chefs are specially trained in the art of preparing the fish without the toxic liver, gonads, and skin. Nevertheless, there are numerous poisonings each year caused by the binding of tetrodotoxin to the voltage-gated Na^+ channels, which prevents action potentials. Symptoms include facial numbness, nausea, vomiting, and abdominal pain followed by increasing paralysis, first of the limbs and then of the respiratory muscles. Cardiac dysfunction and coma can occur if the individual survives long enough. Death, which occurs in 50% of cases, can occur as soon as 4 to 6 hours after ingestion (Benzer, 2015).

Section Summary

- At rest, neurons have an electrical charge across the membrane of –70 mV (resting potential), with the inside being more negative than the outside.
- The resting potential results from the balance between two competing forces on K^+ ions. Electrostatic pressure moves K^+ inward because it is attracted by negatively charged molecules trapped inside the cell. The concentration gradient for K^+ pushes ions out of the cell in an effort to distribute them evenly.
- The Na^+–K^+ pump also helps to maintain the negative membrane potential by exchanging three Na^+ ions (moved out of the cell) for two K^+ ions (taken in).
- Local potentials are small, short-lived changes in membrane potential found largely on the soma and dendrites after the opening of ligand-gated channels.
- Excitatory postsynaptic potentials (EPSPs), or depolarizations, occur when ligand-gated Na^+ channels open and allow Na^+ to enter the cell on its concentration gradient, making the cell slightly more positive and bringing the membrane potential closer to the threshold for firing. Opening Cl^- channels allows Cl^- to enter on its concentration gradient, making the cell more negative and farther from the threshold, causing hyperpolarizations called inhibitory postsynaptic potentials (IPSPs). When ligand-gated K^+ channels open, K^+ exits on its concentration gradient, leaving the cell more negative inside and farther from the threshold producing an IPSP.
- The summation of all EPSPs and IPSPs occurring at any single moment in time occurs at the axon hillock. If the threshold (–50 mV) is reached, voltage-gated Na^+ channels open, allowing large amounts of Na^+ to enter the cell to produce the massive depolarization known as the action potential.
- At the peak of the action potential (+40 mV), voltage-gated Na^+ channels close and cannot be opened until they reset at the resting potential, so no action potential can occur during this time (the absolute refractory period).
- As the cell becomes more positive inside, voltage-gated K^+ channels open and K^+ exits from the cell, bringing the membrane potential back toward resting levels. The overshoot by K^+ causes the cell to be more polarized than normal, so it is more difficult to reach the threshold to generate another action potential (relative refractory period).
- The action potential moves down the length of the axon by sequential opening of voltage-gated Na^+ channels.
- In myelinated axons, regeneration of the action potential occurs only at the nodes of Ranvier, producing a rapid, saltatory conduction that is more energy efficient because the Na^+–K^+ pump needs to exchange ions only at the nodes.
- The characteristics of local and action potentials are summarized in Table 2.2.

Organization of the Nervous System

Thus far we have described the structure of individual neurons and their ability to conduct electrical signals. Clearly, neurons never function individually but form interacting circuits referred to as *neural networks*. Such complexity allows us to make coordinated responses to changes in the environment. For example, as we perceive a potential danger, we suddenly become vigilant and more acutely aware of our surroundings. Meanwhile, internal organs prepare us for action by elevating heart rate, blood pressure, available energy sources, and so forth. Most of us will also calculate the probable outcome of fighting or running before taking a defensive or aggressive stance. Even simple responses require complex coordination of multiple nuclei in the brain and spinal cord. The following section describes the organization of neurons into brain regions that serve specific functions. This section provides only the highlights of functional neuroanatomy and emphasizes those brain structures that receive more attention in subsequent chapters. **BOX 2.3** provides a quick review of the terms used to describe the location of structures in the nervous system.

BOX 2.3 The Cutting Edge

Finding Your Way in the Nervous System

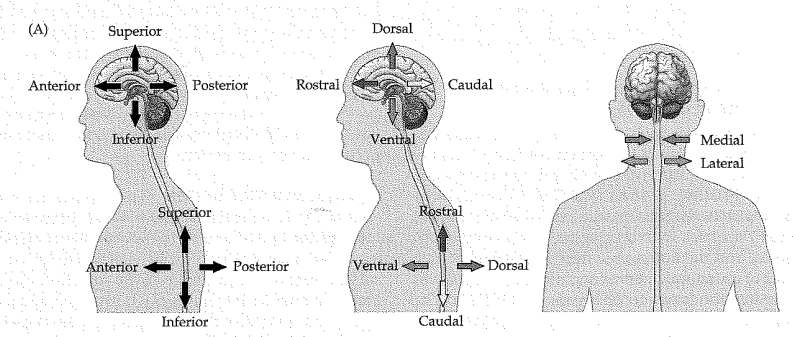
To discuss anatomical relationships, a systematic method to describe location in three dimensions is needed. The directions are based on the **neuraxis**, an imaginary line beginning at the base of the spinal cord and ending at the front of the brain. For most animals, the neuraxis is a straight line; however, because humans walk upright, the neuraxis bends, changing the relationship of the brain to the spinal cord (**Figure A**). For this reason, both the top of the head and the back of the body are called **dorsal**; **ventral** refers to the underside of the brain and the front surface of the body. To avoid confusion, sometimes the top of the human brain is described as **superior** and the bottom as **inferior**. In addition, the head end of the nervous system is **anterior** or **rostral**, and the tail end is **posterior** or **caudal**. Finally, **medial** means "toward the center or midline of the body," and **lateral** means "toward the side." We can describe the location of any brain area using three pairs of dimensional descriptors: dorsal/ventral, anterior/posterior and medial/lateral.

Much of our knowledge about the structure of the nervous system comes from examining two-dimensional slices (**Figure B**). The orientation of the slice (or **section**) is typically in any one of three different planes:

- **Horizontal** sections are slices parallel to the horizon.
- **Sagittal** sections are cut on the plane that bisects the nervous system into right and left halves. The **midsagittal** section is the slice that divides the brain into left and right symmetrical pieces.
- **Coronal** (or **frontal**) sections are cut parallel to the face.

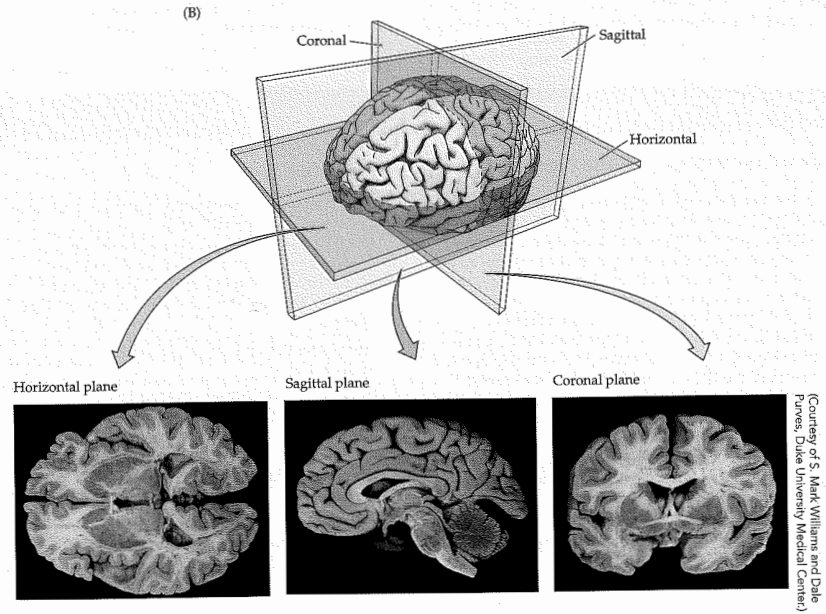
Identifying specific structures in these different views takes a good deal of experience. However, computer-assisted evaluation allows us to visualize

(*Continued*)



BOX 2.3 The Cutting Edge *(continued)*

the brain of a living human in far greater detail than was previously possible. Magnetic resonance imaging (MRI) and computerized tomography (CT) not only provide detailed anatomical images of brain slices but also reconstruct three-dimensional images of the brain using mathematical techniques. Positron emission tomography (PET) and functional MRI (fMRI) provide a view of the functioning brain by mapping blood flow or glucose utilization in various disease states, after drug administration, and during other experimental manipulations. These visualization techniques are described in Chapter 4, the chapter on methods in research.



(Courtesy of S. Mark Williams and Dale Purves, Duke University Medical Center.)

The nervous system comprises the central and peripheral divisions

The nervous system includes the central nervous system, or CNS (the brain and spinal cord), and the peripheral nervous system, or PNS (all nerves outside the CNS) (**FIGURE 2.16A**). The PNS in turn can be further divided into the somatic system, which controls voluntary muscles with both spinal nerves and cranial nerves, and the autonomic nervous system, which consists of autonomic nerves and some cranial nerves that control the function of organs and glands. The autonomic nervous system has both sympathetic and parasympathetic divisions, which help the organism to respond to changing energy demands. **FIGURE 2.16B** provides an overall view of the divisions of the nervous system. We begin by looking more closely at the peripheral nervous system.

SOMATIC NERVOUS SYSTEM Each spinal nerve consists of many neurons, some of which carry sensory information and others motor information; hence they are called *mixed nerves*. Within each mixed nerve, sensory information is carried from the surface of the body and from muscles into the dorsal horn of the spinal cord by neurons that have their cell bodies in the dorsal root ganglia (**FIGURE 2.17**). These signals going into the

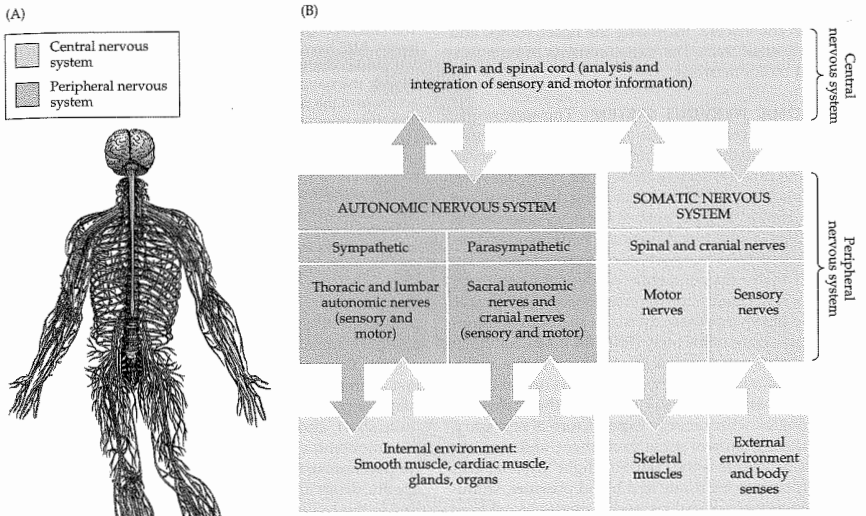


FIGURE 2.16 The central and peripheral nervous systems (A) The brain and spinal cord, shown in yellow, make up the CNS. The peripheral nervous system, shown in purple, connects all parts of the body to the CNS. (B) Organization of the nervous system: internal and external environments send sensory information by way of peripheral nerves to the CNS, where neural circuits analyze and integrate the information before sending signals to regulate muscle and internal organ function.

spinal cord are called **sensory afferents**. Mixed nerves also have motor neurons, which are cells beginning in the ventral horn of the spinal cord and ending on skeletal muscles. These are called **motor efferents** and are responsible for voluntary movements.

The 12 pairs of cranial nerves that project from the brain provide functions similar to those provided by the spinal nerves, except that they serve primarily the head and neck; hence they carry sensory information such as vision, touch, and taste into the brain and control muscle movement needed for things like chewing and laughing. They differ from the spinal nerves in that they are not all mixed nerves; several are dedicated to only sensory or only motor function. In addition, several of the cranial nerves innervate glands and organs rather than skeletal muscles; this means that they are part of the autonomic nervous system (see the next section). The vagus nerve (cranial nerve X) is unique among the

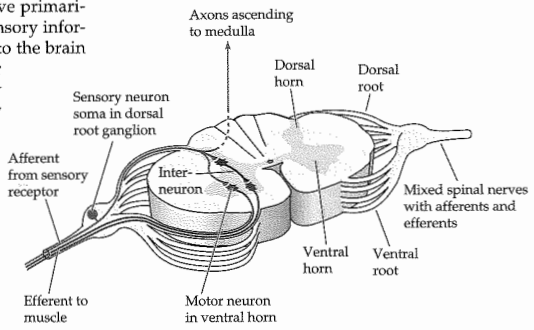


FIGURE 2.17 Spinal nerves of the peripheral nervous system Cross section of the spinal cord shows mixed spinal nerves with sensory afferents entering the dorsal horn and motor efferents leaving the ventral horn to innervate skeletal muscles. Note that the soma for the afferent neuron is in the dorsal root ganglion.

cranial nerves because it communicates with numerous organs in the viscera, including the heart, lungs, and gastrointestinal tract. The vagus consists of both sensory and motor neurons.

AUTONOMIC NERVOUS SYSTEM The autonomic nerves, collectively called the *autonomic nervous system* (ANS), regulate the internal environment by innervating smooth muscles such as those in the heart, intestine, urinary bladder, and glands, including the adrenal and salivary glands. The purpose of the ANS is to control digestive processes, blood pressure, body temperature, and other functions that provide or conserve energy appropriate to the environmental needs of the organism. The ANS is divided into two components, the sympathetic and parasympathetic divisions, and both divisions serve most organs of the body (**FIGURE 2.18**). Although their functions usually work in opposition to one another, control of our internal environment is not an all-or-none affair. Instead, activity of the **sympathetic** division predominates when energy expenditure is necessary, such as during times of stress, excitement, and exertion; hence its nickname is the "fight-or-flight" system. This system increases heart rate and blood pressure, stimulates secretion of adrenaline, and increases blood flow to skeletal muscles, among other effects. The **parasympathetic** division predominates at times when energy reserves can be conserved and stored for later use; hence this system increases salivation, digestion, and storage of glucose and other nutrients and also slows heart rate and decreases respiration.

In addition to contrasting functions, the two branches of the ANS have anatomical differences, including points of origin in the CNS. The cell bodies of the efferent sympathetic neurons are in the ventral horn of the spinal cord at the thoracic and lumbar regions (see Figure 2.18). Their axons project for a relatively short distance before they synapse with a cluster of cell bodies called *sympathetic ganglia*. Some of these ganglia are lined up very close to the spinal cord; others such as the celiac ganglion are located somewhat farther away. These preganglionic fibers release the neurotransmitter acetylcholine onto cell bodies in the ganglia. These postganglionic cells project their axons for a relatively long distance to the target tissues, where they release the neurotransmitter norepinephrine.

In contrast, the cell bodies of the efferent parasympathetic neurons are located either in the brain (cranial nerves III, VII, IX, and X) or in the ventral horn of the spinal cord at the sacral region. Preganglionic neurons travel long distances to synapse on cells in the parasympathetic ganglia that are not neatly lined up along the spinal cord but are close to individual target organs. The preganglionic fibers release acetylcholine, just as the sympathetic preganglionics do. However, parasympathetic postganglionic neurons, which are quite short, also release acetylcholine. Understanding the autonomic nervous system is especially important for psychopharmacologists because many psychotherapeutic drugs alter either norepinephrine or acetylcholine in the brain to relieve symptoms, but by altering those same neurotransmitters in the peripheral nerves, these drugs often produce annoying or dangerous side effects, such as elevated blood pressure, dry mouth, and urinary problems (all related to autonomic function). **TABLE 2.3** summarizes the differences between the two divisions of the ANS.

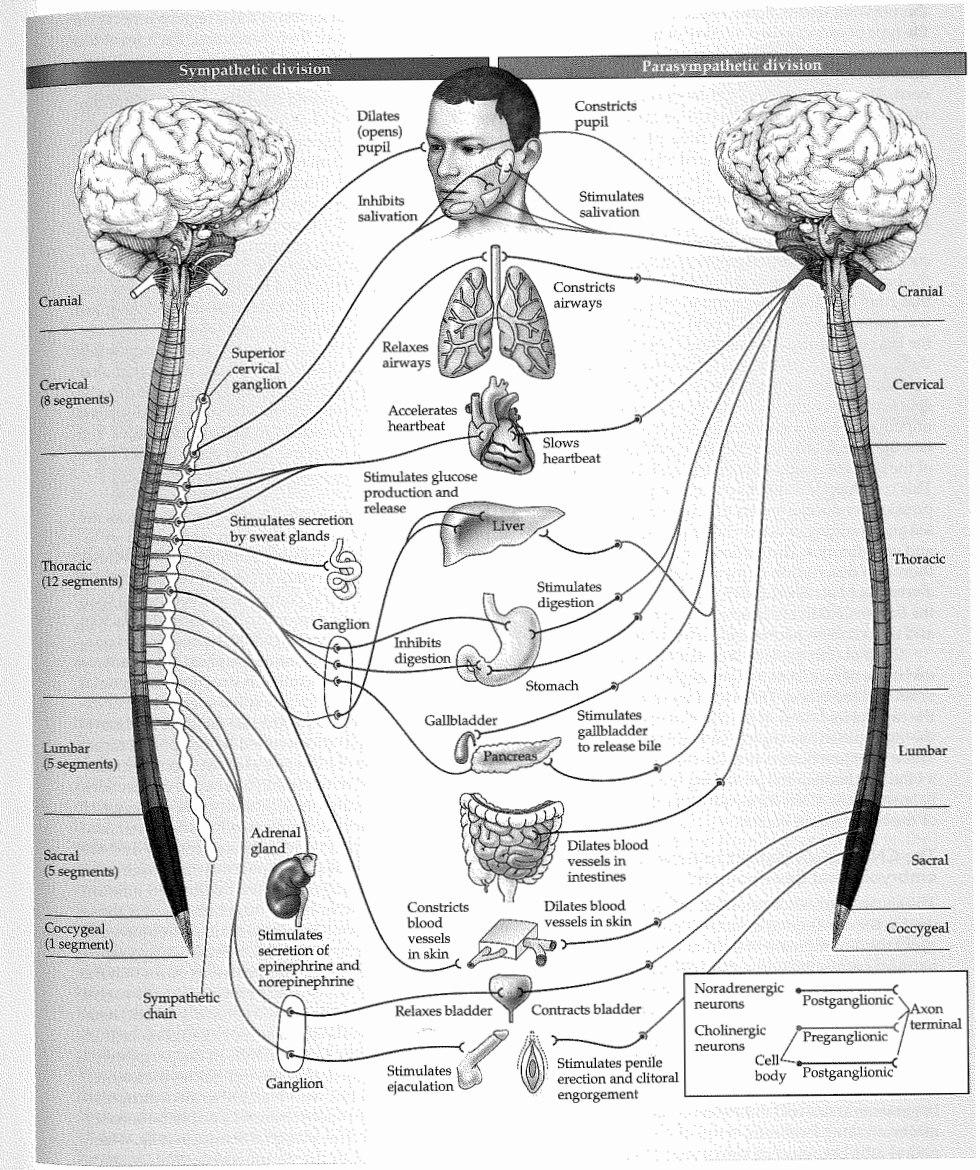
FIGURE 2.18 Autonomic nervous system (ANS) ▶
The internal organs, smooth muscles, and glands served by the ANS have both sympathetic and parasympathetic regulation. The two divisions have opposing effects on the organs; the sympathetic effects prepare the individual for action, and the parasympathetic effects serve to generate and store energy and reduce energy expenditure. Acetylcholine is the neurotransmitter released in all autonomic ganglia because preganglionic fibers are cholinergic neurons. At the target organs, the parasympathetic neurons release acetylcholine once again, while sympathetic neurons (noradrenergic neurons) release norepinephrine. Their anatomical and neurotransmitter differences are described in the text and are summarized in Table 2.3.

CNS functioning is dependent on structural features

The tough bone of the skull and vertebrae maintains the integrity of the delicate tissue of the brain and spinal cord. Three layers of tissue called **meninges** lie just within the bony covering and provide additional protection. The outermost layer, which is also the toughest, is the **dura mater**. The **arachnoid**, just below the dura, is a membrane with a weblike sublayer (subarachnoid space) filled with cerebrospinal fluid (CSF). Finally, the **pia mater** is a thin layer of tissue that sits directly on

TABLE 2.3 Characteristics of the Sympathetic and Parasympathetic Divisions of the ANS

Sympathetic	Parasympathetic
Energy mobilization	Energy conservation and storage
Origin in thoracic and lumbar spinal cord	Origin in the brain and sacral spinal cord
Relatively short preganglionic fibers; long postganglionics	Long preganglionic fibers ending near organs; short postganglionics
Releases acetylcholine in ganglia and norepinephrine at target	Releases acetylcholine at both ganglia and target



the nervous tissue. Some readers may have heard of the type of cancer called meningioma. It should now be apparent to you that this cancer is a tumor that forms on these layers of tissue protecting the brain and spinal cord. The vast majority of tumors of this type are benign (i.e., nonmalignant) and slow growing and often require no treatment unless their growth causes significant symptoms such as headaches, double vision, loss of smell, or weakness. The symptoms that occur are dependent on their anatomic location and the compression of nearby structures.

The CSF not only surrounds the brain and spinal cord but also fills the irregularly shaped cavities within the brain, called **cerebral ventricles**, and the channel that runs the length of the spinal cord, called the **central canal**. CSF is formed by the choroid plexus within the lateral ventricle of each hemisphere and flows to the third and fourth ventricles before moving into the subarachnoid space to bathe the exterior of the brain and spinal cord (see Figure 1.7A). When this flow of CSF is impeded by a tumor, infection, or congenital abnormalities, the fluid builds up in the brain, causing compression of the delicate neural tissue surrounding the ventricles. This condition is called hydrocephalus. The brain compression produces a variety of symptoms, including nausea and vomiting, blurred vision, problems with balance and coordination, drowsiness, and memory loss. For a thorough description of the disorder, see the NIH *Hydrocephalus Fact Sheet* (NIH, 2013). A brief video from the Boston Children's Hospital describes hydrocephalus and the common neurosurgical treatment (Warf, 2011).

CSF not only protects the brain but also helps in the exchange of nutrients and waste products between the brain and the blood. This exchange is possible because the capillaries found in the choroid plexus do not have the tight junctions typical of capillaries in the brain. These tight junctions constitute the blood–brain barrier, a vital mechanism for protecting the delicate chemical balance in the CNS. Return to Chapter 1 for a review of the blood–brain barrier.

The CNS has six distinct regions reflecting embryological development

The six anatomical divisions of the adult CNS are evident in the developing embryo. It is important to know about the development of the brain because exposure to harmful events, including therapeutic and illicit drugs, environmental toxins, and stress, will have different outcomes depending on the timing of the insult and the developmental event occurring at that time. You will read more about this in later chapters on clinical disorders and in the chapter on alcohol. The CNS starts out as a fluid-filled tube that soon develops three enlargements at one end that become the adult hindbrain, midbrain, and forebrain, while the remainder of the neural tube becomes the spinal cord (**FIGURE 2.19A**). The structural organization of these regions reflects the hierarchical nature of their functions. Each level has overlapping functions, and higher levels partially replicate the functions of lower ones but provide increased behavioral complexity and refined nervous system control. The fluid-filled chamber itself becomes the ventricular system in the brain and the central canal in the spinal cord. Within 2 months of conception, further subdivisions occur: the hindbrain enlargement develops two swellings, as does the forebrain. These divisions, in ascending order, are the spinal cord, myelencephalon, metencephalon, mesencephalon, diencephalon, and telencephalon. Each region can be further subdivided into clusters of cell bodies, called **nuclei**, and their associated bundles of axons, called **tracts**. (In the PNS, they are called **ganglia** and **nerves**, respectively.) These interconnecting networks of cells will be the focus of much of the remainder of this book, because drugs that alter brain function, that is, psychotropic drugs, modify the interactions of these neurons. The principal divisions of the CNS are summarized in **FIGURE 2.19B,C**. You may be interested in seeing a brief animation of brain development on the Companion Website.

NEUROTROPHIC FACTORS Neurotrophic factors are proteins that act as neuron growth factors and influence not only neuron growth, but also cell differentiation and survival. Nervous system development and maintenance of synaptic connections over the life span are dependent on the presence of neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3, and neurotrophin-4/5. Although similar in structure and general function, neurotrophins show some specificity. For example, NGF, the first neurotrophic factor to be discovered, is synthesized and secreted by peripheral target organs and guides the development of axonal processes of nearby neurons to establish synaptic connections with the target organ. Additionally, the presence of neurotrophic factors determines which neuronal connections survive and which are unnecessary and are eliminated by cell death. Apparently, the large population of neurons competes for the limited amount of neurotrophic factor in the target tissue, and those that are not supported by access to neurotrophins die, while those that respond to NGF establish appropriate synaptic connections. This process ensures that the number of connections is appropriate for the target tissue. NGF guides the growth of sympathetic neurons and a subpopulation of sensory ganglion cells. A second neurotrophic factor, BDNF, in the periphery is released from skeletal muscles and guides motor neuron development and survival. Other neurotrophins aid the survival of other subsets of peripheral sensory neurons. It is also clear that glial Schwann cells, which myelinate neurons of the peripheral nervous system, release a growth factor when their axon is damaged. The growth factor in this case leads to regeneration of the damaged axon. In the CNS, neurotrophins like BDNF may be released by target neurons (rather than organs) to maintain appropriate synaptic connections, but in some cases, the neurotrophin acts on the same neuron that produces it for autoregulation. Additionally, in some cases, neurotrophic factors are transported from the soma to the axon terminals, where their release modifies nearby cell bodies or nerve terminals of other neurons. For example, neurotrophins determine which of the cell dendrites grow and which retract, a process that influences synaptic activity and plasticity, quite independent of their role in cell survival. Research into the involvement of neurotrophic factors in mood disorders has suggested the neurotrophic hypothesis of depression and other psychiatric disorders. The importance of neurotrophic factors as potential therapeutic agents for neurodegenerative diseases such as Alzheimer's disease (see Chapter 20) and psychiatric disorders (see Chapter 18) will be discussed further in later chapters.

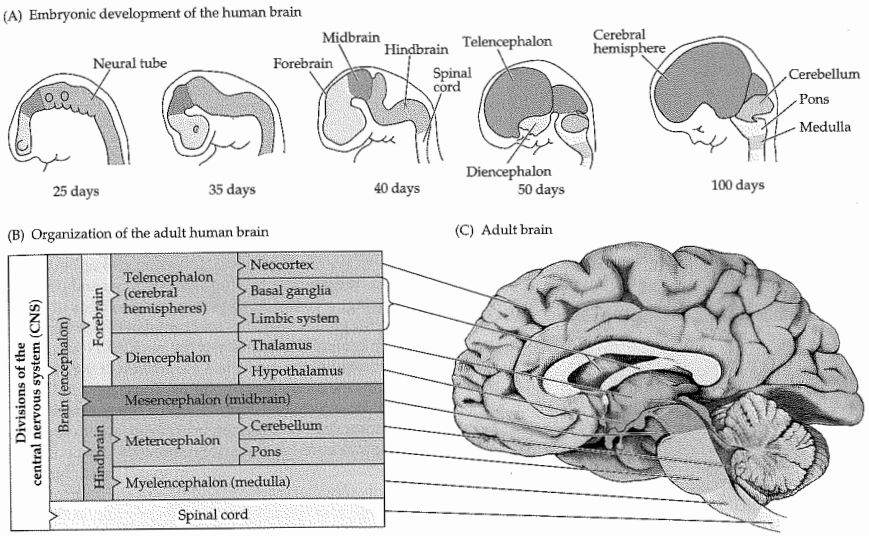


FIGURE 2.19 Divisions of the central nervous system (A) Beginning with the primitive neural tube in the human embryo, the CNS develops rapidly. By day 50 of gestation, the six divisions of the adult CNS are apparent in the fetus. (B) The organization of the CNS (brain and spinal cord) presented in the table is color-coded to match the divisions shown in the adult brain (sagittal section) (C).

SPINAL CORD The spinal cord is made up of gray and white matter. The former appears butterfly shaped in cross section (**FIGURE 2.20A**) and is called *gray matter* because the large numbers of cell bodies in this region appear dark on histological examination. The cell bodies in the dorsal horn receive information from sensory afferent neurons entering the spinal cord and cell bodies of motor neurons in the ventral horn send efferents to skeletal muscles. The white matter surrounding the butterfly-shaped gray matter is made up of myelinated axons of ascending pathways that conduct sensory information to the brain, as well as myelinated axons of descending pathways from higher centers to the motor neurons that initiate muscle contraction (**FIGURE 2.20B**).

As we move up the spinal cord and enter the skull, the spinal cord enlarges and becomes the **brainstem**. Examination of the ventral surface of the brain (**FIGURE 2.21A**) shows that the brainstem with its three principal parts—medulla, pons, and midbrain—is clearly visible. The brainstem contains the reticular formation, a large network of cells and interconnecting fibers that extends up the core of the brainstem for most of its length (described later in the section on the metencephalon). Additionally, the brainstem is the origin of numerous cranial nerves that receive sensory information from the skin and joints of the face, head, and neck, as well as providing motor control to the

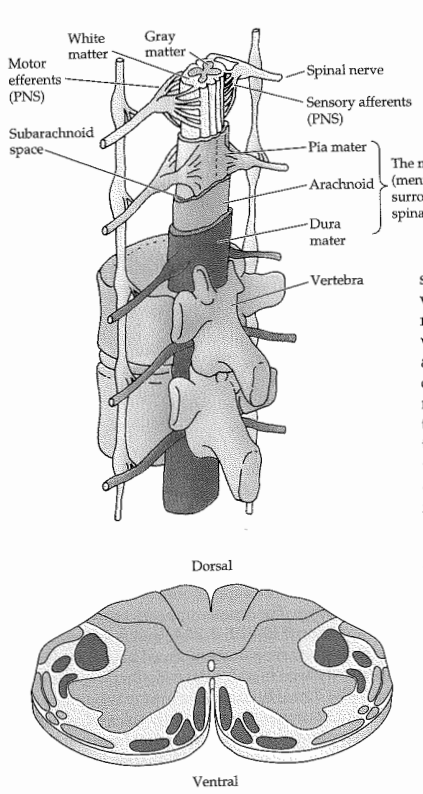


FIGURE 2.20 Spinal cord (A) A view of the spinal cord showing its relationship to the protective layers of meninges and the bony vertebrae. Note the clearly defined gray matter and white matter in cross section. (B) Schematic diagram of the ascending sensory tracts (blue) and the descending motor tracts (red).

muscles in that region. A significant volume of the brainstem is made up of ascending and descending axons coursing between the spinal cord and higher brain regions. The relationships of the structures of the brainstem are apparent in the midsagittal view (**FIGURE 2.21B**).

MYELENCEPHALON The first major structure of the brainstem that we encounter is the myelencephalon, or medulla. Within the **medulla**, multiple cell groups regulate vital functions, including heart rate, digestion, respiration, blood pressure, coughing, and vomiting. When an individual dies from a drug overdose, the cause is most often depression of the respiratory center in the medulla. Also located in the medulla is the **area postrema**, or the vomiting center, described in Chapter 1 as a cluster of cells with a reduced blood–brain barrier that initiates vomiting in response to toxins in the blood. Drugs in the opioid class such as morphine act on the area postrema and produce vomiting, a common unpleasant side effect of treatment for pain. The nuclei for cranial nerves XI and XII, which control the muscles of the neck and tongue, are also located in the medulla. One portion of the medulla contains the medullary pyramids. These pyramids (two ridgelike structures) contain motor fibers that start in the motor region of the cerebral cortex and descend to the spinal cord, so they are named the corticospinal tract. These neurons synapse on spinal motor neurons described earlier. From 80% to 90% of the corticospinal neurons cross to the other side of the brain in the pyramids, explaining why the left motor cortex controls all voluntary movement on the right side of the body while the right motor cortex controls the left.

METENCEPHALON Two large structures within the metencephalon are the pons and the cerebellum (see Figure 2.21). Within the central core of the pons and extending rostrally into the midbrain and caudally into the medulla is the **reticular formation**. The reticular formation is not really a structure but a collection of perhaps 100 small nuclei forming a network that plays an important role in arousal, attention, sleep, and muscle tone, as well as in some cardiac and respiratory reflexes. One nucleus, called the **locus coeruleus**, is of particular importance to psychopharmacology because it is a cluster of cell bodies that distribute their axons to many areas of the forebrain. These cells are the principal source of all neurons that release the neurotransmitter norepinephrine from their terminals. When active, these cells cause arousal, increased vigilance, and attention. Drugs such as amphetamine enhance their function, causing sleeplessness and enhanced alertness.

Other cell groups within the pons that also belong to the reticular formation are the **dorsal** and **median raphe nuclei**. These two clusters of cells are the source of most of the neurons in the CNS that use serotonin as their neurotransmitter. Together, cell bodies in the dorsal and median raphe send axons releasing serotonin to virtually all forebrain areas and function in the regulation of diverse processes, including sleep,

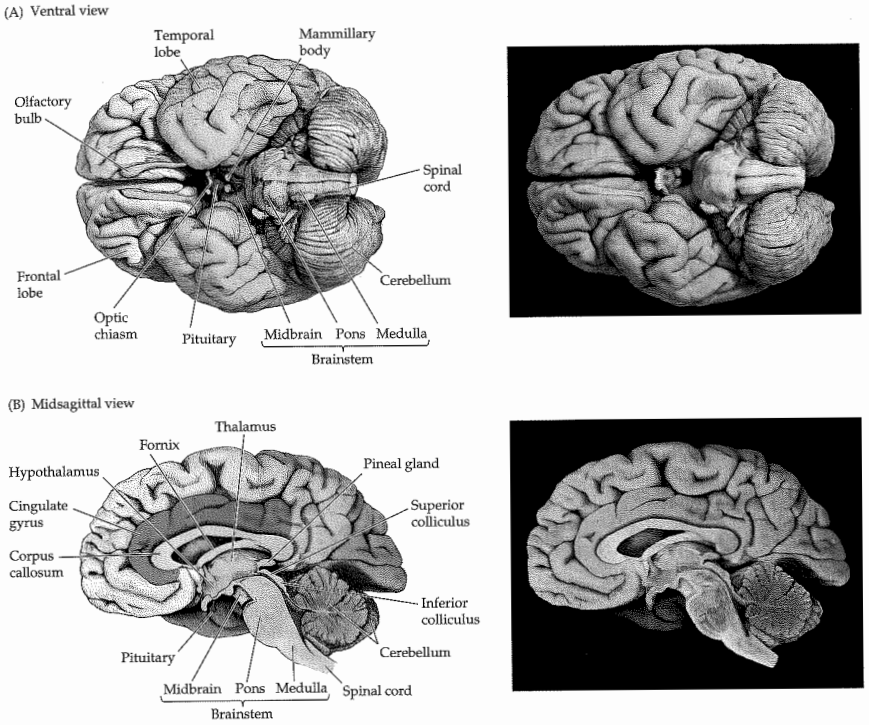


FIGURE 2.21 Two views of the human brain The drawings on the left in each panel label the structural features that are visible on the ventral external surface (A) and the midsagittal (midline) section (B). The right side of each panel shows the same view of a human postmortem brain specimen. (Courtesy of S. Mark Williams and Dale Purves, Duke University Medical Center.)

aggression and impulsiveness, neuroendocrine functions, and emotion. Because it has a generally inhibitory effect on CNS function, serotonin may maintain behaviors within specific limits. Drugs such as LSD (lysergic acid diethylamide) produce their dramatic hallucinogenic effects by inhibiting the inhibitory functions of the raphe nuclei (see Chapter 15).

The **cerebellum** is a large foliated structure on the dorsal surface of the brain that connects to the pons by several large bundles of axons called **cerebellar peduncles**. The cerebellum is a significant sensorimotor center and receives visual, auditory, and somatosensory input, as well as information about body position and balance, from the vestibular system. By coordinating sensory information with motor information received from the cerebral cortex, the cerebellum coordinates and smoothes out movements by timing and patterning skeletal muscle contractions. In addition, the cerebellum allows us to make corrective movements to maintain our balance and posture. Damage to the cerebellum produces poor coordination and jerky movements. Drugs such as alcohol at moderate doses inhibit the function of the cerebellum and cause slurred speech and staggering.

MESENCEPHALON The midbrain has two divisions: the tectum and the tegmentum. The tectum, the dorsalmost structure, consists of the superior colliculi, which are part of the visual system, and the inferior colliculi, which are part of the auditory system (see Figure 2.21B). These nuclei are involved in reflexes such as the

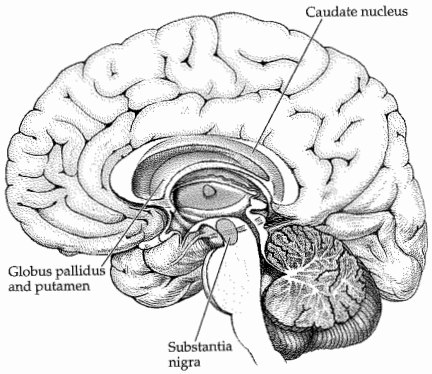


FIGURE 2.22 The basal ganglia These four structures form neural pathways that utilize dopamine as their neurotransmitter. These neural circuits constitute a system for motor control.

pupillary reflex to light, eye movement, and reactions to moving stimuli.

Within the **tegmentum** are several structures that are particularly important to psychopharmacologists. The first is the **periaqueductal gray** (**PAG**), which surrounds the cerebral aqueduct that connects the third and fourth ventricles. The PAG is one of the areas that are important for the modulation of pain. Local electrical stimulation of these cells produces analgesia but no change in the ability to detect temperature, touch, or pressure. The PAG is rich in opioid receptors, making it an important site for morphine-induced analgesia. Chapter 11 describes the importance of natural opioid neuropeptides and the PAG in pain regulation. The PAG is also important in sequencing species-specific actions, such as defensive rage and predation.

The **substantia nigra** is a cluster of cell bodies whose relatively long axons innervate the striatum, a component of the basal ganglia (**FIGURE 2.22**). These cells constitute one of several important neural pathways that utilize dopamine as their neurotransmitter. This pathway is called the nigrostriatal tract. (The names of neural pathways often combine the site of origin of the fibers with their termination site, hence *nigrostriatal*, meaning "substantia nigra to striatum.") This neural circuit is critical for the initiation and modulation of movement. Cell death in the substantia nigra is the cause of Parkinson's disease—a disorder characterized by tremor, rigidity, and inability to initiate movements. An adjacent cluster of dopaminergic cells in the midbrain is the **ventral tegmental area** (**VTA**). Some of these cells project axons to the septum, olfactory tubercle, nucleus accumbens, amygdala, and other limbic structures in the forebrain (see the section on the telencephalon below). Hence these cells form the mesolimbic tract (note that *meso* refers to "midbrain"). Other cells in the VTA project to structures in the prefrontal cortex, cingulate cortex, and entorhinal areas and are considered the mesocortical tract. All three of these dopamine pathways are of significance in our discussions of Parkinson's disease (see Chapter 20), drug addiction (see Chapter 9), and schizophrenia (see Chapter 19).

DIENCEPHALON The two major structures in the diencephalon are the thalamus and the hypothalamus. The **thalamus** is a cluster of nuclei that first process and then distribute sensory and motor information to the appropriate portion of the cerebral cortex. For example, the lateral geniculate nucleus of the thalamus receives visual information from the eyes before projecting it to the primary visual cortex. Most incoming signals are integrated and modified before they are sent on to the cortex. The functioning of the thalamus helps the cortex to direct its attention to selectively important sensory messages while diminishing the significance of others; hence the thalamus helps to regulate levels of awareness.

The second diencephalic structure, the **hypothalamus**, lies ventral to the thalamus at the base of the brain. Although it is much smaller than the thalamus, it is made up of many small nuclei that perform functions critical for survival (**FIGURE 2.23**). The hypothalamus receives a wide variety of information about the internal environment and, in coordination with closely related structures in the limbic system (see the section on the telencephalon below), initiates various mechanisms important for limiting the variability of the body's internal states (i.e., they are responsible for homeostasis). Several nuclei are involved in maintaining body temperature and salt–water balance. Other nuclei modulate hunger, thirst, energy metabolism, reproductive behaviors, and emotional responses such as aggression. The hypothalamus directs behaviors for adjusting to these changing needs by controlling both the autonomic nervous system and the endocrine system and organizing behaviors in coordination with other brain areas. Axons from nuclei in the hypothalamus descend into the brainstem to the nuclei of the cranial nerves that provide parasympathetic control. Additionally, other axons descend farther into the spinal cord to influence sympathetic nervous system function. Other hypothalamic nuclei communicate with the contiguous pituitary gland by two methods: neural control of the posterior pituitary and hormonal control of the anterior pituitary. By regulating the endocrine hormones, the hypothalamus has widespread and prolonged effects on body physiology. Of particular significance to psychopharmacology is the role of the paraventricular nucleus in regulating

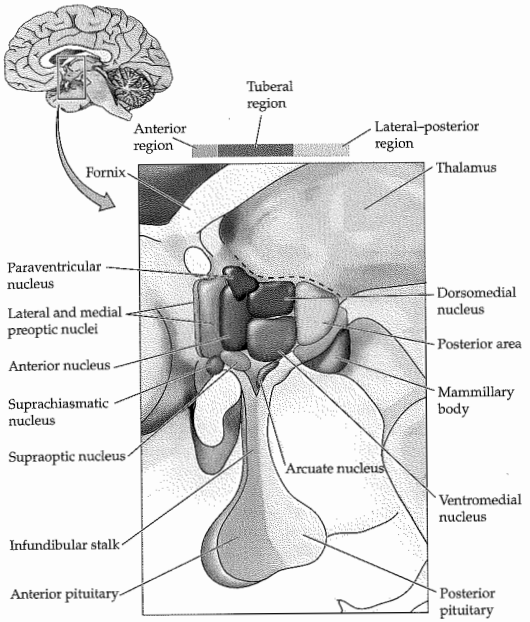


FIGURE 2.23 Hypothalamus The hypothalamus is a cluster of nuclei at the base of the forebrain that is often subdivided into three groups based on region: anterior, tuberal, and lateral–posterior. Each of the nuclei has its own complex pattern of neural connections and regulates one or several components of homeostatic function and motivated behavior.

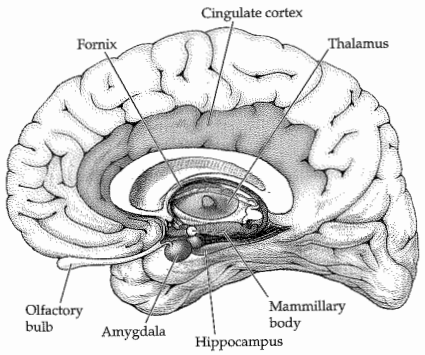


FIGURE 2.24 Limbic system Multiple subcortical structures interconnect to form the limbic system, which is critical for learning, memory, emotional responses, and motivation. Rich connections of limbic areas with association areas of the cortex contribute to decision making and planning.

the hormonal response to stress, because stress has a major impact on our behavior and vulnerability to psychiatric disorders. **BOX 2.4** describes the neuroendocrine response to stress and previews its significance for psychiatric ills and their treatment.

TELENCEPHALON The cerebral hemispheres make up the largest region of the brain and include the external cerebral cortex, the underlying white matter, and subcortical structures belonging to the basal ganglia and limbic system. The **basal ganglia** include the caudate, putamen, and globus pallidus and, along with the substantia nigra in the midbrain, comprise a system for motor control (see Figure 2.22). Drugs administered to control symptoms of Parkinson's disease act on this group of structures.

The **limbic system** is a complex neural network that is involved in integrating emotional responses and regulating motivated behavior and learning. The limbic system includes the limbic cortex, which is located on the medial and interior surface of the cerebral hemispheres and is transitional between allocortex (phylogenetically older cortex) and neocortex (the more recently evolved six-layer cortex). A significant portion of the limbic cortex is the cingulate. Chapter 11 describes the importance of the anterior portion of the cingulate in mediating the emotional component of pain. Some of the significant subcortical limbic structures are the amygdala, nucleus accumbens, and hippocampus, which is connected to the mammillary bodies and the septal nuclei by the fornix, the major tract of the limbic system (**FIGURE 2.24**). The **hippocampus** is most closely associated with the establishment of new long-term memories, spatial memory and contextual memory and has been the focus of research into Alzheimer's disease and its treatment, as you will read in Chapter 7. Additionally, the vulnerability of the hippocampus to high levels of stress hormones suggests its involvement in clinical depression and antidepressant drug treatment (see Chapter 18). The **amygdala** plays a central role in coordinating the various components of emotional

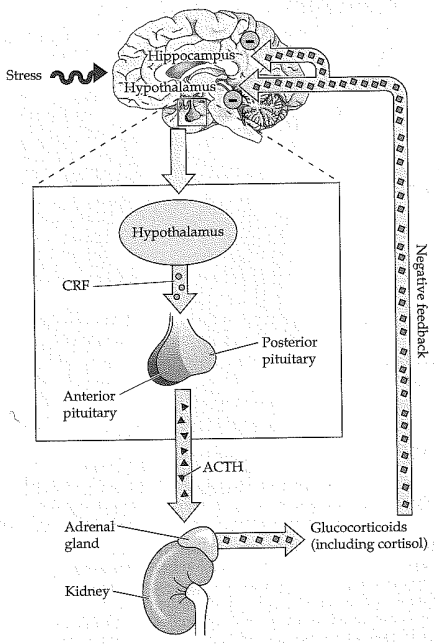
BOX 2.4 Of Special Interest

Neuroendocrine Response to Stress

The principal neuroendocrine response to stress is often referred to as the HPA axis because it depends on the interaction of the hypothalamus (H), the pituitary (P) gland, and the adrenal (A) gland. HPA axis activation is one part of complex emotional responses orchestrated by the amygdala. In essence, stress causes the secretion of corticotropin-releasing factor (CRF) by the paraventricular nucleus of the hypothalamus into the blood vessels ending in the anterior pituitary (see **Figure**). The binding of CRF in that gland causes the release of adrenocorticotropic hormone (ACTH) into the general blood circulation. ACTH subsequently binds to the adrenal cortex to increase the secretion of cortisol and other glucocorticoids, all of which contribute to the mobilization of energy to cope with stress or exertion. Under optimum conditions, cortisol feeds back to the hypothalamus (and hippocampus) to shut down HPA activation and return cortisol levels to normal. It also acts on the anterior pituitary (not shown) to reduce the production of ACTH.

Although HPA activity is critical for survival and adaptation to the environment, overuse of this adaptive mechanism leads to damaging changes to the brain and body. Damaging effects of prolonged cortisol response include such events as lower inflammatory response causing slower wound healing and immune system suppression. Stress has also been linked to an exacerbation of autoimmune diseases such as multiple sclerosis, gastric problems, diabetes, elevated blood pressure, premature aging, and many other disorders. In addition, stress affects neuron structure and brain function.

Several later chapters in this text will describe the relationship between stress and alcohol use disorder, the damaging effect of stress on cells in the hippocampus and its relationship to clinical depression, and the impact of early life traumas that alter the set point of the HPA axis, making it overly responsive to stressors later in life. The differential activation of stress response circuitry in men and women will also be addressed in the chapter on anxiety disorders. In Chapter 19, you will learn how stress-induced epigenetic events may alter the expression of a gene that is linked to the cognitive deficits characteristic of schizophrenia. All of these issues point to the critical need to evaluate more thoroughly the significant interaction between psychiatric and systemic medical disorders with the hope for potential new approaches to prevent and treat disabling conditions.



responses through its profuse connections with the olfactory system, hypothalamus (which is sometimes included in the limbic system, even though it is a diencephalic structure), thalamus, hippocampus, striatum, and brainstem nuclei, as well as portions of the neocortex, such as the orbitofrontal cortex. The amygdala and associated limbic areas play a prominent role in our discussions of antidepressants, alcohol, and antianxiety drugs. Chapters that describe the reinforcing value of abused substances also focus on limbic structures, notably the **nucleus accumbens**.

The cerebral cortex is divided into four lobes, each having primary, secondary, and tertiary areas

The cerebral cortex is a layer of tissue that covers the cerebral hemispheres. In humans, the cortex (or "bark") is heavily convoluted and has deep grooves called

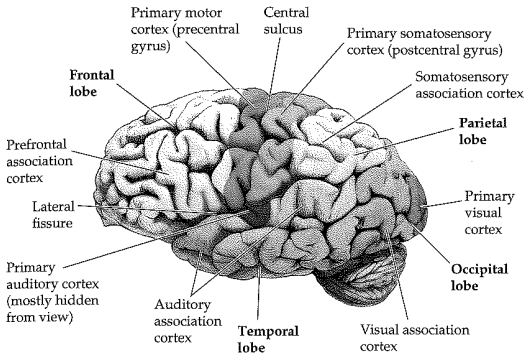


FIGURE 2.25 Lateral view of the exterior cerebral cortex The four lobes of the cerebral cortex are shown with distinct colors. Within each lobe is a primary area (darker in color) and secondary and tertiary association cortices. The caudal-most three lobes carry out sensory functions: vision (occipital), auditory (temporal), and somatosensory (parietal). The frontal lobe serves as the executive mechanism that plans and organizes behavior and initiates the appropriate sequence of actions.

fissures, smaller grooves called **sulci**, and bulges of tissue between called **gyri**. Thus the bulge of tissues immediately posterior to the central sulcus is the postcentral gyrus. The convolutions of the cortex greatly enlarge its surface area, to approximately 2.5 square feet. Only about one-third of the surface of the cortex is visible externally; the remaining two-thirds is hidden in the sulci and fissures. **FIGURE 2.25** shows some of the external features of the cerebral cortex. There may be as many as 100 billion cells in the cortex, arranged in six layers horizontal to the surface. Since these layers have large numbers of cell bodies, they appear gray; hence they are the gray matter of the cerebral cortex. Each layer can be identified by cell type, size, density, and arrangement. Beneath the six layers, the white matter of the cortex consists of millions of axons that connect one part of the cortex with another or connect cortical cells to other brain structures. One of the largest of these pathways is the **corpus callosum** (see Figure 2.21B). It connects corresponding areas in the two hemispheres, which are separated by a deep groove, the medial longitudinal fissure. In addition to the horizontal layers, the cortex has a vertical arrangement of cells that form slender vertical columns running through the entire thickness of the cortex. These vertically oriented cells and their synaptic connections apparently provide functional units for integration of information between various cortical regions.

The central sulcus and the lateral fissure (see Figure 2.25) visually divide the cortex into four distinct lobes in each hemisphere: the **parietal lobe**, **occipital lobe**, and **temporal lobe**, all of which are sensory in function, and the **frontal lobe**, which is responsible for movement and executive planning. Within each lobe is a small primary area, adjacent secondary cortex, and tertiary areas called *association cortex*. Within the occipital lobe is the primary visual cortex, which receives visual information from the thalamus that originates in the retina of the eye. The primary auditory cortex receives auditory information and is located in the temporal lobe; the primary somatosensory cortex, which receives information about body senses such as touch, temperature, and pain, is found in the parietal lobe just posterior to the central sulcus. Neither the gustatory cortex, which involves taste sensations, nor the primary olfactory area, which receives information regarding the sense of smell, is visible on the surface, but both lie within the folds of the cortex. The **primary cortex** of each lobe provides conscious awareness of sensory experience and the initial cortical processing of sensory qualities. Except for olfaction, all sensory information arrives in the appropriate primary cortex via projection neurons from the thalamus. In addition, except for olfaction, sensory information from the left side of the body goes to the right cerebral hemisphere first, and information from the right side goes to the left hemisphere. Visual information is somewhat different in that the left half of the visual field of each eye goes to the right occipital lobe and the right half of the visual field of each eye goes to the left occipital lobe.

Adjacent to each primary area is **secondary cortex**, which consists of neuronal circuits responsible for analyzing information transmitted from the primary area and providing recognition (or perception) of the stimulus. These areas are also the regions where memories are stored. Farther from the primary areas are association areas that lay down more-complex memories that involve multiple sensory systems such that our memories are not confined to a single sensory system but integrate multiple characteristics of the event. For example, many of us remember pieces of music from the past that automatically evoke visual memories of the person we shared it with, or the time in our lives when it was popular. These **tertiary association areas**

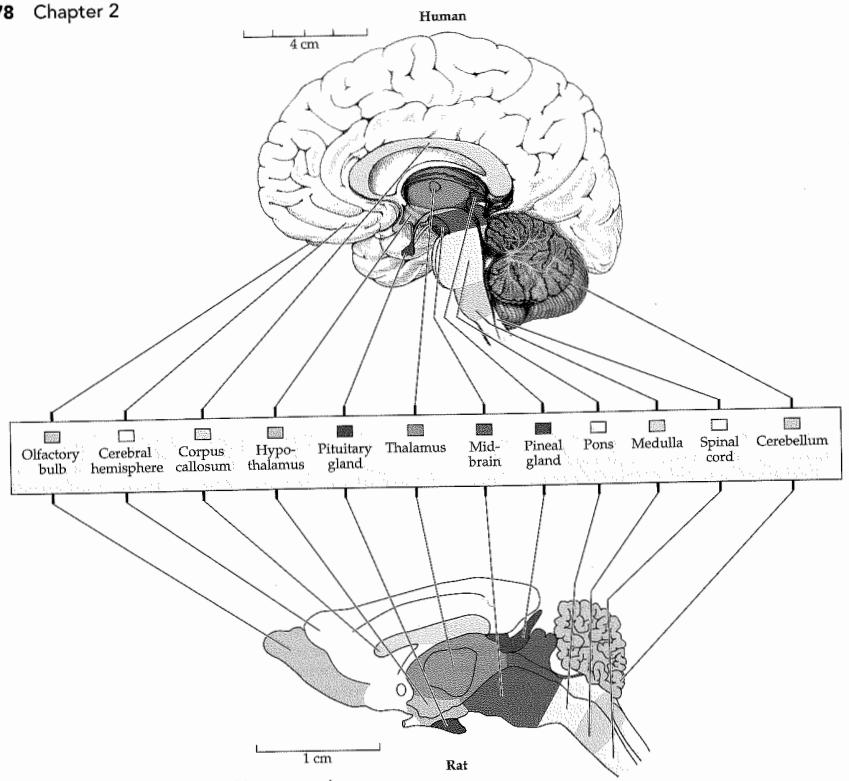


FIGURE 2.26 Comparison of human and rat brains Midsagittal views of the right hemispheres of human and rat brains show extensive similarities in brain structures and their relative topographic location. The brains differ in that the cerebral hemispheres are relatively much larger in the human brain, while the rat has a relatively larger midbrain and olfactory bulb. The rat brain has been enlarged about six times in linear dimensions relative to the human brain. (From Breedlove et al., 2010.)

are often called the parietal–temporal–occipital association cortex because they represent the interface of the three sensory lobes and provide the higher-order perceptual functions needed for purposeful action.

Within the frontal lobe, the primary motor cortex mediates voluntary movements of the muscles of the limbs and trunk. Neurons originating in primary motor cortex directly, or in several steps, project to the spinal cord to act on spinal motor neurons that end on muscle fibers. As was true for the sensory systems, the motor neurons beginning in the frontal cortex are crossed, meaning that areas of the right primary motor cortex control movements of limbs on the left side of the body, and vice versa. Adjacent to the primary motor cortex is the secondary motor cortex, where memories for well-learned motor sequences are stored. Neurons in this area connect directly to the primary motor cortex to direct movement. The rest of the frontal lobe comprises the prefrontal cortex, which receives sensory information from the other cortices via the large bundles of white matter running below the gray matter. Emotional and motivational input is contributed to the prefrontal cortex by limbic and other subcortical structures. The prefrontal cortex is critical for making decisions, planning actions, and evaluating optional strategies. Impaired prefrontal function is characteristic of several psychiatric disorders, including borderline personality disorder, memory loss after traumatic brain injury, attention deficit hyperactivity disorder, and others. The significance of this brain region for the symptoms and treatment of schizophrenia is discussed in Chapter 19.

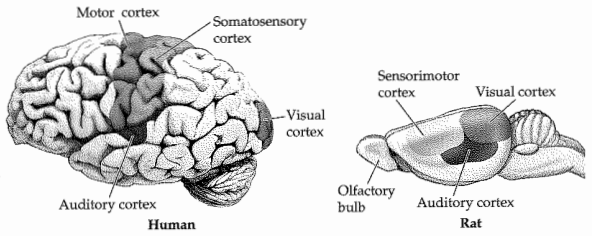


FIGURE 2.27 Lateral view of the left hemisphere of human and rat brains Note that the expanded human cortex does not involve the primary sensory or motor cortex (colored areas). Human cortical expansion involves the secondary and tertiary association areas that are responsible for higher-order perception and cognition. (After Bear et al., 2007.)

Rat and human brains have many similarities and some differences

Since the rat is one of the most commonly used animals in neuroscience and psychopharmacological research, it may be helpful to compare the neuroanatomy of the rat brain with that of the human brain. Overall, there has been great conservation of brain structures during the evolution of mammals. The basic mammalian brain plan draws on the common ancestry of mammals and is the model for the human brain. In fact, looking farther back in the evolutionary tree, all vertebrates show a striking similarity. Despite differences in absolute and relative sizes of the whole brain, all mammalian brains have the same major subdivisions, which are topographically organized in relatively the same locations with similar neural connections among structures. **FIGURE 2.26** shows the striking correspondence of brain structures in the brains of rats and humans. Extensive similarities can also be found for individual nuclei, fiber tracts, and types of cells, although human neurons are much larger than rat neurons and have more elaborate dendritic trees.

Despite the many similarities, there are also notable differences. What differs among mammals is the relative size of the brain regions, which likely reflects the environmental conditions encountered by each species and the importance of the functions of specific brain regions for adaptation of the species. For example, rats have relatively larger olfactory bulbs than humans, apparently because a very sensitive sense of smell provided evolutionary advantages for survival for these nocturnal rodents. More striking is the difference in cerebral cortex. The paired cerebral hemispheres occupy a much greater proportion of the brain in the human than in the rat. The six-layered nature of the neocortex (the outermost layers of the cerebral hemispheres) is characteristic of all mammals, and it is the newest part of the cerebral cortex to evolve. In humans, the surface area of the neocortex is approximately 2322 cm^2 (2.5 ft^2), which explains why the surface must bend and fold to fit within the skull, producing the extensively convoluted surface. As much as two-thirds of the neocortex is not visible on the surface but is buried in the grooves. In contrast, the surface of the rat cerebral cortex is smooth and has no gyri or fissures (**FIGURE 2.27**). It is also clear from Figure 2.27 that the expanded surface area of the human cortex does not involve the primary sensory areas (pink, green, and orange), which are the first cortical areas to receive input from ascending sensory pathways, nor does it involve the primary motor cortex (blue). Instead, one can see enlargement of the secondary sensory association areas responsible for the complex sensory processing, perception, and function (e.g., speech) of which humans are capable. Additionally, tertiary association areas of the cortex are greatly expanded, reflecting the human capacity for cognitive processing, reasoning, abstract thinking, and decision making.

Section Summary

- The central nervous system (CNS) includes the brain and the spinal cord. The remaining nerves of the body constitute the peripheral nervous system (PNS).
- The PNS is divided into the somatic nervous system, which includes spinal nerves that transmit sensory and motor information for skeletal muscles, and the autonomic nervous system, which serves smooth muscles, glands, and visceral organs.
- The autonomic nervous system has two divisions: the sympathetic, which serves to mobilize energy for times of "fight-or-flight"; and the parasympathetic, which reduces energy usage and stores reserves.
- The CNS is protected by a bony covering, three layers of meninges (dura, arachnoid, and pia), and cerebrospinal fluid.
- Neurotrophic factors are neuronal growth factors that guide the development of neurons, regulate dendritic growth and retraction, and aid in survival of neurons.
- The CNS can be divided into six regions containing multiple nuclei and their associated axons,

which form interconnecting neural circuits: spinal cord, myelencephalon, metencephalon, mesencephalon, diencephalon, and telencephalon.

- The gray matter of the spinal cord constitutes cell bodies that receive sensory information and cell bodies of motor neurons that serve muscles. The white matter consists of tracts of myelinated axons that carry signals in the ascending direction, to the brain, and the descending direction, for cortical control of the spinal cord.
- Continuous with the spinal cord is the myelencephalon, or medulla, which contains nuclei that serve vital functions for survival, such as respiration, heart rate, and vomiting.
- The metencephalon includes two major structures. The cerebellum functions to maintain posture and balance and provides fine motor control and coordination. The pons contains several nuclei that represent the origins of most of the tracts utilizing the neurotransmitters norepinephrine (the locus coeruleus) and serotonin (the raphe nuclei).
- Beginning in the medulla, running through the pons, and extending into the midbrain is the reticular formation—a network of interconnected nuclei that control arousal, attention, and survival functions.
- The mesencephalon, or midbrain, contains nuclei that control sensory reflexes such as pupillary constriction. Other nuclei (substantia nigra and ventral tegmental area) are the cell bodies of neurons that form three major dopaminergic tracts. The periaqueductal gray organizes behaviors such as defensive rage and predation and serves as an important pain-modulating center.
- The diencephalon contains the thalamus, which relays information to the cerebral cortex, and the hypothalamus, which is important for maintaining homeostasis of physiological functions and for modulating motivated behaviors, including eating, aggression, reproduction, and so forth. The many nuclei that constitute the hypothalamus control both the autonomic nervous system and the endocrine system.
- The telencephalon includes both the cerebral cortex and multiple subcortical structures, including the basal ganglia and the limbic system. The basal ganglia modulate movement.
- The limbic system is made up of several brain structures with perfuse interconnections that modulate emotion, motivation, and learning. Some of the prominent limbic structures are the amygdala, hippocampus, nucleus accumbens, and limbic cortex.
- The six-layered cerebral cortex is organized into four lobes: the occipital, temporal, and parietal, which are the sensory lobes involved in perception and memories, and the frontal, which regulates motor movements and contains the "executive mechanism" for planning, evaluating, and making strategies.
- Although there are differences in absolute and relative size, rat and human brains have the same major subdivisions, which are topographically organized in similar locations. Rat brains have relatively larger olfactory bulbs and midbrains. Human brains have expanded secondary and tertiary association areas of the cerebral cortex that serve higher-order sensory perception and cognitive functions.

STUDY QUESTIONS

1. What are embryonic stem cells? Describe several potential benefits from stem cell research.
2. Name the three major external features of neurons and their basic functions.
3. What is myelin and why is it important to neuron function?
4. Briefly describe the two stages of protein synthesis as well as epigenetic modification of gene expression.
5. Describe the role of the cytoskeleton in normal axoplasmic transport and its contribution to Alzheimer's disease.
6. Compare and contrast ligand-gated and voltage-gated ion channels.
7. Name the four types of glial cells, and describe their basic functions.
8. What is the resting membrane potential, and what is responsible for it? Be sure to describe the establishment of the equilibrium potential for potassium.
9. How are local potentials generated? Why is summation or integration so important to neuronal signaling?

STUDY QUESTIONS (*continued*)

10. What happens at the axon hillock to generate an action potential? Describe the movement of ions during an action potential. What is responsible for the absolute refractory period and the relative refractory period?
11. Why is saltatory conduction so much more rapid and energy efficient than conduction on nonmyelinated axons?
12. Compare the characteristics of local potentials and action potentials.
13. Describe the somatic nervous system and its functions. Discuss the autonomic nervous system, and compare the sympathetic and parasympathetic divisions.
14. Describe the four protective features of the CNS: skull, meninges, cerebrospinal fluid, and blood–brain barrier.
15. What are the principal functions of neurotrophic factors?
16. Describe the basic functions and cell groups in the spinal cord, medulla, pons, and cerebellum.
17. What are the important functions of the periaqueductal gray, substantia nigra, and ventral tegmental area? How do the latter two nuclei control dopamine function?
18. What is the role of the hypothalamus in survival? Be sure to describe autonomic nervous system regulation as well as control of both anterior and posterior pituitary. How does it help us cope with stress?
19. What is the limbic system? How do the hippocampus and amygdala modify our behavior?
20. How is the cerebral cortex organized? What is the distinction between primary, secondary, and tertiary cortical regions?
21. What are the most significant differences between rat and human brains?

Go to the *Psychopharmacology* Companion Website at oup-arc.com/access/meyer-3e for animations, web boxes, flashcards, and other study aids.