NEUROSCIENCE

Exploring the Brain

Enhanced Fourth Edition

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CHAPTER FIVE

Synaptic Transmission

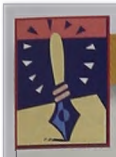
INTRODUCTION

In Chapters 3 and 4, we discussed how mechanical energy, such as a thumbtack entering your foot, can be converted into a neural signal. First, specialized ion channels of the sensory nerve endings allow positive charge to enter the axon. If this depolarization reaches threshold, then action potentials are generated. Because the axonal membrane is excitable and has voltage-gated sodium channels, action potentials can propagate without decrement up the long sensory nerves. For this information to be processed by the rest of the nervous system, however, these neural signals must be passed on to other neurons—for example, the motor neurons that control muscle contraction, as well as neurons in the brain and spinal cord that lead to a coordinated reflex response. By the end of the nineteenth century, it was recognized that this transfer of information from one neuron to another occurs at specialized sites of contact. In 1897, English physiologist Charles Sherrington gave these sites their name: synapses. The process of information transfer at a synapse is called **synaptic transmission**.

The physical nature of synaptic transmission was debated for almost a century. One attractive hypothesis, which nicely explained the speed of synaptic transmission, was that it was simply electrical current flowing from one neuron to the next. The existence of such **electrical synapses** was finally proven in the late 1950s by Edwin Furshpan and David Potter, American physiologists who were studying the nervous system of crayfish at University College London, and Akira Watanabe, who was studying the neurons of lobster at the Tokyo Medical and Dental University. We now know that electrical synapses are common in the brains of invertebrates and vertebrates, including mammals.

An alternative hypothesis about the nature of synaptic transmission, also dating back to the 1800s, was that chemical neurotransmitters transfer information from one neuron to another at the synapse. Solid support for the concept of **chemical synapses** was provided in 1921 by Otto Loewi, then the head of the Pharmacology Department at the University of Graz in Austria. Loewi showed that electrical stimulation of axons innervating the frog's heart caused the release of a chemical that could mimic the effects of neuron stimulation on the heartbeat (Box 5.1). Later, Bernard Katz and his colleagues at University College London conclusively demonstrated that fast transmission at the synapse between a motor neuron axon and skeletal muscle was chemically mediated. By 1951, John Eccles of the Australian National University was studying the physiology of synaptic transmission within the mammalian central nervous system (CNS) using a new tool, the glass microelectrode. These experiments indicated that many CNS synapses also use a chemical transmitter; in fact, chemical synapses comprise the majority of synapses in the brain. During the last decade, new methods of studying the molecules involved in synaptic transmission have revealed that synapses are far more complex than most neuroscientists anticipated.

Synaptic transmission is a large and fascinating topic. The actions of psychoactive drugs, the causes of mental disorders, the neural bases of learning and memory—indeed, all the operations of the nervous system—cannot be understood without knowledge of synaptic transmission. Therefore, we've devoted several chapters to this topic, mainly focusing on chemical synapses. In this chapter, we begin by exploring the basic mechanisms of synaptic transmission. What do different types of synapse look like? How are neurotransmitters synthesized and stored, and how are they released in response to an action potential in the axon terminal? How do neurotransmitters act on the postsynaptic membrane? How do single neurons integrate the inputs provided by the thousands of synapses that impinge upon them?



BOX 5.1 OF SPECIAL INTEREST

Otto Loewi's Dream

One of the more colorful stories in the history of neuroscience comes from Otto Loewi, who, working in Austria in the 1920s, showed definitively that synaptic transmission between nerves and the heart is chemically mediated. The heart has two types of innervation; one type speeds the beating of the heart, and the other slows it. The latter type of innervation is supplied by the vagus nerve. Loewi isolated a frog heart with the vagal innervation still intact, stimulated the nerve electrically, and observed the expected effect: the slowing of the heartbeat. The critical demonstration that this effect was chemically mediated came when he applied the solution that had bathed this heart to a second isolated frog heart and found that the beating of this one also slowed.

The idea for this experiment had actually come to Loewi in a dream. Below is his own account:

> In the night of Easter Sunday, 1921, I awoke, turned on the light, and jotted down a few notes on a tiny slip of paper. Then, I fell asleep again. It occurred to me at six o'clock in the morning that during the night I had written down something most important, but I was unable to decipher the scrawl. That Sunday was the most desperate day in my whole scientific life. During the next night, however, I awoke again, at three o'clock, and I remembered what it was. This time I did not take any risk; I got up immediately, went to the laboratory, made the experiment on the frog's heart, described above, and at five o'clock the chemical transmission of the nervous impulse was conclusively proved. . . . Careful consideration in daytime would undoubtedly have rejected the kind of experiment I performed, because it would have seemed most unlikely that if a nervous impulse released a transmitting agent, it would do so not just in sufficient quantity to influence the effector organ, in my case the heart, but indeed in such an excess that it could partly escape into the fluid which filled the heart, and could therefore be detected. Yet the whole nocturnal concept of the experiment was based on this eventuality, and the result proved to be positive, contrary to expectation. (Loewi, 1953, pp. 33–34.)

The active compound, which Loewi called *vagusstoff* (literally "vagus substance" in German), turned out to be acetylcholine. As we see in this chapter, acetylcholine is also a transmitter at the synapse between nerve and skeletal muscle. Unlike at the heart, acetylcholine applied to skeletal muscle causes excitation and contraction.

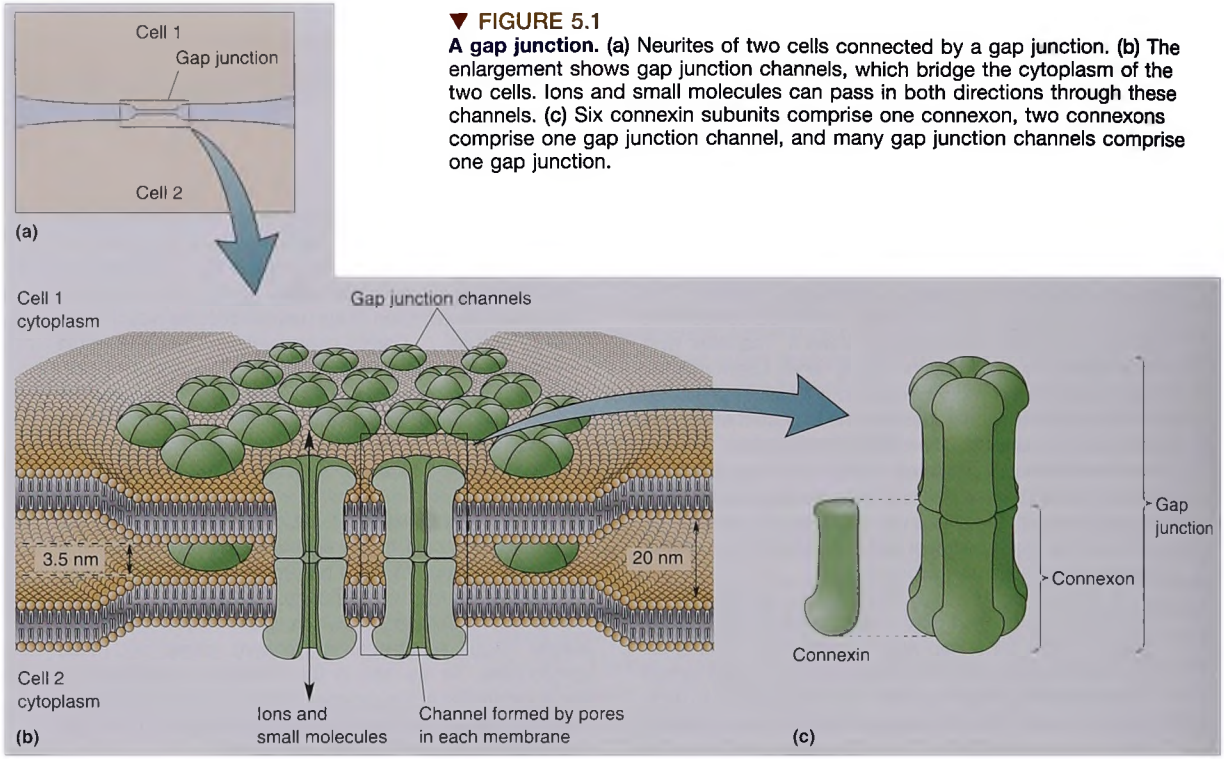
TYPES OF SYNAPSES

We introduced the synapse in Chapter 2. A synapse is the specialized junction where one part of a neuron contacts and communicates with another neuron or cell type (such as a muscle or glandular cell). Information generally flows in one direction, from a neuron to its target cell. The first neuron is said to be *presynaptic*, and the target cell is said to be *postsynaptic*. Let's take a closer look at the different types of synapse.

Electrical Synapses

Electrical synapses are relatively simple in structure and function, and they allow the direct transfer of ionic current from one cell to the next. Electrical synapses occur at specialized sites called **gap junctions**. Gap junctions occur between cells in nearly every part of the body and interconnect many non-neural cells, including epithelial cells, smooth and cardiac muscle cells, liver cells, some glandular cells, and glia.

When gap junctions interconnect neurons, they can function as electrical synapses. At a gap junction, the membranes of two cells are separated by only about 3 nm, and this narrow gap is spanned by clusters of special proteins called *connexins*. There are about 20 different subtypes of connexins, about half of which occur in the brain. Six connexin subunits combine to form a channel called a *connexon*, and two connexons (one from each cell) meet and combine to form a *gap junction channel* (Figure 5.1). The channel allows ions to pass directly from the cytoplasm of one cell

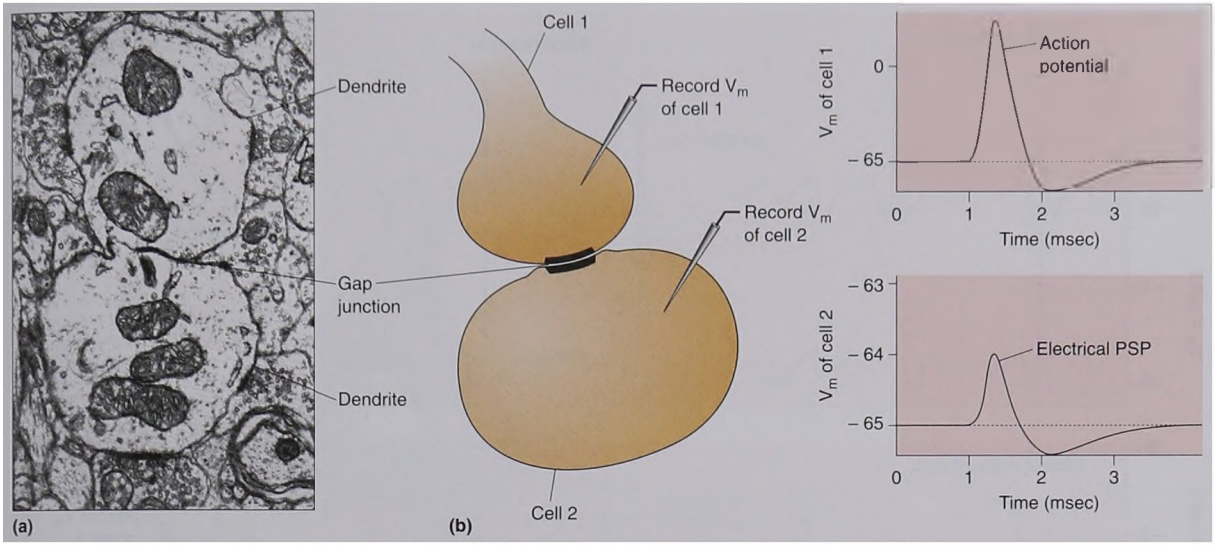


▼ FIGURE 5.1
A gap junction. (a) Neurites of two cells connected by a gap junction. (b) The enlargement shows gap junction channels, which bridge the cytoplasm of the two cells. Ions and small molecules can pass in both directions through these channels. (c) Six connexin subunits comprise one connexon, two connexons comprise one gap junction channel, and many gap junction channels comprise one gap junction.

to the cytoplasm of the other. The pore of most gap junction channels is relatively large. Its diameter is about 1–2 nm, big enough for all the major cellular ions and many small organic molecules to pass through.

Most gap junctions allow ionic current to pass equally well in both directions; therefore, unlike the vast majority of chemical synapses, electrical synapses are bidirectional. Because electrical current (in the form of ions) can pass through these channels, cells connected by gap junctions are said to be *electrically coupled*. Transmission at electrical synapses is very fast and, if the synapse is large, nearly fail-safe. Thus, an action potential in the presynaptic neuron can produce, with very little delay, an action potential in the postsynaptic neuron. In invertebrate species, such as the crayfish, electrical synapses are sometimes found between sensory and motor neurons in neural pathways mediating escape reflexes. This mechanism enables an animal to beat a hasty retreat when faced with a dangerous situation.

Studies in recent years have revealed that electrical synapses are common in every part of the mammalian CNS (Figure 5.2a). When two neurons are electrically coupled, an action potential in the presynaptic neuron causes a small amount of ionic current to flow across the gap junction channels into the other neuron. This current causes an electrically mediated **postsynaptic potential (PSP)** in the second neuron (Figure 5.2b). Note that, because most electrical synapses are bidirectional, when that second neuron generates an action potential, it will in turn induce a PSP in the first neuron. The PSP generated by a single electrical synapse in the mammalian brain is usually small—about 1 mV or less at its peak—and may not, by itself, be large enough to trigger an action



▲ FIGURE 5.2
Electrical synapses. (a) A gap junction interconnecting the dendrites of two neurons constitutes an electrical synapse. **(b)** An action potential generated in one neuron causes a small amount of ionic current to flow through gap junction channels into a second neuron, inducing an electrical PSP. (Source: Part a from Sloper and Powell, 1978.)

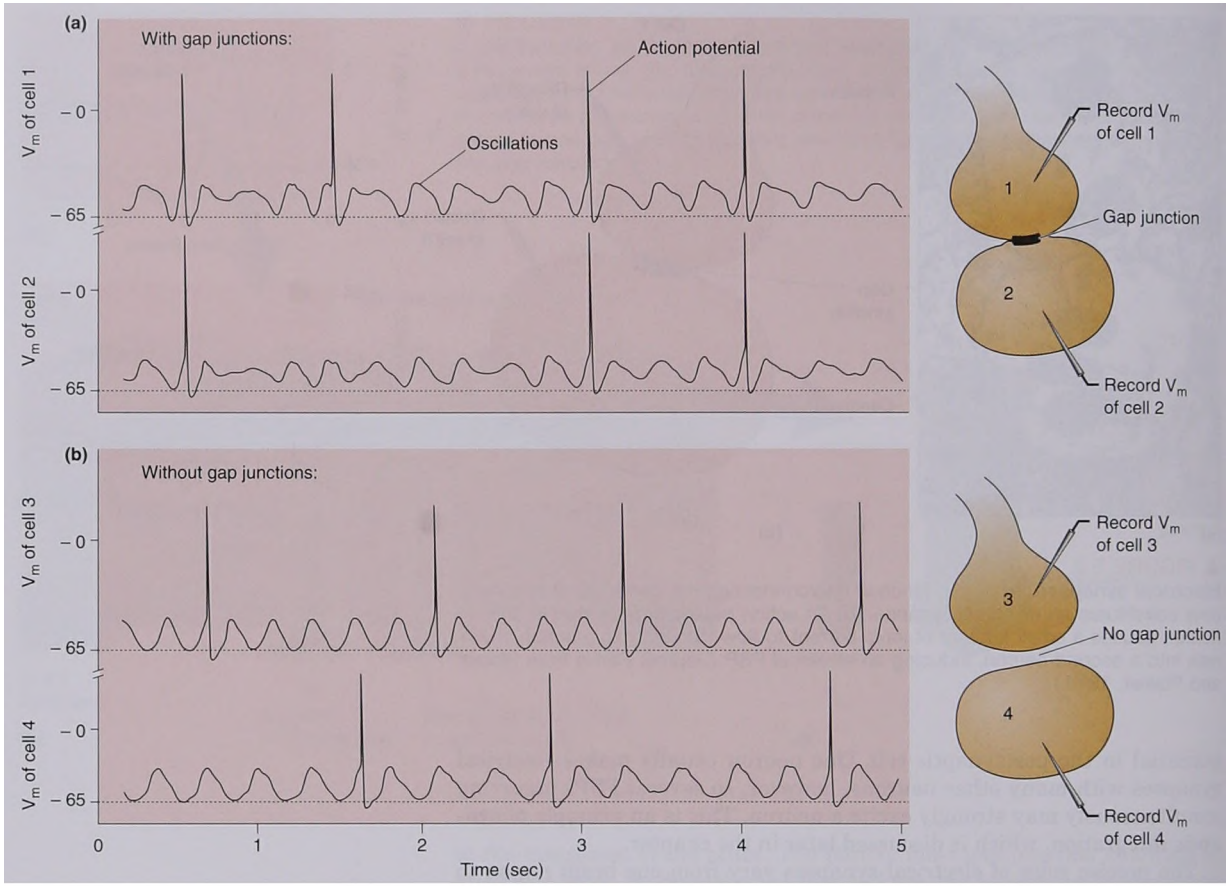
potential in the postsynaptic cell. One neuron usually makes electrical synapses with many other neurons, however, so several PSPs occurring simultaneously may strongly excite a neuron. This is an example of synaptic integration, which is discussed later in the chapter.

The precise roles of electrical synapses vary from one brain region to another. They are often found where normal function requires that the activity of neighboring neurons be highly synchronized. For example, neurons in a brain stem nucleus called the *inferior olive* can generate both small oscillations of membrane voltage and, more occasionally, action potentials. These cells send axons to the cerebellum and are important in motor control. They also make gap junctions with one another. Current that flows through gap junctions during membrane oscillations and action potentials serves to coordinate and synchronize the activity of inferior olivary neurons (Figure 5.3a), and this in turn may help to control the fine timing of motor control. Michael Long and Barry Connors, working at Brown University, found that genetic deletion of a critical gap junction protein called *connexin36* (Cx36) did not alter the neurons' ability to generate oscillations and action potentials but did abolish the synchrony of these events because of the loss of functional gap junctions (Figure 5.3b).

Gap junctions between neurons and other cells are particularly common early in development. Evidence suggests that during prenatal and postnatal brain development, gap junctions allow neighboring cells to share both electrical and chemical signals that may help coordinate their growth and maturation.

Chemical Synapses

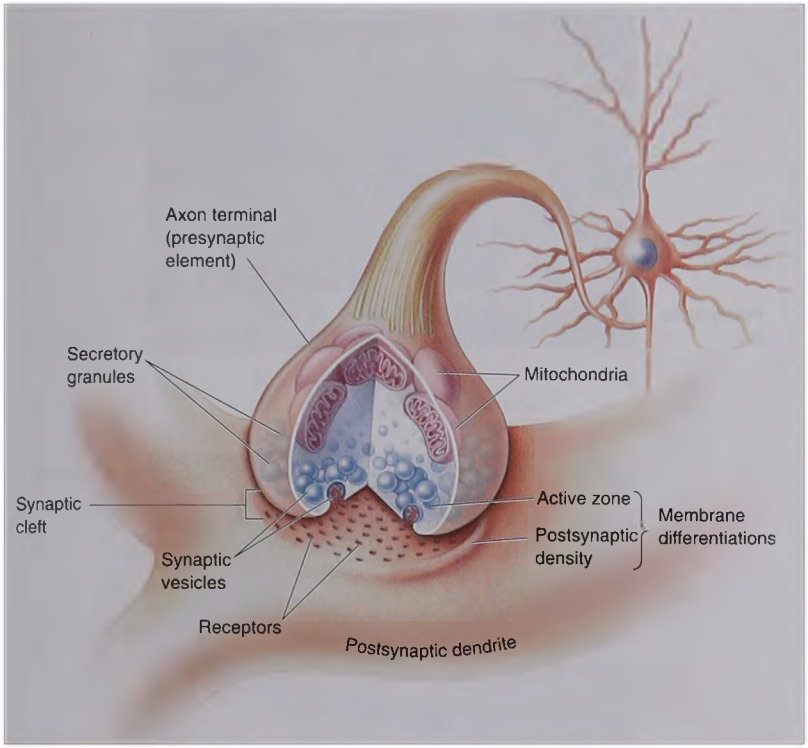
Most synaptic transmission in the mature human nervous system is chemical, so the remainder of this chapter and the next will now focus exclusively on chemical synapses. Before we discuss the different types of



▲ FIGURE 5.3
Electrical synapses can help neurons to synchronize their activity. Certain brain stem neurons generate small, regular oscillations of V_m and occasional action potentials. (a) When two neurons are connected by gap junctions (cells 1 and 2), their oscillations and action potentials are well synchronized. (b) Similar neurons with no gap junctions (cells 3 and 4) generate oscillations and action potentials that are entirely uncoordinated. (Source: Adapted from Long et al., 2002, p. 10903.)

chemical synapses, let's take a look at some of their universal characteristics (Figure 5.4).

The presynaptic and postsynaptic membranes at chemical synapses are separated by a *synaptic cleft* that is 20–50 nm wide, 10 times the width of the separation at gap junctions. The cleft is filled with a matrix of fibrous extracellular protein. One function of this matrix is to serve as a "glue" that binds the pre- and postsynaptic membranes together. The presynaptic side of the synapse, also called the *presynaptic element*, is usually an axon terminal. The terminal typically contains dozens of small membrane-enclosed spheres, each about 50 nm in diameter, called *synaptic vesicles* (Figure 5.5a). These vesicles store neurotransmitter, the chemical used to communicate with the postsynaptic neuron. Many axon terminals also contain larger vesicles, each about 100 nm in diameter, called **secretory granules**. Secretory granules contain soluble protein that appears dark in the electron microscope, so they are sometimes called large, **dense-core vesicles** (Figure 5.5b).

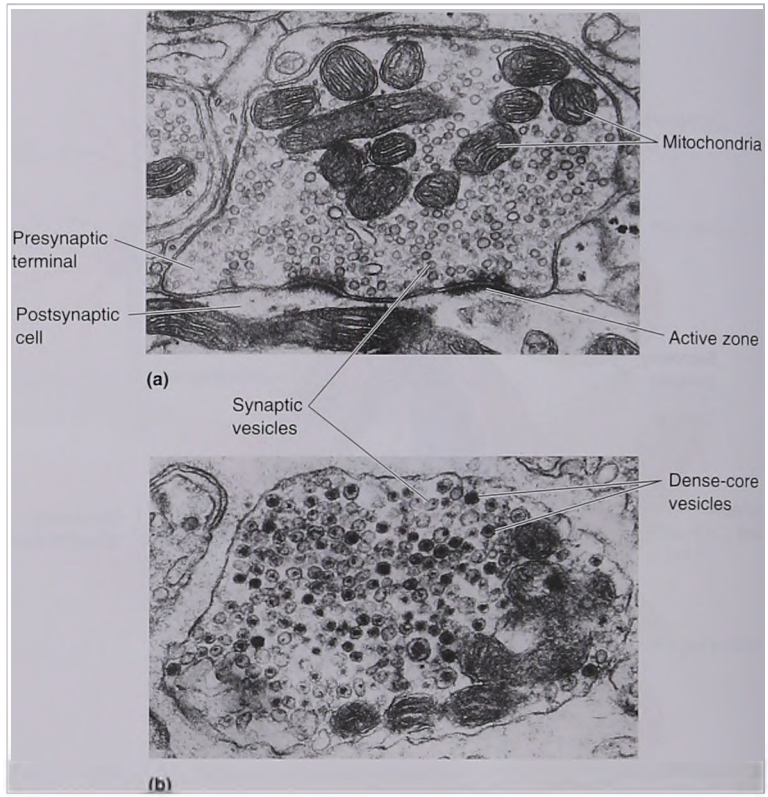


▲ FIGURE 5.4
The components of a chemical synapse.

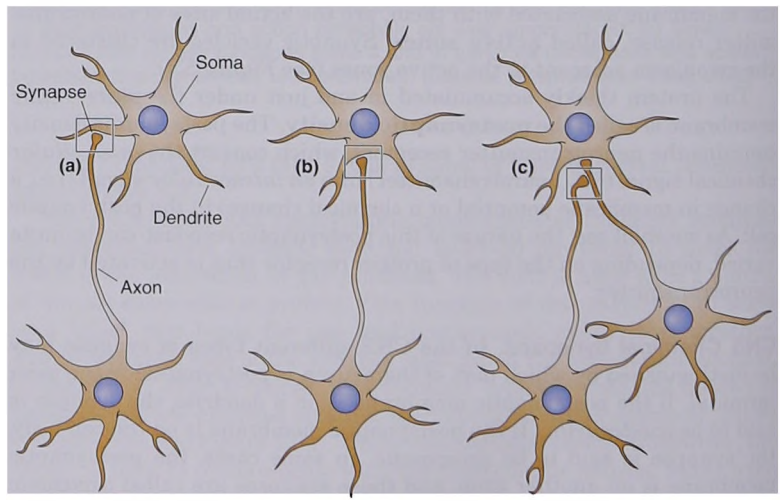
Dense accumulations of protein adjacent to and within the membranes on either side of the synaptic cleft are collectively called **membrane differentiations**. On the *presynaptic* side, proteins jutting into the cytoplasm of the terminal along the intracellular face of the membrane sometimes look like a field of tiny pyramids. The pyramids, and the membrane associated with them, are the actual sites of neurotransmitter release, called **active zones**. Synaptic vesicles are clustered in the cytoplasm adjacent to the active zones (see Figure 5.4).

The protein thickly accumulated in and just under the *postsynaptic* membrane is called the **postsynaptic density**. The postsynaptic density contains the neurotransmitter receptors, which convert the *intercellular* chemical signal (i.e., neurotransmitter) into an *intracellular* signal (i.e., a change in membrane potential or a chemical change) in the postsynaptic cell. As we shall see, the nature of this postsynaptic response can be quite varied, depending on the type of protein receptor that is activated by the neurotransmitter.

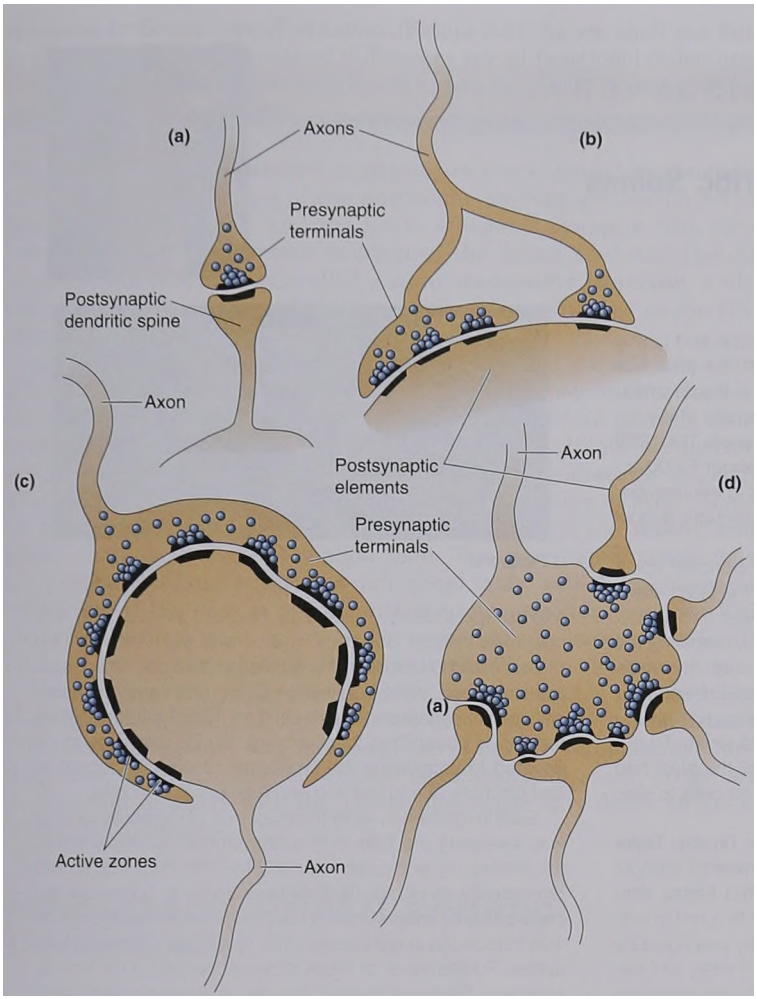
CNS Chemical Synapses. In the CNS, different types of synapse may be distinguished by which part of the neuron is postsynaptic to the axon terminal. If the postsynaptic membrane is on a dendrite, the synapse is said to be *axodendritic*. If the postsynaptic membrane is on the cell body, the synapse is said to be *axosomatic*. In some cases, the postsynaptic membrane is on another axon, and these synapses are called *axoaxonic* (Figure 5.6). When a presynaptic axon contacts a postsynaptic dendritic spine, it is called *axospinous* (Figure 5.7a). In certain specialized neurons, *dendrites* actually form synapses with one another; these are called



▲ FIGURE 5.5
Chemical synapses, as seen with the electron microscope. (a) A fast excitatory synapse in the CNS. (b) A synapse in the PNS, with numerous dense-core vesicles. (Source: Part a adapted from Heuser and Reese, 1977, p. 262; part b adapted from Heuser and Reese, 1977, p. 278.)



▲ FIGURE 5.6
Synaptic arrangements in the CNS. (a) An axodendritic synapse. (b) An axosomatic synapse. (c) An axoaxonic synapse.



▲ FIGURE 5.7
Various shapes and sizes of CNS synapses. (a) Axospinous synapse: A small presynaptic axon terminal contacts a postsynaptic dendritic spine. Notice that presynaptic terminals can be recognized by their many vesicles, and postsynaptic elements have postsynaptic densities. (b) An axon branches to form two presynaptic terminals, one larger than the other, and both contact a postsynaptic soma. (c) An unusually large axon terminal contacts and surrounds a postsynaptic soma. (d) An unusually large presynaptic axon terminal contacts five postsynaptic dendritic spines. Notice that larger synapses have more active zones.

dendrodendritic synapses. The sizes and shapes of CNS synapses also vary widely (Figure 5.7a-d). The finest details of synaptic structure can be studied only under the powerful magnification of the electron microscope (Box 5.2).

CNS synapses may be further classified into two general categories based on the appearance of their presynaptic and postsynaptic membrane differentiations. Synapses in which the membrane differentiation on the postsynaptic side is thicker than that on the presynaptic side are called *asymmetrical synapses*, or *Gray's type I synapses*; those in which the membrane differentiations are of similar thickness are called *symmetrical*

BOX 5.2 PATH OF DISCOVERY

For the Love of Dendritic Spines

by Kristen M. Harris

The first time I looked through the microscope and saw a dendritic spine, it was love at first sight, and the affair has simply never ended. I was a graduate student in the new neurobiology and behavior program at the University of Illinois, and it was indeed an exciting time in neuroscience. The 1979 Society for Neuroscience meeting had only about 5,000 attendees (attendance is now about 25,000), and the member number I obtained during my first year of graduate school was and remains 2500.

I had hoped to discover what a "learned" dendritic spine looks like by training animals and then using the Golgi staining method to quantify changes in spine number and shape. Eagerly, I developed a high-throughput project, preparing the brains from many rats at once, sectioning through the whole brains, checking that the silver staining had worked, and then storing the tissue sections in butanol while engaging undergraduates to help mount them on microscope slides. To our dismay, we found several months later that all the silver had been dissolved out of the cells. There were no cells to see, and the project died an untimely death.

I was fortunate, however, to meet Professor Timothy Teyler at a Gordon Research Conference. He had recently brought the hippocampal slice preparation to the United States from Norway and was moving his lab from Harvard to a new medical school in Rootstown, Ohio. I was completely enamored by the experimental control that brain slices might offer, so I developed a Golgi-slice procedure and moved to complete my PhD with Teyler. This time, I prepared one slice at a time, and as can be seen in Figure A, the spines were exquisitely visible. Unfortunately, accurate counts and shape measurements of the tiny spines were just beyond the resolution of light microscopy.

While I was a graduate student, I talked my way into the esteemed summer course in neurobiology at the Marine Biological Laboratories in Woods Hole, Massachusetts. There I first learned serial-section three-dimensional electron microscopy (3DEM). I was truly hooked. With 3DEM, one could reconstruct dendrites, axons, and glia, and not only measure and count dendritic spines but also see where synapses formed, what was inside them, and how glia associated with synapses (Figure B). The 3DEM platform offers enormous possibilities for discovery. My life continues to be devoted to uncovering the processes of synapse formation and plasticity during learning and memory in the brain.

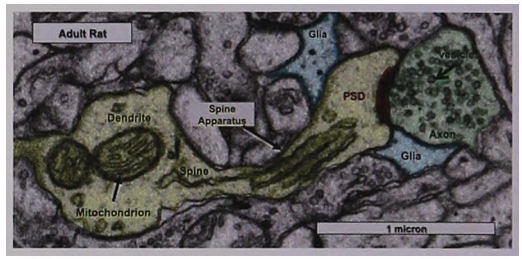


Figure B

Early in my career, while the revolution of molecular biology was sweeping the field, only a rare student or fellow scientist shared my enthusiasm for 3DEM. That bias has shifted dramatically as neuroscientists have come to recognize the importance of understanding how molecules work in consort with intracellular organelles in small spaces like dendrites and spines. Furthermore, all maps of neural circuitry must include synapses. These endeavors have drawn scientists from nearly every field, making 3DEM even more exciting as many of the imaging and reconstruction processes previously done manually are being automated. Figure C shows a recent 3DEM rendering, with color-coding of organelles and synaptic components. It is indeed thrilling to be part of this growth. New findings abound regarding the plasticity of synapse structure during normal changes in brain function and as altered by diseases that tragically affect who we are as human beings.

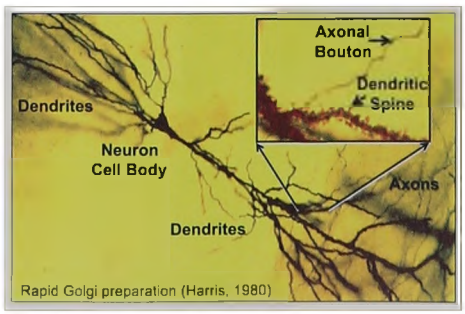


Figure A

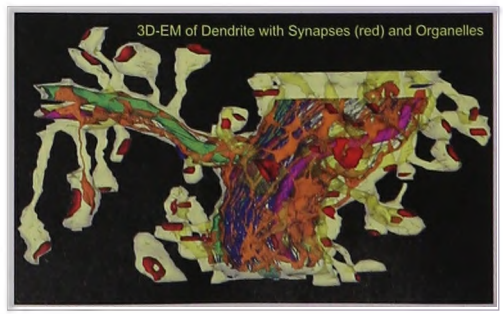
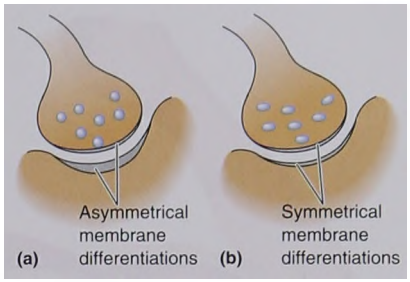


Figure C

synapses, or *Gray's type II synapses* (Figure 5.8). As we shall see later in the chapter, these structural differences reveal functional differences. Gray's type I synapses are usually excitatory, while Gray's type II synapses are usually inhibitory.



▲ FIGURE 5.8
Two categories of CNS synaptic membrane differentiations. (a) A Gray's type I synapse is asymmetrical and usually excitatory. (b) A Gray's type II synapse is symmetrical and usually inhibitory.

The Neuromuscular Junction. Synaptic junctions also exist outside the CNS. For example, axons of the autonomic nervous system innervate glands, smooth muscle, and the heart. Chemical synapses also occur between the axons of motor neurons of the spinal cord and skeletal muscle. Such a synapse is called a **neuromuscular junction**, and it has many of the structural features of chemical synapses in the CNS (Figure 5.9).

Neuromuscular synaptic transmission is fast and reliable. An action potential in the motor axon always causes an action potential in the muscle cell it innervates. This reliability is accounted for, in part, by structural specializations of the neuromuscular junction. Its most important specialization is its size—it is one of the largest synapses in the body. The presynaptic terminal also contains a large number of active zones. In addition, the postsynaptic membrane, also called the **motor endplate**, contains a series of shallow folds. The presynaptic active zones are precisely aligned with these junctional folds, and the postsynaptic membrane of the folds is packed with neurotransmitter receptors. This structure ensures that many neurotransmitter molecules are focally released onto a large surface of chemically sensitive membrane.

Because neuromuscular junctions are more accessible to researchers than CNS synapses, much of what we know about the mechanisms of synaptic transmission was first established here. Neuromuscular junctions are also of considerable clinical significance; diseases, drugs, and poisons that interfere with this chemical synapse have direct effects on vital bodily functions.

PRINCIPLES OF CHEMICAL SYNAPTIC TRANSMISSION

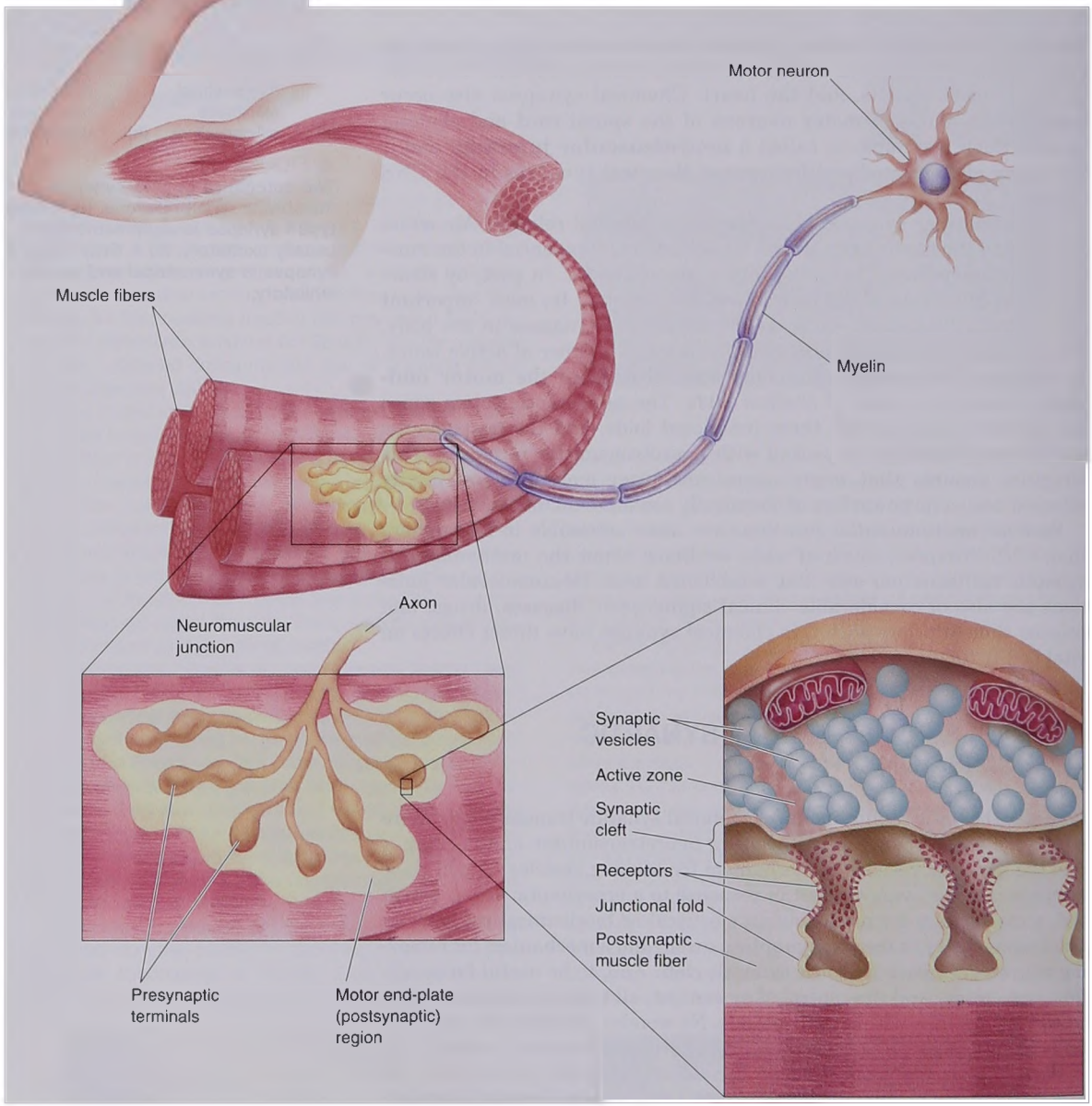
Consider the basic requirements of chemical synaptic transmission. There must be a mechanism for synthesizing neurotransmitter and packing it into the synaptic vesicles, a mechanism for causing vesicles to spill their contents into the synaptic cleft in response to a presynaptic action potential, a mechanism for producing an electrical or biochemical response to neurotransmitter in the postsynaptic neuron, and a mechanism for removing neurotransmitter from the synaptic cleft. And, to be useful for sensation, perception, and the control of movement, all these things must often occur very rapidly, within milliseconds. No wonder physiologists were initially skeptical about the existence of chemical synapses in the brain!

Fortunately, thanks to several decades of research on the topic, we now understand how many of these aspects of synaptic transmission are so efficiently carried out. Here we'll present a general survey of the basic principles. In Chapter 6, we will take a more detailed look at the individual neurotransmitters and their modes of postsynaptic action.

Neurotransmitters

Since the discovery of chemical synaptic transmission, researchers have been identifying neurotransmitters in the brain. Our current understanding is that the major neurotransmitters fall into one of three chemical

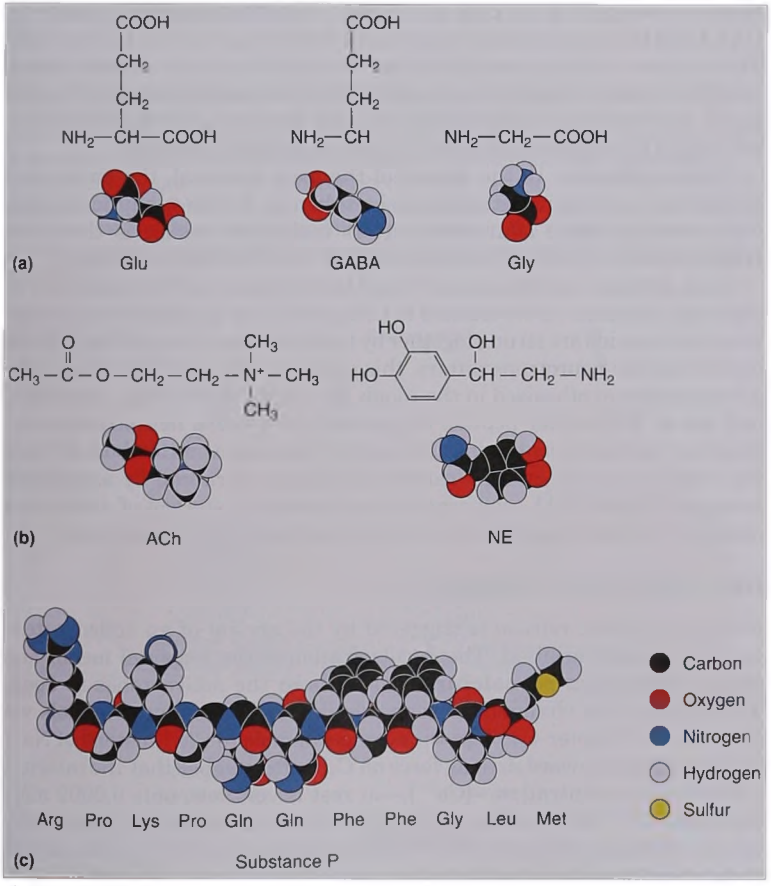
◀ FIGURE 5.9
The neuromuscular junction. The postsynaptic membrane, known as the motor end-plate, contains junctional folds with numerous neurotransmitter receptors.



categories: (1) *amino acids*, (2) *amines*, and (3) *peptides* (Table 5.1). Some representatives of these categories are shown in Figure 5.10. The amino acid and amine neurotransmitters are all small organic molecules containing at least one nitrogen atom, and they are stored in and released from synaptic vesicles. Peptide neurotransmitters are large molecules—chains of amino acids—stored in and released from secretory granules. As discussed earlier, secretory granules and synaptic vesicles are frequently observed in

TABLE 5.1 **The Major Neurotransmitters**

Amino Acids	Amines	Peptides
Gamma-aminobutyric acid (GABA)	Acetylcholine (ACh)	Cholecystokinin (CCK)
Glutamate (Glu)	Dopamine (DA)	Dynorphin
Glycine (Gly)	Epinephrine	Enkephalins (Enk)
	Histamine	*N*-acetylaspartylglutamate (NAAG)
	Norepinephrine (NE)	Neuropeptide Y
	Serotonin (5-HT)	Somatostatin
		Substance P
		Thyrotropin-releasing hormone
		Vasoactive intestinal polypeptide (VIP)



▲ FIGURE 5.10
Representative neurotransmitters. **(a)** The amino acid neurotransmitters glutamate, GABA, and glycine. **(b)** The amine neurotransmitters acetylcholine and norepinephrine. **(c)** The peptide neurotransmitter substance P. (For the abbreviations and chemical structures of amino acids in substance P, see Figure 3.4b.)

the same axon terminals. Consistent with this observation, peptides often exist in the same axon terminals that contain amine or amino acid neurotransmitters. As we'll discuss in a moment, these different neurotransmitters are released under different conditions.

Different neurons in the brain release different neurotransmitters. The speed of synaptic transmission varies widely. Fast forms of synaptic transmission last from about 10–100 msec, and at most CNS synapses are mediated by the amino acids **glutamate (Glu)**, **gamma-aminobutyric acid (GABA)**, or **glycine (Gly)**. The amine **acetylcholine (ACh)** mediates fast synaptic transmission at all neuromuscular junctions. Slower forms of synaptic transmission may last from hundreds of milliseconds to minutes; they can occur in the CNS and in the periphery and are mediated by transmitters from all three chemical categories.

Neurotransmitter Synthesis and Storage

Chemical synaptic transmission requires that neurotransmitters be synthesized and ready for release. Different neurotransmitters are synthesized in different ways. For example, glutamate and glycine are among the 20 amino acids that are the building blocks of protein (see Figure 3.4b); consequently, they are abundant in all cells of the body, including neurons. In contrast, GABA and the amines are made primarily by the neurons that release them. These neurons contain specific enzymes that synthesize the neurotransmitters from various metabolic precursors. The synthesizing enzymes for both amino acid and amine neurotransmitters are transported to the axon terminal, where they locally and rapidly direct transmitter synthesis.

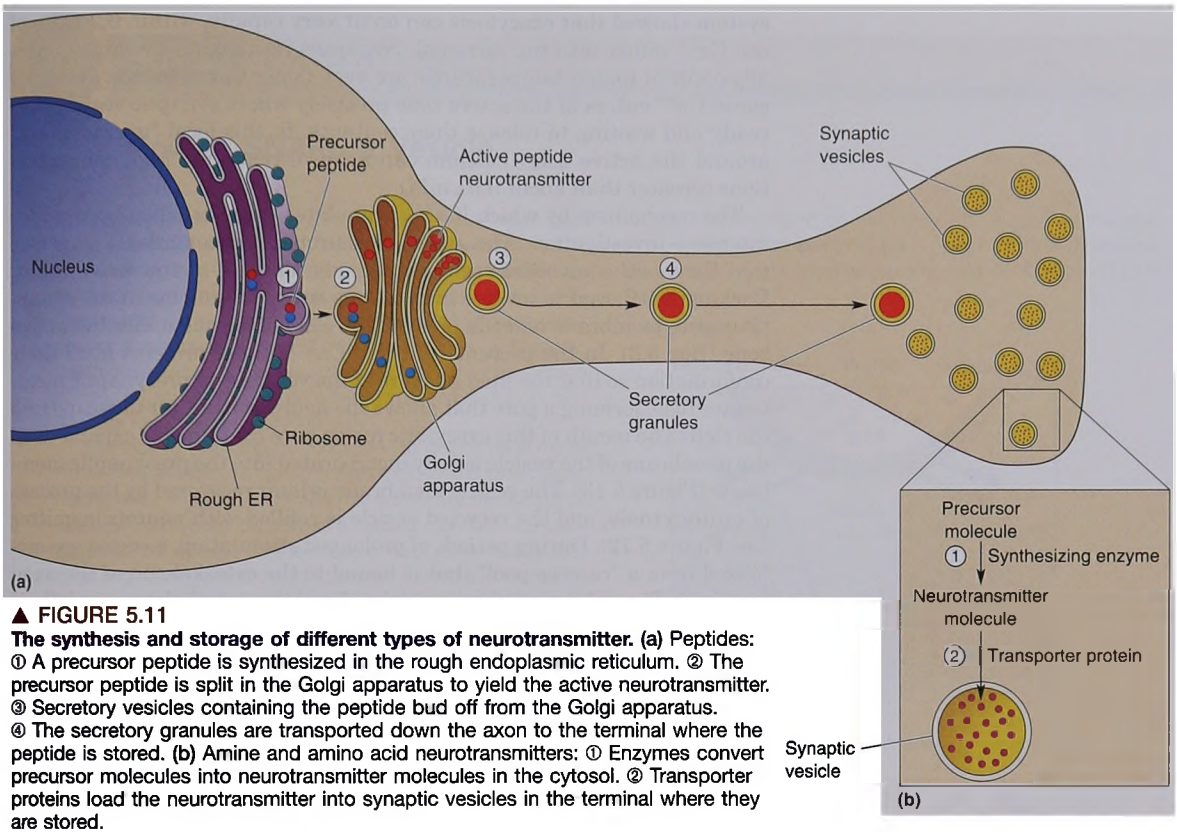
Once synthesized in the cytosol of the axon terminal, the amino acid and amine neurotransmitters must be taken up by the synaptic vesicles. Concentrating these neurotransmitters inside the vesicle is the job of **transporters**, special proteins embedded in the vesicle membrane.

Quite different mechanisms are used to synthesize and store peptides in secretory granules. As we learned in Chapters 2 and 3, peptides are formed when amino acids are strung together by the ribosomes of the cell body. In the case of peptide neurotransmitters, this occurs in the rough ER. Generally, a long peptide synthesized in the rough ER is split in the Golgi apparatus, and one of the smaller peptide fragments is the active neurotransmitter. Secretory granules containing the peptide neurotransmitter bud off from the Golgi apparatus and are carried to the axon terminal by axoplasmic transport. Figure 5.11 compares the synthesis and storage of amine and amino acid neurotransmitters with that of peptide neurotransmitters.

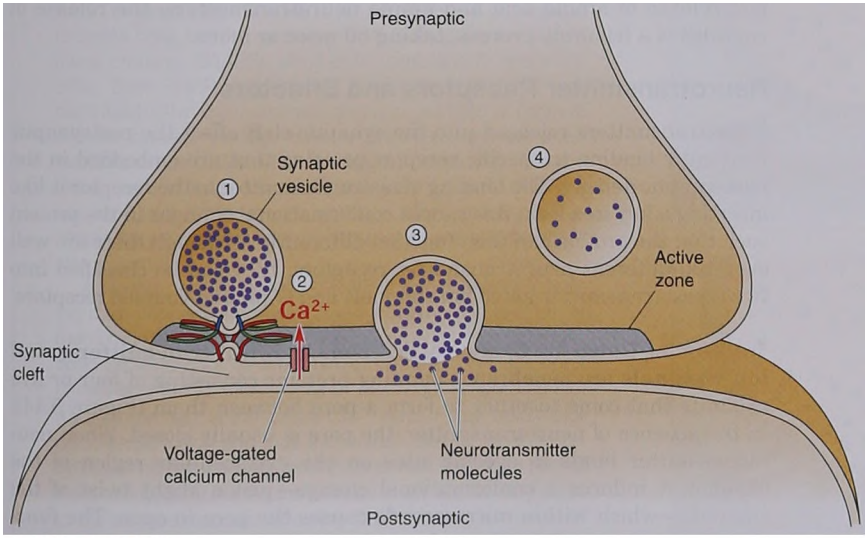
Neurotransmitter Release

Neurotransmitter release is triggered by the arrival of an action potential in the axon terminal. The depolarization of the terminal membrane causes **voltage-gated calcium channels** in the active zones to open. These membrane channels are very similar to the sodium channels we discussed in Chapter 4, except they are permeable to Ca^{2+} instead of Na^{+}. There is a large inward driving force on Ca^{2+}. Remember that the internal calcium ion concentration—$[Ca^{2+}]_i$—at rest is very low, only 0.0002 mM; therefore, Ca^{2+} will flood the cytoplasm of the axon terminal as long as the calcium channels are open. The resulting elevation in $[Ca^{2+}]_i$ is the signal that causes neurotransmitter to be released from synaptic vesicles.

The vesicles release their contents by a process called **exocytosis**. The membrane of the synaptic vesicle fuses to the presynaptic membrane at the active zone, allowing the contents of the vesicle to spill out into the synaptic cleft (Figure 5.12). Studies of a giant synapse in the squid nervous



▲ FIGURE 5.11
The synthesis and storage of different types of neurotransmitter. (a) Peptides: ① A precursor peptide is synthesized in the rough endoplasmic reticulum. ② The precursor peptide is split in the Golgi apparatus to yield the active neurotransmitter. ③ Secretory vesicles containing the peptide bud off from the Golgi apparatus. ④ The secretory granules are transported down the axon to the terminal where the peptide is stored. (b) Amine and amino acid neurotransmitters: ① Enzymes convert precursor molecules into neurotransmitter molecules in the cytosol. ② Transporter proteins load the neurotransmitter into synaptic vesicles in the terminal where they are stored.



▲ FIGURE 5.12
The release of neurotransmitter by exocytosis. ① A synaptic vesicle loaded with neurotransmitter, in response to ② an influx of Ca^{2+} through voltage-gated calcium channels, ③ releases its contents into the synaptic cleft by the fusion of the vesicle membrane with the presynaptic membrane, and ④ is eventually recycled by the process of endocytosis.

system showed that exocytosis can occur very rapidly, within 0.2 msec of the Ca^{2+} influx into the terminal. Synapses in mammals, which generally occur at higher temperatures, are even faster. Exocytosis is quick because Ca^{2+} enters at the active zone precisely where synaptic vesicles are ready and waiting to release their contents. In this local "microdomain" around the active zone, calcium can achieve relatively high concentrations (greater than about 0.01 mM).

The mechanism by which $[Ca^{2+}]_i$ stimulates exocytosis has been under intensive investigation. The speed of neurotransmitter release suggests that the vesicles involved are those already "docked" at the active zones. Docking is believed to involve interactions between proteins in the synaptic vesicle membrane and the presynaptic cell membrane under the active zone (Box 5.3). In the presence of high $[Ca^{2+}]_i$, these proteins alter their conformation so that the lipid bilayers of the vesicle and presynaptic membranes fuse, forming a pore that allows the neurotransmitter to escape into the cleft. The mouth of this exocytotic fusion pore continues to expand until the membrane of the vesicle is fully incorporated into the presynaptic membrane (Figure 5.13). The vesicle membrane is later recovered by the process of **endocytosis**, and the recycled vesicle is refilled with neurotransmitter (see Figure 5.12). During periods of prolonged stimulation, vesicles are mobilized from a "reserve pool" that is bound to the cytoskeleton of the axon terminal. The release of these vesicles from the cytoskeleton, and their docking to the active zone, is also triggered by elevations of $[Ca^{2+}]_i$.

Secretory granules also release peptide neurotransmitters by exocytosis, in a calcium-dependent fashion, but typically not at the active zones. Because the sites of granule exocytosis occur at a distance from the sites of Ca^{2+} entry, peptide neurotransmitters are usually not released in response to every action potential invading the terminal. Instead, the release of peptides generally requires high-frequency trains of action potentials, so that the $[Ca^{2+}]_i$ throughout the terminal can build to the level required to trigger release away from the active zones. Unlike the fast release of amino acid and amine neurotransmitters, the release of peptides is a leisurely process, taking 50 msec or more.

Neurotransmitter Receptors and Effectors

Neurotransmitters released into the synaptic cleft affect the postsynaptic neuron by binding to specific receptor proteins that are embedded in the postsynaptic density. The binding of neurotransmitter to the receptor is like inserting a key in a lock; this causes conformational changes in the protein such that the protein can then function differently. Although there are well over 100 different neurotransmitter receptors, they can be classified into two types: transmitter-gated ion channels and G-protein-coupled receptors.

Transmitter-Gated Ion Channels. Receptors known as **transmitter-gated ion channels** are membrane-spanning proteins consisting of four or five subunits that come together to form a pore between them (Figure 5.14). In the absence of neurotransmitter, the pore is usually closed. When neurotransmitter binds to specific sites on the extracellular region of the channel, it induces a conformational change—just a slight twist of the subunits—which within microseconds causes the pore to open. The functional consequence of this depends on which ions can pass through the pore.

Transmitter-gated channels generally do not show the same degree of ion selectivity as do voltage-gated channels. For example, the ACh-gated ion channels at the neuromuscular junction are permeable to both Na^+ and K^+. Nonetheless, as a rule, if the open channels are permeable to

BOX 5.3 BRAIN FOOD

How to SNARE a Vesicle

Yeasts are single-cell organisms valued for their ability to make dough rise and grape juice ferment into wine. Remarkably, the humble yeasts have some close similarities to the chemical synapses in our brain. Recent research has shown that the proteins controlling secretion in both yeast cells and synapses have only minor differences. Apparently, these molecules are so generally useful that they have been conserved across more than a billion years of evolution, and they are found in all eukaryotic cells.

The trick to fast synaptic function is to deliver neurotransmitter-filled vesicles to just the right place—the presynaptic membrane—and then cause them to fuse at just the right time, when an action potential delivers a pulse of high Ca^{2+} concentration to the cytosol. This process of exocytosis is a special case of a more general cellular problem, *membrane trafficking*. Cells have many types of membranes, including those enclosing the whole cell, the nucleus, endoplasmic reticulum, Golgi apparatus, and various types of vesicles. To avoid intracellular chaos, each of these membranes needs to be moved and delivered to specific locations within the cell. After delivery, one type of membrane often has to fuse with another type. A common molecular machinery has evolved for the delivery and fusion of all these membranes, and small variations in these molecules determine how and when membrane trafficking takes place.

The specific binding and fusion of membranes seem to depend on the SNARE family of proteins, which were first found in yeast cells. SNARE is an acronym too convoluted to define here, but the name perfectly defines the function of these proteins: SNAREs allow one membrane to snare another. Each SNARE peptide has a lipid-loving end that embeds itself within the membrane and a longer tail that projects into the cytosol. Vesicles have "v-SNAREs," and the outer membrane has "t-SNAREs" (for target membrane). The cytosolic ends of these two complementary types of SNAREs can bind very tightly to one another, allowing a vesicle to "dock" very close to a presynaptic membrane and nowhere else (Figure A).

Although complexes of v-SNAREs and t-SNAREs form the main connection between vesicle membrane and target membrane, a large and bewildering array of other presynaptic proteins stick to this SNARE complex. We still don't understand the functions of all of them, but *synaptotagmin*, a vesicle protein, is the critical Ca^{2+} sensor that rapidly triggers vesicle fusion and thus transmitter release. On the presynaptic membrane side, calcium channels may form part of the docking complex. As the calcium channels are very close to the docked vesicles, inflowing Ca^{2+} can trigger transmitter release with astonishing speed—within about 60 μsec in a mammalian synapse at body temperature. The brain has several varieties of synaptotagmins, including one that is specialized for exceptionally fast synaptic transmission.

We have a way to go before we understand all the molecules involved in synaptic transmission. In the meantime, we can count on yeasts to provide delightful brain food (and drink) for thought.

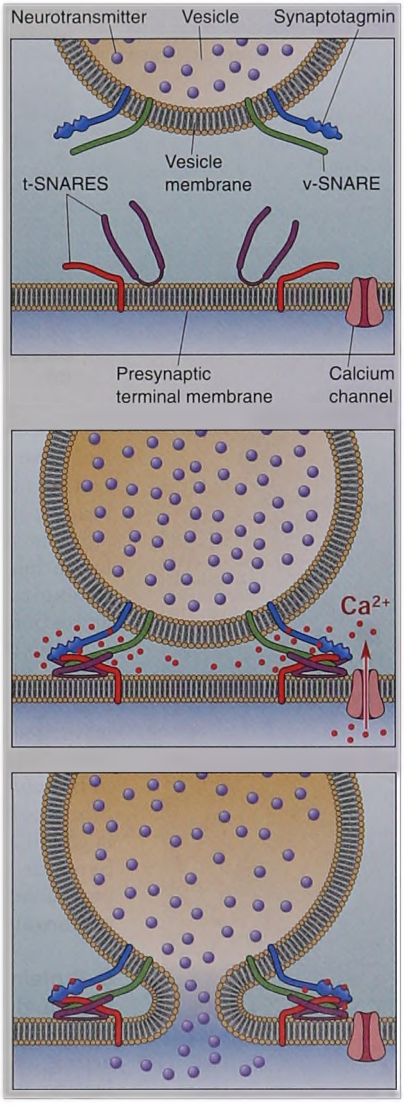
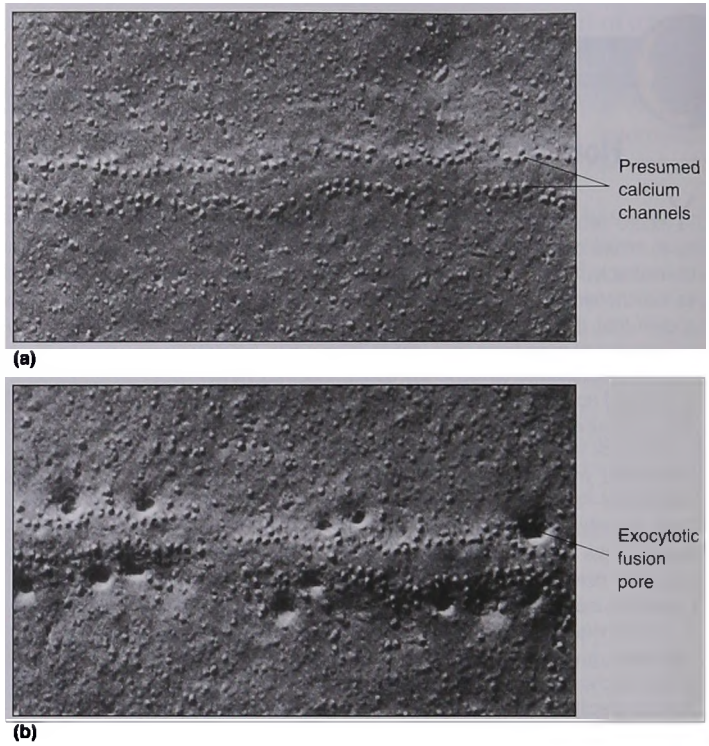
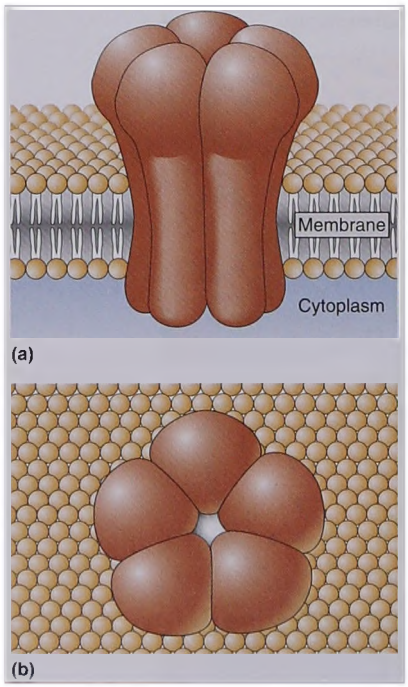


Figure A
SNAREs and vesicle fusion.



▶ FIGURE 5.13
A "receptor's eye" view of neurotransmitter release. (a) This is a view of the extracellular surface of the active zone of a neuromuscular junction in frog. The particles are believed to be calcium channels. (b) In this view, the presynaptic terminal had been stimulated to release neurotransmitter. The exocytotic fusion pores are where synaptic vesicles have fused with the presynaptic membrane and released their contents. (Source: Heuser and Reese, 1973.)



▲ FIGURE 5.14
The structure of a transmitter-gated ion channel. (a) Side view of an ACh-gated ion channel. (b) Top view of the channel, showing the pore at the center of the five subunits.

Na^+, the net effect will be to depolarize the postsynaptic cell from the resting membrane potential (Box 5.4). Because it tends to bring the membrane potential toward threshold for generating action potentials, this effect is said to be *excitatory*. A transient postsynaptic membrane depolarization caused by the presynaptic release of neurotransmitter is called an **excitatory postsynaptic potential (EPSP)** (Figure 5.15). Synaptic activation of ACh-gated and glutamate-gated ion channels causes EPSPs.

If the transmitter-gated channels are permeable to Cl^-, the usual net effect will be to hyperpolarize the postsynaptic cell from the resting membrane potential (because the chloride equilibrium potential is usually negative; see Chapter 3). Because it tends to bring the membrane potential away from threshold for generating action potentials, this effect is said to be *inhibitory*. A transient hyperpolarization of the postsynaptic membrane potential caused by the presynaptic release of neurotransmitter is called an **inhibitory postsynaptic potential (IPSP)** (Figure 5.16). Synaptic activation of glycine-gated or GABA-gated ion channels cause an IPSP. We'll discuss EPSPs and IPSPs in more detail shortly when we explore the principles of synaptic integration.

G-Protein-Coupled Receptors. Fast chemical synaptic transmission is mediated by amino acid and amine neurotransmitters acting on transmitter-gated ion channels. However, all three types of neurotransmitter, acting on **G-protein-coupled receptors**, can also have slower, longer lasting, and much more diverse postsynaptic actions. This type of transmitter action involves three steps:

1. Neurotransmitter molecules bind to receptor proteins embedded in the postsynaptic membrane.

BOX 5.4 BRAIN FOOD

Reversal Potentials

In Chapter 4, we saw that when the membrane voltage-gated sodium channels open during an action potential, Na^+ enters the cell, causing the membrane potential to rapidly depolarize until it approaches the sodium equilibrium potential, E_{Na}, about 40 mV. Unlike the voltage-gated channels, however, many transmitter-gated ion channels are not permeable to a single type of ion. For example, the ACh-gated ion channel at the neuromuscular junction is permeable to both Na^+ and K^+. Let's explore the functional consequence of activating these channels.

In Chapter 3, we learned that the membrane potential, V_m, can be calculated using the Goldman equation, which takes into account the relative permeability of the membrane to different ions (see Box 3.3). If the membrane were equally permeable to Na^+ and K^+, as it would be if many ACh- or glutamate-gated channels were open, then V_m would have a value between E_{Na} and E_K, around 0 mV. Therefore, ionic current would flow through the channels in a direction that brings the membrane potential toward 0 mV. If the membrane potential were <0 mV before ACh was applied, as is usually the case, the direction of net current flow through the ACh-gated ion channels would be *inward*, causing a depolarization. However, if the membrane potential were >0 mV before ACh was applied, the direction of net current flow through the ACh-gated ion channels would be *outward*, causing the membrane potential to become less positive.

Ionic current flow at different membrane voltages can be graphed, as shown in Figure A. Such a graph is called an *I-V plot* (I: current; V: voltage). The critical value of membrane potential at which the direction of current flow reverses is called the *reversal potential*. In this case, the reversal potential would be 0 mV. The experimental determination of a reversal potential, therefore, helps tell us which types of ions the membrane is permeable to.

If, by changing the relative permeability of the membrane to different ions, a neurotransmitter causes V_m to move toward a value that is more positive than the action potential threshold, the neurotransmitter action would be termed excitatory. As a rule, neurotransmitters that open a channel permeable to Na^+ are excitatory. If a neurotransmitter causes V_m to take on a value that is more negative than the action potential threshold, the neurotransmitter action would be termed inhibitory. Neurotransmitters that open a channel permeable to Cl^- tend to be inhibitory, as are neurotransmitters that open a channel permeable only to K^+.

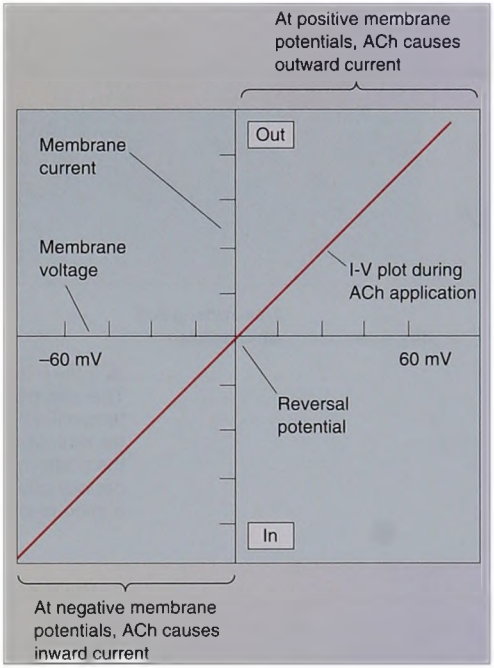
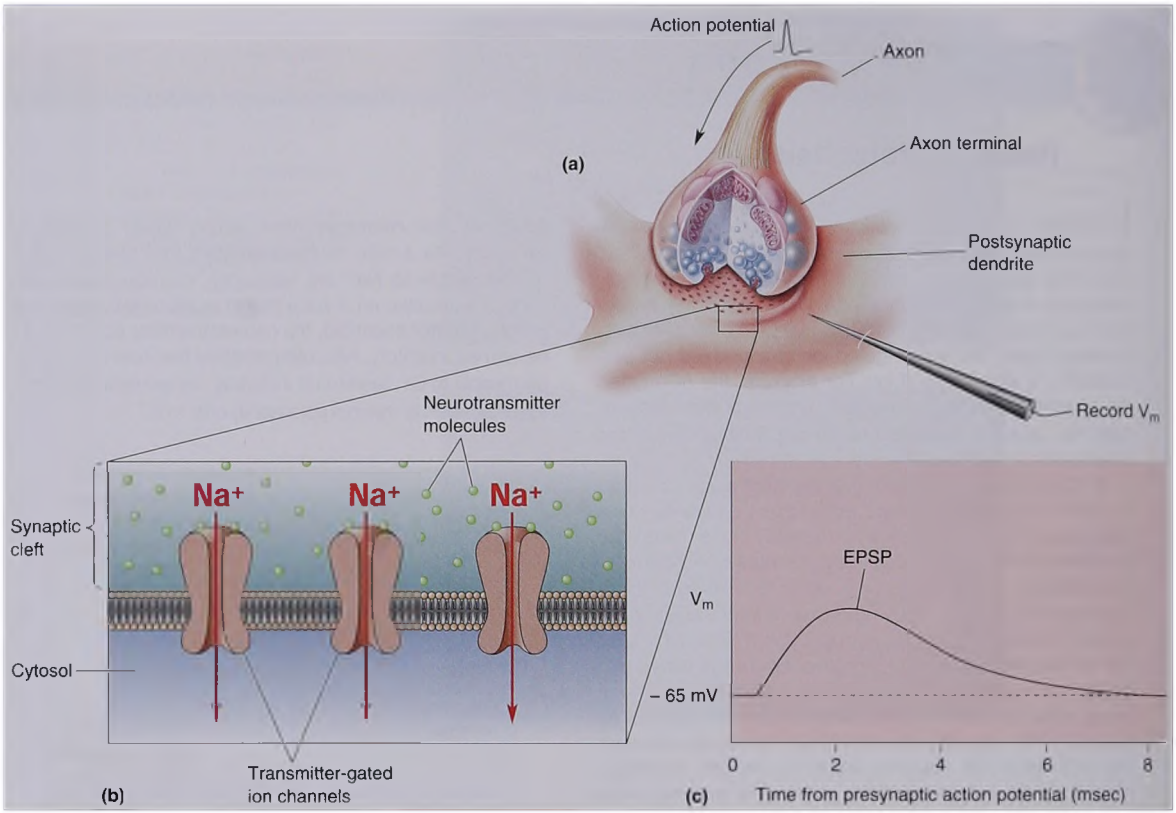


Figure A

2. The receptor proteins activate small proteins, called **G-proteins**, which are free to move along the intracellular face of the postsynaptic membrane.
3. The activated G-proteins activate "effector" proteins.

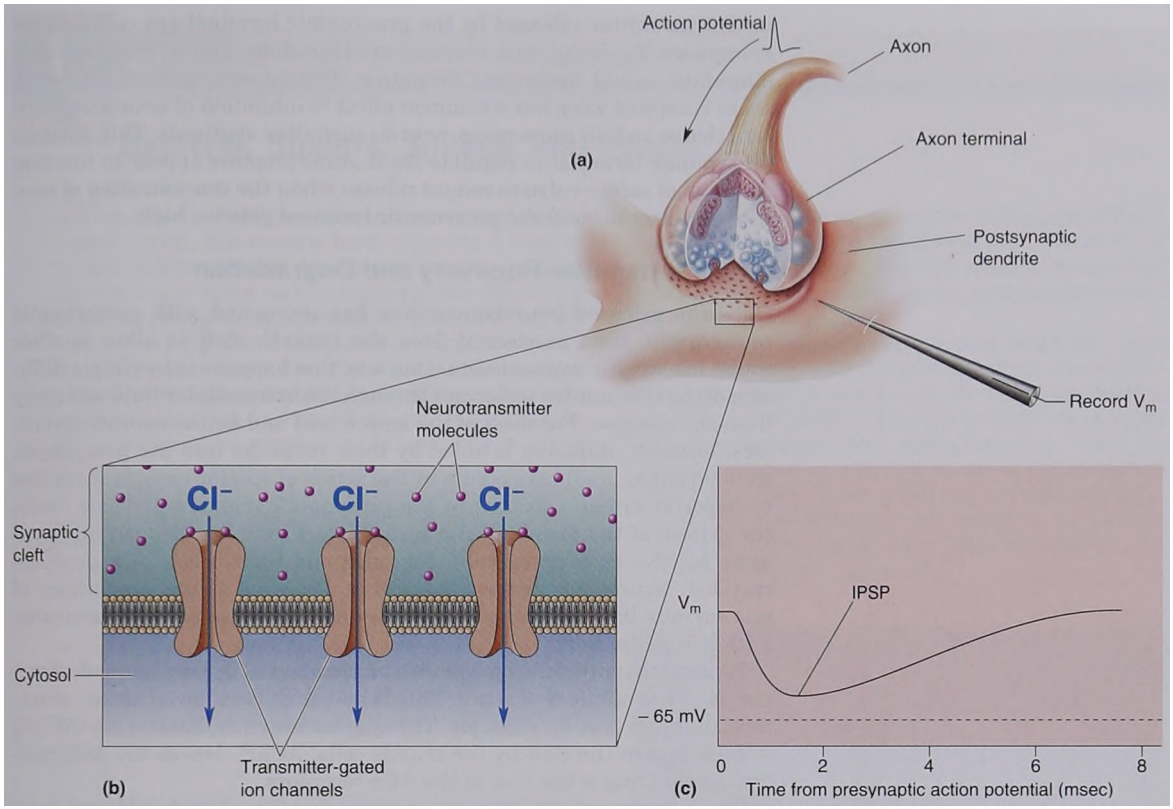
Effector proteins can be G-protein-gated ion channels in the membrane (Figure 5.17a), or they can be enzymes that synthesize molecules called **second messengers** that diffuse away in the cytosol (Figure 5.17b). Second messengers can activate additional enzymes in the cytosol that can regulate ion channel function and alter cellular metabolism. Because G-protein-coupled receptors can trigger widespread metabolic effects, they are often referred to as **metabotropic receptors**.



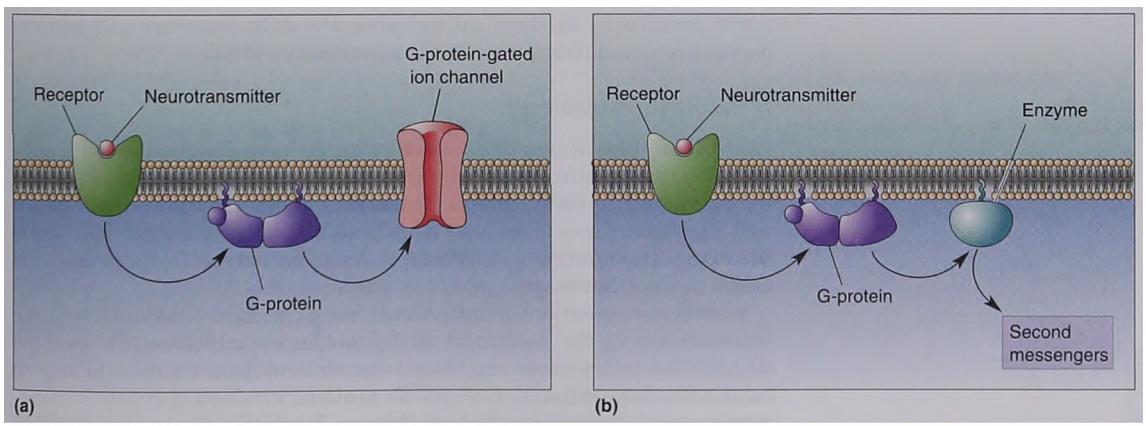
▲ FIGURE 5.15
The generation of an EPSP. (a) An action potential arriving in the presynaptic terminal causes the release of neurotransmitter. (b) The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. If Na^+ enters the postsynaptic cell through the open channels, the membrane will become depolarized. (c) The resulting change in membrane potential (V_m), as recorded by a microelectrode in the cell, is the EPSP.

We'll discuss the different neurotransmitters, their receptors, and their effectors in more detail in Chapter 6. However, you should be aware that the same neurotransmitter can have different postsynaptic actions, depending on what receptors it binds to. An example is the effect of ACh on the heart and on skeletal muscles. ACh slows the rhythmic contractions of the heart by causing a slow hyperpolarization of the cardiac muscle cells. In contrast, in skeletal muscle, ACh induces contraction by causing a rapid depolarization of the muscle fibers. These different actions are explained by the different receptors involved. In the heart, a metabotropic ACh receptor is coupled by a G-protein to a potassium channel. The opening of the potassium channel hyperpolarizes the cardiac muscle fibers and reduces the rate at which it fires action potentials. In skeletal muscle, the receptor is a transmitter-gated ion channel, specifically an ACh-gated ion channel, permeable to Na^+. The opening of this channel depolarizes the muscle fibers and makes them more excitable.

Autoreceptors. Besides being a part of the postsynaptic density, neurotransmitter receptors are also commonly found in the membrane of the presynaptic axon terminal. Presynaptic receptors that are sensitive to the



▲ FIGURE 5.16
The generation of an IPSP. (a) An action potential arriving in the presynaptic terminal causes the release of neurotransmitter. (b) The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. If Cl^- enters the postsynaptic cell through the open channels, the membrane will become hyperpolarized. (c) The resulting change in membrane potential (V_m), as recorded by a microelectrode in the cell, is the IPSP.



▲ FIGURE 5.17
Transmitter actions at G-protein-coupled receptors. The binding of neurotransmitter to the receptor leads to the activation of G-proteins. Activated G-proteins activate effector proteins, which may be (a) ion channels or (b) enzymes that generate intracellular second messengers.

neurotransmitter released by the presynaptic terminal are called **autoreceptors**. Typically, autoreceptors are G-protein-coupled receptors that stimulate second messenger formation. The consequences of activating these receptors vary, but a common effect is inhibition of neurotransmitter release and, in some cases, neurotransmitter synthesis. This allows a presynaptic terminal to regulate itself. Autoreceptors appear to function as a sort of safety valve to reduce release when the concentration of neurotransmitter around the presynaptic terminal gets too high.

Neurotransmitter Recovery and Degradation

Once the released neurotransmitter has interacted with postsynaptic receptors, it must be cleared from the synaptic cleft to allow another round of synaptic transmission. One way this happens is by simple diffusion of the transmitter molecules through the extracellular fluid and away from the synapse. For most of the amino acid and amine neurotransmitters, however, diffusion is aided by their reuptake into the presynaptic axon terminal. Reuptake occurs by the action of specific neurotransmitter transporter proteins located in the presynaptic membrane. Once inside the cytosol of the terminal, the transmitters may be reloaded into synaptic vesicles or enzymatically degraded and their breakdown products recycled. Neurotransmitter transporters also exist in the membranes of glia surrounding the synapse, which assist in the removal of neurotransmitter from the cleft.

Neurotransmitter action can also be terminated by enzymatic destruction in the synaptic cleft itself. This is how ACh is removed at the neuromuscular junction, for example. The enzyme acetylcholinesterase (AChE) is deposited in the cleft by the muscle cells. AChE cleaves the ACh molecule, rendering it inactive at the ACh receptors.

The importance of transmitter removal from the cleft should not be underestimated. At the neuromuscular junction, for example, uninterrupted exposure to high concentrations of ACh after several seconds leads to a process called *desensitization*, in which, despite the continued presence of ACh, the transmitter-gated channels close. This desensitized state can persist for many seconds even after the neurotransmitter is removed. The rapid destruction of ACh by AChE normally prevents desensitization from occurring. However, if the AChE is inhibited, as it is by various nerve gases used as chemical weapons, the ACh receptors will become desensitized and neuromuscular transmission will fail.

Neuropharmacology

Each of the steps of synaptic transmission we have discussed so far—neurotransmitter synthesis, loading into synaptic vesicles, exocytosis, binding and activation of receptors, reuptake, and degradation—is chemical, and therefore these steps can be affected by specific drugs and toxins (Box 5.5). The study of the effects of drugs on nervous system tissue is called **neuropharmacology**.

Earlier, we mentioned that nerve gases can interfere with synaptic transmission at the neuromuscular junction by inhibiting the enzyme AChE. This interference represents one class of drug action, which is to inhibit the normal function of specific proteins involved in synaptic transmission; such drugs are called **inhibitors**. Inhibitors of neurotransmitter receptors, called **receptor antagonists**, bind to the receptors and block (antagonize) the normal action of the transmitter. An example of a receptor antagonist is curare, an arrow-tip poison traditionally used by South American natives to paralyze their prey. Curare binds tightly to the ACh

BOX 5.5 OF SPECIAL INTEREST

Bacteria, Spiders, Snakes, and People

What do the bacteria *Clostridium botulinum*, black widow spiders, cobras, and humans have in common? They all produce toxins that attack the chemical synaptic transmission that occurs at the neuromuscular junction. Botulism is caused by several kinds of botulinum neurotoxins that are produced by the growth of *C. botulinum* in improperly canned foods. (The name comes from the Latin word for "sausage" because of the early association of the disease with poorly preserved meat.) Botulinum toxins are very potent blockers of neuromuscular transmission; it has been estimated that as few as 10 molecules of the toxins are enough to inhibit a cholinergic synapse. Botulinum toxins are extraordinarily specific enzymes that destroy certain of the SNARE proteins in the presynaptic terminals, which are critical for transmitter release (see Box 5.3). This specific action of the toxins made them important tools in the early research on SNAREs.

Although its mechanism of action is different, black widow spider venom also exerts deadly effects by affecting transmitter release (Figure A). The venom contains latrotoxin, which first increases, and then eliminates, ACh release at the neuromuscular junction. Electron microscopic examination of synapses poisoned with black widow spider venom reveals that the axon terminals are swollen and the synaptic vesicles are missing. The action of latrotoxin, a protein molecule, is not entirely understood. Venom binds with proteins on the outside of the presynaptic membrane and forms a membrane pore that depolarizes the terminal and allows Ca^{2+} to enter and trigger rapid and total depletion of transmitter. In some cases, the venom can induce transmitter release even without the need for Ca^{2+}, perhaps by interacting directly with neurotransmitter release proteins.

The bite of the Taiwanese cobra also results in the blockade of neuromuscular transmission in its victim, by yet another mechanism. One of the active compounds in the snake's venom, called *α-bungarotoxin*, is a peptide that binds so tightly to the postsynaptic nicotinic ACh receptors that it takes days to be removed. Often, there is not time for its removal, however, because cobra toxin prevents the activation of nicotinic receptors by ACh, thereby paralyzing the respiratory muscles of its victims.

We humans have synthesized a large number of chemicals that poison synaptic transmission at the neuromuscular junction. Originally motivated by the search for chemical warfare agents, this effort led to the development of a new class of compounds called *organophosphates*. These are irreversible inhibitors of AChE. By preventing the degradation of ACh, they cause it to accumulate and probably kill victims by causing a desensitization of ACh receptors. The organophosphates used today as insecticides, like parathion, are toxic to humans only in high doses.

Figure A
Black widow spiders. (Source: Matthews, 1995, p. 174.)

receptors on skeletal muscle cells and blocks the actions of ACh, thereby preventing muscle contraction.

Other drugs bind to receptors, but instead of inhibiting them, they mimic the actions of the naturally occurring neurotransmitter. These drugs are called **receptor agonists**. An example of a receptor agonist is nicotine, derived from the tobacco plant. Nicotine binds to and activates the ACh receptors in skeletal muscle. In fact, the ACh-gated ion channels in muscle are also called **nicotinic ACh receptors**, to distinguish them from other types of ACh receptors, such as those in the heart, that are not activated by nicotine. There are also nicotinic ACh receptors in the CNS, and these are involved in the addictive effects of tobacco use.

The immense chemical complexity of synaptic transmission makes it especially susceptible to the medical corollary of Murphy's law, which

states that if a physiological process can go wrong, it will go wrong. When chemical synaptic transmission goes wrong, the nervous system malfunctions. Defective neurotransmission is believed to be the root cause of a large number of neurological and psychiatric disorders. The good news is that, thanks to our growing knowledge of the neuropharmacology of synaptic transmission, clinicians have new and increasingly effective therapeutic drugs for treating these disorders. We'll discuss the synaptic basis of some psychiatric disorders, and their neuropharmacological treatment, in Chapter 22.

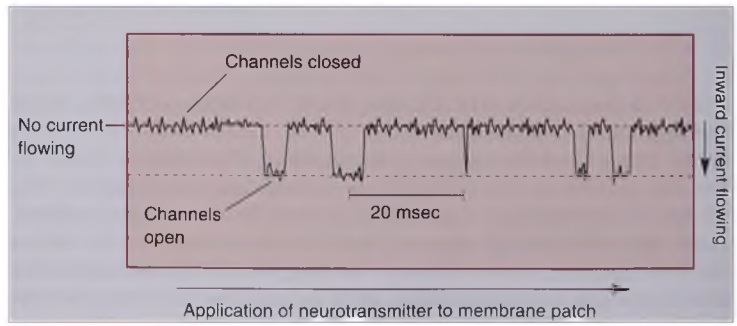
PRINCIPLES OF SYNAPTIC INTEGRATION

Most CNS neurons receive thousands of synaptic inputs that activate different combinations of transmitter-gated ion channels and G-protein-coupled receptors. The postsynaptic neuron integrates all these complex ionic and chemical signals to produce a simple form of output: action potentials. The transformation of many synaptic inputs to a single neuronal output constitutes a neural computation. The brain performs billions of neural computations every second we are alive. As a first step toward understanding how neural computations are performed, let's explore some basic principles of synaptic integration. **Synaptic integration** is the process by which multiple synaptic potentials combine within one postsynaptic neuron.

The Integration of EPSPs

The most elementary postsynaptic response is the opening of a single transmitter-gated channel (Figure 5.18). Inward current through these channels depolarizes the postsynaptic membrane, causing the EPSP. The postsynaptic membrane of one synapse may have from a few tens to several thousands of transmitter-gated channels; how many of these are activated during synaptic transmission depends mainly on how much neurotransmitter is released.

Quantal Analysis of EPSPs. The elementary unit of neurotransmitter release is the contents of a single synaptic vesicle. Vesicles each contain about the same number of transmitter molecules (several thousand); the total amount of transmitter released is some multiple of this number.



▲ FIGURE 5.18
A patch-clamp recording from a transmitter-gated ion channel. Ionic current passes through the channels when the channels are open. In the presence of neurotransmitter, they rapidly alternate between open and closed states. (Source: Adapted from Neher and Sakmann, 1992.)

Consequently, the amplitude of the postsynaptic EPSP is some multiple of the response to the contents of a single vesicle. Stated another way, postsynaptic EPSPs at a given synapse are *quantized*; they are multiples of an indivisible unit, the *quantum*, which reflects the number of transmitter molecules in a single synaptic vesicle and the number of postsynaptic receptors available at the synapse.

At many synapses, exocytosis of vesicles occurs at some very low rate in the absence of presynaptic stimulation. The size of the postsynaptic response to this spontaneously released neurotransmitter can be measured electrophysiologically. This tiny response is a **miniature postsynaptic potential**, often called simply a *mini*. Each mini is generated by the transmitter contents of one vesicle. The amplitude of the postsynaptic EPSP evoked by a presynaptic action potential, then, is simply an integer multiple (i.e., 1×, 2×, 3×, etc.) of the mini amplitude.

Quantal analysis, a method of comparing the amplitudes of miniature and evoked PSPs, can be used to determine how many vesicles release neurotransmitter during normal synaptic transmission. Quantal analysis of transmission at the neuromuscular junction reveals that a single action potential in the presynaptic terminal triggers the exocytosis of about 200 synaptic vesicles, causing an EPSP of 40 mV or more. At many CNS synapses, in striking contrast, the contents of only a *single vesicle* are released in response to a presynaptic action potential, causing an EPSP of only a few tenths of a millivolt.

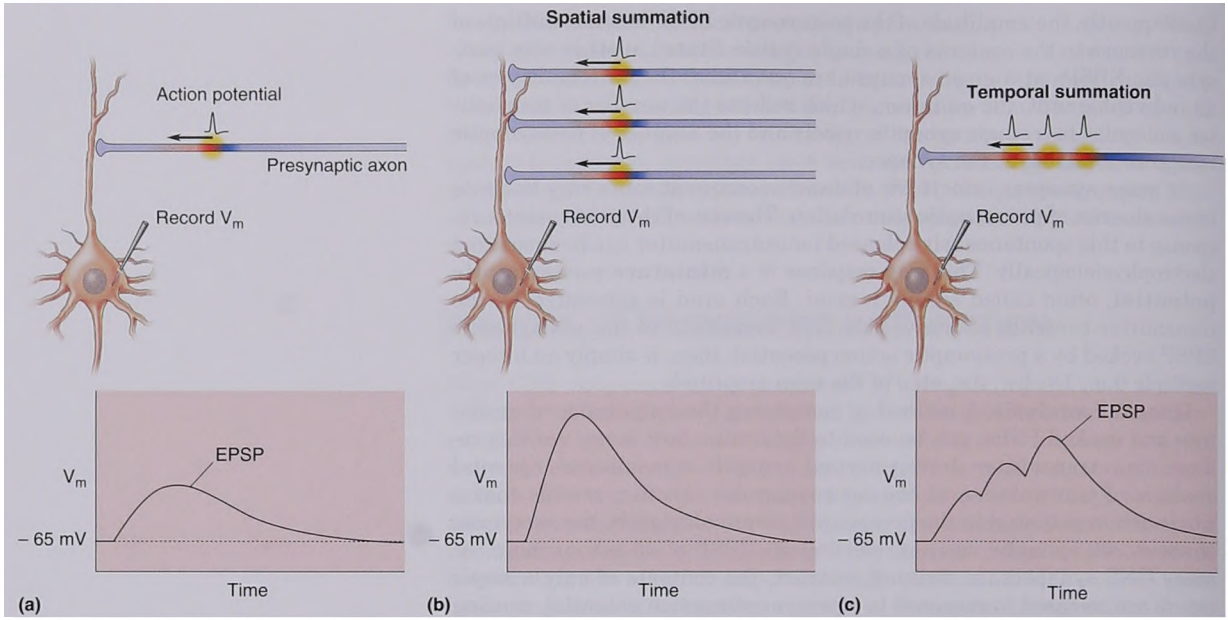
EPSP Summation. The difference between excitatory transmission at neuromuscular junctions and CNS synapses is not surprising. The neuromuscular junction has evolved to be fail-safe; it needs to work every time, and the best way to ensure this is to generate an EPSP of a huge size. On the other hand, if every CNS synapse were, by itself, capable of triggering an action potential in its postsynaptic cell (as the neuromuscular junction can), then a neuron would be little more than a simple relay station. Instead, most neurons perform more sophisticated computations, requiring that many EPSPs add together to produce a significant postsynaptic depolarization. This is what is meant by integration of EPSPs.

EPSP summation represents the simplest form of synaptic integration in the CNS. There are two types of summation: spatial and temporal. **Spatial summation** is the adding together of EPSPs generated simultaneously at many different synapses on a dendrite. **Temporal summation** is the adding together of EPSPs generated at the same synapse if they occur in rapid succession, within about 1–15 msec of one another (Figure 5.19).

The Contribution of Dendritic Properties to Synaptic Integration

Even with the summation of several EPSPs on a dendrite, the depolarization still may not be enough to cause the neuron to fire an action potential. The current entering at the sites of synaptic contact must spread down the dendrite and through the soma and cause the membrane of the spike-initiation zone to be depolarized beyond threshold, before an action potential can be generated. The effectiveness of an excitatory synapse in triggering an action potential, therefore, depends on how far the synapse is from the spike-initiation zone and on the properties of the dendritic membrane.

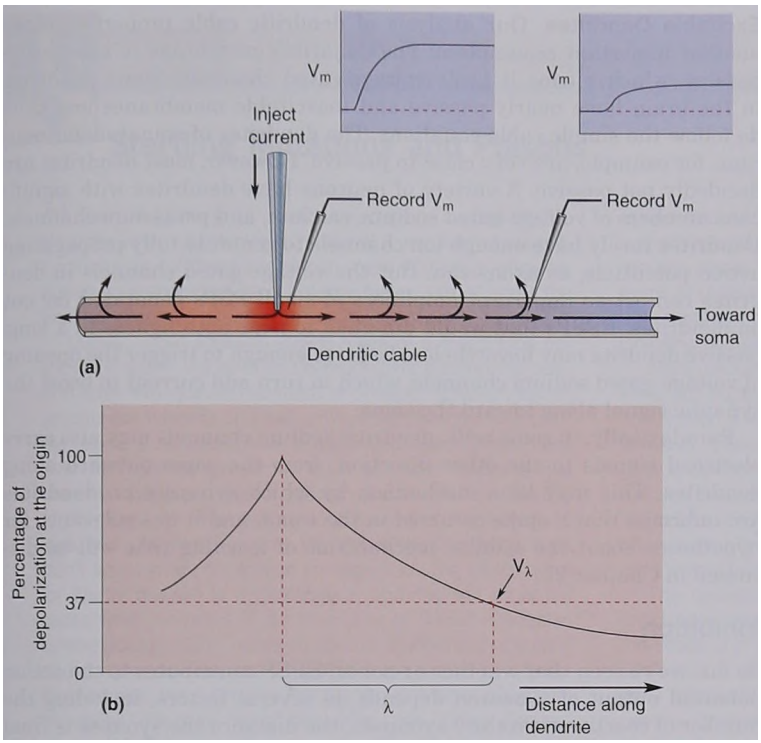
Dendritic Cable Properties. To simplify the analysis of how dendritic properties contribute to synaptic integration, let's assume that dendrites



▲ FIGURE 5.19
EPSP summation. (a) A presynaptic action potential triggers a small EPSP in a postsynaptic neuron. (b) Spatial summation of EPSPs: When two or more presynaptic inputs are active at the same time, their individual EPSPs add together. (c) Temporal summation of EPSPs: When the same presynaptic fiber fires action potentials in quick succession, the individual EPSPs add together.

function as cylindrical cables that are electrically passive, that is, lacking voltage-gated ion channels (in contrast, of course, with axons). Using an analogy introduced in Chapter 4, imagine that the influx of positive charge at a synapse is like turning on the water that will flow down a leaky garden hose (the dendrite). There are two paths the water can take: down the inside of the hose or through the leaks. By the same token, there are two paths that synaptic current can take: down the inside of the dendrite or across the dendritic membrane. As the current proceeds down the dendrite and farther from the synapse, the EPSP amplitude will diminish because of the leakage of ionic current through membrane channels. At some distance from the site of current influx, the EPSP amplitude may eventually approach zero.

The decrease in depolarization as a function of distance along a dendritic cable is plotted in Figure 5.20. In order to simplify the mathematics, in this example, we'll assume the dendrite is infinitely long, unbranched, and uniform in diameter. We will also use a microelectrode to inject a long, steady pulse of current to induce a membrane depolarization. Notice that the amount of depolarization falls off exponentially with increasing distance. Depolarization of the membrane at a given distance (V_x) can be described by the equation $V_x = V_o/e^{x/\lambda}$, where V_o is depolarization at the origin (just under the microelectrode), e (= 2.718 . . .) is the base of natural logarithms, x is distance from the synapse, and λ is a constant that depends on the properties of the dendrite. Notice that when $x = \lambda$, then $V_x = V_o/e$. Put another way, $V_\lambda = 0.37\ (V_o)$. This distance λ, where the depolarization is about 37% of that at the origin, is called the dendritic **length constant**. (Remember that this analysis is an oversimplification. Real dendrites have finite



◀ FIGURE 5.20
Decreasing depolarization as a function of distance along a long dendritic cable. **(a)** Current is injected into a dendrite and the depolarization is recorded. As this current spreads down the dendrite, much of it dissipates across the membrane. Therefore, the depolarization measured at a distance from the site of current injection is smaller than that measured right under it. **(b)** A plot of membrane depolarization as a function of distance along the dendrite. At the distance λ, one length constant, the membrane depolarization (V_λ), is 37% of that at the origin.

lengths, have branches, and tend to taper, and EPSPs are transient—all of which affect the spread of current, and thus the effectiveness of synaptic potentials.)

The length constant is an index of how far depolarization can spread down a dendrite or axon. The longer the length constant, the more likely it is that EPSPs generated at distant synapses will depolarize the membrane at the axon hillock. The value of λ in our idealized, electrically passive dendrite depends on two factors: (1) the resistance to current flowing longitudinally down the dendrite, called the **internal resistance** (r_i); and (2) the resistance to current flowing across the membrane, called the **membrane resistance** (r_m). Most current will take the path of least resistance; therefore, the value of λ will increase as membrane resistance increases because more depolarizing current will flow down the inside of the dendrite rather than "leaking" out the membrane. The value of λ will decrease as internal resistance increases because more current will then flow across the membrane. Just as water will flow farther down a wide hose with few leaks, synaptic current will flow farther down a wide dendrite (low r_i) with few open membrane channels (high r_m).

The internal resistance depends only on the diameter of the dendrite and the electrical properties of the cytoplasm; consequently, it is relatively constant in a mature neuron. The membrane resistance, in contrast, depends on the number of open ion channels, which changes from moment to moment depending on what other synapses are active. The dendritic length constant, therefore, is not constant at all! As we will see in a moment, fluctuations in the value of λ are an important factor in synaptic integration.

Excitable Dendrites. Our analysis of dendritic cable properties made another important assumption: The dendrite's membrane is electrically passive, which means it lacks voltage-gated channels. Some dendrites in the brain have nearly passive and inexcitable membranes and thus do follow the simple cable equations. The dendrites of spinal motor neurons, for example, are very close to passive. However, most dendrites are decidedly not passive. A variety of neurons have dendrites with significant numbers of voltage-gated sodium, calcium, and potassium channels. Dendrites rarely have enough ion channels to generate fully propagating action potentials, as axons can. But the voltage-gated channels in dendrites can act as important amplifiers of small PSPs generated far out on dendrites. EPSPs that would diminish to near nothingness in a long, passive dendrite may nevertheless be large enough to trigger the opening of voltage-gated sodium channels, which in turn add current to boost the synaptic signal along toward the soma.

Paradoxically, in some cells, dendritic sodium channels may also carry electrical signals in the other direction, from the soma outward along dendrites. This may be a mechanism by which synapses on dendrites are informed that a spike occurred in the soma, and it has relevance for hypotheses about the cellular mechanisms of learning that will be discussed in Chapter 25.

Inhibition

So far, we've seen that whether or not an EPSP contributes to the action potential output of a neuron depends on several factors, including the number of coactive excitatory synapses, the distance the synapse is from the spike-initiation zone, and the properties of the dendritic membrane. Of course, not all synapses in the brain are excitatory. The action of some synapses is to take the membrane potential away from action potential threshold; these are called *inhibitory synapses*. Inhibitory synapses exert a powerful control over a neuron's output (Box 5.6).

IPSPs and Shunting Inhibition. The postsynaptic receptors under most inhibitory synapses are very similar to those under excitatory synapses; they're transmitter-gated ion channels. The only important differences are that they bind different neurotransmitters (either GABA or glycine) and that they allow different ions to pass through their channels. The transmitter-gated channels of most inhibitory synapses are permeable to only one natural ion, Cl^-. Opening of the chloride channel allows Cl^- to cross the membrane in a direction that brings the membrane potential toward the chloride equilibrium potential, E_{Cl}, about -65 mV. If the membrane potential were less negative than -65 mV when the transmitter was released, activation of these channels would cause a hyperpolarizing IPSP.

Notice that if the resting membrane potential were already -65 mV, no IPSP would be visible after chloride channel activation because the value of the membrane potential would already equal E_{Cl} (i.e., the reversal potential for that synapse; see Box 5.4). If there is no visible IPSP, is the neuron really inhibited? The answer is yes. Consider the situation illustrated in Figure 5.21, with an excitatory synapse on a distal segment of dendrite and an inhibitory synapse on a proximal segment of dendrite, near the soma. Activation of the excitatory synapse leads to the influx of positive charge into the dendrite. This current depolarizes the membrane as it flows toward the soma. At the site of the active inhibitory synapse, however, the membrane potential is approximately equal to

BOX 5.6 OF SPECIAL INTEREST

Startling Mutations and Poisons

A flash of lightning . . . a thunderclap . . . a tap on the shoulder when you think you're alone! If you are not expecting them, any of these stimuli can make you jump, grimace, hunch your shoulders, and breathe faster. We all know the brief but dramatic nature of the startle response.

Luckily, when lightning strikes twice or a friend taps our shoulder again, we tend to be much less startled the second time. We quickly habituate and relax. However, for an unfortunate minority of mice, cows, dogs, horses, and people, life is a succession of exaggerated startle responses. Even normally benign stimuli, such as hands clapping or a touch to the nose, may trigger an uncontrollable stiffening of the body, an involuntary shout, flexion of the arms and legs, and a fall to the ground. Worse yet, these overreactions don't adapt when the stimuli are repeated. The clinical term for startle disease is *hyperekplexia*, and the first recorded cases were members of a community of French–Canadian lumberjacks in 1878. Hyperekplexia is an inherited condition occurring worldwide, and its sufferers are known by colorful local names: the "Jumping Frenchmen of Maine" (Quebec), "myriachit" (Siberia), "latah" (Malaysia), and "Ragin' Cajuns" (Louisiana).

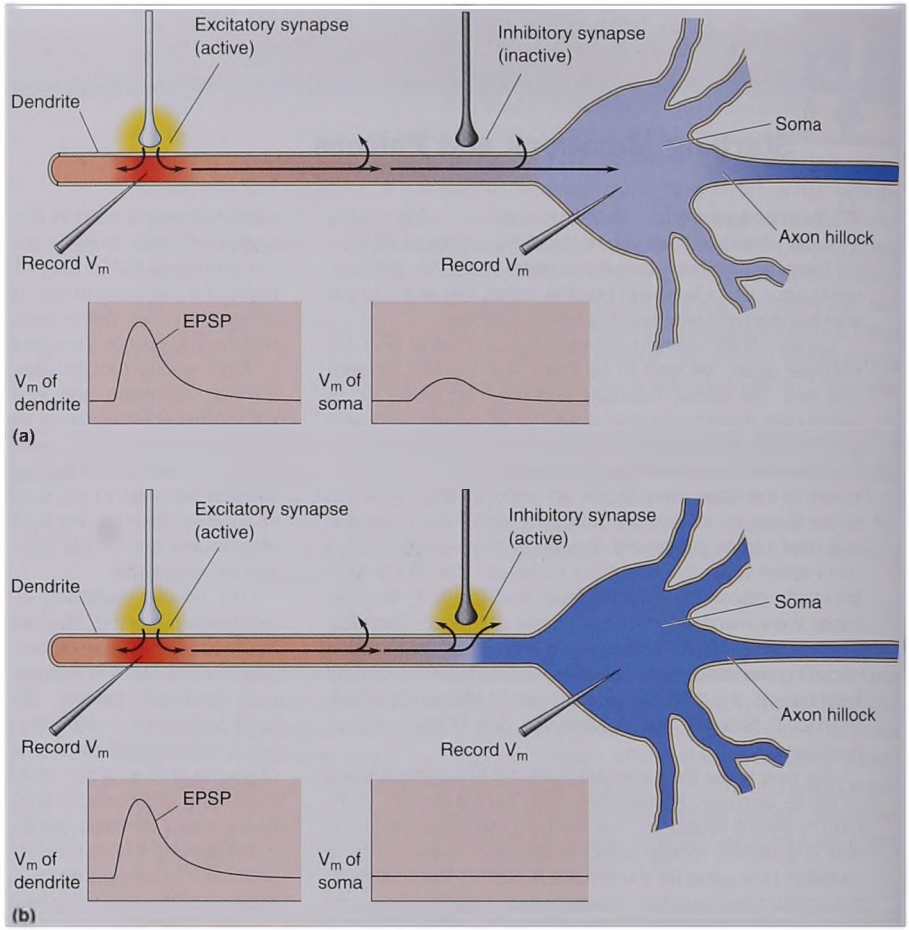
We now know the molecular basis for two general types of startle diseases. Remarkably, both involve defects of inhibitory glycine receptors. The first type, identified in humans and in a mutant mouse called *spasmodic*, is caused by a mutation of a gene for the glycine receptor. The change is the smallest one possible—the abnormal receptors have only one amino acid (out of more than 400) coded wrong—but the result is a chloride channel that opens less frequently when exposed to the neurotransmitter glycine. The second type of startle disease is seen in the mutant mouse *spastic* and in a strain of cattle. In these animals, normal glycine receptors are expressed but in fewer than normal numbers. The two forms of startle disease thus take different routes to the same unfortunate end: The transmitter glycine is less effective at inhibiting neurons in the spinal cord and brain stem.

Most neural circuits depend on a delicate balance of synaptic excitation and inhibition for normal functioning. If excitation is increased or inhibition reduced, then a turbulent and hyperexcitable state may result. An impairment of glycine function yields exaggerated startles; reduced GABA function can lead to the seizures of epilepsy (as discussed in Chapter 19). How can such diseases be treated? There is often a clear and simple logic. Drugs that enhance inhibition can be very helpful.

The genetic mutations of the glycine system resemble strychnine poisoning. Strychnine is a powerful toxin found in the seeds and bark of certain trees and shrubs of the genus *Strychnos*. It was first isolated and identified chemically in the early nineteenth century. Strychnine has traditionally been used by farmers to eradicate pesky rodents and by murderers. It has a simple mechanism of action: It is an antagonist of glycine at its receptor. Mild strychnine poisoning enhances startle and other reflexes and resembles hyperekplexia. High doses nearly eliminate glycine-mediated inhibition in circuits of the spinal cord and brain stem. This leads to uncontrollable seizures and unchecked muscular contractions, spasm and paralysis of the respiratory muscles, and ultimately, death from asphyxiation. It is a painful, agonizing way to die. Since glycine is not a transmitter in the higher centers of the brain, strychnine itself does not impair cognitive or sensory functions.

E_{Cl}, −65 mV. Positive current, therefore, flows outward across the membrane at this site to bring V_m to −65 mV. This synapse acts as an electrical shunt, preventing the current from flowing through the soma to the axon hillock. This type of inhibition is called **shunting inhibition**. The actual physical basis of shunting inhibition is the *inward movement of negatively charged chloride ions,* which is formally equivalent to *outward positive current* flow. Shunting inhibition is like cutting a big hole in the leaky garden hose—more of the water flows down this path of least resistance, out of the hose, before it gets to the nozzle where it can "activate" the flowers in your garden.

Thus, you can see that the action of inhibitory synapses also contributes to synaptic integration. The IPSPs reduce the size of EPSPs, making the postsynaptic neuron less likely to fire action potentials. In addition, shunting inhibition acts to drastically reduce r_m and consequently λ, thus allowing positive current to flow out across the membrane instead of internally down the dendrite toward the spike-initiation zone.



▲ FIGURE 5.21
Shunting inhibition. A neuron receives one excitatory and one inhibitory input. **(a)** Stimulation of the excitatory input causes inward postsynaptic current that spreads to the soma, where it can be recorded as an EPSP. **(b)** When the inhibitory and excitatory inputs are stimulated together, the depolarizing current leaks out before it reaches the soma.

The Geometry of Excitatory and Inhibitory Synapses. Inhibitory synapses in the brain that use GABA or glycine as a neurotransmitter have a morphology characteristic of Gray's type II (see Figure 5.8b). This structure contrasts with excitatory synapses that use glutamate, which have a Gray's type I morphology. This correlation between structure and function has been useful for working out the geometric relationships among excitatory and inhibitory synapses on individual neurons. In addition to being spread over the dendrites, inhibitory synapses on many neurons are found clustered on the soma and near the axon hillock, where they are in an especially powerful position to influence the activity of the postsynaptic neuron.

Modulation

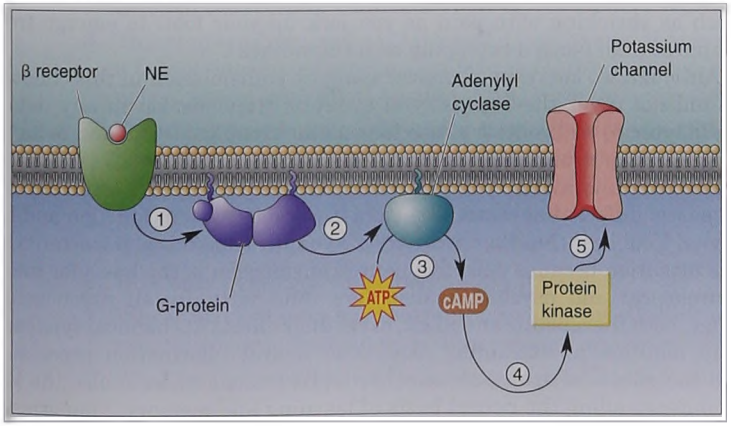
Most of the postsynaptic mechanisms we've discussed so far involve transmitter receptors that are, themselves, ion channels. To be sure, synapses with transmitter-gated channels carry the bulk of the specific information

that is processed by the nervous system. However, there are many synapses with G-protein-coupled neurotransmitter receptors that are not directly associated with an ion channel. Synaptic activation of these receptors does not directly evoke EPSPs and IPSPs but instead *modifies* the effectiveness of EPSPs generated by other synapses with transmitter-gated channels. This type of synaptic transmission is called **modulation**. We'll give you a taste for how modulation influences synaptic integration by exploring the effects of activating one type of G-protein-coupled receptor in the brain, the norepinephrine beta (β) receptor.

The binding of the amine neurotransmitter **norepinephrine (NE)** to the β receptor triggers a cascade of biochemical events within the cell. In short, the β receptor activates a G-protein that, in turn, activates an effector protein, the intracellular enzyme adenylyl cyclase. **Adenylyl cyclase** catalyzes the chemical reaction that converts adenosine triphosphate (ATP), the product of oxidative metabolism in the mitochondria, into a compound called **cyclic adenosine monophosphate**, or **cAMP**, that is free to diffuse within the cytosol. Thus, the *first* chemical message of synaptic transmission (the release of NE into the synaptic cleft) is converted by the β receptor into a *second* message (cAMP); cAMP is an example of a second messenger.

The effect of cAMP is to stimulate another enzyme known as a protein kinase. **Protein kinases** catalyze a chemical reaction called **phosphorylation**, the transfer of phosphate groups (PO_3) from ATP to specific sites on cell proteins (Figure 5.22). The significance of phosphorylation is that it can change the conformation of a protein, thereby changing that protein's activity.

In some neurons, one of the proteins that is phosphorylated when cAMP concentration rises is a particular type of potassium channel in the dendritic membrane. Phosphorylation causes this channel to close, thereby reducing the membrane K^+ conductance. By itself, this does not cause any dramatic effects on the neuron. But consider the wider consequence: *Decreasing the K^+ conductance increases the dendritic membrane resistance and therefore increases the length constant.* It is like wrapping the leaky garden hose in duct tape; more water can flow down the inside of the hose and less leaks out the sides. As a consequence of increasing λ, distant or weak excitatory synapses will become more effective in depolarizing the spike-initiation zone beyond threshold; the cell will become *more excitable*. Thus, the binding of NE to β receptors produces little change in membrane potential but greatly increases the response produced by another neurotransmitter at an excitatory synapse. Because this effect



◀ FIGURE 5.22
Modulation by the NE β receptor. ① The binding of NE to the receptor activates a G-protein in the membrane. ② The G-protein activates the enzyme adenylyl cyclase. ③ Adenylyl cyclase converts ATP into the second messenger cAMP. ④ cAMP activates a protein kinase. ⑤ The protein kinase causes a potassium channel to close by attaching a phosphate group to it.

involves several biochemical intermediaries, it can last far longer than the presence of the modulatory transmitter itself.

We have described one particular G-protein-coupled receptor and the consequences of activating it in one type of neuron. But it is important to recognize that other types of receptors can lead to the formation of other types of second messenger molecules. Activation of each of these receptor types will initiate a distinct cascade of biochemical reactions in the postsynaptic neuron that do not always include phosphorylation and decreases in membrane conductance. In fact, cAMP in a different cell type with different enzymes may produce functionally opposite changes in the excitability of cells.

In Chapter 6, we will describe more examples of synaptic modulation and their mechanisms. However, you can already see that modulatory forms of synaptic transmission offer an almost limitless number of ways that information encoded by presynaptic impulse activity can be transformed and used by the postsynaptic neuron.

CONCLUDING REMARKS

This chapter has covered the basic principles of chemical synaptic transmission. The action potential that arose in the sensory nerve when you stepped on that thumbtack in Chapter 3, and that swept along the axon in Chapter 4, has now reached the axon terminal in the spinal cord. The depolarization of the terminal triggered the presynaptic entry of Ca^{2+} through voltage-gated calcium channels, which then stimulated exocytosis of the contents of synaptic vesicles. Liberated neurotransmitter diffused across the synaptic cleft and attached to specific receptors in the postsynaptic membrane. The transmitter (probably glutamate) caused transmitter-gated channels to open, which allowed positive charge to enter the postsynaptic dendrite. Because the sensory nerve was firing action potentials at a high rate, and because many synapses were activated at the same time, the EPSPs summed to bring the spike-initiation zone of the postsynaptic neuron to threshold, and this cell then generated action potentials. If the postsynaptic cell is a motor neuron, this activity will cause the release of ACh at the neuromuscular junction and muscle contraction to jerk your foot away from the tack. If the postsynaptic cell is an interneuron that uses GABA as a neurotransmitter, the activity of the cell will result in inhibition of its synaptic targets. If this cell uses a modulatory transmitter such as NE, the activity could cause lasting changes in the excitability or metabolism of its synaptic targets. It is this rich diversity of chemical synaptic interactions that allows complex behaviors (such as shrieking with pain as you jerk up your foot) to emerge from simple stimuli (such as stepping on a thumbtack).

Although we surveyed chemical synaptic transmission in this chapter, we did not cover the *chemistry* of synaptic transmission in any detail. In Chapter 6, we'll take a closer look at the chemical "nuts and bolts" of different neurotransmitter systems. In Chapter 15, after we've examined the sensory and motor systems in Part II, we'll explore the contributions of several different neurotransmitters to nervous system function and behavior. You'll see that the chemistry of synaptic transmission warrants all this attention because defective neurotransmission is the basis for many neurological and psychiatric disorders. And virtually all psychoactive drugs, both therapeutic and illicit, exert their effects at chemical synapses.

In addition to explaining aspects of neural information processing and the effects of drugs, chemical synaptic transmission is also the key to understanding the neural basis of learning and memory. Memories of

past experiences are established by modification of the effectiveness of chemical synapses in the brain. This chapter suggests possible sites of modification, ranging from changes in presynaptic Ca^{2+} entry and neurotransmitter release to alterations in postsynaptic receptors or excitability. As we shall see in Chapter 25, all of these changes are likely to contribute to the storage of information by the nervous system.

KEY TERMS

Introduction
synaptic transmission (p. 110)
electrical synapse (p. 110)
chemical synapse (p. 110)

Types of Synapses
gap junction (p. 111)
postsynaptic potential (PSP) (p. 112)
secretory granule (p. 114)
dense-core vesicle (p. 114)
membrane differentiation (p. 115)
active zone (p. 115)
postsynaptic density (p. 115)
neuromuscular junction (p. 119)
motor end-plate (p. 119)

Principles of Chemical Synaptic Transmission
glutamate (Glu) (p. 122)
gamma-aminobutyric acid (GABA) (p. 122)
glycine (Gly) (p. 122)
acetylcholine (ACh) (p. 122)
transporters (p. 122)
voltage-gated calcium channel (p. 122)
exocytosis (p. 122)
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transmitter-gated ion channels (p. 124)
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G-protein-coupled receptors (p. 126)
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receptor agonists (p. 131)
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Principles of Synaptic Integration
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modulation (p. 139)
norepinephrine (NE) (p. 139)
adenylyl cyclase (p. 139)
cyclic adenosine monophosphate (cAMP) (p. 139)
protein kinases (p. 139)
phosphorylation (p. 139)

REVIEW QUESTIONS

1. What is meant by quantal release of neurotransmitter?
2. You apply ACh and activate nicotinic receptors on a muscle cell. Which way will current flow through the receptor channels when $V_m = -60$ mV? When $V_m = 0$ mV? When $V_m = 60$ mV? Why?
3. This chapter discussed a GABA-gated ion channel that is permeable to Cl^-. GABA also activates a G-protein-coupled receptor, called the *$GABA_B$ receptor*, which causes potassium-selective channels to open. What effect would $GABA_B$ receptor activation have on the membrane potential?
4. You think you have discovered a new neurotransmitter, and you are studying its effect on a neuron. The reversal potential for the response caused by the new chemical is −60 mV. Is this substance excitatory or inhibitory? Why?
5. A drug called *strychnine*, isolated from the seeds of a tree native to India and commonly used as rat poison, blocks the effects of glycine. Is strychnine an agonist or an antagonist of the glycine receptor?
6. How does nerve gas cause respiratory paralysis?
7. Why is an excitatory synapse on the soma more effective in evoking action potentials in the postsynaptic neuron than an excitatory synapse on the tip of a dendrite?
8. What are the steps that lead to increased excitability in a neuron when NE is released presynaptically?

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