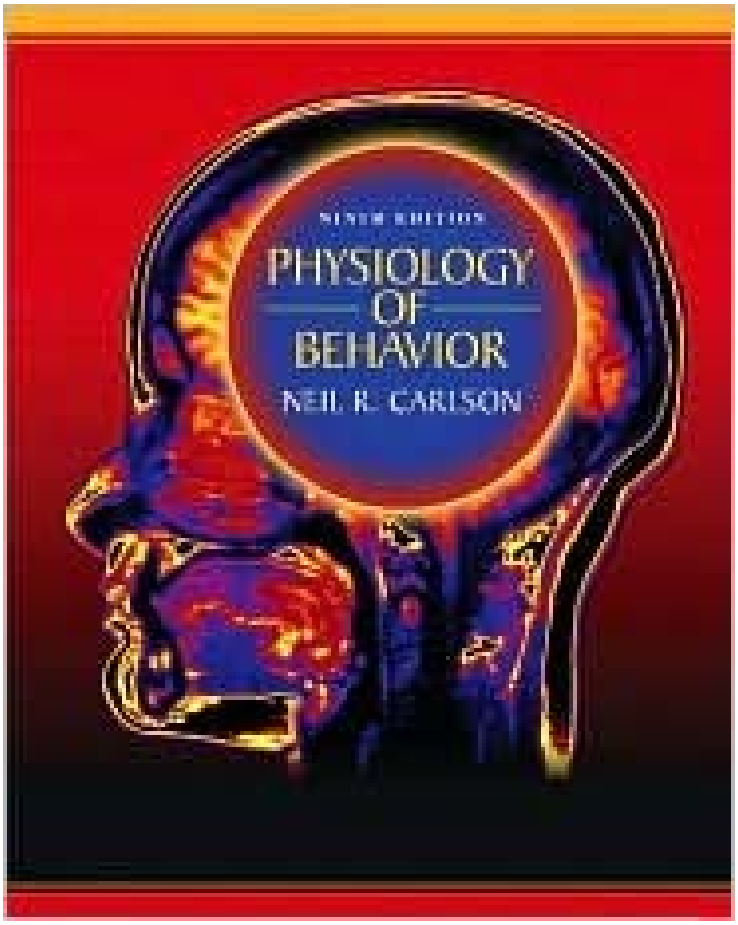
NINTH EDITION
PHYSIOLOGY
OF
BEHAVIOR
NEIL R. CARLSON

Kathryn D. was getting desperate. All her life she had been healthy and active, eating wisely and keeping fit with sports and regular exercise. She went to her health club almost every day for a session of low-impact aerobics, followed by a swim. But several months ago, she began having trouble keeping up with her usual schedule. At first, she found herself getting tired toward the end of her aerobics class. Her arms, particularly, seemed to get heavy. Then when she entered the pool and started swimming, she found that it was hard to lift her arms over her head; she abandoned the crawl and the backstroke and did the sidestroke and breaststroke instead. She did not have any flulike symptoms, so she told herself that she needed more sleep and perhaps she should eat a little more.

Over the next few weeks, however, things only got worse. Aerobics classes were becoming an ordeal. Her instructor became concerned and suggested that Kathryn see her doctor. She did so, but he could find nothing wrong with her. She was not anemic, showed no signs of an infection, and seemed to be well nourished. He asked how things were going at work.

"Well, lately I've been under some pressure," she said. "The head of my department quit a few weeks ago, and I've taken over his job temporarily. I think I have a chance of getting the job permanently, but I feel as if my bosses are watching me to see whether I'm good enough for the job." Kathryn and her physician agreed that increased stress could be the cause of her problem. "I'd prefer not to give you any medication at this time," he said, "but if you don't feel better soon we'll have a closer look at you."

She *did* feel better for a while, but then all of a sudden her symptoms got worse. She quit going to the health club and found that she even had difficulty finishing a day's work. She was certain that people were noticing that she was no longer her lively self, and she was afraid that her chances for the promotion were slipping away. One afternoon she tried to look up at the clock on the wall and realized that she could hardly see—her eyelids were drooping, and her head felt as if it weighed a hundred pounds. Just then, one of her supervisors came over to her desk, sat down, and asked her to fill him in on the progress she had been making on a new project. As she talked, she found herself getting weaker and weaker. Her jaw was getting tired, even her tongue was getting tired, and her voice was getting weaker. With a sudden feeling of fright she realized that the act of breathing seemed to take a lot of effort. She managed to finish the interview, but immediately afterward she packed up her briefcase and left for home, saying that she had a bad headache.

She telephoned her physician, who immediately arranged for her to go to the hospital to be seen by Dr. T., a neurologist. Dr. T. listened to a description of her symptoms and examined her briefly. She said to Kathryn, "I think I know what may be causing your symptoms. I'd like to give you an injection and watch your reaction." She gave some orders to the nurse, who left the room and came back with a syringe. Dr. T. took it, swabbed Kathryn's arm, and injected the drug. She started questioning Kathryn about her job. Kathryn answered slowly, her voice almost a whisper. As the questions continued, she realized that it was getting easier and easier to talk. She straightened her back and took a deep breath. Yes, she was sure. Her strength was returning! She stood up and raised her arms above her head. "Look," she said, her excitement growing. "I can do this again. I've got my strength back! What was that you gave me? Am I cured?"

The brain is the organ that moves the muscles. That might sound simplistic, but ultimately, movement—or, more accurately, behavior—is the primary function of the nervous system. To make useful movements, the brain must know what is happening outside, in the environment. Thus, the body also contains cells that are specialized for detecting environmental events. Of course, complex animals such as we do not react automatically to events in our environment; our brains are flexible enough that we behave in different ways, according to present circumstances and those we experienced in the past. Besides perceiving and acting, we can remember and decide. All these abilities are made possible by the billions of cells found in the nervous system or controlled by them.

This chapter describes the structure and functions of the most important cells of the nervous system. Information, in the form of light, sound waves, odors, tastes, or contact with objects, is gathered from the environment by specialized cells called **sensory neurons.** Movements are accomplished by the contraction of muscles, which are controlled by **motor neurons.** (The term *motor* is used here in its original sense to refer to movement, not to a mechanical engine.) And in between sensory neurons and motor neurons come the **interneurons**—neurons that lie entirely within the central nervous system.

sensory neuron A neuron that detects changes in the external or internal environment and sends information about these changes to the central nervous system.

motor neuron A neuron located within the central nervous system that controls the contraction of a muscle or the secretion of a gland.

interneuron A neuron located entirely within the central nervous system.

Local interneurons form circuits with nearby neurons and analyze small pieces of information *Relay interneurons* connect circuits of local interneurons in one region of the brain with those in other regions. Through these connections, circuits of neurons throughout the brain perform functions essential to tasks such as perceiving, learning, remembering, deciding, and controlling complex behaviors. How many neurons are there in the human nervous system? I have seen estimates of between 100 billion and 1000 billion, but no one has counted them yet.

To understand how the nervous system controls behavior, we must first understand its parts—the cells that compose it. Because this chapter deals with cells, you need not be familiar with the structure of the nervous system, which is presented in Chapter 3. However, you need to know that the nervous system consists of two basic divisions: the central nervous system and the peripheral nervous system. The **central nervous system (CNS)** consists of the parts that are encased by the bones of the skull and spinal column: the brain and the spinal cord. The **peripheral nervous system (PNS)** is found outside these bones and consists of the nerves and most of the sensory organs.

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 neurons in the central nervous system 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. Most neurons 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. (***Animation 2.1, Neurons and Supporting Cells,*** illustrates the information presented in the following section.)

See the interactive CD

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.

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 an action potential 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 of 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 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.***) Bipolar neurons are usually sensory; that is, their dendrites

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central nervous system (CNS) The brain and spinal cord.

peripheral nervous system (PNS) The part of the nervous system outside the brain and spinal cord, including the nerves attached to the brain and spinal cord.

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.

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

FIGURE 2.1

The principal parts of a multipolar neuron.

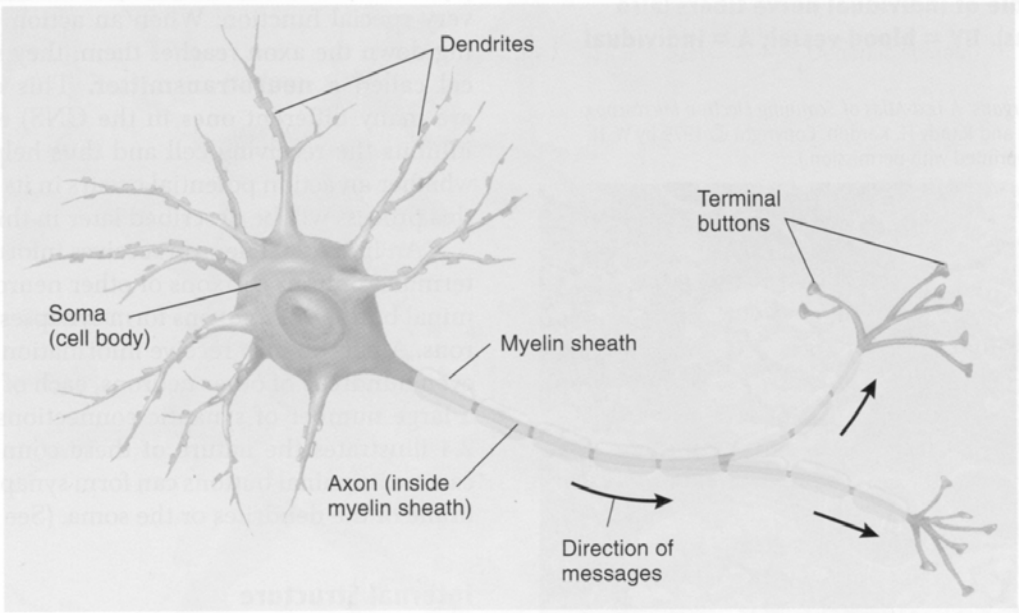
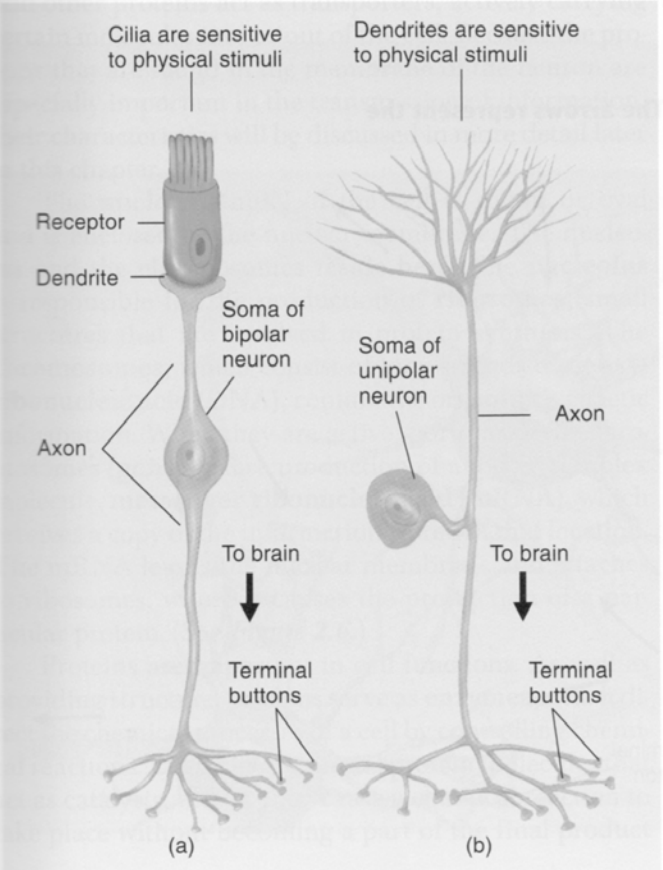


FIGURE 2.2

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).



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) outside 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.

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 2.3.***) 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.

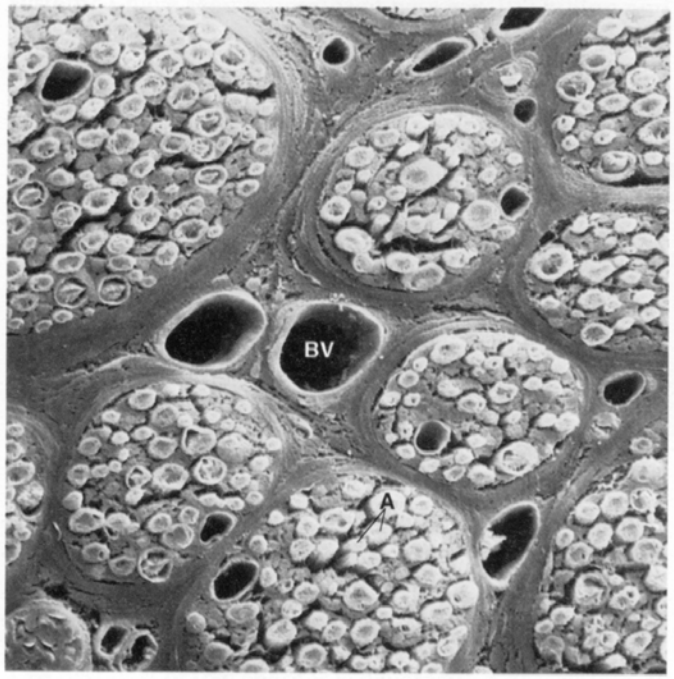
Terminal Buttons. Most axons divide and branch many times. At the ends of the twigs are found little

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

FIGURE 2.3

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 with permission.)



knobs called **terminal buttons.** (Some neuroscientists prefer the original French word *bouton,* and others simply refer to them as *terminals.*) Terminal buttons have a very special function: When an action potential traveling down the axon reaches them, they secrete a chemical called a **neurotransmitter.** This chemical (there are many different ones in the CNS) either excites or inhibits the receiving cell and thus helps to 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 2.4 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 2.4.***)

Internal Structure

Figure 2.5 illustrates the internal structure of a typical multipolar neuron. (See ***Figure 2.5.***) The **membrane** defines the boundary of the cell. It consists of a double layer of lipid (fatlike) molecules. Embedded in the membrane 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

FIGURE 2.4

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

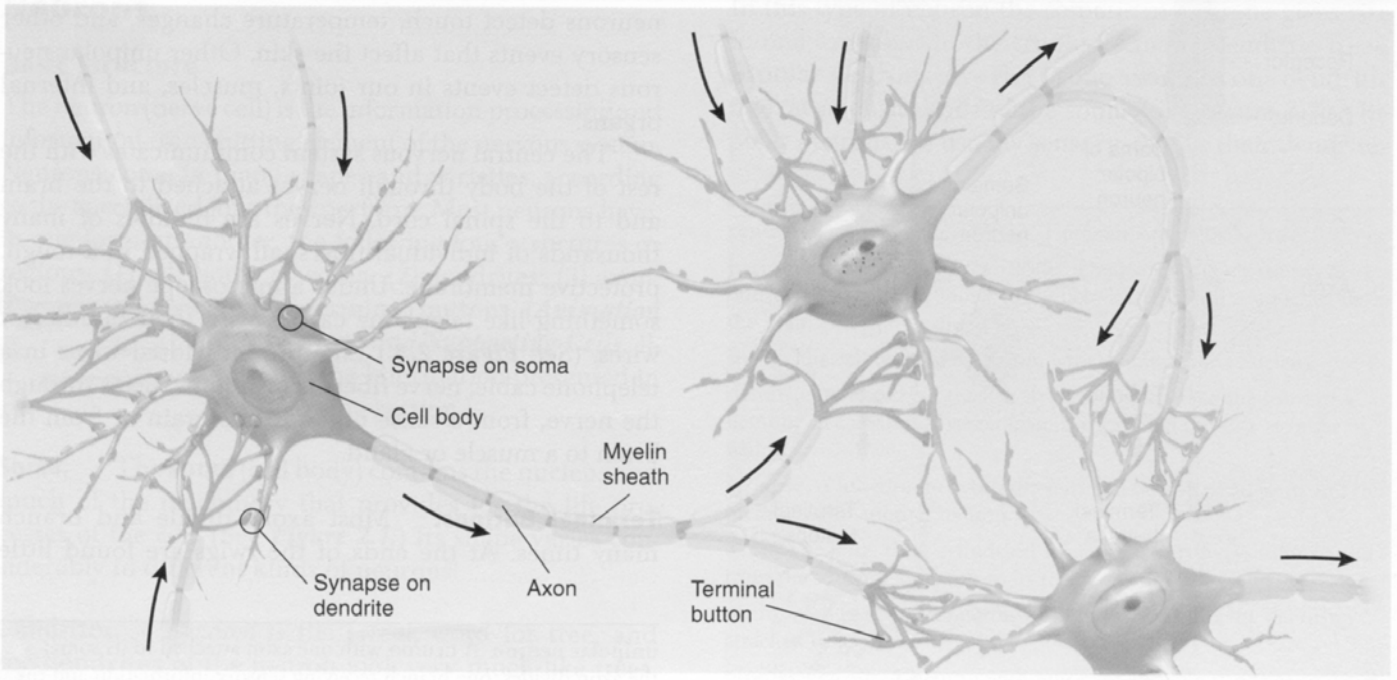
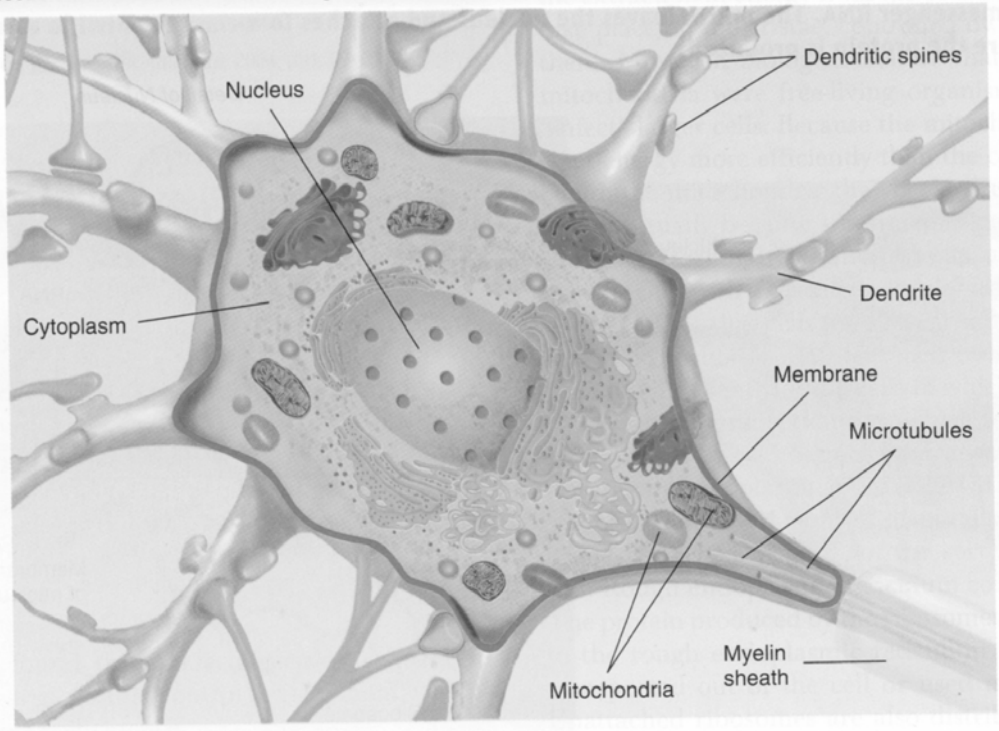


FIGURE 2.5

The principal internal structures of a multipolar neuron.



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 proteins that are found in the membrane of the neuron are especially important in the transmission of information, their characteristics will be discussed in more detail later in this chapter.

The **nucleus** ("nut") of the cell is round or oval and is enclosed by the nuclear membrane. The nucleolus and the chromosomes reside here. The **nucleolus** is responsible for the production of **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 2.6.***)

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 ingredients needed to synthesize an enormous variety of compounds, the

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

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.

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.

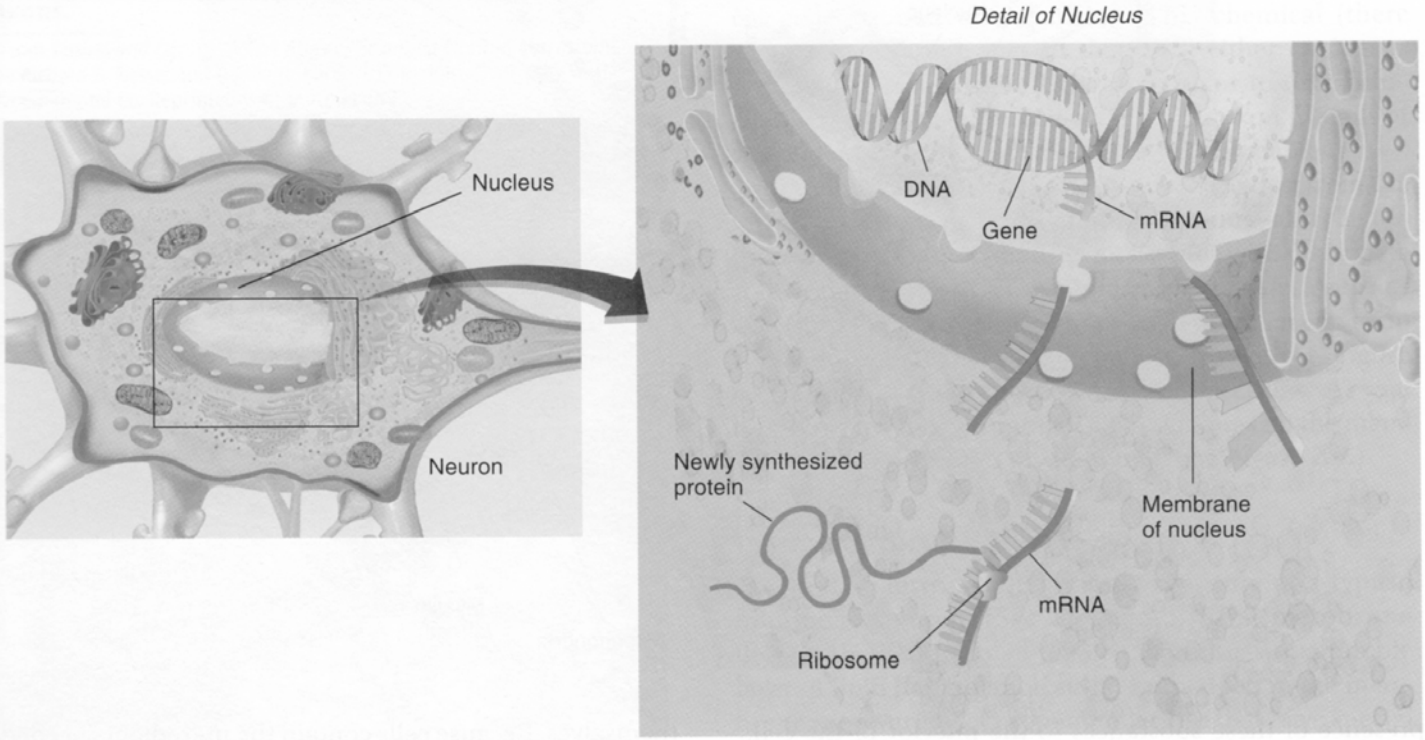
gene The functional unit of the chromosome, which directs synthesis of one or more proteins.

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.

FIGURE 2.6

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.



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 enzymes that put them together; the enzymes that are 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.)

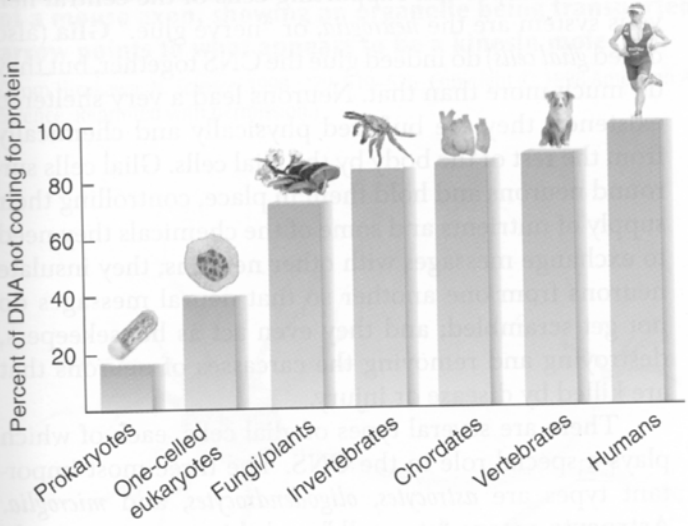
As you undoubtedly know, the sequence of the human genome—along with that of several other plants and animals—has been determined. (The *genome* is the sequence of nucleotide bases on the chromosomes that provide the information needed to synthesize all the proteins that can be produced by a particular organism.) Biologists were surprised to learn that the number of genes was not correlated with the complexity of the organism (Mattick, 2004). For example, *C. elegans,* a simple worm that consists of about 1000 cells, has 19,000 genes, whereas humans have around 25,000 genes. The research also revealed that the genomes of most vertebrates contained much "junk" DNA, which did not contain information needed to produce proteins. For example, only about 1.5 percent of the human genome encodes for proteins. At first, molecular geneticists assumed that "junk" DNA was a leftover from our evolutionary history and that only those sequences of DNA that encoded for proteins were useful. However, further research found that the amount of non-protein-coding DNA did correlate well with the complexity of an organism and that many of these sequences have been conserved for millions of years. In other words, it started looking as though "junk" DNA was not junk after all. (See ***Figure 2.7.***)

A study by Woolfe et al. (2005) illustrates the longevity of most non-coding DNA. They compared the genomes of the human and the pufferfish. The common ancestor of these two species lived many millions of years ago, which means that if non-coding DNA is really just useless, leftover junk, then random mutations should have produced many changes in their sequences. However, Woolfe and his colleagues found 1400 highly conserved non-coding sequences, many of which were over 90 percent identical in humans and pufferfish. In

FIGURE 2.7

Percentage of DNA that does not code for proteins in various categories of living organisms.

(Adapted from Mattick, J. S. *Scientific American*, 2004, *291*, 60–67.)



addition, they found that these conserved sequences were located near genes that control development, which is unlikely to be a coincidence.

What do these non-coding sequences of DNA do? Although their sequences can be transcribed into RNA, this RNA does not result in the production of protein. Instead, **non-coding RNA (ncRNA)** appears to have functions of it own. For example, when most genes become active, segments of DNA are transcribed into molecules of messenger RNA, and then other molecules cut the mRNA into pieces, discard some parts, and splice the remaining pieces together. The protein is then made from the resulting chunk of mRNA. The cutting and splicing are accomplished by molecular complexes called *spliceosomes,* and one of the constituents of spliceosomes is non-coding RNA. Molecules of ncRNA also attach to—and modify—proteins that regulate gene expression (Szymanski et al., 2003; Storz, Altuvia, and Wassarman, 2005). Thus, the human genome, more broadly defined to include non-coding RNA, is much larger than biologists previously believed.

The bulk of the cell consists of cytoplasm. **Cytoplasm** is complex and varies considerably across types of cells, but it can most easily be characterized as a jellylike, semiliquid substance that fills the space outlined by the membrane. It contains small, specialized structures, just as the body contains specialized organs. The generic term for these structures is *organelle,* "little organ." The most important organelles 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 that are involved in the extraction of energy from the breakdown of nutrients take place on the cristae, controlled by enzymes located there. 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 cells they infected could, the mitochondric they became useful to the cells and eventually became a permanent part of them. Cells provide mitochondria with nutrients, and mitochondria provide cells with a special molecule—**adenosine triphosphate (ATP)**—that cells use as their immediate source of energy. Mitochondria contain their own DNA and reproduce independently of the cells in which they reside.

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. 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

non-coding RNA (ncRNA) A form of RNA that does not encode for protein, but has functions of its own.

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

mitochondrion An organelle that is 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.

secretes its products, it uses a process called **exocytosis** (*exo,* "outside"; *cyto,* "cell"; *-osis,* "process"). Briefly stated, the container migrates to the inside of the outer membrane of the cell, fuses with it, and bursts, spilling its contents into the fluid surrounding the cell. As we will see, neurons communicate with one another by secreting chemicals by this means. Therefore, 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 protein filaments arranged around a hollow core.

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 (Yildiz et al., 2004). Energy is supplied by ATP molecules produced by the mitochondria. (See ***Figure 2.8.***) 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.

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. 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 nutrients and 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 disease or injury.

There are several types of glial cells, each of which plays a special role in the CNS. The three most important types are *astrocytes, oligodendrocytes,* and *microglia.* **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 to control the chemical composition of the fluid surrounding neurons by actively taking up or releasing substances whose concentrations must be kept within critical levels. As we will see later, they are involved in establishing structures responsible for communication between neurons. Finally, astrocytes are involved in providing nourishment to neurons.

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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.

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

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

microtubule (*my kro* ***too*** *byool*) 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.

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.

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

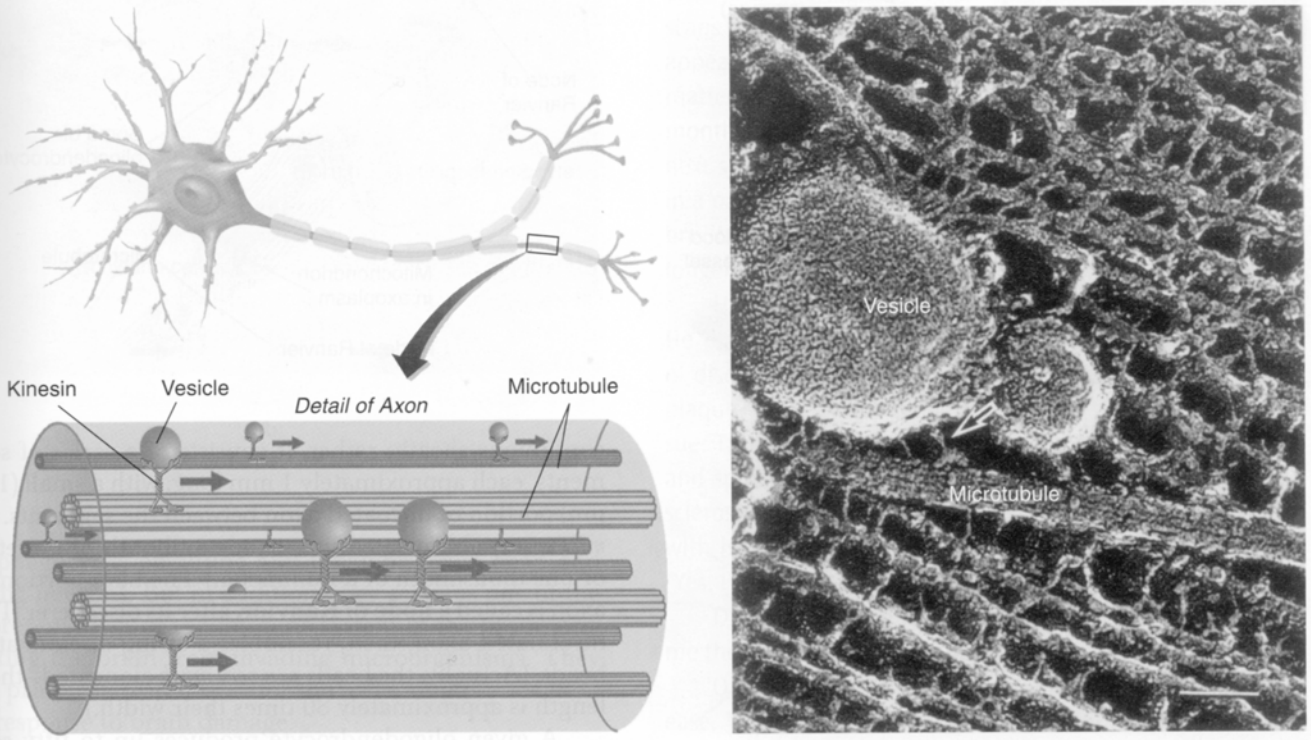
glia (***glee*** *ah*) The supporting cells of the central nervous system.

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.

FIGURE 2.8

Fast axoplasmic transport. (a) 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. (b) A photomicrograph of a mouse axon, showing an organelle being transported along a microtubule. The arrow points to what appears to be a kinesin molecule.

(From Hirokawa, N. *Science,* 1998, *279,* 519–526. Copyright © 1998 American Association for the Advancement of Science. Reprinted with permission.)



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 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 supplied 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: Although neurons receive some glucose directly from capillaries, they receive most of their nutrients from astrocytes. Astrocytes 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. (Tsacopoulos and Magistretti, 1996; Magistretti et al., 1999; Brown, Tekkök, and Ransom, 2004). Apparently, this process provides neurons with a fuel that they can metabolize even more rapidly than glucose. 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. (See ***Figure 2.9.***)

Besides transporting chemicals to neurons, astrocytes serve as the matrix that holds neurons in place—the "nerve glue," so to speak. These cells also surround and isolate synapses, limiting the dispersion of neurotransmitters that are released by the terminal buttons.

When cells in the central nervous system die, certain kinds of astrocytes take up the task of cleaning away the debris. These cells are able to travel around the CNS;

FIGURE 2.9

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

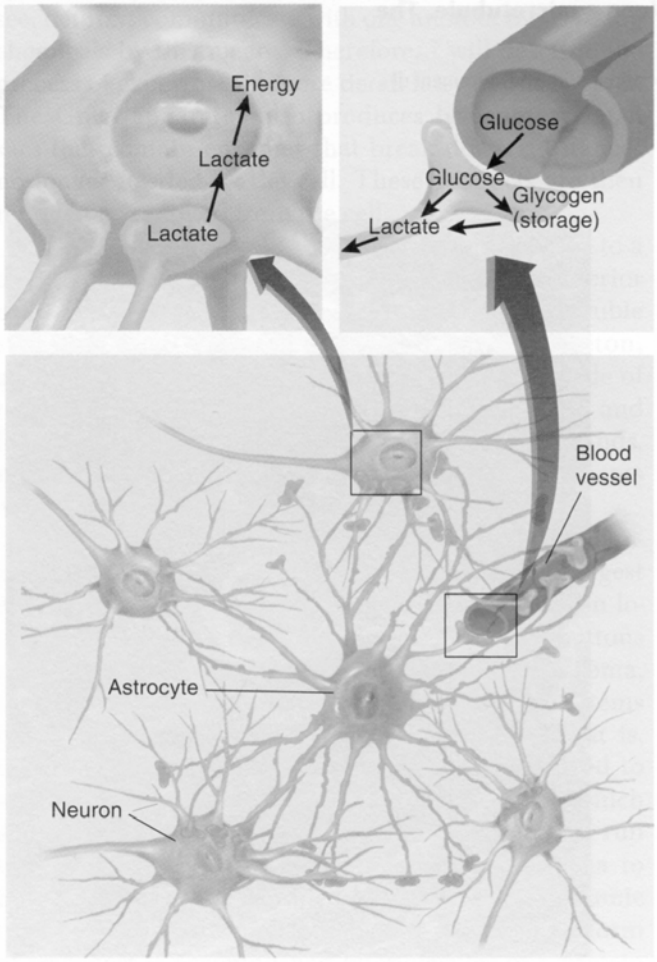
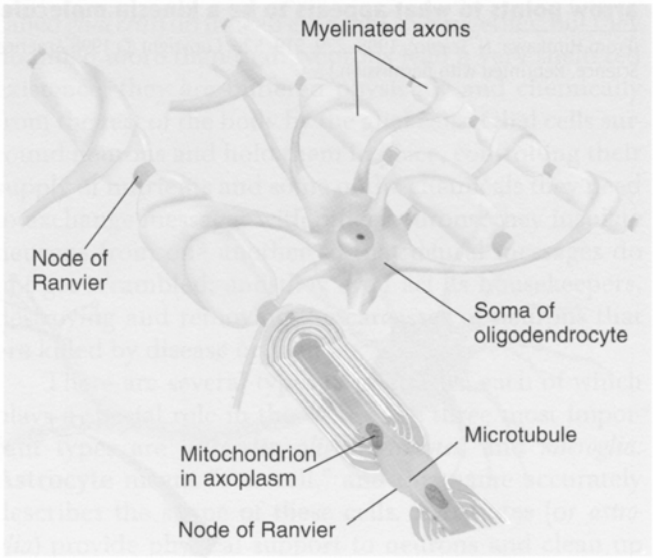


FIGURE 2.10

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.



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.

The principal function of **oligodendrocytes** is to provide support to axons and to produce the **myelin sheath,** which insulates most axons from one another. (Very small 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. (Actually, the beads are *very much* elongated–their length is approximately 80 times their width.)

A given oligodendrocyte produces up to fifty 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 ***Figures 2.10*** and ***2.11a.***)

As their name indicates, **microglia** are the smallest of the glial cells. Like some types of astrocytes, they act

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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.

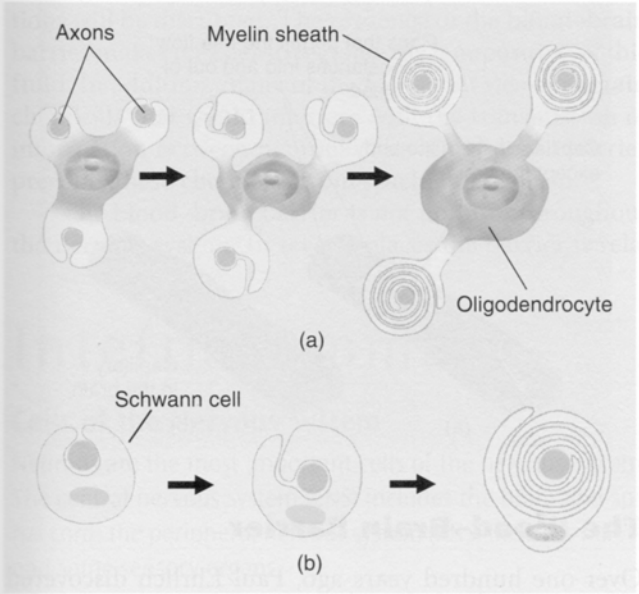
myelin sheath (***my** a lin*) A sheath that surrounds axons and insulates them, preventing messages from spreading between adjacent axons.

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

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

FIGURE 2.11

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.



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.

Dr. C., a retired neurologist, had been afflicted with multiple sclerosis for more than two decades when she died of a heart attack. One evening, twenty-three years previously, she and her husband had had dinner at their favorite restaurant. As they were leaving, she stumbled and almost fell. Her husband joked, "Hey, honey, you shouldn't have had that last glass of wine." She smiled at his attempt at humor, but she knew better—her clumsiness wasn't brought on by the two glasses of wine she had drunk with dinner. She suddenly realized that she had been ignoring some symptoms that she should have recognized.

The next day, she consulted with one of her colleagues, who agreed that her own tentative diagnosis was probably correct: Her symptoms fit those of multiple sclerosis. She had experienced fleeting problems with double vision, she sometimes felt unsteady on her feet, and she occasionally noticed tingling sensations in her right hand. None of these symptoms was serious, and they lasted for only a short while, so she ignored them—or perhaps denied to herself that they were important.

A few weeks after Dr. C.'s death, a group of medical students and neurological residents gathered in an autopsy room at the medical school. Dr. D., the school's neuropathologist, displayed a stainless-steel tray on which were lying a brain and a spinal cord. "These belonged to Dr. C.," he said. "Several years ago she donated her organs to the medical school." Everyone looked at the brain more intently, knowing that it had animated an esteemed clinician and teacher whom they all knew by reputation, if not personally. Dr. D. led his audience to a set of light boxes on the wall, to which several MRI scans had been clipped. He pointed out some white spots that appeared on one scan. "This scan clearly shows some white-matter lesions, but they are gone on the next one, taken six months later. And here is another one, but it's gone on the next scan. The immune system attacked the myelin sheaths in a particular region, and then glial cells cleaned up the debris. MRI doesn't show the lesions then, but the axons can no longer conduct their messages."

He picked up Dr. C.'s brain and cut it in several slices. He picked one up. "Here, see this?" He pointed out a spot of discoloration in a band of white matter. This is a sclerotic plaque—a patch that feels harder than the surrounding tissue. There are many of them, located throughout the brain and spinal cord, which is why the disease is called multiple sclerosis." He picked up the spinal cord, felt along its length with his thumb and forefinger, and then stopped and said, "Yes, I can feel a plaque right here."

Dr. D. put the spinal cord down and said, "Who can tell me the etiology of this disorder?"

One of the students spoke up. "It's an autoimmune disease. The immune system gets sensitized to the body's own myelin protein and periodically attacks it, causing a variety of different neurological symptoms. Some say that a childhood viral illness somehow causes the immune system to start seeing the protein as foreign."

"That's right," said Dr. D. "The primary criterion for the diagnosis of multiple sclerosis is the presence of neurological symptoms disseminated in time and space. The symptoms don't all occur at once, and they can be caused only by damage to several different parts of the nervous system, which means that they can't be the result of a stroke."

Schwann Cells

In the central nervous system the oligodendrocytes support axons and produce myelin. In the peripheral nervous system the **Schwann cells** perform the same functions. Most axons in the PNS are myelinated. The

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

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 2.11b.***)

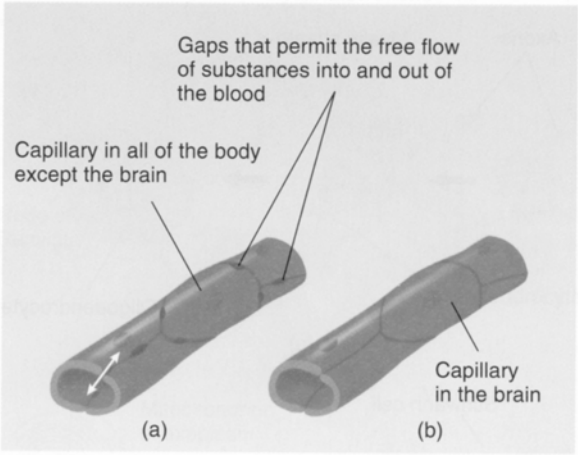
Schwann cells also differ from their CNS counterparts, the oligodendrocytes, in an important way. As we saw, a nerve consists of a bundle of many myelinated axons, all covered in a sheath of tough, elastic connective tissue. If damage occurs to such a nerve, Schwann cells aid in the digestion of the 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.

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 axons in the CNS and the PNS results from differences in the characteristics of the supporting cells, not from differences in the axons.

There is another difference between oligodendrocytes of the CNS and Schwann cells of the PNS: the chemical composition of the myelin protein they produce. The immune system of people with multiple sclerosis attacks only the myelin protein produced by oligodendrocytes; thus, the myelin of the peripheral nervous system is spared.

FIGURE 2.12

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.



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 fluid-filled 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 capillaries that surrounds the cells of the body. In the central nervous system the capillaries lack these gaps; therefore, many substances cannot leave the blood. Thus, the walls of the capillaries in the brain constitute the blood–brain barrier. (See ***Figure 2.12.***) Other substances must be actively transported through the capillary walls by special proteins. For example, glucose transporters bring the brain its fuel, and other transporters rid the brain of toxic waste products (Rubin and Staddon, 1999).

blood–brain barrier A semipermeable barrier between the blood and the brain produced by the cells in the walls of the brain's capillaries.

What is the function of the blood–brain barrier? As we will see, transmission of messages from place to place in the brain depends on a delicate balance between substances within neurons and in the extracellular fluid that surrounds them. If the composition of the extracellular fluid is changed even slightly, the transmission of these messages will be disrupted, which means that brain functions will be disrupted. The presence of the blood–brain barrier makes it easier to regulate the composition of this fluid. In addition, many of the foods that we eat contain chemicals that would interfere with the transmission of information between neurons. The blood–brain barrier prevents these chemicals from reaching the brain.

The blood–brain barrier is not uniform throughout the nervous system. In several places the barrier is relatively permeable, allowing substances that are 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 causing too much damage.

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.

InterimSummary

Cells of the Nervous System

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, junctions between the terminal buttons of one neuron and the somatic or dendritic membrane of another. When an action potential travels down an axon, its terminal buttons secrete a chemical that has either an excitatory or an inhibitory effect on the neurons with which they communicate. Ultimately, the effects of these excitatory and inhibitory synapses cause behavior, in the form of muscular contractions.

Neurons contain a quantity of cytoplasm, enclosed in a membrane. Embedded in the membrane are protein molecules that have special functions, such as the detection of hormones or neurotransmitters or 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 and other protein fibers, which compose the cytoskeleton and help to 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. Recent evidence indicates that only a small proportion of the human genome is devoted to the production of protein; the rest (formerly called "junk" DNA) is involved in the production of non-coding RNA, which has a variety of functions.

Neurons are supported by the glial cells of the central nervous system and the supporting cells of the peripheral nervous system. In the CNS astrocytes provide support and nourishment, regulate the composition of the fluid that surrounds neurons, and 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. In 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.

Thought Question

The fact that the mitochondria in our cells were originally microorganisms that infected our very remote ancestors points out that evolution can involve interactions between two or more species. Many species have other organisms living inside them; in fact, the bacteria in our intestines are necessary for our good health. Some microorganisms can exchange genetic information, so adaptive mutations developed in one species can be adopted by another. Is it possible that some of the features of the cells of our nervous system were bequeathed to our ancestors by other species?

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 neurotransmitter. The details of synaptic transmission—the communication between neurons—will be described in the next section. As we will see in this section, an action potential consists of a series of alterations in the membrane of the axon that permit various substances to move between the interior of the axon and the fluid surrounding it. These exchanges produce electrical currents. (***Animation 2.2, The Action Potential,*** illustrates the information presented in the following section.)

See the interactive CD

Neural Communication: An Overview

Before I begin my discussion of the action potential, let's step back and see how neurons 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), multipolar 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 2.13.***) The terminal buttons of the sensory neuron release a neurotransmitter that excites the interneuron, causing it to send messages down its axon. The terminal buttons of the interneuron release a neurotransmitter 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 neurotransmitter, the muscle cells contract, causing the hand to move away from the hot object. (See ***Figure 2.13.***)

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 walking 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. 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 2.14 shows how this information reaches the spinal cord. As you can see, an axon from a neuron in the

FIGURE 2.13

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.

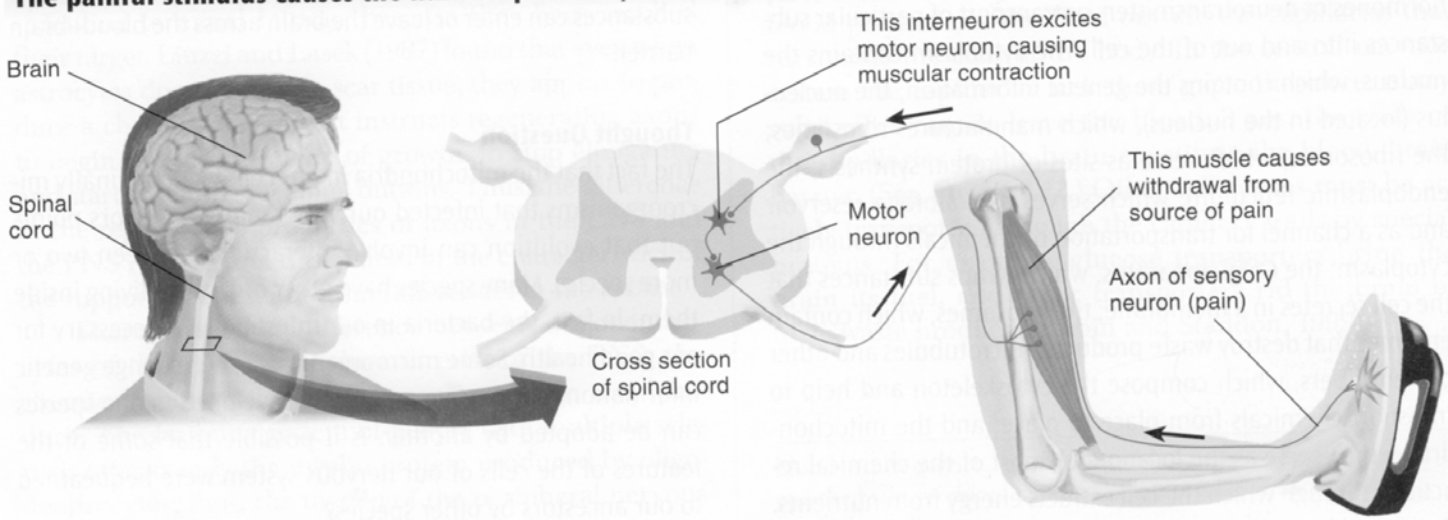
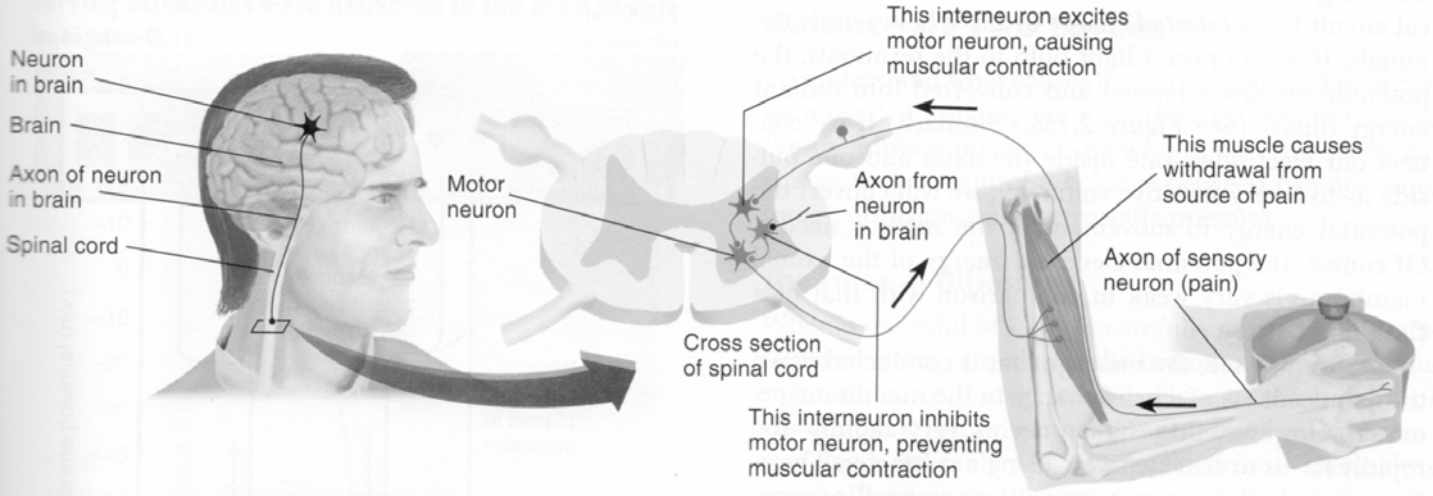


FIGURE 2.14

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



brain reaches the spinal cord, where its terminal buttons form synapses with an inhibitory interneuron. When the neuron in the brain becomes active, its terminal buttons excite this inhibitory interneuron. The interneuron releases an inhibitory neurotransmitter, 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 onto it. (See ***Figure 2.14.***)

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 2.14 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.

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 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 2.15a.***) 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

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.

–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 2.15b.***) 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 in comparison with that of a flashlight battery.

As we will see, the message that is conducted down the axon consists of a brief change in the membrane potential. However, this change occurs very rapidly—too rapidly for us to see if we were using a voltmeter. Therefore, 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, as long as the axon is not disturbed, the oscilloscope draws a straight horizontal line at –70 mV. 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 2.16.***) 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

FIGURE 2.15

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.

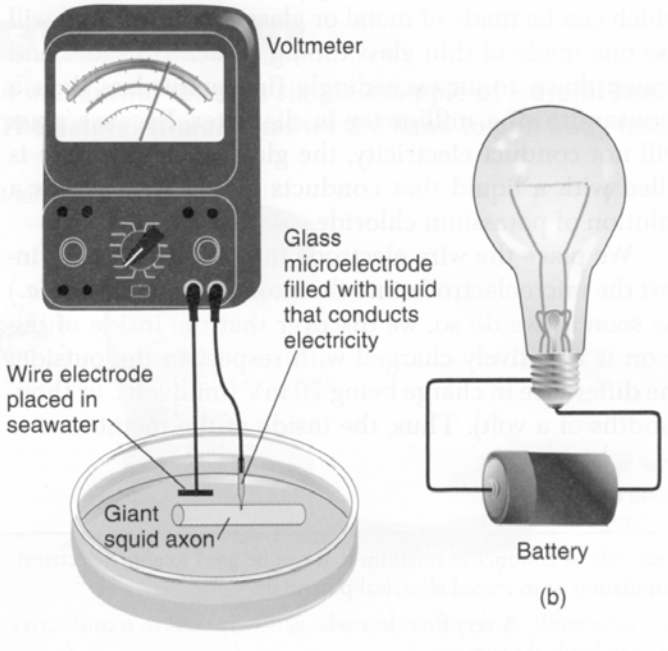
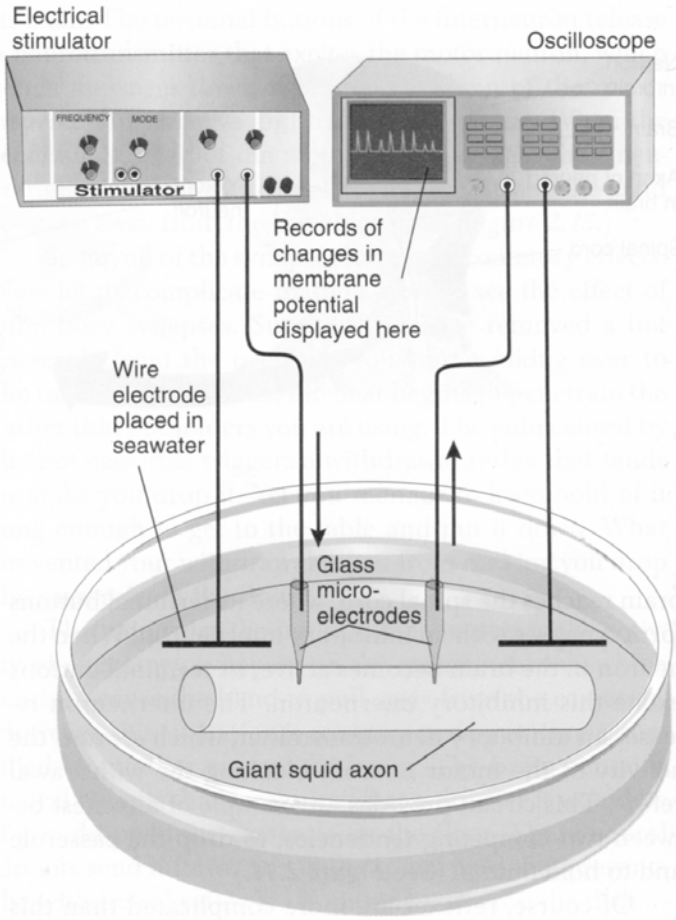


FIGURE 2.16

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



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

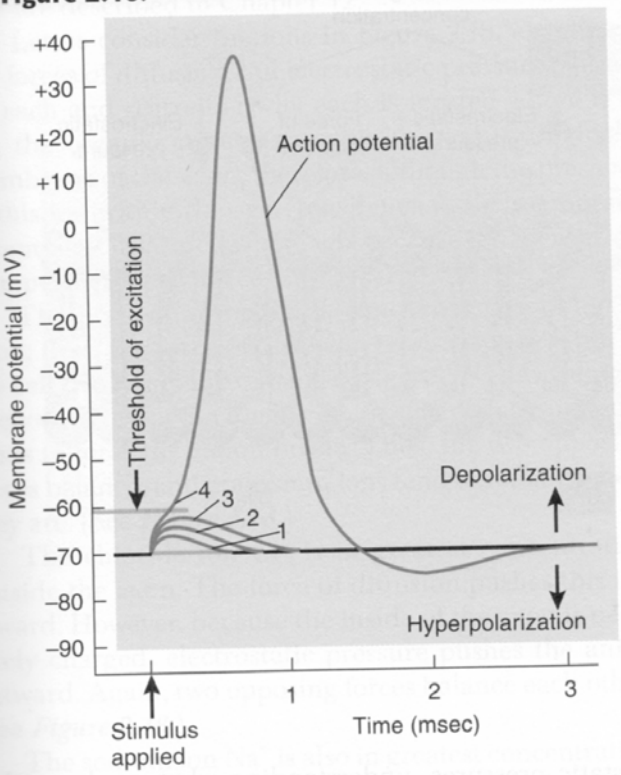
oscilloscope A laboratory instrument that is capable of displaying a graph of voltage as a function of time on the face of a cathode ray tube.

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.

FIGURE 2.17

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 2.16.



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 2.17 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 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 2.17.***)

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.

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 them from doing so, molecules will 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

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 to produce an action potential.

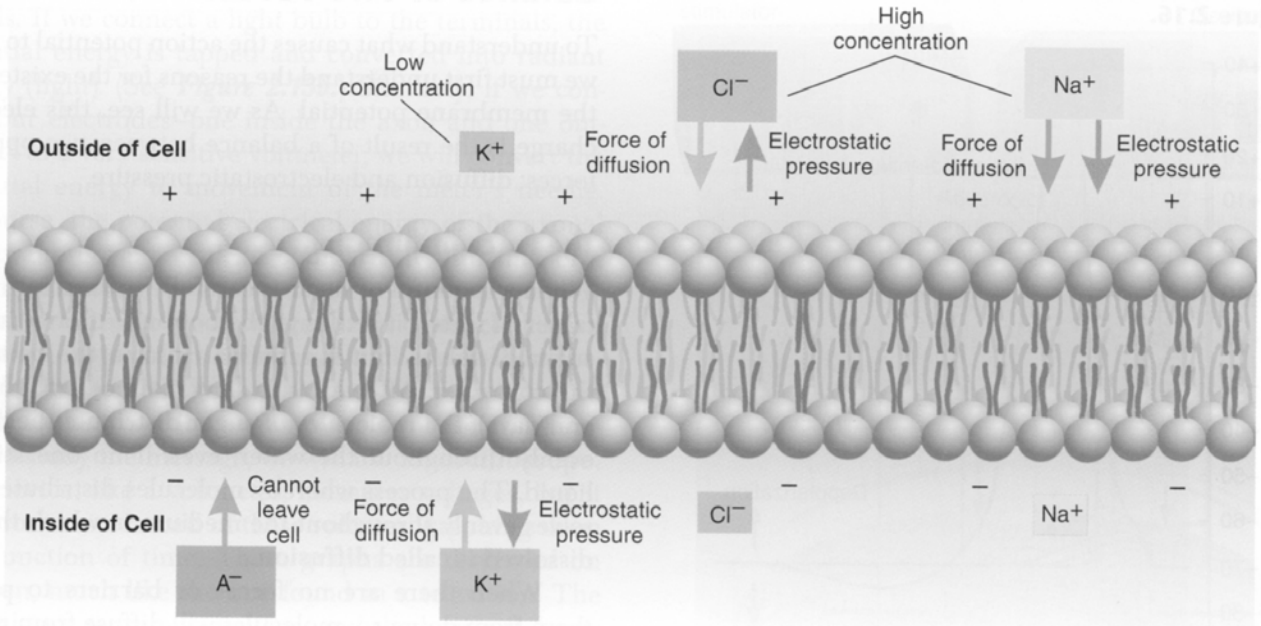
diffusion Movement of molecules from regions of high concentration to regions of low concentration.

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.

FIGURE 2.18

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



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. 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 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 2.18 indicate the relative concentrations of these four ions. (See ***Figure 2.18.***) The easiest way to remember which ion is found where is to recall that the fluid that surrounds our cells

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.

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 2.18, 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 contributes to the membrane potential, 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, and potassium ions tend to remain where they are. (See ***Figure 2.18.***)

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 2.18.***)

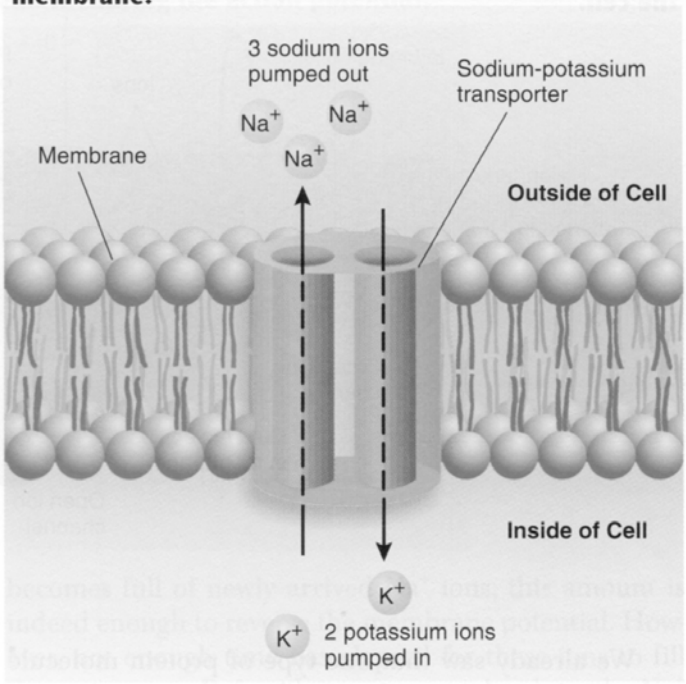
The sodium ion Na^+ is also in greatest concentration outside the axon, so it, like Cl^-, is pushed into the cell by the force of diffusion. But unlike chloride, the sodium ion is *positively* charged. Therefore, electrostatic pressure does *not* prevent Na^+ from entering the cell; indeed, the negative charge inside the axon *attracts* Na^+. (See ***Figure 2.18.***)

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 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 protein molecules embedded in the membrane, driven by energy provided by molecules of ATP produced by the mitochondria. 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 2.19.***)

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

FIGURE 2.19

A sodium–potassium transporter, situated in the cell membrane.



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.

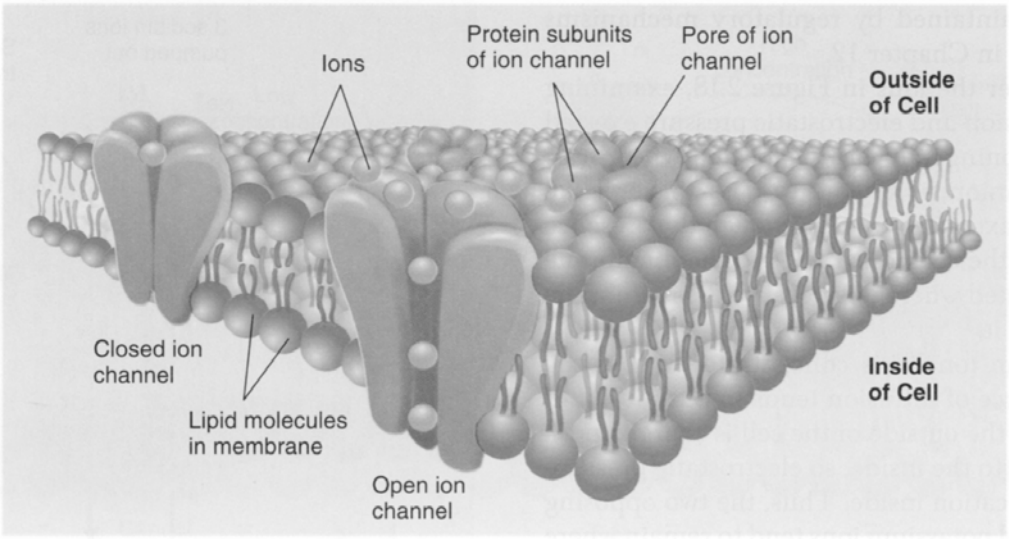
The Action Potential

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 increase in the permeability of the membrane to Na^+ (allowing these ions to rush into the cell) is immediately followed by a transient increase in the permeability of the membrane to K^+ (allowing these ions to rush out of the cell). What is responsible for these transient increases in permeability?

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

FIGURE 2.20

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



We already saw that one type of protein molecule embedded in the membrane—the sodium–potassium transporter—actively pumps sodium ions out of the cell and pumps potassium ions into it. Another type of protein molecule provides an opening that permits ions to enter or leave the cells. These molecules provide **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 2.20.***) Neural membranes contain many thousands of ion channels. For example, the giant squid axon contains several hundred 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 sodium channel can admit up to 100 million ions per second when it is open. Thus, the permeability of a membrane to a particular ion at a given moment is determined by the number of ion channels that are open.

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 2.21.***)

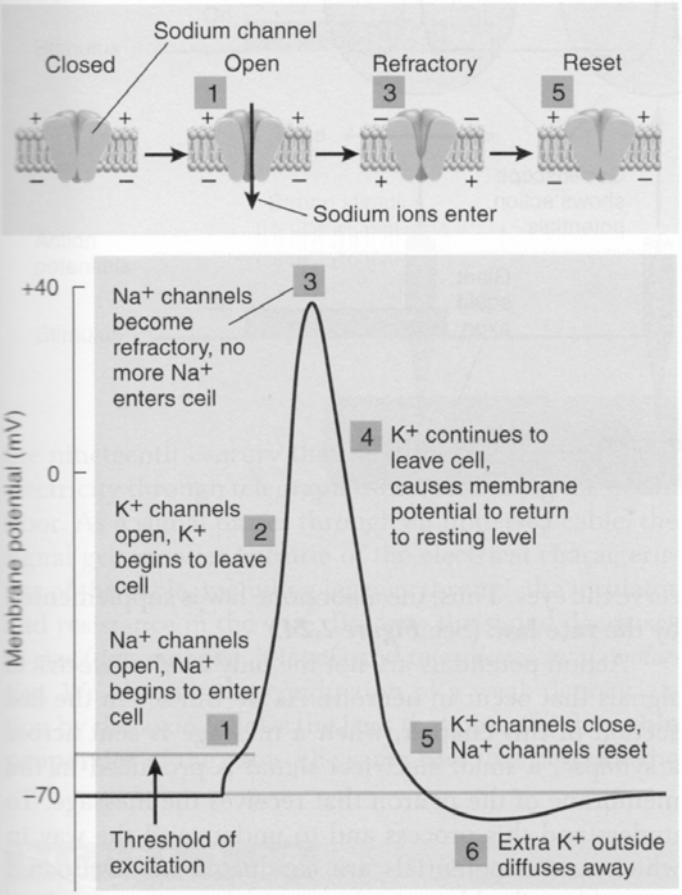
1. As soon as the threshold of excitation is reached, the sodium channels in the membrane open and Na^+ rushes in, propelled by the forces of diffusion and electrostatic pressure. The opening of these channels is triggered by reduction of the membrane potential (depolarization); they open at the point at which an action potential begins: the threshold of excitation. Because these 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 mV 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*—the channels become blocked and 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 *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. Once the membrane potential returns to normal, the potassium channels are closed, and no more potassium leaves the cell. At around this time, the so-

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

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

FIGURE 2.21

The movements of ions during the action potential. The shaded box at the top shows the opening of sodium channels at the threshold of excitation, their refractory condition at the peak of the action potential, and their resetting when the membrane potential returns to normal.



dium channels reset so that another depolarization can cause them to open again.

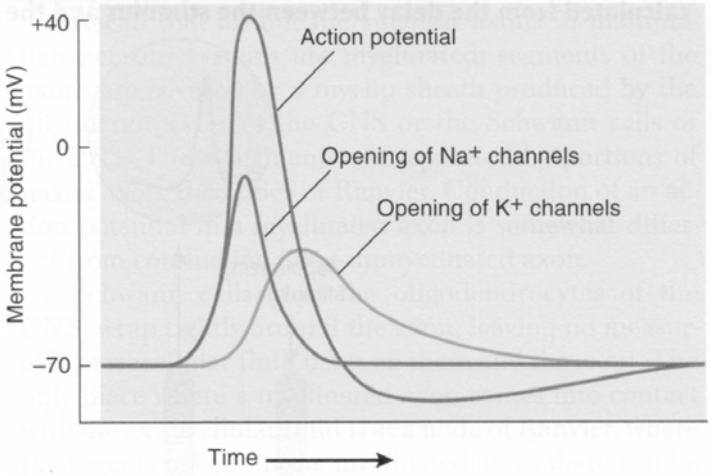
6. The membrane actually overshoots its resting value (–70 mV) and only gradually returns to normal. The accumulation of K^+ ions outside the membrane are responsible for this temporary hyperpolarization. The extra ions K^+ soon diffuse away, and the membrane potential returns to –70 mV. Eventually, sodium–potassium transporters remove the Na^+ ions that leaked in and retrieve the K^+ ions that leaked out.

Figure 2.22 illustrates the changes in permeability of the membrane to sodium and potassium ions during the action potential. (See ***Figure 2.22.***)

How much ionic flow is there? The increased permeability of the membrane 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 layer of fluid immediately inside the axon

FIGURE 2.22

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



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.

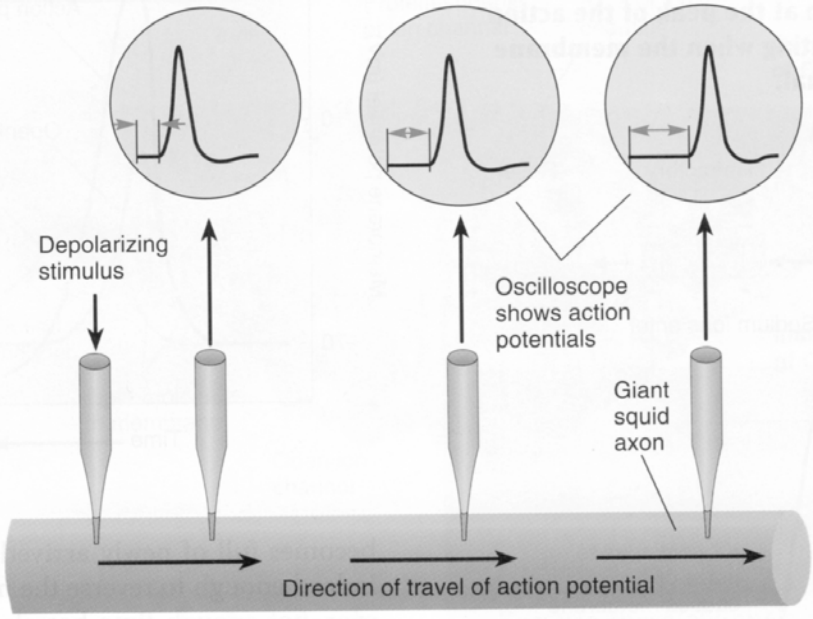
Experiments have shown that an action potential temporarily increases the number of Na^+ ions inside the giant squid axon by 0.0003 percent. Although the concentration just inside the membrane is high, the total number of ions entering the cell is very small relative to the number already there. This means that 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. Without the activity of sodium-potassium transporters the concentration of sodium ions in the axoplasm would eventually increase enough 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

FIGURE 2.23

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.



the action potential travels, it remains constant in size. (See ***Figure 2.23.***)

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; and once triggered, it is transmitted down the axon to its end. An action potential always remains the same size, without growing or diminishing. And when an action potential reaches a point where the axon branches, it splits but does not diminish in size. An 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 2.24.***)

Action potentials are not the only kind of electrical signals that occur in neurons. As we will 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 in which action potentials are conducted in myelinated axons (described later in this section), we must see how signals other than action potentials are conducted. To do so, we produce a weak, 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 stimulus produces a disturbance in the membrane potential that becomes smaller as it moves away from the point of stimulation. (See ***Figure 2.25.***)

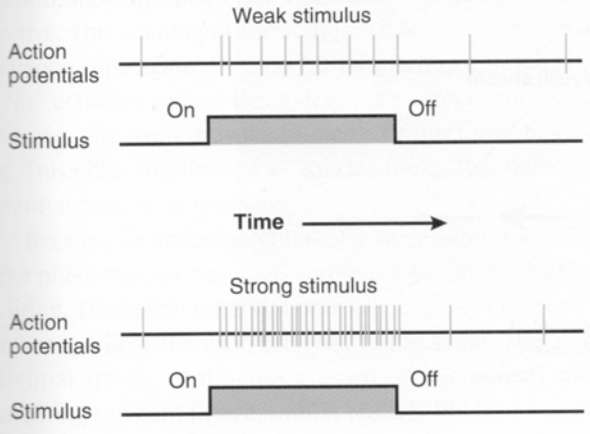
The transmission of the weak, subthreshold depolarization is *passive.* Neither sodium channels nor potassium channels open or close. The axon is acting like an electrical cable, carrying along the current that started at one end. This property of the axon follows laws discovered in

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 2.24

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.



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 weak 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 into 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 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,

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

FIGURE 2.25

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.

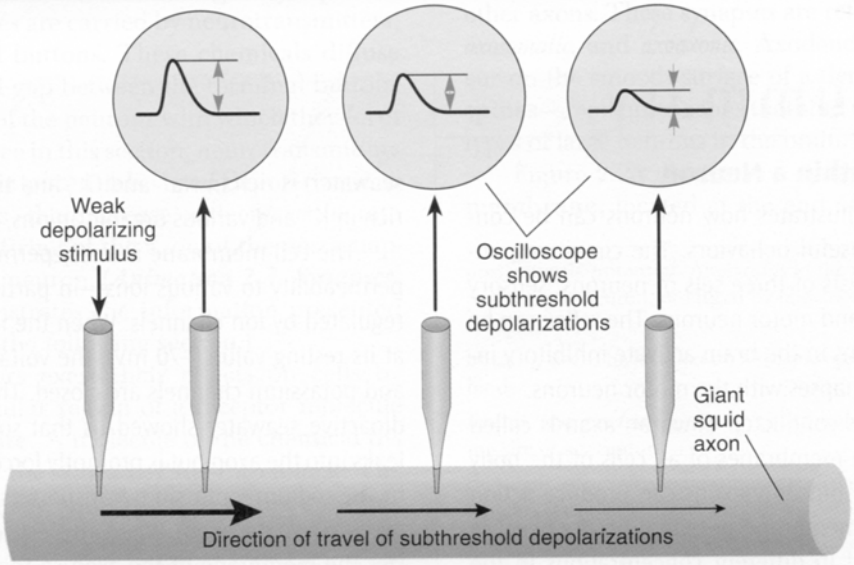
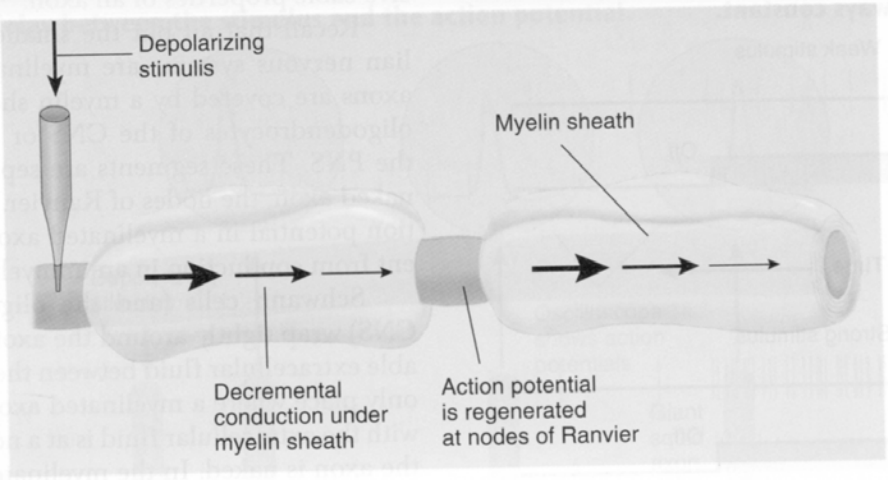


FIGURE 2.26

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



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, appearing to hop from node to node, is called **saltatory conduction,** from the Latin *saltare,* "to leap, to dance." (See ***Figure 2.26.***)

Saltatory conduction confers two advantages. The first is economic. Sodium ions enter axons during action potentials, and these ions must eventually be removed. Sodium–potassium transporters must be located along the entire length of unmyelinated axons because Na^+ enters everywhere. However, because Na^+ can enter myelinated axons only at the nodes of Ranvier, much less gets in, and consequently, much less has to be pumped out again. Therefore, myelinated axons expend much less energy to maintain their 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 (kilometers per hour). At that speed a signal can get from one end of an axon to the other without much delay.

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

InterimSummary

Communication Within a Neuron

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.

The message that is 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 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 axon). When an electrical stimulator depolarizes the membrane of the axon so that its potential reaches the threshold of excitation, voltage-dependent sodium chan-

nels 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 the inside becomes positive. The opening of the sodium channels is temporary; they soon close again. The depolarization 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. (If the axon divides, an 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 a new action potential is triggered. This mechanism saves a considerable amount of energy because sodium-potassium transporters are not needed along the myelinated portions of the axon, and saltatory conduction is faster.

Thought Question

The evolution of the human brain, with all its complexity, depended on many apparently trivial mechanisms. For example, what if cells had not developed the ability to manufacture myelin? Unmyelinated axons must be very large if they are to transmit action potentials rapidly. How big would the human brain have to be if oligodendrocytes did not produce myelin? *Could* the human brain as we know it have evolved without myelin?

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 in which neurons can communicate with each other. These communications make it possible for circuits of neurons to gather sensory information, make plans, and initiate behaviors.

The primary means of communication between neurons is *synaptic transmission*—the transmission of messages from one neuron to another through a synapse. As we saw, these messages are carried by neurotransmitters, released by terminal buttons. These chemicals 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, neurotransmitters produce **postsynaptic potentials**—brief depolarizations or hyperpolarizations—that increase or decrease the rate of firing of the axon of the postsynaptic neuron. (***Animation 2.3, Synapses,*** illustrates the information presented in the following section.)

See the interactive CD

Neurotransmitters 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 neurotransmitter are complementary. A chemical that attaches to a binding site is called a **ligand,** from *ligare,* "to bind." Neurotransmitters are natural ligands, produced and released by neurons. 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 2.27.***)

Figure 2.28 illustrates a synapse. The **presynaptic membrane,** located at the end of the terminal button,

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

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

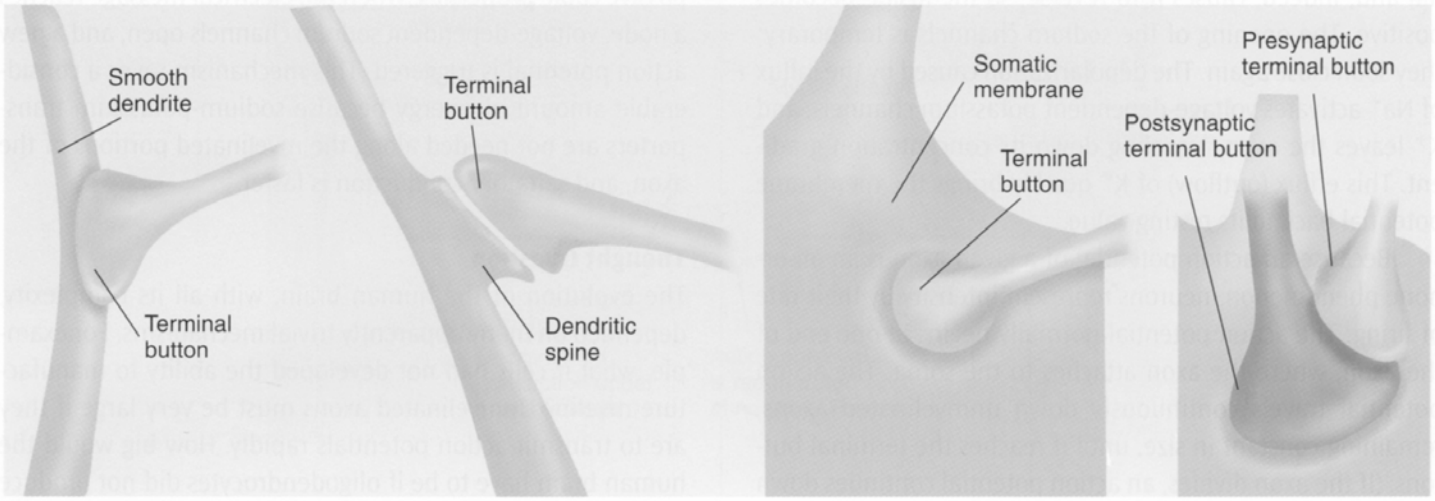
ligand (***lye** gand* or ***ligg** and*) A chemical that binds with the binding site of a receptor.

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

presynaptic membrane The membrane of a terminal button that lies adjacent to the postsynaptic membrane and through which the neurotransmitter is released.

FIGURE 2.27

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).



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 20 nm wide. (A nanometer (nm) is one billionth of a meter.) The synaptic cleft contains extracellular fluid, through which the neurotransmitter diffuses. A meshwork of filaments crosses the synaptic cleft and keeps the presynaptic and postsynaptic membranes in alignment. (See ***Figure 2.28.***)

As you may have noticed in Figure 2.28, two prominent structures are located in the cytoplasm of the terminal button: mitochondria and synaptic vesicles. We also see microtubules, which are responsible for transporting material between the soma and terminal button. The presence of mitochondria implies that the terminal 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 neurotransmitter. They range in number from a few dozen to several hundred. The membrane of small synaptic vesicles consists of approximately 10,000 lipid molecules into which are inserted about 200 protein molecules. *Transport proteins* fill vesicles with the neurotransmitter, and *trafficking proteins* are involved in the release of neurotransmitter and recycling of the vesicles. Synaptic vesicles are found in greatest numbers around the part of the presynaptic membrane that faces the synaptic cleft—near the **release zone,** the region from which the neurotransmitter is released. In many terminal buttons we see a scattering of large, dense-core synaptic vesicles. These vesicles contain one of a number of different peptides, the functions of which are described later in this chapter. (See ***Figures 2.28*** and ***2.29.***)

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, some are also produced from recycled material in the terminal button. Large synaptic vesicles are produced only in the soma and are 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 neurotransmitters in the synaptic cleft—and protein filaments that hold the receptors in place. (See ***Figures 2.28*** and ***2.29.***)

Release of Neurotransmitter

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 presynaptic membrane fuse with the membrane and then break open, spilling

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

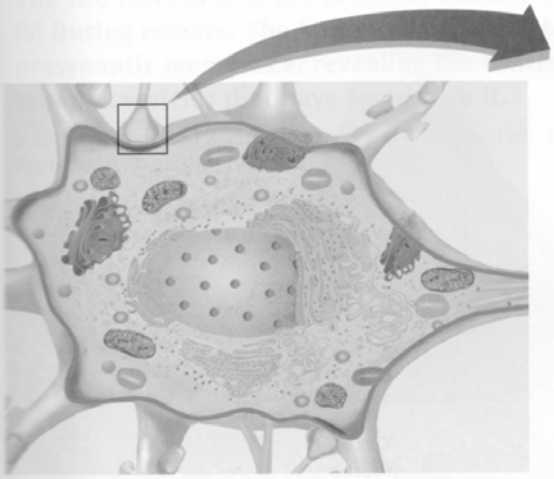
synaptic cleft The space between the presynaptic membrane and the postsynaptic membrane.

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

release zone A region of the interior of the presynaptic membrane of a synapse to which synaptic vesicles attach and release their neurotransmitter into the synaptic cleft.

FIGURE 2.28

Details of a synapse.



Neuron

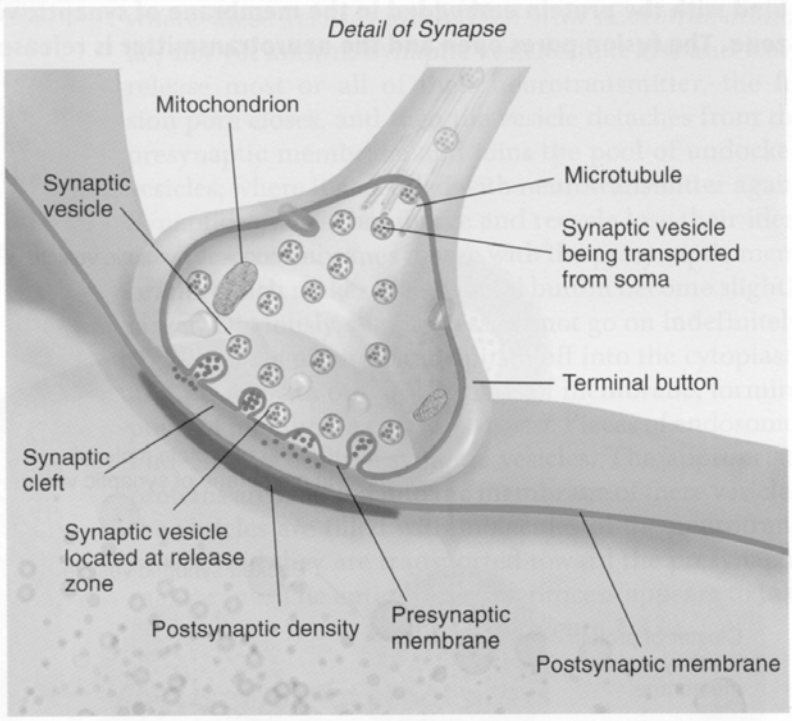


FIGURE 2.29

A photograph from an electron microscope, showing a cross section of a synapse. The terminal button contains many synaptic vesicles, filled with the neurotransmitter, and a single large dense-core vesicle, filled with a peptide.

(From De Camilli, P. et al., in *Synapses,* edited by W. M. Cowan, T. C. Südhof, and C. F. Stevens. Baltimore, MD: Johns Hopkins University Press, 2001. Reprinted with permission.)

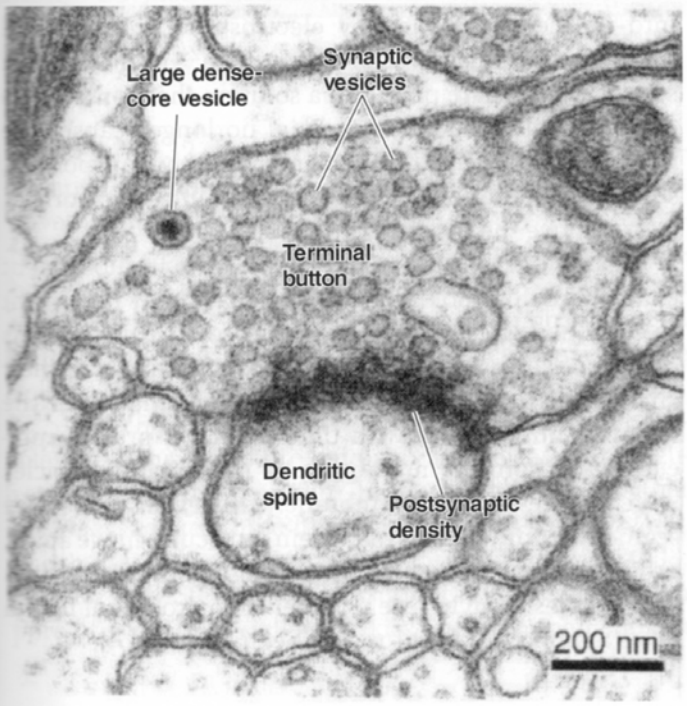


FIGURE 2.30

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. Reprinted with permission.)

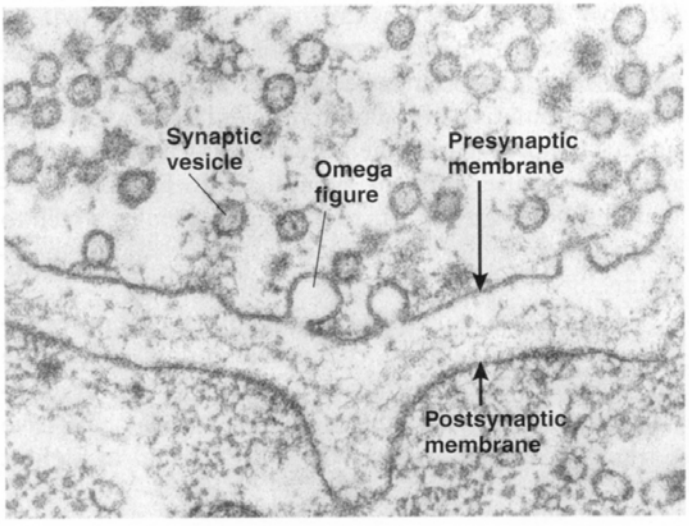
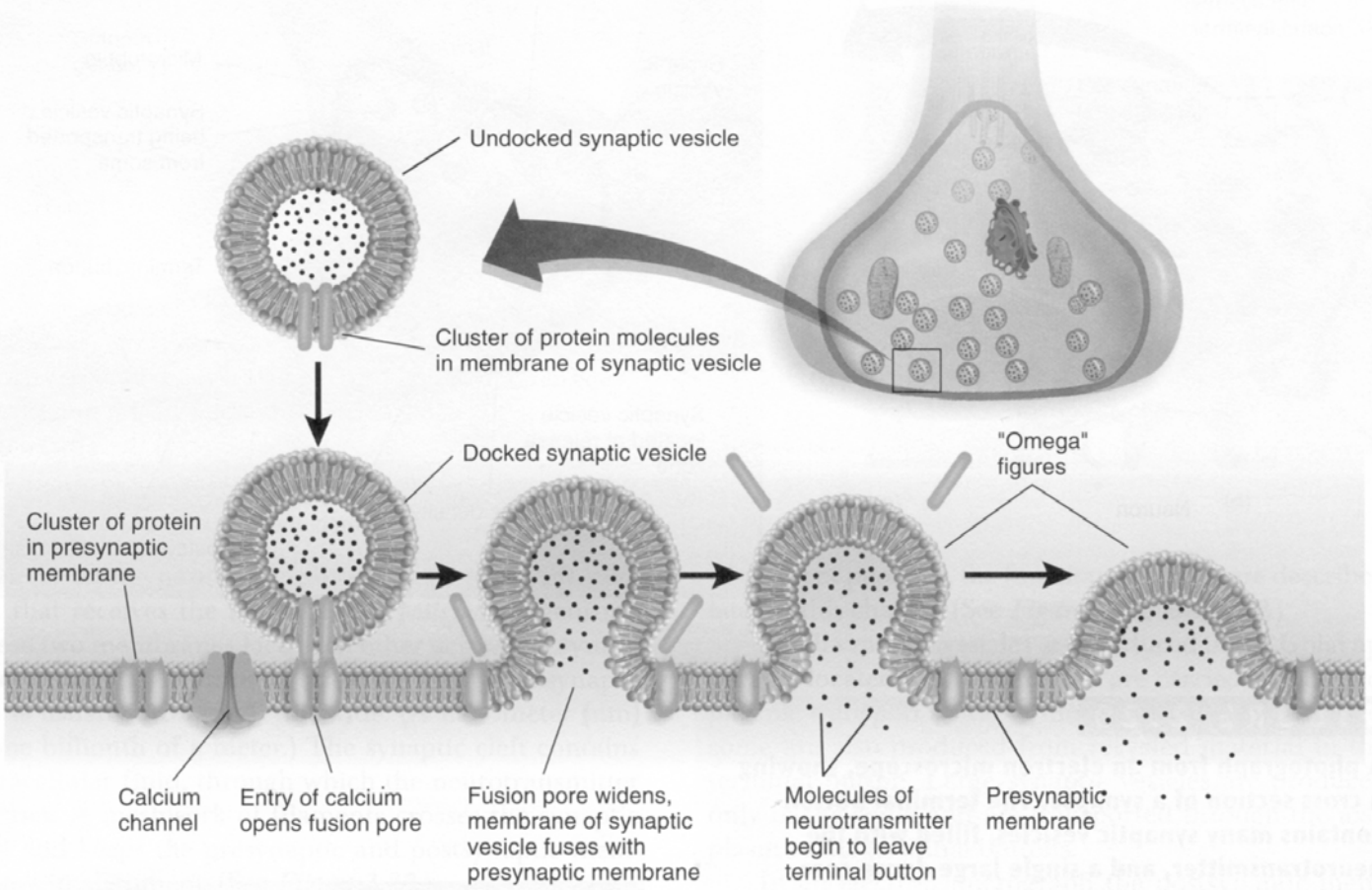


FIGURE 2.31

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 neurotransmitter is released into the synaptic cleft.



their contents into the synaptic cleft. Figure 2.30 shows a portion of a frog's neuromuscular junction—the synapse between a terminal button and a muscle fiber. The axon has just been stimulated, and synaptic vesicles in the terminal button are in the process of releasing the neurotransmitter. Note that some vesicles are fused with the presynaptic membrane, forming the shape of an omega (Ω). (See ***Figure 2.30.***)

How does an action potential cause synaptic vesicles to release the neurotransmitter? The process begins when a population of synaptic vesicles become "docked" against the presynaptic membrane, ready to release their neurotransmitter into the synaptic cleft. Docking is accomplished when clusters of protein molecules attach to other protein molecules located in the presynaptic membrane. (See ***Figure 2.31.***)

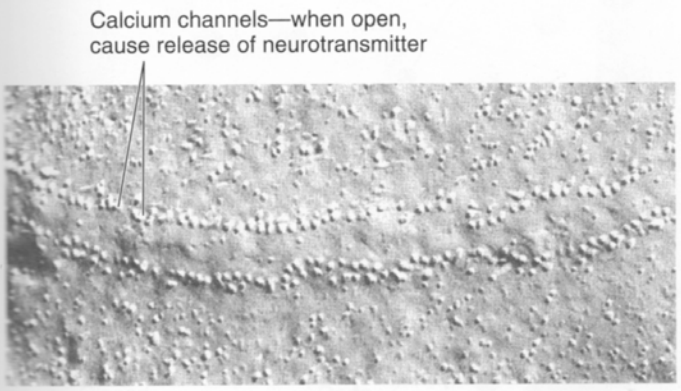
The release zone of the presynaptic membrane contains voltage-dependent calcium channels. When the membrane of the terminal button is depolarized by an arriving action potential, the calcium channels open. Like sodium ions, calcium ions (Ca^{2+}) are located in highest concentration in the extracellular 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 neurotransmitter. (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, calcium ions play many important roles in biological processes within cells. Calcium ions can bind with various types of proteins, changing their characteristics. Some of the calcium ions that enter the terminal button bind 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. The process of fusion takes approximately 0.1 msec. (See ***Figure 2.31.***)

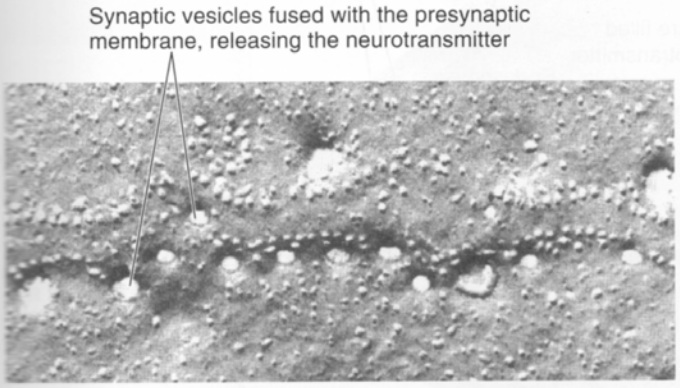
FIGURE 2.32

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 before 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. Reprinted with permission.)



(a)



(b)

Figure 2.32 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 2.32.***)

What happens to the membrane of the synaptic vesicles after they have broken open and released the neurotransmitter they contain? In the brain it appears that the release takes three forms: *kiss and stay, kiss and leave,* and *merge and recycle* (Aravanis, Pyle, and Tsien, 2003; Gandhi and Stevens, 2003; Südhof, 2004). The fusion pore of synaptic vesicles that kiss and stay open enough for some of the molecules of neurotransmitter to diffuse into the synaptic cleft. Then the fusion pore closes again, and the vesicle remains in a docked position. How and where these vesicles are refilled with neurotransmitter are not yet known. Synaptic vesicles that kiss and leave release most or all of their neurotransmitter, the fusion pore closes, and then the vesicle detaches from the presynaptic membrane and joins the pool of undocked vesicles, where it gets filled with neurotransmitter again. Synaptic vesicles that merge and recycle lose their identity. Their membranes merge with the presynaptic membrane, which makes the terminal button become slightly larger. Obviously, this process cannot go on indefinitely, so little buds of membrane pinch off into the cytoplasm and merge with other little buds of membrane, forming pools of membrane called *endosomes.* Pieces of endosomes bud off and become synaptic vesicles. The appropriate proteins are inserted into the membrane of these vesicles, the vesicles are filled with molecules of the neurotransmitter, and they are transported toward the presynaptic membrane. The entire recycling process appears to take approximately one minute. (See ***Figure 2.33.***)

Activation of Receptors

How do molecules of the neurotransmitter 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 located in 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 neurotransmitter 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 will describe it first. Figure 2.34 illustrates 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 2.34.***)

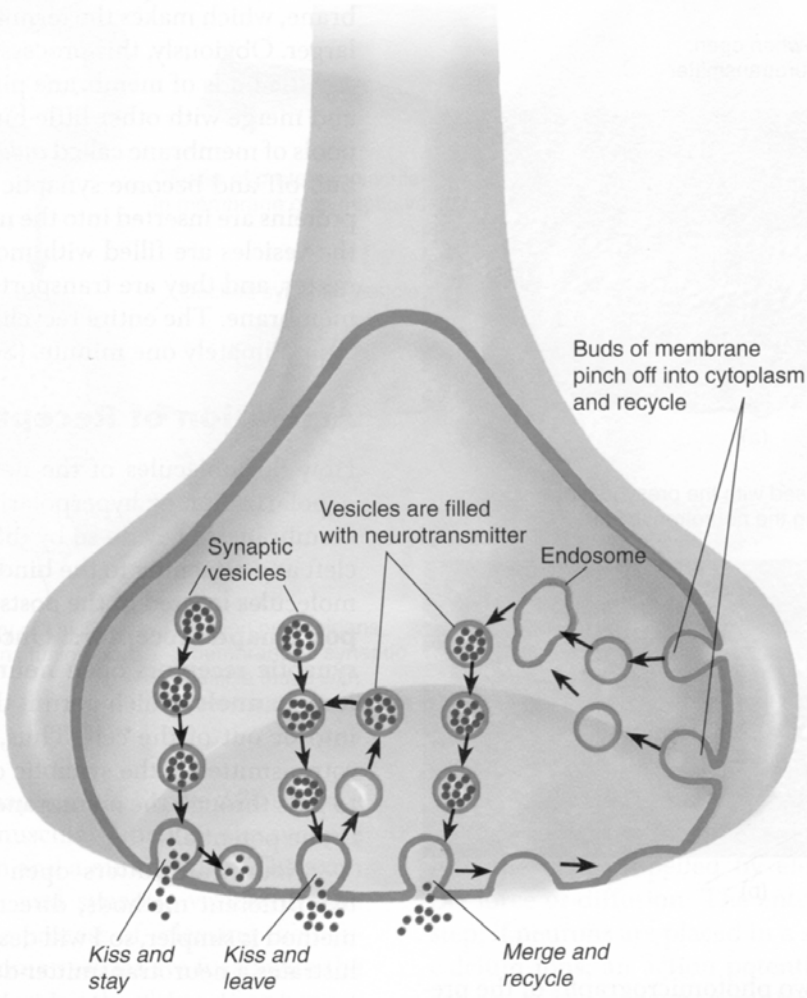
postsynaptic receptor A receptor molecule in the postsynaptic membrane of a synapse that contains a binding site for a neurotransmitter.

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

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.

FIGURE 2.33

The fate of synaptic vesicles that have released neurotransmitter into the synaptic cleft. (a) In "kiss and stay," the vesicle fuses with the postsynaptic membrane and releases some neurotransmitter, and then the fusion pore closes, sealing the vesicular membrane again. The vesicle remains in place. (b) In "kiss and leave," the vesicle releases neurotransmitter and reseals but it leaves the docking site and mixes with other vesicles in the terminal button. (c) In "merge and recycle," the vesicle completely fuses with the postsynaptic membrane, losing its identity. Extra membrane from fused vesicles pinches off into the cytoplasm and forms endosomes, from which new vesicles are produced.



Ionotropic receptors were first discovered in the organ that produces electrical current in *Torpedo,* the electric ray, where they occur 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 neurotransmitter called *acetylcholine,* contain sodium channels. When these channels are open, sodium ions enter the cell and depolarize the membrane.

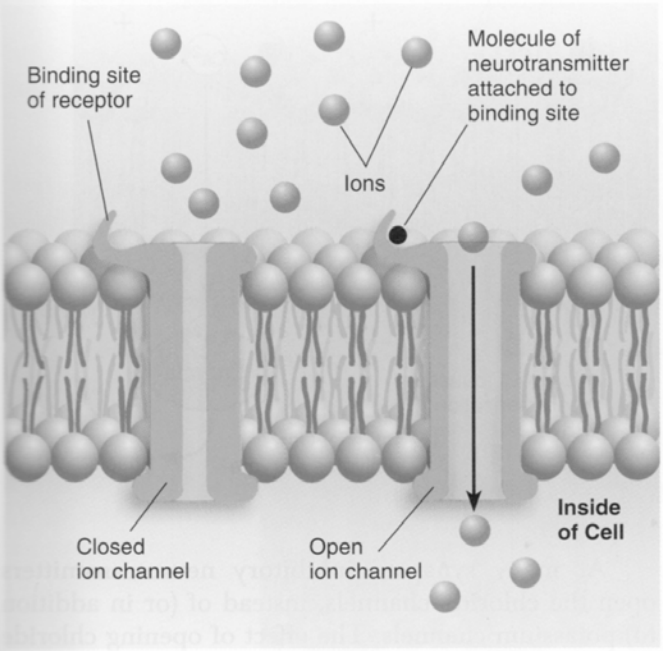
The indirect method is more complicated. Some receptors do not open ion channels directly but instead start a chain of chemical events. These receptors are called **metabotropic receptors** because they involve steps that require that the cell expend metabolic energy. Metabotropic receptors are located in close proximity to another protein attached to the membrane—a **G protein.** When a molecule of the neurotransmitter

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.

FIGURE 2.34

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.



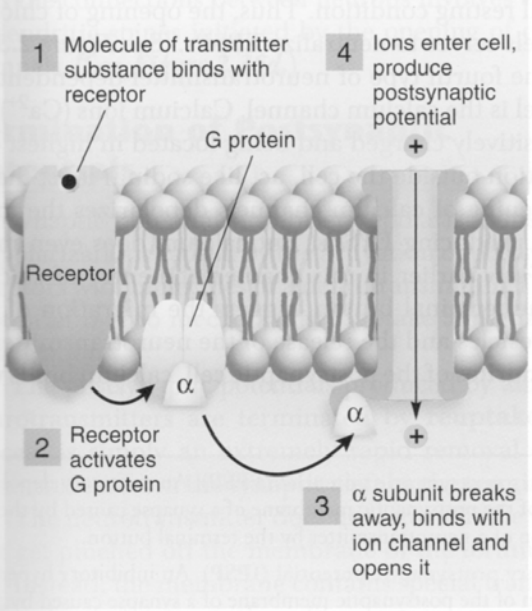
binds with the receptor, the receptor activates a G protein situated inside the membrane next to the receptor. When activated, the G protein activates an enzyme that stimulates the production of a chemical called a **second messenger.** (The neurotransmitter is the first messenger.) Molecules of the second messenger travel through the cytoplasm, attach themselves to nearby ion channels, and cause them to open. Compared with postsynaptic potentials produced by ionotropic receptors, those produced by metabotropic receptors take longer to begin and last longer. (See ***Figure 2.35.***)

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 regions of the neuron and initiate biochemical changes that affect the functions of the cell. They can even turn specific genes on or off, thus initiating or terminating production of particular proteins.

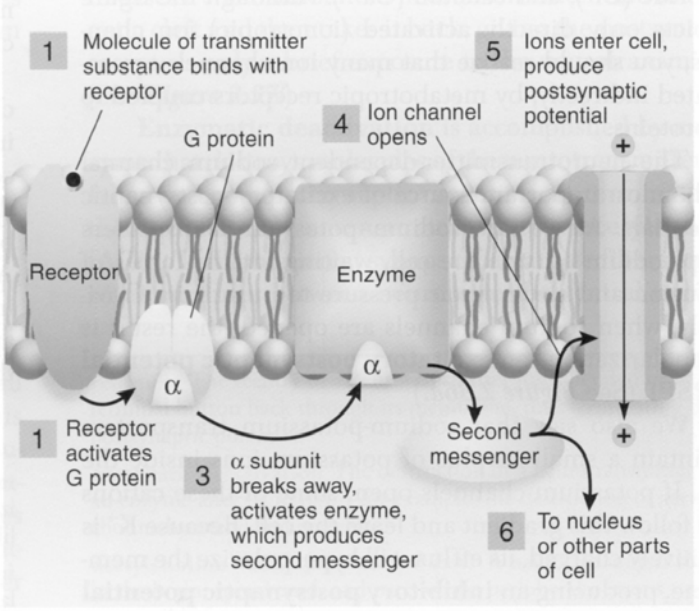
second messenger A chemical produced when a G protein activates an enzyme; carries a signal that results in the opening of the ion channel or causes other events to occur in the cell.

FIGURE 2.35

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.



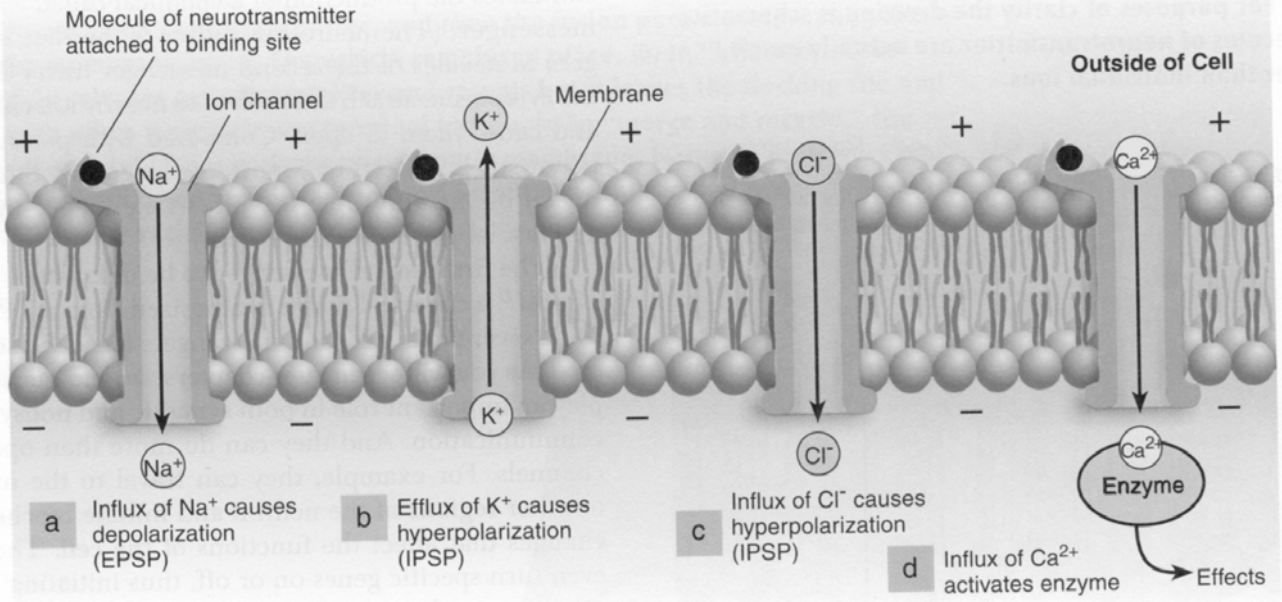
(a)



(b)

FIGURE 2.36

Ionic movements during postsynaptic potentials.



Postsynaptic Potentials

As I mentioned earlier, 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.*

As Figure 2.36 shows, four major types of neurotransmitter-dependent ion channels are 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 2.36a.***)

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, producing an **inhibitory postsynaptic potential (IPSP).** (See ***Figure 2.36b.***)

At many synapses inhibitory neurotransmitters 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 2.36c.***)

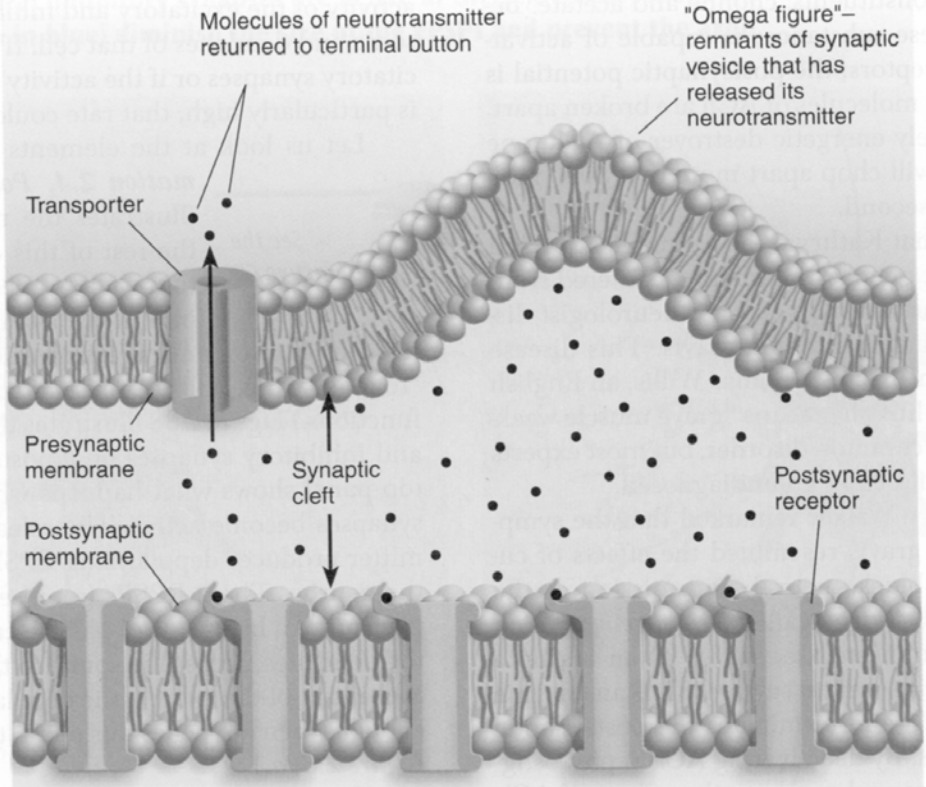
The fourth type of neurotransmitter-dependent ion channel is the calcium channel. Calcium ions (Ca^{2+}), being positively charged and being located in highest concentration outside the cell, act like sodium ions; that is, the opening of calcium channels depolarizes the membrane, producing EPSPs. But 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 neurotransmitter. In the dendrites of the postsynaptic cell, calcium binds with

excitatory postsynaptic potential (EPSP) An excitatory depolarization of the postsynaptic membrane of a synapse caused by the liberation of a neurotransmitter by the terminal button.

inhibitory postsynaptic potential (IPSP) An inhibitory hyperpolarization of the postsynaptic membrane of a synapse caused by the liberation of a neurotransmitter by the terminal button.

FIGURE 2.37

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



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 2.36d.***)

Termination of Postsynaptic Potentials

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

The postsynaptic potentials produced by almost all neurotransmitters are terminated by **reuptake.** This process is simply an extremely rapid removal of neurotransmitter from the synaptic cleft by the terminal button. The neurotransmitter 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 neurotransmitter 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 neurotransmitter into the synaptic cleft and then takes it back, giving the postsynaptic receptors only a brief exposure to the neurotransmitter. (See ***Figure 2.37.***)

Enzymatic deactivation is accomplished by an enzyme that destroys molecules of the neurotransmitter. As far as we know, postsynaptic potentials are terminated in this way for only one neurotransmitter: **acetylcholine (ACh).** Transmission at synapses on muscle fibers and at some synapses between neurons in the central nervous

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

enzymatic deactivation The destruction of a neurotransmitter 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.

system 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 5000 molecules of ACh each second.

You will recall that Kathryn, the woman featured in the case history that opened this chapter, suffered from progressive muscular weakness. As her neurologist discovered, Kathryn had myasthenia gravis. This disease was first described in 1672 by Thomas Willis, an English physician. The term literally means "grave muscle weakness." It is not a very common disorder, but most experts believe that many mild cases go undiagnosed.

In 1934 Dr. Mary Walker remarked that the symptoms of myasthenia gravis resembled the effects of curare, a poison that blocks neural transmission at the synapses on muscles. A drug called *physostigmine,* which deactivates acetylcholinesterase, serves as an antidote for curare poisoning. As we just saw, AChE is an enzyme that destroys the ACh and terminates the postsynaptic potentials it produces. By deactivating AChE, physostigmine greatly increases and prolongs the effects of ACh on the postsynaptic membrane. Thus, it increases the strength of synaptic transmission at the synapses on muscles and reverses the effects of curare. (Chapter 4 will say more about both curare and physostigmine.)

Dr. Walker reasoned that if physostigmine reversed the effects of curare poisoning, perhaps it would also reverse the symptoms of myasthenia gravis. She tried it, and it did within a matter of a few minutes. Later, pharmaceutical companies discovered drugs that could be taken orally and that produced longer-lasting effects. Nowadays, an injectable drug is used to make the diagnosis (as in Kathryn's case), and an oral drug is used to treat it. Unfortunately, no cure has yet been found for myasthenia gravis.

Like multiple sclerosis, myasthenia gravis is an autoimmune disease. For some reason the immune system becomes sensitized against the protein that makes up acetylcholine receptors. Almost as fast as new ACh receptors are produced, the immune system destroys them.

Effects of Postsynaptic Potentials: Neural Integration

We have seen how neurons are interconnected by means of synapses, how action potentials trigger the release of neurotransmitters, 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. (Remember, "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. If there are no active excitatory synapses or if the activity of inhibitory synapses is particularly high, that rate could be close to zero.

Let us look at the elements of this process. (***Animation 2.4, Postsynaptic Potentials,*** illustrates the material presented in the rest of this chapter.) 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 2.38 illustrates the effects of excitatory and inhibitory synapses on a postsynaptic neuron. The top panel shows what happens when several excitatory synapses become active. The release of the neurotransmitter produces depolarizing EPSPs in the dendrites of the neuron. These EPSPs (represented in red) are then transmitted, by means of passive cable properties, down the dendrites, across the soma, to the *axon hillock* located at the base of the axon. If the depolarization is still strong enough when it reaches this point, the axon will fire. (See ***Figure 2.38a.***)

See the interactive CD

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 2.38b.***)

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 activity of inhibitory synapses goes up, the rate of firing will go down.

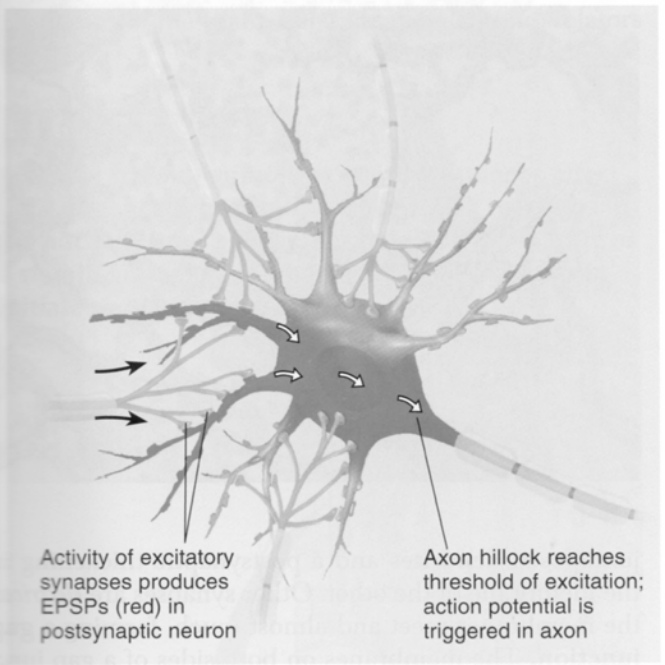
Note that *neural* inhibition (that is, an inhibitory postsynaptic potential) does not always produce *behavioral* inhibition. For example, suppose a group of neurons inhibits a particular movement. If these neurons are inhibited, they will no longer suppress the behavior. Thus, inhibition of the inhibitory neurons makes the behavior more likely to occur. Of course, the same is true for neural excitation. *Excitation* of neurons that *inhibit* a behavior suppresses that behavior. For example, when

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.

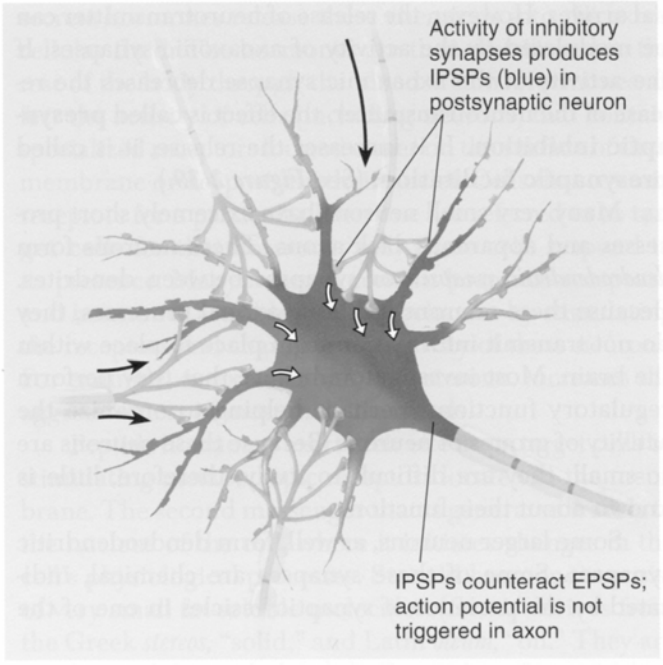
neural integration The process by which inhibitory and excitatory postsynaptic potentials summate and control the rate of firing of a neuron.

FIGURE 2.38

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.



(a)



(b)

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 damaged, 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 neurotransmitter 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 neurotransmitters. Many neurons also possess receptors that respond to the neurotransmitter that *they themselves* release, called **autoreceptors.**

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. In most cases these autoreceptors do not control ion channels. Thus, when stimulated by a molecule of the neurotransmitter, autoreceptors do not produce changes in the membrane potential of the terminal button. Instead, they regulate internal processes, including the synthesis and release of the neurotransmitter. (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 neurotransmitter in the extracellular fluid in the vicinity of the neuron causes a decrease in the rate of synthesis or release of the neurotransmitter. Most investigators believe that autoreceptors are part of a regulatory system that controls the amount of neurotransmitter that is 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, they alter the amount of neurotransmitter

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

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 neurotransmitter by a terminal button is initiated by an action potential. Normally, a particular terminal button releases a fixed amount of neurotransmitter each time an action potential arrives. However, the release of neurotransmitter can be modulated by the activity of axoaxonic synapses. If the activity of the axoaxonic synapse decreases the release of the neurotransmitter, the effect is called **presynaptic inhibition.** If it increases the release, it is called **presynaptic facilitation.** (See ***Figure 2.39.***)

Many very small neurons have extremely short processes and apparently lack axons. These neurons form *dendrodendritic synapses,* or synapses between dendrites. Because these 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; therefore, 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 2.40.***) 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 2.39

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

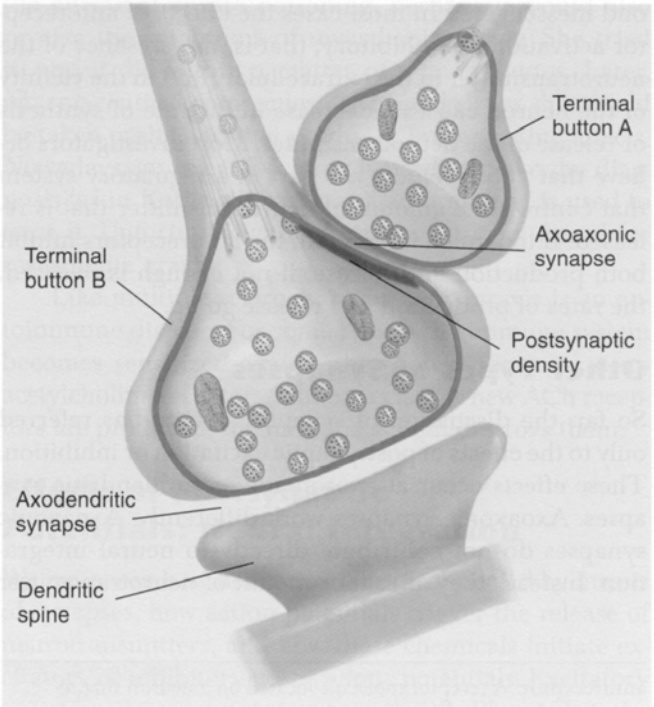
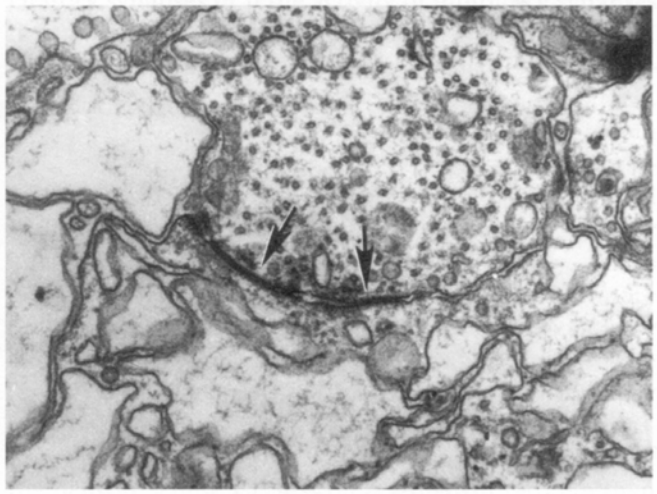


FIGURE 2.40

A gap junction, which permits direct electrical coupling between the membranes of adjacent neurons.

(Adapted from Bennett, M. V. L., and Pappas, G. D. *The Journal of Neuroscience,* 1983, *3,* 748–761.)



Nonsynaptic Chemical Communication

Neurotransmitters are released by terminal buttons of neurons and bind with receptors in the membrane of another cell located a very short distance away. The communication at each synapse is private. **Neuromodulators**

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.

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

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.

are chemicals released by neurons that travel farther and are dispersed more widely than are neurotransmitters. Most neuromodulators are **peptides,** chains of amino acids that are linked together by chemical attachments called *peptide bonds* (hence their name). Neuromodulators are secreted in larger amounts and diffuse for longer distances, modulating the activity of many neurons in a particular part of the brain. For example, neuromodulators affect general behavioral states such as vigilance, fearfulness, and sensitivity to pain. Chapter 4 discusses the most important neurotransmitters and neuromodulators.

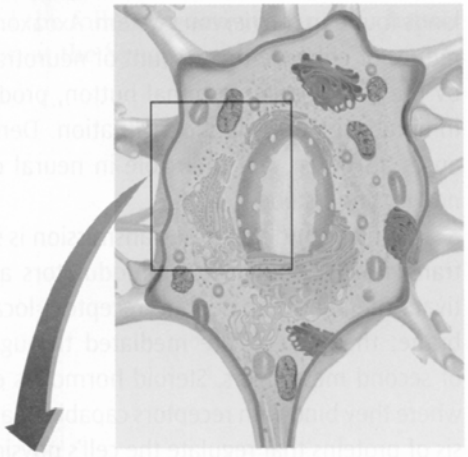
Hormones are secreted by cells of **endocrine glands** (from the Greek *endo-,* "within," and *krinein,* "to secrete") or by cells located in various organs, such as the stomach, the intestines, the kidneys, and the brain. Cells that secrete hormones release these chemicals into the extracellular fluid. 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. 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.

Peptide hormones 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. **Steroid** hormones consist of very small fat-soluble molecules. (*Steroid* derives from the Greek *stereos,* "solid," and Latin *oleum,* "oil." They are synthesized from chole*sterol.*) 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 2.41.***)

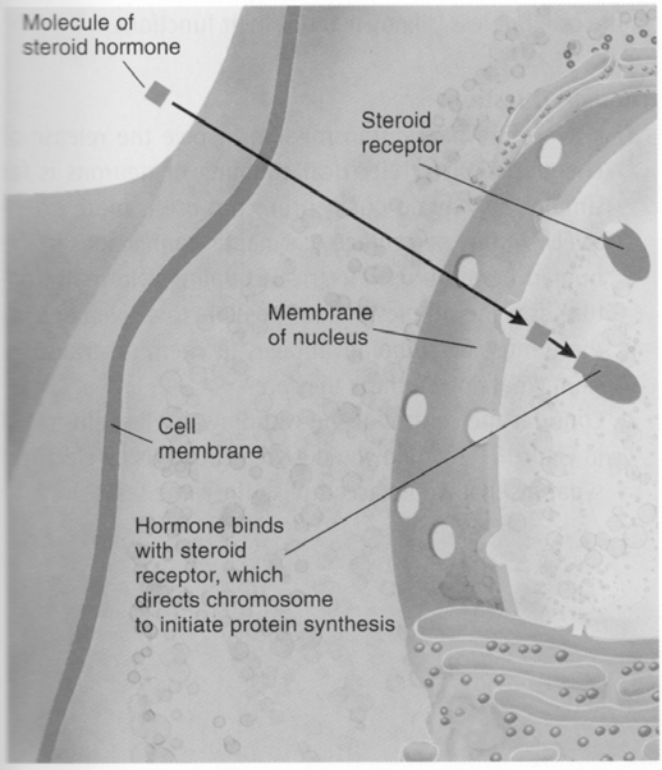
In the past few years investigators have discovered the presence of steroid receptors in terminal buttons and around the postsynaptic membrane of some neurons. These steroid receptors influence synaptic transmission, and they do so rapidly. Exactly how they work is still not known.

FIGURE 2.41

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.



Detail of Cell



peptide A chain of amino acids joined together by peptide bonds. Most neuromodulators, and some hormones, consist of peptide molecules.

hormone A chemical substance that is released by an endocrine gland that has effects on target cells in other organs.

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 other chemical signal.

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

InterimSummary

Communication Between Neurons

Synapses consist of junctions between the terminal buttons of one neuron and the membrane; another neuron, a muscle cell, or a gland cell. When an action potential is transmitted down an axon, the terminal buttons at the end release a neurotransmitter, a chemical that produces either depolarizations (EPSPs) or hyperpolarizations (IPSPs) of the postsynaptic membrane. The rate of firing of the axon of the postsynaptic neuron 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.*

Terminal buttons contain 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 release the neurotransmitter. Some vesicles briefly "kiss" and stay attached to the release zone, others "kiss" and leave, and others completely fuse with the presynaptic membrane. The membrane contributed by these vesicles pinches off into the cytoplasm and is recycled in the production of new vesicles.

The activation of postsynaptic receptors by molecules of a neurotransmitter 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 chemical called a second messenger.

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 when K^+ leaves the cell or Cl^- enters it. The entry of Ca^{2+} produces EPSPs, but even more important, it activates special enzymes that cause physiological changes in the postsynaptic cell.

Postsynaptic potentials are normally very 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 neurotransmitter are removed from the synaptic cleft by means of transporters located in the presynaptic membrane. This retrieval process is called reuptake.

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

Axosomatic and axodendritic synapses are not the only kinds found in the nervous system. Axoaxonic synapses either reduce or enhance the amount of neurotransmitter released by the postsynaptic terminal button, producing presynaptic inhibition or presynaptic facilitation. 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 elsewhere in the cell, but less is known about their functions.

Thought Questions

1. Why does synaptic transmission involve the release of chemicals? Direct electrical coupling of neurons is far simpler, so why do our neurons not use it more extensively? (A tiny percentage of synaptic connections in the human brain do use electrical coupling.) Normally, nature uses the simplest means possible to a given end, so there must be some advantages to chemical transmission. What do you think they are?
2. Consider the control of the withdrawal reflex illustrated in Figure 2.14. Could you design a circuit using electrical synapses that would accomplish the same tasks?

SUGGESTED READINGS

Aidley, D. J. *The Physiology of Excitable Cells,* 4th ed. Cambridge, England: Cambridge University Press, 1998.

Cowan, W. M., Südhof, T. C., and Stevens, C. F. *Synapses.* Baltimore, MD: Johns Hopkins University Press, 2001.

Kandel, E. R., Schwartz, J. H., and Jessell, T. M. *Principles of Neural Science,* 4th ed. New York: McGraw-Hill, 2000.

Nicholls, J. G., Martin, A. R., Fuchs, P. A., and Wallace, B. G. *From Neuron to Brain,* 4th ed. Sunderland, MA: Sinauer, 2001.

ADDITIONAL RESOURCES

The Companion Website for this text contains additional resources, including Practice Tests and Weblinks with up-to-date information about topics discussed in this chapter.

www.ablongman.com/carlsonpob9e

You will also find the following activity for this chapter on the site: Action at the Synapse.