

Structure and Function of the Nervous System

ONE DAY IN 1963, neuroscientist Jose Delgado coolly stood in a bullring in Córdoba, Spain, facing a charging bull. He did not sport the Spanish matador's typical gear of toreador pants, jacket, and sword, however. Instead, he stepped into the ring in slacks and a pullover sweater—and, for effect, a matador's cape—while holding a small electronic device in his hand. He was about to see if it worked.

The bull turned and charged, but Delgado stood his ground, his finger on the device's button. Then he pushed it. The bull skidded to a stop, standing a few feet before the scientist (**Figure 2.1**). The now placid bull stood there looking at Delgado, who gazed back, smiling. This otherwise ordinary bull had one odd feature that gave Delgado confidence: a surgically implanted electric stimulator in its caudate nucleus. The device in Delgado's hand was a radio transmitter that he had built to activate the stimulator. By stimulating the bull's caudate nucleus, Delgado had turned off its aggression.

What motivated Delgado's unusual scientific experiment? Years before, Delgado had been horrified by the increasingly popular frontal lobotomy surgical procedure that destroyed brain tissue—and along with it, its function—in order to treat mental disorders. He was interested in finding a more conservative approach to treating these disorders through electrical stimulation. Using his knowledge of the electrical properties of neurons, neuroanatomy, and brain function, Delgado designed the first remote-controlled neural implants ever to be used. Exceedingly controversial at the time, they were the forerunners of the now common intracranial devices that are used for stimulating the brain to treat disorders such as Parkinson's disease, chronic pain, neuromuscular dysfunction, and other maladies.

Delgado understood that the nervous system uses electrochemical signaling for communication. He also understood that inside the brain, neurons and their long-distance projections (axons) form intricate wiring patterns. An electrical signal

BIG Questions

- What are the elementary building blocks of the brain?
- How is information coded and transmitted in the brain?
- What are the organizing principles of the brain?
- What does the brain's structure tell us about its function and the behaviors it supports?



FIGURE 2.1 Jose Delgado halting a charging bull by remote control.

initiated at one location can travel to another location to trigger the contraction of a muscle, or the initiation or cessation of a behavior. This knowledge is the foundation on which all theories of neuronal signaling are built.

Our goal as cognitive neuroscientists is to figure out what the 89 billion neurons of the human brain do and how their collective action enables us to walk, talk, and imagine the unimaginable. We can approach the biological system that is the brain from several levels of analysis: from atomic, molecular, and cellular levels upward to circuit, network, system, and cognitive levels, and finally, to the highest levels, involving the interactions of humans with each other—our familial, societal, and cultural lives.

Since all theories of how the brain enables the mind must ultimately mesh with the actual nuts and bolts of the nervous system, and what it can and cannot do, we need to understand the basics of neurons. We must appreciate the structure and function of neurons on the individual level, as well as when they are strung together into the circuits, networks, and systems that form the brain and the nervous system as a whole. Thus, for us, it is important to understand the basic physiology of neurons and the anatomy of the nervous system. In this chapter we review the principles of brain structure that support cognition. In chapters that follow, we look at what results from the activity within and among specific brain circuits, networks, and systems (e.g., perception, cognition, emotion, and action).

2.1 The Cells of the Nervous System

The nervous system is composed of two main classes of cells: neurons and glial cells. **Neurons** are the basic signaling units that transmit information throughout the nervous system. As Santiago Ramón y Cajal and others of his time deduced, neurons take in information, make a “decision” about it following some relatively simple rules, and then, by changes in their activity levels, pass the signal along to other neurons or muscles. Neurons vary in their form, location, and interconnectivity within the nervous system (**Figure 2.2**), and these variations are closely related to their functions. **Glial cells** serve various functions in the nervous system, providing structural support and electrical insulation to neurons and modulating neuronal activity. We begin with a quick look at glial cells, after which we will turn our focus back to neurons.

Glial Cells

There are roughly as many glial cells in the brain as there are neurons. The central nervous system has three main types of glial cells: astrocytes, microglial cells, and oligodendrocytes (**Figure 2.3**). *Astrocytes* are large glial cells with round or radially symmetrical forms; they surround neurons and are in close contact with the brain’s vasculature. An astrocyte makes contact with blood vessels at specializations called end feet, which permit the astrocyte to transport ions across the vascular wall.

The astrocytes create a barrier, called the **blood–brain barrier (BBB)**, between the tissues of the central nervous system and the blood. The BBB restricts the diffusion of microscopic objects (such as most bacteria) and large hydrophilic molecules in the blood from entering the neural tissue, but it allows the diffusion of small hydrophobic molecules, such as oxygen, carbon dioxide, and hormones. Many drugs and certain neuroactive agents, including dopamine and norepinephrine, when placed in the blood, cannot cross the BBB. Thus, it plays a vital role in protecting the central nervous system from blood-borne agents such as chemical compounds and also pathogens.

Evidence gathered over the past decade suggests that astrocytes also have an active role in brain function. In vitro studies indicate that they respond to and release neurotransmitters and other neuroactive substances that affect neuronal activity and modulate synaptic strength. In vivo studies found that when astrocyte activity is blocked, neuronal activity increases, supporting the notion that neuronal activity is moderated by astrocyte activity (Schummers et al., 2008). It is hypothesized that

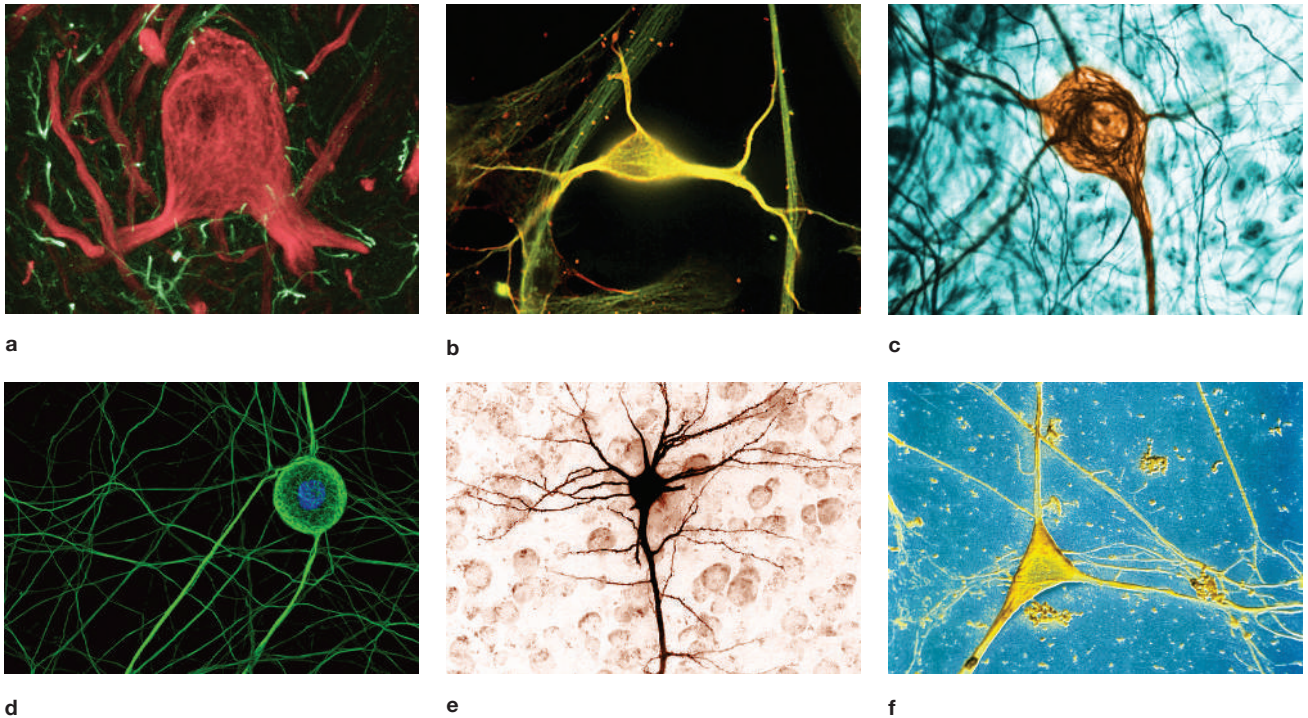
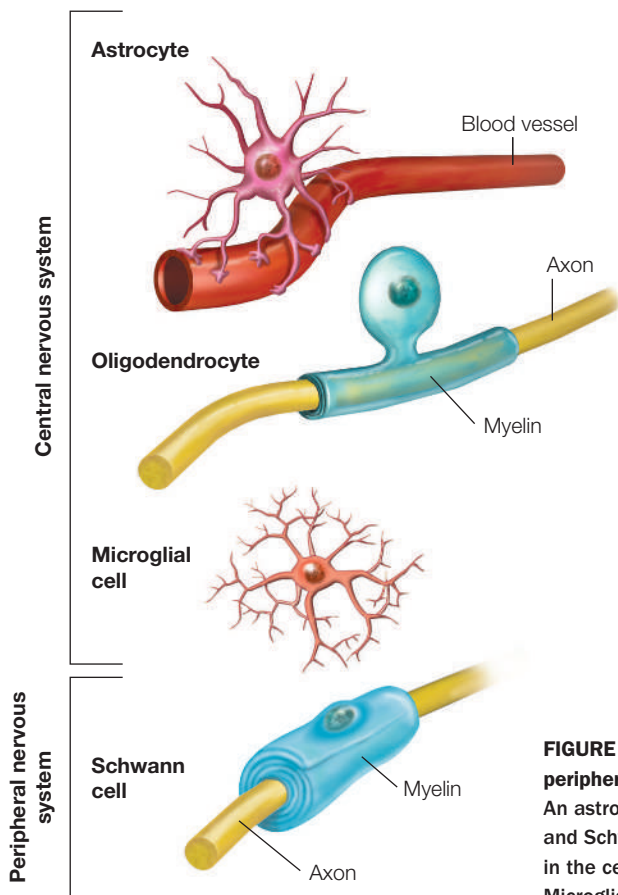


FIGURE 2.2 Mammalian neurons show enormous anatomical variety.

(a) Neuron (red) from the vestibular area of the brain. Glial cells are the thin, lighter structures (confocal light micrograph). (b) Hippocampal neuron (yellow; fluorescent micrograph). (c) Neuron (brown) in mouse dorsal root ganglion of the spinal cord (transmission electron micrograph). (d) Neuron in cell culture from dorsal root ganglia of an embryonic rat (fluorescent micrograph). (e) Pyramidal neuron from the brain. (f) Multipolar neuron cell body from human cerebral cortex (scanning electron micrograph).



astrocytes either directly or indirectly regulate the reuptake of neurotransmitters.

Glial cells also form the fatty substance called **myelin** in the nervous system. In the central nervous system, *oligodendrocytes* form myelin; in the peripheral nervous system, *Schwann cells* carry out this task (Figure 2.3). Both glial cell types create myelin by wrapping their cell membranes around the axon in a concentric manner during development and maturation. The cytoplasm in that portion of the glial cell is squeezed out, leaving layers of the lipid bilayer of the glial cell sheathing the membrane. Myelin is a good electrical insulator, preventing loss of electrical current across the cell membrane. It increases the speed and distance that information can travel along a neuron.

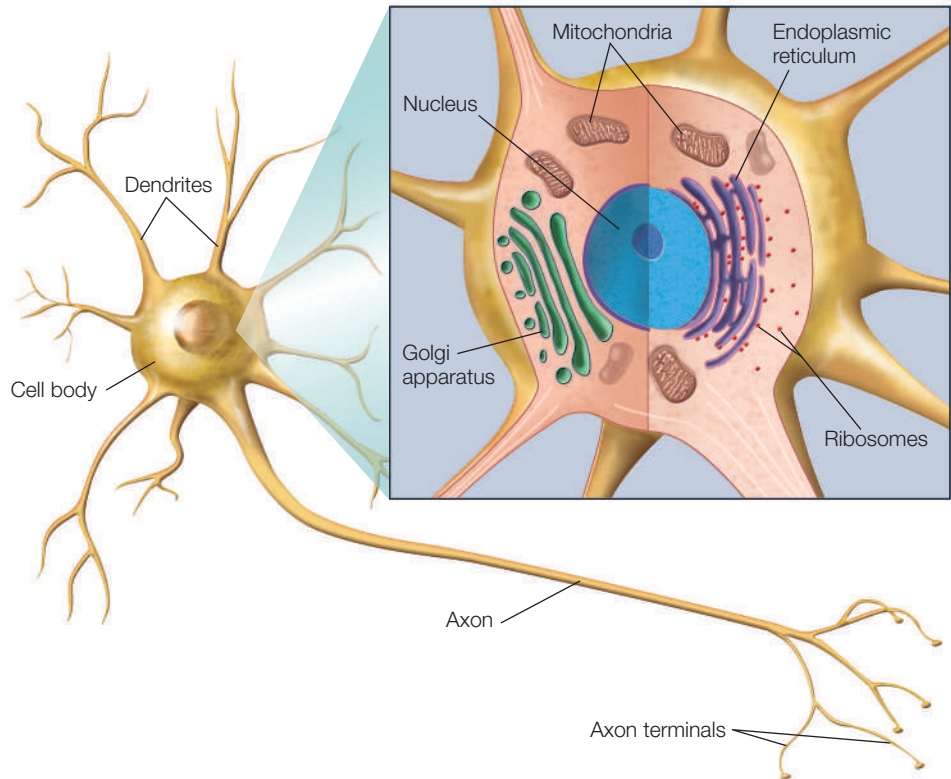
Microglial cells, which are small and irregularly shaped (Figure 2.3), are phagocytes that devour and remove damaged cells. Unlike many cells in the central nervous system, microglial cells can proliferate even in adults (as do other glial cells).

FIGURE 2.3 Various types of glial cells in the mammalian central and peripheral nervous systems.

An astrocyte is shown with end feet attached to a blood vessel. Oligodendrocytes and Schwann cells produce myelin around the axons of neurons (oligodendrocytes in the central nervous system, Schwann cells in the peripheral nervous system). Microglial cells dispose of damaged cells.

FIGURE 2.4 Idealized mammalian neuron.

A neuron is composed of three main parts: a cell body, dendrites, and an axon. The cell body contains the cellular machinery for the production of proteins and other macromolecules. Like other cells, the neuron contains a nucleus, endoplasmic reticulum, ribosomes, mitochondria, Golgi apparatus, and other intracellular organelles (inset). The dendrites and axon are extensions of the cell membrane and contain cytoplasm continuous with the cytoplasm inside the cell body.



Neurons

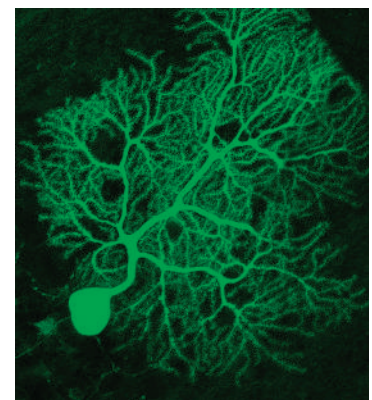
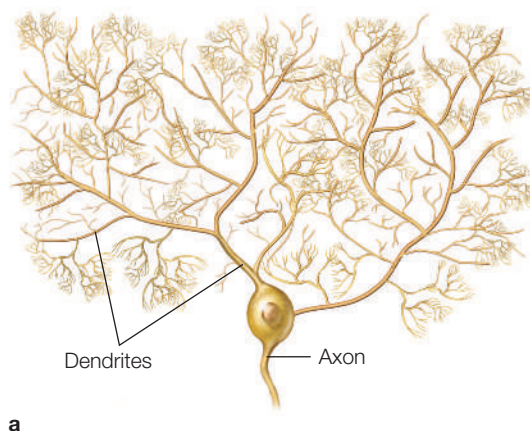
The standard cellular components found in almost all eukaryotic cells are also found in neurons (as well as in glial cells). A cell membrane encases the cell body (in neurons, it is sometimes called the **soma**; Greek for “body”), which contains the metabolic machinery that maintains the neuron: nucleus, endoplasmic reticulum, cytoskeleton, mitochondria, Golgi apparatus, and other common intracellular organelles (**Figure 2.4**). These structures are suspended in cytoplasm, the salty intracellular fluid that is made up of a combination of ions (molecules or atoms that have either a positive or negative electrical charge)—predominantly ions of potassium, sodium, chloride, and calcium—as well as molecules such as proteins.

The neuron itself, like any other cell, sits in a bath of salty extracellular fluid, which is made up of a mixture of the same types of ions.

In addition, however, neurons possess unique cyto- logical features and physiological properties that enable them to transmit and process information rapidly. The two predominant cellular components unique to neurons are the dendrites and the axon. **Dendrites** are branching extensions of the neuron that receive inputs from other neurons. They have many varied and complex forms, depending on the type and location of the neuron. The arborizations may look like the branches and twigs of an oak tree, as seen in the complex dendritic structures of the cerebellar Purkinje cells (**Figure 2.5**), or they may be

FIGURE 2.5 Soma and dendritic tree of a Purkinje cell from the cerebellum.

The Purkinje cells are arrayed in rows in the cerebellum. Each one has a large dendritic tree that is wider in one direction than the other. (a) Drawing of Purkinje cell as viewed in a cross section through a cerebellar folium. (b) Confocal micrograph of a Purkinje cell from mouse cerebellum. The cell is visualized using fluorescence methods.

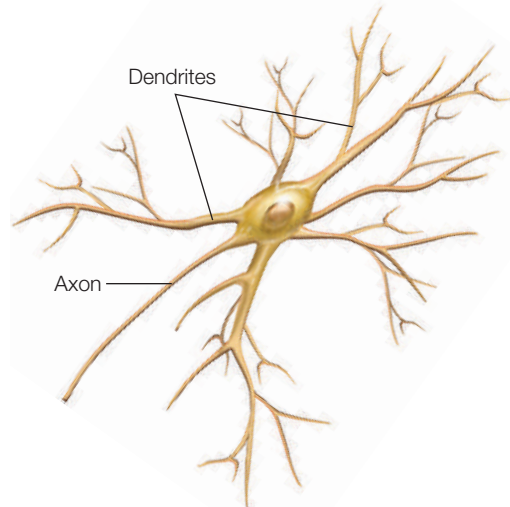


a

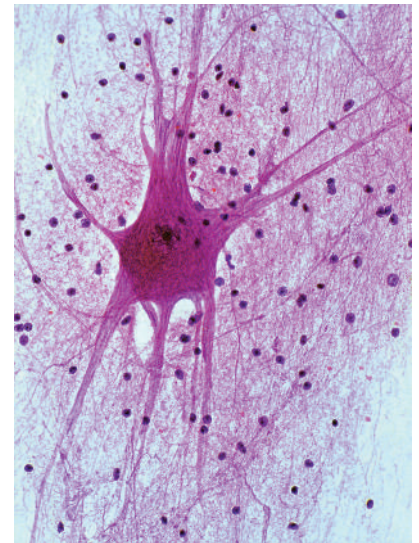
b

FIGURE 2.6 Spinal motor neuron.

(a) Neurons located in the ventral horn of the spinal cord send their axons out the ventral root to make synapses on muscle fibers. (b) A spinal cord motor neuron stained with cresyl echt violet stain.



a



b

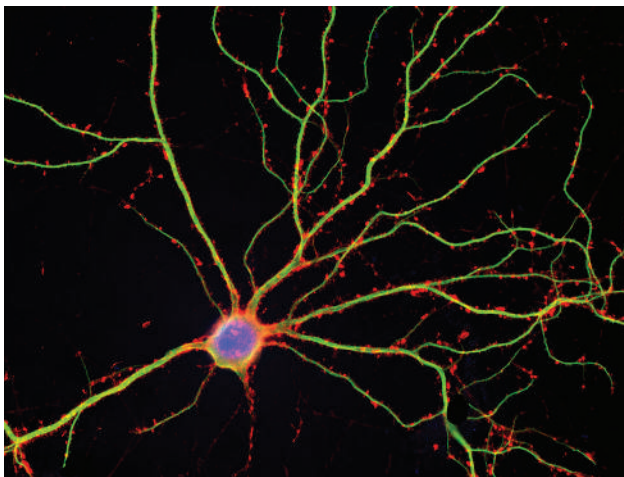


FIGURE 2.7 Dendritic spines on cultured rat hippocampal neurons. This neuron has been triple stained to reveal the cell body (blue), dendrites (green), and spines (red).

much simpler, such as the dendrites in spinal motor neurons (**Figure 2.6**). Most dendrites also have specialized processes called **spines**, little knobs attached by small necks to the surface of the dendrites, where the dendrites receive inputs from other neurons (**Figure 2.7**).

The **axon** is a single process that extends from the cell body. This structure represents the output side of the neuron. Electrical signals travel along the length of the axon to its end, the axon terminals, where the neuron transmits the signal to other neurons or other targets. Transmission occurs at the **synapse**, a specialized structure where two neurons come into close contact so that chemical or electrical signals can be passed from one cell to the next. Some axons branch to form **axon collaterals** that can transmit signals to more than one cell (**Figure 2.8**).

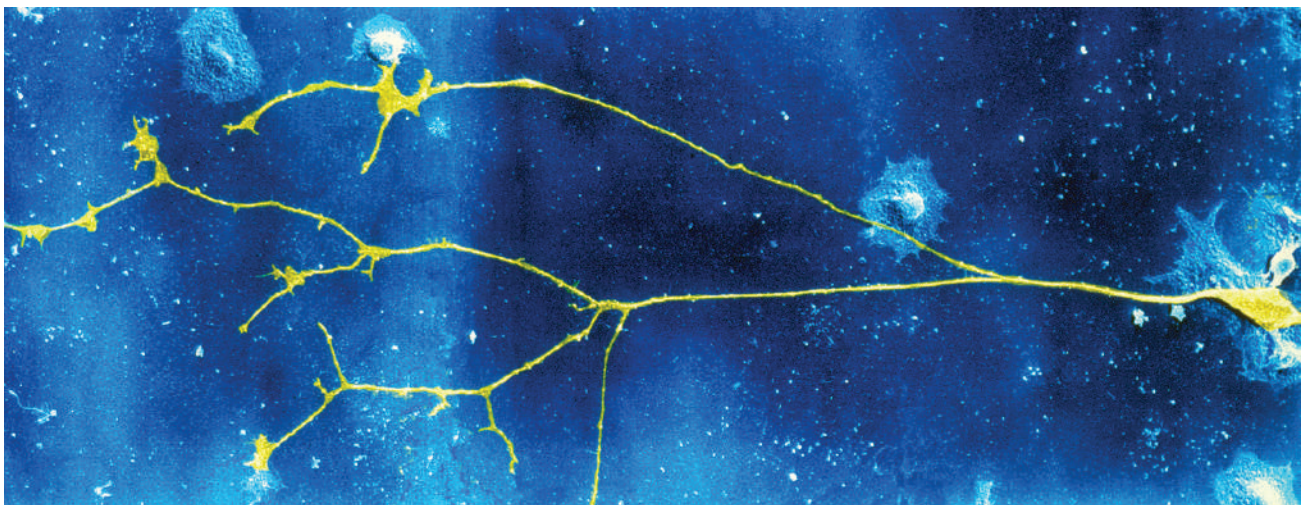


FIGURE 2.8 Axons can take different forms.

A neuron (far right) and its axon collaterals (left half of image) are shown stained in yellow. The cell body (at far right) gives rise to an axon, which branches, forming collaterals that can make contact with many different neurons.

Many axons are wrapped in layers of myelin. Along the length of the axons, there are evenly spaced gaps in the myelin; these gaps are commonly referred to as nodes of Ranvier (see Figure 2.12). Later, when we look at how signals move down an axon, we will explore the role of myelin and the nodes of Ranvier in accelerating signal transmission.

Neuronal Signaling

Neurons receive, evaluate, and transmit information. These processes are referred to as *neuronal signaling*. Information that is received by the neuron at its input synapses passes through the cell body and then, via the axon, to output synapses on the axon terminals. At these output synapses, information is transferred across synapses from one neuron to the next neuron; or to nonneuronal cells such as those in muscles or glands; or to other targets, such as blood vessels.

Within a neuron, information moves from input synapses to output synapses through changes in the electrical state of the neuron caused by the flow of electrical currents within the neuron and across its neuronal membrane. *Between* neurons, information transfer across synapses is typically mediated chemically by neurotransmitters (signaling molecules); these synapses are called *chemical synapses*. At *electrical synapses*, however, signals between neurons travel via transsynaptic electrical currents. Regarding information flow, neurons are referred to as either presynaptic or postsynaptic in relation to any particular synapse. *Most neurons are both presynaptic and postsynaptic*: They are **presynaptic** when their axon's output synapses make connections onto other neurons or targets, and they are **postsynaptic** when other neurons make a connection at input synapses onto their dendrites or elsewhere on the receiving neuron.

THE MEMBRANE POTENTIAL The process of signaling has several stages. Let's return to Delgado's bull, whose neurons process information in the same way ours do. The bull is snorting about in the dirt, head down, when suddenly a sound wave—produced by Delgado entering the ring—courses down its auditory canal and hits the tympanic membrane (eardrum). The resultant stimulation of the auditory receptor cells (auditory hair cells) generates neuronal signals that are transmitted via the auditory pathways to the brain. At each stage of this ascending auditory pathway, neurons receive inputs on their dendrites that typically cause them to generate signals that are transmitted to the next neuron in the pathway.

How does the neuron generate these signals, and what are these signals? To answer these questions, we

have to understand several things about neurons. First, energy is needed to generate the signals. Second, this energy is in the form of an electrical potential across the neuronal membrane. This electrical potential is defined as the difference in voltage across the neuronal membrane or, put simply, the voltage inside the neuron versus outside the neuron. Third, these two voltages depend on the concentrations of potassium, sodium, and chloride ions, as well as on charged protein molecules both inside and outside of the cell. Fourth, when a neuron is in its resting state and not actively signaling, the inside of a neuron is more negatively charged than the outside. The voltage difference across the neuronal membrane in the resting state is typically about -70 millivolts (mV) inside, which is known as the *resting potential* or **resting membrane potential**. This electrical-potential difference means that the neuron has at its disposal a kind of battery; and like a battery, the stored energy can be used to do work—signaling work (**Figure 2.9**).

How does the neuron generate and maintain this resting potential, and how does it use it for signaling? To answer these questions about function, we first need to examine the structures in the neuron that are involved in signaling. The bulk of the *neuronal membrane* is a bilayer of fatty lipid molecules that separates the cytoplasm from the extracellular milieu. Because the membrane is composed of lipids, it does not dissolve in the watery environments found inside and outside of the neuron, and it blocks the flow of water-soluble substances between the inside and the outside. It prevents ions, proteins, and other water-soluble molecules from moving across it. To understand neuronal signaling, we must focus on ions. This point is important: The lipid membrane maintains the separation of intracellular and extracellular ions and electrical charge that ultimately permits neuronal communication.

The neuronal membrane, though, is not merely a lipid bilayer. The membrane is peppered with transmembrane proteins, some of which serve as conduits for ions to move across the membrane (Figure 2.9, inset). These proteins are of two main types: ion channels and ion pumps. **Ion channels**, as we will see, are proteins with a pore through the center, and they allow certain ions to flow down their electrochemical and concentration gradients. **Ion pumps** use energy to actively transport ions across the membrane against their concentration gradients—that is, from regions of low concentration to regions of higher concentration.

Ion channels. The transmembrane passageways created by ion channels are formed from the three-dimensional structure of these proteins. These hydrophilic channels selectively permit one type of ion to pass through the membrane. The ion channels of concern to us—the ones found in neurons—are selective for sodium, potassium,

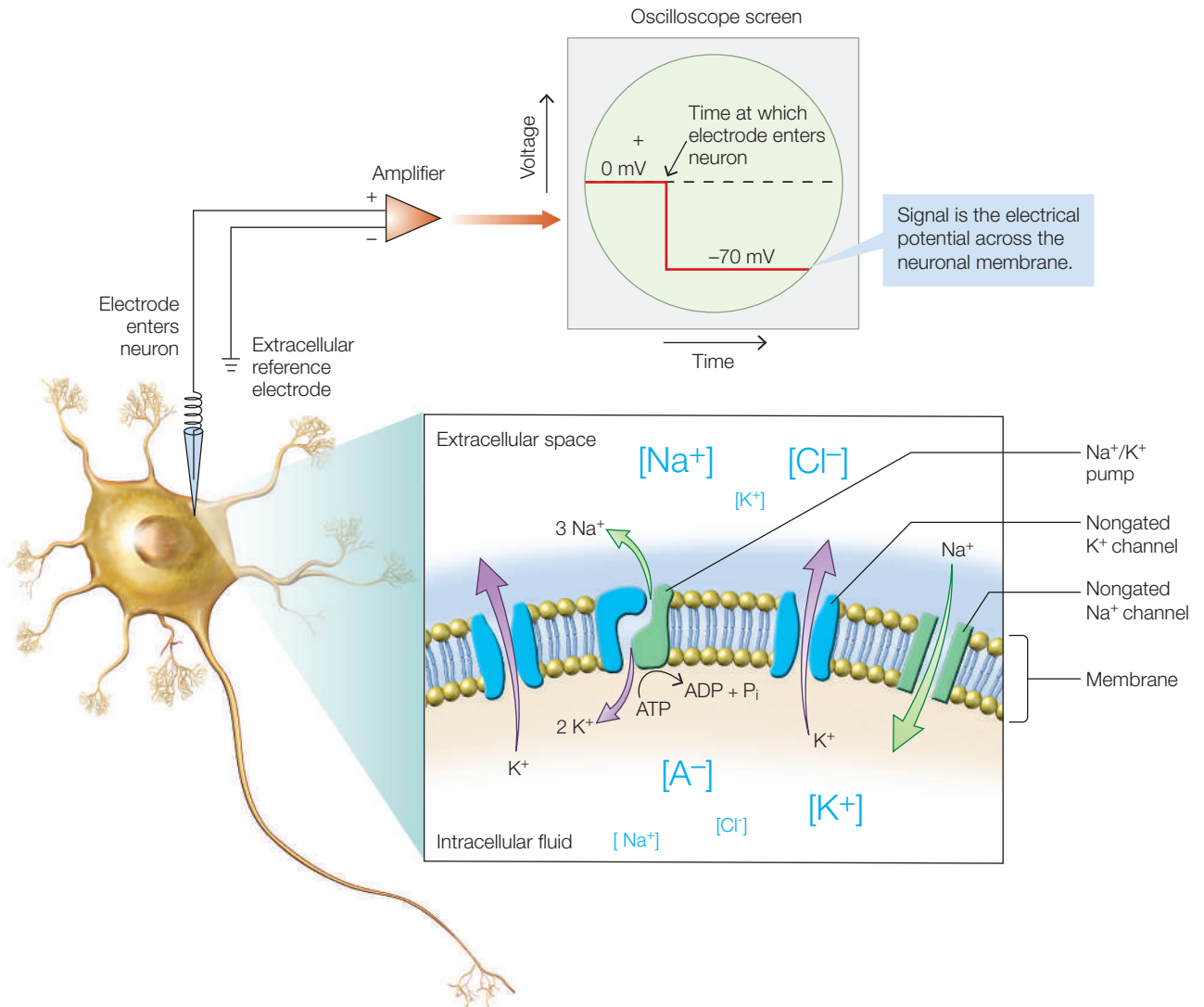


FIGURE 2.9 Ion channels in a segment of neuronal membrane and measuring resting membrane potential.

Idealized neuron (left), shown with an intracellular recording electrode penetrating the neuron. The electrode measures the difference between the voltage inside versus outside the neuron, and this difference is amplified and displayed on an oscilloscope screen (top). The oscilloscope screen shows voltage over time. Before the electrode enters the neuron, the voltage difference between the electrode and the extracellular reference electrode is zero, but when the electrode is pushed into the neuron, the difference becomes -70 mV, which is the resting membrane potential. The resting membrane potential arises from the asymmetrical distribution of ions of sodium (Na^+), potassium (K^+), and chloride (Cl^-), as well as of charged protein molecules (A^-), across the neuron's cell membrane (inset).

calcium, or chloride ions (Na^+ , K^+ , Ca^{2+} , and Cl^- , respectively; Figure 2.9, inset). The extent to which a particular ion can cross the membrane through a given ion channel is referred to as its **permeability**. This characteristic of ion channels gives the neuronal membrane the attribute of *selective permeability*. (Selective permeability is actually a property of all cells in the body; as part of cellular homeostasis, it enables cells to maintain internal chemical stability.) The neuronal membrane is more permeable to K^+ than to Na^+ (or other) ions—a property that contributes to the resting membrane potential, as we will learn shortly. The membrane permeability to K^+ is

larger because there are many more K^+ -selective channels than any other type of ion channel.

Unlike most cells in the body, neurons are excitable, meaning that their membrane permeability can change (because the membranes have ion channels that are capable of changing their permeability for a particular ion). Such proteins are called *gated ion channels*. They open or close in response to changes in nearby transmembrane voltage, or to chemical or physical stimuli. In contrast, ion channels that are unregulated, and hence always allow the associated ion to pass through, are known as *nongated ion channels*.

Ion pumps. Under normal conditions, Na^+ and Cl^- concentrations are greater outside the cell, and K^+ concentrations are greater inside the cell. You may be wondering why K^+ ions don't flow out of the neuron—down their concentration gradient—until the K^+ ion concentrations inside and outside the cell are equal. We could ask the corresponding question for all other ions.

To combat this drive toward equilibrium, neurons use *active transport* proteins known as ion pumps. In particular, neurons use a Na^+/K^+ pump that pumps Na^+ ions out of the cell and K^+ ions into the cell (Figure 2.9, inset). Because this process moves ions up their concentration gradients, the mechanism requires energy. Each pump is an enzyme that hydrolyzes adenosine triphosphate (ATP) for energy. For each molecule of ATP that is hydrolyzed, enough energy is produced to move three Na^+ ions out of the cell and two K^+ ions into the cell (Figure 2.10).

The concentration gradients create forces due to the unequal distribution of ions. The force of the Na^+ concentration gradient acts to push Na^+ from an area of high concentration to one of low concentration (from outside to inside), while the K^+ concentration gradient acts to push K^+ also from an area of high concentration to an area of low concentration (from inside to outside)—the very thing the pump is working against. With both positively and negatively charged ions inside and outside the cell, why is the voltage different inside versus outside the neuron?

The inside and outside voltages are different because the membrane is more permeable to K^+ than to Na^+ . The force of the K^+ concentration gradient pushes some K^+ out of the cell, leaving the inside of the neuron slightly more negative than the outside. This difference creates another force, an **electrical gradient**, because each K^+ ion carries one unit of positive charge out of the neuron as it moves across the membrane. These

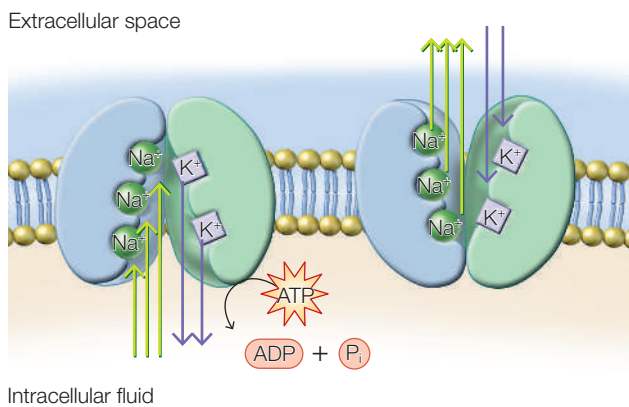


FIGURE 2.10 Ion pumps transport ions across the membrane. The Na^+/K^+ pump preserves the cell's resting potential by maintaining a larger concentration of K^+ inside the cell and Na^+ outside the cell. The pump uses ATP as energy.

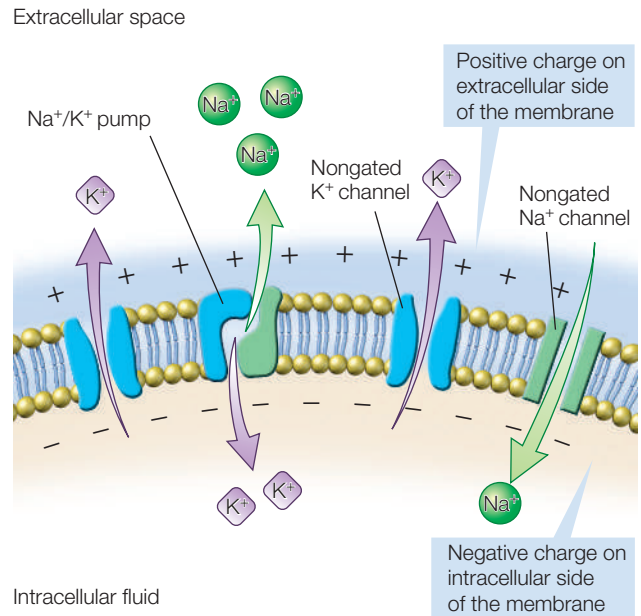


FIGURE 2.11 Selective permeability of the membrane. The membrane's selective permeability to some ions, and the concentration gradients formed by active pumping, lead to a difference in electrical potential across the membrane; this is the *resting membrane potential*. The membrane potential, represented here by the positive charges outside the neuron along the membrane and the negative charges inside along the membrane, is the basis for the transmembrane voltage difference shown in Figure 2.9.

two gradients (electrical and ionic concentration) are in opposition to one another with respect to K^+ (Figure 2.11).

As negative charge builds up along the inside of the membrane (and an equivalent positive charge forms along the extracellular side), the positively charged K^+ ions outside of the cell are drawn electrically back into the neuron through the same ion channels that are allowing K^+ ions to leave the cell by diffusion. Eventually, the force of the concentration gradient pushing K^+ out through the K^+ channels is equal to the force of the electrical gradient driving K^+ in. When that happens, the opposing forces are said to reach *electrochemical equilibrium*. The difference in charge thus produced across the membrane is the resting membrane potential, that -70 mV difference. The value for the resting membrane potential of any cell can be calculated by using knowledge from electrochemistry, provided that the concentrations of ions inside and outside the neuron are known.

THE ACTION POTENTIAL We now understand the basis of the energy source that neurons can use for signaling. Next we want to learn how this energy can be used to transmit information within a neuron, from its dendrites, which receive inputs from other neurons, to its axon terminals, where it signals to the next neuron(s)

in the chain. The process begins when synapses on a neuron's dendrites receive a signal (e.g., a neurotransmitter binding to a receptor), resulting in the opening of ion channels in the dendrite, which causes ionic currents to flow. For excitatory synaptic inputs, *excitatory postsynaptic potentials (EPSPs)* occur in the dendrite, and ionic currents flow through the volume of the neuron's cell body. If these currents happen to be strong enough to reach distant axon terminals, then the process of neuronal signaling is complete. In the vast majority of cases, however, the distance from dendrites to axon terminals is too great for the EPSP to have any effect. Why?

The small electrical current produced by the EPSP is passively conducted through the cytoplasm of the dendrite, cell body, and axon. Passive current conduction is called **electrotonic conduction** or *decremental conduction*: “decremental” because it diminishes with distance from its origin—the synapse on the dendrites, in this case. The maximum distance a passive current will flow in a neuron is only about 1 mm. In most neurons, a millimeter is too short to effectively conduct electrical signals, although sometimes, like in a structure such as the retina, a millimeter is sufficient to permit neuron-to-neuron communication via decremental conduction. Most of the time, however, the reduction in signal intensity with decremental conduction means that long-distance

communication within a neuron from dendrite to axon terminal will fail (your toes would be in trouble, for example, because they are about 1 meter from the spinal cord and close to 2 meters from the brain). How does the neuron solve this problem of decremental conduction and the need to conduct signals over long distances?

Neurons evolved a clever mechanism to regenerate and pass along the signal received at synapses on the dendrite: the **action potential**. It works something like 19th-century firefighters in a bucket brigade. An action potential is a rapid depolarization and repolarization of a small region of the membrane on the neuron's output via its axon caused by the opening and closing of ion channels.

An action potential is a different process from the EPSP and the ionic currents involved in decremental conduction. The action potential doesn't decrement after only 1 mm. Action potentials enable signals to travel for meters with no loss in signal strength, because they continually regenerate the signal at each patch of membrane on the axon. This is one reason why giraffes and blue whales can have neurons whose axon terminals may be many meters from their dendrites.

The action potential is able to regenerate itself because of the presence of **voltage-gated ion channels** located in the neuronal membrane (**Figure 2.12a**, inset). The densest concentration of ion channels is found at the

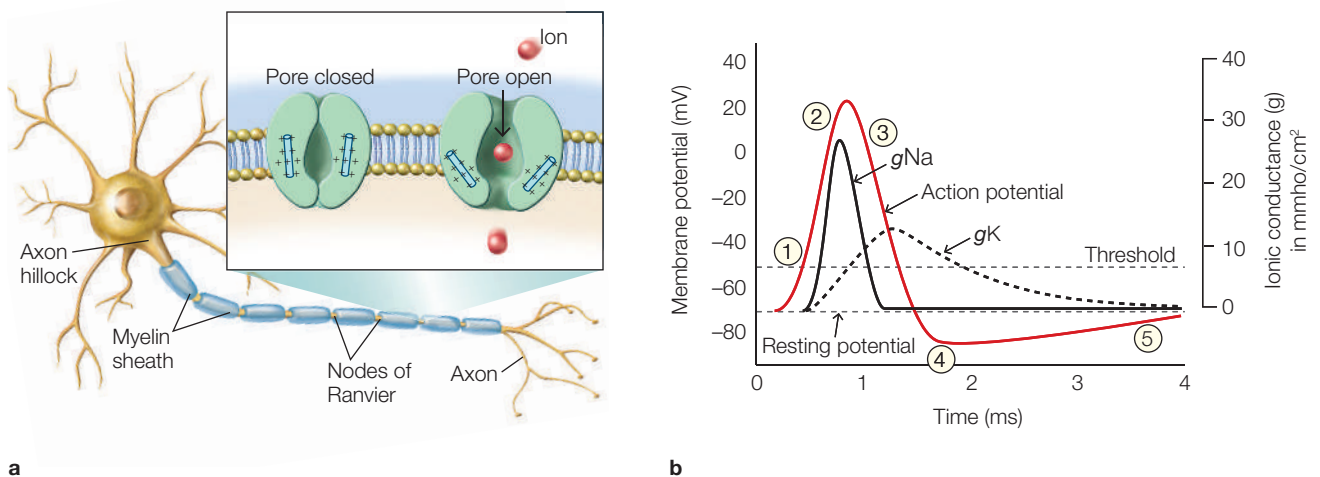


FIGURE 2.12 The neuronal action potential, voltage-gated ion channels, and changes in channel conductance.

(a) An idealized neuron with myelinated axon and axon terminals. Voltage-gated ion channels located in the spike-triggering zone at the axon hillock and along the extent of the axon at the nodes of Ranvier open and close rapidly, changing their conductance to specific ions (e.g., Na^+), altering the membrane potential and resulting in the action potential (inset). (b) The relative time course of changes in membrane voltage during an action potential, and the underlying causative changes in membrane conductance to Na^+ (g_{Na}) and K^+ (g_{K}). The initial depolarizing phase of the action potential (red line) is mediated by increased Na^+ conductance (black line), and the later repolarizing, descending phase of the action potential is mediated by an increase in K^+ conductance (dashed line) that occurs when the K^+ channels open. The Na^+ channels have closed during the last part of the action potential, when repolarization by the K^+ current is taking place. The action potential undershoots the resting membrane potential at the point where the membrane becomes more negative than the resting membrane potential.

spike-triggering zone in the **axon hillock**, a specialized region of the neuronal soma where the axon emerges. As its name denotes, the spike-triggering zone initiates the action potential. (The term *spike* is shorthand for an action potential because it represents a rapid change and a peak in the depolarization of the membrane potential, and it actually looks like a spike when viewed as a recording displayed on an oscilloscope or computer screen.) Ion channels are also found along the axon. In myelinated axons, voltage-gated ion channels along the axon's length are restricted to the **nodes of Ranvier**. Named after the French histologist and anatomist Louis-Antoine Ranvier, who first described them, they are regular intervals along the axon where gaps in myelination occur (Figure 2.12a).

How does the spike-triggering zone initiate an action potential? The passive electrical currents that are generated following EPSPs on multiple distant dendrites sum together at the axon hillock. This current flows across the neuronal membrane in the spike-triggering zone, depolarizing the membrane. If the depolarization is strong enough, meaning that the membrane moves from its resting potential of about -70 mV to a less negative value of approximately -55 mV, then an action potential is triggered. We refer to this **depolarized** membrane potential value as the **threshold** for initiating an action potential. **Figure 2.12b** illustrates an idealized action potential. The numbered circles in the figure correspond to the numbered events in the next paragraph. Each event alters a small region of the membrane's permeability for Na^+ and K^+ as a result of the opening and closing of voltage-gated ion channels.

When the threshold (Figure 2.12b, event 1) is reached, voltage-gated Na^+ channels open and Na^+ flows rapidly into the neuron. This influx of positive ions further depolarizes the neuron, opening additional voltage-gated Na^+ channels; thus, the neuron becomes more depolarized (2), continuing the cycle by causing even more Na^+ channels to open. This process is called the Hodgkin-Huxley cycle. This rapid, self-reinforcing cycle, lasting only about 1 ms, generates the large depolarization that is the first portion of the action potential. Next, the voltage-gated K^+ channels open, allowing K^+ to flow out of the neuron down its concentration gradient. This outward flow of positive ions begins to shift the membrane potential back toward its resting potential (3). The opening of the K^+ channels outlasts the closing of the Na^+ channels, causing a second repolarizing phase of the action potential; this repolarization drives the membrane potential toward the equilibrium potential of K^+ , which is even more negative than the resting potential. The **equilibrium potential** is the membrane potential at which there is no net flux of a given ion. As a result,

the membrane is temporarily **hyperpolarized**: At about -80 mV, the membrane potential is more negative than both the resting membrane potential and the threshold required for triggering an action potential (4). Hyperpolarization causes the K^+ channels to close, in response to which the membrane potential gradually returns to its resting state (5).

During this transient hyperpolarization state, the voltage-gated Na^+ channels are unable to open, and no other action potential can be generated. This is known as the *absolute refractory period*. It is followed by the *relative refractory period*, during which the neuron can generate action potentials, but only with larger-than-normal depolarizing currents. The entire **refractory period** lasts only a couple of milliseconds and has two consequences. One is that the neuron's speed for generating action potentials is limited to about 200 action potentials per second. The other is that the passive current that flows from the action potential cannot reopen the ion-gated channels that generated it. The passive current, however, does flow down the axon with enough strength to depolarize the membrane a bit farther on, where the ion channels are not in a refractory state, opening voltage-gated channels in this next portion of the membrane. The result is that the action potential moves down the axon in one direction only—from the axon hillock toward the axon terminal.

That is the story of the self-regenerating action potential as it propagates itself down an axon, sometimes traveling several meters in the process. But traveling far is not the end of the story. Action potentials must also travel quickly if a person wants to run, or a bull wants to charge, or a very large animal (think blue whale) simply wants to react in a reasonable amount of time. Accelerated transmission of the action potential is accomplished in myelinated axons. The thick lipid sheath of myelin (Figure 2.12a) surrounding the membrane of myelinated axons makes the axon super-resistant to voltage loss. The high electrical resistance allows passive currents generated by the action potential to be shunted farther down the axon. The result is that action potentials do not have to be generated as often, and they can be spread out along the axon at wider intervals.

Indeed, action potentials in myelinated axons need occur only at the nodes of Ranvier, where myelination is interrupted. As a result, the action potential appears to jump down the axon at great speed, from one node of Ranvier to the next. We call this **saltatory conduction** (the term is derived from the Latin word *saltare*, meaning “to jump or leap”). The importance of myelin for efficient neuronal conduction is notable when it is damaged or lost, which is what happens in multiple sclerosis (MS).

There is one more interesting tidbit concerning action potentials: Because they always have the same amplitude, they are said to be *all-or-none* phenomena. Since one action potential has the same amplitude as any other, the strength of the action potential does not communicate anything about the strength of the stimulus that initiated it. The intensity of a stimulus (e.g., a sensory signal) is communicated by the *rate of firing* of the action potentials: More intense stimuli elicit higher action-potential firing rates.

NEURAL OSCILLATIONS So far, we have presented an idealized situation: A neuron is sitting in a resting state, awaiting inputs that might cause it to experience EPSPs and action potentials at the axon hillock that move down the axon to transmit signals. But most neurons actually fire at a continuous baseline rate. This rate is different in different types of neurons, and it can be the result of either intrinsic properties of the neuron itself or activity in small neural circuits or larger neural networks. These neuronal oscillations are important for understanding some of the signals we can receive from electrodes placed in an intact brain or on the surface of the scalp. Because postsynaptic potentials like EPSPs can be recorded from populations of neurons, they are another measure of neuronal activity in addition to recordings of action potentials. In Chapter 3 we describe how these postsynaptic potentials, and not the action potentials, are the sources of electrical signals that can be recorded from the cortical surface or scalp in humans and animals using electroencephalography.

TAKE-HOME MESSAGES

- Glial cells form myelin around the axons of neurons. Myelin enables the rapid transmission of action potentials down an axon and increases the distance over which transmission can occur.
- Neurons communicate with other neurons and cells at specialized structures called synapses, where chemical and electrical signals can be conveyed between neurons.
- The electrical gradient across a neuron's membrane results from the asymmetrical distribution of ions. The electrical difference across the membrane is the basis of the resting potential, the voltage difference across the neuronal membrane during rest (i.e., not during any phase of the action potential).
- Ion channels, formed by transmembrane proteins, can be either passive (always open) or gated (open only in the presence of electrical, chemical, or physical stimuli).
- Synaptic inputs result in postsynaptic potentials, and current to flow in the postsynaptic neuron.
- Postsynaptic currents can depolarize the axon hillock region, generating an action potential.

- Action potentials are all-or-none phenomena: The amplitude of the action potential does not depend on the size of the triggering depolarization, as long as that depolarization reaches the threshold for initiating the action potential.
- Nodes of Ranvier are the spaces between sheaths of myelin where voltage-gated Na^+ and K^+ channels are located and action potentials occur.
- Postsynaptic potentials lead to action potentials but also can be measured from large populations of neurons by electrodes located some distance away, such as the scalp, as when the oscillatory signals in an electroencephalogram (EEG) are being recorded.

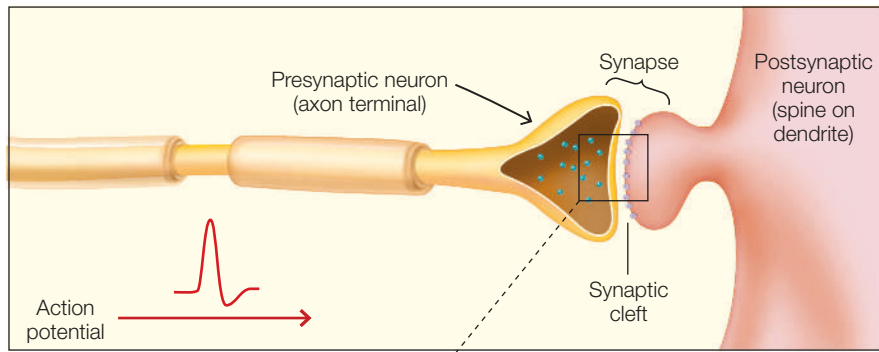
2.2 Synaptic Transmission

Neurons communicate with other neurons, with muscles, or with glands at synapses, and the transfer of a signal from the axon terminal of one neuron to the next neuron is called *synaptic transmission*. There are two major kinds of synapses—chemical and electrical—each using very different mechanisms for synaptic transmission.

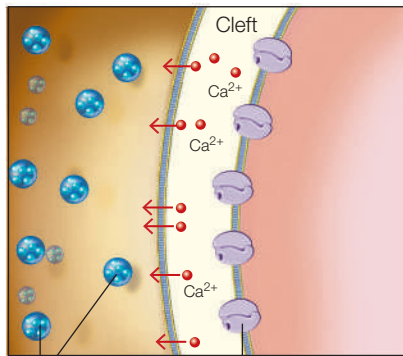
Chemical Transmission

Most neurons send a signal to the cell across the synapse by releasing chemical neurotransmitters into the **synaptic cleft**, the gap between neurons at the synapse. The general mechanism is as follows: The arrival of the action potential at the axon terminal leads to depolarization of the terminal membrane, causing voltage-gated Ca^{2+} channels to open. The opening of these channels triggers small **vesicles** containing neurotransmitter to fuse with the membrane at the synapse and release the transmitter into the synaptic cleft. Different neurons produce and release different neurotransmitters, and some may release more than one type at a time, in what is called co-transmission. The transmitter diffuses across the cleft and, on reaching the postsynaptic membrane, binds with specific receptors embedded in it (**Figure 2.13**).

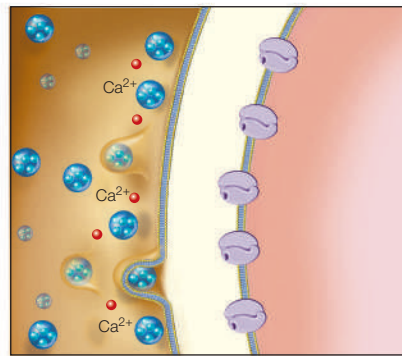
There are two types of postsynaptic receptors: ligand-gated ion channels where neurotransmitter binding directly gates (opens) the ion channel, and G protein-coupled receptors (GPCRs) where biochemical signals indirectly cause the gating of ion channels; G proteins are those that bind the guanine nucleotides GDP and GTP (guanosine di- and triphosphate) and act as molecular switches in cells. Specific neurotransmitters bind to each type of postsynaptic receptor. In ligand-gated ion channels, binding induces a conformational change in the receptor. The change in shape opens an ion channel, resulting in an influx of ions



- ① Action potential depolarizes the terminal membrane, which causes Ca^{2+} to flow into the cell.
- ② Ca^{2+} causes vesicles to bind with cell membrane.



Vesicles containing neurotransmitter Receptors in postsynaptic membrane



- ③ Neurotransmitter is released by exocytosis into the synaptic cleft.
- ④ Transmitter binds with receptor.

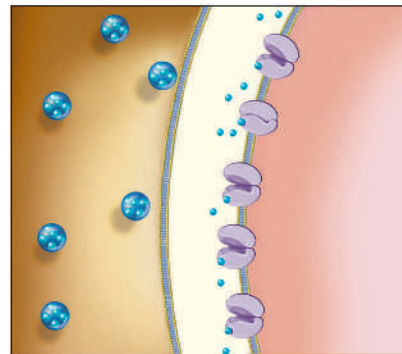
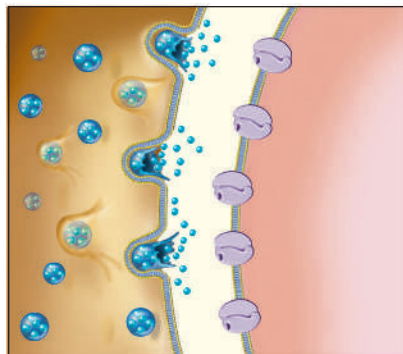


FIGURE 2.13 Neurotransmitter release at the synapse, into the synaptic cleft.

The synapse consists of various specializations where the presynaptic and postsynaptic membranes are close together. When the action potential invades the axon terminals, it causes voltage-gated Ca^{2+} channels to open (1), triggering vesicles to bind to the presynaptic membrane (2). Neurotransmitter is released into the synaptic cleft by exocytosis and diffuses across the cleft (3). Binding of the neurotransmitter to receptor molecules in the postsynaptic membrane completes the process of transmission (4).

leading to either depolarization (excitation) or hyperpolarization (inhibition) of the postsynaptic cell (**Figure 2.14**). Hyperpolarization of the postsynaptic neuron produces an inhibitory postsynaptic potential (IPSP).

Excitatory and inhibitory neurons are also capable of modulating functions through the GPCRs. There are over 1,000 different GPCRs, giving us an idea of the complexity of the system. The particular GPCRs that are present depend on the neuron and where it is located. Each type of GPCR is activated by a specific signaling molecule, which could be a neurotransmitter, a neuropeptide (a small protein-like molecule secreted by neurons or glial cells), or a neurosteroid, among other possible signals.

When a signaling molecule specifically binds to its GPCR, the conformational change activates a G protein within the cell, which in turn activates or regulates a specific target protein, typically an enzyme, which produces a diffusible molecule of some sort called a *second messenger*. The second messenger, in turn, triggers a biochemical cascade of reactions. While directly gated channels mediate fast signaling, measured in milliseconds, GPCR-mediated signaling is slower, occurring over hundreds of milliseconds or even seconds and producing longer-lasting modulatory changes to the functional state. For example, the neurotransmitter epinephrine binds to a particular GPCR. Once bound, a G protein is activated that seeks

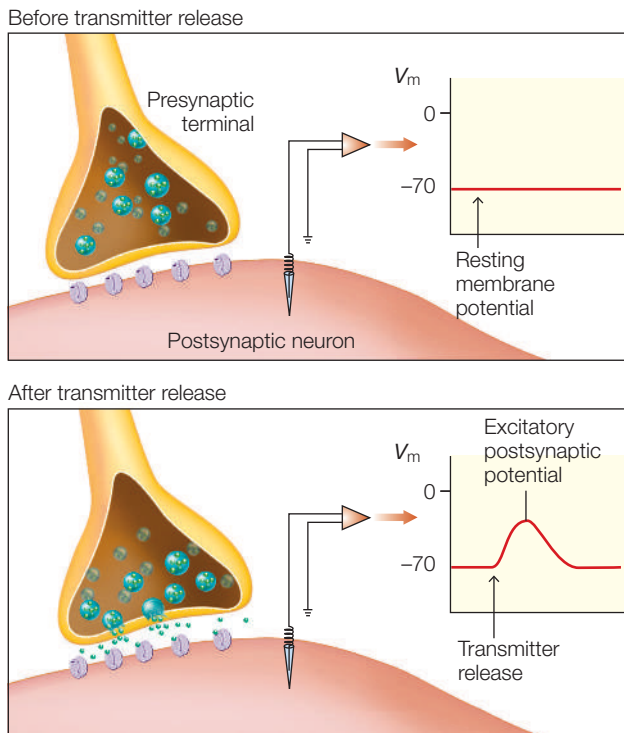


FIGURE 2.14 Neurotransmitter leading to a postsynaptic potential. The binding of neurotransmitter to the postsynaptic membrane receptors changes the membrane potential (V_m). These postsynaptic potentials can be either excitatory (depolarizing the membrane), as shown here, or inhibitory (hyperpolarizing the membrane).

out the protein adenylate cyclase and activates it. Activated adenylate cyclase turns ATP into cAMP (cyclic adenosine monophosphate), which acts as a second messenger of information instructing the postsynaptic neuron.

NEUROTRANSMITTERS While you may have heard of a few of the classic **neurotransmitters**, more than 100 have been identified. What makes a molecule a neurotransmitter?

- It is synthesized by and localized within the presynaptic neuron, and stored in the presynaptic terminal before release.
- It is released by the presynaptic neuron when action potentials depolarize the terminal (mediated primarily by Ca^{2+}).
- The postsynaptic neuron contains receptors specific for it.
- When artificially applied to a postsynaptic cell, it elicits the same response that stimulating the presynaptic neuron would.

Biochemical classification of neurotransmitters. Some neurotransmitters are amino acids: aspartate, gamma-aminobutyric acid (GABA), glutamate, and glycine. Another category of neurotransmitters, called *biogenic amines*, includes dopamine, norepinephrine, and epinephrine (these three are known as the catecholamines), serotonin

(5-hydroxytryptamine), and histamine. Acetylcholine (ACh) is a well-studied neurotransmitter that is in its own biochemical class. Another large group of neurotransmitters consists of slightly larger molecules, the *neuropeptides*, which are made up of strings of amino acids. More than 100 neuropeptides are active in the mammalian brain, and they are divided into five groups:

1. *Tachykinins* (brain-gut peptides, which are peptides secreted by endocrine cells and enteric neurons in the GI tract and also neurons in the central nervous system). This group includes substance P, which affects vasoconstriction and is a spinal neurotransmitter involved in pain.
2. *Neurohypophyseal hormones*. Oxytocin and vasopressin are in this group. The former is involved in mammary functions and has been tagged the “love hormone” for its role in pair bonding and maternal behaviors; the latter is an antidiuretic hormone.
3. *Hypothalamic releasing hormones*. This group includes corticotropin-releasing hormone, involved in the stress response; somatostatin, an inhibitor of growth hormone; and gonadotropin-releasing hormone, involved with the development, growth, and functioning of the body’s reproductive processes.
4. *Opioid peptides*. This group is named for its similarity to opiate drugs, and these peptides bind to opiate receptors. It includes the endorphins and enkephalins.
5. *Other neuropeptides*. This group includes peptides that do not fit neatly into another category, such as insulins, secretins (e.g., glucagon), and gastrins.

Some neurons produce only one type of neurotransmitter, but others produce multiple kinds. Neurons that do produce particular neurotransmitters sometimes form distinct systems, such as the cholinergic system, the noradrenergic system, the dopaminergic system, and the serotonergic system. When a neurotransmitter system is activated, large areas of the brain can be affected (**Figure 2.15**). Neurons that produce more than one type of transmitter may release them together or separately, depending on the conditions of stimulation. For example, the rate of stimulation by the action potential can induce the release of a specific neurotransmitter.

Functional classification of neurotransmitters. As mentioned earlier, the effect of a neurotransmitter on the postsynaptic neuron is determined by the postsynaptic receptor’s properties rather than by the transmitter itself. A particular neurotransmitter may have more than one type of postsynaptic receptor to which it binds, mediating different responses. Thus, the same neurotransmitter released from the same presynaptic neuron onto two different postsynaptic cells might cause one to increase

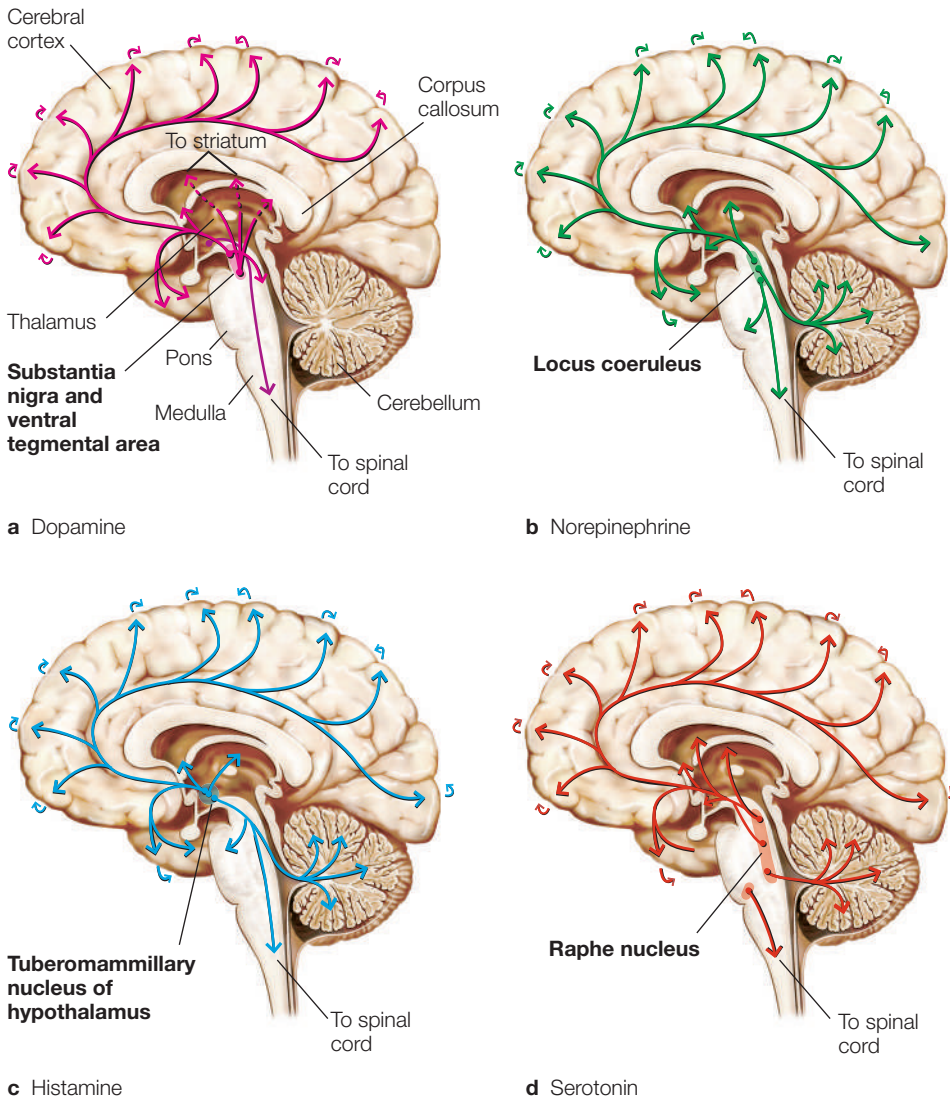


FIGURE 2.15 Major projection pathways of the biogenic amine neurotransmitter systems in the human brain.

Shown are the projections of the dopamine (a), norepinephrine (b), histamine (c), and serotonin (d) systems using the neurotransmitters. The views are midsagittal cuts through the human brain, showing the medial surface of the right hemisphere; the frontal pole is at left. In each image, the primary source of the biogenic amine is in bold type.

firing and the other to decrease firing, depending on the receptors to which the transmitter binds.

The effects also depend on the concentration of the transmitter; the type, number, and density of the receptors; whether, when, and which co-neurotransmitters are also released; and the long-range connections of the neuron. For example, if different co-transmitters are released—one binding to a directly gated receptor with fast signaling and the other to a GPCR with slower signaling—they may produce opposite actions, and their overall combined effect may produce many possible outcomes, even complementary effects. Nevertheless, neurotransmitters can be classified not only biochemically, but also by the *typical effect* that they induce in the postsynaptic neuron.

Neurotransmitters that usually have an excitatory effect include ACh, the catecholamines, glutamate, histamine, serotonin, and some of the neuropeptides. Neurotransmitters that are typically inhibitory include GABA, glycine, and some of the neuropeptides. Some

neurotransmitters act directly to excite or inhibit a post-synaptic neuron, but other neurotransmitters act only in concert with other factors. These are sometimes referred to as *conditional neurotransmitters* because their action is conditioned on the presence of another transmitter in the synaptic cleft or activity in the neural circuit. These types of mechanisms permit the nervous system to achieve complex modulations of information processing by modulating neurotransmission.

Some common neurotransmitters and their functions.

The primary players in the balancing act between excitation and inhibition are glutamate and GABA. *Glutamate* is released by the pyramidal cells of the cortex, the most common cortical neurons. As a result, glutamate is the most prevalent neurotransmitter and is found in most of the fast excitatory synapses in the brain and spinal cord. A few different types of receptors bind glutamate, and some of these are found in modifiable synapses (i.e., ones that can change in strength) involved in learning and memory. Too much