CELLS OF THE NERVOUS SYSTEM

The first part of this chapter is devoted to a description of the most important cells of the nervous system—neurons and their supporting cells—and to the blood–brain barrier, which provides them with chemical isolation from the rest of the body.

Neurons

Basic Structure

The neuron (nerve cell) is the information-processing and information-transmitting element of the nervous system. Neurons come in many shapes and varieties, according to the specialized jobs they perform. Neurons usually have, in one form or another, the following four structures or regions: (1) cell body, or soma; (2) dendrites; (3) axon; and (4) terminal buttons.

Soma. The **soma** (cell body) contains the nucleus and much of the machinery that provides for the life processes of the cell. (See ***Figure 2.1.***) Its shape varies considerably in different kinds of neurons.

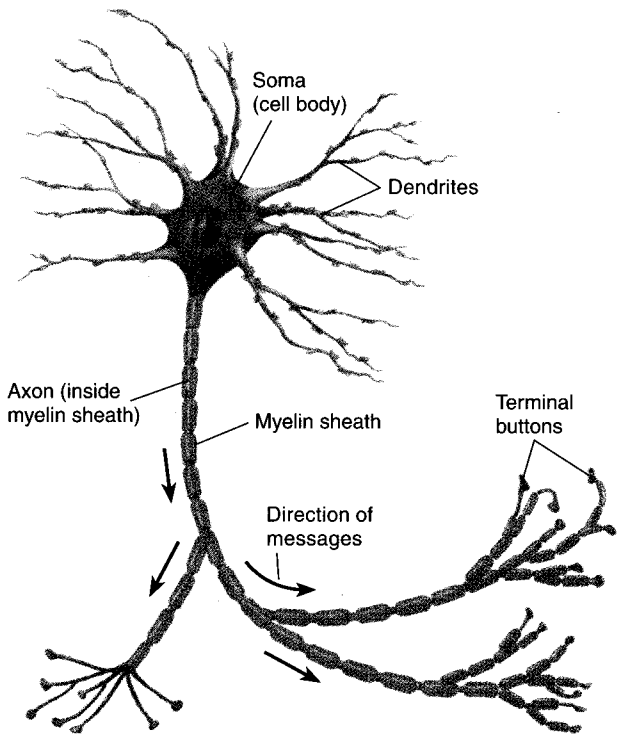

Figure 2.1
The principal parts of a multipolar neuron.

Dendrites. *Dendron* is the Greek word for tree, and the **dendrites** of the neuron look very much like trees. (See ***Figure 2.1.***) Neurons "converse" with one another, and dendrites serve as important recipients of these messages. The messages that pass from neuron to neuron are transmitted across the **synapse,** a junction between the terminal buttons (described later) of the sending cell and a portion of the somatic or dendritic membrane of the receiving cell. (The word *synapse* derives from the Greek *sunaptein,* "to join together.") Communication at a synapse proceeds in one direction: from the terminal button to the membrane of the other cell. (Like many general rules, this one has some exceptions. As we will see in Chapter 4, some synapses pass information in both directions.)

Axon. The **axon** is a long, slender tube, often covered by a *myelin sheath.* (The myelin sheath is described later.) The axon carries information from the cell body to the terminal buttons. (See ***Figure 2.1.***) The basic message it carries is called an *action potential.* This function is an important one and will be described in more detail later in the chapter. For now, it suffices to say that it is a brief electrical/chemical event that starts at the end of the axon next to the cell body and travels toward the terminal buttons. The action potential is like a brief pulse; in a given axon, the action potential is always the same size and duration. When it reaches a point where the axon branches, it splits but does not diminish in size. Each branch receives a *full-strength* action potential.

Like dendrites, axons and their branches come in different shapes. In fact, the three principal types of neurons are classified according to the way in which their axons and dendrites leave the soma. The neuron depicted in Figure 2.1 is the most common type found in the central nervous system; it is a **multipolar neuron.** In this type of neuron the somatic membrane gives rise to one axon but to the trunks

soma The cell body of a neuron, which contains the nucleus.

dendrite A branched, treelike structure attached to the soma of a neuron; receives information from the terminal buttons of other neurons.

synapse A junction between the terminal button of an axon and the membrane of another neuron.

axon The long, thin, cylindrical structure that conveys information from the soma of a neuron to its terminal buttons.

multipolar neuron A neuron with one axon and many dendrites attached to its soma.

of many dendritic trees. **Bipolar neurons** give rise to one axon and one dendritic tree, at opposite ends of the soma. (See *Figure 2.2a.*) These neurons are usually sensory; that is, their dendrites detect events occurring in the environment and communicate information about these events to the central nervous system.

The third type of nerve cell is the **unipolar neuron.** It has only one stalk, which leaves the soma and divides into two branches a short distance away. (See *Figure 2.2b.*) Unipolar neurons, like bipolar neurons, transmit sensory information from the environment to the CNS. The arborizations (treelike branches) farther from the CNS are dendrites; the arborizations within the CNS end in terminal buttons. The dendrites of most unipolar neurons detect touch, temperature changes, and other sensory events that affect the skin. Other unipolar neurons detect events in our joints, muscles, and internal organs.

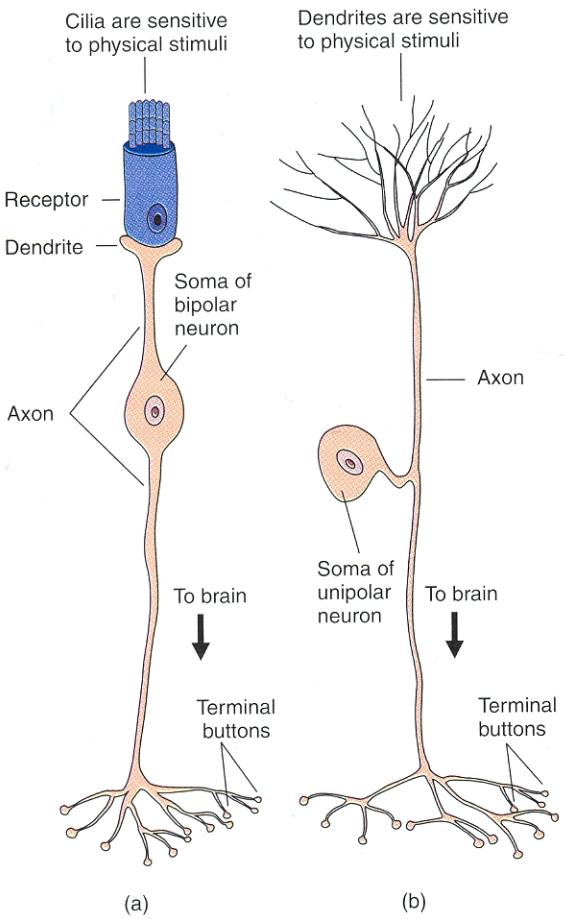

Figure 2.2
Neurons. (a) A bipolar neuron, primarily found in sensory systems (for example, vision and audition). (b) A unipolar neuron, found in the somatosensory system (touch, pain, and the like).

Terminal Buttons. Most axons divide and branch many times. At the ends of the twigs are found little knobs called **terminal buttons.** (Some neuroscientists prefer the original French word *bouton.*) Terminal buttons have a very special function: When an action potential traveling down the axon reaches them, they secrete a chemical called a **transmitter substance,** also known as a **neurotransmitter.** This chemical (there are many different ones in the CNS) either excites or inhibits the receiving cell and thus helps determine whether an action potential occurs in its axon. Details of this process will be described later in this chapter.

An individual neuron receives information from the terminal buttons of axons of other neurons—and the terminal buttons of *its* axons form synapses with other neurons. A neuron may receive information from dozens or even hundreds of other neurons, each of which can form a large number of synaptic connections with it. Figure 2.3 illustrates the nature of these connections. As you can see, terminal buttons can form synapses on the membrane of the dendrites or the soma. (See *Figure 2.3.*)

Internal Structure

Figure 2.4 illustrates the internal structure of a typical multipolar neuron. (See *Figure 2.4* on page 24.) The **membrane** defines the boundary of the cell. It consists of a double layer of lipid (fatlike) molecules. Floating in it are a variety of protein molecules that have special functions. Some proteins detect substances outside the cell (such as hormones) and pass information about the presence of these substances to the interior of the cell. Other proteins control access to the interior of the cell, permitting some substances to enter but barring others. Still other proteins act as transporters, actively carrying certain molecules into or out of the cell. Because the membrane of the neuron is especially important in the transmission of information,

bipolar neuron A neuron with one axon and one dendrite attached to its soma.

unipolar neuron A neuron with one axon attached to its soma; the axon divides, with one branch receiving sensory information and the other sending the information into the central nervous system.

terminal button The bud at the end of a branch of an axon; forms synapses with another neuron; sends information to that neuron.

transmitter substance/neurotransmitter A chemical that is released by a terminal button; has an excitatory or inhibitory effect on another neuron.

membrane A structure consisting principally of lipid molecules that defines the outer boundaries of a cell and also constitutes many of the cell organelles, such as the Golgi apparatus.

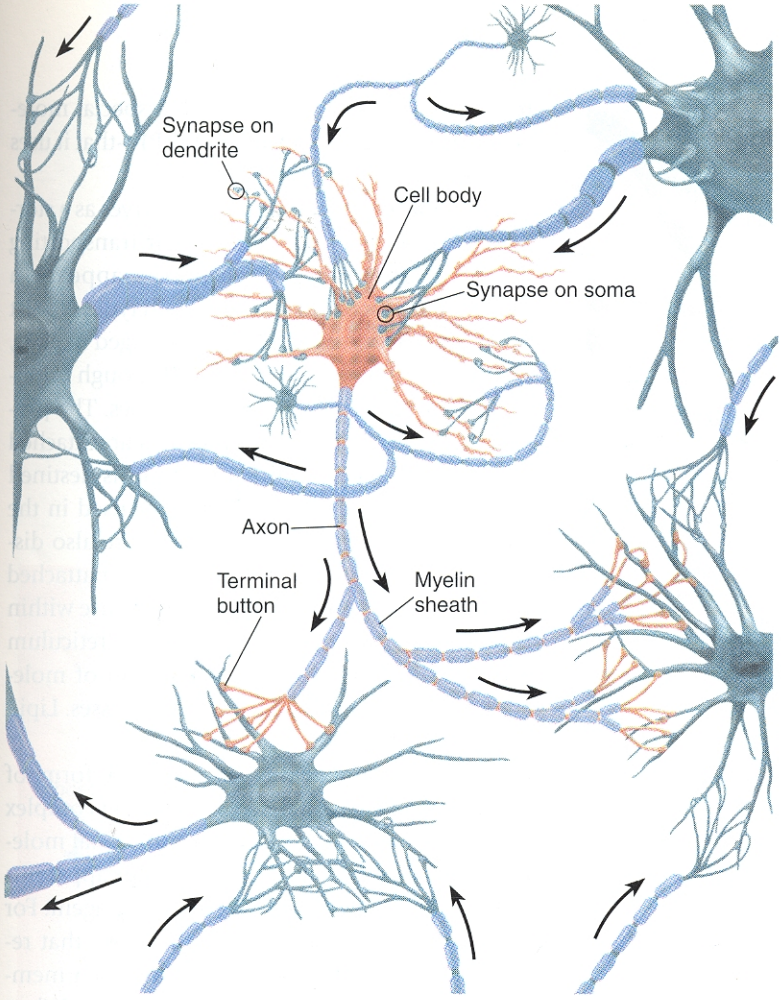

Figure 2.3
An overview of the synaptic connections between neurons. The arrows represent the directions of the flow of information.

its characteristics will be discussed in more detail later in this chapter.

The **nucleus** ("nut") of the cell is round or oval and is covered by the nuclear membrane. The nucleolus and the chromosomes reside here. The **nucleolus** manufactures **ribosomes,** small structures that are involved in protein synthesis. The **chromosomes,** which consist of long strands of **deoxyribonucleic acid (DNA),** contain the organism's genetic information. When they are active, portions of the chromosomes (**genes**) cause production of another complex molecule, **messenger ribonucleic acid (mRNA),** which receives a copy of the information stored at that location. The mRNA leaves the nuclear membrane and attaches to ribosomes, where it causes the production of a particular protein. (See *Figure 2.5* on page 25.)

Proteins are important in cell functions. As well as providing structure, proteins serve as **enzymes,** which direct the chemical processes of a cell by controlling chemical reactions. Enzymes are special protein molecules that act as catalysts; that is, they cause a chemical reaction to take place without becoming a part of the final product themselves. Because cells contain the constituents needed to synthesize an enormous variety of compounds, the ones that cells actually do produce depend primarily on the particular enzymes that are present. Furthermore, there are enzymes that break molecules apart as well as put them together; the enzymes present in a particular region of a cell thus determine which molecules remain intact. For example,

$$A + B \underset{Y}{\overset{X}{\rightleftharpoons}} AB$$

In this reversible reaction the relative concentrations of enzymes X and Y determine whether the complex substance AB or its constituents, A and B, will predominate. Enzyme X makes A and B join together; enzyme Y splits AB apart. (Energy may also be required to make the reactions proceed.)

The bulk of the cell consists of cytoplasm. **Cytoplasm** is complex and varies considerably across types of cells, but it can be most easily characterized as a jellylike, semiliquid substance that fills the space outlined by the mem-

nucleus A structure in the central region of a cell, containing the nucleolus and chromosomes.

nucleolus *(new **clee** o lus)* A structure within the nucleus of a cell that produces the ribosomes.

ribosome *(**ry** bo soam)* A cytoplasmic structure, made of protein, that serves as the site of production of proteins translated from mRNA.

chromosome A strand of DNA, with associated proteins, found in the nucleus; carries genetic information.

deoxyribonucleic acid (DNA) *(dee ox ee **ry** bo new **clay** ik)* A long, complex macromolecule consisting of two interconnected helical strands; along with associated proteins, strands of DNA constitute the chromosomes.

gene The functional unit of the chromosome, which directs synthesis of one or more proteins.

messenger ribonucleic acid (mRNA) A macromolecule that delivers genetic information concerning the synthesis of a protein from a portion of a chromosome to a ribosome.

enzyme A molecule that controls a chemical reaction, combining two substances or breaking a substance into two parts.

cytoplasm The viscous, semiliquid substance contained in the interior of a cell.

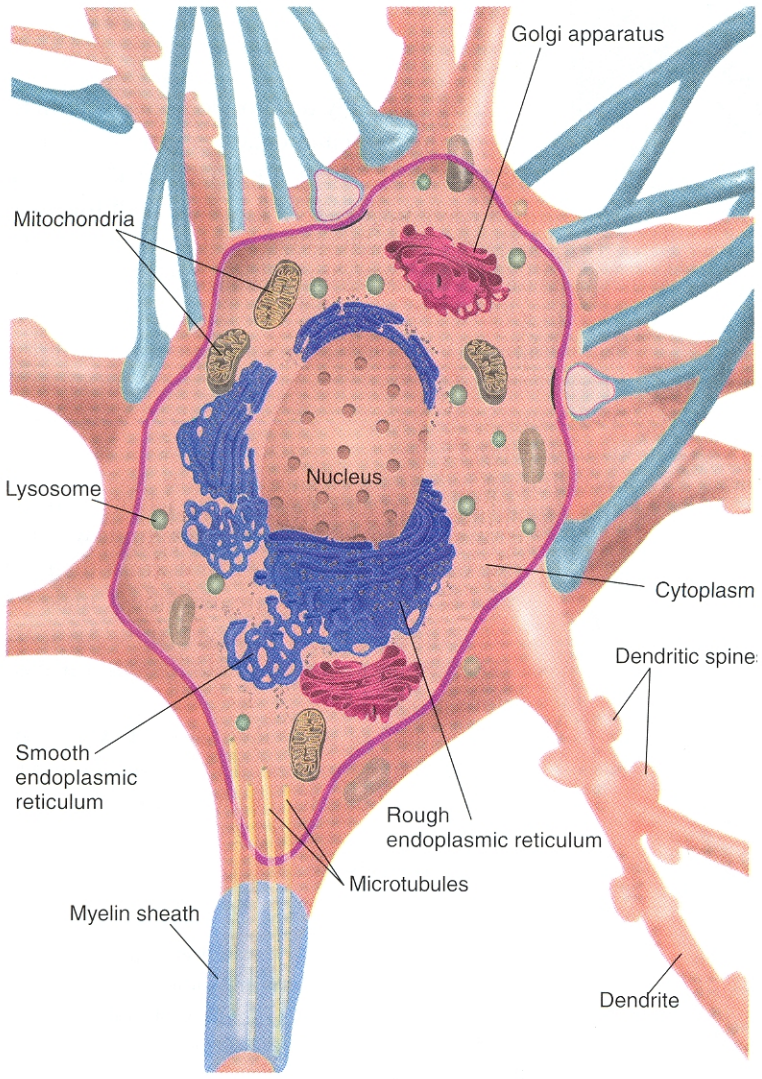

Figure 2.4
The principal internal structures of a multipolar neuron.

brane. It contains small, specialized structures, just as the body contains specialized organs. The most important of these are described next.

Mitochondria (singular: mitochondrion) are shaped like oval beads and are formed of a double membrane. The inner membrane is wrinkled, and the wrinkles make up a set of shelves *(cristae)* that fill the inside of the bead. Mitochondria perform a vital role in the economy of the cell; many of the biochemical steps involved in the extraction of energy from the breakdown of nutrients take place on the cristae. Most cell biologists believe that many eons ago mitochondria were free-living organisms that came to "infect" larger cells. Because the mitochondria could extract energy more efficiently than the larger cells, they became useful to them and eventually became a permanent part of the cells. The cell provides mitochondria with nutrients, and the mitochondria provide the cell with a special molecule—**adenosine triphosphate (ATP)**—that it uses as its immediate source of energy.

Endoplasmic reticulum, which serves as a storage reservoir and as a channel for transporting chemicals through the cytoplasm, appears in two forms: rough and smooth. Both types consist of parallel layers of membrane, arranged in pairs, of the sort that encloses the cell. Rough endoplasmic reticulum contains ribosomes. The protein produced by the ribosomes that are attached to the rough endoplasmic reticulum is destined to be transported out of the cell or used in the membrane. Unattached ribosomes are also distributed around the cytoplasm; the unattached variety appears to produce protein for use within the neuron. The smooth endoplasmic reticulum provides channels for the segregation of molecules involved in various cellular processes. Lipid (fatlike) molecules are produced here.

The **Golgi apparatus** is a special form of smooth endoplasmic reticulum. Some complex molecules, made up of simpler individual molecules, are assembled here. The Golgi apparatus also serves as a wrapping or packaging agent. For example, secretory cells (such as those that release hormones) wrap their product in a membrane produced by the Golgi apparatus. When the cell secretes its products, it uses a process called **exocytosis** (*exo*, "outside"; *cyto*, "cell"; *-osis*, "process"). Briefly stated, the container migrates to the outer membrane of the cell, fuses with it, and bursts, spilling the product into the fluid sur-

mitochondria An organelle responsible for extracting energy from nutrients.

adenosine triphosphate (ATP) *(ah **den** o seen)* A molecule of prime importance to cellular energy metabolism; its breakdown liberates energy.

endoplasmic reticulum Parallel layers of membrane found within the cytoplasm of a cell. Rough endoplasmic reticulum contains ribosomes and is involved with production of proteins that are secreted by the cell. Smooth endoplasmic reticulum is the site of synthesis of lipids and provides channels for the segregation of molecules involved in various cellular processes.

Golgi apparatus *(**goal** jee)* A complex of parallel membranes in the cytoplasm that wraps the products of a secretory cell.

exocytosis *(**ex** o sy **toe** sis)* The secretion of a substance by a cell through means of vesicles; the process by which neurotransmitters are secreted.

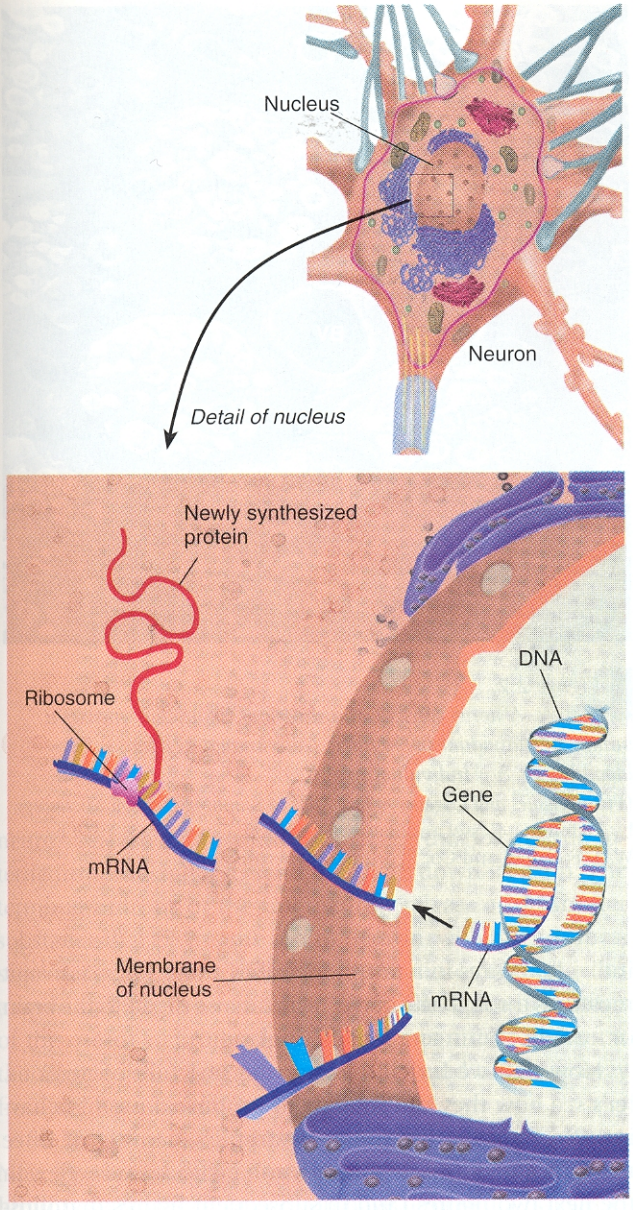

Figure 2.5
Protein synthesis. When a gene is active, a copy of the information is made onto a molecule of messenger RNA. The mRNA leaves the nucleus and attaches to a ribosome, where the protein is produced.

rounding the cell. As we will see, neurons are secretory cells; they communicate with one another by secreting chemicals by this means. Thus, I will describe the process of exocytosis in more detail later in this chapter. The Golgi apparatus also produces **lysosomes,** small sacs that contain enzymes that break down substances no longer needed by the cell. These products are then recycled or excreted from the cell.

If a neuron grown in a tissue culture is exposed to a detergent, the lipid membrane and much of the interior of the cell dissolve away, leaving a matrix of insoluble strands of protein. This matrix, called the **cytoskeleton,** gives the neuron its shape. The cytoskeleton is made of three kinds of protein strands, linked to each other and forming a cohesive mass. The thickest of these strands, **microtubules,** are bundles of thirteen filaments arranged around a hollow core. Each filament consists of long chains of beads of a protein called *tubulin.* **Neurofilaments** are made of long, continuous strands of protein similar to those found in hair. **Microfilaments,** the thinnest fibers found in the cytoskeleton, consist of a double strand of *actin,* one of the proteins responsible for muscular contractions. Microfilaments form a meshwork just inside the membrane that holds membrane-bound proteins in place.

Axons can be extremely long, relative to their diameter and the size of the soma. For example, the longest axon in a human stretches from the foot to a region located in the base of the brain. Because terminal buttons need some items that can be produced only in the soma, there must be a system that can transport these items rapidly and efficiently through the axoplasm (that is, the cytoplasm of the axon). This system is referred to as **axoplasmic transport,** an active process by which substances are propelled along microtubules that run the length of the axon. Movement from the soma to the terminal buttons is called **anterograde** axoplasmic transport. (*Antero-* means "toward the front.") This form of transport is accomplished by molecules of a protein called *kinesin.* In the cell body, kinesin molecules, which resemble a pair of legs and feet, attach to the item being transported down the axon. The kinesin molecule then walks down a microtubule, carrying the cargo to its destination.

lysosome *(**lye** so soam)* An organelle surrounded by membrane; contains enzymes that break down waste products.

cytoskeleton Formed of microtubules, neurofilaments, and microfilaments, linked to each other and forming a cohesive mass that gives a cell its shape.

microtubule *(my kro **too** bule)* A long strand of bundles of protein filaments arranged around a hollow core; part of the cytoskeleton and involved in transporting substances from place to place within the cell.

neurofilament One of the fibers of the cytoskeleton, made of long, continuous strands of protein similar to those found in hair.

microfilament The thinnest of the fibers of the cytoskeleton; forms a meshwork just inside the membrane that holds membrane-bound proteins in place.

axoplasmic transport An active process by which substances are propelled along microtubules that run the length of the axon.

anterograde In a direction along an axon from the cell body toward the terminal buttons.

Energy is supplied by ATP molecules produced by the mitochondria. (See ***Figure 2.6.***) Another protein, *dynein*, carries substances from the terminal buttons to the soma, a process known as **retrograde** axoplasmic transport. Anterograde axoplasmic transport is remarkably fast: up to 500 mm per day. Retrograde axoplasmic transport is about half as fast as anterograde transport.

Neural Communication: An Overview

The central nervous system communicates with the rest of the body through nerves attached to the brain and to the spinal cord. Nerves are bundles of many thousands of individual fibers, all wrapped in a tough, protective membrane. Under a microscope, nerves look something like telephone cables, with their bundles of wires. (See ***Figure 2.7.***) Like the individual wires in a telephone cable, nerve fibers transmit messages through the nerve, from a sense organ to the brain or from the brain to a muscle or gland.

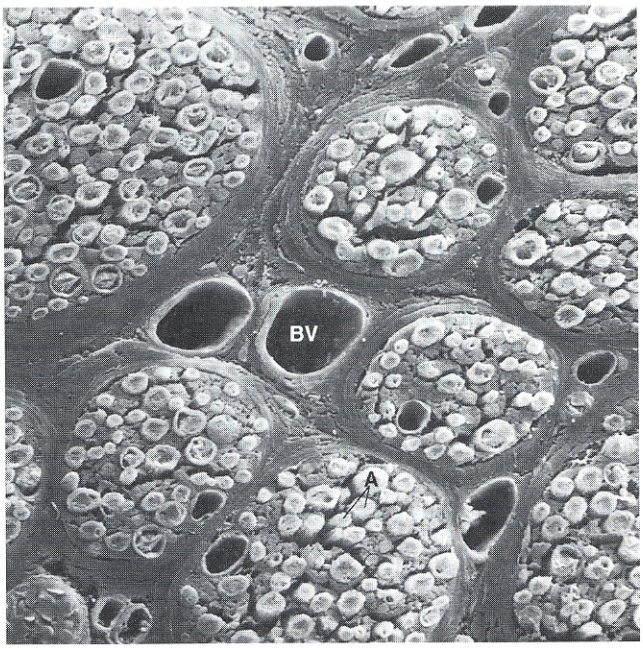

Figure 2.7
Nerves. A nerve consists of a sheath of tissue that encases a bundle of individual nerve fibers (also known as axons). BV = blood vessel; A = individual axons.
(From *Tissues and Organs: A Text-Atlas of Scanning Electron Microscopy*, by Richard G. Kessel and Randy H. Kardon. Copyright © 1979 by W.H. Freeman and Co. Reprinted by permission.)

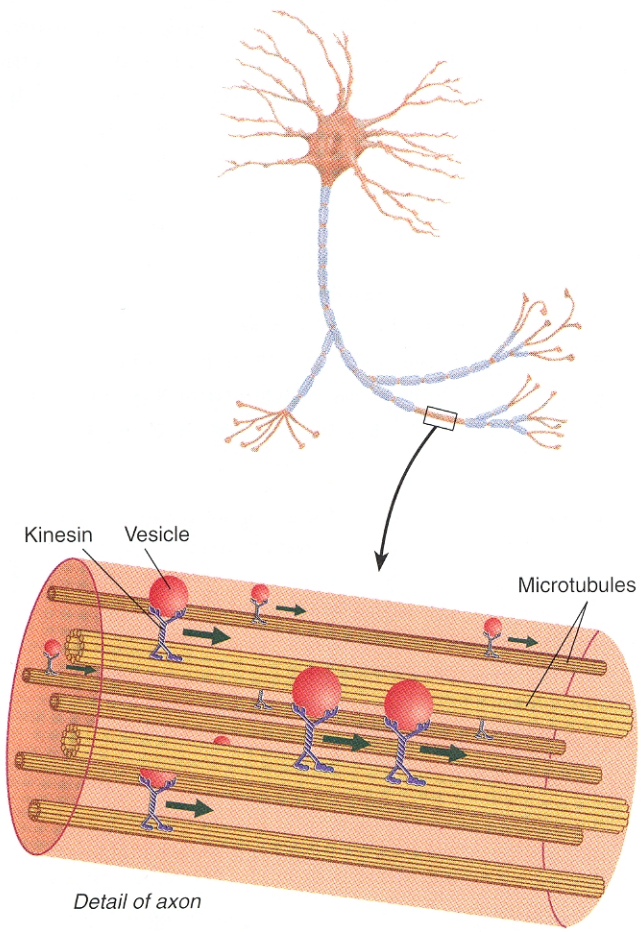

Figure 2.6
Fast axoplasmic transport. Kinesin molecules "walk" down a microtubule, carrying their cargo from the soma to the terminal buttons. Another protein, dynein, carries substances from the terminal buttons to the soma.

Now that we have looked at the structure of neurons, let's see how they can interact to produce a useful behavior. We begin by examining a simple assembly of three neurons and a muscle that control a withdrawal reflex. In the next two figures (and in subsequent figures that illustrate simple neural circuits) neurons are depicted in shorthand fashion as several-sided stars. The points of these stars represent dendrites, and only one or two terminal buttons are shown at the end of the axon. The sensory neuron in this example detects painful stimuli. When its dendrites are stimulated by a noxious stimulus (such as contact with a hot object), it sends messages down the axon to the terminal buttons, which are located in the spinal cord. (You will recognize this cell as a unipolar neuron; see ***Figure 2.8.***) The terminal buttons of the sensory

retrograde In a direction along an axon from the terminal buttons toward the cell body.

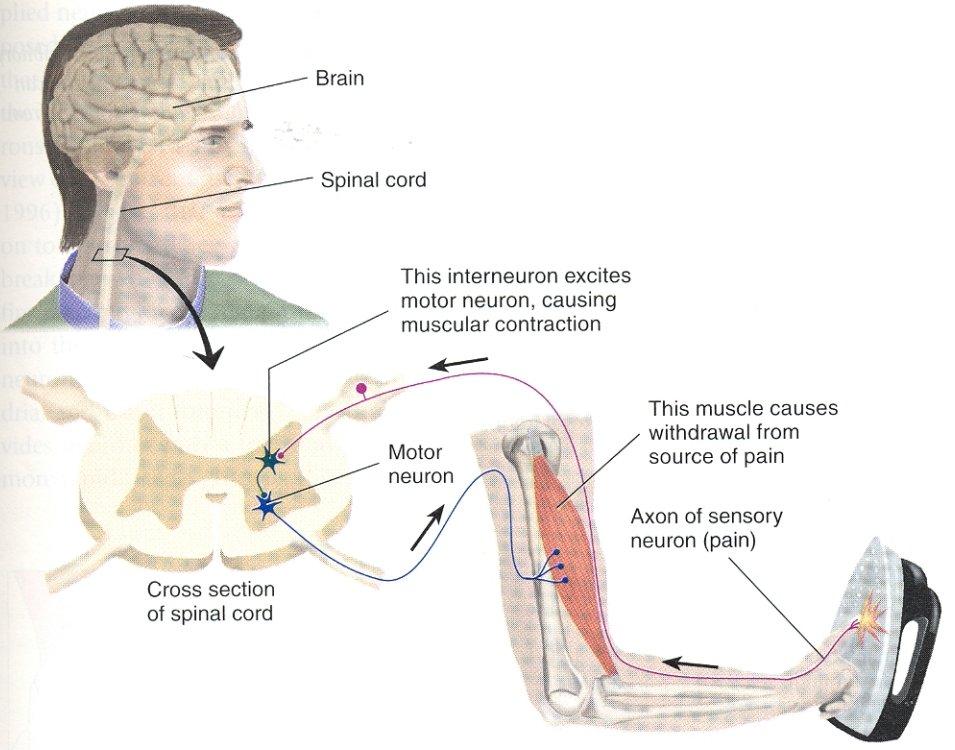

Figure 2.8
A withdrawal reflex, a simple example of a useful function of the nervous system. The painful stimulus causes the hand to pull away from the hot iron.

neuron release a transmitter substance that excites the interneuron, causing it to send messages down its axon. The terminal buttons of the interneuron release a transmitter substance that excites the motor neuron, which sends messages down its axon. The axon of the motor neuron joins a nerve and travels to a muscle. When the terminal buttons of the motor neuron release their transmitter substance, the muscle cells contract, causing the hand to move away from the hot object. (See ***Figure 2.8.***)

So far, all of the synapses have had excitatory effects. Now let us complicate matters a bit to see the effect of inhibitory synapses. Suppose you have removed a hot casserole from the oven. As you start over to the table to put it down, the heat begins to penetrate the rather thin potholders you are using. The pain caused by the hot casserole triggers a withdrawal reflex that tends to make you drop it. And yet you manage to keep hold of it long enough to get to the table and put it down. What prevented your withdrawal reflex from making you drop the casserole on the floor?

The pain from the hot casserole increases the activity of excitatory synapses on the motor neurons, which tends to cause the hand to pull away from the casserole. However, this excitation is counteracted by *inhibition*, supplied by another source—the brain. The brain contains neural circuits that recognize what a disaster it would be if you dropped the casserole on the floor. These neural circuits send information to the spinal cord that prevents the withdrawal reflex from making you drop the dish.

Figure 2.9 shows how this information reaches the spinal cord. As you can see, an axon from a neuron in the brain reaches the spinal cord, where its terminal buttons form synapses with an inhibitory interneuron. When the neuron in the brain becomes active, it excites this inhibitory interneuron. The interneuron releases an inhibitory transmitter substance, which *decreases* the activity of the motor neuron, blocking the withdrawal reflex. This circuit provides an example of a contest between two competing tendencies: to drop the casserole and to hold on to it. (See ***Figure 2.9.***)

Of course, reflexes are more complicated than this description, and the mechanisms that inhibit them are even more so. And thousands of neurons are involved in this process. The five neurons shown in Figure 2.9 represent many others: Dozens of sensory neurons detect the hot object, hundreds of interneurons are stimulated by their activity, hundreds of motor neurons produce the contraction—and thousands of neurons in the brain must become active if the reflex is to be inhibited. Yet this simple model provides an overview of the process of neural communication, which is described in more detail later in this chapter.

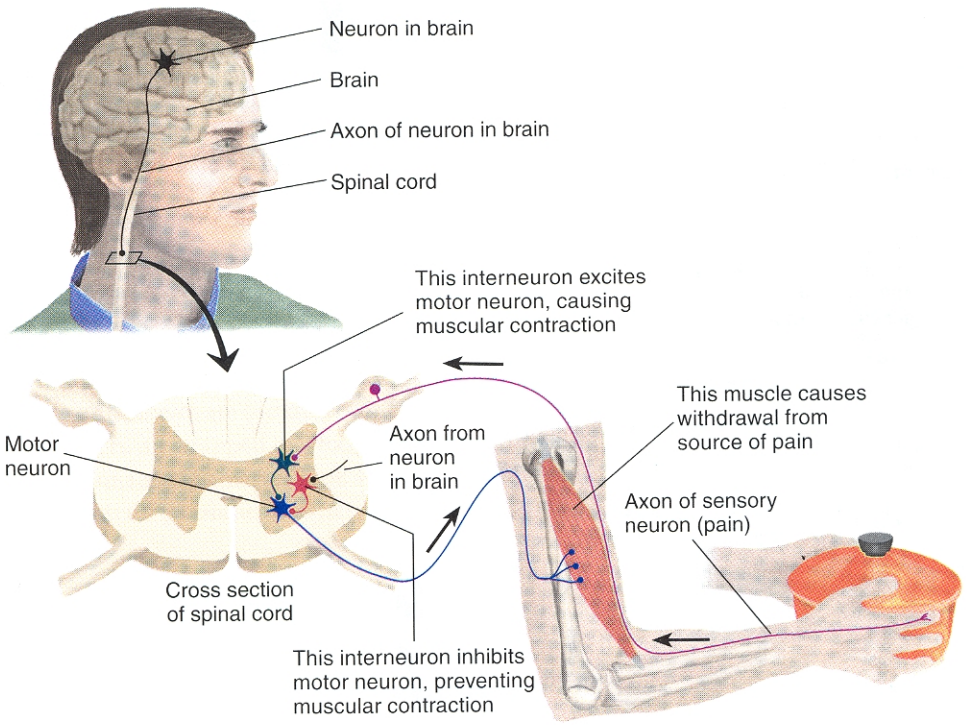

Figure 2.9
The role of inhibition. Inhibitory signals arising from the brain can prevent the withdrawal reflex from causing the person to drop the casserole.

Supporting Cells

Neurons constitute only about half the volume of the CNS. The rest consists of a variety of supporting cells. Because neurons have a very high rate of metabolism but have no means of storing nutrients, they must constantly be supplied with nutrients and oxygen or they will quickly die. Unlike most other cells of the body, neurons cannot be replaced when they die. Thus, the role played by the cells that support and protect neurons is very important to our existence.

Glia

The most important supporting cells of the central nervous system are the *neuroglia*, or "nerve glue." **Glia** (also called *glial cells*) do indeed glue the CNS together, but they do much more than that. Neurons lead a very sheltered existence; they are buffered physically and chemically from the rest of the body by the glial cells. Glial cells surround neurons and hold them in place, controlling their supply of some of the chemicals they need to exchange messages with other neurons; they insulate neurons from one another so that neural messages do not get scrambled; and they even act as housekeepers, destroying and removing the carcasses of neurons that are killed by injury or that die as a result of old age.

There are several types of glial cells, each of which plays a special role in the CNS. The two most important types are *astrocytes* and *oligodendrocytes*. **Astrocyte** means "star cell," and this name accurately describes the shape of these cells. Astrocytes (or *astroglia*) provide physical support to neurons and clean up debris within the brain. They produce some chemicals that neurons need to fulfill their functions. They help control the chemical composition of the fluid surrounding neurons by actively taking up or releasing substances whose concentrations must be kept within critical levels. Finally, astrocytes are involved in providing nourishment to neurons.

Some of the astrocyte's processes (the arms of the star) are wrapped around blood vessels; other processes are wrapped around parts of neurons, so that the somatic and dendritic membranes of neurons are largely surrounded by astrocytes. This arrangement suggested to the Italian histologist Camillo Golgi (1844–1926) that astrocytes sup-

glia (*glee ah*) The supporting cells of the central nervous system.

astrocyte A glial cell that provides support for neurons of the central nervous system, provides nutrients and other substances, and regulates the chemical composition of the extracellular fluid.

plied neurons with nutrients from the capillaries and disposed of their waste products (Golgi, 1903). He thought that nutrients passed from capillaries to the cytoplasm of the astrocytes and then through the cytoplasm to the neurons. Recent evidence suggests that Golgi was right. A review of the current literature (Tsacopoulos and Magistretti, 1996) suggests that astrocytes do more than pass glucose on to neurons: They receive glucose from capillaries and break it down to *lactate,* the chemical produced during the first step of glucose metabolism. They then release lactate into the extracellular fluid that surrounds neurons, and neurons take up the lactate, transport it to their mitochondria, and use it for energy. Presumably, this process provides neurons with a fuel that they can metabolize even more rapidly than glucose. (See ***Figure 2.10.***) In addition, astrocytes store a small amount of a carbohydrate called *glycogen* that can be broken down to glucose and then to lactate when the metabolic rate of neurons in their vicinity is especially high.

Besides having a possible role in transporting chemicals to neurons, astrocytes serve as the matrix that holds neurons in place. These cells also surround and isolate synapses, limiting the dispersion of transmitter substances that are released by the terminal buttons.

Neurons occasionally die for unknown reasons or are killed by head injury or stroke. Certain kinds of astrocytes then take up the task of cleaning away the debris. These cells are able to travel around the CNS; they extend and retract their processes (*pseudopodia,* or "false feet") and glide about the way amoebas do. When these astrocytes contact a piece of debris from a dead neuron, they push themselves against it, finally engulfing and digesting it. We call this process **phagocytosis** (*phagein,* "to eat"; *kutos,* "cell"). If there is a considerable amount of injured tissue to be cleaned up, astrocytes will divide and produce enough new cells to do the task. Once the dead tissue is broken down, a framework of astrocytes will be left to fill in the vacant area, and a specialized kind of astrocyte will form scar tissue, walling off the area.

Oligodendrocytes are residents of the CNS, and their principal function is to provide support to axons and to produce the **myelin sheath,** which insulates most axons from one another. (Some axons are not myelinated and lack this sheath.) Myelin, 80 percent lipid and 20 percent protein, is produced by the oligodendrocytes in the form of a tube surrounding the axon. This tube does not form a continuous sheath; rather, it consists of a series of segments, each approximately 1 mm long, with a small (1–2 µm) portion of uncoated axon between the segments. (A *micrometer,* abbreviated µm, is one-millionth of a meter, or one-thousandth of a millimeter.) The bare portion of axon is called a **node of Ranvier,** after its discoverer. The myelinated axon, then, resembles a string of elongated beads.

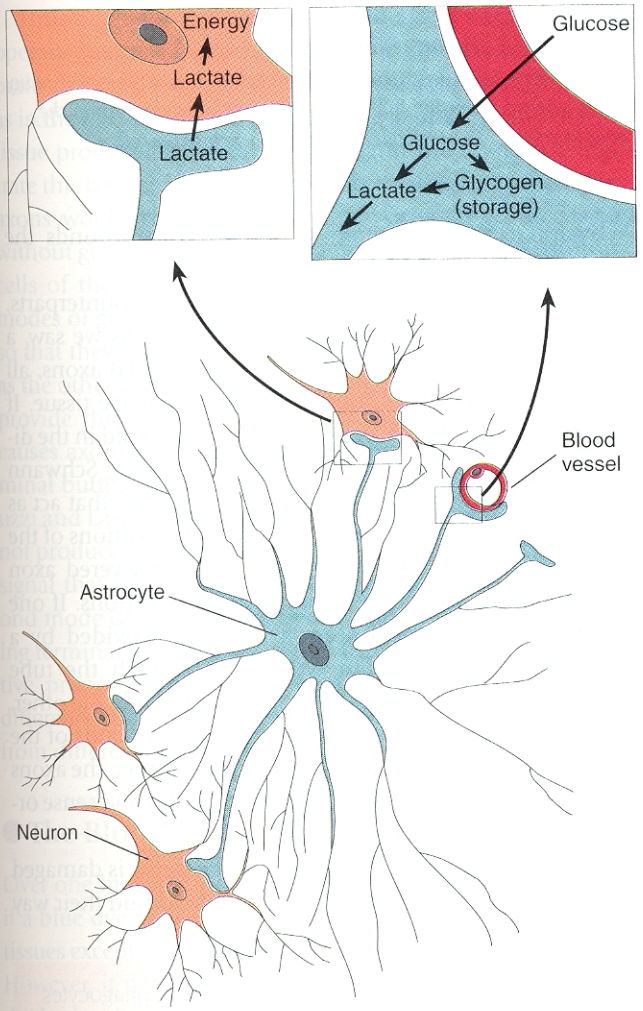

Figure 2.10
Structure and location of astrocytes, whose processes surround capillaries and neurons of the central nervous system.

phagocytosis *(**fagg** o sy **toe** sis)* The process by which cells engulf and digest other cells or debris caused by cellular degeneration.

oligodendrocyte *(oh li go **den** droh site)* A type of glial cell in the central nervous system that forms myelin sheaths.

myelin sheath *(**my** a lin)* A sheath that surrounds axons and insulates them, preventing messages from spreading between adjacent axons.

node of Ranvier *(**raw** vee ay)* A naked portion of a myelinated axon, between adjacent oligodendroglia or Schwann cells.

(Actually, the beads are *very much* elongated—their length is approximately 80 times their width.)

A given oligodendrocyte produces several segments of myelin. During the development of the CNS, oligodendrocytes form processes shaped something like canoe paddles. Each of these paddle-shaped processes then wraps itself many times around a segment of an axon and, while doing so, produces layers of myelin. Each paddle thus becomes a segment of an axon's myelin sheath. (See ***Figure 2.11.***)

As their name indicates, **microglia** are the smallest of the glial cells. Like some types of astrocytes, they act as phagocytes, engulfing and breaking down dead and dying neurons. But in addition, they serve as one of the representatives of the immune system in the brain, protecting the brain from invading microorganisms. They are primarily responsible for the inflammatory reaction in response to brain damage.

Schwann Cells

In the CNS the oligodendrocytes support axons and produce myelin. In the PNS the **Schwann cells** perform the same functions. Most axons in the PNS are myelinated. The myelin sheath occurs in segments, as it does in the CNS; each segment consists of a single Schwann cell, wrapped many times around the axon. In the CNS the oligodendrocytes grow a number of paddle-shaped processes that wrap around a number of axons. In the PNS a Schwann cell provides myelin for only one axon, and the entire Schwann cell—not merely a part of it—surrounds the axon. (See ***Figure 2.12.***)

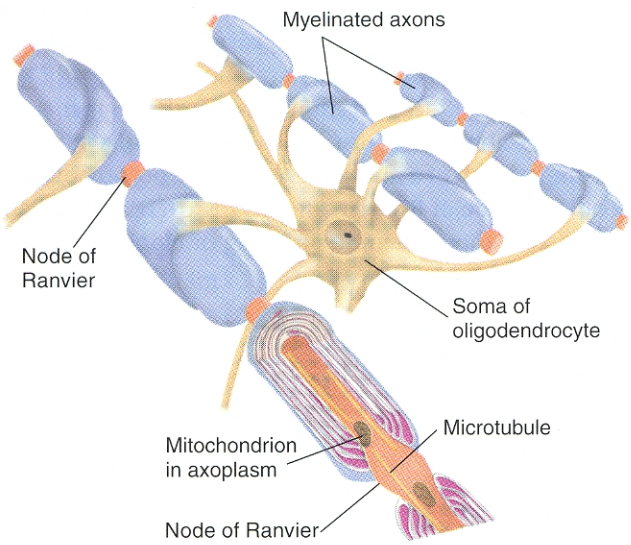

Figure 2.11
An oligodendrocyte, which forms the myelin that surrounds many axons in the central nervous system. Each cell forms one segment of myelin for several adjacent axons.

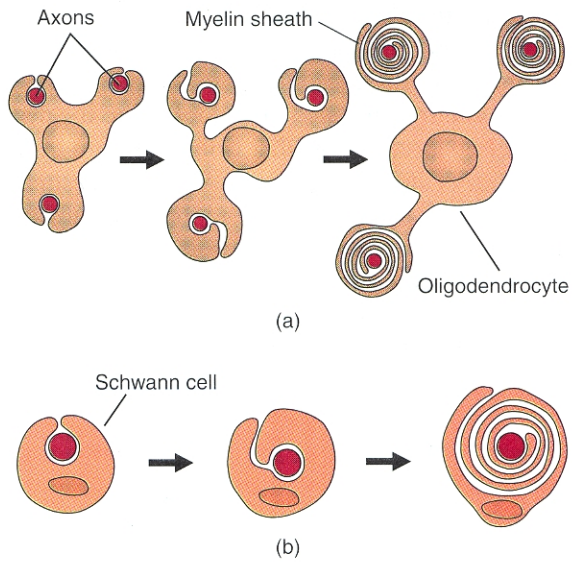

Figure 2.12
Formation of myelin. During development, a process of an oligodendrocyte or an entire Schwann cell tightly wraps itself many times around an individual axon and forms one segment of the myelin sheath. (a) Oligodendrocyte. (b) Schwann cell.

Schwann cells also differ from their CNS counterparts, the oligodendrocytes, in an important way. As we saw, a nerve consists of a bundle of many myelinated axons, all covered in a sheath of tough, elastic connective tissue. If damage occurs to such a nerve, Schwann cells aid in the digestion of the dead and dying axons. Then the Schwann cells arrange themselves in a series of cylinders that act as guides for regrowth of the axons. The distal portions of the severed axons die, but the stump of each severed axon grows sprouts, which then spread in all directions. If one of these sprouts encounters a cylinder provided by a Schwann cell, the sprout will grow through the tube quickly (at a rate of up to 3–4 mm a day), while the other, nonproductive sprouts wither away. If the cut ends of the nerve are still located close enough to each other, the axons will reestablish connections with the muscles and sense organs they previously served.

On the other hand, if a section of the nerve is damaged beyond repair, the axons will not be able to find their way

microglia The smallest of glial cells; act as phagocytes and protect the brain from invading microorganisms.

Schwann cell A cell in the peripheral nervous system that is wrapped around a myelinated axon, providing one segment of its myelin sheath.

to the original sites of innervation. In such cases neurosurgeons can sew the cut ends of the nerve together, if not too much of the nerve has been damaged. (Nerves are flexible and can be stretched a bit.) If too long a section has been lost, and if the nerve was an important one (controlling hand muscles, for example), a piece of nerve about the same size as the lost section can be taken from another part of the body. Because many nerves overlap in the area of tissue they innervate, neurosurgeons have no trouble finding a branch of a nerve that the patient can lose without ill effect. The surgeon, using a special microscope and very delicate instruments, grafts this piece of nerve to the damaged one. Of course, the axons in the excised and transplanted piece of nerve die away, but the tubes produced by the Schwann cells guide the sprouts of the damaged nerve and help them find their way back to the affected muscles—in this case, to the hand muscles.

Unfortunately, the glial cells of the CNS are not as cooperative as the supporting cells of the PNS. If axons in the brain or spinal cord are damaged, new sprouts will form, as in the PNS. However, the budding axons encounter scar tissue produced by the astrocytes, and they cannot penetrate this barrier. Even if the sprouts could get through, the axons would not reestablish their original connections without guidance similar to that provided by the Schwann cells of the PNS. During development, axons have two modes of growth. The first mode causes them to elongate so that they reach their target, which could be as far away as the other end of the brain or spinal cord. Schwann cells provide this signal to injured axons. The second mode causes axons to stop elongating and begin sprouting terminal buttons, because they have reached their target. Liuzzi and Lasek (1987) found that even when astrocytes do not produce scar tissue, they appear to produce a chemical signal that instructs regenerating axons to begin the second mode of growth: to stop elongating and start sprouting terminal buttons. Thus, the difference in the regenerative properties of the CNS and the PNS results from differences in the characteristics of the supporting cells, not from differences in the neurons.

The Blood–Brain Barrier

Over one hundred years ago, Paul Ehrlich discovered that if a blue dye is injected into an animal's bloodstream, all tissues except the brain and spinal cord will be tinted blue. However, if the same dye is injected into the ventricles of the brain, the blue color will spread throughout the CNS (Bradbury, 1979). This experiment demonstrates that a barrier exists between the blood and the fluid that surrounds the cells of the brain—the **blood–brain barrier.**

Some substances can cross the blood-brain barrier; others cannot. Thus, it is *selectively permeable* (*per,* "through"; *meare,* "to pass"). In most of the body the cells that line the capillaries do not fit together absolutely tightly. Small gaps are found between them that permit the free exchange of most substances between the blood plasma and the fluid outside the blood vessels that surrounds the cells. In the central nervous system the capillaries lack these gaps, and thus, many substances cannot leave the blood. Other substances, such as glucose (the primary fuel of the central nervous system), must be actively transported through the capillary walls, carried by special proteins. (See ***Figure 2.13.***)

The messages that are conveyed from place to place in the nervous system involve movements of substances through the membranes of neurons. If the composition of

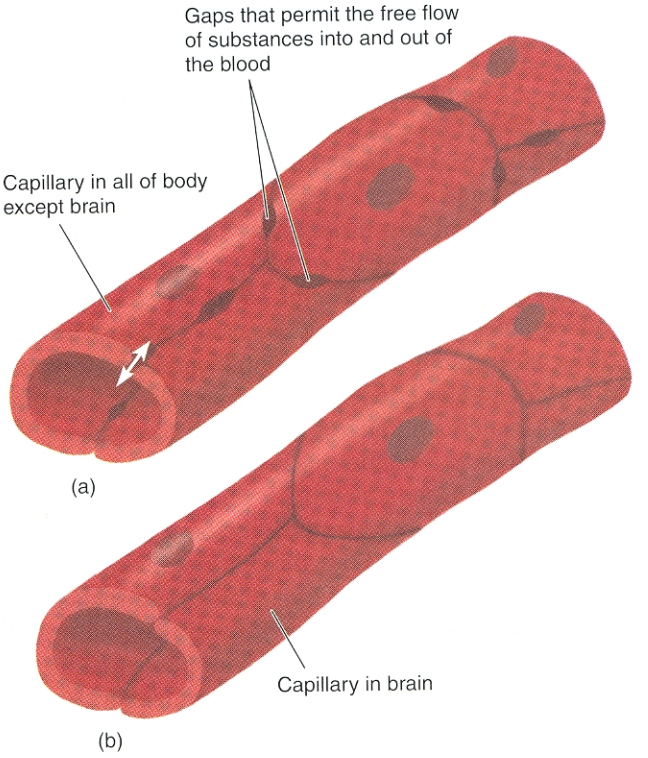

Figure 2.13
The blood–brain barrier. (a) The cells that form the walls of the capillaries in the body outside the brain have gaps that permit the free passage of substances into and out of the blood. (b) The cells that form the walls of the capillaries in the brain are tightly joined.

blood–brain barrier A semipermeable barrier produced by the cells in the walls of the capillaries in the brain.

the fluid that bathes neurons is changed even slightly, the transmission of these messages will be disrupted. Thus, if this fluid is not closely regulated, the brain cannot function normally. The presence of the blood-brain barrier makes it easier to regulate the composition of this fluid.

The blood-brain barrier is not uniform throughout the nervous system. In several places the barrier is relatively permeable, allowing substances excluded elsewhere to cross freely. For example, the **area postrema** is a part of the brain that controls vomiting. The blood-brain barrier is much weaker there, permitting neurons in this region to detect the presence of toxic substances in the blood. A poison that enters the circulatory system from the stomach can thus stimulate this area to initiate vomiting. If the organism is lucky, the poison can be expelled from the stomach before it causes too much damage.

Interim Summary

Neurons are the most important cells of the nervous system. The central nervous system (CNS) includes the brain and spinal cord; the peripheral nervous system (PNS) includes nerves and some sensory organs.

Neurons have four principal parts: dendrites, soma (cell body), axon, and terminal buttons. They communicate by means of synapses, located at the ends of the axons. When an action potential travels down an axon, the terminal buttons secrete a chemical that has either an excitatory or an inhibitory effect on the neuron with which it communicates. Ultimately, the effects of these excitatory and inhibitory synapses cause behavior, in the form of muscular contraction.

Neurons contain a quantity of clear cytoplasm, enclosed in a membrane. Embedded in the membrane are protein molecules that have special functions, such as the transport of particular substances into and out of the cell. The cytoplasm contains the nucleus, which contains the genetic information; the nucleolus (located in the nucleus), which manufactures ribosomes; the ribosomes, which serve as sites of protein synthesis; the endoplasmic reticulum, which serves as a storage reservoir and as a channel for transportation of chemicals through the cytoplasm; the Golgi apparatus, which wraps substances that the cell secretes in a membrane; the lysosomes, which contain enzymes that destroy waste products; microtubules, neurofilaments, and microfilaments, which compose the cytoskeleton and help transport chemicals from place to place; and the mitochondria, which serve as the location for most of the chemical reactions through which the cell extracts energy from nutrients.

The withdrawal reflex illustrates how neurons can be connected to accomplish useful behaviors. The circuit responsible for this reflex consists of three sets of neurons: sensory neurons, interneurons, and motor neurons. The reflex can be suppressed when neurons in the brain activate inhibitory interneurons that form synapses with the motor neurons.

Neurons are supported by the glial cells of the central nervous system and the satellite cells of the peripheral nervous system. Within the CNS, astrocytes provide the primary support and also remove debris and form scar tissue in the event of tissue damage. Microglia are phagocytes that serve as the representatives of the immune system. Oligodendrocytes form myelin, the substance that insulates axons, and also support unmyelinated axons. Within the PNS, support and myelin are provided by the Schwann cells.

In most organs, molecules freely diffuse between the blood within the capillaries that serve them and the extracellular fluid that bathes their cells. The molecules pass through gaps between the cells that line the capillaries. The walls of the capillaries of the CNS lack these gaps; consequently, fewer substances can enter or leave the brain across the blood-brain barrier.

Communication within a Neuron

This section describes the nature of communication *within* a neuron—the way an action potential is sent from the cell body down the axon to the terminal buttons, informing them to release some transmitter substance. The details of synaptic transmission—the communication between neurons—will be described in the next section. As we shall see in this section, an action potential consists of a series of alterations in the membrane of the axon that permit various chemicals to move between the interior of the axon and the fluid surrounding it. These exchanges produce electrical currents.

Measuring Electrical Potentials of Axons

Let's examine the nature of the message that is conducted along the axon. To do so, we obtain an axon that is large enough to work with. Fortunately, nature has provided the neuroscientist with the giant squid axon (the giant axon of

area postrema *(poss **tree** ma)* A region of the medulla where the blood–brain barrier is weak; poisons can be detected there and can initiate vomiting.

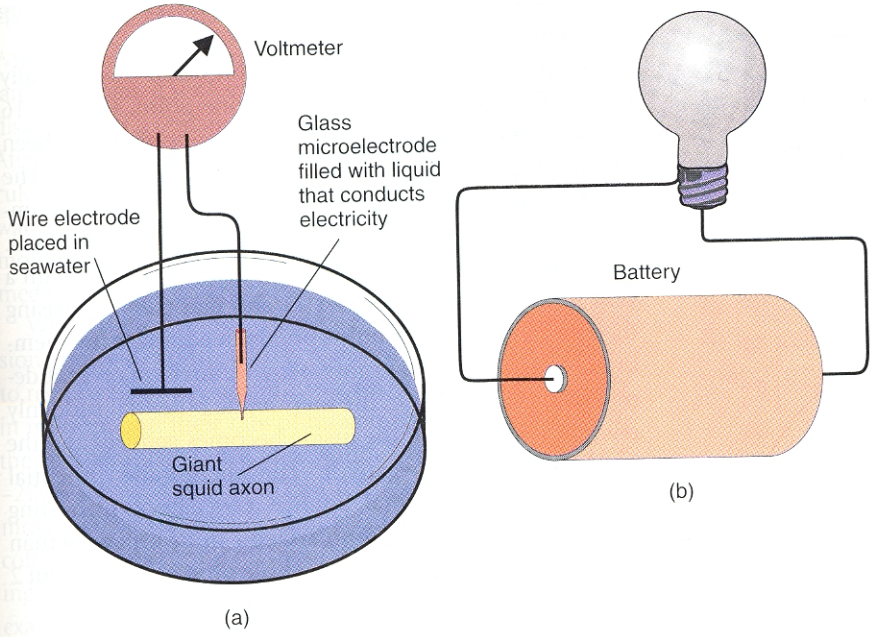

Figure 2.14
Measuring electrical charge. (a) A voltmeter detecting the charge across a membrane of an axon. (b) A light bulb detecting the charge across the terminals of a battery.

a squid, not the axon of a giant squid!). This axon is about 0.5 mm in diameter, which is hundreds of times larger than the largest mammalian axon. (This large axon controls an emergency response: sudden contraction of the mantle, which squirts water through a jet and propels the squid away from a source of danger.) We place an isolated giant squid axon in a dish of seawater, in which it can exist for a day or two.

To measure the electrical charges generated by an axon, we will need to use a pair of electrodes. **Electrodes** are electrical conductors that provide a path for electricity to enter or leave a medium. One of the electrodes is a simple wire that we place in the seawater. The other one, which we use to record the message from the axon, has to be special. Because even a giant squid axon is rather small, we must use a tiny electrode that will record the membrane potential without damaging the axon. To do so, we use a microelectrode.

A **microelectrode** is simply a very small electrode, which can be made of metal or glass. In this case we will use one made of thin glass tubing, which is heated and drawn down to an exceedingly fine point, less than a thousandth of a millimeter in diameter. Because glass will not conduct electricity, the glass microelectrode is filled with a liquid that conducts electricity, such as a solution of potassium chloride.

We place the wire electrode in the seawater and insert the microelectrode into the axon. (See ***Figure 2.14a***.) As soon as we do so, we discover that the inside of the axon is negatively charged with respect to the outside; the difference in charge being 70 mV (millivolts, or thousandths of a volt). Thus, the inside of the membrane is –70 mV. This electrical charge is called the **membrane potential.** The term *potential* refers to a stored-up source of energy—in this case, electrical energy. For example, a flashlight battery that is not connected to an electrical circuit has a *potential* charge of 1.5 V between its terminals. If we connect a light bulb to the terminals, the potential energy is tapped and converted into radiant energy (light). (See ***Figure 2.14b***.) Similarly, if we connect our electrodes—one inside the axon and one outside it—to a very sensitive voltmeter, we will convert the potential energy to movement of the meter's needle. Of course, the potential electrical energy of the axonal membrane is very weak, compared with that of a flashlight battery.

As we shall see, the message that is conducted down the axon consists of a brief change in the membrane potential.

electrode A conductive medium that can be used to apply electrical stimulation or to record electrical potentials.

microelectrode A very fine electrode, generally used to record activity of individual neurons.

membrane potential The electrical charge across a cell membrane; the difference in electrical potential inside and outside the cell.

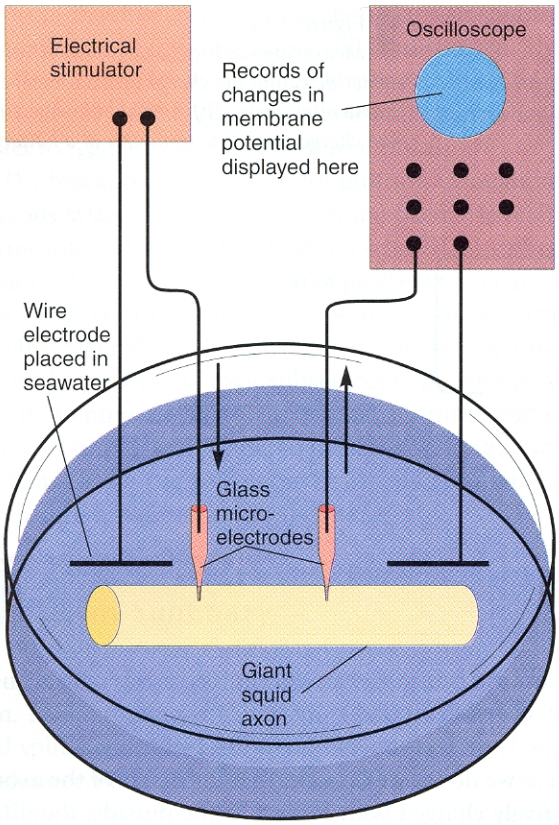

Figure 2.15
The means by which an axon can be stimulated while its membrane potential is being recorded.

However, this change occurs very rapidly—too rapidly for us to see if we were using a voltmeter. Thus, to study the message, we will use an **oscilloscope.** This device, like a voltmeter, measures voltages, but it also produces a record of these voltages, graphing them as a function of time. These graphs are displayed on a screen, much like the one found in a television. The vertical axis represents voltage, and the horizontal axis represents time, going from left to right.

Once we insert our microelectrode into the axon, the oscilloscope draws a straight horizontal line at –70 mV, as long as the axon is not disturbed. This electrical charge across the membrane is called, quite appropriately, the **resting potential.** Now let us disturb the resting potential and see what happens. To do so, we will use another device—an electrical stimulator that allows us to alter the membrane potential at a specific location. (See *Figure 2.15.*) The stimulator can pass current through another microelectrode that we have inserted into the axon. Because the inside of the axon is negative, a positive charge applied to the inside of the membrane produces a **depolarization.** That is, it takes away some of the electrical charge across the membrane near the electrode, reducing the membrane potential.

Let us see what happens to an axon when we artificially change the membrane potential at one point. Figure 2.16 shows a graph drawn by an oscilloscope that has been monitoring the effects of brief depolarizing stimuli. The graphs of the effects of these separate stimuli are superimposed on the same drawing so that we can compare them. We deliver a series of depolarizing stimuli, starting with a very weak stimulus (number 1) and gradually increasing their strength. Each stimulus briefly depolarizes the membrane potential a little more. Finally, after we present depolarization number 4, the membrane potential suddenly reverses itself, so that the inside becomes *positive* (and the outside becomes negative). The membrane potential quickly returns to normal, but first it overshoots the resting potential, becoming **hyperpolarized**—more polarized than normal—for a short time. The whole process takes about 2 msec (milliseconds). (See *Figure 2.16.*)

This phenomenon, a very rapid reversal of the membrane potential, is called the **action potential.** It constitutes the message carried by the axon from the cell body to the terminal buttons. The voltage level that triggers an action potential—which was achieved only by depolarizing shock number 4—is called the **threshold of excitation.**

The Membrane Potential: Balance of Two Forces

To understand what causes the action potential to occur, we must first understand the reasons for the existence of the membrane potential. As we will see, this electrical charge is the result of a balance between two opposing forces: diffusion and electrostatic pressure.

oscilloscope A laboratory instrument capable of displaying a graph of voltage as a function of time on the face of a cathode ray tube.

resting potential The membrane potential of a neuron when it is not being altered by excitatory or inhibitory postsynaptic potentials; approximately –70 mV in the giant squid axon.

depolarization Reduction (toward zero) of the membrane potential of a cell from its normal resting potential.

hyperpolarization An increase in the membrane potential of a cell, relative to the normal resting potential.

action potential The brief electrical impulse that provides the basis for conduction of information along an axon.

threshold of excitation The value of the membrane potential that must be reached in order to produce an action potential.

The Force of Diffusion

When a spoonful of sugar is carefully poured into a container of water, it settles to the bottom. After a time the sugar dissolves, but it remains close to the bottom of the container. After a much longer time (probably several days), the molecules of sugar distribute themselves evenly throughout the water, even if no one stirs the liquid. The process whereby molecules distribute themselves evenly throughout the medium in which they are dissolved is called **diffusion.**

When there are no forces or barriers to prevent diffusion, molecules diffuse from regions of high concentration to regions of low concentration. Molecules are constantly in motion, and their rate of movement is proportional to the temperature. Only at absolute zero [0 K (kelvin) = −273.15 C = −459.7 F] do molecules cease their random movement. At all other temperatures they move about, colliding and veering off in different directions, thus pushing one another away. The result of these collisions in the example of sugar and water is to force sugar molecules upward (and to force water molecules downward), away from the regions in which they are most concentrated.

The Force of Electrostatic Pressure

When some substances are dissolved in water, they split into two parts, each with an opposing electrical charge. Substances with this property are called **electrolytes;** the charged particles into which they decompose are called **ions.** Ions are of two basic types: *Cations* have a positive charge, and *anions* have a negative charge. For example, when sodium chloride (NaCl, table salt) is dissolved in water, many of the molecules split into sodium cations (Na^+) and chloride anions (Cl^-). (I find that the easiest way to keep the terms *cation* and *anion* straight is to think of the cation's plus sign as a cross, and remember the superstition of a black *cat* crossing your path.)

As you have undoubtedly learned, particles with the same kind of charge repel each other (+ repels +, and − repels −), but particles with different charges are attracted to each other (+ and − attract). Thus, anions repel anions, cations repel cations, but anions and cations attract each other. The force exerted by this attraction or repulsion is called **electrostatic pressure.** Just as the force of diffusion moves molecules from regions of high concentration to regions of low concentration, electrostatic pressure moves ions from place to place: Cations are pushed away from regions with an excess of cations, and anions are pushed away from regions with an excess of anions.

Ions in the Extracellular and Intracellular Fluid

The fluid within cells (**intracellular fluid**) and the fluid surrounding them (**extracellular fluid**) contain different ions.

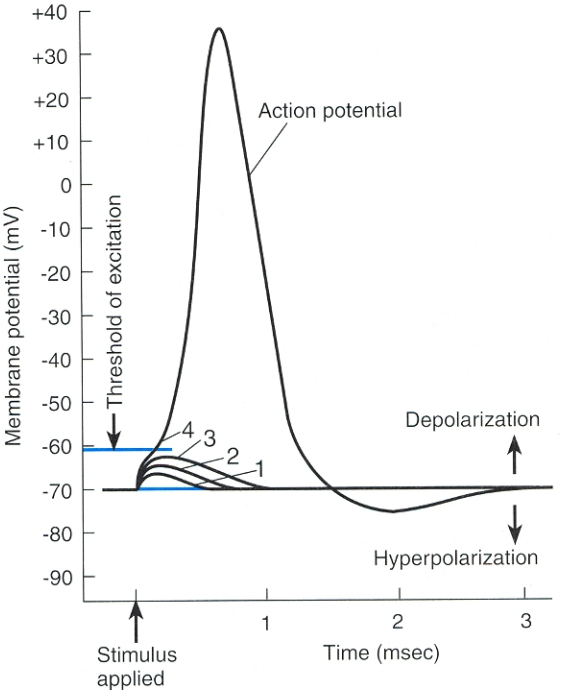

Figure 2.16
An action potential. These results would be seen on an oscilloscope screen if depolarizing stimuli of varying intensities were delivered to the axon shown in Figure 2.15.

The forces of diffusion and electrostatic pressure contributed by these ions give rise to the membrane potential. Because the membrane potential is produced by a balance between the forces of diffusion and electrostatic pressures, understanding what produces this potential requires that we know the concentration of the various ions in the extracellular and intracellular fluids.

There are several important ions in these fluids. I will discuss four of them here: organic anions (symbolized by A^-), chloride ions (Cl^-), sodium ions (Na^+), and potassium ions (K^+). The Latin words for sodium and potassium are *natrium* and *kalium;* hence, they are abbreviated *Na* and *K,* respectively. Organic anions—negatively charged proteins and intermediate products of the cell's metabolic

diffusion Movement of molecules from regions of high concentration to regions of low concentration.
electrolyte An aqueous solution of a material that ionizes—namely, a soluble acid, base, or salt.
ion A charged molecule. *Cations* are positively charged, and *anions* are negatively charged.
electrostatic pressure The attractive force between atomic particles charged with opposite signs, or the repulsive force between atomic particles charged with the same sign.
intracellular fluid The fluid contained within cells.
extracellular fluid Body fluids located outside of cells.

processes—are found only in the intracellular fluid. Although the other three ions are found in both the intracellular and extracellular fluids, K^+ is found predominantly in the intracellular fluid, whereas Na^+ and Cl^- are found predominantly in the extracellular fluid. The sizes of the boxes in Figure 2.17 indicate the relative concentrations of these four ions. (See ***Figure 2.17.***) The easiest way to remember which ion is found where is to recall that the fluid that surrounds our cells is similar to seawater, which is predominantly a solution of salt, NaCl. The primitive ancestors of our cells lived in the ocean; thus, the seawater was their extracellular fluid. Our extracellular fluid thus resembles seawater, produced and maintained by regulatory mechanisms that are described in Chapter 12.

Let us consider the ions in Figure 2.17, examining the forces of diffusion and electrostatic pressure exerted on each and reasoning why each is located where it is. A^-, the organic anion, is unable to pass through the membrane of the axon; therefore, although the presence of this ion within the cell affects the other ions, it is located where it is because the membrane is impermeable to it.

The potassium ion K^+ is concentrated within the axon; thus, the force of diffusion tends to push it out of the cell. However, the outside of the cell is charged positively with respect to the inside, so electrostatic pressure tends to force the cation inside. Thus, the two opposing forces balance. (See ***Figure 2.17.***)

The chloride ion Cl^- is in greatest concentration outside the axon. The force of diffusion pushes this ion inward. However, because the inside of the axon is negatively charged, electrostatic pressure pushes the anion outward. Again, two opposing forces balance each other. (See ***Figure 2.17.***)

The sodium ion Na^+ is also in greatest concentration outside the axon, so it, like Cl^-, is pushed into the cell by the force of diffusion. But unlike chloride, the sodium ion is *positively* charged. Therefore, electrostatic pressure does *not* prevent Na^+ from entering the cell; indeed, the negative charge inside the axon *attracts* Na^+. (See ***Figure 2.17.***)

How can Na^+ remain in greatest concentration in the extracellular fluid, despite the fact that both forces (diffusion and electrostatic pressure) tend to push it inside? The simplest explanation would be that the membrane is impermeable to Na^+, as it is to A^-, the organic anion. This possibility can be tested with the following experiment. A giant squid axon is placed in a dish of seawater containing some radioactive Na^+, is allowed to sit a while, and is then removed and washed off. The axon is now found to be radioactive, which shows that Na^+ *can* pass through the membrane, because some of the radioactive Na^+ in the seawater found its way into the axon.

Although the axon contains radioactive Na^+, analysis of its cytoplasm (which can be squeezed out like toothpaste from a tube) shows that the concentration of Na^+ is unchanged. This analysis indicates that although some molecules of Na^+ entered the axon, an equal number left again, keeping the concentration constant. But as we know, the forces of diffusion and electrostatic pressure tend to push Na^+ into the cell. It is easy to understand why the axon became radioactive—these forces pushed some radioactive sodium ions in. But what pushed an equal number of Na^+ ions out again, against these two forces?

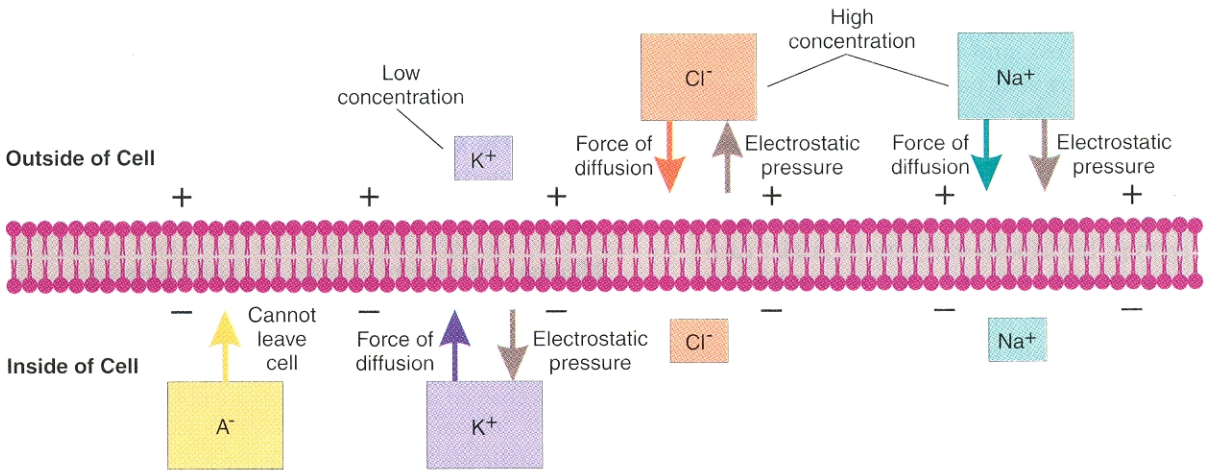

Figure 2.17
The relative concentration of some important ions inside and outside the neuron and the forces acting on them.

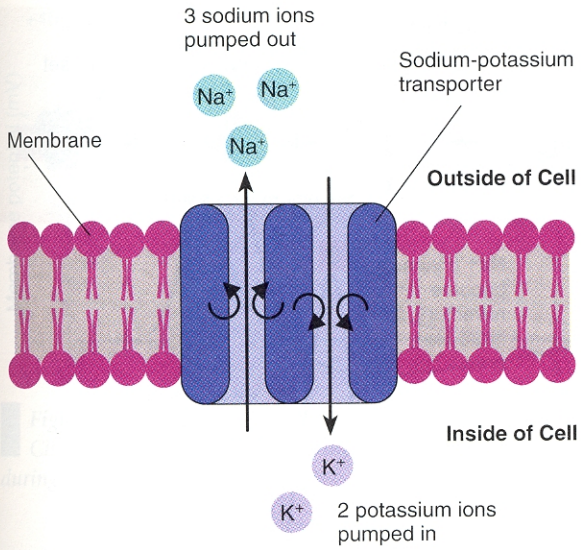

Figure 2.18
A sodium-potassium transporter, situated in the cell membrane.

The answer is this: Another force, provided by the *sodium-potassium pump*, continuously pushes Na^+ out of the axon. The sodium-potassium pump consists of a large number of individual protein molecules situated in the membrane, driven by energy provided by the mitochondria as they metabolize the cell's nutrients. These molecules, known as **sodium-potassium transporters,** exchange Na^+ for K^+, pushing three sodium ions out for every two potassium ions they push in. (See *Figure 2.18.*)

Because the membrane is not very permeable to Na^+, sodium-potassium transporters very effectively keep the intracellular concentration of Na^+ low. By transporting K^+ into the cell, they also increase the intracellular concentration of K^+ somewhat. The membrane is approximately 100 times more permeable to K^+ than to Na^+, so the increase is slight; but as we will see when we study the process of neural inhibition later in this chapter, it is very important. The transporters that make up the sodium-potassium pump use considerable energy: Up to 40 percent of a neuron's metabolic resources are used to operate them. Neurons, muscle cells, glia—in fact, most cells of the body—have sodium-potassium transporters in their membrane.

The Action Potential

As we saw, the forces of both diffusion and electrostatic pressure tend to push Na^+ into the cell. However, the membrane is not very permeable to this ion, and sodium-potassium transporters continuously pump out Na^+, keeping the intracellular level of Na^+ low. But imagine what would happen if the membrane suddenly became permeable to Na^+. The forces of diffusion and electrostatic pressure would cause Na^+ to rush into the cell. This sudden influx (inflow) of positively charged ions would drastically change the membrane potential. Indeed, experiments have shown that this mechanism is precisely what causes the action potential: A brief drop in the membrane resistance to Na^+ (allowing these ions to rush into the cell) is immediately followed by a transient drop in the membrane resistance to K^+ (allowing these ions to rush out of the cell).

I said earlier that the membrane consists of a double layer of lipid molecules in which are floating many different kinds of protein molecules. One class of protein molecules provides a way for ions to enter or leave the cells. These molecules constitute **ion channels,** which contain passages ("pores") that can open or close. When an ion channel is open, a particular type of ion can flow through the pore and thus can enter or leave the cell. (See *Figure 2.19.*) Neural membranes contain many thousands of ion channels. For example, the giant squid axon contains from 100 to 600 sodium channels in each square micrometer of membrane. (There are one million square micrometers in a square millimeter; thus, a patch of axonal membrane the size of a lowercase letter "o" in this book would contain several hundred million sodium channels.) Each open sodium channel can admit up to 100 million ions per second. The permeability of a membrane to a particular ion at a given moment is determined by the number of ion channels that are open. (By the way, cell biologists have discovered approximately 75 different types of ion channels, and more will undoubtedly be discovered.)

The following numbered paragraphs describe the movements of ions through the membrane during the action potential. The numbers on the figure correspond to the numbers of the paragraphs that follow. (See *Figure 2.20.*)

1. As soon as the threshold of excitation is reached, the sodium channels in the membrane open and Na^+ rushes in, propelled by the forces of diffusion and electrostatic pressure. The opening of these channels is triggered by the depolarization of the membrane potential; they open at the threshold of excitation. Because these

sodium-potassium transporter A protein found in the membrane of all cells that extrudes sodium ions from and transports potassium ions into the cell.

ion channel A specialized protein molecule that permits specific ions to enter or leave cells.

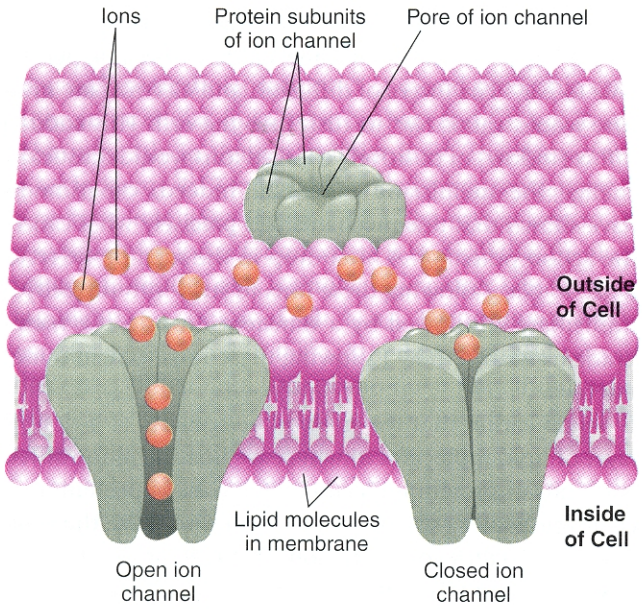

Figure 2.19
Ion channels. When they are open, ions can pass through them, entering or leaving the cell.

channels are opened by changes in the membrane potential, they are called **voltage-dependent ion channels.** The influx of positively charged sodium ions produces a rapid change in the membrane potential, from –70 to +40 mV.

2. The membrane of the axon contains voltage-dependent potassium channels, but these channels are less sensitive than voltage-dependent sodium channels. That is, they require a greater level of depolarization before they begin to open. Thus, they begin to open later than the sodium channels.
3. At about the time the action potential reaches its peak (in approximately 1 msec), the sodium channels become *refractory*—they cannot open again until the membrane once more reaches the resting potential. At this time, then, no more Na^+ can enter the cell.
4. By now, the voltage-dependent potassium channels in the membrane are open, letting K^+ ions move freely through the membrane. At this time, the inside of the axon is now *positively* charged, so K^+ is driven out of the cell by diffusion and by electrostatic pressure. This outflow of cations causes the membrane potential to return toward its normal value. As it does so, the potassium channels begin to close again.
5. As the membrane potential returns to normal, the potassium channels close, and no more potassium leaves the cell.

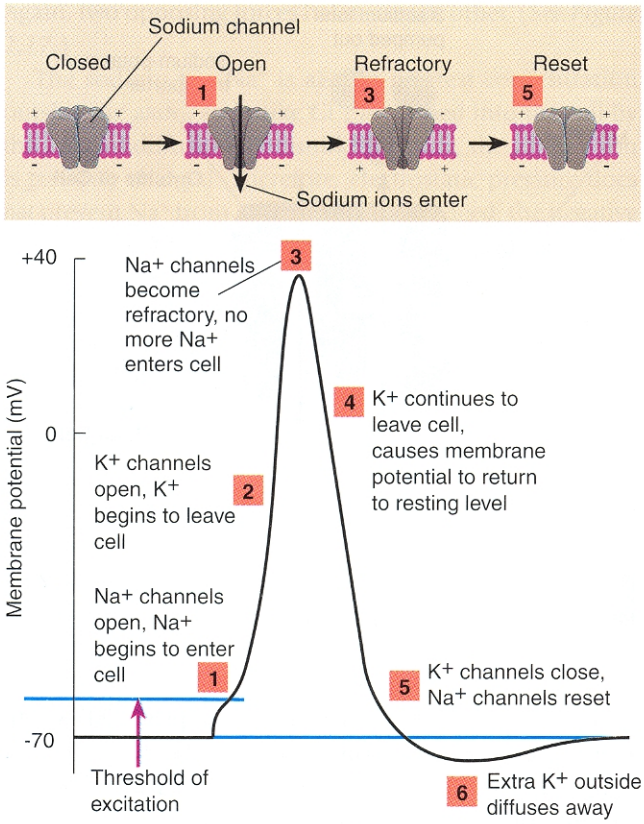

Figure 2.20
The movements of ions during the action potential.

6. The membrane actually overshoots its resting value (–70 mV) and only gradually returns to normal. The accumulation of K^+ ions outside the membrane causes it to become temporarily hyperpolarized. These extra ions soon diffuse away, and the membrane potential returns to –70 mV. Eventually, sodium-potassium transporters remove the Na^+ that leaked in and retrieve the K^+ that leaked out.

Figure 2.21 summarizes the changes in permeability of the membrane to sodium and potassium ions during the action potential. (See ***Figure 2.21.***)

How much ionic flow is there? The drop in membrane resistance to Na^+ is brief, and diffusion over any appreciable distance takes some time. Thus, when I say "Na^+ rushes in," I do not mean that the axoplasm becomes flooded with Na^+. At the peak of the action potential a very thin

voltage-dependent ion channel An ion channel that opens or closes according to the value of the membrane potential.

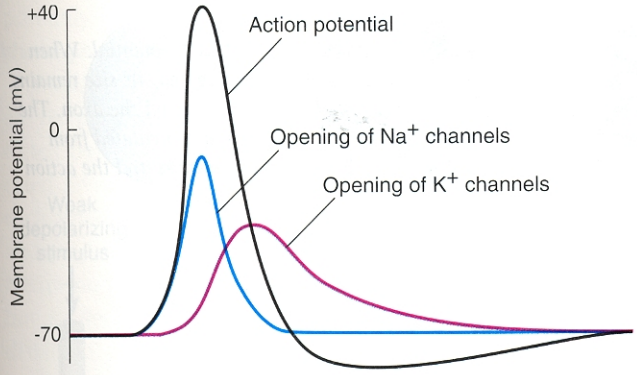

Figure 2.21
Changes in the permeability of the membrane to Na^+ and K^+ during the action potential.

layer of fluid immediately inside the axon becomes full of newly arrived Na^+ ions; this amount is indeed enough to reverse the membrane potential. However, not enough time has elapsed for these ions to fill the entire axon. Before that event can take place, the Na^+ channels close and K^+ starts flowing out.

Experiments have shown that an action potential temporarily increases the number of Na^+ ions inside the giant squid axon by 0.0003 percent. Although the concentration just inside the membrane is high, the total number of ions entering the cell is very small, relative to the number already there. On a short-term basis, sodium-potassium transporters are not very important. The few Na^+ ions that manage to leak in diffuse into the rest of the axoplasm, and the slight increase in Na^+ concentration is hardly noticeable. However, sodium-potassium transporters are important on a long-term basis, because in many axons action potentials occur at a very high rate. Without the activity of sodium-potassium transporters, the concentration of sodium ions in the axoplasm would increase enough so that the axon would no longer be able to function.

Conduction of the Action Potential

Now that we have a basic understanding of the resting membrane potential and the production of the action potential, we can consider the movement of the message down the axon, or *conduction of the action potential.* To study this phenomenon, we again make use of the giant squid axon. We attach an electrical stimulator to an electrode at one end of the axon and place recording electrodes, attached to oscilloscopes, at different distances from the stimulating electrode. Then we apply a depolarizing stimulus to the end of the axon and trigger an action potential. We record the action potential from each of the electrodes, one after the other. Thus, we see that the action potential is conducted down the axon. As the action potential travels, it remains constant in size. (See *Figure 2.22.*)

This experiment establishes a basic law of axonal conduction: the **all-or-none law.** This law states that an action potential either occurs or does not occur; once triggered, it is transmitted down the axon to its end. An action potential always remains the same size, without growing or diminishing. In fact, the axon will transmit an action potential in either direction, or even in both directions, if it is started in the middle of the axon's length. However, because action potentials in living animals always start at the end attached to the soma, axons normally carry one-way traffic.

As you know, the strength of a muscular contraction can vary from very weak to very forceful, and the strength of a stimulus can vary from barely detectable to very intense. We know that the occurrence of action potentials in axons controls the strength of muscular contractions and represents the intensity of a physical stimulus. But if the action potential is an all-or-none event, how can it represent information that can vary in a continuous fashion? The answer is simple: A single action potential is not the basic element of information; rather, variable information is represented by an axon's *rate of firing.* (In this context, *firing* refers to the production of action potentials.) A high rate of firing causes a strong muscular contraction, and a strong stimulus (such as a bright light) causes a high rate of firing in axons that serve the eyes. Thus, the all-or-none law is supplemented by the **rate law.** (See *Figure 2.23.*)

Action potentials are not the only kind of electrical signals that occur in neurons. As we shall see in the last section of this chapter, when a message is sent across a synapse, a small electrical signal is produced in the membrane of the neuron that receives the message. To understand this process, and to understand the way that action potentials are conducted in myelinated axons (described later in this section), we must see how such signals other than action potentials are conducted. To do so, we produce a subthreshold depolarization (too small to produce an action potential) at one end of an axon and record its effects from electrodes placed along the axon. We find that the

all-or-none law The principle that once an action potential is triggered in an axon, it is propagated, without decrement, to the end of the fiber.

rate law The principle that variations in the intensity of a stimulus or other information being transmitted in an axon are represented by variations in the rate at which that axon fires.

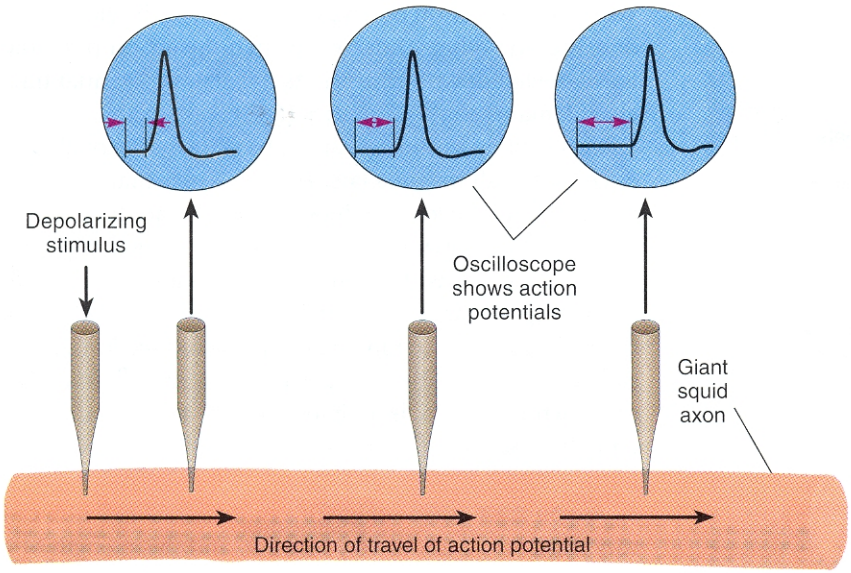

Figure 2.22
Conduction of the action potential. When an action potential is triggered, its size remains undiminished as it travels down the axon. The speed of conduction can be calculated from the delay between the stimulus and the action potential.

stimulus produces a disturbance in the membrane potential that becomes smaller as it moves away from the point of stimulation. (See ***Figure 2.24.***)

The transmission of the small, subthreshold depolarization is *passive.* Neither sodium channels nor potassium channels are opening or closing. The axon is acting like an electrical cable, carrying along the current started at one end. This property of the axon follows laws discovered in the nineteenth century that describe the conduction of electricity through telegraph cables laid along the ocean floor. As a signal passes through an undersea cable, the signal gets smaller because of the electrical characteristics of the cable, including leakage through the insulator and resistance in the wire. Because the signal decreases in size (decrements), it is referred to as *decremental conduction.* We say that the conduction of a small depolarization by the axon follows the laws that describe the **cable properties** of the axon—the same laws that describe the electrical properties of an undersea cable. And because hyperpolarizations never trigger action potentials, these disturbances, too, are transmitted by means of the passive cable properties of an axon.

Recall that all but the smallest axons in mammalian nervous systems are myelinated; segments of the axons are covered by a myelin sheath produced by the oligodendrocytes of the CNS or the Schwann cells of the PNS. These segments are separated by portions of naked axon, the nodes of Ranvier. Conduction of an action potential in a myelinated axon is somewhat different from conduction in an unmyelinated axon.

Schwann cells (and the oligodendrocytes of the CNS) wrap tightly around the axon, leaving no measurable extracellular fluid between them and the axon. The only place where a myelinated axon comes in contact with the extracellular fluid is at a node of Ranvier, where the axon is naked. In the myelinated areas there can be no inward flow of Na^+ when the sodium channels open, because there *is* no extracellular sodium. How, then, does the "action potential" travel along the area of axonal membrane

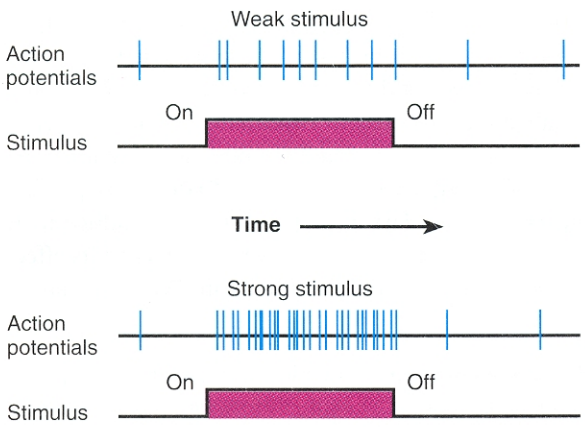

Figure 2.23
The rate law. The strength of a stimulus is represented by the rate of firing of an axon. The size of each action potential is always constant.

cable properties The passive conduction of electrical current, in a decremental fashion, down the length of an axon.

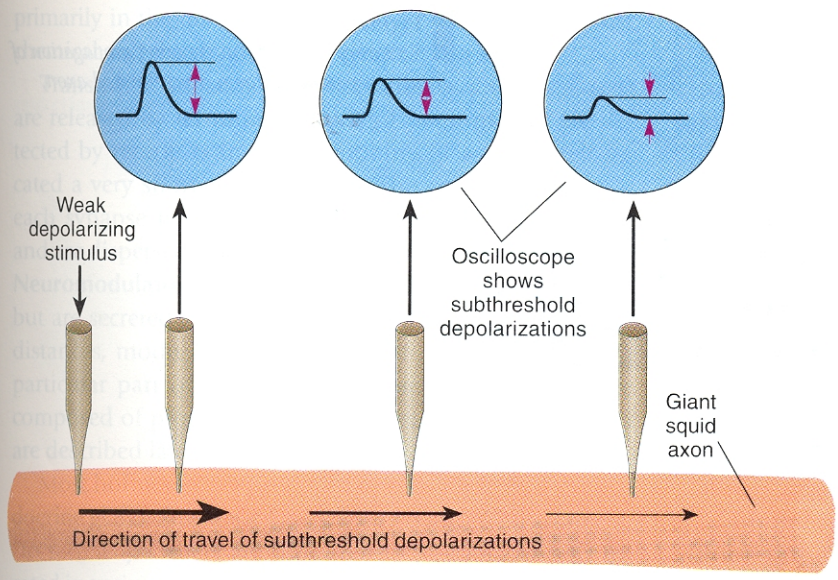

Figure 2.24
Decremental conduction. When a subthreshold depolarization is applied to the axon, the disturbance in the membrane potential is largest near the stimulating electrode and gets progressively smaller at distances farther along the axon.

covered by myelin sheath? You guessed it—by cable properties. The axon passively conducts the electrical disturbance from the action potential to the next node of Ranvier. The disturbance gets smaller, but it is still large enough to trigger an action potential at the node. The action potential gets retriggered, or repeated, at each node of Ranvier and is passed, by means of cable properties of the axon, along the myelinated area to the next node. Such conduction, hopping from node to node, is called **saltatory conduction,** from the Latin *saltare,* "to dance." (See *Figure 2.25.*)

Saltatory conduction confers two advantages. The first is economic. Energy must be expended by sodium- potassium transporters to get rid of the excess Na^+ that enters the axon during the action potential. Sodium-potassium transporters must be located along an unmyelinated axon because Na^+ enters everywhere. However, because Na^+ can enter a myelinated axon only at the nodes of Ranvier, much less gets in and, consequently, much less has to be pumped out again. Therefore, a myelinated axon expends much less energy to maintain its sodium balance.

The second advantage to myelin is speed. Conduction of an action potential is faster in a myelinated axon because the transmission between the nodes, which occurs by means of the axon's cable properties, is very fast. Increased speed enables an animal to react faster and (undoubtedly) to think faster. One of the ways to increase the speed of conduction is to increase size. Because it is so large, the unmyelinated squid axon, with a diameter of 500 µm, achieves a conduction velocity of approximately 35 m/sec (meters per second). However, the same speed is achieved by a myelinated cat axon with a diameter of a mere 6 µm. The fastest myelinated axon, 20 µm in diameter, can conduct action potentials at a speedy 120 m/sec, or 432 km/h. At that speed a signal can get from one end of an axon to the other without much delay.

Interim Summary

The message conducted down an axon is called an action potential. The membranes of all cells of the body are electrically charged, but only axons can produce action potentials. The resting membrane potential occurs because various ions are located in different concentrations in the fluid inside and outside the cell. The extracellular fluid (like seawater) is rich in Na^+ and Cl^-, and the intracellular fluid is rich in K^+ and various organic anions, designated as A^-.

The cell membrane is freely permeable to water, but its permeability to various ions—in particular, Na^+ and K^+—is regulated by ion channels. When the membrane potential is at its resting value (–70 mV), the gates of the voltage-dependent sodium and potassium channels are closed. The experiment with radioactive seawater showed us that some Na^+ continuously leaks into the axon but is promptly forced out of the cell again by the sodium-potassium transporters (which also pump potassium *into* the

saltatory conduction Conduction of action potentials by myelinated axons. The action potential "jumps" from one node of Ranvier to the next.

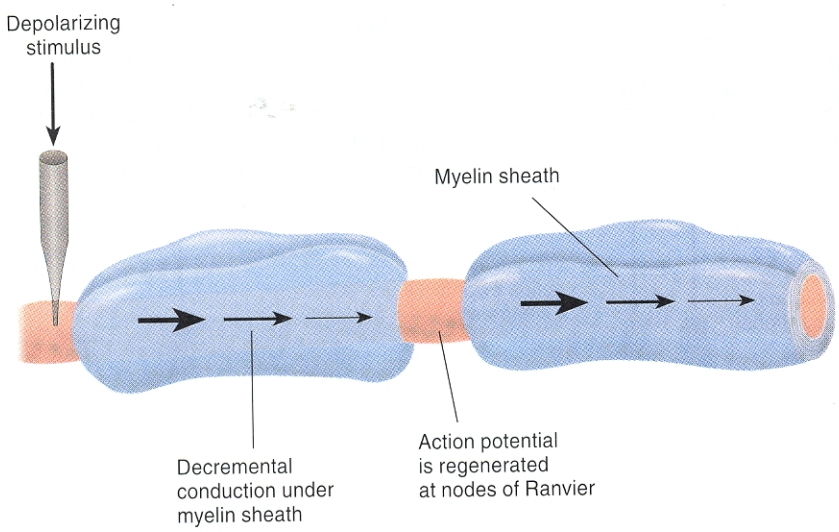

Figure 2.25
Saltatory conduction, showing propagation of an action potential down a myelinated axon.

axon). When an electrical stimulator depolarizes the membrane potential of the axon so that it reaches the threshold of excitation, voltage-dependent sodium channels open and Na^+ rushes into the cell, driven by the force of diffusion and by electrostatic pressure. The entry of the positively charged ions further reduces the membrane potential and, indeed, causes it to reverse, so that the inside becomes positive. The opening of the sodium channels is temporary; they soon close again. The depolarization of the membrane potential caused by the influx of Na^+ activates voltage-dependent potassium channels, and K^+ leaves the axon, traveling down its concentration gradient. This efflux (outflow) of K^+ quickly brings the membrane potential back to its resting value.

Because an action potential of a given axon is an all-or-none phenomenon, neurons represent intensity by their rate of firing. The action potential normally begins at one end of the axon, where the axon attaches to the soma. The action potential travels continuously down unmyelinated axons, remaining constant in size, until it reaches the terminal buttons. (When the axon divides, the action potential continues down each branch.) In myelinated axons, ions can flow through the membrane only at the nodes of Ranvier, because the axons are covered everywhere else with myelin, which isolates them from the extracellular fluid. Thus, the action potential is conducted from one node of Ranvier to the next by means of passive cable properties. When the electrical message reaches a node, voltage-dependent sodium channels open, and the action potential reaches full strength again. This mechanism saves a considerable amount of energy because sodium-potassium transporters are not needed along the myelinated portions of the axons, and saltatory conduction is faster.

COMMUNICATION BETWEEN NEURONS

Now that you know about the basic structure of neurons and the nature of the action potential, it is time to describe the ways that neurons can interact, gathering sensory information and initiating a behavior. As we have seen, neurons communicate by means of synapses, and the medium used for these messages is the chemical released by terminal buttons. These chemicals, called *transmitter substances* (or *neurotransmitters*), diffuse across the fluid-filled gap between the terminal buttons and the membranes of the neurons with which they form synapses. As we will see in this section, the transmitter substances produce **postsynaptic potentials**—brief depolarizations or hyperpolarizations—that increase or decrease the rate of firing of the axon of the postsynaptic neuron.

The Concept of Chemical Transmission

Chemicals are used to transmit information between cells. These chemicals—transmitter substances, neuromodulators, and hormones—control the behavior of cells or organs. All these methods of transmission require the presence of cells that release the chemical and specialized protein molecules (receptors) that detect their presence. These methods differ

postsynaptic potential Alterations in the membrane potential of a postsynaptic neuron, produced by liberation of transmitter substance at the synapse.

primarily in the distance between the cell that secretes the chemical and the receptors that detect its presence.

Transmitter substances (often called *neurotransmitters*) are released by terminal buttons of neurons and are detected by receptors in the membrane of another cell located a very short distance away. The communication at each synapse is private. Neuromodulators travel farther and are dispersed more widely than are neurotransmitters. **Neuromodulators,** too, are released by terminal buttons but are secreted in larger amounts and diffuse for longer distances, modulating the activity of many neurons in a particular part of the brain. Most neuromodulators are composed of proteinlike molecules called *peptides,* which are described later in this chapter.

Most hormones are produced in cells located in the **endocrine glands** (from the Greek *endo-*, "within," and *krinein,* "to secrete"). Others are produced by specialized cells located in various organs, such as the stomach, the intestines, the kidneys, and the brain. Cells that secrete hormones release these chemicals into the extracellular fluid. The hormones are then distributed to the rest of the body through the bloodstream. Hormones affect the activity of cells (including neurons) that contain specialized receptors located either on the surface of their membrane or deep within their nuclei. (Both types are described later in this chapter.) Cells that contain receptors for a particular hormone are referred to as **target cells** for that hormone; only these cells respond to its presence. Many neurons contain hormone receptors, and hormones are able to affect behavior by stimulating the receptors and changing the activity of these neurons. For example, a sex hormone, testosterone, increases the aggressiveness of most male mammals.

Neurotransmitters, neuromodulators, and hormones exert their effects on cells by attaching to a particular region of a receptor molecule called the **binding site.** A molecule of the chemical fits into the binding site the way a key fits into a lock; the shape of the binding site and the shape of the molecule of the transmitter substance are complementary. (A chemical that attaches to a binding site is called a **ligand,** from *ligare,* "to bind.") Neurotransmitters, neuromodulators, or hormones are natural ligands, produced by cells of the body. But other chemicals found in nature (primarily in plants or in the poisonous venoms of animals) can serve as ligands, too. In addition, artificial ligands can be produced in the laboratory. These chemicals are discussed in Chapter 4, which deals with drugs and their effects.

Structure of Synapses

As you have already learned, synapses are junctions between the terminal buttons at the ends of the axonal branches of one neuron and the membrane of another. Synapses can occur in three places: on dendrites, on the soma, and on other axons. These synapses are referred to as *axodendritic, axosomatic,* and *axoaxonic.* Axodendritic synapses can occur on the smooth surface of a dendrite or on **dendritic spines**—small protrusions that stud the dendrites of several types of large neurons in the brain. (See *Figure 2.26.*)

Figure 2.27 illustrates a synapse. The **presynaptic membrane,** located at the end of the terminal button, faces the **postsynaptic membrane,** located on the neuron that receives the message (the *postsynaptic* neuron). These two membranes face each other across the **synaptic cleft,** a gap that varies in size from synapse to synapse but is usually around 200 Å wide. (An ångström, Å, is one ten-millionth of a millimeter.) The synaptic cleft contains extracellular fluid, through which the transmitter substance diffuses. (See *Figure 2.27* on page 45.)

As you may have noticed in Figure 2.27, three prominent structures are located in the cytoplasm of the terminal button: mitochondria, synaptic vesicles, and a cisterna. We also see microtubules, which are responsible for transporting material between the soma and terminal button. The presence of mitochondria implies that the terminal

neuromodulator A naturally secreted substance that acts like a neurotransmitter except that it is not restricted to the synaptic cleft but diffuses through the extracellular fluid.

endocrine gland A gland that liberates its secretions into the extracellular fluid around capillaries and hence into the bloodstream.

target cell The type of cell that is directly affected by a hormone or nerve fiber.

binding site The location on a receptor protein to which a ligand binds.

ligand *(**ligh** gand* or *__ligg__ and)* A chemical that binds with the binding site of a receptor.

dendritic spine A small bud on the surface of a dendrite, with which a terminal button from another neuron forms a synapse.

presynaptic membrane The membrane of a terminal button that lies adjacent to the postsynaptic membrane.

postsynaptic membrane The cell membrane opposite the terminal button in a synapse; the membrane of the cell that receives the message.

synaptic cleft The space between the presynaptic membrane and the postsynaptic membrane.

synaptic vesicle *(**vess** i kul)* A small, hollow, beadlike structure found in terminal buttons; contains molecules of a neurotransmitter.

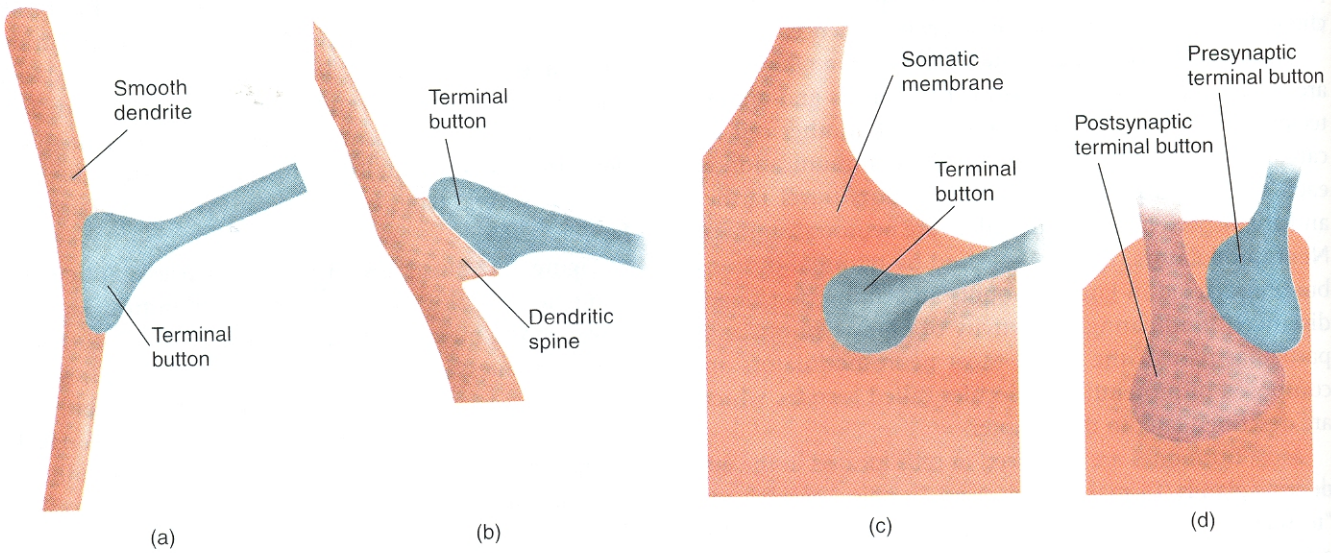

Figure 2.26
Types of synapses. Axodendritic synapses can occur on the smooth surface of a dendrite (a) or on dendritic spines (b). Axosomatic synapses occur on somatic membrane (c). Axoaxonic synapses consist of synapses between two terminal buttons (d).

button needs energy to perform its functions. **Synaptic vesicles** are small, rounded objects in the shape of spheres or ovoids. (The term *vesicle* means "little bladder.") Many terminal buttons contain two types of synaptic vesicles, large and small. Small synaptic vesicles (found in all terminal buttons) contain molecules of the transmitter substance. These vesicles are found in greatest numbers around the part of the presynaptic membrane that faces the synaptic cleft—next to the **release zone,** the region from which transmitter substance is released. In many terminal buttons, we see a scattering of large synaptic vesicles. These vesicles contain one of a number of different neuropeptides, the functions of which are described later in this chapter. (See *Figure 2.27.*)

Small synaptic vesicles are produced in the Golgi apparatus located in the soma and are carried by fast axoplasmic transport to the terminal button. As we will see, they are also produced from recycled material in the terminal button by the **cisternae,** collections of membrane similar to the Golgi apparatus. Large synaptic vesicles are produced in the soma and transported through the axoplasm to the terminal buttons.

In an electron micrograph the postsynaptic membrane under the terminal button appears somewhat thicker and more dense than the membrane elsewhere. This postsynaptic density is caused by the presence of receptors—specialized protein molecules that detect the presence of transmitter substances in the synaptic cleft. (See *Figure 2.27.*)

Release of Transmitter Substance

When action potentials are conducted down an axon (and down all of its branches), something happens inside all of the terminal buttons: A number of small synaptic vesicles located just inside the postsynaptic membrane fuse with the membrane and then break open, spilling their contents into the synaptic cleft.

Heuser and colleagues (Heuser, 1977; Heuser et al., 1979) obtained photomicrographs that illustrate this process. Because the release of transmitter substance is a very rapid event, taking only a few msec to occur, special procedures are needed to stop the action so that the details can be studied. The experimenters electrically stimulated the nerve attached to an isolated frog muscle and then dropped the muscle against a block of pure copper that had been cooled to 4 K (approximately −453° F). Contact with the supercooled metal froze the outer layer of tissue in 2 msec or less. The ice held the components of the terminal buttons in place until they could be chemically stabilized and examined with an electron microscope. Figure 2.28 shows a por-

release zone A region of the interior of the postsynaptic membrane of a synapse to which synaptic vesicles attach and release their neurotransmitter into the synaptic cleft.
cisterna A part of the Golgi apparatus; through the process of pinocytosis, it receives portions of the presynaptic membrane and recycles them into synaptic vesicles.

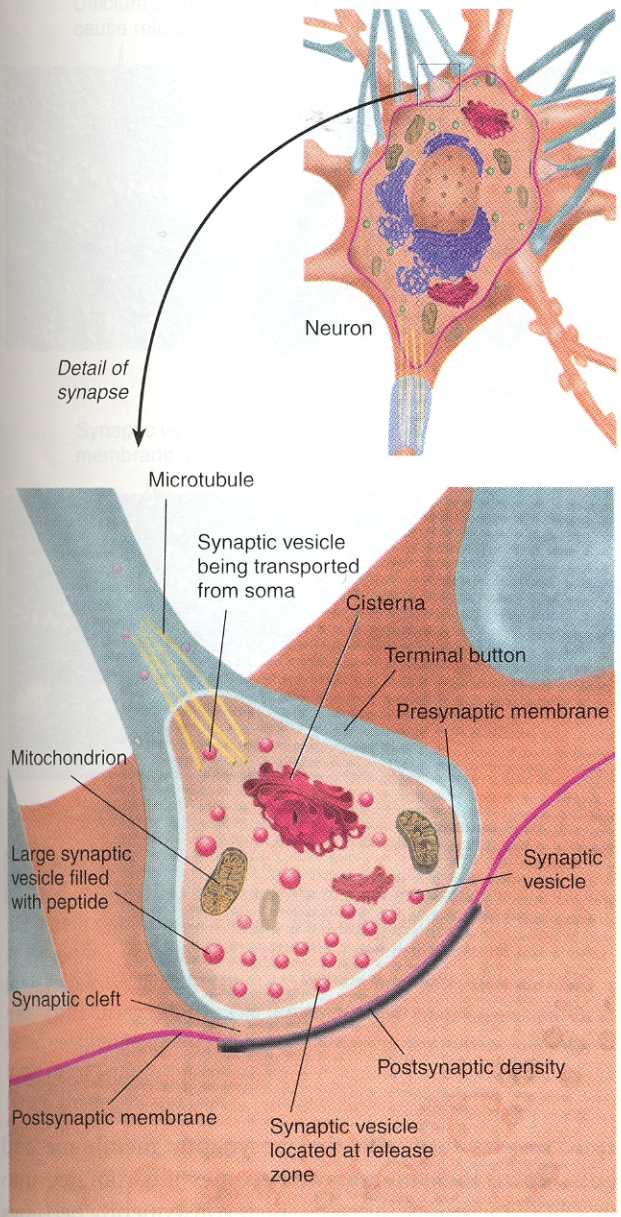

Figure 2.27
Details of a synapse.

tion of the synapse in cross section; note the vesicles that appear to be fused with the presynaptic membrane, forming the shape of an omega (Ω). (See ***Figure 2.28.***)

How does an action potential cause synaptic vesicles to release the transmitter substance? Based on experiments with secretory cells in a variety of different species, Almers (1990) suggested the following model. Some synaptic vesicles are "docked" against the presynaptic membrane, ready to release their transmitter substance into the synaptic cleft. Docking is accomplished when clusters of protein molecules attach to protein molecules located in the presynaptic membrane. (See ***Figure 2.29.***)

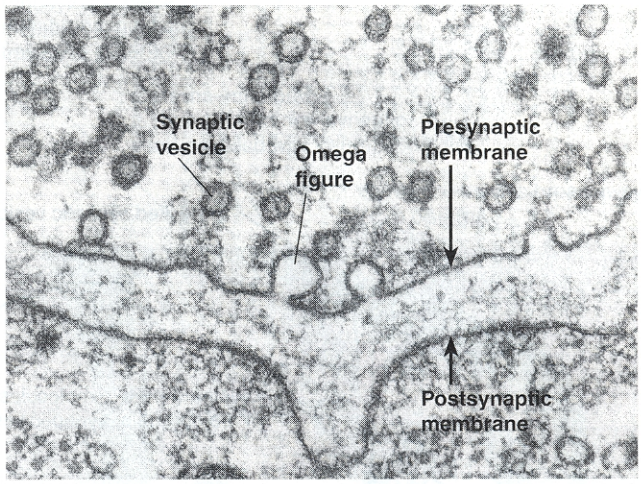

Figure 2.28
A photograph from an electron microscope, showing a cross section of a synapse. The omega-shaped figures are synaptic vesicles fusing with the presynaptic membranes of terminal buttons that form synapses with frog muscle.
(From Heuser, J.E., in *Society for Neuroscience Symposia, Vol. II,* edited by W.M. Cowan and J.A. Ferrendelli. Bethesda, MD: Society for Neuroscience, 1977.)

The release zone of the presynaptic membrane contains voltage-dependent calcium channels. When the membrane of the terminal button is depolarized by an arriving action potential, the calcium channels open. Like sodium ions, calcium ions (Ca^{2+}) are located in highest concentration in the extracellular fluid. Thus, when the voltage-dependent calcium channels open, Ca^{2+} flows into the cell, propelled by electrostatic pressure and the force of diffusion. The entry of Ca^{2+} is an essential step; if neurons are placed in a solution that contains no calcium ions, an action potential no longer causes the release of the transmitter substance. (Calcium transporters, similar in operation to sodium-potassium transporters, later remove the intracellular Ca^{2+}.)

As we will see later in this chapter and in subsequent chapters of this book, the calcium ion plays many important roles in biological processes within cells. The calcium ion can bind with various types of proteins, changing their characteristics. According to Almers (1990), the calcium that enters the terminal button binds with the clusters of protein molecules that join the membrane of the synaptic vesicles with the presynaptic membrane. This event makes the segments of the clusters of protein molecules move apart, producing a *fusion pore*—a hole through both membranes that enables them to fuse together. (See ***Figure 2.29.***)

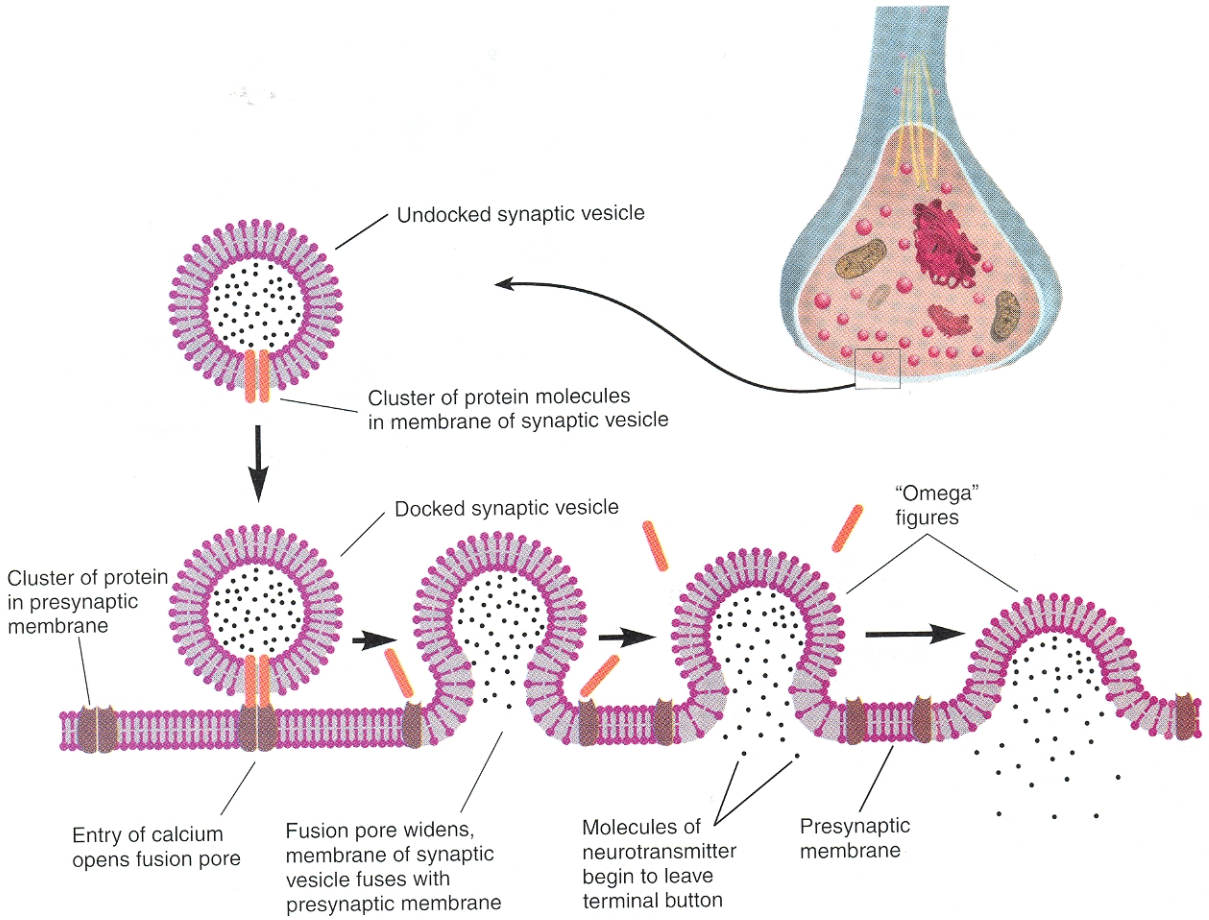

Figure 2.29
Release of neurotransmitter. An action potential opens calcium channels. Calcium ions enter and bind with the protein embedded in the membrane of synaptic vesicles docked at the release zone. The fusion pores open and the transmitter substance is released into the synaptic cleft. The membrane of the vesicles fuses with that of the terminal button.

Figure 2.30 shows two photomicrographs of the presynaptic membrane, before and after the fusion pores have opened. We see the face of the presynaptic membrane as it would be viewed from the postsynaptic membrane. As you can see, the synaptic vesicles are aligned in a row along the release zone. The small bumps arranged in lines on each side of the synaptic vesicles appear to be voltage-dependent calcium channels. (See ***Figure 2.30.***)

What happens to the membrane of the synaptic vesicles after they have broken open and released the transmitter substance they contain? Every time some transmitter substance is released the membrane of the terminal button gains the membrane of the synaptic vesicles that fuse with it and becomes slightly larger. Obviously, this process cannot go on indefinitely, or else the terminal buttons would get enormously big. The answer is that the membrane is recycled. Heuser and Reese (1973) proposed that as the synaptic vesicles fuse with the presynaptic membrane and burst open, their membrane becomes incorporated into that of the terminal button, which consequently becomes larger. Therefore, if the proper size of the terminal button is to be maintained, some membrane must be removed. Heuser and Reese obtained evidence that suggested that at the point of junction between the axon and the terminal button, little buds of membrane pinch off into the cytoplasm, in a process called **pinocytosis.** The buds of membrane migrate to the cisternae and fuse with them, pooling the lipid molecules in their membrane with that of the cisternae. Then new synaptic vesicles are produced as beads of membrane break off from the cisternae. These vesicles are

pinocytosis *(pee no sy **toh** sis)* The pinching off of a bud of cell membrane, which travels to the interior of the cell.

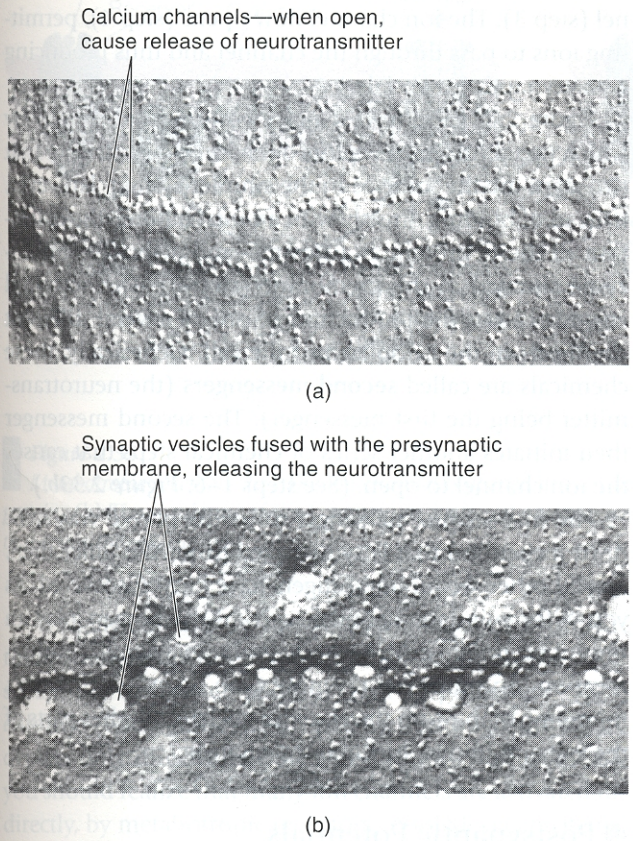

Figure 2.30
Photomicrographs of the release of neurotransmitter by a terminal button that forms a synapse with a frog muscle. The views are of the surface of the fusion zone of the terminal button. (a) Just prior to release. The two rows of dots are probably calcium channels. (b) During release. The larger circles are holes in the presynaptic membrane, revealing the contents of the synaptic vesicles that have fused with it.
(From Heuser, J., and Reese, T. *Journal of Cell Biology*, 1981, *88*, 564–580.)

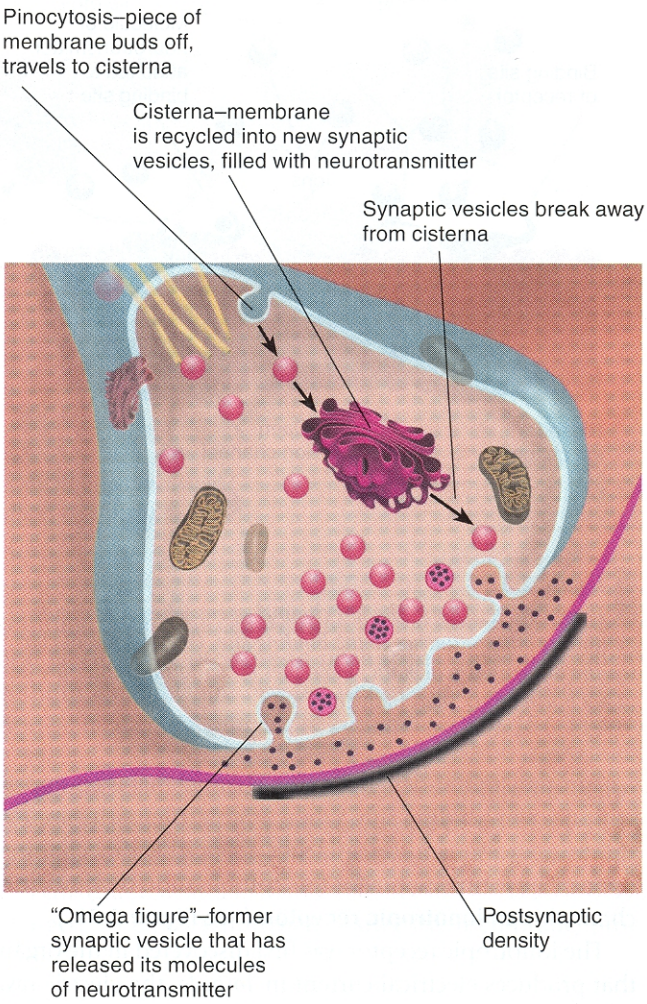

Figure 2.31
Recycling of the membrane of synaptic vesicles that have released neurotransmitter into the synaptic cleft.

then filled with molecules of transmitter substance, the appropriate proteins are inserted into the membrane, and they are transported toward the presynaptic membrane. (See *Figure 2.31.*)

Activation of Receptors

How do molecules of the transmitter substance produce a depolarization or hyperpolarization in the postsynaptic membrane? They do so by diffusing across the synaptic cleft and attaching to the binding sites of special protein molecules attached to the postsynaptic membrane, called **postsynaptic receptors.** Once binding occurs, the postsynaptic receptors open **neurotransmitter-dependent ion channels,** which permit the passage of specific ions into or out of the cell. Thus, the presence of the transmitter substance in the synaptic cleft allows particular ions to pass through the membrane, changing the local membrane potential.

Neurotransmitters open ion channels by at least two different methods, direct and indirect. The direct method is simpler, so I shall describe it first. Figure 2.32 illustrates

postsynaptic receptor A receptor molecule in the postsynaptic membrane of a synapse that contains a binding site for a neurotransmitter.

neurotransmitter-dependent ion channel An ion channel that opens when a molecule of a neurotransmitter binds with a postsynaptic receptor.

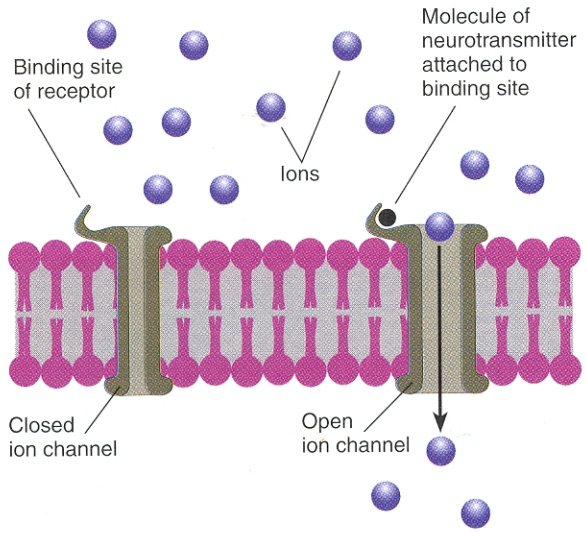

Figure 2.32
Ionotropic receptors. The ion channel opens when a molecule of neurotransmitter attaches to the binding site. For purposes of clarity, the drawing is schematic; molecules of neurotransmitter are actually much larger than individual ions.

a neurotransmitter-dependent ion channel that is equipped with its own binding site. When a molecule of the appropriate neurotransmitter attaches to it, the ion channel opens. The formal name for this combination receptor/ion channel is an **ionotropic receptor.** (See *Figure 2.32.*)

The ionotropic receptor was first discovered in the organ that produces electrical current in *Torpedo,* the electric ray, where it occurs in great number. (The electric ray is a fish that generates a powerful electrical current, not some kind of Star Wars weapon.) These receptors, which are sensitive to a transmitter substance called *acetylcholine,* contain sodium channels. When these channels are open, sodium ions enter the cell.

The indirect method is more complicated. Most receptors do not open ion channels directly but instead start a chain of chemical events. These receptors are called **metabotropic receptors** because they involve steps that require that the cell expend energy. Metabotropic receptors are located in close proximity to another protein attached to the membrane—a **G protein.** Figure 2.33(a) shows the simplest type of metabotropic receptor. (See *Figure 2.33,* and note that the numbers in the color squares correspond to the step numbers in the description that follows.) When a molecule of the transmitter substance binds with the receptor (step 1), the receptor activates a G protein situated nearby (step 2). An inactive G protein consists of three subunits. When activated, the α subunit breaks away from the others and attaches to a special binding site of an ion channel (step 3). The ion channel now opens (step 4), permitting ions to pass through the channel and thus producing a postsynaptic potential.

Figure 2.33(b) shows a more complicated system by which metabotropic receptors open ion channels. The first two steps are the same as in the simpler system. However, instead of binding directly with an ion channel, the α subunit of the G protein attaches to—and activates—an enzyme situated in the membrane (step 3). The activated enzyme causes the production of one of several different chemicals in the cytoplasm of the cell. Generically, these chemicals are called **second messengers** (the neurotransmitter being the first messenger). The second messenger then initiates another series of chemical steps that causes the ion channel to open. (See steps 1–6, *Figure 2.33b.*)

The first second messenger to be discovered was *cyclic AMP,* a chemical that is synthesized from ATP. Since then, several other second messengers have been discovered. As you will see in later chapters, second messengers play an important role in both synaptic and nonsynaptic communication. And they can do more than open ion channels; for example, they can travel to the nucleus or other parts of the cell and initiate biochemical changes.

Postsynaptic Potentials

As we saw, postsynaptic potentials can be either depolarizing (excitatory) or hyperpolarizing (inhibitory). What determines the nature of the postsynaptic potential at a particular synapse is not the neurotransmitter itself. Instead, it is determined by the characteristics of the postsynaptic receptors—in particular, *by the particular type of ion channel they open.*

ionotropic receptor *(eye on oh **trow** pik)* A receptor that contains a binding site for a neurotransmitter and an ion channel that opens when a molecule of the neurotransmitter attaches to the binding site.

metabotropic receptor *(meh tab oh **trow** pik)* A receptor that contains a binding site for a neurotransmitter; activates an enzyme that begins a series of events that opens an ion channel elsewhere in the membrane of the cell when a molecule of the neurotransmitter attaches to the binding site.

G protein A protein coupled to a metabotropic receptor; conveys messages to other molecules when a ligand binds with and activates the receptor.

second messenger A chemical produced when a G protein activates an enzyme; carries a signal that results in the opening of the ion channel or causes other events to occur in the cell.

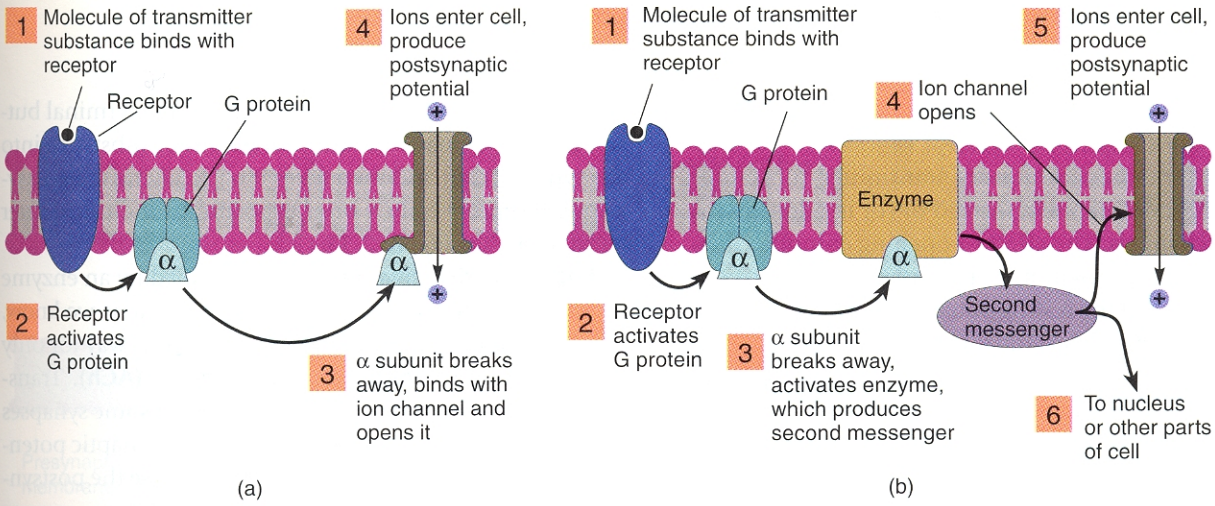

Figure 2.33
Metabotropic receptors. (a) The ion channel is opened directly by the α subunit of an activated G protein. (b) The α subunit of the G protein activates an enzyme, which produces a second messenger that opens the ion channel.

As Figure 2.34 shows, there are four major types of neurotransmitter-dependent ion channels found in the postsynaptic membrane: sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}). Although the figure depicts only directly activated (ionotropic) ion channels, you should realize that many ion channels are activated indirectly, by metabotropic receptors coupled to G proteins.

The neurotransmitter-dependent sodium channel is the most important source of excitatory postsynaptic potentials. As we saw, sodium-potassium transporters keep sodium outside the cell, waiting for the forces of diffusion and electrostatic pressure to push it in. Obviously, when sodium channels are opened, the result is a depolarization—an *excitatory postsynaptic potential (EPSP)*. (See ***Figure 2.34a.***)

We also saw that sodium-potassium transporters maintain a small surplus of potassium ions inside the cell. If potassium channels open, some of these cations will follow this gradient and leave the cell. Because K^+ is positively charged, its efflux will hyperpolarize the membrane, pro-

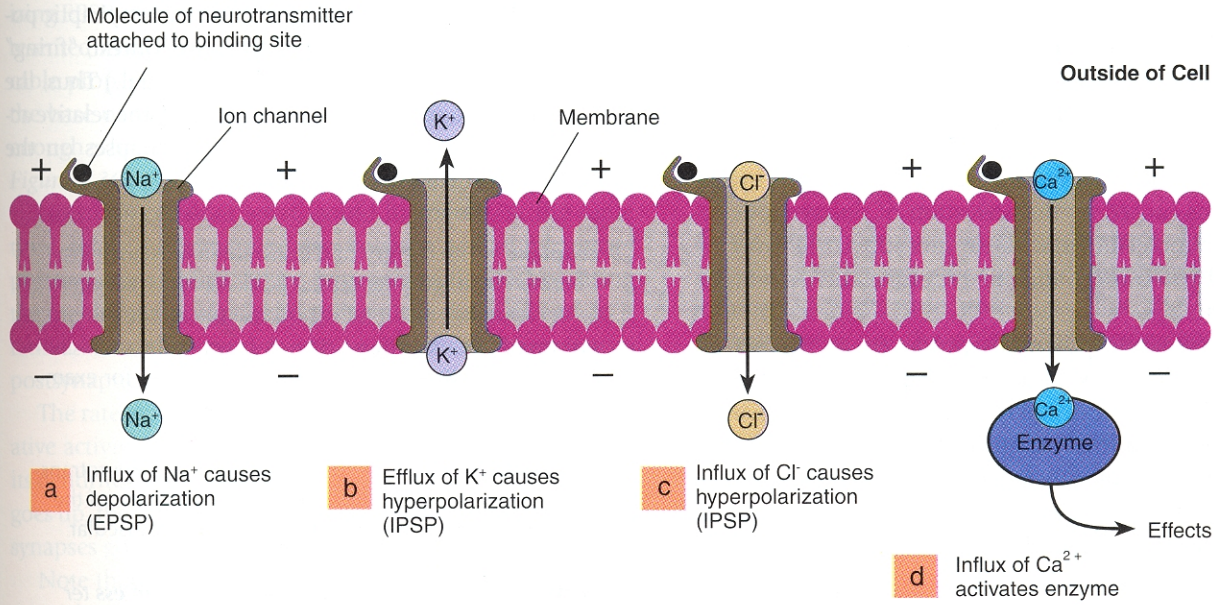

Figure 2.34
Ionic movements during postsynaptic potentials.

ducing an *inhibitory postsynaptic potential* (IPSP). (See ***Figure 2.34b.***)

At many synapses, inhibitory transmitter substances open the chloride channels, instead of (or in addition to) potassium channels. The effect of opening chloride channels depends on the membrane potential of the neuron. If the membrane is at the resting potential, nothing happens, because (as we saw earlier) the forces of diffusion and electrostatic pressure balance perfectly for the chloride ion. However, if the membrane potential has already been depolarized by the activity of excitatory synapses located nearby, then the opening of chloride channels will permit Cl^- to enter the cell. The influx of anions will bring the membrane potential back to its normal resting condition. Thus, the opening of chloride channels serves to neutralize EPSPs. (See ***Figure 2.34c.***)

The fourth type of neurotransmitter-dependent ion channel is the calcium channel. Calcium ions (Ca^{2+}), being positively charged and being located in highest concentration outside the cell, act like sodium ions; that is, the opening of calcium channels depolarizes the membrane, producing EPSPs. But calcium does even more. As we saw earlier in this chapter, the entry of calcium into the terminal button triggers the migration of synaptic vesicles and the release of the transmitter substance. In the dendrites of the postsynaptic cell, calcium binds with and activates special enzymes. These enzymes have a variety of effects, including the production of biochemical and structural changes in the postsynaptic neuron. As we will see in Chapter 14, one of the ways that learning affects the connections between neurons involves changes in dendritic spines initiated by the opening of calcium channels. (See ***Figure 2.34d.***)

Termination of Postsynaptic Potentials

Postsynaptic potentials are brief depolarizations or hyperpolarizations caused by the activation of postsynaptic receptors with molecules of a transmitter substance. They are kept brief by two mechanisms: reuptake and enzymatic deactivation.

The postsynaptic potentials produced by almost all transmitter substances are terminated by **reuptake.** This process is simply an extremely rapid removal of transmitter substance from the synaptic cleft by the terminal button. The transmitter substance does not return in the vesicles that get pinched off the membrane of the terminal button. Instead, the membrane contains special transporter molecules that draw on the cell's energy reserves to force molecules of the transmitter substance from the synaptic cleft directly into the cytoplasm—just as sodium-potassium transporters move Na^+ and K^+ across the membrane. When an action potential arrives, the terminal button releases a small amount of transmitter substance into the synaptic cleft and then takes it back, giving the postsynaptic receptors only a brief exposure to the transmitter substance. (See ***Figure 2.35.***)

Enzymatic deactivation is accomplished by an enzyme that destroys the transmitter molecule. As far as we know, postsynaptic potentials are terminated in this way for only one transmitter substance—**acetylcholine (ACh).** Transmission at synapses on muscle fibers and at some synapses between neurons is mediated by ACh. Postsynaptic potentials produced by ACh are short-lived because the postsynaptic membrane at these synapses contains an enzyme called **acetylcholinesterase (AChE).** AChE destroys ACh by cleaving it into its constituents—choline and acetate. Because neither of these substances is capable of activating postsynaptic receptors, the postsynaptic potential is terminated once the molecules of ACh are broken apart. AChE is an extremely energetic destroyer of ACh; one molecule of AChE will chop apart more that five thousand molecules of ACh each second.

Effects of Postsynaptic Potentials: Neural Integration

We have seen how neurons are interconnected by means of synapses, how action potentials trigger the release of transmitter substances, and how these chemicals initiate excitatory or inhibitory postsynaptic potentials. Excitatory postsynaptic potentials increase the likelihood that the postsynaptic neuron will fire; inhibitory postsynaptic potentials decrease this likelihood. (In this context, "firing" refers to the occurrence of an action potential.) Thus, the rate at which an axon fires is determined by the relative activity of the excitatory and inhibitory synapses on the soma and dendrites of that cell.

reuptake The reentry of a transmitter substance just liberated by a terminal button back through its membrane, thus terminating the postsynaptic potential.

enzymatic deactivation The destruction of a transmitter substance by an enzyme after its release—for example, the destruction of acetylcholine by acetylcholinesterase.

acetylcholine (ACh) *(a see tul **koh** leen)* A neurotransmitter found in the brain, spinal cord, and parts of the peripheral nervous system; responsible for muscular contraction.

acetylcholinesterase (AChE) *(a see tul koh lin **ess** ter ace)* The enzyme that destroys acetylcholine soon after it is liberated by the terminal buttons, thus terminating the postsynaptic potential.

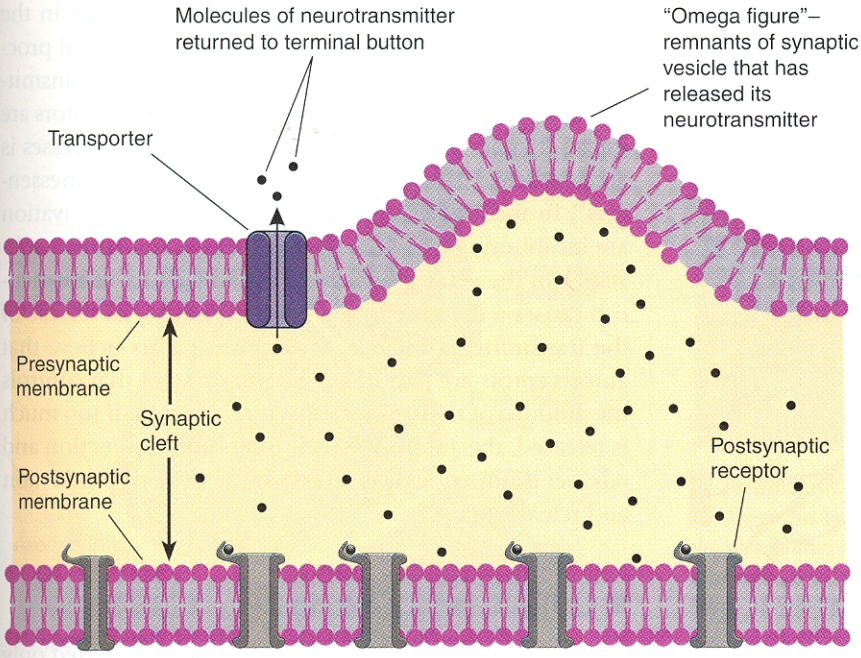

Figure 2.35
Reuptake. Molecules of a neurotransmitter that has been released into the synaptic cleft are transported back into the terminal button.

Let us look at the elements of this process. The interaction of the effects of excitatory and inhibitory synapses on a particular neuron is called **neural integration.** (*Integration* means "to make whole," in the sense of combining two or more functions.) Figure 2.36 illustrates the effects of excitatory and inhibitory synapses. The top panel shows what happens when several excitatory synapses become active. The release of the transmitter substance produces depolarizing EPSPs in the dendrites of neuron A. These EPSPs (represented in red) are then transmitted, by means of passive cable properties, down the dendrites, across the soma, to the base of the axon. If the depolarization is still strong enough when it reaches this point, the axon will fire. (See *Figure 2.36a.*)

Now let's consider what would happen if, at the same time, inhibitory synapses also become active. Inhibitory postsynaptic potentials are hyperpolarizing—they bring the membrane potential away from the threshold of excitation. Thus, they tend to cancel the effects of excitatory postsynaptic potentials. (See *Figure 2.36b.*)

The rate at which a neuron fires is controlled by the relative activity of the excitatory and inhibitory synapses on its dendrites and soma. If the activity of excitatory synapses goes up, the rate of firing will go up. If the rate of inhibitory synapses goes up, the rate of firing will go down.

Note that *neural* inhibition (that is, an inhibitory postsynaptic potential) does not always produce *behavioral* inhibition. For example, suppose a group of neurons inhibits a particular movement. If these neurons are inhibited, they will no longer suppress the behavior. Thus, inhibition of the inhibitory neurons makes the behavior more likely to occur. Of course, the same is true for neural excitation. Neural *excitation* of neurons that *inhibit* a behavior suppresses that behavior. For example, when we are dreaming, a particular set of inhibitory neurons in the brain becomes active and prevents us from getting up and acting out our dreams. (As we will see in Chapter 9, if these neurons are destroyed, people *will* act out their dreams.) Neurons are elements in complex circuits; without knowing the details of these circuits, one cannot predict the effects of the excitation or inhibition of one set of neurons on an organism's behavior.

Autoreceptors

Postsynaptic receptors detect the presence of a transmitter substance in the synaptic cleft and initiate excitatory or inhibitory postsynaptic potentials. But the postsynaptic membrane is not the only location of receptors that respond to transmitter substances. Many neurons also possess receptors that respond to the transmitter substance that *they* release, called **autoreceptors.**

neural integration The process by which inhibitory and excitatory postsynaptic potentials summate and control the rate of firing of a neuron.

autoreceptor A receptor molecule located on a neuron that responds to the neurotransmitter released by that neuron.

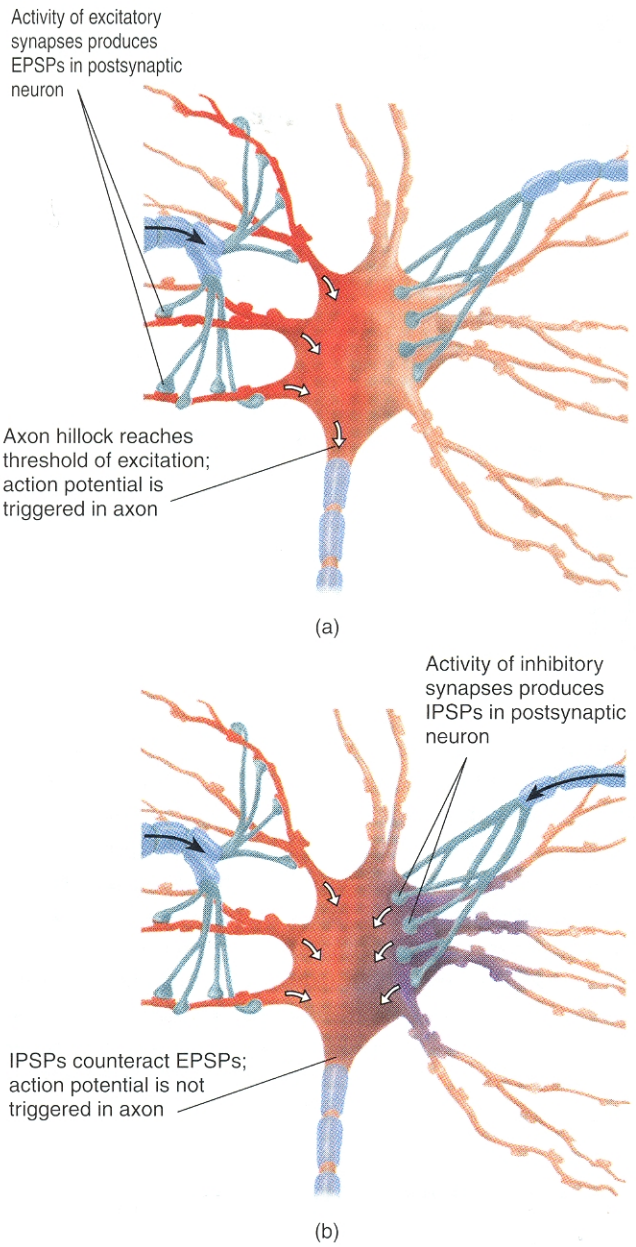

Figure 2.36
Neural integration. (a) If several excitatory synapses are active at the same time, the EPSPs they produce (shown in red) summate as they travel toward the axon, and the axon fires. (b) If several inhibitory synapses are active at the same time, the IPSPs they produce (shown in blue) diminish the size of the EPSPs and prevent the axon from firing.

Autoreceptors can be located on the membrane of any part of the cell, but in this discussion we will consider those located on the terminal button. As far as we know, autoreceptors do not control ion channels. Thus, when stimulated by a molecule of the appropriate transmitter substance, autoreceptors do not produce changes in the membrane potential. Instead, they regulate internal processes, including the synthesis and release of the transmitter substance. (As you may have guessed, autoreceptors are metabotropic; the control they exert on these processes is accomplished through G proteins and second messengers.) In most cases the effects of autoreceptor activation are inhibitory; that is, the presence of the transmitter substance in the extracellular fluid in the vicinity of the neuron causes a decrease in the rate of synthesis or release of the transmitter substance. Most investigators believe that autoreceptors are part of a regulatory system that controls the amount of transmitter substance released. If too much is released, the autoreceptors inhibit both production and release; if not enough is released, the rates of production and release go up.

Other Types of Synapses

So far, the discussion of synaptic activity has referred only to the effects of postsynaptic excitation or inhibition. These effects occur at axosomatic or axodendritic synapses. Axoaxonic synapses work differently. Axoaxonic synapses do not contribute directly to neural integration. Instead, axoaxonic synapses alter the amount of transmitter substance released by the terminal buttons of the postsynaptic axon. They can produce presynaptic modulation: presynaptic inhibition or presynaptic facilitation.

As you know, the release of a transmitter substance by a terminal button is initiated by an action potential. Normally, a particular terminal button releases a fixed amount of transmitter substance each time an action potential arrives. However, the release of transmitter substance can be modulated by the activity of axoaxonic synapses. If the activity of the axoaxonic synapse decreases the release of the transmitter substance, the effect is called **presynaptic inhibition.** If it increases the release, it is called **presynaptic facilitation.** (See *Figure 2.37.*)

Many very small neurons have extremely short processes and apparently lack axons. These neurons form *dendrodendritic synapses,* or synapses between dendrites. Because these

presynaptic inhibition The action of a presynaptic terminal button in an axoaxonic synapse; reduces the amount of neurotransmitter released by the postsynaptic terminal button.

presynaptic facilitation The action of a presynaptic terminal button in an axoaxonic synapse; increases the amount of neurotransmitter released by the postsynaptic terminal button.

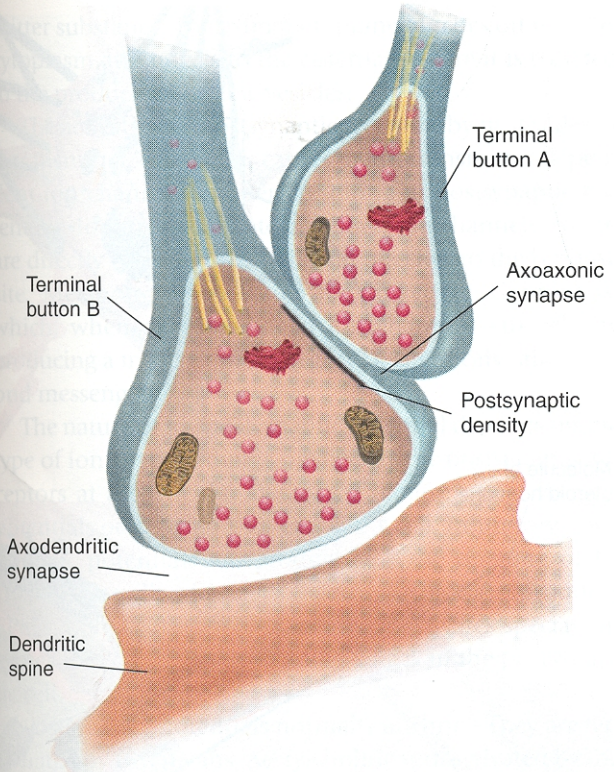

Figure 2.37
An axoaxonic synapse. The activity of terminal button A can increase or decrease the amount of neurotransmitter released by terminal button B.

neurons lack long axonal processes, they do not transmit information from place to place within the brain. Most investigators believe that they perform regulatory functions, perhaps helping to organize the activity of groups of neurons. Because these neurons are so small, they are difficult to study; thus, little is known about their function.

Some larger neurons, as well, form dendrodendritic synapses. Some of these synapses are chemical, indicated by the presence of synaptic vesicles in one of the juxtaposed dendrites and a postsynaptic thickening in the membrane of the other. Other synapses are *electrical;* the membranes meet and almost touch, forming a **gap junction.** The membranes on both sides of a gap junction contain channels that permit ions to diffuse from one cell to another. Thus, changes in the membrane potential of one neuron induce changes in the membrane of the other. (See *Figure 2.38.*) Although most gap junctions in vertebrate synapses are dendrodendritic, axosomatic and axodendritic gap junctions also occur. Gap junctions are common in invertebrates; their function in the vertebrate nervous system is not known.

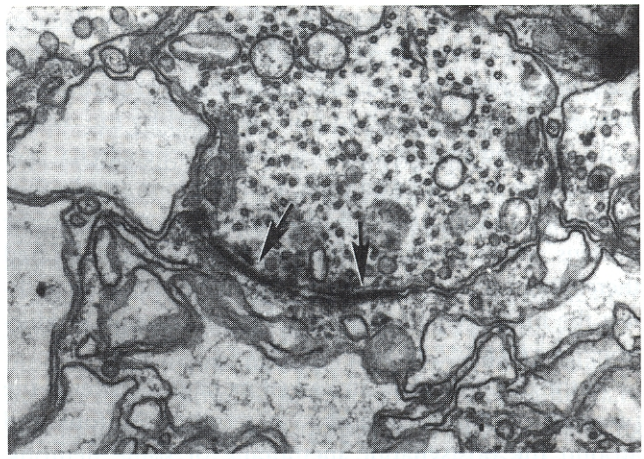

Figure 2.38
A gap junction, which permits direct electrical coupling between the membranes of adjacent neurons.
(From Bennett, M.V.L., and Pappas, G.D. *The Journal of Neuroscience,* 1983, 3, 748–761.)

Nonsynaptic Chemical Communication

Not all chemical communication takes place at synapses. Neurons possess receptors for a variety of substances in the membrane of all parts of the cell—and even in their nucleus. These receptors are sensitive to neuromodulators and to hormones.

Some of these receptors are ionotropic in nature and contain binding sites for several different molecules, including both neurotransmitters and neuromodulators. (The best known example, the $GABA_A$ receptor, is described in Chapter 4.) But most of the receptors found in the membrane are metabotropic—coupled to a G protein that generates a second messenger that produces changes in the cell's physiological processes.

First, let us consider receptors for hormones. Endocrine glands produce two classes of hormones: peptides and steroids. **Peptides** are chains of amino acids that are linked together by special chemical links called *peptide bonds* (hence their name). For example, insulin and the hormones of the pituitary gland are peptides. Peptides exert their effects on target cells by stimulating metabotropic receptors located in the membrane. The second messenger that is generated travels to the nucleus of the cell, where it initiates changes in the cell's physiological processes.

gap junction A special junction between cells that permits direct communication by means of electrical coupling.

peptide A chain of amino acids joined together by peptide bonds.

Steroids consist of very small fat-soluble molecules. (*Steroid* derives from *stereos*, "solid," and *oleum*, "oil." They are synthesized from cholesterol.) Examples of steroid hormones include the sex hormones secreted by the ovaries and testes and the hormones secreted by the adrenal cortex. Because steroid hormones are soluble in lipids, they pass easily through the cell membrane. They travel to the nucleus, where they attach themselves to receptors located there. The receptors, stimulated by the hormone, then direct the machinery of the cell to alter its protein production. (See ***Figure 2.39.***)

In the past few years, investigators have discovered the presence of steroid receptors in terminal buttons and around the postsynaptic membrane of some neurons. These steroid receptors influence synaptic transmission, and they do so rapidly. Exactly how these steroid receptors work is still not known.

Interim Summary

Synapses consist of junctions between the terminal buttons of one neuron and the membrane—usually the somatic or dendritic membrane—of another. When an action potential is transmitted down an axon, the terminal buttons at the end release a transmitter substance, a chemical that produces either depolarizations (EPSPs) or hyperpolarizations (IPSPs) of the postsynaptic membrane. The rate of firing of the axon of the postsynaptic cell is determined by the relative activity of the excitatory and inhibitory synapses on the membrane of its dendrites and soma—a phenomenon known as *neural integration.*

Chemical communication takes place between a cell that secretes a chemical and one that contains receptors for that chemical. The communication can involve neurotransmitters, neuromodulators, or hormones; the distance varies from the space that separates the presynaptic and postsynaptic membrane to the space that separates cells at different locations in the body. Neurotransmitters, neuromodulators, and hormones act on cells by attaching to the binding sites of receptors and initiating chemical changes in these cells.

Synapses consist of junctions between the terminal buttons of one neuron and the membrane—usually the somatic or dendritic membrane—of another. The terminal button contains synaptic vesicles. Most terminal buttons contain two sizes of vesicles, the smaller of which are found in greatest numbers around the release zone of the presynaptic membrane. When an action potential is transmitted down an axon, the depolarization opens voltage-dependent calcium channels, which permit Ca^{2+} to enter. The calcium ions bind with the clusters of protein molecules in the membranes of synaptic vesicles already docked at the release zone. The protein clusters spread apart, causing the vesicles to break open and fuse their membrane with that of the terminal button, thus releasing the trans-

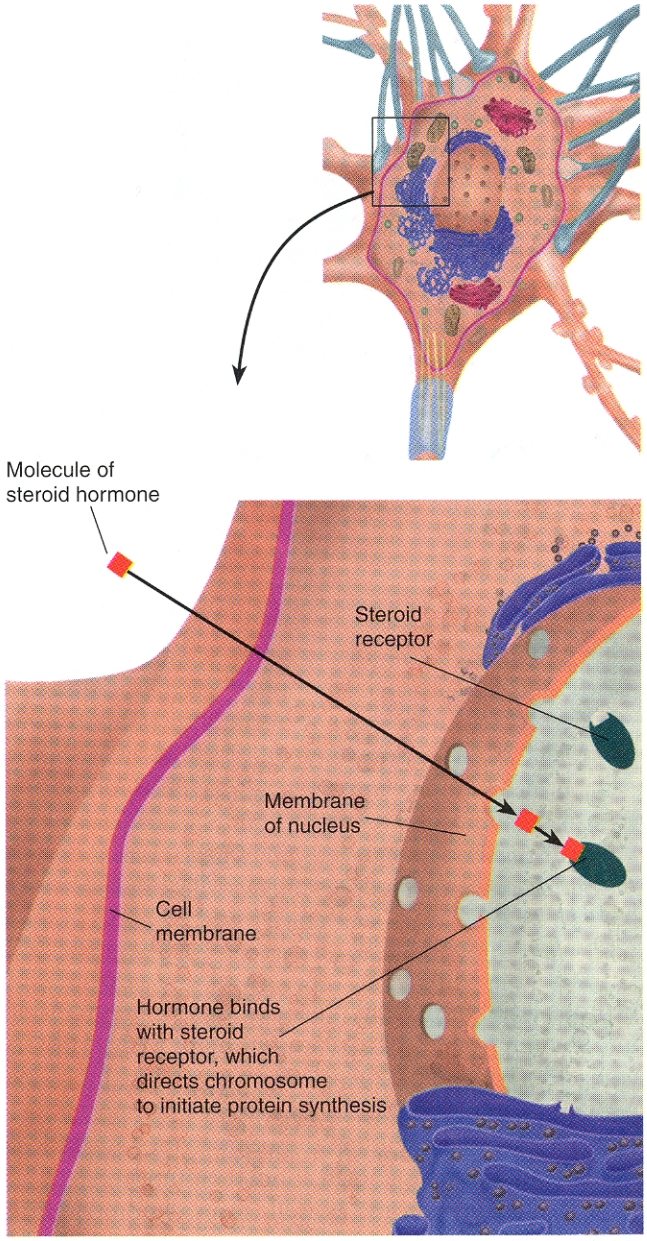

Figure 2.39
Action of steroid hormones. Steroid hormones affect their target cells by means of specialized receptors in the nucleus. Once a receptor binds with a molecule of a steroid hormone, it causes genetic mechanisms to initiate protein synthesis.

steroid A chemical of low molecular weight, derived from cholesterol. Steroid hormones affect their target cells by attaching to receptors found within the cell.

mitter substance. The extra membrane pinches off into the cytoplasm and travels to the cisternae, where it is recycled in the production of new vesicles.

The activation of postsynaptic receptors by molecules of a transmitter substance causes neurotransmitter-dependent ion channels to open, resulting in postsynaptic potentials. Ionotropic receptors contain ion channels, which are directly opened when a ligand attaches to the binding site. Metabotropic receptors are linked to G proteins, which, when activated, open ion channels—usually by producing a member of a category of chemicals called second messengers.

The nature of the postsynaptic potential depends on the type of ion channel that is opened by the postsynaptic receptors at a particular synapse. Excitatory postsynaptic potentials occur when Na^+ enters the cell. Inhibitory postsynaptic potentials are produced by the opening of K^+ channels or Cl^- channels. The entry of Ca^{2+} produces EPSPs, but even more importantly, it activates special enzymes that cause physiological changes in the postsynaptic cell.

Postsynaptic potentials normally are brief. They are terminated by two means. Acetylcholine is deactivated by the enzyme acetylcholinesterase. In all other cases (as far as we know) molecules of the transmitter substance are removed from the synaptic cleft by means of transporters located in the presynaptic membrane, which transport the molecules back into the cytoplasm. This retrieval process is called reuptake.

The presynaptic membrane, as well as the postsynaptic membrane, contains receptors that detect the presence of a transmitter substance. Presynaptic receptors, also called autoreceptors, monitor the quantity of transmitter substance that a neuron releases and, apparently, regulate the amount that is synthesized or released.

Axosomatic and axodendritic synapses are not the only kinds found in the nervous system. Axoaxonic synapses produce presynaptic inhibition or presynaptic facilitation by blocking or promoting the opening of calcium channels in the terminal button, thus reducing or enhancing the amount of transmitter substance that is liberated. Dendrodendritic synapses also exist, but their role in neural communication is not yet understood.

Nonsynaptic chemical transmission is similar to synaptic transmission. Peptide neuromodulators and hormones activate metabotropic peptide receptors located in the membrane; their effects are mediated through the production of second messengers. Steroid hormones enter the nucleus, where they bind with receptors capable of altering the synthesis of proteins that regulate the cell's physiological processes. These hormones also bind with receptors located outside the nucleus, but less is known about their functions.

Suggested Readings

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Nicholls, J. G., Martin, A. R., Wallace, B. G., and Kuffler, S. W. *From Neuron to Brain,* 3rd ed. Sunderland, MA: Sinauer, 1992.