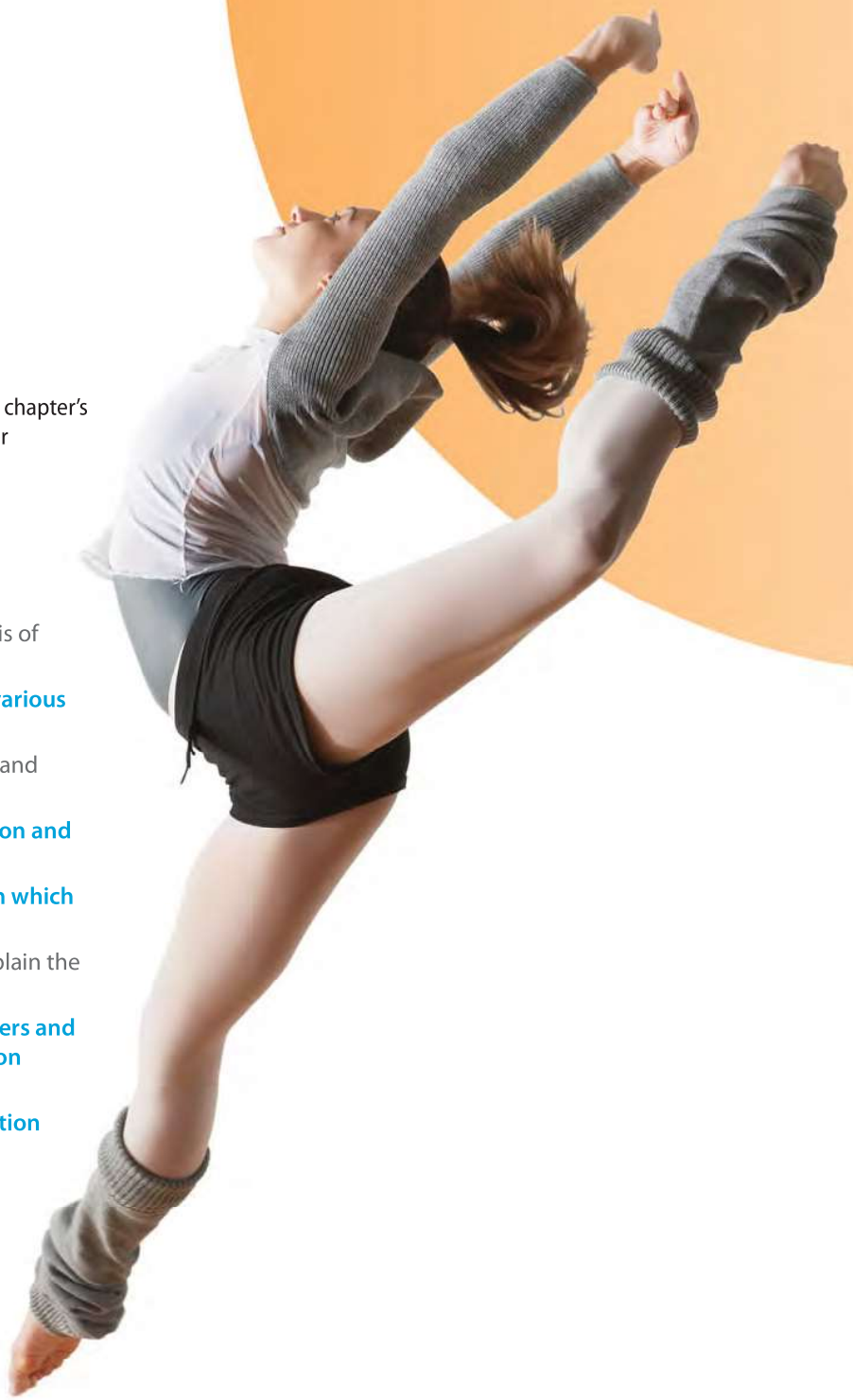
12 Neural Tissue



Learning Outcomes

These Learning Outcomes correspond by number to this chapter's sections and indicate what you should be able to do after completing the chapter.

12-1 Describe the **anatomical and functional divisions** of the nervous system.

12-2 Sketch and label the **structure of a typical neuron**, describe the **functions of each component**, and classify neurons on the basis of their structure and function.

12-3 Describe the locations and functions of the **various types of neuroglia**.

12-4 Explain how the **resting potential** is created and maintained.

12-5 Describe the events involved in the **generation and propagation of an action potential**.

12-6 Discuss the factors that affect the **speed with which action potentials are propagated**.

12-7 Describe the **structure of a synapse**, and explain the mechanism involved in **synaptic activity**.

12-8 Describe the **major types of neurotransmitters and neuromodulators**, and discuss their **effects on postsynaptic membranes**.

12-9 Discuss the interactions that enable **information processing** to occur in **neural tissue**.

Clinical Notes

Spotlight

An Introduction to Neural Tissue

The nervous system includes all the neural tissue in the body. p. 137 The basic functional units of the nervous system are individual cells called **neurons.** Neurons perform all of the communication, information processing, and control functions of the nervous system. Supporting cells, called **neuroglia** (noo-RŌG-lē-uh or noo-rō-GLĒ-uh; *glia*, glue) or *glial cells*, have functions essential to the survival and functionality of neurons and to preserving the physical and biochemical structure of neural tissue. They separate and protect the neurons, provide a supportive framework for neural tissue, act as phagocytes, and help regulate the composition of the interstitial fluid. Neuroglia far outnumber neurons.

Neural tissue, with supporting blood vessels and connective tissues, forms the organs of the nervous system: the brain; the spinal cord; the receptors in complex sense organs, such as the eye and ear; and the *nerves* that link the nervous system with other systems.

12-1 The nervous system has anatomical and functional divisions

We can look at the nervous system from anatomical and functional perspectives.

The Anatomical Divisions of the Nervous System

Viewed anatomically, the nervous system has two divisions: the central nervous system and the peripheral nervous system. The **central nervous system (CNS)** consists of the spinal cord and brain. These complex organs include not only neural tissue, but also blood vessels and the various connective tissues that provide physical protection and support.

The CNS is responsible for integrating, processing, and coordinating sensory data and motor commands. Sensory data convey information about conditions inside or outside the body. Motor commands control or adjust the activities of peripheral organs, such as skeletal muscles. When you stumble, for example, the CNS integrates information about your balance and the position of your limbs and then coordinates your recovery by sending motor commands to appropriate skeletal muscles—all in a split second and without your conscious effort. The CNS—specifically, the brain—is also the seat of higher functions, such as intelligence, memory, learning, and emotion.

The **peripheral nervous system (PNS)** includes all the neural tissue outside the CNS. The PNS delivers sensory information to the CNS and carries motor commands to peripheral tissues and systems. Bundles of axons, or *nerve fibers*, carry sensory information and motor commands in the PNS. Such bundles, with associated blood vessels and connective tissues, are called *peripheral nerves*, or simply **nerves.** Nerves connected to the brain are called **cranial nerves,** and those attached to the spinal cord are called **spinal nerves.**

The Functional Divisions of the Nervous System

We can divide the PNS into afferent and efferent divisions, each with different functions. The **afferent division** (*afferens*, to bring to) of the PNS brings sensory information *to* the CNS from receptors in peripheral tissues and organs. **Receptors** are sensory structures that either detect changes in the environment (internal or external) or respond to specific stimuli. Our receptors range from the slender cytoplasmic extensions of single cells to complex receptor organs, such as the eye and ear. Receptors may be neurons or specialized cells of other tissues. p. 154

The **efferent division** (*effero*, to bring out) of the PNS carries motor commands *from* the CNS to muscles, glands, and adipose tissue. These target organs, which respond by *doing* something, are called **effectors.** The efferent division has both somatic and autonomic components:

- The **somatic nervous system (SNS)** controls skeletal muscle contractions. *Voluntary* contractions are under conscious control. For example, you exert conscious control over your arm as you raise a full glass of water to your lips. *Involuntary* contractions may be simple, automatic responses or complex movements, but they are controlled at the subconscious level, outside your awareness. For instance, if you accidentally place your hand on a hot stove, you will withdraw it immediately, usually before you even notice any pain. This type of automatic response is called a **reflex.**
- The **autonomic nervous system (ANS),** or *visceral motor system*, provides automatic regulation of smooth muscle, cardiac muscle, glandular secretions, and adipose tissue at the subconscious level. The ANS includes a *sympathetic division* and a *parasympathetic division*, which commonly have antagonistic effects. For example, activity of the sympathetic division accelerates the heart rate, whereas parasympathetic activity slows the heart rate.

Now that you have an overview of the nervous system, let's look at the structure of neural tissue and the functional principles that govern neural activities. We begin with neurons, the basic functional units of the nervous system.

Checkpoint

1. Identify the two anatomical divisions of the nervous system.
2. Identify the two functional divisions of the peripheral nervous system, and cite their primary functions.
3. Identify the two components of the efferent division of the PNS.
4. What would be the effect of damage to the afferent division of the PNS?

See the blue Answers tab at the back of the book.

12-2 Neurons are nerve cells specialized for intercellular communication

Let's examine the structure of a representative neuron and see how it is specialized for intercellular communication before we consider the structural and functional classifications of neurons.

12

The Structure of Neurons

Neurons have a variety of shapes. **Figure 12–1** shows a *multipolar neuron*, the most common type of neuron in the central nervous system. Each multipolar neuron has a large *cell body*, several short, branched *dendrites*, and a single, long *axon*, ending in terminal branches called *telodendria*.

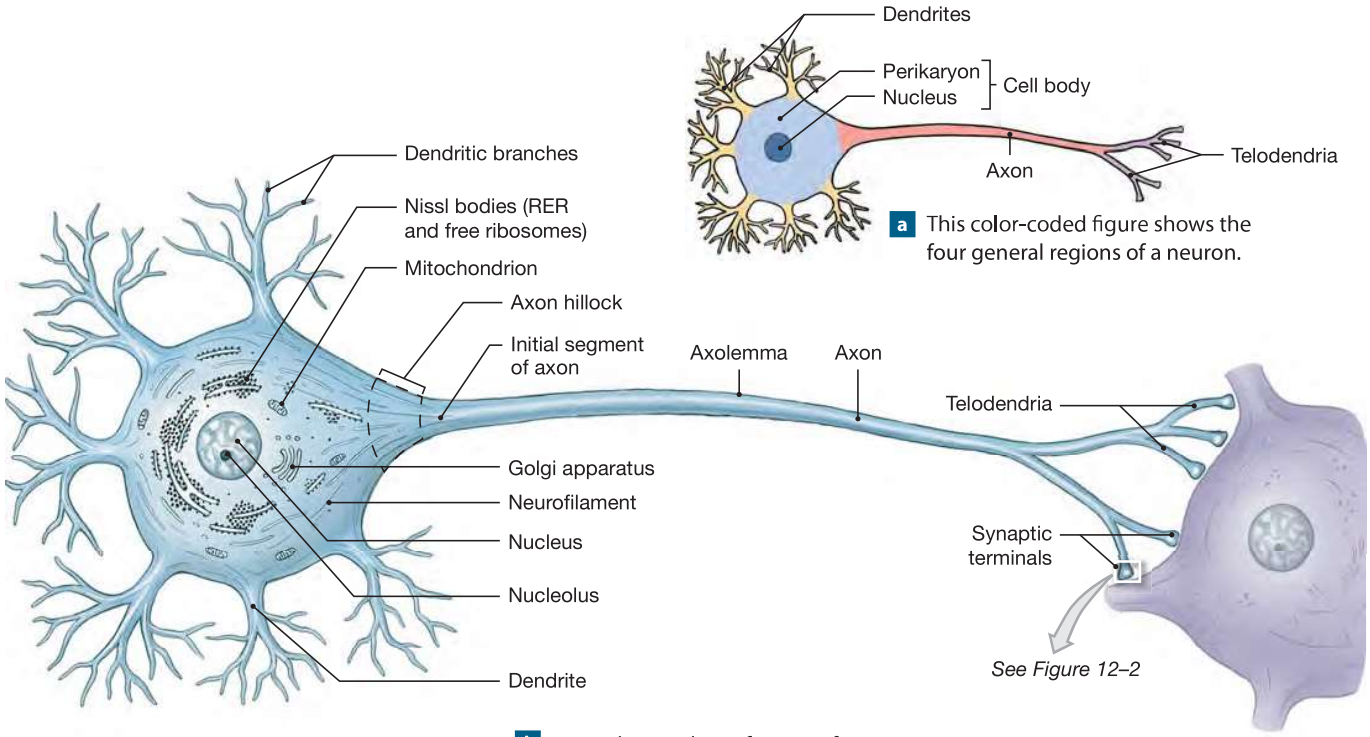
The Cell Body

The **cell body**, or *soma*, contains a large, round nucleus with a prominent nucleolus (**Figure 12–1**). The cytoplasm surrounding the nucleus is the **perikaryon** (per-i-KAR-ē-on; *peri*, around + *karyon*, nucleus). The cytoskeleton of the perikaryon contains **neurofilaments** and **neurotubules,** which are similar to the intermediate filaments and microtubules of other types of cells. Bundles of neurofilaments, called **neurofibrils,** extend into the dendrites and axon, providing internal support for them.

The perikaryon contains organelles that provide energy and synthesize organic materials, especially the chemical neurotransmitters that are important in cell-to-cell communication. p. 292 The numerous mitochondria, free and fixed ribosomes, and membranes of rough endoplasmic reticulum (RER) give the perikaryon a coarse, grainy appearance. Mitochondria generate ATP to meet the high energy demands of an active neuron. The ribosomes and RER synthesize proteins.

Some areas of the perikaryon contain clusters of RER and free ribosomes. These regions, which stain darkly, are called *Nissl bodies*, after the German microscopist Franz Nissl who first described them. Nissl bodies give a gray color to areas contain-

Figure 12–1 The Anatomy of a Multipolar Neuron.



ing neuron cell bodies—the *gray matter* seen in gross dissection of the brain and spinal cord.

Most neurons lack centrioles, important organelles that help to organize the cytoskeleton, and microtubules that move chromosomes during mitosis. p. 99 As a result, typical CNS neurons cannot divide. For this reason, they cannot be replaced if lost to injury or disease. Neural stem cells persist in the adult nervous system, but they are typically inactive except in the nose, where the regeneration of olfactory (smell) receptors maintains our sense of smell, and in the *hippocampus*, a part of the brain involved in storing memories. Researchers are investigating the control mechanisms that trigger neural stem cell activity, with the goal of preventing or reversing neuron loss due to trauma, disease, or aging.

Dendrites and Axons

A variable number of slender, sensitive processes (extensions) known as **dendrites** extend out from the cell body (**Figure 12–1**). Dendrites play key roles in intercellular communication. Typical dendrites are highly branched, and each branch bears fine 0.5- to 1-μm-long studded processes called *dendritic spines*. In the CNS, a neuron receives information from other neurons primarily at the dendritic spines, which represent 80–90 percent of the neuron's total surface area.

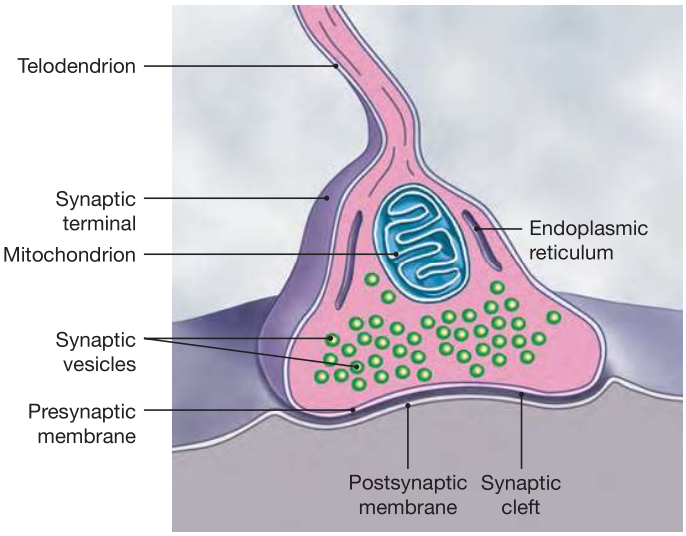
An **axon** is a long cytoplasmic process capable of propagating an electrical impulse known as an *action potential*. p. 292 The **axoplasm** (AK-sō-plazm), or cytoplasm of the axon, contains neurofibrils, neurotubules, small vesicles, lysosomes, mitochondria, and various enzymes. The **axolemma** (*lemma*, husk), a specialized portion of the plasma membrane, surrounds the axoplasm. In the CNS, the axolemma may be exposed to the interstitial fluid or, as we'll see, it may be covered by the processes of neuroglia. The base, or **initial segment,** of the axon in a multipolar neuron joins the cell body at a thickened region known as the **axon hillock** (**Figure 12–1**).

An axon may branch along its length, producing side branches known as **collaterals.** Collaterals enable a single neuron to communicate with several other cells. The main axon trunk and any collaterals end in a series of fine extensions called **telodendria** (tel-ō-DEN-drē-uh; *telo-*, end + *dendron*, tree) or *terminal branches*. The telodendria, in turn, end at **synaptic terminals** (also called synaptic knobs, axon terminals, and synaptic boutons), which play a role in communication with another cell (**Figure 12–1**).

The Synapse

Each synaptic terminal is part of a **synapse,** a specialized site where the neuron communicates with another cell (**Figure 12–2**). Every synapse involves two cells: (1) the *presynaptic cell*, which sends a message and includes the synaptic terminal; and (2) the *postsynaptic cell*, which receives the message. Typically, a narrow space called the *synaptic cleft* separates the two cells. p. 292

Figure 12–2 The Structure of a Typical Synapse.
A diagrammatic view of a typical synapse between two neurons.



In communication between two cells, the synaptic terminal of the presynaptic cell most commonly releases chemicals called **neurotransmitters** into the synaptic cleft. Inside the synaptic terminal, neurotransmitters are contained in *synaptic vesicles*. As we saw in Chapter 10, neurotransmitter release is triggered by electrical events, such as the arrival of an action potential. The neurotransmitters then flood the synaptic cleft and affect the activity of the postsynaptic cell.

The presynaptic cell is usually a neuron. (Specialized receptor cells may form synaptic connections with the dendrites of neurons, a topic we describe in Chapter 15.) The postsynaptic cell can be either a neuron or another type of cell. One neuron may communicate with another at a synapse on a dendrite, on the cell body, or along the length of the axon of the receiving cell. A synapse between a neuron and a muscle cell is called a **neuromuscular junction.** p. 290 At a **neuroglandular junction,** a neuron controls or regulates the activity of a secretory (gland) cell. Neurons also *innervate* (are distributed to) a variety of other cell types, such as adipocytes (fat cells). We consider the nature of that innervation in later chapters.

The structure of the synaptic terminal varies with the type of postsynaptic cell. A relatively simple, round synaptic terminal occurs where the postsynaptic cell is another neuron. At a synapse, the narrow synaptic cleft separates the **presynaptic membrane,** where neurotransmitters are released, from the **postsynaptic membrane,** which bears receptors for neurotransmitters (**Figure 12–2**). The synaptic terminal at a neuromuscular junction is much more complex.

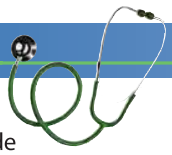
Each synaptic terminal contains mitochondria, portions of the endoplasmic reticulum, and thousands of vesicles filled with

neurotransmitter molecules. The synaptic terminal reabsorbs breakdown products of neurotransmitters formed at the synapse and reassembles them. It also receives a continuous supply of neurotransmitters synthesized in the cell body, along with enzymes and lysosomes.

These materials travel the length of the axon along neurotubules, pulled along by "molecular motors," called *kinesin* and *dynein*, that run on ATP. The movement of materials between the cell body and synaptic terminals is called **axoplasmic transport.** Some materials travel slowly, at rates of a few millimeters per day. This transport mechanism is known as the "slow stream." Vesicles containing neurotransmitters move much more rapidly, traveling in the "fast stream" at 5–10 mm per hour.

Axoplasmic transport occurs in both directions. The flow of materials from the cell body to the synaptic terminal is *anterograde* (AN-ter-ō-grād; *antero-*, forward) *flow,* carried by kinesin. At the same time, other substances are transported toward the cell body in *retrograde* (RET-rō-grād) *flow* (*retro*, backward), carried by dynein. If debris or unusual chemicals appear in the synaptic terminal, retrograde flow soon delivers them to the cell body. There they may then alter the activity of the cell by turning certain genes on or off.

Clinical Note



Rabies *Rabies* is a dramatic example of a clinical condition directly related to retrograde flow. A bite from a rabid animal injects the rabies virus into peripheral tissues, where virus particles quickly enter synaptic terminals and peripheral axons. Retrograde flow then carries the virus into the CNS, with fatal results. Many toxins (including heavy metals), some pathogenic bacteria, and other viruses also bypass CNS defenses through axoplasmic transport.

The Classification of Neurons

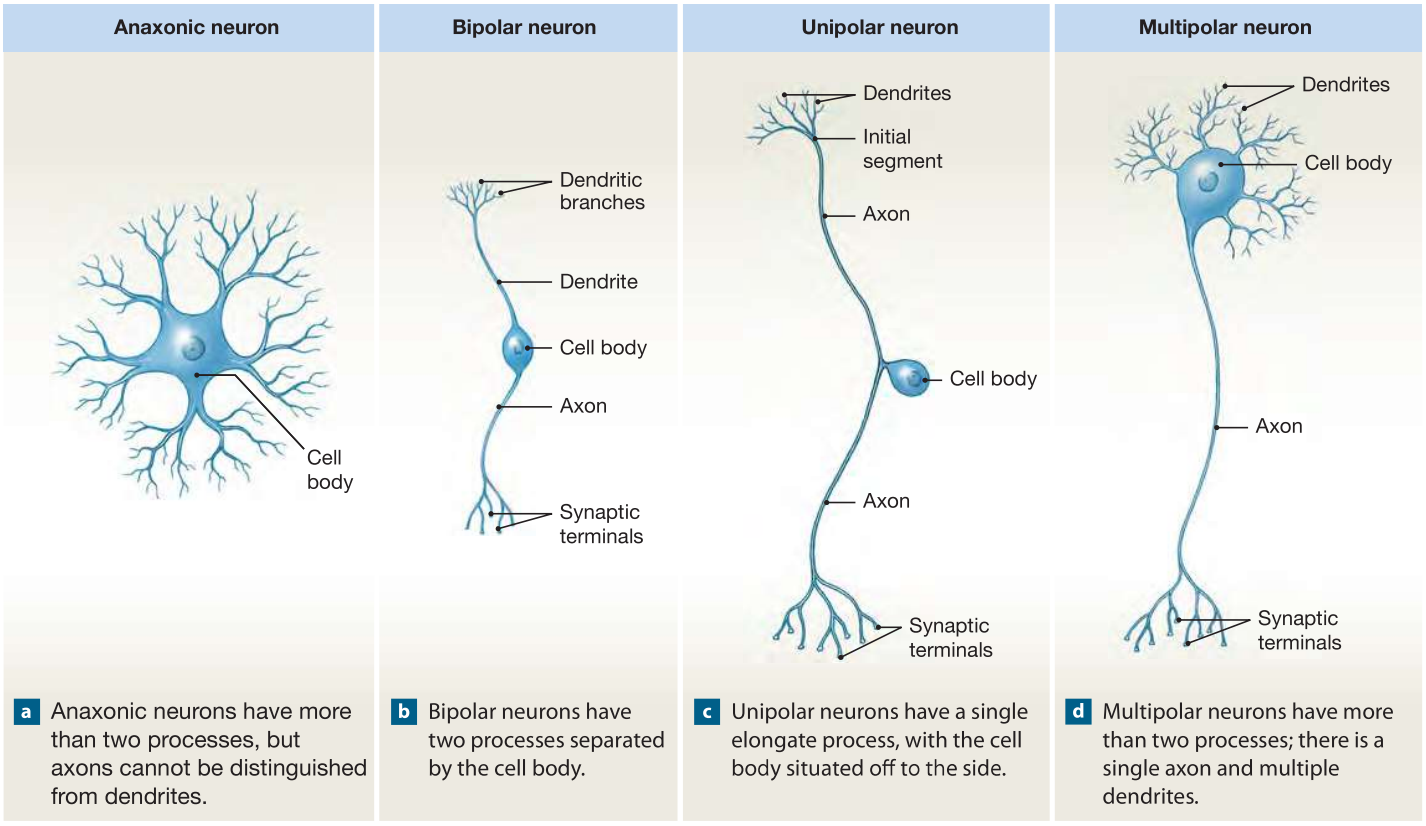
We can group neurons by structure or by function.

Structural Classification of Neurons

Neurons are classified as anaxonic, bipolar, unipolar, or multipolar on the basis of the relationship of the dendrites to the cell body and the axon (**Figure 12–3**):

- **Anaxonic** (an-aks-ON-ik) **neurons** are small and have no anatomical features that distinguish dendrites from axons.

Figure 12–3 **A Structural Classification of Neurons.**



a Anaxonic neurons have more than two processes, but axons cannot be distinguished from dendrites.

b Bipolar neurons have two processes separated by the cell body.

c Unipolar neurons have a single elongate process, with the cell body situated off to the side.

d Multipolar neurons have more than two processes; there is a single axon and multiple dendrites.

All the cell processes look alike. Anaxonic neurons are located in the brain and in special sense organs. Their functions are poorly understood.

- **Bipolar neurons** have two distinct processes—one dendrite that branches extensively into dendritic branches at its distal tip, and one axon—with the cell body between the two. Bipolar neurons are rare. They occur in special sense organs, where they relay information about sight, smell, or hearing from receptor cells to other neurons. Bipolar neurons are small. The largest measure less than 30 μm from end to end.
- In a **unipolar neuron,** or *pseudounipolar neuron*, the dendrites and axon are continuous—basically, fused—and the cell body lies off to one side. In such a neuron, the initial segment lies where the dendrites converge. The rest of the process, which carries action potentials, is usually considered an axon. Most sensory neurons of the peripheral nervous system are unipolar. Their axons may extend a meter or more, ending at synapses in the central nervous system. The longest carry sensations from the tips of the toes to the spinal cord.
- **Multipolar neurons** have two or more dendrites and a single axon. They are the most common neurons in the CNS. All the motor neurons that control skeletal muscles, for example, are multipolar neurons. The axons of multipolar neurons can be as long as those of unipolar neurons, and the longest carry motor commands from the spinal cord to small muscles that move the toes.

Functional Classification of Neurons

Alternatively, we can categorize neurons by function as (1) sensory neurons, (2) motor neurons, or (3) interneurons.

Sensory Neurons. Sensory neurons, or *afferent neurons*, form the afferent division of the PNS. They deliver information from sensory receptors to the CNS. The cell bodies of sensory neurons are located in peripheral *sensory ganglia*. (A *ganglion* is a collection of neuron cell bodies in the PNS.) Sensory neurons are unipolar neurons whose processes, known as **afferent fibers,** extend between a sensory receptor and the central nervous system (spinal cord or brain). The human body's 10 million or so sensory neurons collect information about the external or internal environment. **Somatic sensory neurons** monitor the outside world and our position within it. **Visceral sensory neurons** monitor internal conditions and the status of other organ systems.

Sensory receptors are either the processes of specialized sensory neurons or cells monitored by sensory neurons. We can broadly categorize receptors in three groups:

- **Interoceptors** (*intero-*, inside) monitor the digestive, respiratory, cardiovascular, urinary, and reproductive systems and provide sensations of distension, deep pressure, and pain.
- **Exteroceptors** (*extero-*, outside) provide information about the external environment in the form of touch, temperature, or pressure sensations and the more complex senses of taste, smell, sight, equilibrium, and hearing.
- **Proprioceptors** (prō-prē-ō-SEP-torz) monitor the position and movement of skeletal muscles and joints.

Motor Neurons. Motor neurons, or *efferent neurons*, form the efferent division of the PNS. These neurons carry instructions from the CNS to peripheral effectors in a peripheral tissue, organ, or organ system. The human body has about half a million motor neurons. Axons traveling away from the CNS are called **efferent fibers.** As noted earlier, the two major efferent systems are the somatic nervous system (SNS) and the autonomic (visceral) nervous system (ANS).

The somatic nervous system includes all the **somatic motor neurons** that innervate skeletal muscles. You have conscious control over the activity of the SNS. The cell body of a somatic motor neuron lies in the CNS, and its axon extends into the periphery within a peripheral nerve to innervate skeletal muscle fibers at neuromuscular junctions.

You do not have conscious control over the activities of the ANS. **Visceral motor neurons** innervate all peripheral effectors other than skeletal muscles—that is, smooth muscle, cardiac muscle, glands, and adipose tissue throughout the body. The axons of visceral motor neurons in the CNS innervate a second set of visceral motor neurons in peripheral *autonomic ganglia*. The neurons whose cell bodies are located in those ganglia innervate and control peripheral effectors.

Tips & Tricks

To distinguish between *efferent* and *afferent*, think of the **SAME** principle: **S** is for **s**ensory, **A** is for **a**fferent, **M** is for **m**otor, and **E** is for **e**fferent. This way, you associate the **S** and **A** together and the **M** and **E** together.

To get from the CNS to a visceral effector such as a smooth muscle cell, a signal must travel along one axon, be relayed across a synapse, and then travel along a second axon to its final destination. The axons extending from the CNS to an autonomic ganglion are called *preganglionic fibers*, and axons connecting the ganglion cells with the peripheral effectors are known as *postganglionic fibers*.

Interneurons. The 20 billion or so **interneurons,** or *association neurons*, outnumber all other types of neurons combined. Most are located within the brain and spinal cord, but some are in autonomic ganglia. Interneurons distribute sensory information and coordinate motor activity. One or more interneurons are

located between sensory neurons and motor neurons, and the more complex the response to a given stimulus, the more interneurons are involved. Interneurons also play a part in all higher functions, such as memory, planning, and learning.

We now turn our attention to the neuroglia, cells that support and protect the neurons.

Checkpoint

5. **Name the structural components of a typical neuron.**
6. **Classify neurons according to their structure.**
7. **Classify neurons according to their function.**
8. **Are unipolar neurons in a tissue sample more likely to function as sensory neurons or motor neurons?**

See the blue Answers tab at the back of the book.

12-3 CNS and PNS neuroglia support and protect neurons

Neuroglia are abundant and diverse, and they account for roughly half of the volume of the nervous system. The organization of neural tissue in the CNS differs from that in the PNS, primarily because the CNS contains a greater variety of neuroglial cell types. Histological descriptions have been available for the past century, but the technical problems involved in isolating and manipulating individual glial cells have limited our understanding of their functions. **Figure 12–4** summarizes what we know about the major neuroglial populations in the CNS and PNS.

Neuroglia of the Central Nervous System

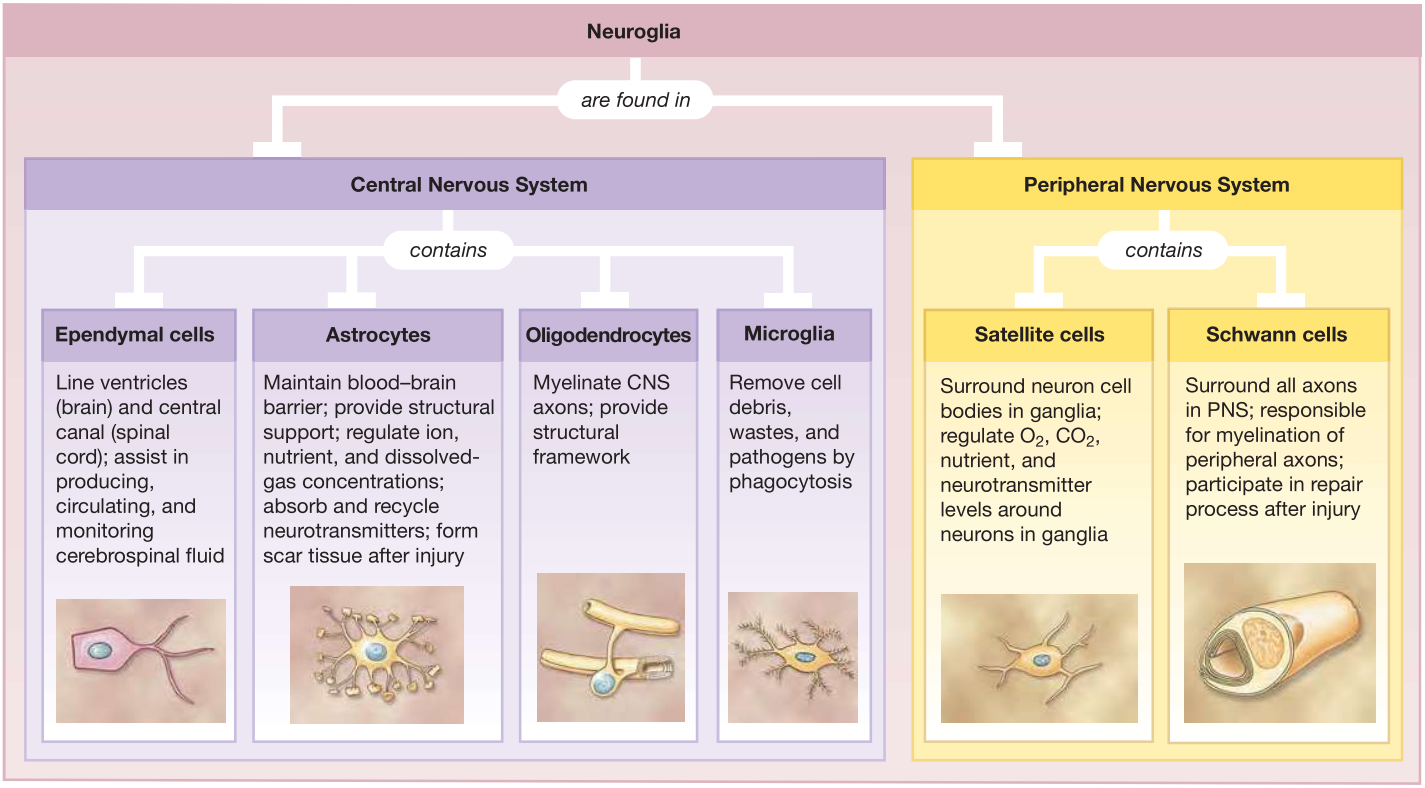
The central nervous system has four types of neuroglia: (1) *ependymal cells*, (2) *astrocytes*, (3) *oligodendrocytes*, and (4) *microglia* (**Figure 12–5**).

Ependymal Cells

A fluid-filled central passageway extends along the longitudinal axis of the spinal cord and brain. **Cerebrospinal fluid (CSF)** fills this passageway and also surrounds the brain and spinal cord. This fluid, which circulates continuously, provides a protective cushion and transports dissolved gases, nutrients, wastes, and other materials. The diameter of the internal passageway varies from one region to another. The narrow passageway in the spinal cord is called the *central canal* (**Figure 12–5a,b**). In several regions of the brain, the passageway forms enlarged chambers called *ventricles*. **Ependymal cells** line the central canal and ventricles, where they form an epithelium known as the **ependyma** (ep-EN-di-muh).

During embryonic development and early childhood, the free surfaces of ependymal cells are covered with cilia. The cilia persist in adults only in small areas within the ventricles of the brain, where

Figure 12–4 An Introduction to Neuroglia.



Clinical Note

Tumors Tumors of the brain, spinal cord, and associated membranes result in approximately 90,000 deaths in the United States each year. Tumors that originate in the central nervous system are called *primary CNS tumors*, to distinguish them from *secondary CNS tumors*, which arise from the metastasis (spread) of cancer cells that originate elsewhere. Roughly 75 percent of CNS tumors are primary tumors. In adults, primary CNS tumors result from the divisions of abnormal neuroglia rather than from the divisions of abnormal neurons, because typical neurons in adults cannot divide. However, through the divisions of stem cells, neurons increase in number until children reach age 4. As a result, primary CNS tumors involving abnormal neurons can occur in young children. Symptoms of CNS tumors vary with the location affected. Treatment may involve surgery, radiation, chemotherapy, or a combination of these procedures.

they help to circulate the CSF. In other areas, the ependymal cells typically have scattered microvilli. In a few parts of the brain, specialized ependymal cells secrete CSF. Other regions of the ependyma may have sensory functions, such as monitoring the composition of the CSF. In adults, the ependyma appears to contain stem cells that can divide to produce additional neurons. The specific regulatory mechanisms involved are now being investigated.

Unlike typical epithelial cells, ependymal cells have slender processes that branch extensively and make direct contact with other neuroglial cells in the surrounding neural tissue. The functions of these connections are not known. During early embryonic development, stem cells line the central canal and ventricles and divide to give rise to neurons and all CNS neuroglia other than microglia.

Astrocytes

Astrocytes (AS-trō-sīts; *astro-*, star + *cyte*, cell) are the largest and most numerous neuroglia in the CNS (**Figure 12–5b**). These cells have a variety of functions, many of them poorly understood:

- *Maintaining the Blood–Brain Barrier.* Compounds dissolved in circulating blood do not have free access to the interstitial fluid of the CNS. Neural tissue must be physically and biochemically isolated from the general circulation, because hormones, amino acids, or other chemicals in the blood can alter neuron function. The endothelial cells lining CNS capillaries control the chemical exchange between the blood and interstitial fluid. These cells create a **blood–brain barrier (BBB)** that isolates the CNS from the general circulation.

  The slender cytoplasmic extensions of astrocytes end in expanded "feet," processes that wrap around capillaries. These processes form a complete blanket around the capillaries, interrupted only where other neuroglia come in contact with the capillary walls. Astrocytes secrete chemicals that are somehow responsible for maintaining the special permeability characteristics of endothelial cells. (We discuss the blood–brain barrier further in Chapter 14.)
- *Creating a Three-Dimensional Framework for the CNS.* Astrocytes are packed with microfilaments that extend across the breadth of the cell and its processes. This extensive cytoskeleton helps astrocytes to provide a structural framework for the neurons of the brain and spinal cord.
- *Repairing Damaged Neural Tissue.* In the CNS, damaged neural tissue seldom regains normal function. However, astrocytes that move into an injury site can make structural repairs that stabilize the tissue and prevent further injury. We discuss neural damage and repair in a later section.
- *Guiding Neuron Development.* Astrocytes in the embryonic brain appear to be involved in directing both the growth and interconnection of developing neurons.
- *Controlling the Interstitial Environment.* Astrocytes appear to adjust the composition of interstitial fluid by several means: (1) regulating the concentration of sodium ions, potassium ions, and carbon dioxide; (2) providing a "rapid-transit system" for transporting nutrients, ions, and dissolved gases between capillaries and neurons; (3) controlling the volume of blood flow through the capillaries; (4) absorbing and recycling some neurotransmitters; and (5) releasing chemicals that enhance or suppress communication across synaptic terminals.

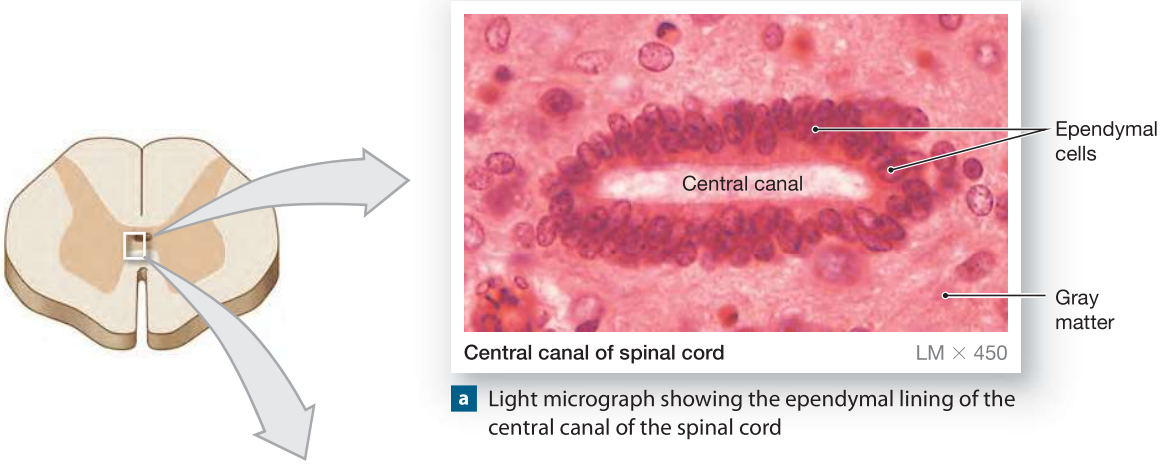
Oligodendrocytes

Like astrocytes, **oligodendrocytes** (ol-i-gō-DEN-drō-sīts; *oligo-*, few) have slender cytoplasmic extensions, but the cell bodies of oligodendrocytes are smaller, with fewer processes, than astrocytes (**Figure 12–5b**). The processes of oligodendrocytes generally are in contact with the exposed surfaces of neurons. The functions of processes ending at the neuron cell body have yet to be determined. Much more is known about the processes that end on the surfaces of axons. Many axons in the CNS are completely sheathed in these processes, which insulate them from contact with the extracellular fluid.

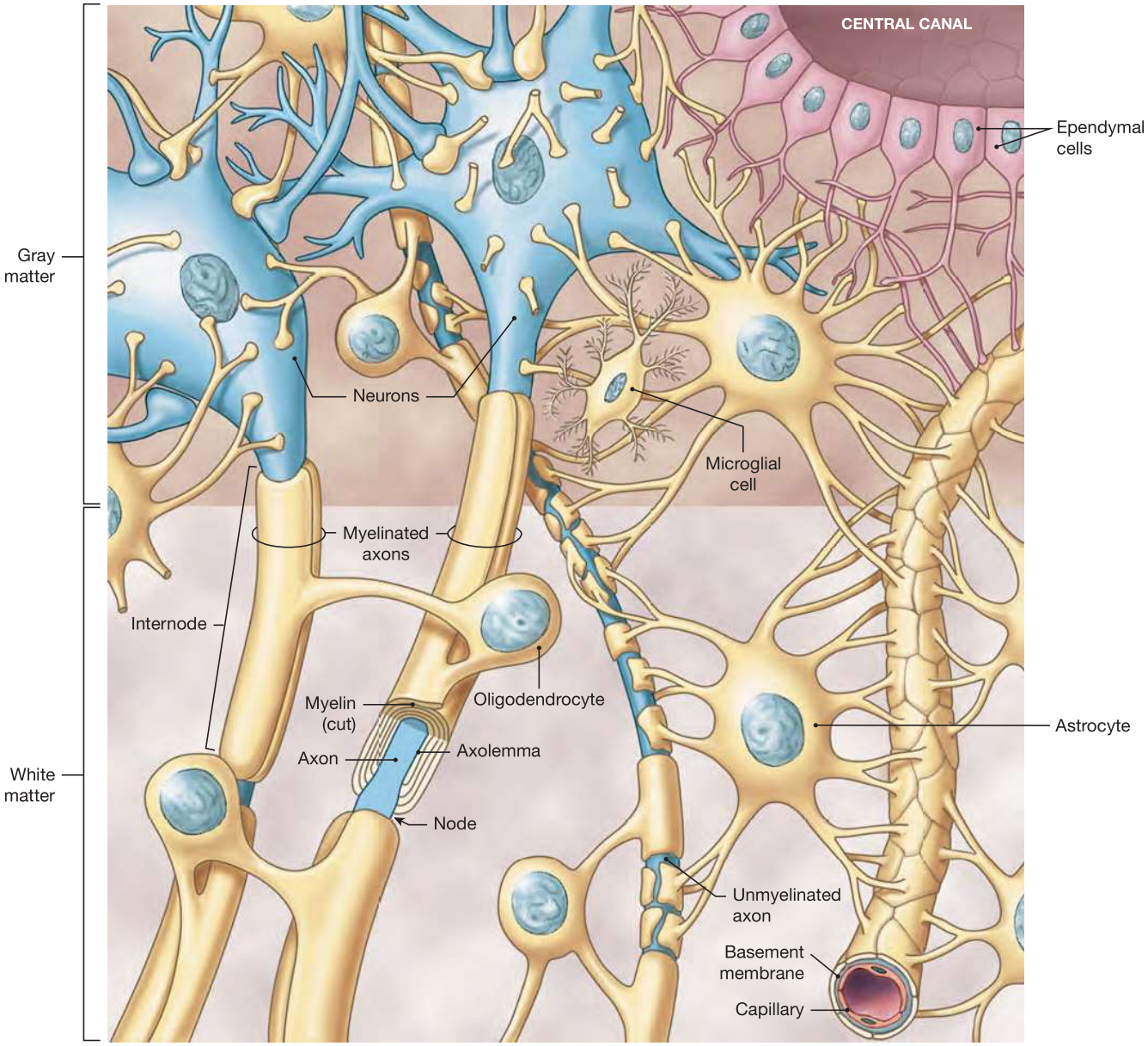
Near the tip of each process, the plasma membrane of the oligodendrocyte expands to form an enormous pad, and the cytoplasm there becomes very thin. This flattened "pancake" somehow gets wound around the axolemma, forming concentric layers of plasma membrane (**Figure 12–5b**). This membranous wrapping, called **myelin** (MĪ-e-lin), serves as electrical insulation and increases the speed at which an action potential travels along the axon. (We describe this mechanism in a later section.)

Many oligodendrocytes cooperate in forming a **myelin sheath** along the length of an axon. Such an axon is said to be **myelinated.** Each oligodendrocyte myelinates segments of several axons. The fairly large areas of the axon that are wrapped in

Figure 12–5 Neuroglia in the CNS.



a Light micrograph showing the ependymal lining of the central canal of the spinal cord



b A diagrammatic view of neural tissue in the CNS, showing relationships between neuroglia and neurons

Clinical Note — Demyelination

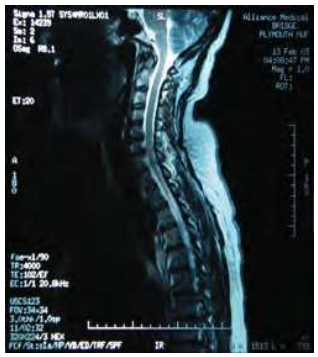
Stripping the fat

Demyelination is the progressive destruction of myelin sheaths, both in the CNS and in the PNS. The result is a loss of sensation and motor control that leaves affected regions numb and paralyzed. Many unrelated conditions that result in the destruction of myelin can cause symptoms of demyelination.

Chronic exposure to heavy-metal ions, such as arsenic, lead, or mercury, can cause **heavy-metal poisoning,** leading to damage of neuroglia and to demyelination. As demyelination occurs, the affected axons deteriorate, and the condition becomes irreversible.

Diphtheria (dif-THER-ē-uh; *diphthera*, leather + *-ia*, disease) is a disease that results from a bacterial infection. In the nervous system, diphtheria toxin damages Schwann cells and destroys myelin sheaths in the PNS. The resulting demyelination leads to sensory and motor problems that can ultimately produce a fatal paralysis. Due to an effective vaccine, cases are relatively rare in countries with adequate health care.

Multiple sclerosis (skler-Ō-sis; *sklerosis*; hardness), or **MS,** is a disease characterized by recurrent incidents of demyelination that affects axons in the optic nerve, brain, and spinal cord. Common signs and symptoms include partial loss of vision and problems with speech, balance, and general motor coordination, including bowel and urinary bladder control. The time between incidents and degree of recovery varies from case to case. In about one-third of all cases, the disorder is progressive, and each incident leaves a greater degree of functional impairment. The first attack typically occurs in individuals 30–40 years old. The incidence among women is 1.5 times that among men. In some patients, corticosteroid or interferon injections have slowed the progression of the disease.



Guillain–Barré (ghee-yan bah-ray) **syndrome** is an autoimmune disorder characterized by demyelination of peripheral nerves. The signs and symptoms include weakness or tingling of the legs that spreads to the arms. They typically increase in severity, leading to paralysis. When breathing is affected, the patient is placed on a ventilator. The disorder affects both sexes equally and each year afflicts 1 of every 100,000 Americans. A virus appears to trigger the syndrome, because the onset is usually within a few days or weeks of a respiratory or gastrointestinal infection, or occasionally after surgery or immunization. Most patients fully recover, but some continue to have residual weakness.

myelin are called **internodes** (*inter*, between). Internodes are typically 1–2 mm in length. The small gaps of a few micrometers that separate adjacent internodes are called **nodes,** or *nodes of Ranvier* (rahn-vē-Ā). An axon's branches originate at nodes.

In dissection, myelinated axons appear glossy white, primarily because of the lipids in the myelin. As a result, regions dominated by myelinated axons are known as the **white matter** of the CNS. Not all axons in the CNS are myelinated, however. **Unmyelinated** axons may not be completely covered by the processes of neuroglia. Such axons are common where short axons and collaterals form synapses with densely packed neuron cell bodies. Areas containing neuron cell bodies, dendrites, and unmyelinated axons have a dusky gray color, and make up the **gray matter** of the CNS.

In sum, oligodendrocytes play a role in structural organization by tying clusters of axons together. These neuroglia also improve the functioning of neurons by wrapping axons within a myelin sheath.

Tips & Tricks

The overall color of CNS tissue is related to its structure and function. **Gr**ay matter has a **gr**eat concentration of neuron cell bodies and is a region of inte**gr**ation. **Wh**ite matter has a **wh**ole lot of myelinated axons and **wh**isks nerve impulses.

Microglia

The least numerous and smallest neuroglia in the CNS are phagocytic cells called **microglia** (mī-KRŌG-lē-uh). ↩ pp. 94–95 Their slender processes have many fine branches (**Figure 12–5b**). These cells can migrate through neural tissue. Microglia appear early in embryonic development, originating from mesodermal stem cells related to stem cells that produce monocytes and macrophages. ↩ pp. 122, 127 Microglia migrate into the CNS as the nervous system forms. There they remain, acting as a wandering janitorial service and police force by engulfing cellular debris, waste products, and pathogens.

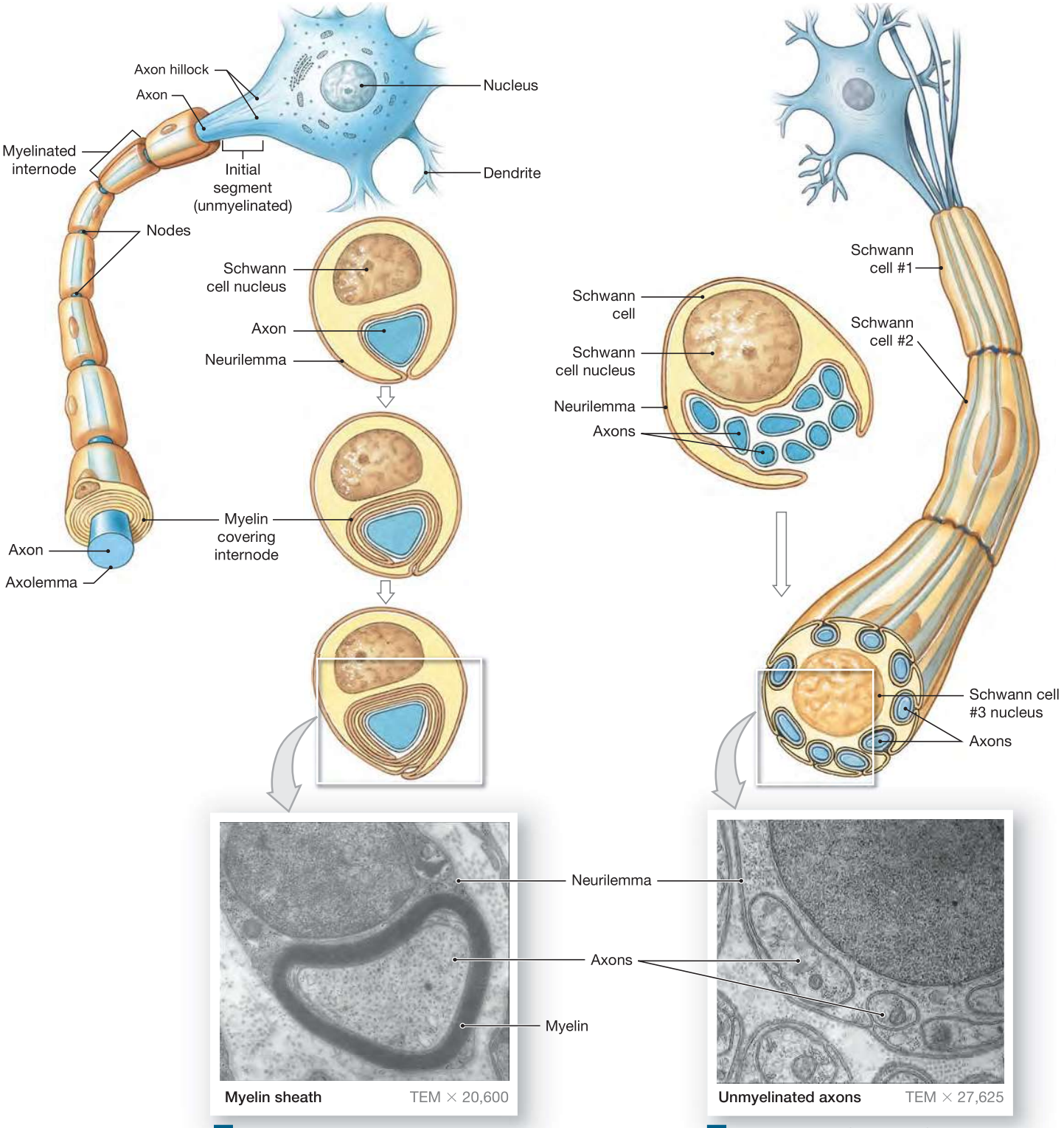
Neuroglia of the Peripheral Nervous System

Recall that the cell bodies of neurons in the PNS are clustered in masses called **ganglia** (singular, *ganglion*). The processes of neuroglia completely insulate neuronal cell bodies and most axons in the PNS from their surroundings. The two types of neuroglia in the PNS are satellite cells and Schwann cells.

Satellite cells, or *amphicytes* (AM-fi-sīts), surround neuron cell bodies in ganglia. They regulate the environment around the neurons, much as astrocytes do in the CNS.

Schwann cells, or *neurilemma cells*, form a sheath around peripheral axons (**Figure 12–6**). Wherever a Schwann cell covers an axon, the outer surface of the Schwann cell is called the

Figure 12–6 Schwann Cells and Peripheral Axons.



a A myelinated axon, showing the organization of Schwann cells along the length of the axon. Also shown are stages in the formation of a myelin sheath by a single Schwann cell along a portion of a single axon.

b The enclosing of a group of unmyelinated axons by a single Schwann cell. A series of Schwann cells is required to cover the axons along their entire length.

neurilemma (noor-i-LEM-uh). Most axons in the PNS, whether myelinated or unmyelinated, are shielded from contact with interstitial fluids by Schwann cells.

A Schwann cell can myelinate only one segment of a single axon (**Figure 12–6a**), whereas an oligodendrocyte in the CNS may myelinate portions of several adjacent axons (**Figure 12–5b**). However, a Schwann cell can *enclose* segments of several unmyelinated axons (**Figure 12–6b**). A series of Schwann cells is required to enclose an axon along its entire length.

Neural Responses to Injuries

What happens when a neuron is injured? It responds to injury in a very limited fashion. In the cell body, the Nissl bodies disperse and the nucleus moves away from its centralized location as the cell increases its rate of protein synthesis. If the neuron recovers its functional abilities, it will regain its normal appearance.

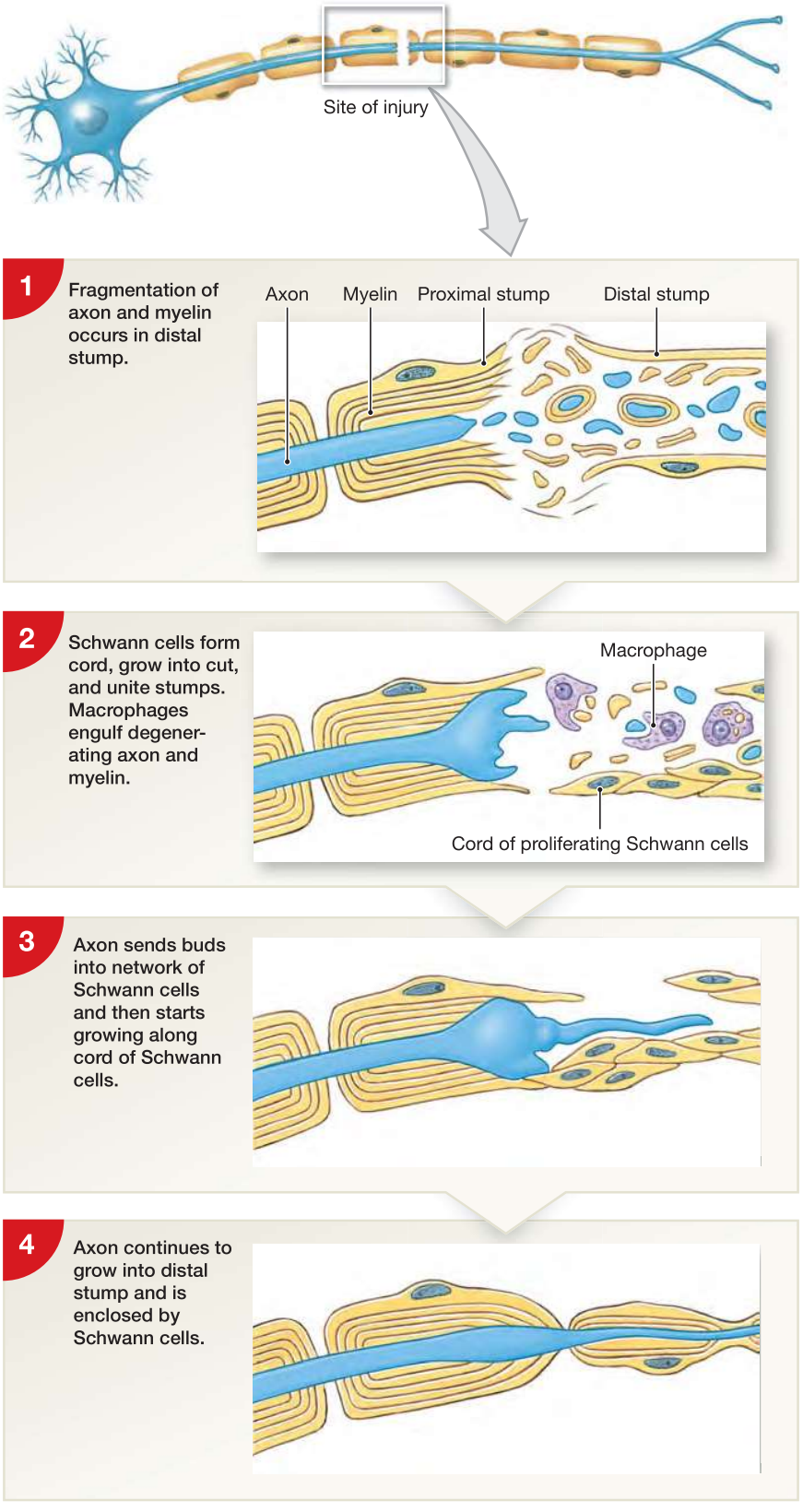
The key to recovery appears to be events in the axon. If, for example, the pressure applied during a crushing injury produces a local decrease in blood flow and oxygen, the affected axonal membrane becomes unexcitable. If the pressure is alleviated after an hour or two, the neuron will recover within a few weeks. More severe or prolonged pressure produces effects similar to those caused by cutting the axon.

In the PNS, Schwann cells play a part in repairing damaged nerves. In the process known as **Wallerian degeneration,** the axon distal to the injury site degenerates, and macrophages migrate into the area to clean up the debris (**Figure 12–7**). The Schwann cells do not degenerate. Instead, they proliferate and form a solid cellular cord that follows the path of the original axon. As the neuron recovers, its axon grows into the site of injury, and the Schwann cells wrap around the axon.

If the axon grows alongside the appropriate cord of Schwann cells, it may eventually reestablish its normal synaptic contacts. However, if it stops growing or wanders off in some new direction, normal function will not return. The growing axon is most likely to arrive at its appropriate destination if the cut edges of the original nerve bundle remain in contact.

Limited regeneration can occur in the CNS, but the situation is more complicated because

Figure 12–7 Peripheral Nerve Regeneration after Injury.



(1) many more axons are likely to be involved, (2) astrocytes produce scar tissue that can prevent axon growth across the damaged area, and (3) astrocytes release chemicals that block the regrowth of axons.

Checkpoint

9. **Identify the neuroglia of the central nervous system.**
10. **Identify the neuroglia of the peripheral nervous system.**
11. **Which type of neuroglia would increase in number in the brain tissue of a person with a CNS infection?**

See the blue Answers tab at the back of the book.

12-4 The transmembrane potential is the electrical potential of the cell's interior relative to its surroundings

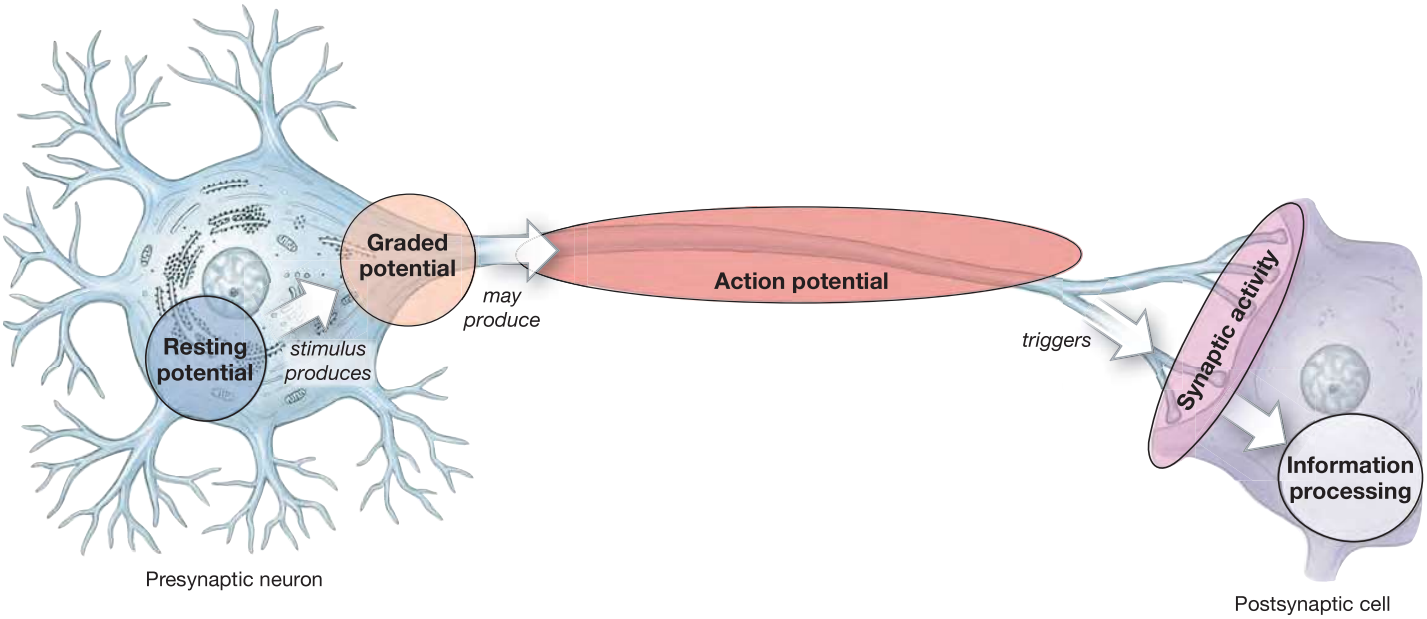
In Chapter 3, we introduced the concepts of the *transmembrane potential* (or *membrane potential*) and the *resting potential*, two characteristic features of all cells. p. 96 In this discussion, we focus on the membranes of neurons, but many of the principles discussed apply to other types of cells as well.

The important membrane processes we will be examining are the resting potential, graded potential, action potential, synaptic activity, and information processing (**Figure 12–8**).

- *Resting potential* All living cells have a transmembrane potential that varies from moment to moment depending on the activities of the cell. The *resting potential* is the transmembrane potential of a resting cell. All neural activities begin with a change in the resting potential of a neuron.
- *Graded potential* A typical stimulus produces a temporary, localized change in the resting potential. The effect, which decreases with distance from the stimulus, is called a *graded potential*.
- *Action potential* If the graded potential is large enough, it triggers an *action potential* in the membrane of the axon. An action potential is an electrical impulse that is propagated (spread) along the surface of an axon and does not diminish as it moves away from its source. This impulse travels along the axon to one or more synapses.
- *Synaptic activity* then produces graded potentials in the plasma membrane of the postsynaptic cell. The presynaptic cell typically releases neurotransmitters, such as ACh. These chemicals bind to receptors on the postsynaptic plasma membrane, changing its permeability and producing graded potentials. The mechanism is comparable to that of the neuromuscular junction, described in Chapter 10. p. 292
- *Information processing* The response of the postsynaptic cell ultimately depends on what the stimulated receptors do and what other stimuli are influencing the cell at the same time. The integration of stimuli at the level of the individual cell is the simplest form of *information processing* in the nervous system.

When you understand each of these processes, you will know how neurons deal with information and communicate with one another and with peripheral effectors.

Figure 12–8 An Overview of Neural Activities.



The Transmembrane Potential

Chapter 3 introduced three important concepts regarding the transmembrane potential:

1. *The extracellular fluid (ECF) and intracellular fluid (cytosol) differ greatly in ionic composition.* The extracellular fluid contains high concentrations of sodium ions (Na^+) and chloride ions (Cl^-), whereas the cytosol contains high concentrations of potassium ions (K^+) and negatively charged proteins.
2. *Cells have selectively permeable membranes.* If the plasma membrane were freely permeable, diffusion would continue until all the ions were evenly distributed across the membrane and a state of equilibrium existed. But an even distribution does not occur, because cells have selectively permeable membranes. ↩ p. 86 Ions cannot freely cross the lipid portions of the plasma membrane. They can enter or leave the cell only through membrane channels. Many kinds of membrane channels exist, each with its own properties. At the resting potential, or transmembrane potential of an undisturbed cell, ions move through *leak channels*—membrane channels that are always open. ↩ pp. 87–88 Active transport mechanisms, such as the sodium–potassium exchange pump, also move specific ions into or out of the cell. ↩ p. 92
3. *Membrane permeability varies by ion.* The cell's passive and active transport mechanisms do not ensure an equal distribution of charges across its membrane, because membrane permeability varies by ion. For example, negatively charged proteins inside the cell are too large to cross the membrane, and it is easier for K^+ to diffuse out of the cell through a potassium leak channel than it is for Na^+ to enter the cell through a sodium leak channel. As a result, the membrane's inner surface has an excess of negative charges with respect to the outer surface.

Both passive and active forces act across the plasma membrane to determine the transmembrane potential at any moment. **Figure 12–9** shows the membrane at the normal resting potential.

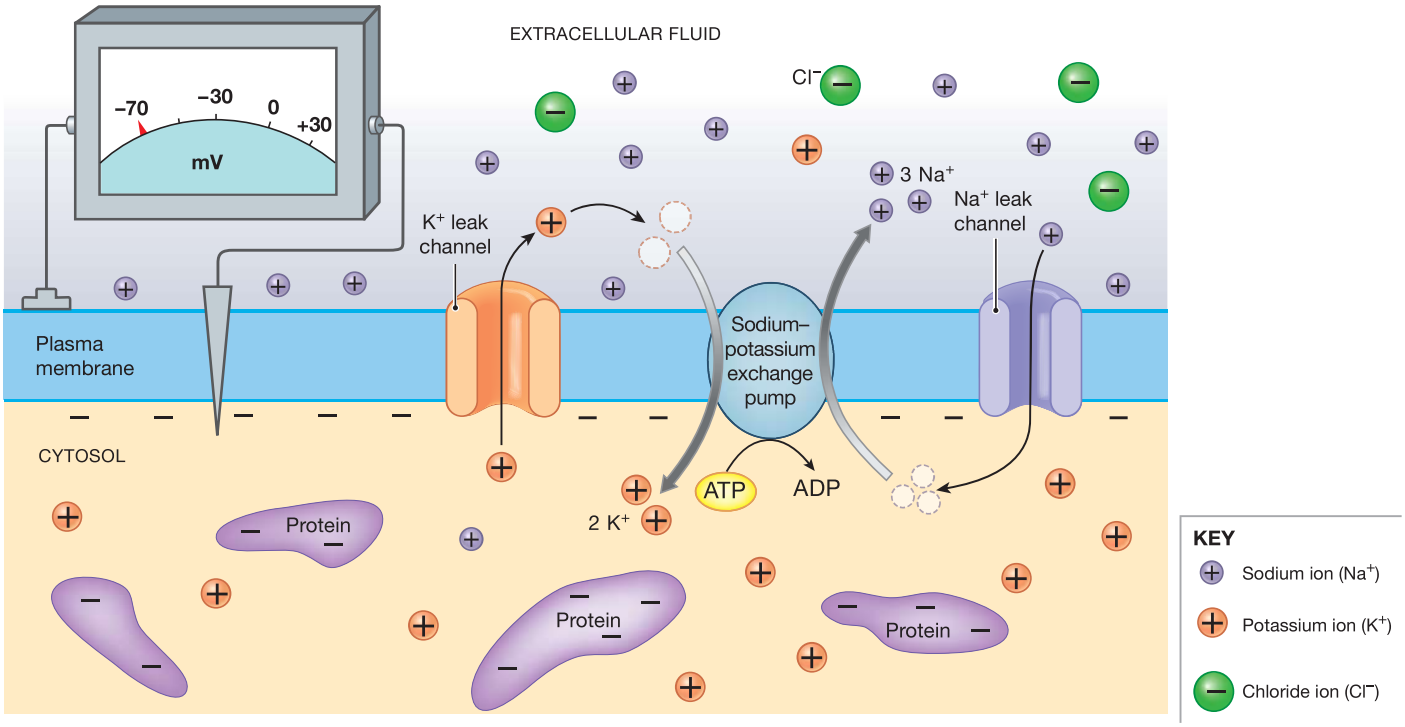
Passive Forces Acting across the Plasma Membrane

The passive forces acting across the plasma membrane are both chemical and electrical in nature.

Chemical Gradients. Because the intracellular concentration of potassium ions (K^+) is relatively high, these ions tend to move out of the cell through open potassium channels. The movement is driven by a concentration gradient, or *chemical gradient*. ↩ p. 86 Similarly, a chemical gradient for sodium ions (Na^+) tends to drive those ions *into* the cell.

Electrical Gradients. Potassium ions leave the cytoplasm more rapidly than sodium ions enter because the plasma membrane is much more permeable to potassium than to sodium. As a result,

Figure 12–9 The Resting Potential is the Transmembrane Potential of an Undisturbed Cell.



the cytosol along the interior of the membrane exhibits a net loss of positive charges, leaving an excess of negatively charged proteins. At the same time, the extracellular fluid near the outer surface of the plasma membrane displays a net gain of positive charges. The positive and negative charges are separated by the plasma membrane, which restricts the free movement of ions. Whenever positive and negative ions are held apart, a *potential difference* arises.

We measure the size of a potential difference in millivolts (mV; thousandths of a volt). The resting potential varies widely, depending on the type of cell, but averages about 70 mV for many cells, including most neurons. We will use this value in our discussion, usually expressing it as –70 mV (**Figure 12–9**). The minus sign shows that the inner surface of the plasma membrane is negatively charged with respect to the exterior.

Positive and negative charges attract one another. If nothing separates them, oppositely charged ions will move together and eliminate the potential difference between them. A movement of charges to eliminate a potential difference is called a **current.** If a barrier (such as a plasma membrane) separates the oppositely charged ions, the amount of current depends on how easily the ions can cross the membrane. The **resistance** of the membrane is a measure of how much the membrane restricts ion movement. If the resistance is high, the current is very small, because few ions can cross the membrane. If the resistance is low, the current is very large, because ions flood across the membrane. The resistance of a plasma membrane can change as ion channels open or close. The changes result in currents that bring ions into or out of the cytoplasm.

The Electrochemical Gradient. Electrical gradients can either reinforce or oppose the chemical gradient for each ion. The **electrochemical gradient** for a specific ion is the sum of the chemical and electrical forces acting on that ion across the plasma membrane. The electrochemical gradients for K^+ and Na^+ are the primary factors affecting the resting potential of most cells, including neurons. Let's consider the forces acting on each ion independently.

The intracellular concentration of potassium ions is relatively high, whereas the extracellular concentration is very low. Therefore, the chemical gradient for potassium ions tends to drive them out of the cell, as indicated by the orange arrow in **Figure 12–10a.** However, the electrical gradient opposes this movement, because K^+ inside and outside of the cell are attracted to the negative charges on the inside of the plasma membrane, and repelled by the positive charges on the outside of the plasma membrane. The white arrow in **Figure 12–10a** indicates the size and direction of this electrical gradient. The chemical gradient is strong enough to overpower the electrical gradient, but the electrical gradient weakens the force driving K^+ out of the cell. The peach arrow represents the net driving force.

If the plasma membrane were freely permeable to K^+ but impermeable to other positively charged ions, potassium ions would continue to leave the cell until the electrical gradient (opposing the exit of K^+ from the cell) was as strong as the chemical gradient (driving K^+ out of the cell). The transmembrane potential at which there is no net movement of a particular ion across the plasma membrane is called the *equilibrium potential* for that ion. For potassium ions, this equilibrium occurs at a transmembrane potential of about –90 mV, as illustrated in **Figure 12–10b**. The resting membrane potential is typically –70 mV, a value close to the equilibrium potential for K^+. The difference is due primarily to Na^+ leaking continuously into the cell.

Tips & Tricks

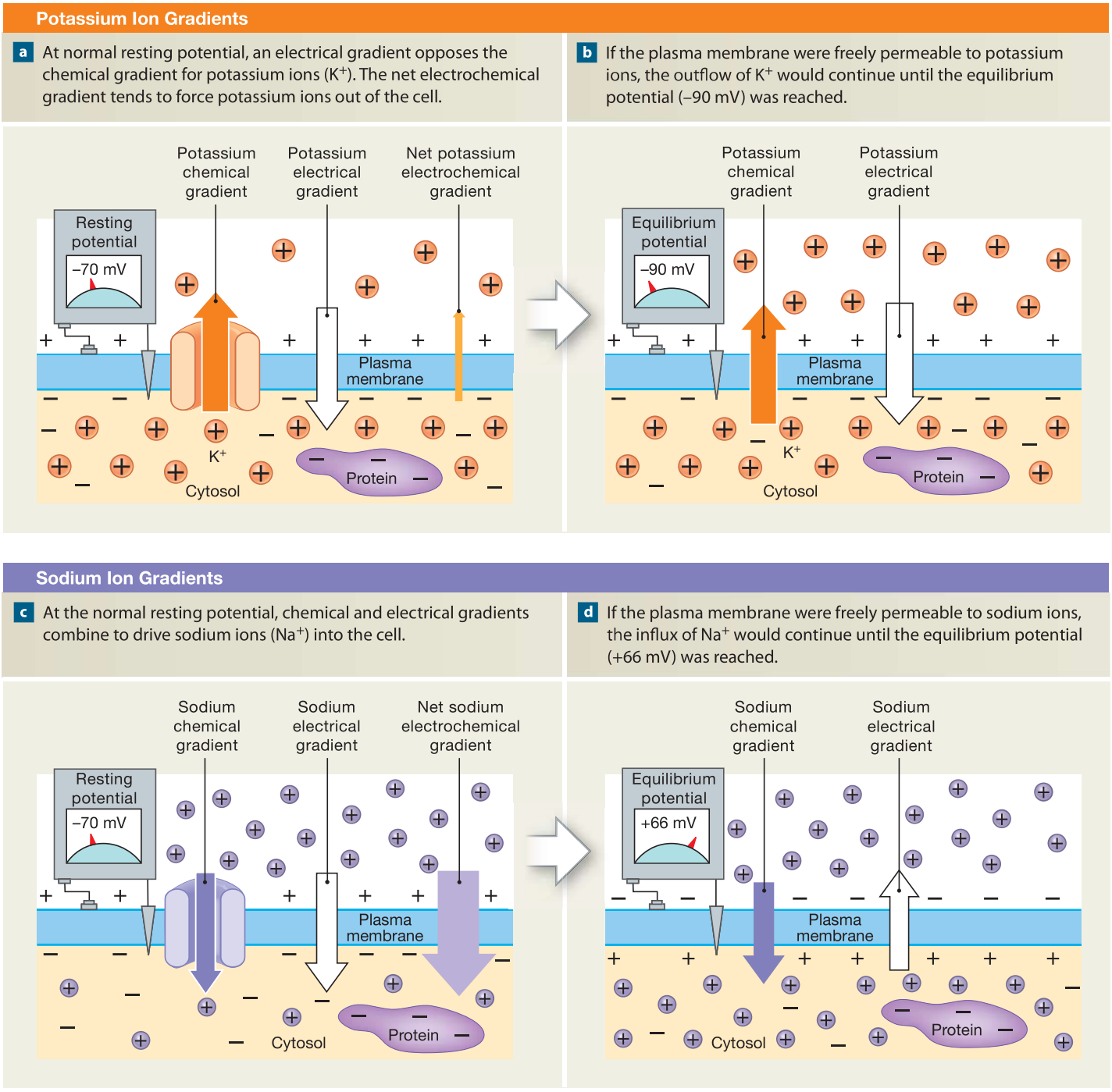
To remember the relative distribution of ions across the resting cell membrane, associate **N**egative with i**N**side and p**O**sitive with the **O**utside.

The sodium ion concentration is relatively high in the extracellular fluid, but inside the cell it is extremely low. As a result, there is a strong chemical gradient driving Na^+ into the cell (the black arrow in **Figure 12–10c**). In addition, the extracellular sodium ions are attracted by the excess of negative charges on the inner surface of the plasma membrane. The white arrow in **Figure 12–10c** shows the relative size and direction of this electrical gradient. Both electrical forces and chemical forces drive Na^+ into the cell, and the lavender arrow represents the net driving force.

If the plasma membrane were freely permeable to Na^+, these ions would continue to cross it until the interior of the cell contained enough excess positive charges to reverse the electrical gradient. In other words, ion movement would continue until the interior developed such a strongly positive charge that repulsion between the positive charges would prevent any further net movement of Na^+ into the cell. The equilibrium potential for Na^+ is approximately +66 mV, as shown in **Figure 12–10d**. The resting potential is nowhere near that value, because the resting membrane permeability to Na^+ is very low, and because ion pumps in the plasma membrane eject sodium ions as fast as they cross the membrane.

An electrochemical gradient is a form of *potential energy*. p. 96 Potential energy is stored energy—the energy of position, as exists in a stretched spring, a charged battery, or water behind a dam. Without a plasma membrane, diffusion would eliminate all electrochemical gradients. In effect, the plasma membrane acts like a dam across a river. Without the dam, water would simply respond to gravity and flow downstream, gradually losing energy. With the dam in place, even a small opening releases water under tremendous pressure. Similarly, any stimulus that increases the permeability of the plasma membrane to sodium or potassium

Figure 12–10 Electrochemical Gradients for Potassium and Sodium Ions.



ions produces sudden and dramatic ion movement. For example, a stimulus that opens sodium ion channels triggers a rush of Na^+ into the cell. Note that the nature of the stimulus does not determine the amount of ion movement: If the stimulus opens the door, the electrochemical gradient does the rest.

Active Forces across the Membrane: The Sodium–Potassium Exchange Pump

We can compare a cell to a leaky fishing boat loaded with tiny fish floating in the sea. The hull represents the plasma membrane; the fish, K^+; and the ocean water, Na^+. As the boat rumbles and rolls,

water comes in through the cracks, and fish swim out. If the boat is to stay afloat and the catch kept, we must pump the water out and recapture the lost fish.

Similarly, at the normal resting potential, the cell must bail out sodium ions that leak in and recapture potassium ions that leak out. The "bailing" takes place through the activity of an exchange pump powered by ATP. The ion pump involved is the carrier protein *sodium–potassium ATPase*. ↩ p. 92 This pump exchanges three intracellular sodium ions for two extracellular potassium ions. At the normal resting potential, this pump ejects sodium ions as quickly as they enter the cell. In this way, the activity of the exchange pump exactly balances the passive forces of diffusion, and the resting potential remains stable because the ionic concentration gradients are maintained.

Table 12–1 summarizes the important features of the resting potential.

Table 12–1 The Resting Potential

- Because the plasma membrane is highly permeable to potassium ions, the resting potential of approximately –70 mV is fairly close to –90 mV, the equilibrium potential for K^+.
- The electrochemical gradient for sodium ions is very large, but the membrane's permeability to these ions is very low. Consequently, Na^+ has only a small effect on the normal resting potential, making it just slightly less negative than the equilibrium potential for K^+.
- The sodium–potassium exchange pump ejects 3 Na^+ ions for every 2 K^+ ions that it brings into the cell. It serves to stabilize the resting potential when the ratio of Na^+ entry to K^+ loss through passive channels is 3:2.
- At the normal resting potential, these passive and active mechanisms are in balance. The resting potential varies widely with the type of cell. A typical neuron has a resting potential of approximately –70 mV.

Changes in the Transmembrane Potential

As noted previously, the resting potential is the transmembrane potential of an "undisturbed" cell. Recall that it exists because (1) the cytosol differs from extracellular fluid in chemical and ionic composition, and (2) the plasma membrane is selectively permeable. Yet cells are dynamic structures that continually modify their activities, either in response to external stimuli or to perform specific functions. The transmembrane potential is equally dynamic, rising or falling in response to temporary changes in membrane permeability. Those changes result from the opening or closing of specific membrane channels.

Membrane channels control the movement of ions across the plasma membrane. We will focus on the permeability of the membrane to sodium and potassium ions. These ions are the primary determinants of the transmembrane potential of many cell types, including neurons. Sodium and potassium ion channels are either passive or active.

Passive channels, or **leak channels,** are always open. However, their permeability can vary from moment to moment as the proteins that make up the channel change shape in response to local conditions. As noted earlier, leak channels are important in establishing the normal resting potential of the cell (**Figure 12–9**).

Plasma membranes also contain **active channels,** often called **gated channels,** which open or close in response to specific stimuli. Each gated channel can be in one of three states: (1) closed but capable of opening, (2) open (**activated**), or (3) closed and incapable of opening (**inactivated**).

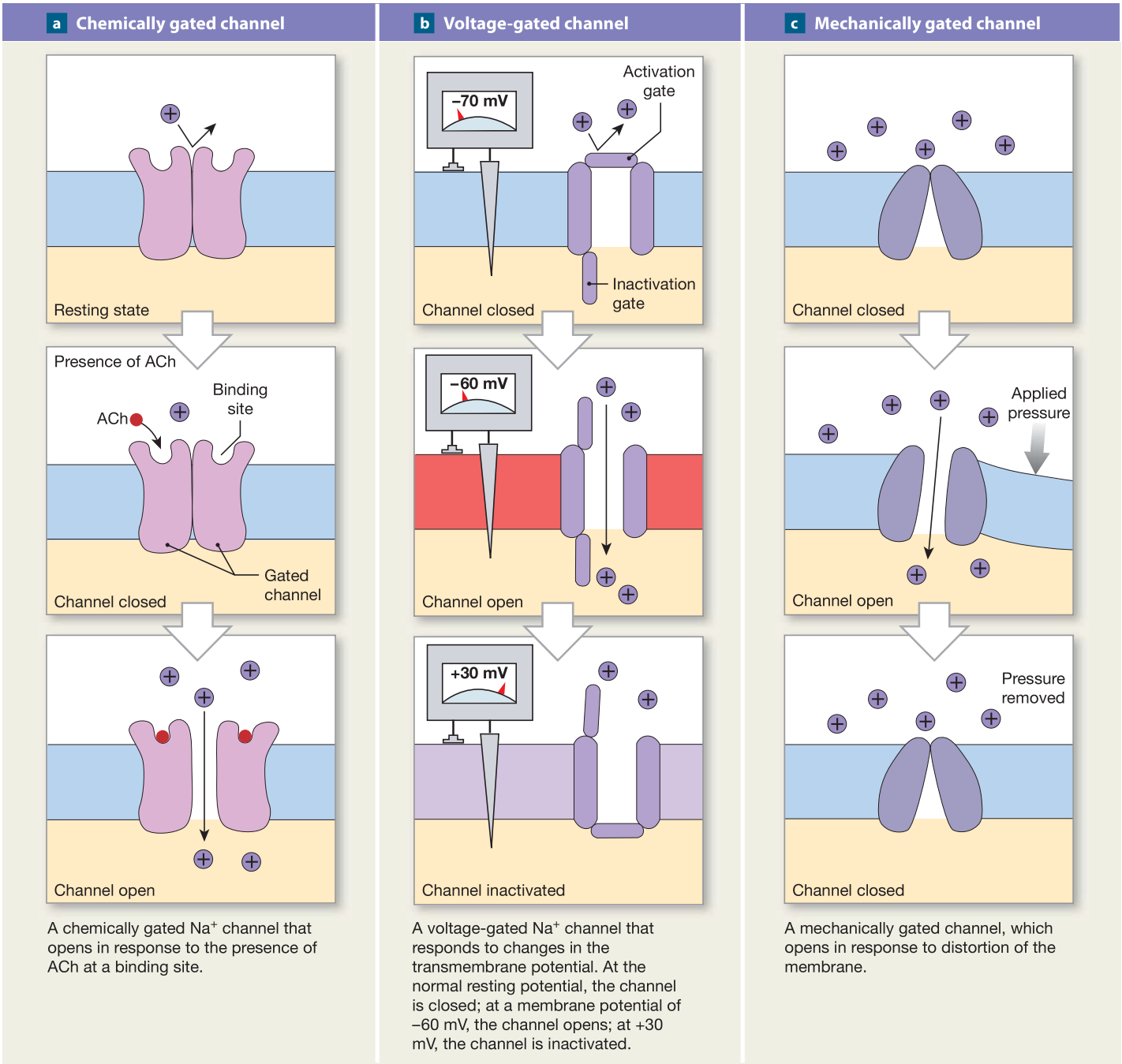
Three classes of gated channels exist: chemically gated channels, voltage-gated channels, and mechanically gated channels.

1. **Chemically gated channels** open or close when they bind specific chemicals (**Figure 12–11a**). The receptors that bind acetylcholine (ACh) at the neuromuscular junction are chemically gated channels. ↩ p. 293 Chemically gated channels are most abundant on the dendrites and cell body of a neuron, the areas where most synaptic communication occurs.
2. **Voltage-gated channels** open or close in response to changes in the transmembrane potential. They are characteristic of areas of **excitable membrane,** a membrane capable of generating and conducting an action potential. Examples of excitable membranes are the axons of unipolar and multipolar neurons, and the sarcolemma (including T tubules) of skeletal muscle fibers and cardiac muscle cells. ↩ pp. 292, 313 The most important voltage-gated channels, for our purposes, are voltage-gated sodium channels, potassium channels, and calcium channels. These sodium channels have two gates that function independently: an *activation gate* that opens on stimulation, letting sodium ions into the cell, and an *inactivation gate* that closes to stop the entry of sodium ions (**Figure 12–11b**).
3. **Mechanically gated channels** open or close in response to physical distortion of the membrane surface (**Figure 12–11c**). Such channels are important in sensory receptors that respond to touch, pressure, or vibration. We discuss these receptors in more detail in Chapter 15.

At the resting potential, most gated channels are closed. When gated channels open, the rate of ion movement across the plasma membrane increases, changing the transmembrane potential.

The distribution of membrane channels varies from one region of the plasma membrane to another, affecting how and where a cell responds to specific stimuli. For example, chemically gated sodium channels are widespread on the surfaces of a neuron, but voltage-gated sodium channels are most abundant on the axon, its branches, and the synaptic terminals. Mechanically gated channels are typically located only on the dendrites of sensory neurons. In later sections you will see how these differences in distribution affect the way the neurons function.

Figure 12–11 Gated Channels.



A chemically gated Na^+ channel that opens in response to the presence of ACh at a binding site.

A voltage-gated Na^+ channel that responds to changes in the transmembrane potential. At the normal resting potential, the channel is closed; at a membrane potential of −60 mV, the channel opens; at +30 mV, the channel is inactivated.

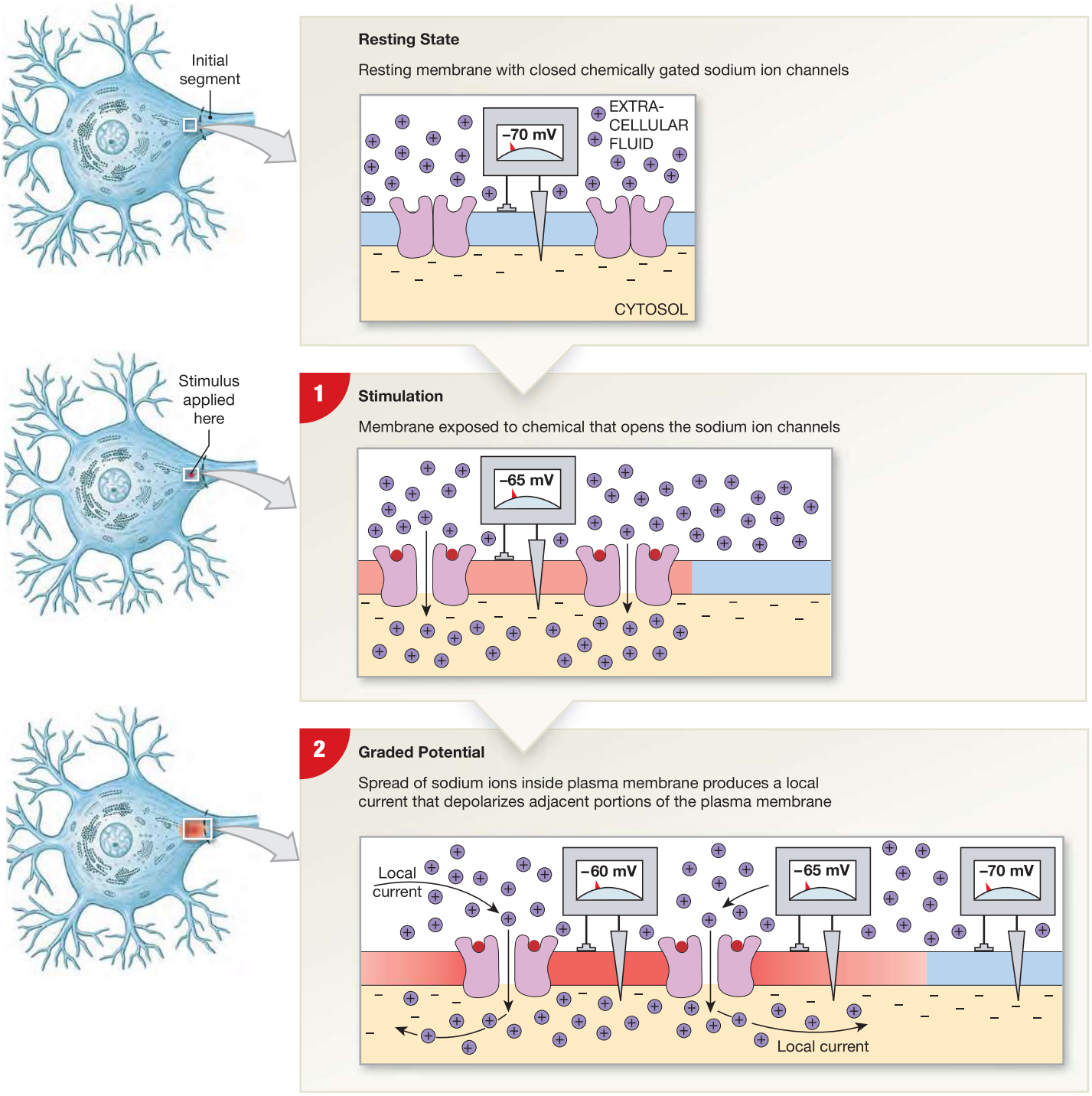
A mechanically gated channel, which opens in response to distortion of the membrane.

Graded Potentials

Graded potentials, or *local potentials*, are changes in the transmembrane potential that cannot spread far from the site of stimulation. Any stimulus that opens a gated channel produces a graded potential. **Figure 12–12** shows what happens when a resting membrane is exposed to a chemical that opens chemically gated sodium channels.

1 Sodium ions enter the cell and are attracted to the negative charges along the inner surface of the membrane. As these additional positive charges spread out, the transmembrane potential shifts toward 0 mV. Any shift from the resting potential toward a more positive potential is called a **depolarization.** Note that this term applies to changes in potential from −70 mV to smaller negative values (−65 mV,

Figure 12–12 Graded Potentials. The depolarization radiates in all directions away from the source of stimulation. For clarity, only gated channels are shown; leak channels are present, but are not responsible for the production of graded potentials. Color changes in the plasma membrane indicate that the resting potential has been disturbed and that the transmembrane potential is no longer –70 mV.



–45 mV, –10 mV), as well as to membrane potentials above 0 mV (+10 mV, +30 mV). In all these changes, the membrane potential becomes more positive.

2 As the plasma membrane depolarizes, sodium ions are released from its outer surface. These ions, along with other extracellular sodium ions, then move toward the open channels, replacing ions that have already entered the cell. This movement of positive charges parallel to the inner and outer surfaces of a membrane is called a **local current.**

In a graded potential, the degree of depolarization decreases with distance away from the stimulation site. Why? The depolarization lessens with distance because the cytosol offers considerable resistance to ion movement, and because some of the sodium ions entering the cell then move back out across the membrane through sodium leak channels. At some distance from the entry point, the effects on the transmembrane potential are undetectable.

The maximum change in the transmembrane potential is proportional to the size of the stimulus, which determines the number of open sodium channels. The more open channels, the more sodium ions enter the cell, the greater the membrane area affected, and the greater the degree of depolarization.

When a chemical stimulus is removed and normal membrane permeability is restored, the transmembrane potential soon returns to resting levels. The process of restoring the normal resting potential after depolarization is called **repolarization** (Figure 12–13). Repolarization typically involves a combination of ion movement through membrane channels and the activities of ion pumps, especially the sodium–potassium exchange pump.

What happens to the transmembrane potential when a gated potassium channel opens? Opening a gated potassium channel has the opposite effect from opening a gated sodium channel. The rate of potassium outflow increases, and the interior of the cell loses positive ions. In other words, the inside of the cell becomes more negative. The loss of positive ions produces **hyperpolarization,** an increase in the negativity of the resting potential, for example, from –70 mV to perhaps –80 mV or more. Again, a local current distributes the effect to adjacent portions of the plasma membrane, and the effect decreases with distance from the open channel or channels.

Graded potentials occur in the membranes of many types of cells—not just nerve and muscle cells, but epithelial cells, gland cells, adipocytes, and a variety of sensory receptors. Graded potentials often trigger specific cell functions. For example, a graded potential at the surface of a gland cell may trigger the exocytosis of secretory vesicles. Similarly, at a neuromuscular junction, the graded depolarization of the motor end plate by ACh triggers an action potential in adjacent portions of the sarcolemma. The motor end plate supports graded potentials, but the rest of the sarcolemma consists of excitable membrane. These areas of membrane are different because they have different gated channels. Table 12–2 summarizes the basic characteristics of graded potentials.

Table 12–2 Graded Potentials

Graded potentials, whether depolarizing or hyperpolarizing, share four basic characteristics:

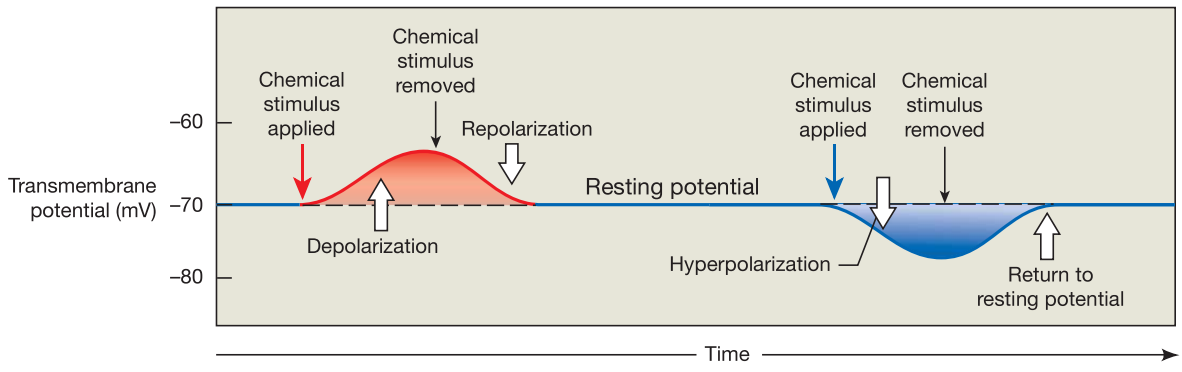
1. The transmembrane potential is most changed at the site of stimulation, and the effect decreases with distance.
2. The effect spreads passively, due to local currents.
3. The graded change in transmembrane potential may involve either depolarization or hyperpolarization. The properties and distribution of the membrane channels involved determine the nature of the change. For example, in a resting membrane, the opening of sodium channels causes depolarization, whereas the opening of potassium channels causes hyperpolarization. That is, the change in transmembrane potential reflects whether positive charges enter or leave the cell.
4. The stronger the stimulus, the greater is the change in the transmembrane potential and the larger is the area affected.

Checkpoint

12. **Define the resting potential.**
13. **What effect would a chemical that blocks the voltage-gated sodium channels in neuron plasma membranes have on a neuron's ability to depolarize?**
14. **What effect would decreasing the concentration of extracellular potassium ions have on the transmembrane potential of a neuron?**

See the blue Answers tab at the back of the book.

Figure 12–13 Depolarization, Repolarization, and Hyperpolarization.



12-5 An action potential is an electrical event

Action potentials are propagated changes in the transmembrane potential that, once initiated, affect an entire excitable membrane. These electrical events are also known as **nerve impulses.** Recall that voltage-gated sodium channels are abundant on the axon, its branches, and its synaptic terminals. The first step in generating an action potential is the opening of voltage-gated sodium ion channels at one site, usually the initial segment of the axon. The movement of sodium ions into the axon depolarizes adjacent sites, triggering the opening of additional voltage-gated channels. The result is a chain reaction that spreads across the surface of the membrane like a line of falling dominoes. In this way, the action potential is propagated along the length of the axon, ultimately reaching the synaptic terminals.

The All-or-None Principle

The transmembrane potential at which an action potential begins is called the **threshold.** Threshold for an axon is typically between –60 mV and –55 mV, corresponding to a depolarization of 10 to 15 mV. A stimulus that shifts the resting membrane potential from –70 mV to –62 mV will not produce an action potential, only a graded depolarization. When such a stimulus is removed, the transmembrane potential returns to the resting level. The depolarization of the initial segment of the axon is caused by local currents resulting from the graded depolarization of the axon hillock.

The initial depolarization acts like pressure on the trigger of a gun. If you apply a slight pressure, the gun does not fire. It fires only when you apply a certain minimum pressure to the trigger. Once the pressure on the trigger reaches this threshold, the firing pin drops and the gun discharges. At that point, it no longer matters whether you applied the pressure gradually or suddenly or whether you moved just one finger or clenched your entire hand. The speed and range of the bullet that leaves the gun do not change, regardless of the forces that you applied to the trigger.

In the case of an axon or another area of excitable membrane, a graded depolarization is similar to the pressure on the trigger, and the action potential is like the firing of the gun. All stimuli that bring the membrane to threshold generate identical action potentials. In other words, the properties of the action potential are independent of the relative strength of the depolarizing stimulus, as long as that stimulus exceeds the threshold. This concept is the **all-or-none principle,** because a given stimulus either triggers a typical action potential, or none at all. The all-or-none principle applies to all excitable membranes.

Now let's take a closer look at how action potentials are generated and propagated. Generation and propagation are closely related concepts, in terms of both time and space: An action potential must be generated at one site before it can be propagated away from that site.

Generation of Action Potentials

Spotlight Figure 12–14 diagrams the steps involved in generating an action potential from the resting state. At the normal resting potential, the activation gates of the voltage-gated sodium channels are closed. The steps are as follows: (1) depolarization to threshold, (2) activation of sodium channels and rapid depolarization, (3) inactivation of sodium channels and activation of potassium channels, and (4) closing of potassium channels.

The Refractory Period

The membrane does not respond normally to additional depolarizing stimuli from the time an action potential begins until the normal resting potential has stabilized. This period is known as the **refractory period** of the membrane. The membrane cannot respond to further stimulation from the moment the voltage-gated sodium channels open at threshold until sodium channel inactivation ends, because all the voltage-gated sodium channels either are already open or are inactivated. This first part of the refractory period, called the **absolute refractory period,** lasts 0.4–1.0 msec. The smaller the axon diameter, the longer the duration. The **relative refractory period** begins when the sodium channels regain their normal resting condition, and continues until the transmembrane potential stabilizes at resting levels. Another action potential can occur in this period if the membrane is sufficiently depolarized. That depolarization, however, requires a larger-than-normal stimulus, because (1) the local current must deliver enough Na^+ to counteract the exit of positively charged K^+ through open voltage-gated K^+ channels, and (2) the membrane is hyperpolarized to some degree through most of the relative refractory period.

Tips & Tricks

Flushing a toilet provides a useful analogy for an action potential. Nothing happens while you press the handle, until the water starts to flow (threshold is reached). After that, the amount of water that is released is independent of how hard or quickly you pressed the handle (all-or-none principle). Finally, you cannot flush the toilet again until the tank refills (refractory period).

The Role of the Sodium–Potassium Exchange Pump

In an action potential, depolarization results from the influx of Na^+, and repolarization involves the loss of K^+. Over time, the sodium–potassium exchange pump returns intracellular and

extracellular ion concentrations to prestimulation levels. Compared with the total number of ions inside and outside the cell, however, the number involved in a single action potential is insignificant. Tens of thousands of action potentials can occur before intracellular ion concentrations change enough to disrupt the entire mechanism. For this reason, the exchange pump is not essential to any single action potential.

However, a maximally stimulated neuron can generate action potentials at a rate of 1000 per second. Under these circumstances, the exchange pump is needed to keep ion concentrations within acceptable limits over a prolonged period. The sodium– potassium exchange pump requires energy in the form of ATP. Each time the pump exchanges two extracellular potassium ions for three intracellular sodium ions, one molecule of ATP is broken down to ADP. Recall that the transmembrane protein of the exchange pump is *sodium–potassium ATPase*, which gets the energy to pump ions by splitting a phosphate group from a molecule of ATP, forming ADP. If the cell runs out of ATP, or if a metabolic poison inactivates sodium–potassium ATPase, the neuron will soon stop functioning.

Propagation of Action Potentials

The events that generate an action potential take place in a small portion of the total membrane surface. But unlike graded potentials, which diminish rapidly with distance, action potentials spread along the entire excitable membrane. To understand how this happens, imagine that you are standing by the doors of a movie theater at the start of a long line. Everyone is waiting for the doors to open. The manager steps outside and says to you, "Let everyone know that we're opening in 15 minutes." How would you spread the news?

If you treated the line as an inexcitable membrane, you would shout, "The doors open in 15 minutes!" as loudly as you could. The closest people in the line would hear the news very clearly, but those farther away might not hear the entire message, and those at the end of the line might not hear you at all.

If, on the other hand, you treated the crowd as an excitable membrane, you would tell the message to the next person in line, with instructions to pass it on. In that way, the message would travel along the line undiminished, until everyone had heard the news. Such a message "moves" as each person repeats it to someone else. Distance is not a factor, and the line can contain 50 people or 5000.

Having each person repeat the message is comparable to the way an action potential spreads along an excitable membrane. An action potential (message) is relayed from one location to another in a series of steps. At each step, the message is repeated. Because the same events take place over and over, the term **propagation** is preferable to the term *conduction*, which suggests a flow of charge similar to that in a conductor such as a copper wire. (In fact, compared to wires, axons are poor conductors of electricity.) Action potentials may travel along an axon by continuous propagation (unmyelinated axons) or by saltatory propagation (myelinated axons).

Continuous Propagation

In an unmyelinated axon, an action potential moves along by **continuous propagation** (**Figure 12–15**). For convenience, think of the membrane as a series of adjacent segments.

The action potential begins at the axon's initial segment. For a brief moment at the peak of the action potential, the transmembrane potential becomes positive rather than negative (1).

A local current then develops as sodium ions begin moving in the cytosol and the extracellular fluid (2). The local current spreads in all directions, depolarizing adjacent portions of the membrane. (The axon hillock cannot respond with an action potential because, like the rest of the cell body, it lacks voltage-gated sodium channels.)

The process then continues in a chain reaction (3 and 4). Each time a local current develops, the action potential moves forward, but not backward, because the previous segment of the axon is still in the absolute refractory period. As a result, an action potential always proceeds away from the site of generation and cannot reverse direction. Eventually, the most distant portions of the plasma membrane are affected.

As in our "movie line" model, the message is relayed from one location to another. At each step along the way, the message is retold, so distance has no effect on the process. The action potential reaching the synaptic terminal is identical to the one generated at the initial segment. The net effect is the same as if a single action potential had traveled across the surface of the membrane.

In continuous propagation, an action potential appears to move across the surface of the membrane in a series of tiny steps. Even though the events at any one location take only about a millisecond, they must be repeated at each step along the way. Continuous propagation along unmyelinated axons occurs at a speed of about 1 meter per second (approximately 2 mph). For a second action potential to occur at the same site, a second stimulus must be applied.

Tips & Tricks

The "wave" performed by fans in a football stadium illustrates the continuous propagation of an action potential. The "wave" moves, but the people remain in place.

Saltatory Propagation

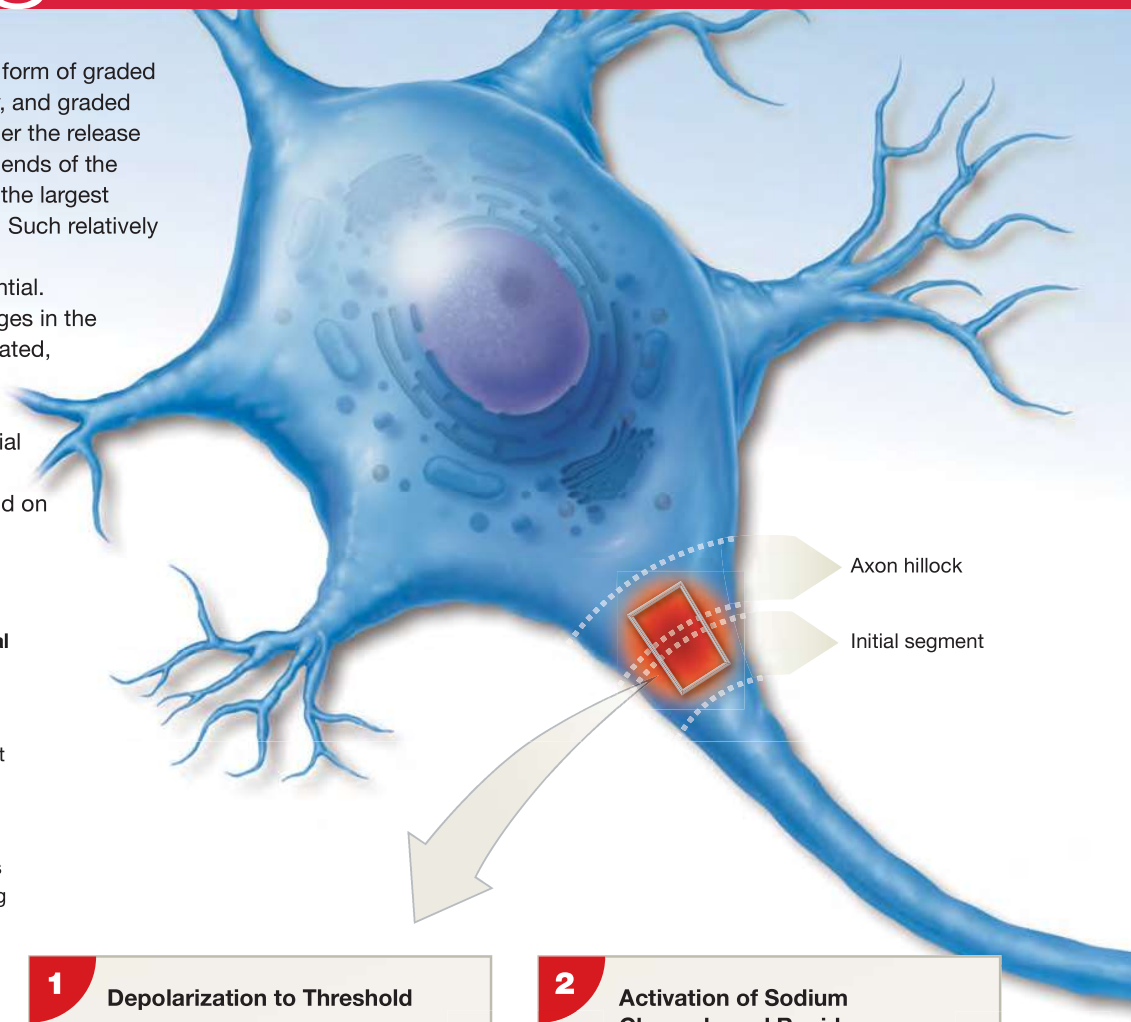
Saltatory propagation (*saltare*, leaping) in the CNS and PNS carries action potentials along an axon much more rapidly than does continuous propagation. To get the general idea, let's return

Spotlight

Figure 12–14

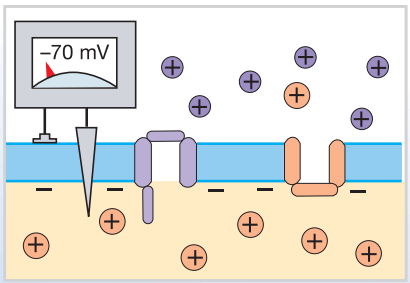
Generation of an Action Potential

Each neuron receives information in the form of graded potentials on its dendrites and cell body, and graded potentials at the synaptic terminals trigger the release of neurotransmitters. However, the two ends of the neuron may be a meter apart, and even the largest graded potentials affect only a tiny area. Such relatively long-range communication requires a different mechanism—the action potential. **Action potentials** are propagated changes in the transmembrane potential that, once initiated, affect an entire excitable membrane. Whereas the resting potential depends on leak channels and the graded potential we considered depends on chemically gated channels, action potentials depend on voltage-gated channels.



Steps in the formation of an action potential at the initial segment of an axon. The first step is a graded depolarizaton caused by the opening of chemically gated sodium ion channels, usually at the axon hillock. Note that when illustrating action potentials, we can ignore both the leak channels and the chemically gated channels, because their properties do not change. The membrane colors in steps 1-4 match the colors of the line graph showing transmembrane potential changes.

Resting Potential



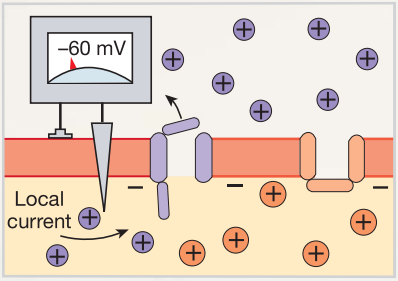
The axolemma contains both voltage-gated sodium channels and voltage-gated potassium channels that are closed when the membrane is at the resting potential.

KEY

⊕ = Sodium ion

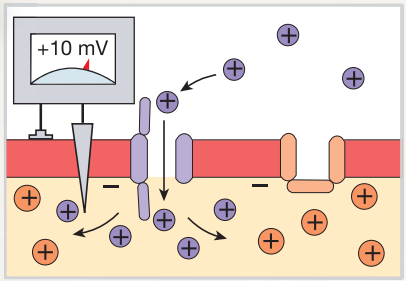
⊕ = Potassium ion

1 Depolarization to Threshold

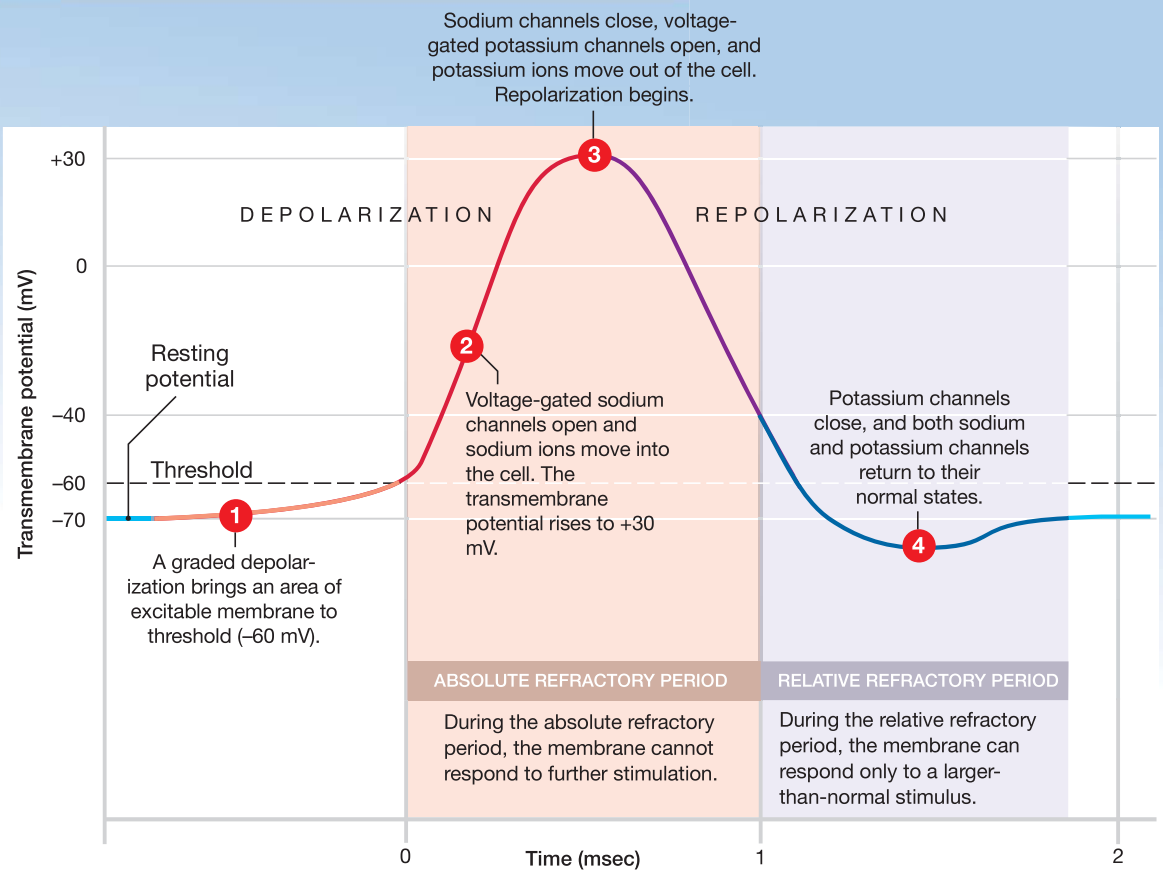


The stimulus that initiates an action potential is a graded depolarization large enough to open voltage-gated sodium channels. The opening of the channels occurs at a transmembrane potential known as the threshold.

2 Activation of Sodium Channels and Rapid Depolarization

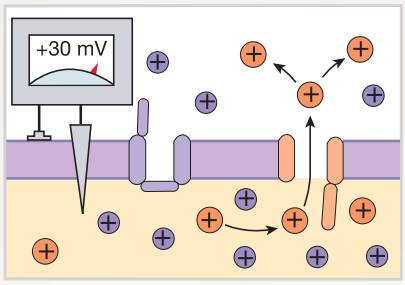


When the sodium channel activation gates open, the plasma membrane becomes much more permeable to Na^+. Driven by the large electrochemical gradient, sodium ions rush into the cytoplasm, and rapid depolarization occurs. The inner membrane surface now contains more positive ions than negative ones, and the transmembrane potential has changed from –60 mV to a positive value.



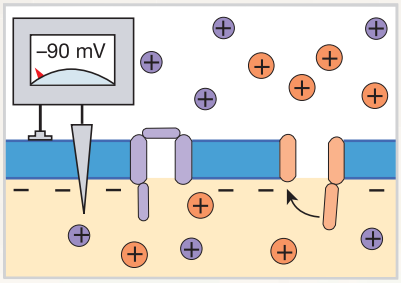
Changes in the transmembrane potential at one location during the generation of an action potential. The circled numbers in the graph correspond to the steps illustrated below.

3 **Inactivation of Sodium Channels and Activation of Potassium Channels**



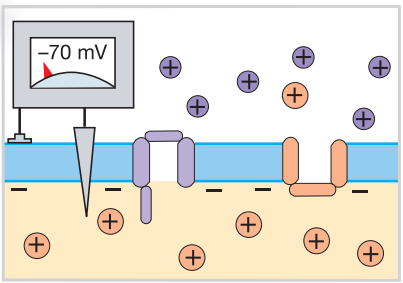
As the transmembrane potential approaches +30 mV, the inactivation gates of the voltage-gated sodium channels close. This step is known as **sodium channel inactivation**, and it coincides with the opening of voltage-gated potassium channels. Positively charged potassium ions move out of the cytosol, shifting the transmembrane potential back toward resting levels. Repolarization now begins.

4 **Closing of Potassium Channels**



The voltage-gated sodium channels remain inactivated until the membrane has repolarized to near threshold levels. At this time, they regain their normal status: closed but capable of opening. The voltage-gated potassium channels begin closing as the membrane reaches the normal resting potential (about –70 mV). Until all of these potassium channels have closed, potassium ions continue to leave the cell. This produces a brief hyperpolarization.

Resting Potential



As the voltage-gated potassium channels close, the transmembrane potential returns to normal resting levels. The action potential is now over, and the membrane is once again at the resting potential.

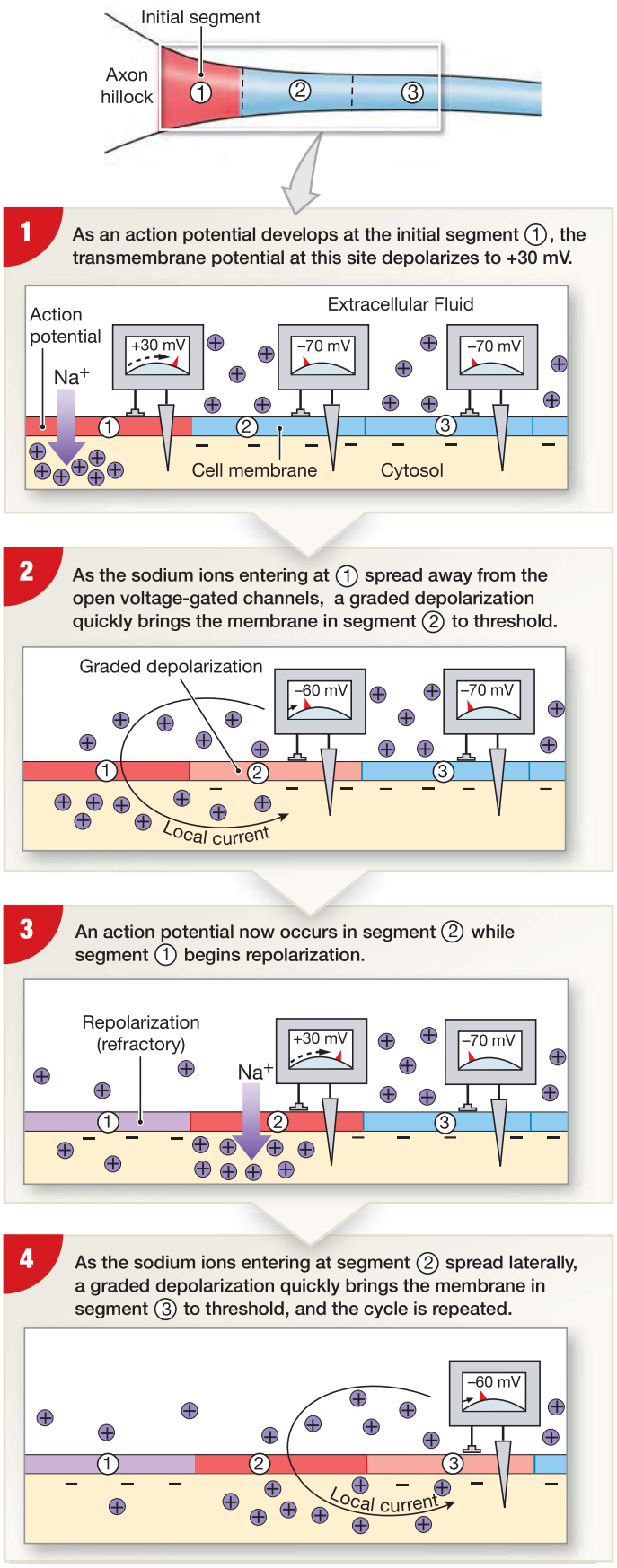


Figure 12–15 **Continuous Propagation of an Action Potential along an Unmyelinated Axon.**

to the line in front of the movie theater, and assume that it takes 1 second to relay the message to another person. In a model of continuous propagation, the people are jammed together. In 4 seconds, four people would hear the news, and the message would move perhaps 2 meters along the line. In a model of saltatory propagation, in contrast, the people in the line are spaced 5 meters apart. So after 4 seconds the same message would move 20 meters.

In a myelinated axon, the "people" are the nodes, and the spaces between them are the internodes wrapped in myelin (**Figure 12–5b** and **12–6a**). Continuous propagation cannot occur along a myelinated axon, because myelin increases resistance to the flow of ions across the membrane. Ions can readily cross the plasma membrane only at the nodes. As a result, only the nodes can respond to a depolarizing stimulus.

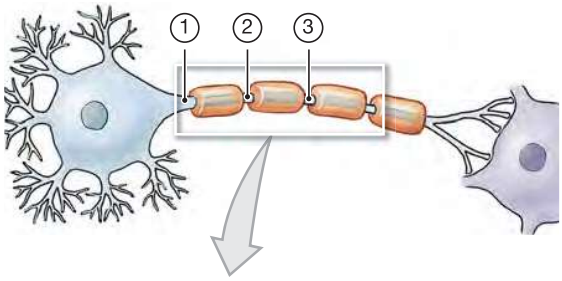
When an action potential appears at the initial segment of a myelinated axon, the local current skips the internodes and depolarizes the closest node to threshold (**Figure 12–16**). Because the nodes may be 1–2 mm apart in a large myelinated axon, the action potential "jumps" from node to node rather than moving along the axon in a series of tiny steps. In addition to being faster, saltatory propagation uses proportionately less energy, because less surface area is involved and fewer sodium ions must be pumped out of the cytoplasm.

Table 12–3 reviews the key differences between graded potentials and action potentials.

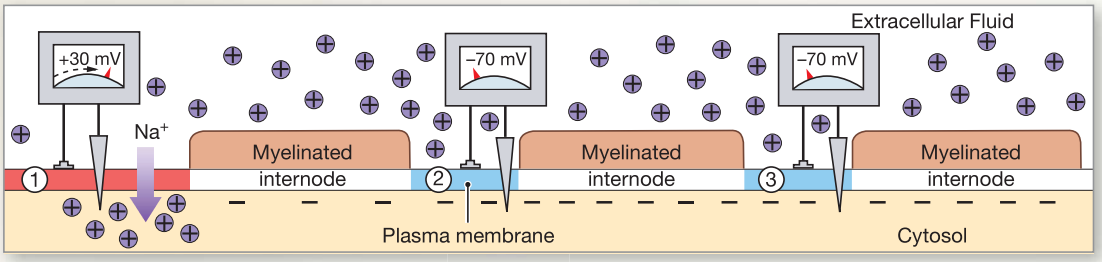
Table 12–3 A Comparison of Graded Potentials and Action Potentials

Graded Potentials	Action Potentials
Depolarizing or hyperpolarizing	Always depolarizing
No threshold value	Depolarization to threshold must occur before action potential begins
Amount of depolarization or hyperpolarization depends on intensity of stimulus	All-or-none; all stimuli that exceed threshold produce identical action potentials
Passive spread from site of stimulation	Action potential at one site depolarizes adjacent sites to threshold
Effect on membrane potential decreases with distance from stimulation site	Propagated along entire membrane surface without decrease in strength
No refractory period	Refractory period occurs
Occur in most plasma membranes	Occur only in excitable membranes of specialized cells such as neurons and muscle cells

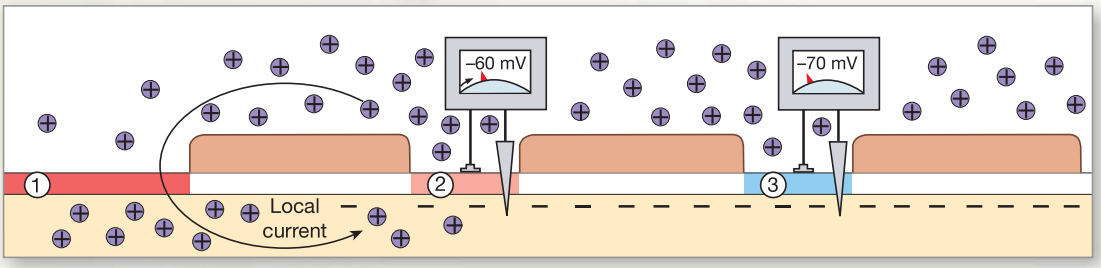
Figure 12–16 Saltatory Propagation along a Myelinated Axon. This process will continue along the entire length of the axon.



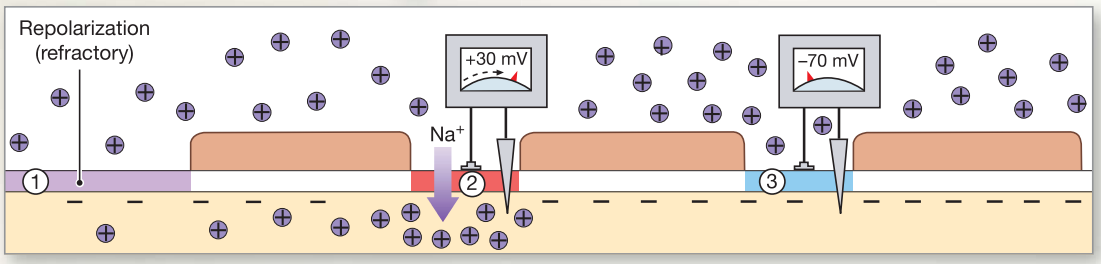
1 An action potential has occurred at the initial segment (1).



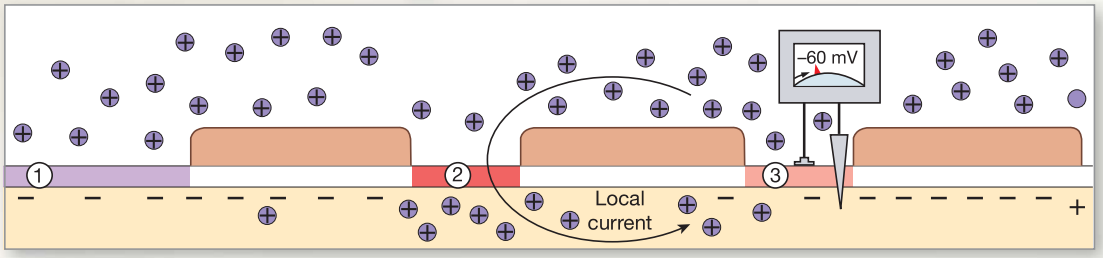
2 A local current produces a graded depolarization that brings the axolemma at the next node to threshold.



3 An action potential develops at node (2).



4 A local current produces a graded depolarization that brings the axolemma at node (3) to threshold.



Checkpoint

15. **Define action potential.**
16. **List the steps involved in the generation and propagation of an action potential.**

See the blue Answers tab at the back of the book.

12-6 Axon diameter, in addition to myelin, affects propagation speed

As we have seen, myelin greatly increases the propagation speed of action potentials. The diameter of the axon also affects the propagation speed, although less dramatically. Axon diameter is important because ions must move through the cytosol in order to depolarize adjacent portions of the plasma membrane. Cytosol offers much less resistance to ion movement than does the plasma membrane. In this instance, an axon behaves like an electrical cable: The larger the diameter, the lower the resistance. (That is why motors with large current demands, such as the starter on a car, an electric stove, or a big air conditioner, use such thick wires.)

We can classify axons into three groups according to the relationships among the diameter, myelination, and propagation speed:

1. **Type A fibers** are the largest myelinated axons, with diameters ranging from 4 to 20 μm. These fibers carry action potentials at speeds of up to 120 meters per second, or 268 mph.
2. **Type B fibers** are smaller myelinated axons, with diameters of 2–4 μm. Their propagation speeds average around 18 meters per second, or roughly 40 mph.
3. **Type C fibers** are unmyelinated and less than 2 μm in diameter. These axons propagate action potentials at the leisurely pace of 1 meter per second, or a mere 2 mph.

The advantage of myelin becomes clear when you compare Type C to Type A fibers and note that the diameter increases tenfold but the propagation speed increases 120 times.

Type A fibers carry sensory information about position, balance, and delicate touch and pressure sensations from the skin surface to the CNS. The motor neurons that control skeletal muscles also send their commands over large, myelinated Type A axons.

Type B fibers and Type C fibers carry information to and from the CNS. They deliver temperature, pain, and general touch and pressure sensations. They also carry instructions to smooth muscle, cardiac muscle, glands, and other peripheral effectors.

Why isn't every axon in the nervous system large and myelinated? The most likely reason is that it would be physically impossible. If all sensory information were carried by large Type A fibers, your peripheral nerves would be the size of garden hoses, and your spinal cord would be the diameter of a garbage can. Instead, only about one-third of all axons carrying sensory information are myelinated, and most sensory information arrives over slender Type C fibers.

In essence, information transfer in the nervous system represents a compromise between conduction time and available space. Messages are routed according to priority: Urgent news—sensory information about things that threaten survival and motor commands that prevent injury—travels over Type A fibers (the equivalent of instant messaging). Less urgent sensory information and motor commands are relayed by Type B fibers (e-mail) or Type C fibers (regular "snail mail").

Checkpoint

17. **What is the relationship between myelin and the propagation speed of action potentials?**
18. **Which of the following axons is myelinated: one that propagates action potentials at 50 meters per second, or one that carries them at 1 meter per second?**

See the blue Answers tab at the back of the book.

12-7 At synapses, communication occurs among neurons or between neurons and other cells

In the nervous system, messages move from one location to another in the form of action potentials (nerve impulses) along axons. To be effective, a message must be not only propagated along an axon but also transferred in some way to another cell. This transfer takes place at synapses.

Synaptic Activity

At a synapse between two neurons, the nerve impulse passes from the **presynaptic neuron** to the **postsynaptic neuron.** Synapses may also involve other types of postsynaptic cells. For example, the neuromuscular junction is a synapse where the postsynaptic cell is a skeletal muscle fiber. Now let's take a closer look at the ways that synapses work.

General Properties of Synapses

A synapse may be *electrical*, with direct physical contact between the cells, or *chemical*, involving a neurotransmitter.

Electrical Synapses

At **electrical synapses,** the presynaptic and postsynaptic membranes are locked together at gap junctions (**Figure 4–2**, p. 112). The lipid portions of opposing membranes, separated by only 2 nm, are held in position by binding between integral

membrane proteins called *connexons*. These proteins form pores that permit ions to pass between the cells. Because the two cells are linked in this way, changes in the transmembrane potential of one cell produce local currents that affect the other cell as if the two shared a common membrane. As a result, an electrical synapse propagates action potentials quickly and efficiently from one cell to the next.

Electrical synapses are extremely rare in both the CNS and PNS. They occur in some areas of the brain, including the *vestibular nuclei*, the eye, and in at least one pair of PNS ganglia (the *ciliary ganglia*).

Chemical Synapses

The situation at a **chemical synapse** is far more changeable than that at an electrical synapse, because the cells are not directly coupled. For example, an action potential that reaches an electrical synapse is *always* propagated to the next cell. But at a chemical synapse, an arriving action potential *may or may not* release enough neurotransmitter to bring the postsynaptic neuron to threshold. In addition, other factors may intervene and make the postsynaptic cell more or less sensitive to arriving stimuli. In essence, the postsynaptic cell at a chemical synapse is not a slave to the presynaptic neuron, and its activity can be adjusted, or "tuned," by a variety of factors.

Chemical synapses are by far the most abundant type of synapse. Most synapses between neurons, and all communications between neurons and other types of cells, involve chemical synapses. Normally, communication across a chemical synapse takes place in only one direction: from the presynaptic membrane to the postsynaptic membrane.

Acetylcholine (ACh) is the neurotransmitter that has received the most attention, but there are other important chemical transmitters. Based on their effects on postsynaptic membranes, neurotransmitters are often classified as excitatory or inhibitory. **Excitatory neurotransmitters** cause depolarization and promote the generation of action potentials; whereas **inhibitory neurotransmitters** cause hyperpolarization and suppress the generation of action potentials.

This classification is useful, but not always precise. For example, acetylcholine typically produces a depolarization in the postsynaptic membrane, but acetylcholine released at neuromuscular junctions in the heart has an inhibitory effect, producing a transient hyperpolarization of the postsynaptic membrane. This situation highlights an important aspect of neurotransmitter function: *The effect of a neurotransmitter on the postsynaptic membrane depends on the properties of the receptor, not on the nature of the neurotransmitter*.

Let's continue our discussion of chemical synapses with a look at a synapse that releases the neurotransmitter **acetylcholine (ACh).** Then we will introduce other important neurotransmitters that you will encounter in later chapters.

Cholinergic Synapses

Synapses that release ACh are known as **cholinergic synapses.** The neuromuscular junction is an example of a cholinergic synapse. ↩ p. 292 ACh is the most widespread (and best-studied) neurotransmitter. It is released (1) at all neuromuscular junctions involving skeletal muscle fibers, (2) at many synapses in the CNS, (3) at all neuron-to-neuron synapses in the PNS, and (4) at all neuromuscular and neuroglandular junctions in the parasympathetic division of the ANS.

At a cholinergic synapse between two neurons, the presynaptic and postsynaptic membranes are separated by a synaptic cleft that averages 20 nm (0.02 μm) in width. Most of the ACh in the synaptic terminal is packaged in synaptic vesicles, each containing several thousand molecules of the neurotransmitter. A single synaptic terminal may contain a million such vesicles.

Tips & Tricks

Cholinergic synapses are so named because the neurotransmitter involved is acetyl***choli***ne.

Events at a Cholinergic Synapse

Figure 12–17 diagrams the events that take place at a cholinergic synapse between neurons after an action potential arrives at a synaptic terminal. For convenience, we will assume that this synapse is adjacent to the initial segment of the axon, an arrangement that is easy to illustrate.

1 ***An Action Potential Arrives and Depolarizes the Synaptic Terminal.*** The normal stimulus for neurotransmitter release is the depolarization of the synaptic terminal by the arrival of an action potential.

2 ***Extracellular Calcium Ions Enter the Synaptic Terminal, Triggering the Exocytosis of ACh***. The depolarization of the synaptic terminal briefly opens its voltage-gated calcium channels, allowing calcium ions to rush in. Their arrival triggers exocytosis of ACh into the synaptic cleft. The ACh is released in packets of roughly 3000 molecules, the average number of ACh molecules in a single vesicle. ACh release stops very soon, because active transport mechanisms rapidly remove the calcium ions from the terminal cytoplasm. These ions are either pumped out of the cell or transferred into mitochondria, vesicles, or the endoplasmic reticulum.

3 ***ACh Binds to Receptors and Depolarizes the Postsynaptic Membrane.*** ACh diffuses across the synaptic cleft toward receptors on the postsynaptic membrane. These receptors are chemically gated ion channels. The primary response is an increased permeability to Na^+, producing a depolarization in the postsynaptic membrane that lasts about 20 msec. (These cation channels also let potassium ions out of the cell, but because sodium ions are driven by a much stronger

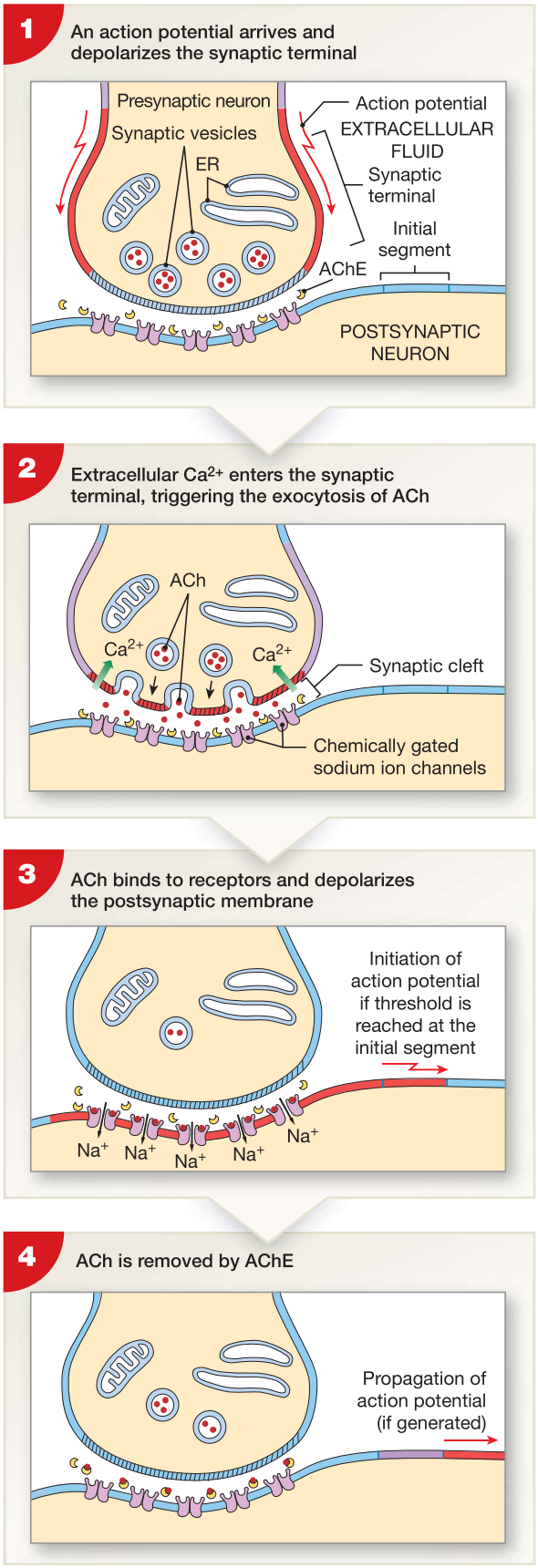


Figure 12–17 Events in the Functioning of a Cholinergic Synapse.

electrochemical gradient, the net effect is a slight depolarization of the postsynaptic membrane.)

This depolarization is a graded potential. The greater the amount of ACh released at the presynaptic membrane, the greater the number of open cation channels in the postsynaptic membrane, and so the larger the depolarization. If the depolarization brings an adjacent area of excitable membrane (such as the initial segment of an axon) to threshold, an action potential appears in the postsynaptic neuron.

4 ***ACh Is Removed by AChE.*** The neurotransmitter's effects on the postsynaptic membrane are temporary, because the synaptic cleft and the postsynaptic membrane contain the enzyme *acetylcholinesterase* (*AChE*, or *cholinesterase*). Roughly half of the ACh released at the presynaptic membrane is broken down before it reaches receptors on the postsynaptic membrane. ACh molecules that bind to receptor sites are generally broken down within 20 msec of their arrival.

AChE breaks down molecules of ACh (by hydrolysis) into **acetate** and **choline.** The choline is actively absorbed by the synaptic terminal and is used to synthesize more ACh, using acetate provided by *coenzyme A (CoA)*. (Recall from Chapter 2 that coenzymes derived from vitamins are required in many enzymatic reactions. ↩ p. 54) Acetate diffusing away from the synapse can be absorbed and metabolized by the postsynaptic cell or by other cells and tissues.

Table 12–4 summarizes the events that occur at a cholinergic synapse.

Synaptic Delay

A **synaptic delay** of 0.2–0.5 msec occurs between the arrival of the action potential at the synaptic terminal and the effect on the postsynaptic membrane. Most of that delay reflects the time involved in calcium influx and neurotransmitter release, not in the neurotransmitter's diffusion—the synaptic cleft is narrow, and neurotransmitters can diffuse across it in very little time.

Although a delay of 0.5 msec is not very long, in that time an action potential may travel more than 7 cm (about 3 in.) along a myelinated axon. When information is being passed along a chain of interneurons in the CNS, the cumulative synaptic delay may exceed the propagation time along the axons. This is why reflexes are important for survival—they involve only a few synapses and thus provide rapid and automatic responses to stimuli. The fewer synapses involved, the shorter the total synaptic delay and the faster the response. The fastest reflexes have just one synapse, with a sensory neuron directly controlling a motor neuron. The muscle spindle reflexes, discussed in Chapter 13, are arranged in this way.

Table 12–4 Synaptic Activity

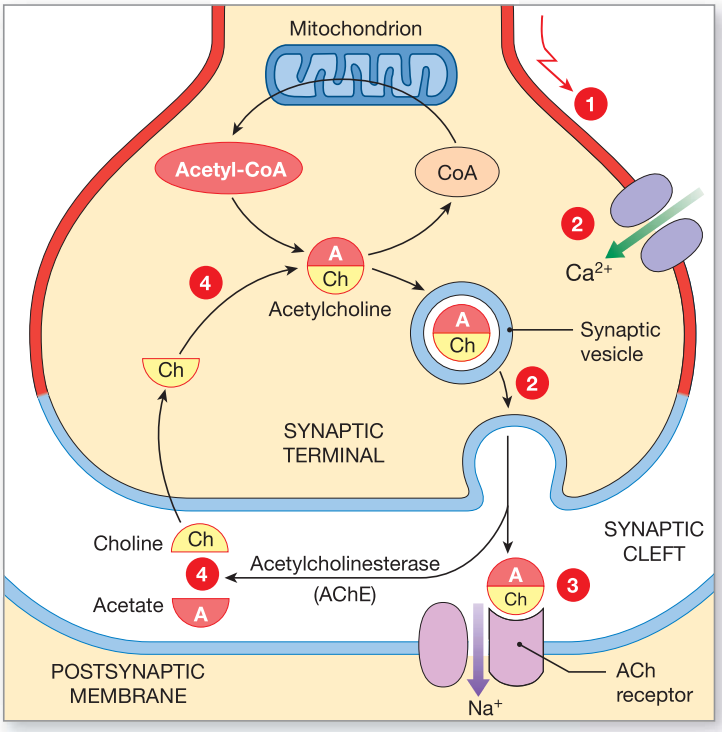
The Sequence of Events at a Typical Cholinergic Synapse:

STEP 1
- An arriving action potential depolarizes the synaptic terminal.

STEP 2
- Calcium ions enter the cytoplasm of the synaptic terminal.
- ACh is released through exocytosis of synaptic vesicles.
- ACh release ceases because calcium ions are removed from the cytoplasm of the synaptic terminal.

STEP 3
- ACh diffuses across the synaptic cleft and binds to receptors on the postsynaptic membrane.
- Chemically gated sodium channels on the postsynaptic membrane open, producing a graded depolarization.

STEP 4
- The depolarization ends as ACh is broken down into acetate and choline by AChE.
- The synaptic terminal reabsorbs choline from the synaptic cleft and uses it to resynthesize ACh.



Synaptic Fatigue

Because ACh molecules are recycled, the synaptic terminal is not totally dependent on the ACh synthesized in the cell body and delivered by axoplasmic transport. But under intensive stimulation, resynthesis and transport mechanisms may not keep up with the demand for neurotransmitter. **Synaptic fatigue** then occurs, and the synapse weakens until ACh has been replenished.

Checkpoint

19. **Describe the general structure of a synapse.**
20. **If a synapse involves direct physical contact between cells, it is termed _____; if the synapse involves a neurotransmitter, it is termed _____.**
21. **What effect would blocking voltage-gated calcium channels at a cholinergic synapse have on synaptic communication?**
22. **One pathway in the central nervous system consists of three neurons, another of five neurons. If the neurons in the two pathways are identical, which pathway will transmit impulses more rapidly?**

See the blue Answers tab at the back of the book.

12-8 Neurotransmitters and neuromodulators have various functions

Now that we have examined the actions of acetylcholine at cholinergic synapses, let's consider the actions of other neurotransmitters, and of neuromodulators, which change the cell's response to neurotransmitters.

The Activities of Other Neurotransmitters

The nervous system relies on a complex form of chemical communication. Each neuron is continuously exposed to a variety of neurotransmitters. Some usually have excitatory effects, while others usually have inhibitory effects. Yet in all cases, the effects depend on the nature of the receptor rather than the structure of the neurotransmitter. (Many drugs affect the nervous system by stimulating receptors that otherwise respond only to neurotransmitters. These drugs can have complex effects on perception, motor control, and emotional states.)

Major categories of neurotransmitters include *biogenic amines*, *amino acids*, *neuropeptides*, *dissolved gases*, and a variety of other compounds. Here we introduce only a few of the most important neurotransmitters, and you will encounter additional examples in later chapters.

- **Norepinephrine** (nor-ep-i-NEF-rin), or **NE,** is a neurotransmitter that is widely distributed in the brain and in portions of the ANS. Norepinephrine is also called *noradrenaline*, and synapses that release NE are known as **adrenergic synapses.** Norepinephrine typically has an excitatory, depolarizing effect on the postsynaptic membrane, but the mechanism is quite distinct from that of ACh, as we will see in Chapter 16.
- **Dopamine** (DŌ-puh-mēn) is a CNS neurotransmitter released in many areas of the brain. It may have either inhibitory or excitatory effects. Inhibitory effects play an important role in our precise control of movements. For example, dopamine release in one portion of the brain prevents the overstimulation of neurons that control skeletal muscle tone. If the neurons that produce dopamine are damaged or destroyed, the result can be the characteristic rigidity and stiffness of *Parkinson's disease*, a condition we describe in Chapter 14. At other sites, dopamine release has excitatory effects. Cocaine inhibits the removal of dopamine from synapses in specific areas of the brain. The resulting rise in dopamine concentrations at these synapses is responsible for the "high" experienced by cocaine users.
- **Serotonin** (ser-ō-TŌ-nin) is another important CNS neurotransmitter. Inadequate serotonin production can have widespread effects on a person's attention and emotional states and may be responsible for many cases of severe chronic depression. *Fluoxetine (Prozac)*, *paroxetine* (*Paxil*), *sertraline* (*Zoloft*), and related antidepressant drugs inhibit the reabsorption of serotonin by synaptic terminals (hence their classification as *s*elective *s*erotonin *r*euptake *i*nhibitors, or *SSRIs*). This inhibition leads to increased serotonin concentrations at synapses, and over time, the increase may relieve the symptoms of depression. Interactions among serotonin, norepinephrine, and other neurotransmitters are thought to be involved in the regulation of sleep and wake cycles.
- **Gamma-aminobutyric** (a-MĒ-nō-bū-TĒR-ik) **acid,** or **GABA,** generally has an inhibitory effect. Roughly 20 percent of the synapses in the brain release GABA, but its functions remain incompletely understood. In the CNS, GABA release appears to reduce anxiety, and some antianxiety drugs work by enhancing this effect.

The functions of many neurotransmitters are not well understood. In a clear demonstration of the principle "the more you look, the more you see," over 100 neurotransmitters have been identified, including certain amino acids, peptides, polypeptides, prostaglandins, and ATP.

In addition, two gases, nitric oxide and carbon monoxide, are known to be important neurotransmitters. **Nitric oxide** (**NO**) is generated by synaptic terminals that innervate smooth muscle in the walls of blood vessels in the PNS, and at synapses in several regions of the brain. **Carbon monoxide** (**CO**), best known as a component of automobile exhaust, is also generated by specialized synaptic terminals in the brain, where it functions as a neurotransmitter.

Neuromodulators

It is convenient to discuss each synapse as if it were releasing only one chemical, but synaptic terminals may release a mixture of active compounds, either through diffusion across the membrane or via exocytosis, along with neurotransmitter molecules. These compounds may have a variety of functions. Those that alter the rate of neurotransmitter release by the presynaptic neuron or change the postsynaptic cell's response to neurotransmitters are called **neuromodulators** (noo-rō-MOD-ū-lā-torz). These substances are typically **neuropeptides,** small peptide chains synthesized and released by the synaptic terminal. Most neuromodulators act by binding to receptors in the presynaptic or postsynaptic membranes and activating cytoplasmic enzymes.

Neuromodulators called **opioids** (Ō-pē-oydz) have effects similar to those of the drugs *opium* and *morphine*, because they bind to the same group of postsynaptic receptors. Four classes of opioids in the CNS are (1) **endorphins** (en-DOR-finz), (2) **enkephalins** (en-KEF-a-linz), (3) **endomorphins,** and (4) **dynorphins** (DĪ-nor-finz). The primary function of opioids is probably to relieve pain. They inhibit the release of the neurotransmitter *substance P* at synapses that relay pain sensations. Dynorphins have far more powerful pain-relieving effects than morphine or the other opioids.

Tips & Tricks

Endorphins are so named because they act like ***endo***genous (coming from within the body) m***orphin***e.

In general, neuromodulators (1) have long-term effects that are relatively slow to appear; (2) trigger responses that involve a number of steps and intermediary compounds; (3) may affect the presynaptic membrane, the postsynaptic membrane, or both; and (4) can be released alone or along with a neurotransmitter. **Figure 12–18** shows how neurotransmitters and neuromodulators work. **Table 12–5** lists major neurotransmitters and neuromodulators of the brain and spinal cord, and their primary effects (if known). In practice, it can be very difficult to distinguish neurotransmitters from neuromodulators on either biochemical or functional grounds: A neuropeptide may function in one site as a neuromodulator and in another

as a neurotransmitter. For this reason, Table 12–5 does not distinguish between neurotransmitters and neuromodulators.

How Neurotransmitters and Neuromodulators Work

Functionally, neurotransmitters and neuromodulators fall into one of three groups: (1) *compounds that have a direct effect on membrane potential*, (2) *compounds that have an indirect effect on membrane potential*, or (3) *lipid-soluble gases that exert their effects inside the cell*.

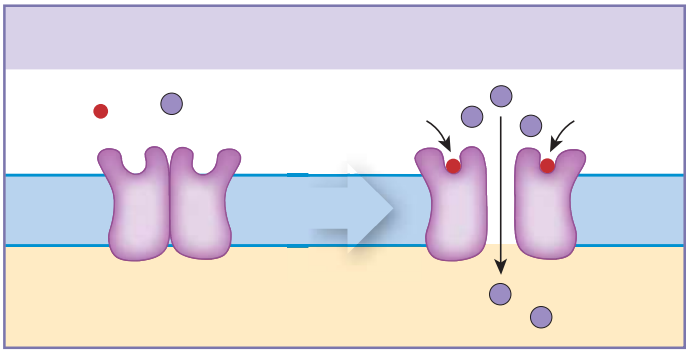
Compounds that have direct effects on membrane potential open or close gated ion channels (Figure 12–18a). Examples include ACh and the amino acids *glycine* and *aspartate*. Because these neurotransmitters alter ion movement across the membrane, they are said to have *ionotropic effects*. A few neurotransmitters, notably glutamate, GABA, NE, and serotonin, have both direct and indirect effects, because these compounds target two different classes of receptors. The direct effects are ionotropic. The indirect effects, which involve changes in the metabolic activity of the postsynaptic cell, are called *metabotropic*.

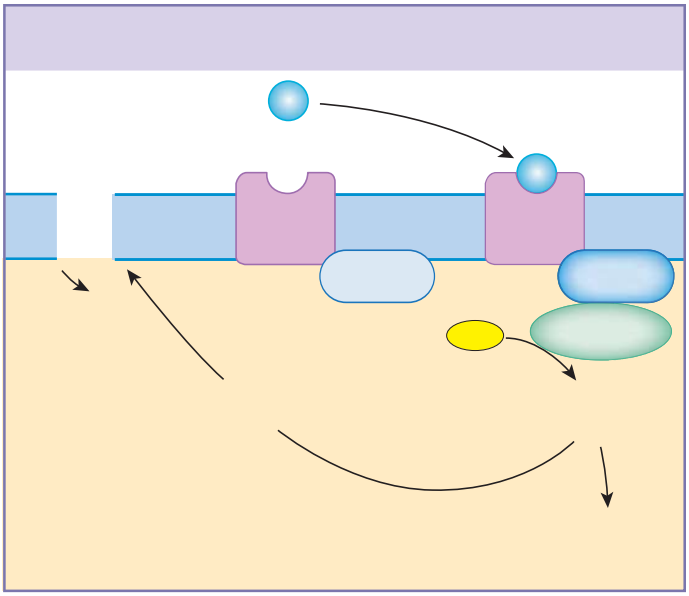
Compounds that have an indirect effect on membrane potential work through intermediaries known as *second messengers*. The neurotransmitter represents a *first messenger*, because it delivers the message to receptors on the plasma membrane or within the cell. Second messengers are ions or molecules that are produced or released inside the cell when a first messenger binds to one of these receptors.

Many neurotransmitters—including epinephrine, norepinephrine, dopamine, serotonin, histamine, and GABA—and many neuromodulators bind to receptors in the plasma membrane. In these instances, the link between the first messenger and the second messenger involves a **G protein,** an enzyme complex coupled to a membrane receptor. The name *G protein* refers to the fact that these proteins bind GTP, a high-energy compound introduced in Chapter 2. p. 57 Several types of G protein exist, but each type includes an enzyme that is "turned on" when an extracellular compound binds to its associated receptor at the cell surface.

Figure 12–18b shows one possible result of this binding: the activation of the enzyme **adenylate cyclase.** This enzyme converts ATP, the energy currency of the cell, to *cyclic-AMP*, a ring-shaped form of the compound AMP that was introduced in Chapter 2. p. 56 The conversion takes place at the inner surface of the plasma membrane. Cyclic-AMP (cAMP) is a second messenger that may open membrane channels, activate intracellular enzymes, or both, depending on the nature of the postsynaptic cell. This is only an overview of the function of one type of G protein. We examine several types of G proteins more closely in later chapters.

Two lipid-soluble gases, nitric oxide (NO) and carbon monoxide (CO), are known to be important neurotransmitters in specific regions of the brain. Because they can diffuse





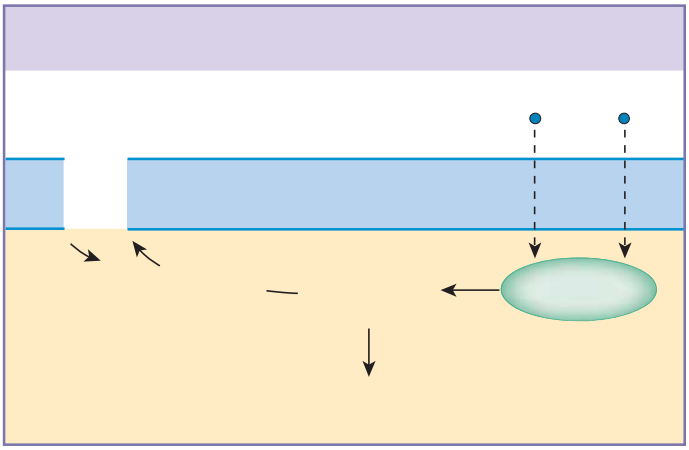


Table 12–5 Representative Neurotransmitters and Neuromodulators

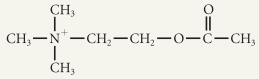
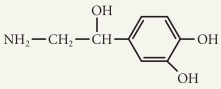
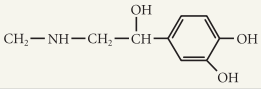
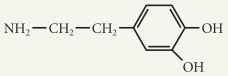
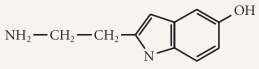
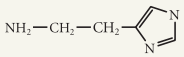
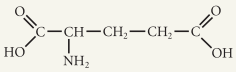
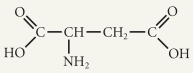
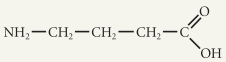
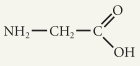
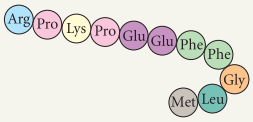
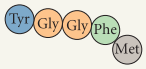
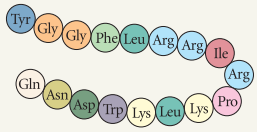
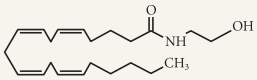
Class and Neurotransmitter	Chemical Structure	Mechanism of Action	Location(s)	Comments
Acetylcholine		Primarily direct, through binding to chemically gated channels	CNS: Synapses throughout brain and spinal cord PNS: Neuromuscular junctions; preganglionic synapses of ANS; neuroglandular junctions of parasympathetic division and (rarely) sympathetic division of ANS; amacrine cells of retina	Widespread in CNS and PNS; best known and most studied of the neurotransmitters
BIOGENIC AMINES				
Norepinephrine		Indirect: G proteins and second messengers	CNS: Cerebral cortex, hypothalamus, brain stem, cerebellum, spinal cord PNS: Most neuromuscular and neuroglandular junctions of sympathetic division of ANS	Involved in attention and consciousness, control of body temperature, and regulation of pituitary gland secretion
Epinephrine		Indirect: G proteins and second messengers	CNS: Thalamus, hypothalamus, midbrain, spinal cord	Uncertain functions
Dopamine		Indirect: G proteins and second messengers	CNS: Hypothalamus, midbrain, limbic system, cerebral cortex, retina	Regulation of subconscious motor function; receptor abnormalities have been linked to development of schizophrenia
Serotonin		Primarily indirect: G proteins and second messengers	CNS: Hypothalamus, limbic system, cerebellum, spinal cord, retina	Important in emotional states, moods, and body temperature; several illicit hallucinogenic drugs, such as Ecstasy, target serotonin receptors
Histamine		Indirect: G proteins and second messengers	CNS: Neurons in hypothalamus, with axons projecting throughout the brain	Receptors are primarily on presynaptic membranes; functions in sexual arousal, pain threshold, pituitary hormone secretion, thirst, and blood pressure control
AMINO ACIDS				
Excitatory: **Glutamate**		Indirect: G proteins and second messengers Direct: opens calcium/sodium channels on pre- and postsynaptic membranes	CNS: Cerebral cortex and brain stem	Important in memory and learning; most important excitatory neurotransmitter in the brain
Aspartate		Direct or indirect (G proteins), depending on type of receptor	CNS: Cerebral cortex, retina, and spinal cord	Used by pyramidal cells that provide voluntary motor control over skeletal muscles
Inhibitory: **Gamma-aminobutyric acid (GABA)**		Direct or indirect (G proteins), depending on type of receptor	CNS: Cerebral cortex, cerebellum, interneurons throughout brain and spinal cord	Direct effects: open Cl^- channels; indirect effects: open K^+ channels and block entry of Ca^{2+}
Glycine		Direct: Opens Cl^- channels	CNS: Interneurons in brain stem, spinal cord, and retina	Produces postsynaptic inhibition; the poison *strychnine* produces fatal convulsions by blocking glycine receptors

Table 12–5 Representative Neurotransmitters and Neuromodulators

Class and Neurotransmitter	Chemical Structure	Mechanism of Action	Location(s)	Comments
NEUROPEPTIDES				
Substance P		Indirect: G proteins and second messengers	CNS: Synapses of pain receptors within spinal cord, hypothalamus, and other areas of the brain PNS: Enteric nervous system (network of neurons along the digestive tract)	Important in pain pathway, regulation of pituitary gland function, control of digestive tract reflexes
Neuropeptide Y	*36-amino-acid peptide*	Indirect: G proteins and second messengers	CNS: hypothalamus PNS: sympathetic neurons	Stimulates appetite and food intake
Opioids **Endorphins**	*31-amino-acid peptide*	Indirect: G proteins and second messengers	CNS: Thalamus, hypothalamus, brain stem, retina	Pain control; emotional and behavioral effects poorly understood
Enkephalins		Indirect: G proteins and second messengers	CNS: Basal nuclei, hypothalamus, midbrain, pons, medulla oblongata, spinal cord	Pain control; emotional and behavioral effects poorly understood
Endomorphin	*9- or 10-amino-acid peptide*	Indirect: G proteins and second messengers	CNS: Thalamus, hypothalamus, basal nuclei	Pain control; emotional and behavioral effects poorly understood
Dynorphin		Indirect: G proteins and second messengers	CNS: Hypothalamus, midbrain, medulla oblongata	Pain control; emotional and behavioral effects poorly understood
PURINES				
ATP, GTP	*(see Figure 2–24)*	Direct or indirect (G proteins), depending on type of receptor	CNS: Spinal cord PNS: Autonomic ganglia	
Adenosine	*(see Figure 2–24)*	Indirect: G proteins and second messengers	CNS: Cerebral cortex, hippocampus, cerebellum	Produces drowsiness; stimulatory effect of caffeine is due to inhibition of adenosine activity
HORMONES				
ADH, oxytocin, insulin, glucagon, secretin, CCK, GIP, VIP, inhibins, ANP, BNP, and many others	Peptide containing fewer than 200 amino acids	Typically indirect: G proteins and second messengers	CNS: Brain (widespread)	Numerous, complex, and incompletely understood
GASES				
Carbon monoxide (CO)	C = 0	Indirect: By diffusion to enzymes activating second messengers	CNS: Brain PNS: Some neuromuscular and neuroglandular junctions	Localization and function poorly understood
Nitric oxide (NO)	N = 0	Indirect: By diffusion to enzymes activating second messengers	CNS: Brain, especially at blood vessels PNS: Some sympathetic neuromuscular and neuroglandular junctions	
LIPIDS				
Anandamide		Indirect: G proteins and second messengers	CNS: cerebral cortex, hippocampus, cerebellum	Euphoria, drowsiness, appetite; receptors are targeted by the active ingredient in marijuana

Checkpoint

23. Differentiate between a neurotransmitter and a neuromodulator.
24. Identify the three functional groups into which neurotransmitters and neuromodulators fall.

See the blue Answers tab at the back of the book.

12-9 Individual neurons process information by integrating excitatory and inhibitory stimuli

A single neuron may receive information across thousands of synapses. As we have seen, some of the neurotransmitters arriving at the postsynaptic cell at any moment may be excitatory, and others may be inhibitory. So how does the neuron respond? The net effect on the transmembrane potential of the cell body—specifically, in the area of the axon hillock—determines how the neuron responds from moment to moment. If the net effect is a depolarization at the axon hillock, that depolarization affects the transmembrane potential at the initial segment. If threshold is reached at the initial segment, an action potential is generated and propagated along the axon.

Thus it is really the axon hillock that integrates the excitatory and inhibitory stimuli affecting the cell body and dendrites at any given moment. This integration process, which determines the rate of action potential generation at the initial segment, is the simplest level of **information processing** in the nervous system. The excitatory and inhibitory stimuli are integrated through interactions between *postsynaptic potentials*, which we discuss next. Higher levels of information processing involve interactions among neurons and among groups of neurons. We address these topics in later chapters.

Postsynaptic Potentials

Postsynaptic potentials are graded potentials that develop in the postsynaptic membrane in response to a neurotransmitter. (**Figure 12–13** illustrated graded depolarizations and hyperpolarizations.) Two major types of postsynaptic potentials develop at neuron-to-neuron synapses: excitatory postsynaptic potentials and inhibitory postsynaptic potentials.

An **excitatory postsynaptic potential,** or **EPSP,** is a graded depolarization caused by the arrival of a neurotransmitter at the postsynaptic membrane. An EPSP results from the opening of chemically gated membrane channels that lead to depolarization of the plasma membrane. For example, the graded depolarization produced by the binding of ACh is an EPSP. Because it is a graded potential, an EPSP affects only the area immediately surrounding the synapse, as shown in **Figure 12–12**.

We have already noted that not all neurotransmitters have an excitatory (depolarizing) effect. An **inhibitory postsynaptic potential,** or **IPSP,** is a graded hyperpolarization of the postsynaptic membrane. For example, an IPSP may result from the opening of chemically gated potassium channels. While the hyperpolarization continues, the neuron is said to be **inhibited,** because a larger-than-usual depolarizing stimulus is needed to bring the membrane potential to threshold. A stimulus that shifts the transmembrane potential by 10 mV (from –70 mV to –60 mV) would normally produce an action potential, but if the transmembrane potential were reset at –85 mV by an IPSP, the same stimulus would depolarize it to only –75 mV, which is below threshold.

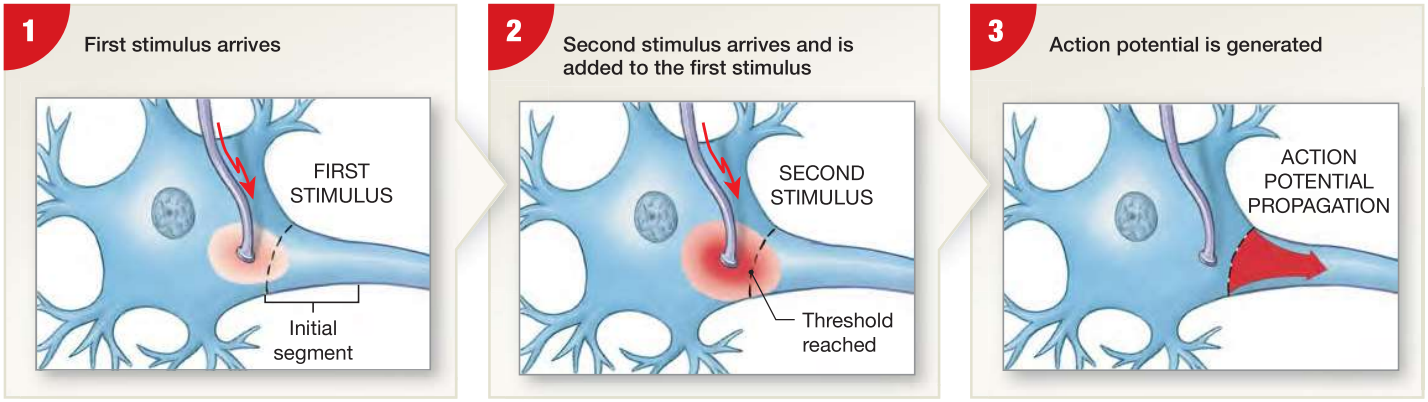
Summation

An individual EPSP has a small effect on the transmembrane potential, typically producing a depolarization of about 0.5 mV at the postsynaptic membrane. Before an action potential will arise in the initial segment, local currents must depolarize that region by at least 10 mV. Therefore, a single EPSP will not result in an action potential, even if the synapse is on the axon hillock. But individual EPSPs combine through the process of **summation,** which integrates the effects of all the graded potentials that affect one portion of the plasma membrane. The graded potentials may be EPSPs, IPSPs, or both. We will consider EPSPs in our discussion. Two forms of summation exist: temporal summation and spatial summation (**Figure 12–19**).

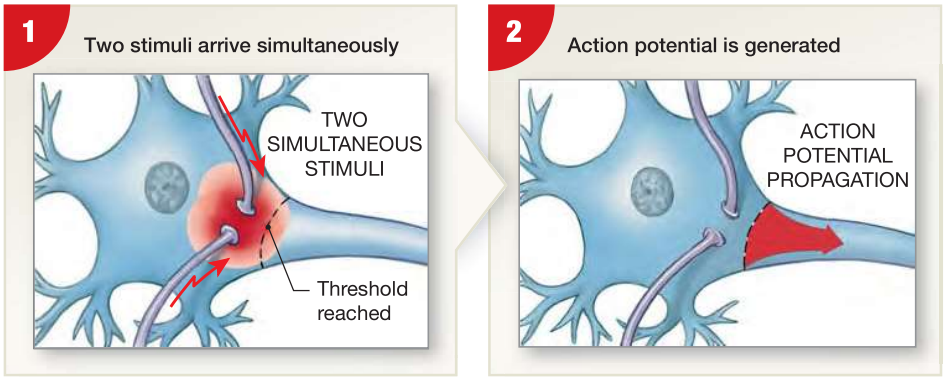
Temporal summation (*tempus*, time) is the addition of stimuli occurring in rapid succession at a *single synapse* that is active *repeatedly*. This form of summation can be likened to using a bucket to fill up a bathtub: You can't fill the tub with a single bucket of water, but you will fill it eventually if you keep repeating the process. In the case of temporal summation, the water in a bucket corresponds to the sodium ions that enter the cytoplasm during an EPSP. A typical EPSP lasts about 20 msec, but under maximum stimulation an action potential can reach the synaptic terminal each millisecond. **Figure 12–19a** shows what happens when a second EPSP arrives before the effects of the first EPSP have disappeared: The effects of the two are combined. Every time an action potential arrives, a group of vesicles discharges ACh into the synaptic cleft, and every time more ACh molecules arrive at the postsynaptic membrane, more chemically gated channels open, and the degree of depolarization increases. In this way, a series of small steps can eventually bring the initial segment to threshold.

Spatial summation occurs when simultaneous stimuli applied at different locations have a cumulative effect on the transmembrane potential. In other words, spatial summation involves *multiple synapses* that are active *simultaneously*. In terms of our bucket analogy, you could fill the bathtub immediately if 50 friends emptied their buckets into it all at the same time.

Figure 12–19 Temporal and Spatial Summation.



a Temporal Summation. Temporal summation occurs on a membrane that receives two depolarizing stimuli from the same source in rapid succession. The effects of the second stimulus are added to those of the first.



b Spatial Summation. Spatial summation occurs when sources of stimulation arrive simultaneously, but at different locations. Local currents spread the depolarizing effects, and areas of overlap experience the combined effects.

In spatial summation, more than one synapse is active at the same time (**Figure 12–19b**), and each "pours" sodium ions across the postsynaptic membrane, producing a graded potential with localized effects. At each active synapse, the sodium ions that produce the EPSP spread out along the inner surface of the membrane and mingle with those entering at other synapses. As a result, the effects on the initial segment are cumulative. The degree of depolarization depends on how many synapses are active at any moment, and on their distance from the initial segment. As in temporal summation, an action potential results when the transmembrane potential at the initial segment reaches threshold.

Facilitation

Now consider a situation in which summation of EPSPs is under way, but the initial segment has not been depolarized to threshold. The closer the initial segment gets to threshold, the easier it will be for the *next* depolarizing stimulus to trigger an action potential. A neuron whose transmembrane potential shifts closer to threshold is said to be **facilitated.** The larger the degree of facilitation, the smaller is the additional stimulus needed to trigger an action potential. In a highly facilitated neuron, even a small depolarizing stimulus produces an action potential.

Facilitation can result from the summation of EPSPs or from the exposure of a neuron to certain drugs in the extracellular fluid. For example, the nicotine in cigarettes stimulates postsynaptic ACh receptors, producing prolonged EPSPs that facilitate CNS neurons. Nicotine also increases the release of another neurotransmitter, dopamine, producing feelings of pleasure and reward, thereby leading to addiction.

Summation of EPSPs and IPSPs

Like EPSPs, IPSPs combine spatially and temporally. EPSPs and IPSPs reflect the activation of different types of chemically gated channels, producing opposing effects on the transmembrane potential. The antagonism between IPSPs and EPSPs is

important in cellular information processing. In terms of our bucket analogy, EPSPs put water into the bathtub, and IPSPs take water out. If more buckets add water than remove water, the water level in the tub rises. If more buckets remove water, the level falls. If a bucket of water is removed every time another bucket is dumped in, the level remains stable. Comparable interactions between EPSPs and IPSPs determine the transmembrane potential at the boundary between the axon hillock and the initial segment (**Figure 12–20**).

Neuromodulators, hormones, or both can change the postsynaptic membrane's sensitivity to excitatory or inhibitory neurotransmitters. By shifting the balance between EPSPs and IPSPs, these compounds promote facilitation or inhibition of CNS and PNS neurons.

Presynaptic Inhibition and Presynaptic Facilitation

Inhibitory or excitatory responses may occur not only at synapses involving the cell body and dendrites, but also at synapses found along an axon or its collaterals. At an *axoaxonic* (axon to axon) *synapse*, a synapse occurs between the axons of two neurons. An axoaxonic synapse at the synaptic terminal can either decrease (inhibit) or increase (facilitate) the rate of neurotransmitter release at the presynaptic membrane. In one form of **presynaptic inhibition,** the release of GABA inhibits the opening of voltage-gated calcium channels in the synaptic terminal (**Figure 12–21a**). This inhibition reduces the amount of neurotransmitter released when an action potential arrives there, and thus reduces the effects of synaptic activity on the postsynaptic membrane.

In **presynaptic facilitation,** activity at an axoaxonic synapse increases the amount of neurotransmitter released when an action potential arrives at the synaptic terminal (**Figure 12–21b**). This increase enhances and prolongs the neurotransmitter's effects on the postsynaptic membrane. The neurotransmitter *serotonin* is involved in presynaptic facilitation. In the presence of serotonin released at an axoaxonic synapse, voltage-gated calcium channels remain open longer.

The Rate of Generation of Action Potentials

In the nervous system, complex information is translated into action potentials that are propagated along axons. On arrival, the message is often interpreted solely on the basis of the frequency of action potentials. For example, action potentials arriving at a neuromuscular junction at the rate of 1 per second may produce a series of isolated twitches in the associated skeletal muscle fiber, but at the rate of 100 per second they cause a sustained tetanic contraction. Similarly, you may perceive a few action potentials per second along a sensory fiber as a feather-light touch, but you would perceive hundreds of action potentials per second along that same axon as unbearable pressure. In general, the degree of sensory stimulation or the strength of the motor response is proportional to the frequency of action potentials. In this section, we examine factors that vary the rate of generation of action potentials. .

If a graded potential briefly depolarizes the axon hillock such that the initial segment reaches its threshold, an action potential is propagated along the axon. But what happens when the axon hillock *remains* depolarized past threshold for an extended period? The longer the initial segment remains above

Figure 12–20 Interactions between EPSPs and IPSPs. At time 1, a small depolarizing stimulus produces an EPSP. At time 2, a small hyperpolarizing stimulus produces an IPSP of comparable magnitude. If the two stimuli are applied simultaneously, as they are at time 3, summation occurs. Because the two are equal in size but have opposite effects, the membrane potential remains at the resting level. If the EPSP were larger, a net depolarization would result; if the IPSP were larger, a net hyperpolarization would result instead.

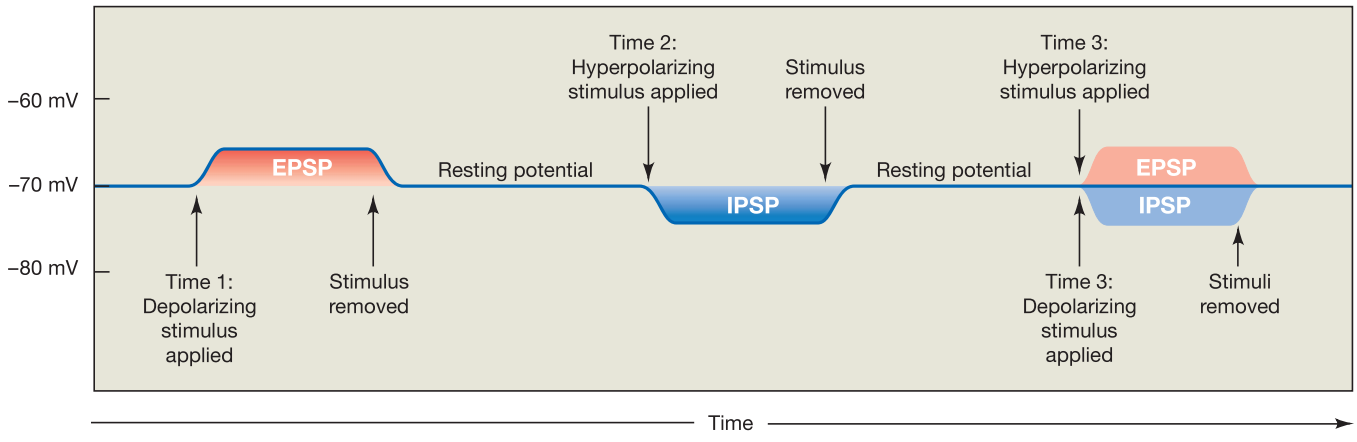
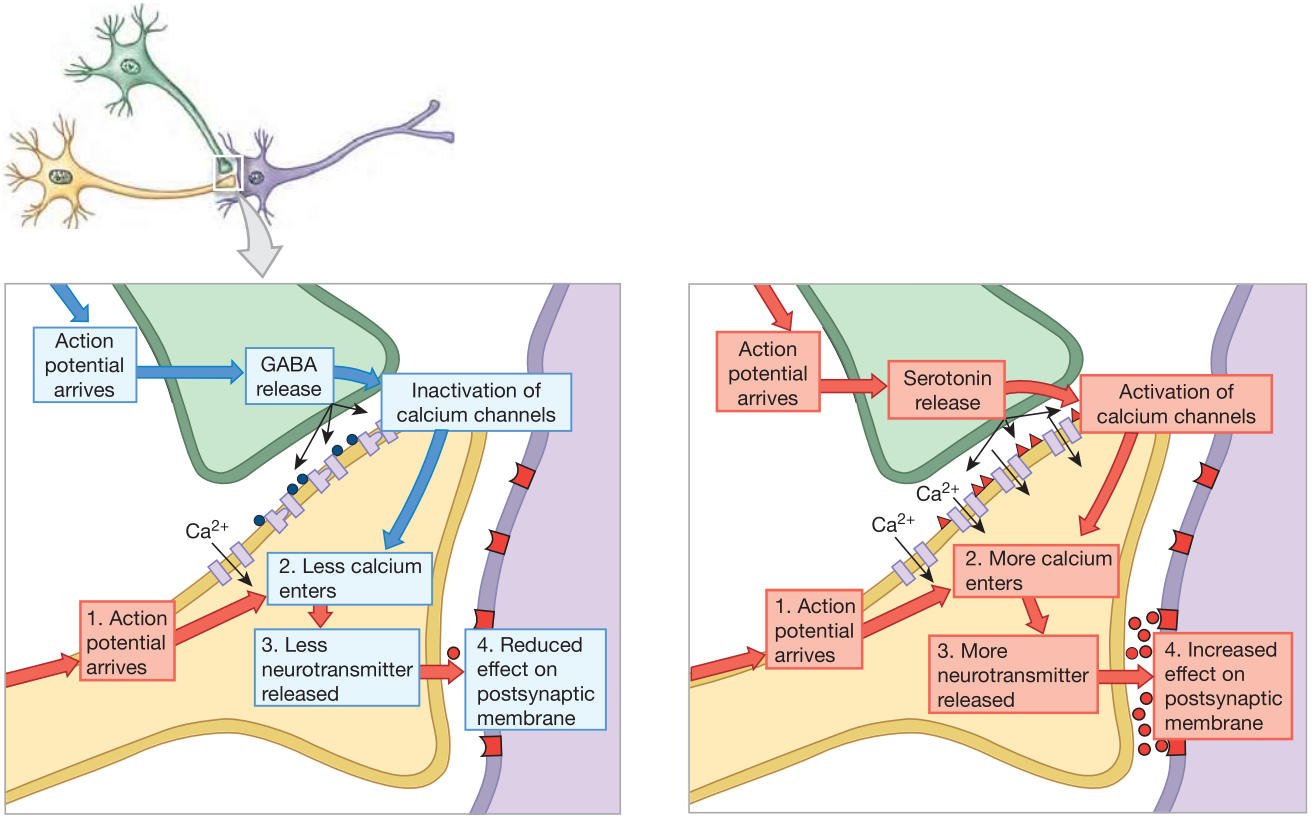


Figure 12–21 Presynaptic Inhibition and Presynaptic Facilitation.



a Presynaptic inhibition

b Presynaptic facilitation

threshold, the more action potentials it produces. The *frequency* of action potentials depends on the degree of depolarization above threshold: The greater the degree of depolarization, the higher the frequency of action potentials. The membrane can respond to a second stimulus as soon as the absolute refractory period ends. Holding the membrane above threshold has the same effect as applying a second, larger-than-normal stimulus.

Action potentials can be generated at a maximum rate when the relative refractory period has been completely eliminated. For this reason, the maximum theoretical frequency of action potentials is established by the duration of the absolute refractory period. The absolute refractory period is shortest in large-diameter axons, in which the *theoretical* maximum frequency of action potentials is 2500 per second. However, the highest frequencies recorded from axons in the body range between 500 and 1000 per second.

Table 12–6 summarizes the basic principles of information processing.

Table 12–6 Information Processing

- Information is relayed in the form of action potentials. In general, the degree of sensory stimulation or the strength of the motor response is proportional to the frequency of action potentials.
- The neurotransmitters released at a synapse may have either excitatory or inhibitory effects. The effect on the axon's initial segment reflects a summation of the stimuli that arrive at any moment. The frequency of generation of action potentials is an indication of the degree of sustained depolarization at the axon hillock.
- Neuromodulators can alter either the rate of neurotransmitter release or the response of a postsynaptic neuron to specific neurotransmitters.
- Neurons may be facilitated or inhibited by extracellular chemicals other than neurotransmitters or neuromodulators.
- The response of a postsynaptic neuron to the activation of a presynaptic neuron can be altered by (1) the presence of neuromodulators or other chemicals that cause facilitation or inhibition at the synapse, (2) activity under way at other synapses affecting the postsynaptic cell, and (3) modification of the rate of neurotransmitter release through presynaptic facilitation or presynaptic inhibition.

You are now familiar with the basic components of neural tissue, and the origin and significance of action potentials. In later chapters we consider higher levels of anatomical and functional organization within the nervous system, examine information processing at these levels, and see how a single process—the generation of action potentials—can be responsible for the incredible diversity of sensations and movements that we experience each day.

Checkpoint

25. **One EPSP depolarizes the initial segment from a resting potential of –70 mV to –65 mV, and threshold is at –60 mV. Will an action potential be generated?**
26. **Given the situation in Checkpoint 25, if a second, identical EPSP occurs immediately after the first, will an action potential be generated?**
27. **If the two EPSPs in Checkpoint 26 occurred simultaneously, what form of summation would occur?**

See the blue Answers tab at the back of the book.

Related Clinical Terms

anesthetic: An agent that produces a local or general loss of sensation including feelings of pain.
anticholinesterase drug: A drug that blocks the breakdown of ACh by AChE.
atropine: A drug that prevents ACh from binding to the postsynaptic membrane of cardiac muscle and smooth muscle cells.
d-tubocurarine: A drug, derived from curare, that produces paralysis by preventing ACh from binding to the postsynaptic membrane of skeletal muscle fibers.
dysthymia: A form of clinical depression with a depressed mood for most of the time for at least two years along with at least two of the following signs and symptoms: poor appetite or overeating; insomnia or excessive sleep; low energy or fatigue; low self-esteem; poor concentration or indecisiveness; and hopelessness.
excitotoxicity: Continuous and exaggerated stimulation by a neurotransmitter, especially for the excitatory neurotransmitter glutamate. The nerve cells can become damaged and killed by the over activation of receptors.
neuroblastoma: A malignant tumor composed of neuroblasts, most commonly in the adrenal gland; it is the most common cancer in infancy.
neuropathy: Condition that causes tingling, numbness, and/or pain in parts of the body, notably the hands and feet.
neurotoxin: A compound that disrupts normal nervous system function by interfering with the generation or propagation of action potentials. Examples include *tetrodotoxin (TTX)*, *saxitoxin (STX)*, and *ciguatoxin (CTX)*.
Tay–Sachs disease: A genetic abnormality involving the metabolism of gangliosides, important components of neuron plasma membranes. The result is a gradual deterioration of neurons due to the buildup of metabolic by-products and the release of lysosomal enzymes.

Chapter Review

Study Outline

An Introduction to Neural Tissue p. 375

1. The nervous system includes all the neural tissue in the body. The basic functional unit is the **neuron.**

12-1 The nervous system has anatomical and functional divisions p. 375

2. The anatomical divisions of the nervous system are the **central nervous system (CNS)** (the brain and spinal cord) and the **peripheral nervous system (PNS)** (all the neural tissue outside the CNS). Bundles of **axons** *(nerve fibers)* in the PNS are called **nerves.**
3. Functionally, the PNS can be divided into an **afferent division,** which brings sensory information from **receptors** to the CNS, and an **efferent division,** which carries motor commands to muscles and glands called **effectors.**
4. The efferent division of the PNS includes the **somatic nervous system (SNS),** which controls skeletal muscle contractions, and the **autonomic nervous system (ANS),** which controls smooth muscle, cardiac muscle, adipose tissue, and glandular activity.

12-2 Neurons are nerve cells specialized for intercellular communication p. 376

5. The **perikaryon** of a multipolar neuron contains organelles, including **neurofilaments, neurotubules,** and **neurofibrils.** The **axon hillock** connects the **initial segment** of the **axon** to the **cell body,** or *soma*. The **axoplasm** contains numerous organelles. *(Figure 12–1)*
6. **Collaterals** may branch from an axon, with **telodendria** branching from the axon's tip.
7. A **synapse** is a site of intercellular communication. Telodendria end in **synaptic terminals,** which are also known as synaptic knobs, axon terminals, and synaptic boutons. **Neurotransmitters** released from the synaptic terminals of the presynaptic cell affect the postsynaptic cell, which may be a neuron or another type of cell. *(Figures 12–1, 12–2)*
8. Neurons are structurally classified as **anaxonic, bipolar, unipolar,** or **multipolar.** *(Figure 12–3)*
9. The three functional categories of neurons are sensory neurons, motor neurons, and interneurons.

10. **Sensory neurons,** which form the afferent division of the PNS, deliver information received from **interoceptors, exteroceptors,** and **proprioceptors** to the CNS.
11. **Motor neurons,** which form the efferent division of the PNS, stimulate or modify the activity of a peripheral tissue, organ, or organ system.
12. **Interneurons** *(association neurons)* are always located in the CNS and may be situated between sensory and motor neurons. They distribute sensory inputs and coordinate motor outputs.

12-3 CNS and PNS neuroglia support and protect neurons p. 380

13. The four types of **neuroglia,** or *glial cells,* in the CNS are (1) **ependymal cells,** with functions related to the **cerebrospinal fluid (CSF);** (2) **astrocytes,** the largest and most numerous neuroglia; (3) **oligodendrocytes,** which are responsible for the **myelination** of CNS axons; and (4) **microglia,** or phagocytic cells. *(Figures 12–4, 12–5b)*
14. Neuron cell bodies in the PNS are clustered into **ganglia.**
15. **Satellite cells,** or *amphicytes,* surround neuron cell bodies within ganglia. **Schwann cells** ensheath axons in the PNS. A single Schwann cell may myelinate one segment of an axon or enclose segments of several unmyelinated axons. *(Figure 12–6)*
16. In the PNS, functional repair of axons may follow **Wallerian degeneration.** In the CNS, many factors complicate the repair process and reduce the chances of functional recovery. *(Figure 12–7)*

12-4 The transmembrane potential is the electrical potential of the cell's interior relative to its surroundings p. 386

17. All normal neural signaling depends on events that occur at the plasma membrane. (*Figure 12–8*)
18. The **electrochemical gradient** is the sum of all chemical and electrical forces acting across the plasma membrane. *(Figures 12–9, 12–10)*
19. The sodium–potassium exchange pump stabilizes the resting potential at approximately –70 mV. *(Table 12–1)*
20. The plasma membrane contains **passive (leak) channels,** which are always open, and **active (gated) channels,** which open or close in response to specific stimuli. *(Figure 12–9)*
21. The three types of gated channels are **chemically gated channels, voltage-gated channels,** and **mechanically gated channels.** *(Figure 12–11)*
22. A localized **depolarization** or **hyperpolarization** is a **graded potential** (a change in potential that decreases with distance). *(Figures 12–12, 12–13; Table 12–2)*

12-5 An action potential is an electrical event p. 394

23. An **action potential** arises when a region of excitable membrane depolarizes to its **threshold.** The steps involved, in order, are membrane depolarization to threshold, activation of sodium channels and rapid depolarization, inactivation of sodium channels and activation of potassium channels, and the return to normal permeability. *(Figure 12–14; Spotlight Figure 12–14; Table 12–3)*
24. The generation of an action potential follows the **all-or-none principle.** The **refractory period** lasts from the time an action potential begins until the normal resting potential has returned. *(Spotlight Figure 12–14; Table 12–3)*
25. In **continuous propagation,** an action potential spreads across the entire excitable membrane surface in a series of small steps. *(Figure 12–15)*
26. In **saltatory propagation,** an action potential appears to leap from node to node, skipping the intervening membrane surface. Saltatory propagation carries nerve impulses many times more rapidly than does continuous propagation. *(Figure 12–16)*

12-6 Axon diameter, in addition to myelin, affects propagation speed p. 400

27. Axons are classified as **Type A fibers, Type B fibers,** or **Type C fibers** on the basis of their diameter, myelination, and propagation speed.
28. Compared with action potentials in neural tissue, those in muscle tissue have (1) larger resting potentials, (2) longer-lasting action potentials, and (3) slower propagation of action potentials.

12-7 At synapses, communication occurs among neurons or between neurons and other cells p. 400

29. An action potential traveling along an axon is a **nerve impulse.** At a synapse between two neurons, information passes from the **presynaptic neuron** to the **postsynaptic neuron.**
30. A synapse is either *electrical* (with direct physical contact between cells) or *chemical* (involving a neurotransmitter).
31. **Electrical synapses** occur in the CNS and PNS, but they are rare. At an electrical synapse, the presynaptic and postsynaptic plasma membranes are bound by interlocking membrane proteins at a gap junction. Pores formed by these proteins permit the passage of local currents, and the two neurons act as if they share a common plasma membrane.
32. **Chemical synapses** are far more common than electrical synapses. **Excitatory neurotransmitters** cause depolarization and promote the generation of action potentials, whereas **inhibitory neurotransmitters** cause hyperpolarization and suppress the generation of action potentials.
33. The effect of a neurotransmitter on the postsynaptic membrane depends on the properties of the receptor, not on the nature of the neurotransmitter.
34. **Cholinergic synapses** release the neurotransmitter **acetylcholine (ACh).** Communication moves from the presynaptic neuron to the postsynaptic neuron across a synaptic cleft. A **synaptic delay** occurs because calcium influx and the release of the neurotransmitter takes an appreciable length of time. *(Figure 12–17)*
35. **Choline** released during the breakdown of ACh in the synaptic cleft is reabsorbed and recycled by the synaptic terminal. If stores of ACh are exhausted, **synaptic fatigue** can occur. *(Table 12–4)*

12-8 Neurotransmitters and neuromodulators have various functions p. 403

36. **Adrenergic synapses** release **norepinephrine (NE),** also called *noradrenaline.* Other important neurotransmitters include **dopamine, serotonin,** and **gamma aminobutyric acid (GABA).**
37. **Neuromodulators** influence the postsynaptic cell's response to neurotransmitters. *(Figure 12–18; Table 12–5)*
38. Neurotransmitters can have a direct or indirect effect on membrane potential, and others are lipid-soluble gases that diffuse across the plasma membrane to exert their effects inside the cell. *(Figure 12–18)*

12-9 Individual neurons process information by integrating excitatory and inhibitory stimuli p. 408

39. Excitatory and inhibitory stimuli are integrated through interactions between **postsynaptic potentials.** This interaction is the simplest level of **information processing** in the nervous system.
40. A depolarization caused by a neurotransmitter is an **excitatory postsynaptic potential (EPSP).** Individual EPSPs can combine through **summation,** which can be either **temporal** (occurring at a single synapse when a second EPSP arrives before the effects of the first have disappeared) or **spatial** (resulting from the cumulative effects of multiple synapses at various locations). *(Figure 12–19)*
41. Hyperpolarization of the postsynaptic membrane is an **inhibitory postsynaptic potential (IPSP).**
42. The most important determinants of neural activity are EPSP–IPSP interactions. *(Figure 12–20)*
43. In **presynaptic inhibition,** GABA release at an *axoaxonic synapse* inhibits the opening of voltage-gated calcium channels in the synaptic terminal. This inhibition reduces the amount of neurotransmitter released when an action potential arrives at the synaptic terminal. *(Figure 12–21a)*
44. In **presynaptic facilitation,** activity at an axoaxonic synapse increases the amount of neurotransmitter released when an action potential arrives at the synaptic terminal. This increase enhances and prolongs the effects of the neurotransmitter on the postsynaptic membrane. *(Figure 12–21b)*
45. The neurotransmitters released at a synapse have excitatory or inhibitory effects. The effect on the initial segment reflects an integration of the stimuli arriving at any moment. The frequency of generation of action potentials depends on the degree of depolarization above threshold at the axon hillock. *(Table 12–6)*
46. Neuromodulators can alter either the rate of neurotransmitter release or the response of a postsynaptic neuron to specific neurotransmitters. Neurons may be facilitated or inhibited by extracellular chemicals other than neurotransmitters or neuromodulators. *(Table 12–6)*
47. The effect of a presynaptic neuron's activation on a postsynaptic neuron may be altered by other neurons. *(Table 12–6)*
48. The greater the degree of sustained depolarization at the axon hillock, the higher the frequency of generation of action potentials. At a frequency of about 1000 per second, the relative refractory period has been eliminated, and further depolarization will have no effect. *(Table 12–6)*

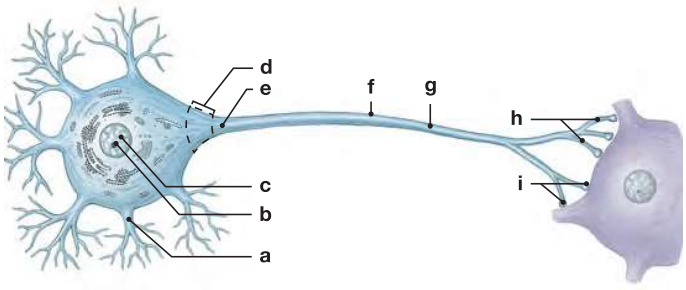
12

Review Questions

See the blue Answers tab at the back of the book.

LEVEL 1 Reviewing Facts and Terms

1. Label the structures in the following diagram of a neuron.



(a) _____
(b) _____
(c) _____
(d) _____
(e) _____
(f) _____
(g) _____
(h) _____
(i) _____

2. Regulation by the nervous system provides
   (a) relatively slow, but long-lasting, responses to stimuli.
   (b) swift, long-lasting responses to stimuli.
   (c) swift, but brief, responses to stimuli.
   (d) relatively slow, short-lived responses to stimuli.
3. In the CNS, a neuron typically receives information from other neurons at its
   (a) axon.
   (b) Nissl bodies.
   (c) dendrites.
   (d) nucleus.
4. Phagocytic cells in neural tissue of the CNS are
   (a) astrocytes.
   (b) ependymal cells.
   (c) oligodendrocytes.
   (d) microglia.
5. The neural cells responsible for the analysis of sensory inputs and coordination of motor outputs are
   (a) neuroglia.
   (b) interneurons.
   (c) sensory neurons.
   (d) motor neurons.
6. Depolarization of a neuron plasma membrane will shift the membrane potential toward
   (a) 0 mV.
   (b) –70 mV.
   (c) –90 mV.
   (d) all of these.
7. What factor determines the direction that ions will move through an open membrane channel?
   (a) the membrane permeability to sodium
   (b) the electrochemical gradient
   (c) intracellular negatively charged proteins
   (d) negatively charged chloride ions in the ECF

8. Receptors that bind acetylcholine at the postsynaptic membrane are
   (a) chemically gated channels.
   (b) voltage-gated channels.
   (c) passive channels.
   (d) mechanically gated channels.
9. What are the major components of (a) the central nervous system? (b) the peripheral nervous system?
10. Which two types of neuroglia insulate neuron cell bodies and axons in the PNS from their surroundings?
11. What three *functional* groups of neurons are found in the nervous system? What is the function of each type of neuron?

LEVEL 2 Reviewing Concepts

12. If the resting membrane potential is –70 mV and the threshold is –55 mV, a membrane potential of –60 mV will
   (a) produce an action potential.
   (b) make it easier to produce an action potential.
   (c) make it harder to produce an action potential.
   (d) hyperpolarize the membrane.
13. Why can't most neurons in the CNS be replaced when they are lost to injury or disease?
14. What is the difference between anterograde flow and retrograde flow?
15. What is the *functional* difference among voltage-gated, chemically gated, and mechanically gated channels?
16. State the all-or-none principle of action potentials.
17. Describe the steps involved in the generation of an action potential.
18. What is meant by saltatory propagation? How does it differ from continuous propagation?
19. What are the structural and functional differences among type A, B, and C fibers?
20. Describe the events that occur during nerve impulse transmission at a typical cholinergic synapse.
21. What is the difference between temporal summation and spatial summation?

LEVEL 3 Critical Thinking and Clinical Applications

22. Harry has a kidney condition that causes changes in his body's electrolyte levels (concentration of ions in the extracellular fluid). As a result, he is exhibiting tachycardia, an abnormally fast heart rate. Which ion is involved, and how does a change in its concentration cause Harry's symptoms?
23. Twenty neurons synapse with a single receptor neuron. Fifteen of the 20 neurons release neurotransmitters that produce EPSPs at the postsynaptic membrane, and the other five release neurotransmitters that produce IPSPs. Each time one of the neurons is stimulated, it releases enough neurotransmitter to produce a 2-mV change in potential at the postsynaptic membrane. If the threshold of the postsynaptic neuron is 10 mV, how many of the excitatory neurons must be stimulated to produce an action potential in the receptor neuron if all five inhibitory neurons are stimulated? (Assume that spatial summation occurs.)
24. In multiple sclerosis, there is intermittent and progressive damage to the myelin sheath of peripheral nerves. This results in poor motor control of the affected area. Why does destruction of the myelin sheath affect motor control?
25. What factor determines the maximum frequency of action potentials that could be conducted by an axon?

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