The Nervous System, Neuronal Excitability, and Homeostasis

The neurons of the nervous system are excitable, a characteristic that allows for the generation of action potentials. Action potentials in neurons contribute to homeostasis by providing these cells with the ability to communicate rapidly over long distances within the body.

Looking back to move ahead

- Ion channels are membrane proteins that contain pores through which specific ions can pass (Section 3.2).
- The Na⁺/K⁺ ATPase is a carrier protein that actively transports three Na⁺ ions out of a cell and two K⁺ ions into a cell (Section 5.3).
- Synaptic signaling refers to communication between a neuron and a target cell by the release of neurotransmitter molecules at a synapse (Section 6.2).
- A G protein is a membrane protein that regulates the activity of membrane enzymes or ion channels during signal transduction (Section 6.4).
Together, the nervous system and the endocrine system share responsibility for maintaining homeostasis. Their objective is the same—to keep controlled conditions within limits that maintain life—but the two systems achieve that objective very differently. The nervous system regulates body activities by responding rapidly using electrical signals known as action potentials; the endocrine system responds more slowly, though no less effectively, by releasing hormones.

Besides helping to maintain homeostasis, the nervous system is also responsible for your perceptions, behaviors, and memories, and initiates all voluntary movements. Because the nervous system is quite complex, different aspects of its function will be considered in several related chapters. This chapter focuses on the organization of the nervous system and the properties of the cells that make up nervous tissue—neurons (nerve cells) and neuroglia (cells that support the activities of neurons). Chapter 8 will examine the functions of the central nervous system (brain and spinal cord), followed by a discussion of how the afferent division of the peripheral nervous system conveys sensory input into the central nervous system from sensory receptors (Chapter 9). Exploration of the nervous system concludes with a discussion of how the efferent division of the peripheral nervous system conveys motor output to muscles and glands (Chapter 10).

7.1 OVERVIEW OF THE NERVOUS SYSTEM

Objectives
- Describe the subdivisions of the nervous system.
- Explain the basic functions of the nervous system.

Organization of the Nervous System

With a mass of only 2 kg (4.5 lb), about 3% of the total body weight, the nervous system is one of the smallest and yet the most complex of the 11 body systems. This intricate network of billions of neurons and even more neuroglia is organized into two main subdivisions: the central nervous system and the peripheral nervous system.

Central Nervous System

The central nervous system (CNS) consists of the brain and spinal cord (Figure 7.1a). The brain is the part of the CNS that is located in the skull. The spinal cord is connected to the brain and is enclosed by the bones of the vertebral column. The CNS processes many different kinds of incoming sensory information. It is also the source of thoughts, emotions, and memories. Most signals that stimulate muscles to contract and glands to secrete originate in the CNS.

Peripheral Nervous System

The peripheral nervous system (PNS) consists of all nervous tissue outside the CNS (Figure 7.1a). Components of the PNS include nerves and sensory receptors. A nerve is a bundle of axons (described shortly) that lies outside the brain and spinal cord. Twelve pairs of cranial nerves emerge from the brain and thirty-one pairs of spinal nerves emerge from the spinal cord. A sensory receptor is a structure that monitors changes in the external or internal environment. Examples of sensory receptors include touch receptors in the skin, olfactory (smell) receptors in the nose, and stretch receptors in the stomach wall.

The PNS is divided into afferent and efferent divisions. The afferent division of the PNS conveys input into the CNS from sensory receptors in the body (Figure 7.1b). This division provides the CNS with sensory information about the somatic senses (tactile, thermal, pain, and proprioceptive sensations), visceral senses (sensations associated with internal organs, such as fullness or the degree of stretch), and special senses (smell, taste, vision, hearing, and equilibrium).

The efferent division of the PNS conveys output from the CNS to effectors (muscles and glands) in the PNS. This division is further subdivided into a somatic nervous system and an autonomic nervous system (Figure 7.1b). The somatic nervous system (SNS) conveys output from the CNS to skeletal muscles only. Because its motor responses can be consciously controlled, the action of this part of the PNS is voluntary. The autonomic nervous system (ANS) conveys output from the CNS to smooth muscle, cardiac muscle, and glands. Since its motor responses are not normally under conscious control, the action of the ANS is involuntary. The ANS is comprised of two branches, the parasympathetic nervous system and the sympathetic nervous system. With a few exceptions, effectors receive innervation from both branches of the ANS, and usually the two branches have opposing actions. For example, neurons of the sympathetic nervous system increase heart rate, and neurons of the parasympathetic nervous system slow it down. In general, the parasympathetic nervous system takes care of “rest-and-digest” activities, and the sympathetic nervous system helps support exercise or emergency actions—the so-called “fight-or-flight” responses.

Functions of the Nervous System

The diverse activities of the nervous system can be grouped into three basic functions: sensory, integrative, and motor.

- **Sensory function.** Sensory receptors detect external or internal stimuli, such as a raindrop landing on your arm or an increase in blood acidity. This sensory information is then conveyed through cranial and spinal nerves of the PNS into the brain and spinal cord of the CNS.

- **Integrative function.** The CNS processes sensory information by analyzing it and making decisions for appropriate responses—an activity known as integration.

- **Motor function.** Once sensory information is integrated, the CNS may elicit an appropriate motor response. In order for this to occur, motor information is conveyed from the CNS through cranial and spinal nerves of the PNS to effectors (muscles and glands). Stimulation of the effectors causes muscles to contract and glands to secrete.

The three basic functions of the nervous system occur, for example, when you answer your cell phone after hearing it ring. The sound of the ringing phone stimulates sensory receptors in
The two main subdivisions of the nervous system are (1) the central nervous system (CNS), which consists of the brain and spinal cord, and (2) the peripheral nervous system (PNS), which consists of all nervous tissue outside the CNS.

What is the function of the afferent division of the PNS?
Chapter 7 The Nervous System and Neuronal Excitability

Checkpoint
1. What are the functions of the CNS?
2. What purpose does the afferent division of the PNS serve?
3. How does the somatic nervous system differ from the autonomic nervous system?
4. Explain the concept of integration and provide an example.

7.2 NERVOUS TISSUE

Objectives
- Describe the functions of neurons and neuroglia.
- Explain the importance of myelination.

Nervous tissue consists of two types of cells: neurons and neuroglia. Neurons, also known as nerve cells, provide most of the unique functions of the nervous system, such as sensing, thinking, remembering, controlling muscle activity, and regulating glandular secretions. Neuroglia support, nourish, and protect neurons and maintain homeostasis in the interstitial fluid that bathes them.

Neurons

In order to appreciate how neurons function in the nervous system, you need to understand the different parts of a neuron and to learn how the various types of neurons in the body are classified.

Parts of a Neuron

Most neurons have three parts: (1) a cell body, (2) dendrites, and (3) an axon (Figure 7.2). The dendrites and axon of a neuron are collectively referred to as neural processes, which extend from the cell body.

Dendrites are short, highly branched structures of a neuron. Because they receive signals from other neurons or from stimuli in the environment, they function as the main input portions of the neuron. Most neurons have numerous dendrites, an aspect that substantially increases the receptive surface area of the cell.

The cell body (soma) contains most of the organelles, including the nucleus. Because of its ability to direct protein synthesis and other cellular activities, the cell body functions as the control center of the neuron. Like dendrites, the cell body also serves as an input portion of the neuron because it can receive signals from other neurons. Throughout the nervous system, the cell bodies of adjacent neurons are often clustered together. A cluster of neuronal cell bodies in the PNS is called a ganglion (singular is ganglia); a similar arrangement of neuronal cell bodies in the CNS is known as a nucleus (plural is nuclei).

Figure 7.2 Parts of a neuron.

A single axon functions as the output portion of the neuron. It generates action potentials and then propagates them toward another neuron, a muscle fiber, or a gland cell. An axon is a long, thin, cylindrical projection that usually connects to the cell body at a cone-shaped region called the axon hillock. In most neurons, action potentials arise at the axon hillock, from which they travel along the axon to their destination. The axon hillock is also known as the trigger zone because of its role in the generation of action potentials. Along the length of an axon, side branches called axon collaterals may extend off. The axon and its collaterals end by dividing into smaller processes called axon terminals.
In most neurons, the tips of the axon terminals swell into **synaptic end bulbs**, which are so-named because they are bulb-shaped structures that can form synapses with other cells. A **synapse** (SIN-aps) is a site of communication between a neuron and a target cell, which can be another neuron, a muscle fiber, or a gland cell. Within the synaptic end bulbs are many tiny membrane-enclosed sacs called **synaptic vesicles** that store chemical **neurotransmitters** (see Figure 7.28a). The arrival of an action potential at the synaptic end bulb ultimately causes the release of neurotransmitters from the synaptic vesicles. The released neurotransmitter molecules, in turn, excite or inhibit the target cell.

In order for an axon to function, materials must move between the cell body and axon terminals, a process known as **axonal transport**. Axonal transport uses proteins called **kinesins** and **dyneins** as “motors” to transport materials along the surfaces of microtubules of the neuron’s cytoskeleton (Figure 7.3). Each of these motor proteins has a region that binds to the particle to be transported and a region that binds to a microtubule. The bound particle is carried by the motor protein as the motor protein uses energy from ATP hydrolysis to “walk” along the surface of the microtubule. Axonal transport moves materials in both directions—away from and toward the cell body. Axonal transport that occurs in an **anterograde** (forward) direction involves kinesins. Anterograde transport moves organelles and synaptic vesicles from the cell body to the axon terminals. Axonal transport that occurs in a **retrograde** (backward) direction

![Figure 7.3 Axonal transport.](image)

**Axonal transport** that occurs in an anterograde (forward) direction involves kinesins; axonal transport that occurs in a retrograde (backward) direction involves dyneins.

**What substances undergo anterograde transport?**
6 Chapter 7 The Nervous System and Neuronal Excitability

Involves dyneins. Retrograde transport moves membrane vesicles and other cellular materials from the axon terminals to the cell body to be degraded or recycled. Substances that enter the neuron at the axon terminals are also moved to the cell body by retrograde transport. These substances include (1) trophic chemicals such as nerve growth factor and (2) harmful agents such as tetanus toxin and the viruses that cause rabies, herpes simplex, and polio.

**Clinical Connection**

Retrograde Transport and Tetanus Toxin

If *Clostridium tetani* bacteria are near a deep cut or puncture wound, they can enter the damaged area and release tetanus toxin. This toxin is then carried by retrograde transport into the CNS. There it ultimately causes activation of neurons that stimulate muscles to contract, which leads to prolonged and painful muscle spasms, a condition called tetanus. This disorder is also known as lockjaw because spasms in the jaw muscles make it difficult to open the mouth. The delay between the release of the toxin and the first appearance of symptoms is due, in part, to the time required for transport of the toxin to the cell body. For this reason, a deep cut or puncture wound in the head or neck is a more serious matter than a similar injury in the leg. The closer the site of injury is to the brain, the shorter the transit time, so treatment must begin quickly.

The length of an axon can vary from one neuron to another. Some neurons have axons as short as just a few microns. Other neurons have axons as long as a meter or more. Adjacent axons of similar lengths are often bundled together with connective tissue. A nerve is a bundle of axons in the PNS, whereas a tract is a bundle of axons in the CNS.

**Classification of Neurons**

Neurons are divided into three functional classes based on the direction in which the action potential is conveyed relative to the CNS (Figure 7.4).

1. **Sensory** or afferent neurons (AF-er-ent) convey action potentials from peripheral parts of the body into the CNS. They constitute the afferent division of the PNS. Most sensory neurons have only one process that extends from their cell bodies. This single process consists of several dendrites and one axon that are fused together. Sensory neurons are associated with sensory receptors that detect a sensory stimulus such as touch, pressure, light, or sound. Sensory receptors are either the dendrites of sensory neurons or separate cells that are located close to sensory neurons. When the dendrites of sensory neurons serve as sensory receptors, they may be encapsulated (surrounded by a connective tissue capsule) or free (not encapsulated). The trigger zone for action potentials is at the junction of the dendrites and the axon of the sensory neuron. Once an action potential is generated, it then propagates along the axon into the CNS.

2. **Motor** or efferent neurons (EF-e-rent) convey action potentials away from the CNS to effectors in the periphery. They comprise the efferent division of the PNS. Most motor neurons have numerous dendrites and one main axon extending from their cell bodies. Depending on the branch of the efferent division of the PNS to which they belong, motor neurons are further classified into two groups: somatic motor neurons and autonomic motor neurons. Somatic motor neurons are part of the somatic nervous system; they convey action potentials to skeletal muscles. Autonomic motor neurons, which are components of the autonomic nervous system, convey action potentials to cardiac muscle, smooth muscle, or glands.

3. **Interneurons** or association neurons are located entirely within the CNS between sensory and motor neurons. Interneurons are responsible for integration—they process incoming sensory information from sensory neurons and then may elicit a motor response by activating the appropriate motor neurons. Like motor neurons, interneurons usually have numerous dendrites and one main axon extending from their cell bodies. About 99% of all neurons in the body are interneurons.

**Neuroglia**

Neuroglia (noo-RO-glè-a) or glia make up about half the volume of the CNS. Their name derives from the idea of early histologists that they were simply the “glue” that held nervous tissue together. We now know that neuroglia are not merely passive bystanders but rather actively participate in the activities of nervous tissue. Generally, neuroglia are smaller than neurons, and they are 5 to 50 times more numerous. In contrast to neurons, glia do not generate or propagate action potentials, and they can multiply and divide in the mature nervous system. In cases of injury or disease, neuroglia multiply to fill in the spaces formerly occupied by neurons. Brain tumors derived from glia, called gliomas, tend to be highly malignant and to grow rapidly. Different types of neuroglia are present in the CNS and PNS.

**Neuroglia of the CNS**

There are four types of neuroglia in the CNS: astrocytes, oligodendrocytes, microglia, and ependymal cells (Figure 7.5).

1. **Astrocytes** (AS-trò-sìts) are the most numerous of the neuroglia. They have processes that wrap around capillaries (the smallest blood vessels) in the CNS. The walls of brain capillaries consist of endothelial cells (see Figure 14.4) that are joined together by tight junctions. In effect, the tight junctions between the endothelial cells create a blood–brain barrier, which isolates neurons of the CNS from harmful agents and other substances in the blood. Astrocyte processes surrounding brain capillaries secrete chemicals that maintain the “tightness” of these tight junctions. Details of the blood–brain barrier are discussed in Chapter 8. Astrocytes also help to maintain the appropriate chemical environment for the generation of action potentials. For example, they regulate the concentration of important ions such as K⁺, take...
7.2 Nervous Tissue

Oligodendrocytes (OL-i-gō-den′-drō-sīts) are responsible for forming and maintaining the myelin sheath around axons of neurons in the CNS. As you will see shortly, the myelin sheath is a multilayered lipid and protein covering around many axons that insulates them and increases the speed of conduction of action potentials.

Figure 7.4 Functional classes of neurons.

Neurons are divided into three functional classes: sensory neurons, interneurons, and motor neurons.

Which functional class of neurons is responsible for integration?

up excess neurotransmitters, and serve as a conduit for the passage of nutrients and other substances between capillaries and neurons. In the embryo, astrocytes secrete chemicals that appear to regulate the growth, migration, and interconnection among neurons in the brain. Astrocytes may also play a role in the formation of neural synapses.
8 Chapter 7 The Nervous System and Neuronal Excitability

Figure 7.5 Neuroglia of the central nervous system (CNS).

The four types of CNS neuroglia are astrocytes, oligodendrocytes, microglia, and ependymal cells.

Schwann cells (SCHVON or SCHWON) (Figure 7.6a) are a type of neuroglia found only in the PNS. They form the myelin sheath around axons of PNS neurons. Schwann cells also participate in axon regeneration, which is more easily accomplished in the PNS than in the CNS.

Myelination

The axons of many neurons are surrounded by a myelin sheath, a multilayered covering composed of lipids and proteins. Like insulation covering an electrical wire, the myelin sheath insulates the axon of a neuron and increases the speed of conduction of action potentials. Two types of neuroglia produce myelin sheaths: Schwann cells (in the PNS) and oligodendrocytes (in the CNS). In the PNS, each Schwann cell wraps about 1 millimeter of a single axon’s length by spiraling many times around the axon (Figure 7.6b). Eventually, as many as 100 layers of Schwann cell membrane surround the axon to form the myelin sheath.

Which CNS neuroglia function as phagocytes?

3. Microglia function as phagocytes. They remove cellular debris formed during normal development of the nervous system and phagocytize microbes and damaged nervous tissue.

4. Ependymal cells (ep-EN-de-mal) line the ventricles of the brain and central canal of the spinal cord. (Ventricles and the central canal are spaces filled with cerebrospinal fluid, which protects and nourishes the brain and spinal cord.) Functionally, ependymal cells produce and assist in the circulation of cerebrospinal fluid.

Neuroglia of the PNS

Ciliated microvilli on the surface of some cells

Node of Ranvier

Axon

Oligodendrocyte

Myelin sheath

Neurons

Ventricle

Astrocyte

Blood capillary

Neuron

Microglial cell

Ependymal cell

Microvillus

Cells of pia mater (inner covering around brain)

Oligodendrocyte

Microglial cell

Astrocytes

Ependymal cell

Ventricle

Oligodendrocyte

Node of Ranvier

Axon

Myelin sheath

Astrocyte

Blood capillary

Neuron

Microglial cell

Ependymal cell

Microvillus

Cells of pia mater (inner covering around brain)

Oligodendrocyte

Microglial cell

Astrocytes

Ependymal cell

Microvillus

Ventricle

Astrocyte

Blood capillary

Neuron

Microglial cell

Ependymal cell

Microvillus

Ventricle

Astrocyte

Blood capillary

Neuron

Microglial cell

Ependymal cell

Microvillus

Ventricle

Astrocyte

Blood capillary

Neuron

Microglial cell

Ependymal cell

Microvillus

Ventricle
Schwann cells form the myelin sheath around axons of neurons in the PNS.

(a) Schwann cells that have formed a myelin sheath around a PNS axon.

(b) Stages in the formation of a myelin sheath.

What is the functional significance of the myelin sheath?
Gaps in the myelin sheath, called **nodes of Ranvier** (RON-vé-ä), appear at intervals along the axon. Each Schwann cell wraps one axon segment between two nodes. In the CNS, an oligodendrocyte myelinites parts of several axons (see Figure 7.5). Each oligodendrocyte puts forth about 15 broad, flat processes that spiral around CNS axons to form the myelin sheath. Nodes of Ranvier are present, but they are fewer in number. Axons in the CNS or PNS that have a myelin sheath are said to be **myelinated**, and those without it are said to be **unmyelinated**.

**CLINICAL CONNECTION**

**Multiple Sclerosis**

**Multiple sclerosis** (MS) is a disease that causes a progressive destruction of myelin sheaths of neurons in the CNS. The condition's name describes its pathology: In *multiple* regions the myelin sheaths deteriorate to *sclerosis*, which are hardened scars or plaques. The destruction of myelin sheaths slows and then short-circuits conduction of action potentials. MS is an autoimmune disease—the body's own immune system spearheads the attack. This disease usually appears between the ages of 20 and 40. The first symptoms may include a feeling of heaviness or weakness in the muscles, abnormal sensations, or double vision. An attack is followed by a period of remission during which the symptoms temporarily disappear. One attack follows another over the years, usually every year or two. The result is a progressive loss of function interspersed with remission periods, during which symptoms abate.

Within the brain and spinal cord are regions that look white, known as **white matter**, and regions that appear gray, called **gray matter** (Figure 7.7). White matter is composed primarily of myelinated axons. The whitish color of myelin gives white matter its name. The gray matter of the nervous system contains neuronal cell bodies, dendrites, unmyelinated axons, axon terminals, and neuroglia. It appears grayish, rather than white, because of the absence of myelin in these areas. The arrangement of gray matter and white matter in the spinal cord and brain is discussed more extensively in Chapter 8.

**Regeneration of Nervous Tissue**

Human neurons have very limited powers of regeneration, the capability to replicate or repair themselves. In the PNS, an axon may undergo repair if the cell body is intact and if the Schwann cells that produce myelination remain active. Schwann cells aid the repair process by forming a **regeneration tube** that guides and stimulates regrowth of the axon. Therefore, a person who injures axons of a nerve in an upper limb, for example, has a good chance of regaining nerve function.

In the CNS, there is little or no repair of an axon after injury. This seems to result from two factors: (1) inhibitory influences

**CLINICAL CONNECTION**

**Neurogenesis**

**Neurogenesis**—the birth of new neurons from undifferentiated stem cells—occurs regularly in some animals. For example, new neurons appear and disappear every year in some songbirds. Until recently, the dogma in humans and other primates was "no new neurons" in the adult brain. Then, in 1998, scientists discovered **neural stem cells** that give rise to new neurons in the adult human hippocampus, an area of the brain that is crucial for learning. Recent evidence indicates that ependymal cells are also a source of neural stem cells. Researchers are currently trying to find ways to stimulate neural stem cells to replace neurons lost through damage or disease and to develop tissue-cultured neurons that can be used for transplantation purposes.

**Figure 7.7** Distribution of gray and white matter in the spinal cord and brain.

White matter consists primarily of myelinated axons of neurons. Gray matter consists of neuronal cell bodies, dendrites, unmyelinated axons, axon terminals, and neuroglia.

What is responsible for the white appearance of white matter?
from neuroglia, particularly oligodendrocytes, and (2) absence of growth-stimulating cues that were present during fetal development. Axons in the CNS are myelinated by oligodendrocytes rather than Schwann cells, and this CNS myelin is one of the factors inhibiting regeneration of neurons. Also, after axonal damage, nearby astrocytes proliferate rapidly, forming a type of scar tissue that acts as a physical barrier to regeneration. Thus, injury of the brain or spinal cord usually is permanent.

Checkpoint
5. Describe the functions of the dendrites, cell body, and axon of a neuron.
6. Discuss the three functional classes of neurons.
7. Explain the functions of astrocytes.
8. Why is there little or no repair of a CNS axon after an injury?

7.3 ELECTRICAL SIGNALS IN NEURONS

Objectives
- Describe the concept of electrical excitability.
- Compare the basic types of ion channels, and explain how they relate to graded potentials and action potentials.
- Explain the factors that determine the resting membrane potential.
- Outline the sequence of events that occurs during an action potential.

Neurons and muscle fibers communicate with one another using two types of electrical signals: (1) graded potentials, which are used for short-distance communication only and (2) action potentials, which allow communication over long distances in the body. Neurons and muscle fibers are considered to be excitable cells because they exhibit electrical excitability, the ability to respond to a stimulus and convert it into an action potential. An action potential that occurs in a neuron is called a nerve action potential or nerve impulse. In most neurons, an action potential causes the release of neurotransmitters, which allow the neuron to communicate with another neuron, a muscle fiber, or a gland. An action potential that occurs in a muscle fiber is called a muscle action potential or muscle impulse. When an action potential occurs in a muscle fiber, the muscle fiber contracts. The details of the nerve action potential are described in this section, and the details of the muscle action potential are discussed in Chapter 11.

To understand the functions of graded potentials and action potentials, consider how the nervous system allows you to feel the smooth surface of the pen you are using to write a letter. The nervous system would respond in the following way (Figure 7.8):

1. As you touch the pen, a graded potential develops in a sensory receptor in the skin of the fingers.
2. The graded potential triggers the axon of the sensory neuron to form a nerve action potential, which travels along the axon into the CNS and ultimately causes the release of neurotransmitter at a synapse with an interneuron.
3. The neurotransmitter stimulates the interneuron to form a graded potential in its dendrites and cell body.
4. In response to the graded potential, the axon of the interneuron forms a nerve action potential. The nerve action potential travels along the axon, which results in neurotransmitter release at the next synapse with another interneuron.
5. This process of neurotransmitter release at a synapse followed by the formation of a graded potential and then a nerve action potential occurs over and over as interneurons in higher parts of the brain (such as the thalamus and cerebral cortex) are activated. Once interneurons in the cerebral cortex, the outer part of the brain, are activated, perception occurs and you are able to feel the smooth surface of the pen touch your fingers. As you will learn in Chapter 8, perception, the conscious awareness of a sensation, is primarily a function of the cerebral cortex.

Suppose that you want to use the pen to write a letter. The nervous system would respond in the following way (Figure 7.8):

6. A stimulus in the brain causes a graded potential to form in the dendrites and cell body of an upper motor neuron, a type of motor neuron that synapses with a lower motor neuron farther down in the CNS in order to contract a skeletal muscle. The graded potential subsequently causes a nerve action potential to occur in the axon of the upper motor neuron, followed by neurotransmitter release.
7. The neurotransmitter generates a graded potential in a lower motor neuron, a type of motor neuron that directly supplies skeletal muscle fibers. The graded potential triggers the formation of a nerve action potential and then release of neurotransmitter at neuromuscular junctions formed with skeletal muscle fibers that control movements of the fingers. A neuromuscular junction (NMJ) is a type of synapse formed between a neuron and a skeletal muscle fiber.
8. The neurotransmitter stimulates the muscle fibers that control finger movements to form muscle action potentials. The muscle action potentials cause these muscle fibers to contract, which allows you to write with the pen.

In order to understand how graded potentials and action potentials are produced, it is important to have a basic knowledge of electricity. The body contains many types of charged particles such as ions, proteins, and the phosphate groups of ATP. Electrical forces exist between these charged particles. Like charges repel each other, and opposite charges attract each other. In some cases, a partition may separate opposite charges.

*An upper motor neuron is actually an interneuron, due to the fact that it is completely located within the CNS. So, the term upper motor neuron is a misnomer, but it continues to be used because this type of cell originates in the upper part of the CNS and it regulates the activity of lower motor neurons. A lower motor neuron, which originates in the lower part of the CNS, is a true motor neuron: It conveys action potentials from the CNS to skeletal muscle fibers in the periphery.
Graded potentials, nerve action potentials, and muscle action potentials are involved in the relay of sensory stimuli, integrative functions, and motor activities.

In which region of the brain does perception primarily occur?
Such a separation of positive and negative charges is a form of potential energy, which can do work. The electrical potential difference between opposite charges that are separated from each other is termed **voltage**, which is measured in units called **volts** or **millivolts** (1 mV = 0.001 V). Most cells, including excitable cells, have a separation of positive and negative charges just across their plasma membranes. The voltage that exists across the plasma membrane of a cell is called **membrane potential** ($V_m$). When a cell is at rest (unstimulated) the voltage that exists across the plasma membrane is specifically termed the **resting membrane potential**. You will soon learn, however, that the membrane potential can change when excitable cells are stimulated. These changes in membrane potential give rise to graded potentials and action potentials, allowing neurons to communicate with other neurons, muscle fibers, or glands.

The membrane potential is like voltage stored in a battery. If you connect the positive and negative terminals of a battery with a piece of wire, electrons will flow along the wire. This flow of charged particles is called **current**. In living cells, the flow of ions (rather than electrons) constitutes the electrical current. Current flow depends on two main factors: (1) voltage (the electrical potential difference between opposite charges that are separated from each other) and (2) the type of substance through which the charges move. **Resistance** is the hindrance to the flow of charges. **Conductors** are substances that permit fast current flow because they have a low resistance. The extracellular and intracellular fluids of the body are good conductors because they consist of ions that carry the current. **Insulators** are substances that decrease current flow because they have a high resistance. The plasma membrane is a good insulator, since membrane lipids have few charged groups and cannot carry current. The effect of voltage and resistance on current is defined by an equation called Ohm’s law (see Physiological Equation box).

The production of graded potentials and action potentials depends on two basic features of the plasma membrane of excitable cells: the presence of specific types of ion channels and the existence of a resting membrane potential.

### Ion Channels

Graded potentials and action potentials occur because the membranes of neurons contain many different kinds of ion channels that open or close in response to specific stimuli. Since the lipid bilayer of the plasma membrane is a good electrical insulator, the main paths for current to flow across the membrane are through the ion channels. When ion channels are open, they allow specific ions to move across the plasma membrane, down their **electrochemical gradient**—a concentration (chemical) difference plus an electrical difference. Recall that ions move from areas of higher concentration to areas of lower concentration (the chemical part of the gradient). Also, positively charged cations move toward a negatively charged area, and negatively charged anions move toward a positively charged area (the electrical aspect of the gradient). As ions move, they create a flow of electrical current that can change the membrane potential.

Ion channels open and close due to the presence of “gates.” The gate is a part of the channel protein that can seal the channel pore shut or move aside to open the pore (see Figure 5.6). The electrical signals produced by neurons rely on four types of ion channels: leak channels, ligand-gated channels, mechanically-gated channels, and voltage-gated channels (Figure 7.9).

1. The gates of **leak channels** randomly alternate between open and closed positions (Figure 7.9a). Typically, plasma membranes have many more potassium ion ($K^+$) leak channels than sodium ion ($Na^+$) leak channels, and the $K^+$ leak channels are leakier than the $Na^+$ leak channels. Thus, the membrane’s permeability to $K^+$ is much higher than its permeability to $Na^+$.

2. A **ligand-gated channel** opens or closes in response to a specific ligand (chemical) stimulus. A wide variety of ligands—including neurotransmitters, hormones, and chemicals in food or an odor—can open or close ligand-gated channels. The neurotransmitter acetylcholine, for example, opens cation channels that allow $Na^+$ and $Ca^{2+}$ to diffuse inward and $K^+$ to diffuse outward (Figure 7.9b).

3. A **mechanically-gated channel** opens or closes in response to mechanical stimulation in the form of touch, pressure, tissue stretching, or vibration (such as sound waves) (Figure 7.9c). The force distorts the channel from its resting position, opening the gate. Examples of mechanically-gated channels are those found in touch receptors and pressure receptors in the skin, in receptors that monitor stretching of internal organs, and in auditory receptors in the ears.

### Physiological Equation

**Ohm’s Law**

<table>
<thead>
<tr>
<th>Physical Law</th>
<th>Description</th>
</tr>
</thead>
</table>
| Ohm’s Law | express the relationship between current, voltage, and resistance:  
\[
I = \frac{V}{R}
\]
where  
$V$ is voltage measured in units called volts (V), and  
$R$ is resistance, which is measured in units called ohms (Ω).  

- **Current** ($I$) is directly proportional to **voltage** ($V$). This means that if voltage increases, current increases and that if voltage decreases, current decreases (assuming that resistance remains constant).
- **Current** ($I$) is inversely proportional to **resistance** ($R$). This means that if resistance increases, current decreases and that if resistance decreases, current increases (assuming that voltage remains constant).

Go to your online course for an expanded Video Explanation of this physiological equation.
Chapter 7 The Nervous System and Neuronal Excitability

Figure 7.9 Ion channels in the plasma membrane. (a) Leak channels randomly open and close. (b) A chemical stimulus—here, the neurotransmitter acetylcholine—opens a ligand-gated channel. (c) A mechanical stimulus opens a mechanically-gated channel. (d) A change in membrane potential opens voltage-gated $K^+$ channels during an action potential.

The electrical signals produced by neurons and muscle fibers rely on four types of ion channels: leak channels, ligand-gated channels, mechanically-gated channels, and voltage-gated channels.

What type of gated channel is activated by a touch on the arm?
7.3 Electrical Signals in Neurons

15

ence in charge across the membrane, the larger the membrane potential (voltage). Notice in Figure 7.10 that the excess charges are located only very close to the membrane. The rest of the extracellular fluid or cytosol contains equal numbers of positive and negative charges and is electrically neutral. It is important to point out that only a tiny fraction of all of the charges in the ECF and cytosol must be separated across the plasma membrane in order to establish the normal resting membrane potential.

By convention, membrane potential always compares the amount of net excess charge inside the cell relative to the outside. In neurons, the resting membrane potential ranges from $-40$ to $-90$ mV. A typical value is $-70$ mV. A cell that exhibits a membrane potential is said to be polarized. Most body cells are polarized; the membrane potential varies from $+5$ mV to $-100$ mV in different types of cells.

4. A voltage-gated channel opens in response to a change in membrane potential (voltage) (Figure 7.9d). Voltage-gated channels participate in the generation and conduction of action potentials.

Table 7.1 presents a summary of the four major types of ion channels in neurons.

### Resting Membrane Potential

The resting membrane potential exists because of an excess of negative ions in the cytosol along the inside surface of the membrane and an equal excess of positive ions in the extracellular fluid (ECF) along the outside surface of the membrane (Figure 7.10). Recall that a separation of positive and negative electrical charges is an electrical potential difference (voltage), which is measured in volts or millivolts. The greater the difference in charge across the membrane, the larger the membrane potential (voltage). Notice in Figure 7.10 that the excess charges are located only very close to the membrane. The rest of the extracellular fluid or cytosol contains equal numbers of positive and negative charges and is electrically neutral. It is important to point out that only a tiny fraction of all of the charges in the ECF and cytosol must be separated across the plasma membrane in order to establish the normal resting membrane potential.

By convention, membrane potential always compares the amount of net excess charge inside the cell relative to the outside. In neurons, the resting membrane potential ranges from $-40$ to $-90$ mV. A typical value is $-70$ mV. A cell that exhibits a membrane potential is said to be polarized. Most body cells are polarized; the membrane potential varies from $+5$ mV to $-100$ mV in different types of cells.

**Figure 7.10** Distribution of charges that produce the resting membrane potential of a neuron.

![Distribution of charges](image)

The resting membrane potential is an electrical potential difference (voltage) that exists across the plasma membrane of an excitable cell under resting conditions.

Does it take a large number of charges to be separated across the plasma membrane in order to establish the normal resting membrane potential?
Chapter 7 The Nervous System and Neuronal Excitability

The resting membrane potential of a neuron can be measured using an instrument known as a voltmeter. During this procedure, the tip of a recording microelectrode is inserted inside the neuron and a reference (ground) electrode is placed outside the neuron in the extracellular fluid. (Electrodes are devices that conduct electrical charges.) The two electrodes are connected to the voltmeter, which detects the electrical potential difference (voltage) across the plasma membrane. By convention, the extracellular fluid is designated as the ground and given a value of 0 mV. This allows the voltmeter to detect the excess electrical charges inside the cell relative to the outside.

Determinants of the Resting Membrane Potential

The resting membrane potential is determined by two major factors:

1. Unequal distribution of ions in the ECF and cytosol. The concentrations of major cations and anions are different outside and inside cells (Figure 7.11). Extracellular fluid (ECF) is rich in Na⁺ and chloride ions (Cl⁻). In cytosol, however, the main cation is K⁺, and the two dominant anions are proteins and the phosphate ions attached to molecules such as the three phosphates in ATP. The symbol A⁻ is used to collectively refer to the negatively charged (anionic) proteins and phosphate ions of the cytosol. The concentrations of selected solutes in extracellular fluid and cytosol (intracellular fluid) are listed in Table 7.2. As you will soon learn, the unequal distribution of ions in the ECF and cytosol establishes the concentration gradients that certain ions use to help generate the resting membrane potential.

2. Differences in membrane permeability to various ions. In neurons at rest, there are differences in membrane permeability to various ions because some ions are able to pass through the membrane via specific leak channels, whereas other ions do not have transport mechanisms allowing them passage through the membrane. In general, the more permeable the plasma membrane is to a particular ion, the greater the influence that ion has on the resting membrane potential. This is due to the fact that ion movement across the membrane can alter the number of negative or positive charges that are located along the inside and outside surfaces of the membrane. Of all the solutes present in the ECF and cytosol, neurons at rest are most permeable to K⁺ ions because K⁺ leak channels are the most abundant type of leak channel in their plasma membranes (Figure 7.11). This high K⁺ permeability allows K⁺ ions to influence the resting membrane potential to a much greater extent than any other type of ion. Resting neurons are also permeable to Na⁺ ions because their plasma membranes contain Na⁺ leak channels (Figure 7.11). However, Na⁺ permeability is lower than K⁺ permeability because there are fewer Na⁺ leak channels than K⁺ leak channels. This means that Na⁺ ions do influence the resting membrane potential of a neuron, but to a lesser extent than K⁺ ions. Neurons at rest are also permeable to Cl⁻ ions due to the presence of Cl⁻ leak channels in their plasma membranes. However, for reasons that will be discussed later in this section, chloride ions do not make a significant contribution to the resting membrane potential in most neurons.
7.3 Electrical Signals in Neurons

**Figure 7.11 Factors that contribute to the resting membrane potential.** Factors that contribute to the inside-negative resting membrane potential of a cell include the unequal distribution of ions in the ECF and cytosol and differences in membrane permeability to various ions. Because the ECF is rich in Na\(^+\) and Cl\(^-\) ions and the cytosol is rich in K\(^+\) ions and A\(^-\) ions (anionic proteins and phosphates), concentration gradients are established. These concentration gradients can be used by certain ions to generate the resting membrane potential. The more permeable the plasma membrane is to a particular ion, the greater the influence that ion has on the resting membrane potential. Of all solutes present in the ECF and cytosol, neurons at rest are most permeable to K\(^+\) and somewhat permeable to Na\(^+\). The permeability of a resting cell is due to the presence of leak channels. The plasma membrane has a large number of K\(^+\) leak channels and a smaller number of Na\(^+\) leak channels. This allows K\(^+\) ions to have a greater influence on the resting membrane potential than Na\(^+\) ions.

The resting membrane potential is determined by two major factors: (1) unequal distribution of ions in the ECF and cytosol and (2) differences in membrane permeability to various ions.

Although resting neurons are permeable to K\(^+\), Na\(^+\), and Cl\(^-\) ions, they are essentially impermeable to Ca\(^{2+}\) ions and the anionic proteins and phosphates (A\(^-\) ions) of the cytosol because plasma membranes of most resting neurons do not have leak channels or other transport mechanisms for these ions. Therefore, Ca\(^{2+}\) and A\(^-\) ions do not have a direct impact on the resting membrane potential. In summary, the resting membrane potential of most neurons is influenced primarily by K\(^+\) ions and to a lesser extent by Na\(^+\) ions, and is not significantly influenced by Cl\(^-\), Ca\(^{2+}\), or A\(^-\) ions.

**Table 7.2 Concentrations of Selected Solutes in Extracellular and Intracellular Fluids**

<table>
<thead>
<tr>
<th>Ion</th>
<th>Extracellular Fluid (mM(^*))</th>
<th>Intracellular Fluid (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K(^+)</td>
<td>5</td>
<td>150</td>
</tr>
<tr>
<td>Na(^+)</td>
<td>145</td>
<td>15</td>
</tr>
<tr>
<td>Cl(^-)</td>
<td>115</td>
<td>5</td>
</tr>
<tr>
<td>A(^-)</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Ca(^{2+})</td>
<td>2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\(^*\)mM = millimolar, which represents the number of millimoles per liter (mmol/L).

**Membrane Potential Generation**

To understand how K\(^+\) and Na\(^+\) ions influence the resting membrane potential, let’s first consider how membrane potential is generated in a hypothetical neuron that is permeable to just one type of ion (either K\(^+\) ions or Na\(^+\) ions). Then you will learn how membrane potential is generated in a real neuron that is permeable to both K\(^+\) and Na\(^+\) ions.
Membrane Potential Generation in a Hypothetical Neuron Permeable Only to Potassium Ions  Suppose that the following conditions exist in a hypothetical neuron (Figure 7.12): (1) Only K⁺ leak channels are present in the plasma membrane, making the membrane permeable just to K⁺ ions; (2) the ECF contains a high concentration of Na⁺ and Cl⁻ ions, and the cytosol contains a high concentration of K⁺ and A⁻ ions; (3) both the ECF and cytosol initially are electrically neutral because each solution starts off with the same total number of positive and negative charges; and (4) since the plasma membrane is permeable only to K⁺ ions, the other ions in the ECF or cytosol cannot move across the membrane. In this scenario, the movement of K⁺ ions across the plasma membrane will generate a membrane potential in the following way (Figure 7.12):

1. The K⁺ leak channels are initially closed and no membrane potential exists. If the K⁺ leak channels of the neuron are initially closed, K⁺ ions cannot move across the plasma membrane. A membrane potential does not exist at this point because there are equal numbers of positive and negative charges in the ECF and cytosol.

2. The K⁺ leak channels open and an inside-negative membrane potential is generated because K⁺ ions move out of the neuron. Opening the K⁺ leak channels allows K⁺ ions to move down their concentration gradient from the cytosol into the ECF. As K⁺ ions move into the ECF, the outside surface of the plasma membrane becomes positively charged. At the same time, the inside surface of the plasma membrane becomes negatively charged because A⁻ ions are left behind in the cytosol and cannot follow the K⁺ ions into the ECF. An inside-negative membrane potential now exists because there is an excess of negative charges along the inside surface of the membrane and an excess of positive charges along the outside surface of the membrane.

3. The membrane potential becomes more negative because K⁺ ions continue to move out of the neuron. As K⁺ ions continue to move out of the neuron, the membrane potential becomes more negative. However, K⁺ movement out of the neuron eventually slows down because the negative membrane potential creates an electrical gradient that favors movement of K⁺ ions from the ECF into the cytosol. Since K⁺ ions are positively charged, they are attracted to the negative charges along the inside surface of the membrane and are repelled by the positive charges along the outside surface of the membrane. As some K⁺ ions leave the neuron moving down their concentration gradient, other K⁺ ions enter the neuron moving down their electrical gradient. At this point, however, there is net movement of K⁺ ions out of the neuron because the magnitude of the K⁺ concentration gradient is greater than the magnitude of the K⁺ electrical gradient.

4. At the potassium equilibrium potential (E_K'), there is no net movement of K⁺ ions into or out of the neuron. As the membrane potential becomes more negative, the magnitude of the K⁺ electrical gradient increases. Eventually, the K⁺ electrical gradient becomes equal in magnitude to the opposing K⁺ concentration gradient and there is no net movement of K⁺ ions into or out of the neuron. The membrane potential that exists at this equilibrium is called the K⁺ equilibrium potential (E_K'); and it is equal to -90 mV. In general, an equilibrium potential is the membrane potential at which the concentration gradient and electrical gradient for a particular ion are equal in magnitude but opposite in direction and there is no net movement of that ion across the plasma membrane. It is important to note that only a tiny number of K⁺ ions pass through the plasma membrane to establish the K⁺ equilibrium potential, which means that the K⁺ concentrations in the cytosol and ECF are not significantly altered during this process.

Membrane Potential Generation in a Hypothetical Neuron Permeable Only to Sodium Ions  Now suppose that the following conditions exist in another hypothetical neuron (Figure 7.13): (1) Only Na⁺ leak channels are present in the plasma membrane, making the membrane permeable just to Na⁺ ions; (2) the ECF contains a high concentration of Na⁺ and Cl⁻ ions, and the cytosol contains a high concentration of K⁺ and A⁻ ions; (3) both the ECF and cytosol initially are electrically neutral because each solution starts off with the same total number of positive and negative charges; and (4) since the plasma membrane is permeable only to Na⁺ ions, the other ions in the ECF or cytosol cannot move across the membrane. In this scenario, the movement of Na⁺ ions across the plasma membrane will generate a membrane potential in the following way (Figure 7.13):

1. The Na⁺ leak channels are initially closed and no membrane potential exists. If the Na⁺ leak channels of the neuron are initially closed, Na⁺ ions cannot move across the plasma membrane. A membrane potential does not exist at this point because there are equal numbers of positive and negative charges in the ECF and cytosol.

2. The Na⁺ leak channels open and an inside-positive membrane potential is generated because Na⁺ ions move into the neuron. Opening the Na⁺ leak channels allows Na⁺ ions to move down their concentration gradient from the cytosol into the ECF. As Na⁺ ions enter the neuron, the inside surface of the plasma membrane becomes positively charged. At the same time, the outside surface of the plasma membrane becomes negatively charged because Cl⁻ ions are left behind in the ECF and cannot follow Na⁺ ions into the cytosol. An inside-positive membrane potential now exists because there is an excess of positive charges along the inside surface of the membrane and an excess of negative charges along the outside surface of the membrane.

3. The membrane potential becomes more positive because Na⁺ ions continue to move into the neuron. As Na⁺ ions continue to move into the neuron, the membrane potential becomes more positive. However, Na⁺ entry into the neuron eventually slows down because the positive membrane potential creates an electrical gradient that favors movement of Na⁺ ions from the cytosol into the ECF. Since Na⁺ ions are positively charged, they are attracted to the negative charges...


**Figure 7.12** Membrane potential generation in a hypothetical neuron permeable only to K⁺ ions.

In a hypothetical neuron that is permeable only to K⁺ ions, an inside-negative membrane potential will be generated if there is net movement of K⁺ ions from the cytosol into the ECF.

1. The K⁺ channels are initially closed and no membrane potential exists.

2. The K⁺ leak channels open and an inside-negative membrane potential is generated because K⁺ ions move out of the neuron.

3. The membrane potential becomes more negative because K⁺ ions continue to move out of the neuron.

4. At the potassium equilibrium potential (E_K), there is no net movement of K⁺ ions into or out of the neuron.

**Question:** Why does the K⁺ electrical gradient favor movement of K⁺ ions from the ECF into the cytosol when an inside-negative membrane potential exists?
Chapter 7 The Nervous System and Neuronal Excitability

Figure 7.13 Membrane potential generation in a hypothetical neuron permeable only to Na\(^+\) ions.

1. The Na\(^+\) leak channels are initially closed and no membrane potential exists.

2. The Na\(^+\) leak channels open and an inside-positive membrane potential is generated because Na\(^+\) ions move into the neuron.

3. The membrane potential becomes more positive because Na\(^+\) ions continue to move into the neuron.

4. At the sodium equilibrium potential (\(E_{Na}\)), there is no net movement of Na\(^+\) ions into or out of the neuron.

Why does the Na\(^+\) electrical gradient favor movement of Na\(^+\) ions from the cytosol into the ECF when an inside-positive membrane potential exists?
on the outside surface of the membrane and are repelled by the positive charges on the inside surface of the membrane. As some Na$^+$ ions enter the neuron moving down their concentration gradient, other Na$^+$ ions leave the neuron moving down their electrical gradient. At this point, however, there is no net movement of Na$^+$ ions into the neuron because the magnitude of the Na$^+$ concentration gradient is greater than the magnitude of the Na$^+$ electrical gradient.

4. At the sodium equilibrium potential ($E_{Na}$), there is no net movement of Na$^+$ ions into or out of the neuron. As the membrane potential becomes more positive, the magnitude of the Na$^+$ electrical gradient increases. Eventually, the Na$^+$ electrical gradient becomes equal in magnitude to the opposing Na$^+$ concentration gradient and there is no net movement of Na$^+$ ions into or out of the neuron. The membrane potential that exists at this equilibrium is called the Na$^+$ equilibrium potential ($E_{Na}$) and it is equal to +60 mV. Since only a tiny number of Na$^+$ ions cross the membrane to form the Na$^+$ equilibrium potential, the Na$^+$ concentrations in the ECF and cytosol are not significantly changed. The equilibrium potential for Na$^+$, K$^+$, or any other ion can be calculated by using the Nernst equation (see Physiological Equation box).

Membrane Potential Generation in a Real Neuron Permeable to Both Potassium and Sodium Ions Unlike the hypothetical neurons that were just described, a real neuron is permeable to both K$^+$ and Na$^+$ ions (Figure 7.14). Recall that a typical neuron has the following characteristics: (1) It is more permeable to K$^+$ ions than to Na$^+$ ions because its plasma membrane contains more K$^+$ leak channels than Na$^+$ leak channels; (2) the ECF contains a high concentration of Na$^+$ and Cl$^-$ ions, and the cytosol contains a high concentration of K$^+$ and A$^-$ ions; and (3) it is impermeable to A$^-$ ions. In order to describe the generation of membrane potential in a real neuron, assume that both the ECF and cytosol initially are electrically neutral because each solution starts off with the same total number of positive and negative charges. You should realize, however, that once the membrane potential is established, the ECF and cytosol will not be electrically neutral because of the separation of positive and negative charges that will exist just across the plasma membrane. In a typical neuron that is more permeable to K$^+$ ions than to Na$^+$ ions, the movement of K$^+$ and Na$^+$ ions across the plasma membrane will generate a membrane potential in the following way (Figure 7.14):

1. The K$^+$ and Na$^+$ leak channels are initially closed and no membrane potential exists. If the K$^+$ and Na$^+$ leak channels of the neuron are initially closed, K$^+$ and Na$^+$ ions cannot move across the plasma membrane. A membrane potential does not exist at this point because there are equal numbers of positive and negative charges in the ECF and cytosol.

2. The K$^+$ and Na$^+$ leak channels open and an inside-negative membrane potential is generated because the number of K$^+$ ions that move out of the neuron is greater than the number of Na$^+$ ions that move into the neuron. Opening the K$^+$ leak channels allows K$^+$ ions to move down their concentration gradient from the cytosol into the ECF. Opening the Na$^+$ leak channels allows Na$^+$ ions to move down their concentration gradient from the ECF into the cytosol. Because the plasma membrane of a neuron is more permeable to K$^+$ ions than to Na$^+$ ions, the number of K$^+$ ions that move out of the neuron is greater than the number of Na$^+$ ions that move into the neuron. In other words, there is net movement of positive charge out of the neuron. Since the amount of K$^+$ ions that enter the ECF is greater than the amount of Na$^+$ ions that enter the

### Physiological Equation

#### Nernst Equation

The equilibrium potential is the membrane potential at which the concentration gradient and the electrical gradient for a particular ion are equal in magnitude and opposite in direction and there is no net movement of that ion across the plasma membrane. If the extracellular and intracellular concentrations of an ion are known, the equilibrium potential for that ion can be calculated by using the Nernst equation:

$$E_x = \frac{zF}{RT} \log \left( \frac{[X]_{\text{out}}}{[X]_{\text{in}}} \right)$$

where $E_x$ is the equilibrium potential of ion X in millivolts at 37°C, $[X]_{\text{out}}$ is the extracellular concentration of ion X in millimoles/liter (mM), $[X]_{\text{in}}$ is the intracellular concentration of ion X in millimoles/liter (mM), and $z$ is the valence of ion X (for K$^+$ and Na$^+$ ions, the valence is +1).

Using the K$^+$ and Na$^+$ concentrations listed in Table 7.2, the K$^+$ and Na$^+$ equilibrium potentials can be calculated using the Nernst equation in the following way:

$$E_{K} = \frac{61}{+1} \log \frac{5}{150} = -90 \text{ mV}$$

$$E_{Na} = \frac{61}{+1} \log \frac{145}{15} = +60 \text{ mV}$$

Go to your online course for an expanded Video Explanation of this physiological equation.
Figure 7.14 Membrane potential generation in a real neuron that is more permeable to K\(^+\) ions than to Na\(^+\) ions.

In a real neuron that is more permeable to K\(^+\) ions than to Na\(^+\) ions, an inside-negative membrane potential is generated because the number of K\(^+\) ions that move out of the neuron is greater than the number of Na\(^+\) ions that move into the neuron.

1. The K\(^+\) and Na\(^+\) leak channels are initially closed and no membrane potential exists.

2. The K\(^+\) and Na\(^+\) leak channels open and an inside-negative membrane potential is generated because the number of K\(^+\) ions that move out of the neuron is greater than the number of Na\(^+\) ions that move into the neuron.

3. The membrane potential becomes more negative because the number of K\(^+\) ions that move out of the neuron continues to surpass the number of Na\(^+\) ions that move into the neuron.

4. The membrane potential of the neuron stabilizes around –70 mV.

Suppose that the plasma membrane of a neuron has more Na\(^+\) leak channels than K\(^+\) leak channels. What effect would this have on the resting membrane potential?
cytosol, the outside surface of the plasma membrane becomes positively charged. At the same time, the inside surface of the plasma membrane becomes negatively charged because A ions are left behind in the cytosol and cannot follow the K ions into the ECF. An inside-negative membrane potential now exists because there is an excess of negative charges along the inside surface of the membrane and an excess of positive charges along the outside surface of the membrane.

3 The membrane potential becomes more negative because the number of K ions that move out of the neuron continues to surpass the number of Na ions that move into the neuron. The continuous movement of more K out of the neuron and less Na into the neuron causes the membrane potential to become more negative. Eventually, K movement out of the neuron slows down and Na entry into the neuron speeds up. This is due to the fact that the negative membrane potential creates an electrical gradient that favors movement of both Na and K ions into the neuron. Because K and Na ions are positively charged, they are attracted to the negative charges along the inside surface of the membrane and are repelled by the positive charges along the outside surface of the membrane. Since both the Na electrical gradient and the Na concentration gradient promote movement of Na ions from the ECF into the cytosol, Na movement into the neuron speeds up. Since the K concentration gradient promotes movement of K ions from the cytosol into the ECF and the K electrical gradient promotes movement of K ions from the ECF into the cytosol, K movement out of the neuron slows down. There is still net movement of K ions out of the neuron, however, because the magnitude of the K concentration gradient is greater than the magnitude of the K electrical gradient.

4 The membrane potential of the neuron stabilizes around −70 mV. With the help of Na+/K+ ATPases (described shortly), the resting membrane potential of the neuron stabilizes when it reaches about −70 mV. At this point, K movement out of the neuron is exactly balanced by Na movement into the neuron and there is no net movement of charge across the membrane. Note that the resting membrane potential (−70 mV) of a neuron is not equal to either the K equilibrium potential (−90 mV) or the Na equilibrium potential (+60 mV). However, the resting membrane potential is closer to the K equilibrium potential than to the Na equilibrium potential. This is due to the fact that a resting neuron is more permeable to K ions than it is to Na ions, which allows K ions to have a greater influence on the resting membrane potential than Na ions. The resting membrane potential of a neuron can be calculated by using the Goldman-Hodgkin-Katz equation (see Physiological Equation box).

Contribution of the Na+/K+ ATPases

Since the resting membrane potential (−70 mV) is not equal to either the K equilibrium potential (−90 mV) or the Na equilibrium potential (+60 mV), some K continuously leaks out of the neuron and some Na continuously leaks into the neuron. Left unchecked, the small outward K leak and the small

### Physiological Equation

Goldman-Hodgkin-Katz Equation

Resting membrane potential is determined by two major factors: (1) an unequal distribution of ions in the ECF and cytosol and (2) differences in membrane permeability to various ions. These factors are expressed mathematically by the Goldman-Hodgkin-Katz (GHK) equation, which can be used to calculate the resting membrane potential of a neuron. Since the resting membrane potential of most neurons is influenced mainly by K and Na ions, a simplified version of the GHK equation is as follows:

\[
V_m = 61 \log \left( \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in}} \right)
\]

where

- \( V_m \) is the resting membrane potential in mV at 37°C,
- \( P_K \) is the potassium membrane permeability value (in most neurons, \( P_K = 1 \)),
- \( P_{Na} \) is the sodium membrane permeability value (in most neurons, \( P_{Na} = 0.04 \)),
- \( [K^+]_{out} \) is the extracellular K concentration in millimoles per liter (mM),
- \( [K^+]_{in} \) is the intracellular K concentration in millimoles per liter (mM),
- \( [Na^+]_{out} \) is extracellular Na concentration in millimoles per liter (mM), and
- \( [Na^+]_{in} \) is intracellular Na concentration in millimoles per liter (mM).

Using the membrane permeability values for K and Na listed above and the K and Na concentrations listed in Table 7.2, the resting membrane potential of a neuron can be calculated using the GHK equation in the following way:

\[
V_m = 61 \log \left( \frac{1(5) + 0.04(145)}{1(150) + 0.04(15)} \right) = -70 \text{ mV}
\]

Note that if the potassium membrane permeability value (\( P_K \)) is set to zero in the GHK equation, then the potassium terms in the GHK equation are eliminated, and the GHK equation becomes the Nernst equation for Na ions. Alternatively, if the sodium membrane permeability value (\( P_{Na} \)) is set to zero in the GHK equation, then the sodium terms in the GHK equation are eliminated, and the GHK equation becomes the Nernst equation for K ions. In essence, the GHK equation is an extended version of the Nernst equation that takes into account the differences in membrane permeability to K ions and Na ions.

Go to your online course for an expanded Video Explanation of this physiological equation.
inward Na\(^+\) leak would eventually dissipate the K\(^+\) and Na\(^+\) concentration gradients. This does not happen because the inward Na\(^+\) leak and outward K\(^+\) leak are offset by the Na\(^+/\)K\(^+\) ATPases (sodium-potassium pumps) (see step 4 in Figure 7.14). Recall from Chapter 5 that the Na\(^+/\)K\(^+\) ATPases maintain the K\(^+\) and Na\(^+\) concentration gradients by expelling three Na\(^+\) ions for each two K\(^+\) ions imported, using energy derived from the hydrolysis of ATP (see Section 5.3). Since these pumps remove more positive charges from the cell than they bring into the cell, they are *electrogenic*, which means they contribute to the negativity of the resting membrane potential. However, their total contribution is very small, only a few millivolts of the total −70 mV resting membrane potential in a typical neuron.

**Existence of the Resting Neuron in a Steady State**

As noted above, the Na\(^+/\)K\(^+\) ATPases help maintain the resting membrane potential by using energy derived from ATP hydrolysis to pump out Na\(^+\) as fast as it leaks in and to bring in K\(^+\) as fast as it leaks out. This means that there is no net charge movement across the membrane of a resting neuron because Na\(^+\) leakage into the cell and K\(^+\) leakage out of the cell are exactly balanced by the constant activity of the Na\(^+/\)K\(^+\) ATPases. Because there is no net charge movement across the membrane and energy is required to maintain this constant condition, the resting neuron exists in a steady state. Recall that when a *steady state* exists, energy is required to keep a particular condition constant (see Section 1.4).

**Chloride Ions and the Resting Membrane Potential**

Neurons at rest are permeable to Cl\(^-\) ions because their plasma membranes contain Cl\(^-\) leak channels. In most neurons, however, Cl\(^-\) ions do not significantly influence the resting membrane potential because there is no net movement of these ions across the plasma membrane though the Cl\(^-\) leak channels. This is ultimately the result of the fact that the plasma membranes of these cells lack active transport mechanisms for maintaining the Cl\(^-\) concentration gradient. Instead, Cl\(^-\) ions passively distribute across the membrane until the chloride equilibrium potential (E\(_{\text{Cl}}\)) becomes the same as the resting membrane potential. In other words, at −70 mV, the Cl\(^-\) concentration gradient (from ECF to cytosol) is equal in magnitude to the opposing Cl\(^-\) electrical gradient (from cytosol to ECF) and there is no net Cl\(^-\) movement across the membrane.

Some neurons, however, do have active transport mechanisms that move Cl\(^-\) ions against their concentration gradient from the cytosol into the ECF. This generates a stronger Cl\(^-\) concentration gradient compared to what would be the case without active Cl\(^-\) transport. Consequently, the magnitude of the Cl\(^-\) concentration gradient becomes greater than the magnitude of the Cl\(^-\) electrical gradient and there is net movement of Cl\(^-\) ions from the ECF into the cytosol of the neuron (via Cl\(^-\) leak channels in the membrane) under resting conditions. This means that E\(_{\text{Cl}}\) is not equal to the resting membrane potential; in fact E\(_{\text{Cl}}\) is more negative than the resting membrane potential in cells that actively transport Cl\(^-\) ions. Since there is net movement of Cl\(^-\) ions across the membrane, Cl\(^-\) ions make a significant contribution to the resting membrane potential in these cells.

**Graded Potentials**

A *graded potential* is a small deviation from the membrane potential that makes the membrane either more polarized (inside more negative) or less polarized (inside less negative). When the response makes the membrane more polarized (inside more negative), it is termed a *hyperpolarizing graded potential* (Figure 7.15a). When the response makes the membrane less polarized (inside less negative), it is termed a *depolarizing graded potential* (Figure 7.15b). The duration of a hyperpolarizing or depolarizing graded potential can last from several msec to several minutes.

**Figure 7.15** Graded potentials. Most graded potentials occur in the dendrites and cell body (areas colored blue in the inset).

During a hyperpolarizing graded potential, the membrane potential is inside more negative than the resting level. During a depolarizing graded potential, the membrane potential is inside less negative than the resting level.

![Hyperpolarizing graded potential](a)

![Depolarizing graded potential](b)

What kind of graded potential describes a change in membrane potential from −70 to −60 mV? From −70 to −80 mV?
A graded potential occurs in a small region of membrane when a stimulus causes mechanically-gated channels or ligand-gated channels to open or close in an excitable cell’s plasma membrane (Figure 7.16). Mechanically-gated channels and ligand-gated channels can be present in the dendrites of sensory neurons, and ligand-gated channels are numerous in the dendrites and cell bodies of interneurons and motor neurons (see Table 7.1). Hence, graded potentials occur mainly in the dendrites and cell body of a neuron.

To say that these electrical signals are graded means that they vary in amplitude (size), depending on the strength of the stimulus (Figure 7.17). Graded potentials are larger or smaller depending on how many ligand-gated or mechanically-gated channels have opened (or closed) and how long each remains open.

**Figure 7.16** Generation of graded potentials in response to the opening of mechanically-gated channels or ligand-gated channels. (a) A mechanical stimulus such as pressure opens a mechanically-gated channel that allows passage of cations (mainly Na\(^+\) and Ca\(^{2+}\)) into the cell and a depolarizing graded potential occurs because the membrane potential becomes inside less negative than at rest. (b) The neurotransmitter acetylcholine (a ligand stimulus) opens a cation channel that allows passage of Na\(^+\), K\(^+\), and Ca\(^{2+}\), but Na\(^+\) inflow is greater than either Ca\(^{2+}\) inflow or K\(^+\) outflow and a depolarizing graded potential occurs because the membrane potential becomes inside less negative than at rest. (c) The neurotransmitter glycine (a ligand stimulus) opens a Cl\(^-\) channel that allows passage of Cl\(^-\) ions into the cell and a hyperpolarizing graded potential occurs because the membrane potential becomes inside more negative than at rest.

Which parts of a neuron contain mechanically-gated channels? Ligand-gated channels?
open. The opening or closing of these ion channels alters the number of specific ions that move across the plasma membrane to cause the graded potential. The amplitude of a graded potential can vary from less than 1 mV to more than 50 mV.

After it is generated, a graded potential spreads along the membrane in both directions away from the stimulus source. The spread of a graded potential is accomplished by local current flow. Local current flow refers to the passive movement of charges from one region of membrane to adjacent regions of membrane due to differences in membrane potential in these regions. To understand how a graded potential spreads along the membrane by local current flow, consider what happens when a ligand stimulus or a mechanical stimulus causes a depolarizing graded potential to form in one of the dendrites of a neuron (Figure 7.18):

1. **A depolarizing graded potential is generated.** A ligand stimulus or a mechanical stimulus generates a depolarizing graded potential in a region of dendrite membrane (membrane region C).

2. **Local current flow occurs.** Local current flow occurs in the cytosol as positive charges move from depolarized membrane region C to the more negative adjacent membrane regions B and D that are still at resting membrane potential. At the same time, local current flow occurs in the ECF as positive charges move from the more positive adjacent membrane regions B and D to the more negative membrane region C.

**Figure 7.17** The graded nature of graded potentials. As the stimulus strength increases (stimuli 1, 2, and 3), the amplitude (size) of each resulting depolarizing graded potential increases. Although not shown, a similar relationship exists between stimulus strength and the amplitude of a hyperpolarizing graded potential.

The amplitude of a graded potential depends on the stimulus strength. The greater the stimulus strength, the larger the amplitude of the graded potential.

![Graph: Membrane potential in millivolts (mV) versus Time in milliseconds (msec)]

**Why does a stronger stimulus cause a larger graded potential than a weaker stimulus?**

**Generation of Action Potentials**

An action potential (AP) or impulse is a sequence of rapidly occurring events that decrease and reverse the membrane potential and then eventually restore it to the resting state. An action potential has two main phases: a depolarizing phase and a repolarizing phase (Figure 7.21a). During the depolarizing phase, or rising phase, the negative membrane potential becomes more positive, reaches zero, and then becomes more negative. The depolarizing phase reaches its peak at +30 mV. The part of the depolarizing phase between 0 mV and +30 mV is called the overshoot. During the repolarizing phase, or falling phase, the membrane potential is restored to the resting state of −70 mV. Following the repolarizing phase there may be an afterhyperpolarizing phase, also called the undershoot, during which the membrane potential temporarily becomes more negative.

**The depolarizing graded potential spreads along the membrane.** As a result of local current flow, adjacent membrane regions B and D become depolarized. In other words, the graded potential spreads along the membrane in both directions away from the stimulus source.

As a graded potential spreads to adjacent regions of membrane by local current flow, it gradually dies out because its charges are lost across the membrane through leak channels. This mode of travel by which graded potentials die out as they spread along the membrane is known as decremental conduction. Figure 7.19 shows that the amplitude of a graded potential decreases as the distance from the graded potential’s point of origin increases. Because they die out within a few millimeters of where they originate, graded potentials are useful for short-distance communication only.

Although an individual graded potential undergoes decremental conduction, it can become stronger and last longer by summat ing with other graded potentials. **Summation** is the process by which graded potentials add together. If two depolarizing graded potentials summate, the net result is a larger depolarizing graded potential (Figure 7.20). If two hyperpolarizing graded potentials summate, the net result is a larger hyperpolarizing graded potential. If two equal but opposite graded potentials summate (one depolarizing and the other hyperpolarizing), they cancel each other out and the overall graded potential disappears. You will learn more about the process of summation later in this chapter.

Graded potentials have different names depending on which type of stimulus causes them and where they occur. For example, when a graded potential occurs in the dendrites or cell body of a neuron in response to a neurotransmitter, it is called a postsynaptic potential (explained in Section 7.4). The graded potentials that occur in sensory receptors are termed receptor potentials or generator potentials, depending on the type of sensory receptor that is involved (explained in Chapter 9). When a graded potential occurs in the plasma membrane of a skeletal muscle fiber at the neuromuscular junction (NMJ), it is called an end plate potential (EPP) (explained in Chapter 11).
**7.3 Electrical Signals in Neurons**

**Figure 7.18** The spread of a depolarizing graded potential by local current flow.

Because of local current flow, a graded potential spreads along the plasma membrane in both directions away from the stimulus source.

1. A depolarizing graded potential is generated.
2. Local current flow occurs.
3. The depolarizing graded potential spreads along the membrane.

**Key:**
- Extracellular fluid
- Cytosol
- Resting membrane potential
- Depolarizing graded potential

**What is local current flow?**
than the resting level. Two types of voltage-gated channels open and then close during an action potential. These channels are present mainly in the axon plasma membrane and axon terminals. The first channels that open, the voltage-gated Na\(^+\) channels, allow Na\(^+\) to rush into the cell, which causes the depolarizing phase. Then voltage-gated K\(^+\) channels open, allowing K\(^+\) to flow out, which produces the repolarizing phase. The afterhyperpolarizing phase occurs when the voltage-gated K\(^+\) channels remain open after the repolarizing phase ends. The duration of the action potential in most neurons is about 1-2 msec.

An action potential occurs in the membrane of the axon when depolarization reaches a certain level termed the threshold (about \(-55\) mV in many neurons). Different neurons may have different thresholds for action potential generation, but the threshold in a particular neuron usually is constant. The generation of an action potential depends on whether a particular stimulus is able to bring the membrane potential to threshold. An action potential will not occur in response to a subthreshold stimulus, a stimulus that is a weak depolarization that cannot bring the membrane potential to threshold (Figure 7.22). However, an action potential will occur in response to a threshold stimulus, a stimulus that is just strong enough to depolarize the membrane to threshold (Figure 7.22). Several action potentials will form in response to a suprathreshold stimulus, a stimulus that is strong enough to depolarize the membrane above threshold (Figure 7.22). Each of the action potentials caused by a suprathreshold stimulus has the same amplitude (size) as an action potential caused by a threshold stimulus. Therefore, once an action potential is generated, the amplitude of an action potential is always the same and does not depend on stimulus intensity. Instead, the greater the stimulus strength above threshold, the greater the frequency of the action potentials until a maximum frequency is reached as determined by the absolute refractory period (described shortly).

As you have just learned, an action potential is generated in response to a threshold stimulus but does not form when there is a subthreshold stimulus. In other words, an action potential either completely occurs or it does not occur at all. This characteristic of an action potential is known as the all-or-none principle.

**Depolarizing Phase**

During the depolarizing phase of the action potential, membrane permeability to Na\(^+\) ions increases (see Figure 7.21b). The depolarizing phase begins when a depolarizing graded potential or some other stimulus causes the membrane of the axon to depolarize to threshold. Once threshold is reached, voltage-gated Na\(^+\) channels open rapidly. Since both the Na\(^+\) concentration and electrical gradients favor inward movement of Na\(^+\), there is a rush of Na\(^+\) ions into the neuron. The inflow of Na\(^+\) causes the membrane potential to move above \(-55\) mV toward the sodium equilibrium potential (E\(_{Na}\)) of \(+60\) mV (see Figure 7.21a). However, the membrane potential never reaches E\(_{Na}\) because
7.3 Electrical Signals in Neurons

**Figure 7.21** The action potential (AP). When a stimulus depolarizes the membrane to threshold (~-55 mV), an AP is generated. The action potential arises at the trigger zone and then propagates along the axon to the axon terminals. The green-colored regions of the neuron in the inset indicate the parts that typically have voltage-gated Na⁺ and K⁺ channels (axon plasma membrane and axon terminals).

An action potential consists of a depolarizing phase and a repolarizing phase, which may be followed by an after-hyperpolarizing phase.

(a) Phases of the action potential

(b) Na⁺ and K⁺ permeability changes during the action potential

Which channels are open during the depolarizing phase? During the repolarizing phase?
**Chapter 7 The Nervous System and Neuronal Excitability**

**Figure 7.22** Stimulus strength and action potential generation. A subthreshold stimulus does not cause an action potential because it does not bring the membrane potential to threshold. However, an action potential does occur in response to a threshold stimulus because a threshold stimulus is just strong enough to depolarize the membrane to threshold. Several action potentials form in response to a suprathreshold stimulus, which depolarizes the membrane above threshold. Each of the action potentials caused by the suprathreshold stimulus has the same amplitude (size) as the action potential caused by the threshold stimulus. For simplicity, the after-hyperpolarizing phase of the action potential is not shown.

An action potential will only occur once the membrane potential reaches threshold.

Will an action potential occur in response to a hyperpolarizing graded potential that spreads from the dendrites or cell body to the trigger zone of the axon of a neuron? Why or why not?

**REAL WORLD ANALOGY**

Comparing the All-or-None Principle of the Action Potential to Pushing the First in a Row of Standing Dominoes

The all-or-none principle of the action potential is similar to pushing the first domino in a long row of standing dominoes. When the push on the first domino is strong enough (when depolarization reaches threshold), that domino falls against the second domino, and the entire row topples (an action potential occurs). Stronger pushes on the first domino produce the identical effect—toppling of the entire row. Thus, pushing on the first domino produces an all-or-none event: The dominoes all fall or none fall.

during the repolarizing phase (described next) the voltage-gated Na⁺ channels close and Na⁺ membrane permeability decreases. This causes the membrane potential to peak at +30 mV at the end of the depolarizing phase. The total change in membrane potential from resting conditions to the end of the depolarizing phase is about 100 mV (from −70 mV to +30 mV).

Each voltage-gated Na⁺ channel has two separate gates, an activation gate and an inactivation gate. In the resting state of a voltage-gated Na⁺ channel, the inactivation gate is open, but the activation gate is closed (step 1 in Figure 7.23). As a result, Na⁺ cannot move into the cell through these channels. At threshold, voltage-gated Na⁺ channels are activated. In the activated state of a voltage-gated Na⁺ channel, both the activation and inactivation gates in the channel are open and Na⁺ inflow begins (step 2 in Figure 7.23). As more channels open, Na⁺ inflow increases, the membrane depolarizes further, and more Na⁺ channels open. This is an example of a positive feedback mechanism. During the few ten-thousandths of a second that the voltage-gated Na⁺ channel is open, about 10,000 Na⁺ ions flow across the membrane and change the membrane potential considerably, but the concentration of Na⁺ hardly changes because of the millions of Na⁺ ions present in the extracellular fluid. The sodium-potassium pumps easily bail out the 10,000 or so Na⁺ ions that enter the cell during a single action potential and maintain the low concentration of Na⁺ inside the cell.

**Repolarizing Phase**

During the repolarizing phase of the action potential, membrane permeability to Na⁺ decreases and membrane permeability to K⁺ increases (see Figure 7.21b). The repolarizing phase begins when the inactivation gates of the voltage-gated Na⁺ channels close (step 3 in Figure 7.23). Now the voltage-gated Na⁺ channel is in an inactivated state. In addition to opening voltage-gated Na⁺ channels, a threshold-level depolarization also opens voltage-gated K⁺ channels (steps 3 and 4 in Figure 7.23).
Given the existence of leak channels for both $\text{K}^+$ and $\text{Na}^+$, could the membrane repolarize if the voltage-gated $\text{K}^+$ channels did not exist?

**Figure 7.23** Changes in ion flow through voltage-gated channels during the depolarizing and repolarizing phases of an action potential. Leak channels and sodium-potassium pumps are not shown.

Inflow of sodium ions ($\text{Na}^+$) causes the depolarizing phase, and outflow of potassium ions ($\text{K}^+$) causes the repolarizing phase of an action potential.
Because the voltage-gated K⁺ channels open more slowly, their opening occurs at about the same time the voltage-gated Na⁺ channels are closing. The slower opening of voltage-gated K⁺ channels and the closing of previously open voltage-gated Na⁺ channels produce the repolarizing phase of the action potential. As the Na⁺ channels are inactivated, Na⁺ inflow slows. At the same time, the K⁺ channels are opening, accelerating K⁺ outflow. Slowing of Na⁺ inflow and acceleration of K⁺ outflow cause the membrane potential to change from +30 mV to −70 mV. As the membrane potential approaches −70 mV, the inactivated Na⁺ channels revert to their resting state.

**After-hyperpolarizing Phase**

While the voltage-gated K⁺ channels are open, outflow of K⁺ may be large enough to cause an after-hyperpolarizing phase of the action potential (see Figure 7.21a). During this phase, the voltage-gated K⁺ channels remain open. The membrane potential becomes even more negative as it approaches the K⁺ equilibrium potential (E_K) of about −90 mV. Once voltage-gated K⁺ channels close, the membrane potential returns to the resting level of −70 mV. Unlike voltage-gated Na⁺ channels, most voltage-gated K⁺ channels do not enter an inactivated state. Instead, they alternate between closed (resting) and open (activated) states.

**Refractory Period**

The period of time after an action potential begins during which an excitable cell cannot generate another action potential in response to a normal threshold stimulus is called the refractory period (see key in Figure 7.21a). During the absolute refractory period, even a very strong stimulus cannot initiate a second action potential. This period coincides with the period of Na⁺ channel activation and inactivation (steps 2 and 3 in Figure 7.23). Inactivated Na⁺ channels cannot reopen; they first must return to the resting state (step 1 in Figure 7.23). In contrast to action potentials, graded potentials do not exhibit a refractory period. The relative refractory period is the period of time during which a second action potential can be initiated, but only if it is greater than the threshold for the cell.

**TOOL OF THE TRADE**

**The Oscilloscope**

An oscilloscope is an instrument that can record the fluctuations of an electrical event across a fluorescent screen. Examples of phenomena that can be seen on an oscilloscope include action potentials of individual neurons, muscle contractions, and electrical activity of the heart. To use an oscilloscope to record the action potential of a neuron, the following procedure is performed: The tip of a recording microelectrode is inserted inside the axon and a reference (ground) electrode is placed outside the axon in the extracellular fluid. The two electrodes are connected to an amplifier (to increase the signal), which in turn is connected to the oscilloscope. As a change in voltage occurs during the action potential, upward and downward deflections are seen on the oscilloscope. Thus, when used in this way, the oscilloscope essentially functions as a voltmeter that records the rapid changes that occur during an action potential.
by a larger-than-normal stimulus. It coincides with the period when the voltage-gated K⁺ channels are still open after inactivated Na⁺ channels have returned to their resting state (see Figure 7.21a).

**Propagation of Action Potentials**

To communicate information from one part of the body to another, action potentials in a neuron must travel from the trigger zone of the axon (their point of origin) to the axon terminals. In contrast to a graded potential, an action potential is not decremental (it does not die out). Instead, an action potential maintains its strength as it spreads along the membrane. This mode of conduction, called **propagation**, depends on positive feedback. When sodium ions flow in, they cause voltage-gated Na⁺ channels in adjacent segments of the membrane to open. Thus, the action potential travels along the membrane rather like the activity of that long row of dominoes. The propagation of an action potential is accomplished by local current flow. Recall from the discussion on graded potentials that local current flow refers to the passive movement of charges from one region of membrane to adjacent regions of membrane due to differences in membrane potential in these regions. In a neuron, an action potential can only propagate along the axon away from the cell body—it cannot propagate back toward the cell body because any region of membrane that has just undergone an action potential is temporarily in the absolute refractory period and cannot generate another action potential. You should realize that it is not the same action potential that propagates along the entire axon. Rather, the action potential regenerates over and over at adjacent regions of membrane from the trigger zone to the axon terminals. Because they can travel along a membrane without dying out, action potentials function in communication over long distances.

To understand how an action potential propagates along the axon by local current flow, consider what happens when a region of axon membrane is depolarized to threshold (Figure 7.24):

1. **The depolarizing phase of the action potential is generated.** When the membrane potential reaches threshold in a region of axon membrane (membrane region C), the depolarizing phase of the action potential is generated. Notice that membrane region B is in the refractory period because an action potential was generated in this region prior to the generation of an action potential in membrane region C.
2. **Local current flow occurs.** Local current flow occurs in the cytosol as positive charges move from depolarized membrane region C to the more negative adjacent membrane regions B and D. At the same time, local current flow occurs in the ECF as positive charges move from adjacent membrane regions B and D to the more negative membrane region C.
3. **The depolarizing phase of the action potential regenerates along the axon.** As a result of local current flow, adjacent membrane region D becomes depolarized. By contrast, adjacent membrane region B does not become depolarized because it was in the refractory period at the time of local current flow (see step 2 of Figure 7.24). Membrane region B eventually returns to resting membrane potential and membrane region C enters the refractory period. Thus, the depolarizing phase of the action potential regenerates along the axon in the direction of the axon terminals.

**Figure 7.25** illustrates the regeneration of all phases of the nerve action potential as the action potential propagates along the axon.

**Continuous and Saltatory Conduction**

There are two types of propagation: continuous conduction and saltatory conduction. The type of action potential propagation described so far is **continuous conduction**, which involves step-by-step depolarization, repolarization, and after-hyperpolarization of each adjacent segment of the plasma membrane (Figure 7.26a). In continuous conduction, ions flow through their voltage-gated channels in each adjacent segment of the membrane. Note that the action potential propagates only a relatively short distance in a few milliseconds. Continuous conduction occurs in unmyelinated axons and in muscle fibers.

Action potentials propagate more rapidly along myelinated axons than along unmyelinated axons. If you compare parts a and b in Figure 7.26 you will see that the action potential propagates much farther along the myelinated axon in the same period of time. **Saltatory conduction** (SAL-ta-tô-ré), the special mode of action potential propagation that occurs along myelinated axons, occurs because of the uneven distribution of voltage-gated channels. Few voltage-gated channels are present in regions where a myelin sheath covers the axon plasma membrane. By contrast, at the nodes of Ranvier (where there is no myelin sheath), the axon plasma membrane has many voltage-gated channels. Hence, current carried by Na⁺ and K⁺ flows across the membrane mainly at the nodes.

When an action potential propagates along a myelinated axon, local current flow occurs through the extracellular fluid surrounding the myelin sheath and through the cytosol from
What prevents local current flow from depolarizing an adjacent region of axon membrane in a backward direction?
7.3 Electrical Signals in Neurons

Figure 7.25 Regeneration of the three phases of the action potential along an unmyelinated axon. Parts (a)–(d) represent the same section of axon membrane at different points in time. The black arrows represent either Na⁺ movement into the neuron or K⁺ movement of the neuron. For simplicity, voltage-gated channels and local current flow are not shown.

Each phase of the action potential sequentially regenerates along the axon of a neuron from the trigger zone to the axon terminals.

Key:
- Resting membrane potential
- Depolarizing phase of action potential
- Repolarizing phase of action potential
- After-hyperpolarizing phase of action potential

Why doesn’t an action potential undergo decremental conduction?
Opening a smaller number of channels only at the nodes, rather than many channels in each adjacent segment of membrane, is a more energy-efficient mode of conduction. Because only small regions of the membrane depolarize and repolarize, minimal inflow of Na\(^+\) and outflow of K\(^+\) occurs each time an action potential passes by. Thus, less ATP is used by sodium-potassium pumps to maintain the low intracellular concentration of Na\(^+\) and the low extracellular concentration of K\(^+\).

**Factors That Affect Conduction Velocity**

The velocity of action potential conduction is affected by two major factors: axon diameter and the presence or absence of myelin.

1. **Axon diameter.** The larger the diameter of the axon, the faster the action potential is conducted. This is because an axon with a large diameter offers less resistance to local current flow, which allows adjacent regions of membrane to be brought to threshold more quickly.
2. Presence or absence of myelin. Conduction of action potentials is more rapid along myelinated axons than along unmyelinated axons. Recall that this is due to the fact that an action potential “leaps” across long segments of membrane of a myelinated axon, whereas it must travel through each adjacent segment of membrane of an unmyelinated axon.

Large-diameter, myelinated axons conduct action potentials at velocities ranging from 12 to 130 m/sec (27 – 280 mi/hr). They carry urgent information such as sensory signals associated with touch, pressure, and position of joints and motor signals that cause contraction of skeletal muscles. By contrast, small-diameter, unmyelinated axons conduct action potentials at velocities ranging from 0.5 to 2 m/sec (1–4 mi/hr). They carry information that is less critical, such as motor signals that cause contraction of smooth muscle in digestive organs.

Encoding of Stimulus Intensity

How can your sensory systems detect stimuli of differing intensities if all action potentials are the same size? Why does a light touch feel different from a slap on the wrist? The main answer to these questions is the frequency of action potentials—how often action potentials are generated at the trigger zone. A light touch generates a low frequency of action potentials. A slap on the wrist elicits action potentials that pass down the axon at a higher frequency. In addition to this “frequency code,” a second factor is the number of sensory neurons recruited (activated) by the stimulus. A slap on the wrist stimulates a larger number of touch-sensitive neurons than does a light touch.

7.3 Electrical Signals in Neurons

Influence of Extracellular Ion Concentration on Neuronal Excitability

The excitability of neurons is influenced by the extracellular concentrations of K⁺, Na⁺, and Ca²⁺ ions.

- Changes in the extracellular K⁺ concentration. An increase in the extracellular K⁺ concentration causes a decrease in the K⁺ concentration gradient across the plasma membrane of a neuron. Consequently, less K⁺ leaves the neuron, which causes the neuron to depolarize. By contrast, a decrease in the extracellular K⁺ concentration causes an increase in the K⁺ concentration gradient across the plasma membrane of the neuron. As a result, more K⁺ leaves the neuron, which causes the neuron to hyperpolarize.

- Changes in the extracellular Na⁺ concentration. An increase in the extracellular Na⁺ concentration causes an increase in the Na⁺ concentration gradient across the plasma membrane of the neuron. Consequently, more Na⁺ enters the neuron, which causes the neuron to depolarize. Conversely, a decrease in the extracellular Na⁺ concentration causes a decrease in the Na⁺ concentration gradient across the plasma membrane of the neuron. As a result, less Na⁺ enters the neuron, which causes the neuron to hyperpolarize.

- Changes in the extracellular Ca²⁺ concentration. The voltage-gated Na⁺ channels of a neuron are sensitive to the extracellular Ca²⁺ concentration. This is because Ca²⁺ ions in the ECF bind to the extracellular surfaces of voltage-gated Na⁺ channels and increase the voltage that these channels require to open. Consequently, an increase in the extracellular Ca²⁺ concentration increases the number of Ca²⁺ ions that bind to the voltage-gated Na⁺ channels. This decreases the excitability of the neuron because the voltage gated Na⁺ channels now require a higher voltage than normal to open. The opposite situation occurs when there is a decrease in the extracellular Ca²⁺ concentration. Less Ca²⁺ in the ECF reduces the number of Ca²⁺ ions that bind to the voltage-gated Na⁺ channels. This increases the excitability of the neuron because the voltage-gated Na⁺ channels are able to open at a lower voltage than normal.

Table 7.3 presents a summary of the differences between graded potentials and action potentials in neurons.

Checkpoint

9. Explain how the resting membrane potential of a neuron is generated.
10. Compare and contrast graded potentials and action potentials.
11. How is saltatory conduction different from continuous conduction?
12. What factors determine the speed of propagation of an action potential?
Section 7.4: Signal Transmission at Synapses

Objectives

- Explain the events of signal transmission at a chemical synapse.
- Distinguish between spatial and temporal summation.
- Give examples of excitatory and inhibitory neurotransmitters, and describe how they act.

Synapses, the sites of communication between two neurons or between a neuron and an effector cell, are essential for homeostasis because they allow information to be filtered and integrated. During the process of learning, the structure and function of particular synapses change. The changes may allow some signals to be transmitted while others are blocked. For example, the changes in your synapses from studying will determine how well you do on your physiology tests! Synapses are also important because some diseases and neurological disorders result from disruptions of synaptic communication, and many therapeutic and addictive chemicals affect the body at these junctions.

At a synapse between two neurons, the neuron sending the signal is called the presynaptic neuron, and the neuron receiving the message is called the postsynaptic neuron. Neural synapses are named based on the parts of the neurons that form the synapse and the direction of information flow. Examples include axodendritic (from axon to dendrite), axosomatic (from axon to cell body), and axoaxonic (from axon to axon) synapses (Figure 7.27). Most neural synapses are either axodendritic or axosomatic.

A synapse may be electrical or chemical. These two types of synapses differ both structurally and functionally.

### Electrical Synapses

At an electrical synapse, action potentials conduct directly between adjacent cells through structures called gap junctions. Each gap junction contains tubular connexons, which function as tunnels that connect the cytosol of the two cells directly (see Figure 3.30c). As ions flow from one cell to the next through the connexons, the action potential spreads from cell to cell. At many electrical synapses, the flow of ions through gap junctions is bidirectional; at other electrical synapses, ions flow through gap junctions only in one direction. Gap junctions are common in visceral smooth muscle, cardiac muscle, and the developing embryo. They also occur in the CNS.

Electrical synapses have two main advantages:

1. **Faster communication.** Because action potentials conduct directly through gap junctions, electrical synapses are faster than chemical synapses. At an electrical synapse, the action potential passes directly from the presynaptic cell to the postsynaptic cell. The events that occur at a chemical synapse take some time and delay communication slightly.

2. **Synchronization.** Electrical synapses can synchronize the activity of a group of neurons or muscle fibers. In other words, a large number of neurons or muscle fibers can produce action potentials in unison if they are connected by gap junctions. The value of synchronized action potentials in the heart or in visceral smooth muscle is coordinated contraction of these fibers to produce a heartbeat or move food through the gastrointestinal tract.

### Chemical Synapses

Although the plasma membranes of presynaptic and postsynaptic neurons in a chemical synapse are close, they do not touch. They are separated by the synaptic cleft, a space of 20–50 nm that is filled with interstitial fluid. Action potentials cannot conduct across the synaptic cleft, so an alternate, indirect form of communication occurs. In response to an action potential, the presynaptic neuron releases a neurotransmitter that diffuses through the fluid in the synaptic cleft and binds to receptors in the plasma membrane of the postsynaptic neuron.

---

1. **Objectives.**
2. **Synapses**
3. **Electrical Synapses**
4. **Chemical Synapses**

---

### Table 7.3: Comparison of Graded Potentials and Action Potentials in Neurons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Graded Potentials</th>
<th>Action Potentials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Origin</strong></td>
<td>Arise mainly in dendrites and cell body.</td>
<td>Arise at trigger zone and propagate along axon.</td>
</tr>
<tr>
<td><strong>Types of channels</strong></td>
<td>Ligand-gated or mechanically-gated ion channels.</td>
<td>Voltage-gated channels for Na⁺ and K⁺.</td>
</tr>
<tr>
<td><strong>Conduction</strong></td>
<td>Decremental (not propagated); permit communication over short distances.</td>
<td>Propagate and thus permit communication over longer distances.</td>
</tr>
<tr>
<td><strong>Amplitude (size)</strong></td>
<td>Depending on stimulus strength, vary from less than 1 mV to more than 50 mV.</td>
<td>All-or-none; typically about 100 mV.</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Typically longer, ranging from several msec to several min.</td>
<td>Shorter, ranging from 1 to 2 msec.</td>
</tr>
<tr>
<td><strong>Polarity</strong></td>
<td>May be hyperpolarizing (inhibitory to generation of an action potential) or depolarizing (excitatory to generation of an action potential).</td>
<td>Always consist of depolarizing phase followed by repolarizing phase and return to resting membrane potential.</td>
</tr>
<tr>
<td><strong>Refractory period</strong></td>
<td>Not present; thus, summation can occur.</td>
<td>Present; thus, summation cannot occur.</td>
</tr>
</tbody>
</table>
A typical chemical synapse transmits a signal as follows (Figure 7.28a):

1. An action potential arrives at a synaptic end bulb of a presynaptic axon.
2. The membrane of the synaptic end bulb contains voltage-gated \( \text{Ca}^{2+} \) channels in addition to the voltage-gated Na\(^+\) and K\(^+\) channels found in other parts of the axon. The depolarizing phase of the action potential opens not only the voltage-gated Na\(^+\) channels, but also the voltage-gated \( \text{Ca}^{2+} \) channels.

The postsynaptic neuron receives the chemical signal and, in turn, produces a postsynaptic potential, a type of graded potential. Thus, the presynaptic neuron converts an electrical signal (action potential) into a chemical signal (released neurotransmitter). The time required for these processes at a chemical synapse, a synaptic delay of about 0.5 msec, is the reason that chemical synapses relay signals more slowly than electrical synapses.
**Figure 7.28** Signal transmission at a chemical synapse. Through exocytosis of synaptic vesicles, a presynaptic neuron releases neurotransmitter molecules. After diffusing across the synaptic cleft, the neurotransmitter binds to receptors in the plasma membrane of the postsynaptic neuron and produces a postsynaptic potential.

At a chemical synapse, a presynaptic neuron converts an electrical signal (action potential) into a chemical signal (neurotransmitter release). The postsynaptic neuron then converts the chemical signal back into an electrical signal (postsynaptic potential).

**Why may electrical synapses work in two directions, but chemical synapses can transmit a signal in only one direction?**
channels. Because calcium ions are more concentrated in the extracellular fluid, \( Ca^{2+} \) flows inward through the open voltage-gated \( Ca^{2+} \) channels.

3. An increase in the \( Ca^{2+} \) concentration inside the synaptic end bulb serves as a signal that triggers exocytosis of the synaptic vesicles. This process involves several proteins, including synaptotagmin and the SNAREs (Soluble \( N \)-ethylmaleimide-sensitive factor Attachment protein REceptors) (Figure 7.28b). Synaptotagmin is found in the membrane of the synaptic vesicle. One of the SNAREs, synaptobrevin, is also located in the synaptic vesicle membrane. Two other SNAREs, syntaxin and SNAP-25, are in the presynaptic membrane. As the SNAREs interact with each other, they dock the synaptic vesicle on the presynaptic membrane. After \( Ca^{2+} \) enters the synaptic end bulb during the depolarizing phase of the action potential, it binds to synaptotagmin. This, in turn, causes synaptotagmin to bind to the SNARE proteins, resulting in fusion of the synaptic vesicle with the presynaptic membrane. As fusion occurs, neurotransmitter molecules within the synaptic vesicles are released into the synaptic cleft. Each synaptic vesicle contains several thousand molecules of neurotransmitter.

4. The neurotransmitter molecules diffuse across the synaptic cleft and bind to neurotransmitter receptors in the postsynaptic neuron's plasma membrane. The receptor shown in Figure 7.28a is part of a ligand-gated channel; in other cases the receptor may be coupled to a separate ion channel in the membrane.

5. Binding of neurotransmitter molecules to the receptor sites on ligand-gated channels opens the channels and allows particular ions to flow across the membrane.

6. As ions flow through the opened channels, the voltage across the membrane changes. This change in membrane voltage is a postsynaptic potential. Depending on which ions the channels admit, the postsynaptic potential may be a depolarization or hyperpolarization. For example, opening of \( Na^{+} \) channels allows inflow of \( Na^{+} \), which causes depolarization. However, opening of \( Cl^- \) or \( K^+ \) channels causes hyperpolarization. Opening \( Cl^- \) channels permits \( Cl^- \) to move into the cell, while opening the \( K^+ \) channels allows \( K^+ \) to move out—in either event, the inside of the cell becomes more negative.

7. When a depolarizing postsynaptic potential reaches threshold, it triggers an action potential in the axon of the postsynaptic neuron.

At most chemical synapses, only one-way information transfer can occur—from a presynaptic neuron to a postsynaptic neuron or an effector, such as a muscle fiber or a gland cell. For example, synaptic transmission at a neuromuscular junction (NMJ) proceeds from a somatic motor neuron to a skeletal muscle fiber (but not in the opposite direction). Only synaptic end bulbs of presynaptic neurons can release neurotransmitter, and only the postsynaptic neuron's membrane has the receptor proteins that can recognize and bind that neurotransmitter. As a result, action potentials move in one direction.

### 7.4 Signal Transmission at Synapses

**Excitatory and Inhibitory Postsynaptic Potentials**

A neurotransmitter causes either an excitatory or an inhibitory graded potential. A neurotransmitter that depolarizes the postsynaptic membrane is excitatory because it brings the membrane closer to threshold (see Figure 7.15a). A depolarizing postsynaptic potential is called an excitatory postsynaptic potential (EPSP). Although a single EPSP normally does not initiate an action potential, the postsynaptic cell does become more excitable. Because it is partially depolarized, it is more likely to reach threshold when the next EPSP occurs.

A neurotransmitter that causes hyperpolarization of the postsynaptic membrane (see Figure 7.15a) is inhibitory. During hyperpolarization, generation of an action potential is more difficult than usual because the membrane potential becomes inside more negative and thus even farther from threshold than in its resting state. A hyperpolarizing postsynaptic potential is termed an inhibitory postsynaptic potential (IPSP).

**Structure of Neurotransmitter Receptors**

As you have just learned, neurotransmitters released from a presynaptic neuron bind to neurotransmitter receptors in the plasma membrane of a postsynaptic cell. Each type of neurotransmitter receptor has one or more binding sites where its specific neurotransmitter binds. When a neurotransmitter binds to the correct receptor, an ion channel opens and a postsynaptic potential (either an EPSP or IPSP) forms in the membrane of the postsynaptic cell. Neurotransmitter receptors are classified as either ionotropic receptors or metabotropic receptors based on whether the neurotransmitter binding site and the ion channel are components of the same protein or are components of different proteins.

**Ionotropic Receptors**

An ionotropic receptor is a type of neurotransmitter receptor that contains both a neurotransmitter binding site and an ion channel. In other words, the neurotransmitter binding site and the ion channel are components of the same protein. An ionotropic receptor is a type of ligand-gated channel (see Figure 7.9b). In the absence of neurotransmitter (the ligand), the ion channel component of the ionotropic receptor is closed. When the correct neurotransmitter binds to the ionotropic receptor, the ion channel opens, and an EPSP or IPSP occurs in the postsynaptic cell.

Many excitatory neurotransmitters bind to ionotropic receptors that contain cation channels (Figure 7.29a). EPSPs result from opening these cation channels. When cation channels open, they allow passage of the three most plentiful cations (\( Na^+ \), \( K^+ \), and \( Ca^{2+} \)) through the postsynaptic cell membrane. However, the amount of \( Na^+ \) that enters the postsynaptic cell is greater than the amount of \( K^+ \) that leaves it because the resting membrane potential of the postsynaptic cell is closer to the potassium equilibrium potential (\( E_k \)) than to the sodium equilibrium potential (\( E_Na \)).
Chapter 7 The Nervous System and Neuronal Excitability

**Figure 7.29 Ionotopic and metabotropic neurotransmitter receptors.** (a) The nicotinic acetylcholine receptor is a type of ionotropic receptor. It contains two binding sites for the neurotransmitter acetylcholine (ACh) and a cation channel. Binding of ACh to this receptor causes the cation channel to open. Opening the cation channel allows passage of the three most plentiful cations (Na\(^+\), K\(^+\), and Ca\(^{2+}\)) through the postsynaptic cell membrane, but Na\(^+\) inflow is greater than either Ca\(^{2+}\) inflow or K\(^+\) outflow and an excitatory postsynaptic potential (EPSP) is generated. The nicotinic ACh receptor is so named because the drug nicotine is an agonist. (b) The GAB\(_A\) receptor is a type of ionotropic receptor. It contains two binding sites for the neurotransmitter GABA and a Cl\(^-\) channel. Binding of GABA to this receptor causes the Cl\(^-\) channel to open. Opening the Cl\(^-\) channel allows a larger number of chloride ions to diffuse inward and an inhibitory postsynaptic potential (IPSP) is generated. (c) The muscarinic acetylcholine receptor is a type of metabotropic receptor. It contains a binding site for the neurotransmitter ACh. Binding of ACh to this receptor activates a G protein, which in turn opens a K\(^+\) channel. Opening the K\(^+\) channel allows a larger number of potassium ions to diffuse out of the cell and an IPSP forms. The muscarinic ACh receptor is so named because the mushroom poison muscarine is an agonist.

An ionotopic receptor is a type of neurotransmitter receptor that contains a neurotransmitter binding site and an ion channel; a metabotropic receptor is a type of neurotransmitter receptor that contains a neurotransmitter binding site and is coupled to a separate ion channel by a G protein.

The neurotransmitter acetylcholine (ACh) is excitatory at some synapses and inhibitory at other synapses. How is this possible?
potential \( (E_{N_0}) \). (Recall that the equilibrium potential of an ion is the membrane potential at which the concentration gradient and electrical gradient for a particular ion are equal in magnitude but opposite in direction and there is no net movement of that ion across the plasma membrane.) In addition, more \( Na^+ \) ions than \( Ca^{2+} \) ions enter the postsynaptic cell because the concentration of \( Na^+ \) ions in the ECF is higher than the concentration of \( Ca^{2+} \) ions in the ECF. Therefore, the net effect of opening cation channels in the postsynaptic cell is that \( Na^+ \) inflow is greater than either \( K^+ \) outflow or \( Ca^{2+} \) inflow and the inside of the postsynaptic cell becomes less negative (depolarized).

Many inhibitory neurotransmitters bind to ionotropic receptors that contain chloride channels (Figure 7.29b). In cells that actively transport \( Cl^- \) ions into the ECF, IPSPs result from opening these \( Cl^- \) channels. When \( Cl^- \) channels open, a larger number of chloride ions diffuse inward because the chloride equilibrium potential \( (E_{Cl}) \) is not equal to the resting membrane potential. The inward flow of \( Cl^- \) ions causes the inside of the postsynaptic cell to become more negative (hyperpolarized). In cells that do not actively transport \( Cl^- \) ions, opening \( Cl^- \) channels does not change the membrane potential because \( E_{Cl} \) is equal to the resting membrane potential and there is no net movement of \( Cl^- \) ions into or out of the cell. However, opening these \( Cl^- \) channels does stabilize the membrane potential and make it more difficult for excitatory neurotransmitters to depolarize the cell.

**Metabotropic Receptors**

A metabotropic receptor is a type of neurotransmitter receptor that contains a neurotransmitter binding site, but lacks an ion channel as part of its structure. However, a metabotropic receptor is coupled to a separate ion channel by a G protein. When a neurotransmitter binds to a metabotropic receptor, the G protein either directly opens (or closes) the ion channel or it may act indirectly by activating an enzyme that produces a second messenger, which in turn opens (or closes) the ion channel (see Section 6.4 for a discussion on G proteins and second messengers). Thus, a metabotropic receptor differs from an ionotropic receptor in that the neurotransmitter binding site and the ion channel are components of different proteins.

Some inhibitory neurotransmitters bind to metabotropic receptors that are linked to \( K^+ \) channels (Figure 7.29c). IPSPs result from the opening of these \( K^+ \) channels. When \( K^+ \) channels open, a larger number of potassium ions diffuse outward. The outward flow of \( K^+ \) ions causes the inside of the postsynaptic cell to become more negative (hyperpolarized).

### Different Postsynaptic Effects for the Same Neurotransmitter

The same neurotransmitter can be excitatory at some synapses and inhibitory at others, depending on the structure of the neurotransmitter receptor to which it binds. For example, at some excitatory synapses acetylcholine (ACH) binds to ionotropic receptors containing cation channels that open and subsequently generate EPSPs in the postsynaptic cell (Figure 7.29a). By contrast, at some inhibitory synapses ACh binds to metabotropic receptors coupled to G proteins that open \( K^+ \) channels, resulting in the formation of IPSPs in the postsynaptic cell (Figure 7.29c).

#### Fast and Slow Responses in Postsynaptic Cells

The time required for a neurotransmitter to induce a postsynaptic potential (either an EPSP or an IPSP) and the duration of that postsynaptic potential are both influenced by whether the neurotransmitter binds to an ionotropic receptor or to a metabotropic receptor. In general, binding of a neurotransmitter to an ionotropic receptor causes a fast response in the postsynaptic cell because activation of an ionotropic receptor quickly opens or closes ion channels in the postsynaptic membrane and the subsequent postsynaptic potential that is generated usually lasts for only a few milliseconds or less. By contrast, binding of neurotransmitter to a metabotropic receptor causes a slow response in the postsynaptic cell because activation of a metabotropic receptor more slowly opens or closes ion channels (since G protein and second messengers are involved) and the subsequent postsynaptic potential that is generated typically lasts for hundreds of milliseconds to several minutes or even longer.

#### Removal of Neurotransmitter

Removal of the neurotransmitter from the synaptic cleft is essential for normal synaptic function. If a neurotransmitter could linger in the synaptic cleft, it would influence the postsynaptic neuron, muscle fiber, or gland cell indefinitely. Neurotransmitter is removed in three possible ways:

- **Diffusion.** Some of the released neurotransmitter molecules diffuse away from the synaptic cleft (Figure 7.30a). Once a neurotransmitter molecule is out of reach of its receptors, it can no longer exert an effect.
- **Enzymatic degradation.** Certain neurotransmitters are inactivated through enzymatic degradation (Figure 7.30b). For example, the enzyme acetylcholinesterase, which is located on the postsynaptic membrane, breaks down acetylcholine in the synaptic cleft.
- **Uptake by cells.** Many neurotransmitters are actively transported back into the neuron that released them (reuptake) (Figure 7.30c). Others are transported into neighboring neuroglia (uptake). The neurons that release norepinephrine, for example, rapidly take up the norepinephrine and recycle it into new synaptic vesicles. The membrane proteins that accomplish such uptake are called neurotransmitter transporters.

#### Spatial and Temporal Summation of Postsynaptic Potentials

A typical neuron in the CNS receives input from 1000 to 10,000 synapses. Integration of these inputs involves summation of the postsynaptic potentials that form in the postsynaptic neuron. Recall that summation is the process by which graded potentials add together. The greater the summation of EPSPs, the
Figure 7.30 Removal of neurotransmitter. A neurotransmitter is removed in three possible ways: (1) diffusion, (2) enzymatic degradation, and (3) uptake by cells.

(a) Diffusion

(b) Enzymatic degradation

(c) Uptake by cells

What is the difference between reuptake and uptake of a neurotransmitter?
greater the chance that threshold will be reached. At threshold, one or more action potentials arise.

There are two types of summation: spatial summation and temporal summation. **Spatial summation** is summation of postsynaptic potentials in response to stimuli that occur at different locations in the membrane of a postsynaptic cell at the same time. For example, spatial summation results from the buildup of neurotransmitter released simultaneously by several presynaptic end bulbs (Figure 7.31a). **Temporal summation** is summation of postsynaptic potentials in response to stimuli that occur at the same location in the membrane of the postsynaptic cell but at different times. For example, temporal summation results from buildup of neurotransmitter released by a single presynaptic end bulb two or more times in rapid succession (Figure 7.31b). Because a typical EPSP lasts about 15 msec, the second (and subsequent) release of neurotransmitter must occur soon after the first one if temporal summation is to occur. Summation is rather like voting on the Internet. Many people voting “yes” or “no” on an issue at the same time can be compared to spatial summation. One person voting repeatedly and rapidly is like temporal summation. Most of the time, spatial and temporal summations act together to influence the chance that a neuron fires an action potential.

**Figure 7.31 Spatial and temporal summation.** (a) When presynaptic neurons 1 and 2 separately cause EPSPs (arrows) in postsynaptic neuron 3, the threshold level is not reached in neuron 3. Spatial summation occurs only when neurons 1 and 2 act simultaneously on neuron 3; their EPSPs sum to reach the threshold level and trigger an action potential. (b) Temporal summation occurs when stimuli applied to the same axon in rapid succession (arrows) cause overlapping EPSPs that sum. When depolarization reaches the threshold level, action potential is triggered.

A single postsynaptic neuron receives input from many presynaptic neurons, some of which release excitatory neurotransmitters and some of which release inhibitory neurotransmitters (Figure 7.32). The sum of all the excitatory and inhibitory effects at any given time determines the effect on the postsynaptic neuron, which may respond in the following ways:

- **EPSP:** If the total excitatory effects are greater than the total inhibitory effects but less than the threshold level of stimulation, the result is an EPSP that does not reach threshold. Following an EPSP, subsequent stimuli can more easily generate an action potential through summation because the neuron is partially depolarized.
- **Action potential(s).** If the total excitatory effects are greater than the total inhibitory effects and threshold is reached, one or more action potentials will be triggered. Action potentials continue to be generated as long as the EPSP is at or above the threshold level.
- **IPSP:** If the total inhibitory effects are greater than the excitatory effects, the membrane hyperpolarizes (IPSP). The result is inhibition of the postsynaptic neuron and an inability to generate an action potential.

Suppose that EPSPs summate in a postsynaptic neuron in response to simultaneous stimulation by the neurotransmitters glutamate, serotonin, and acetylcholine released by three separate presynaptic neurons. Is this an example of spatial or temporal summation?
Chapter 7 The Nervous System and Neuronal Excitability

Figure 7.32 Summation of postsynaptic potentials at the trigger zone of a postsynaptic neuron. Presynaptic neurons 1, 3, and 5 release excitatory neurotransmitters (red dots) that generate excitatory postsynaptic potentials (EPSPs) (red arrows) in the membrane of a postsynaptic neuron. Presynaptic neurons 2 and 4 release inhibitory neurotransmitters (purple dots) that generate inhibitory postsynaptic potentials (IPSPs) (purple arrows) in the membrane of the postsynaptic neuron. The net summation of these EPSPs and IPSPs determines whether an action potential will be generated at the trigger zone of the postsynaptic neuron.

If the net summation of EPSPs and IPSPs is a depolarization that reaches threshold, then an action potential will occur at the trigger zone of a postsynaptic neuron.

Suppose that the net summation of the EPSPs and IPSPs shown in this figure is a depolarization that brings the membrane potential of the trigger zone of the postsynaptic neuron to \(-60\) mV. Will an action potential occur in the postsynaptic neuron?
Presynaptic Modulation

Earlier you learned that an axoaxonic synapse is a type of neural synapse in which the axon of one neuron communicates with the axon of another neuron (see Figure 7.27). An axoaxonic synapse is often used by the nervous system to modulate the amount of neurotransmitter that is released at another synapse. For example, in Figure 7.33 a presynaptic neuron (neuron A) forms an axodendritic synapse with a postsynaptic neuron (neuron C) and is at the receiving end of an axoaxonic synapse with another neuron (neuron B). When neuron B is inactive, neuron A releases a normal amount of neurotransmitter in response to an action potential (Figure 7.33a). The neurotransmitter in turn binds to neurotransmitter receptors in the membrane of neuron C to generate a particular postsynaptic effect. By contrast, when neuron B is active, it functions as a modulating neuron that can either increase or decrease the amount of neurotransmitter released from neuron A (Figure 7.33b,c). The alteration in the amount of neurotransmitter released by a presynaptic neuron is referred to as presynaptic modulation. Examples of presynaptic modulation include presynaptic inhibition and presynaptic facilitation.

During presynaptic inhibition, there is a decrease in the amount of neurotransmitter released from the presynaptic neuron (neuron A in Figure 7.33b). This occurs because neuron B releases neurotransmitter that binds to presynaptic receptors in the membrane of the synaptic end bulb of neuron A. The binding of the neurotransmitter to the presynaptic receptors in turn decreases the amount of Ca\(^2^+\) that enters the synaptic end bulb of neuron A through voltage-gated Ca\(^2^+\) channels when there is an action potential. As a result, neuron A releases less neurotransmitter and the postsynaptic effect on neuron C is reduced.

During presynaptic facilitation, there is an increase in the amount of neurotransmitter released from the presynaptic neuron (neuron A in Figure 7.33c). This also occurs because neuron B releases neurotransmitter that binds to presynaptic receptors in the membrane of the synaptic end bulb of neuron A. In this case, however, binding of the neurotransmitter to the presynaptic receptors increases the amount of Ca\(^2^+\) that enters the synaptic end bulb of neuron A through voltage-gated Ca\(^2^+\) channels when there is an action potential. As a result, neuron A releases more neurotransmitter and the postsynaptic effect on neuron C is enhanced.

Note that neuron B typically causes either presynaptic inhibition of neuron A or presynaptic facilitation of neuron A, but not both types of modulation. The factors that determine whether the modulating neuron causes presynaptic inhibition or presynaptic facilitation of neuron A are (1) the type of neurotransmitter released by the modulating neuron and (2) the type of presynaptic receptors in the membrane of the synaptic end bulb of neuron A. It is also important to note that during either presynaptic inhibition or presynaptic facilitation, neuron B has no direct effect on neuron C. However, neuron B does indirectly affect the activity of neuron C by modulating the amount of neurotransmitter released from neuron A. Presynaptic modulation is an important mechanism utilized by the nervous system because it allows selective regulation of one specific input to a particular neuron. In the case of the synapses shown in Figure 7.33, there is selective regulation of input from neuron A to neuron C.

**Checkpoint**

13. How is neurotransmitter removed from the synaptic cleft?
14. How are excitatory and inhibitory postsynaptic potentials similar and different?
15. Why are action potentials said to be “all-or-none,” and EPSPs and IPSPs are described as “graded”?
16. What is the difference between presynaptic inhibition and presynaptic facilitation?

### 7.5 Neurotransmitters

**Objectives**

- Describe the classes of neurotransmitters.
- Explain the functions of neurotransmitters.

**Neurotransmitters** are the chemical substances that neurons use to communicate with other neurons, muscle fibers, and glands. They are divided into two classes based on size: small-molecule neurotransmitters and neuropeptides (Figure 7.34). The small-molecule neurotransmitters include acetylcholine, amino acids, biogenic amines, purines, gases, and endocannabinoids. The neuropeptides are larger in size; they consist of many amino acids linked together by peptide bonds. Most small-molecule neurotransmitters cause EPSPs or IPSPs by opening or closing ion channels in the postsynaptic membrane. By contrast, some small-molecule neurotransmitters and most neuropeptides do not change the membrane potential of the postsynaptic cell. Instead, these neurotransmitters function as neuromodulators, substances that do not generate EPSPs or IPSPs, but alter the strength of a particular synaptic response. For example, a neuromodulator may act on the postsynaptic cell to alter the cell’s response to a specific neurotransmitter. Alternatively, the neuromodulator may act on the presynaptic cell to alter the synthesis, release, or reuptake of a specific neurotransmitter. The synaptic effects of neuromodulators usually are long-lasting, having a duration of days, months, or even years.

**Small-Molecule Neurotransmitters**

**Acetylcholine**

The best-studied neurotransmitter is acetylcholine (ACh) (Figure 7.34). Neurons that release ACh are called cholinergic neurons (ko¯-lin-ER-jik), which are present in the CNS and PNS. The synthesis, release, and degradation of ACh occurs as follows (Figure 7.35):

- The enzyme choline acetyltransferase (CAT) synthesizes ACh from the precursors acetyl coenzyme A (acetyl CoA) and choline. This reaction occurs in the cytoplasm of the synaptic end bulb of a cholinergic neuron.
Figure 7.33 Examples of presynaptic modulation.

During presynaptic inhibition, there is a decrease in the amount of neurotransmitter released from the presynaptic neuron; during presynaptic facilitation, there is an increase in the amount of neurotransmitter released from the presynaptic neuron.

What kind of synapse is typically associated with presynaptic inhibition or presynaptic facilitation?
### 7.5 Neurotransmitters

**Figure 7.34** Small-molecule neurotransmitters.

Small-molecule neurotransmitters include acetylcholine, amino acids, biogenic amines, purines, gases, and lipids.

<table>
<thead>
<tr>
<th>SMALL-MOLECULE NEUROTRANSMITTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetylcholine</strong></td>
</tr>
<tr>
<td>H₃C — N⁺ — CH₂ — CH₂ — O — CH₃</td>
</tr>
<tr>
<td><strong>Gases</strong></td>
</tr>
<tr>
<td>N.O</td>
</tr>
<tr>
<td>Nitric oxide</td>
</tr>
<tr>
<td><strong>Endocannabinoids</strong></td>
</tr>
<tr>
<td>Example: Anandamide</td>
</tr>
<tr>
<td><strong>Biogenic Amines</strong></td>
</tr>
<tr>
<td>Norepinephrine</td>
</tr>
<tr>
<td>HO — C — CH₂ — NH₂⁺</td>
</tr>
<tr>
<td>Epinephrine</td>
</tr>
<tr>
<td>HO — C — CH₂ — NH₂⁺</td>
</tr>
<tr>
<td>Serotonin</td>
</tr>
<tr>
<td>HO — C — CH₂ — NH₂⁺</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>HO — C — NH₂ — CH₃</td>
</tr>
<tr>
<td><strong>Amino Acids</strong></td>
</tr>
<tr>
<td>Glutamate</td>
</tr>
<tr>
<td>H⁺ — C — COO⁻</td>
</tr>
<tr>
<td>Aspartate</td>
</tr>
<tr>
<td>H⁺ — C — COO⁻</td>
</tr>
<tr>
<td>Gamma aminobutyric acid (GABA)</td>
</tr>
<tr>
<td>H⁺ — CH₃ — CH₂ — COO⁻</td>
</tr>
<tr>
<td>Glycine</td>
</tr>
<tr>
<td>H⁺ — C — COO⁻</td>
</tr>
<tr>
<td><strong>Purines</strong></td>
</tr>
<tr>
<td>Example: ATP</td>
</tr>
<tr>
<td>Adenosine</td>
</tr>
<tr>
<td>Adenine</td>
</tr>
<tr>
<td>HO — C — O — P — O — P — O — P — O —</td>
</tr>
<tr>
<td>Ribose</td>
</tr>
<tr>
<td>Phosphate groups</td>
</tr>
<tr>
<td><strong>Neuropeptides</strong></td>
</tr>
<tr>
<td>Examples:</td>
</tr>
<tr>
<td>Enkephalin</td>
</tr>
<tr>
<td>Substance P</td>
</tr>
</tbody>
</table>

Why are norepinephrine, epinephrine, dopamine, and serotonin classified as biogenic amines?
Chapter 7 The Nervous System and Neuronal Excitability

Figure 7.35 Synthesis, release, and degradation of acetylcholine (ACh). The numbers correspond to events listed in the text.

What happens to the breakdown products of acetylcholine?

1. Once it is synthesized, ACh is transported into a synaptic vesicle, where it is stored.
2. The arrival of an action potential into the synaptic end bulb causes exocytosis of synaptic vesicles and release of ACh into the synaptic cleft.
3. ACh diffuses through the synaptic cleft where it binds to a neurotransmitter receptor. The specific receptor to which acetylcholine binds is called a cholinergic receptor. The binding of ACh to the cholinergic receptor causes a postsynaptic potential (PSP) in the membrane of the postsynaptic cell.
4. ACh is quickly broken down into acetate and choline by the enzyme acetylcholinesterase (AChE), which is located on the postsynaptic membrane. The choline is transported back into the synaptic end bulb, where it is used to synthesize another ACh molecule. The acetate diffuses out of the synaptic cleft and into the blood.

As shown in step 4, ACh released from a cholinergic neuron binds to specific cholinergic receptors in the membrane of the postsynaptic cell. There are two types of cholinergic receptors: nicotinic acetylcholine receptors and muscarinic acetylcholine receptors. Nicotinic acetylcholine receptors are so named because the drug nicotine is an agonist. Nicotine, a natural substance in tobacco leaves, is not a naturally occurring substance in humans and is not normally present in nonsmokers. Muscarinic acetylcholine receptors are so named because the mushroom poison muscarine is an agonist. Note that ACh activates both types of cholinergic receptors. However, nicotine activates only nicotinic ACh receptors and muscarine activates only muscarinic ACh receptors.

Nicotinic ACh receptors are present in some neurons of the CNS, in certain autonomic neurons of the PNS, and in skeletal muscle at the neuromuscular junction. The nicotinic ACh receptor is an ionotropic receptor that contains two binding sites for acetylcholine and a cation channel (see Figure 7.29). Activation of nicotinic ACh receptors causes depolarization (EPSP) and thus excitation of the postsynaptic cell.

Muscarinic ACh receptors are present in some neurons of the CNS and in effectors (cardiac muscle, smooth muscle, and...
glands) innervated by certain autonomic neurons of the PNS. The muscarinic ACh receptor is a metabotropic receptor that is coupled to an ion channel by a G protein. There are several types of muscarinic ACh receptors. Activation of muscarinic ACh receptors causes depolarization (EPSP) or hyperpolarization (IPSP) of the postsynaptic cell, depending on which type of muscarinic ACh receptor is activated. One type of muscarinic ACh receptor opens K+ channels, which leads to hyperpolarization (IPSP) of the postsynaptic cell (see Figure 7.29c).

There are chemical substances that can bind to and block cholinergic receptors. The plant derivative curare blocks nicotinic ACh receptors in skeletal muscle at the neuromuscular junction. As a result, skeletal muscle becomes paralyzed. It can also be used as an antidote for chemical warfare agents that inhibit acetylcholinesterase (AChE). There are also disorders that result from abnormal ACh levels in the brain or from a reduction in the number of functional cholinergic receptors at a synapse. In Alzheimer’s disease, there is a decrease in ACh levels in the brain because of a loss of neurons that liberate ACh (especially in a region of the brain known as the nucleus basalis). In myasthenia gravis, the immune system inappropriately produces antibodies that bind to and block some nicotinic ACh receptors in skeletal muscle at the neuromuscular junction. As a result, muscles become increasingly weaker, fatigue more easily, and may eventually cease to function. For more information on Alzheimer’s disease and myasthenia gravis, see the Clinical Connection on Alzheimer’s disease and the Clinical Connection on Myasthenia Gravis in Section 8.3 and the Clinical Connection on Myasthenia Gravis in Section 11.3.

**Amino Acids**

Several amino acids are neurotransmitters in the CNS: glutamate, aspartate, gamma-aminobutyric acid (GABA), and glycine (see Figure 7.34).

**Glutamate** (glutamic acid) has powerful excitatory effects. Most excitatory neurons in the CNS and perhaps half of the synapses in the brain communicate via glutamate. There are many types of receptors for glutamate. Examples include the AMPA receptor and the NMDA receptor, which are named after the agonists that activate them: AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate) and NMDA (N-methyl-D-aspartate). The AMPA and NMDA receptors are ionotropic receptors that contain cation channels. Binding of glutamate to these receptors opens the cation channels and the consequent inflow of cations (mainly Na+ ions) produces an EPSP. Inactivation of glutamate occurs via reuptake. Glutamate transporters actively transport glutamate back into the synaptic end bulbs and neighboring neuroglia.

Both AMPA and NMDA receptors are thought to be involved in a phenomenon called long-term potentiation (LTP), the process in which transmission at synapses is enhanced (potentiated) for hours or weeks after a brief period of high-frequency stimulation. LTP has been linked to some aspects of memory and has been extensively studied in a region of the brain known as the hippocampus (see Section 8.3). NMDA receptors may also be involved in a process called excitotoxicity — the destruction of neurons through prolonged activation of excitatory synaptic transmission. The most common cause of excitotoxicity is oxygen deprivation of the brain due to ischemia (inadequate blood flow), as happens during a stroke. Lack of oxygen causes the glutamate transporters to fail, and glutamate accumulates in the interstitial spaces between neurons and glia. The accumulated glutamate excessively stimulates NMDA receptors in the membranes of postsynaptic neurons, which causes these neurons to die. In other words, the neurons are literally stimulated to death. Clinical trials are under way to see if NMDA receptor antagonists administered after a stroke can offer some protection from excitotoxicity.

**Aspartate** (aspartic acid) is an excitatory neurotransmitter that is released by certain neurons of the CNS. Aspartate activates some of the same types of neurotransmitter receptors as glutamate (namely the NMDA receptors).

**Gamma-aminobutyric acid (GABA)** is an important inhibitory neurotransmitter that is derived from the amino acid glutamate. GABA is found in the CNS, where it is the most common inhibitory neurotransmitter. As many as one-third of all brain synapses use GABA. There are three types of GABA receptors: GABA_A, GABA_B, and GABA_C. GABA_A and GABA_C receptors are ionotropic receptors that contain Cl− channels (see Figure 7.29b). Activation of GABA_A and GABA_C receptors opens the Cl− channels. As a result, Cl− moves from the ECF into the cytosol and the postsynaptic membrane becomes hyperpolarized (IPSP). GABA_B receptors are metabotropic receptors that are often coupled to K+ channels by G proteins. When GABA_B receptors are activated, the K+ channels open. Consequently, K+ moves from the cytosol into the ECF and the postsynaptic membrane becomes hyperpolarized (IPSP).

Several chemical substances can bind to and subsequently modulate the activity of GABA_A receptors:

- Benzodiazepines such as diazepam (Valium®) and clonazepam (Klonopin®) increase the frequency of opening of the Cl− channels of GABA_A receptors when GABA is present. These drugs have a tranquilizing effect and are used to help reduce anxiety, promote sleep, and treat epilepsy.
- Barbiturates such as phenobarbital and pentobarbital increase the duration of opening of the Cl− channels of the GABA_A receptors when GABA is present. These drugs are used for their sedative and anesthetic effects and to control epilepsy.
- Ethanol, an alcohol, enhances the activity of GABA_A receptors. Consequently, there is an overall inhibition of the nervous system when a person consumes significant amounts of alcohol.

Like GABA, the amino acid glycine is an inhibitory neurotransmitter. About half of the inhibitory synapses in the
spinal cord use glycine; the rest use GABA. Like GABA<sub>A</sub> and GABA<sub>C</sub> receptors, glycine receptors are ionotropic receptors that contain Cl<sup>-</sup> channels. Activation of glycine receptors causes the Cl<sup>-</sup> channels to open. As a result, Cl<sup>-</sup> moves from the ECF into the cytosol and the postsynaptic membrane becomes hyperpolarized (IPSP).

**Clinical Connection**

**Strychnine Poisoning**

The importance of inhibitory neurons can be appreciated by observing what happens when their activity is blocked. Normally, inhibitory neurons in the spinal cord called Renshaw cells release the neurotransmitter glycine at inhibitory synapses with somatic motor neurons. This inhibitory input to their motor neurons prevents excessive contraction of skeletal muscles. *Strychnine* is a lethal poison that binds to and blocks glycine receptors. The normal, delicate balance between excitation and inhibition of motor neurons is disturbed, which causes the motor neurons to generate action potentials without restraint. All skeletal muscles, including the diaphragm, contract fully and remain contracted. Because the diaphragm cannot relax, the victim cannot inhale, resulting in suffocation.

**Biogenic Amines**

Certain amino acids are modified and decarboxylated (carboxyl group removed) to produce the biogenic amines, which include norepinephrine, epinephrine, dopamine, and serotonin (see Figure 7.34).

Norepinephrine, epinephrine, and dopamine are chemically classified as catecholamines (cat-e-KOL-a-mens) because they all contain an amino group (—NH<sub>2</sub>) and a catechol ring, which is composed of six carbons and two adjacent hydroxyl (—OH) groups. The catecholamines are synthesized from the amino acid tyrosine in the cytoplasm of the synaptic end bulb. Catecholamine synthesis involves a series of enzymatic steps that are part of the same biosynthetic pathway (Figure 7.36). Different catecholamines are produced at different steps along this pathway. Not all enzymes of the catecholamine biosynthetic pathway are present in every neuron that synthesizes a catecholamine. The type synthesized depends on which set of enzymes of the catecholamine biosynthetic pathway are present. For example, a neuron that just has the enzymes tyrosine hydroxylase and DOPA decarboxylase synthesizes only dopamine and not norepinephrine or epinephrine. Once they are produced, the catecholamines are stored in synaptic vesicles until an action potential triggers their release. Removal of catecholamines from synapses occurs via reuptake into synaptic end bulbs or enzymatic degradation. Two enzymes that break down catecholamines are catechol-O-methyltransferase (kat-e-kol-ö-meth-il-TRANS-fer-äs) (COMT) and monoamine oxidase (mon-ö-AM-in OK-si-dás) (MAO).

Norepinephrine (NE), also known as noradrenaline, is involved in arousal (awakening from sleep), attention, and regulating mood. Norepinephrine is released by certain neurons in the brain stem and by some autonomic neurons of the PNS. Amphetamines promote the release of norepinephrine from synaptic end bulbs. The stimulant effects that a person experiences after taking amphetamines reflects norepinephrine’s role in arousal. Epinephrine, also known as adrenaline, is released by only a small number of neurons in the brain and has the lowest concentration in the brain of all the catecholamines. Both norepinephrine and epinephrine also serve as hormones. Cells of the adrenal medulla, the inner portion of the adrenal gland, release them into the blood.

Norepinephrine and epinephrine bind to adrenergic receptors (ad-ren-ER-jik) in the postsynaptic membrane. Adrenergic receptors are present in some neurons of the CNS and in effectors (cardiac muscle, smooth muscle, and glands) innervated by certain autonomic neurons of the PNS. Adrenergic receptors are metabotropic receptors that are coupled to ion channels by a G protein. There are two main groups of adrenergic receptors: alpha (α) receptors and beta (β) receptors. These receptors are further classified into subtypes—α<sub>1</sub>, α<sub>2</sub>, β<sub>1</sub>, β<sub>2</sub>, and β<sub>3</sub>—based on the specific responses they elicit and by their selective binding of drugs that activate or block them. Norepinephrine stimulates alpha receptors more strongly than beta receptors; epinephrine is a potent stimulator of both alpha and beta receptors. Activation of adrenergic receptors can cause either excitation or inhibition of the postsynaptic cell, depending on which type of adrenergic receptor is activated. A large variety of drugs can activate or block specific adrenergic receptors. Examples include phenylephrine, which is an agonist at α<sub>1</sub> receptors, and propranolol, which is a nonselective antagonist at β receptors. Adrenergic agonists and antagonists are described in more detail in the discussion of the autonomic nervous system in Chapter 10.

Neurons that release the neurotransmitter dopamine (DA) are present in the brain, especially in the substantia nigra and ventral tegmental area of the midbrain. There are several types of dopamine receptors, all of which are metabotropic. Activation of dopamine receptors can cause either excitation or inhibition of the postsynaptic cell, depending on which type of dopamine receptor is activated. Dopamine is involved in generating emotional responses. In fact, the behavioral disorder schizophrenia has been linked to the accumulation of excess dopamine. People with schizophrenia may have inappropriate or absent emotions, delusions, distortions of reality, paranoia, and hallucinations. Dopamine also plays a role in the formation of addictive behaviors and pleasurable experiences. The drug cocaine produces euphoria—intensely pleasurable feelings—by blocking transporters for dopamine reuptake. This action allows dopamine to linger in synaptic clefts, producing excessive stimulation of certain brain regions. Dopamine is also involved in the regulation of skeletal muscle tone and some aspects of movement due to contraction of skeletal muscles. The tremors (shaking), rigidity (muscular stiffness), and slow movements that occur in Parkinson’s disease are due to degeneration of neurons that release dopamine (see Clinical Connection on Parkinson’s
Serotonin, also known as 5-hydroxytryptamine (5-HT), is released by neurons in the brain stem. Unlike the catecholamines, which are synthesized from the amino acid tyrosine, serotonin is synthesized from the amino acid tryptophan. There are several types of serotonin receptors, most of which are metabotropic. Activation of serotonin receptors can cause either excitation or inhibition of the postsynaptic cell, depending on the type of serotonin receptor that is activated. Removal of serotonin from the synapse occurs by reuptake into synaptic end bulbs. Then the serotonin is degraded by MAO. Serotonin is thought to be involved in sensory perception, temperature regulation, control of mood, appetite, and the induction of sleep.

**Clinical Connection**

Depression is a disorder that affects over 18 million people each year in the United States. People who are depressed feel sad and helpless, have a lack of interest in activities that they once enjoyed, and experience suicidal thoughts. There are several types of depression. A person with major depression experiences symptoms of depression that last for more than two weeks. A person with dysthymia (dis-THÍ-ma) experiences episodes of depression that alternate with periods of feeling normal. A person with bipolar disorder, or manic-depressive illness, experiences recurrent episodes of depression and extreme elation (mania). A person with seasonal affective disorder (SAD) experiences depression during the winter months, when day length is short. Although its exact cause is unknown, research suggests that depression is linked to an imbalance of the neurotransmitters serotonin, norepinephrine, and dopamine in the brain. Factors that may contribute to depression include heredity, stress, chronic illnesses, certain personality traits (such as low self-esteem), and hormonal changes. Medication is the most common treatment for depression. For example, tricyclic antidepressants (TCAs) provide relief from depression by inhibiting the uptake of serotonin and norepinephrine. As a result, these neurotransmitters remain at their synapses for a longer period of time. TCAs are so named because of their three-ringed structure. Examples of TCAs are imipramine (Tofranil®) and amitriptyline (Elavil®). Other drugs used to treat depression include monoamine oxidase inhibitors such as isocarboxazid (Marplan®), phenelzine (Nardil®), and tranylcypromine (Parnate®). These drugs block the degradation of all biogenic amines. This prolongs the activity of serotonin, norepinephrine, and dopamine at their synapses in the brain. Depression can also be treated with drugs called selective serotonin reuptake inhibitors (SSRIs). By inhibiting reuptake of serotonin by serotonin transporters, SSRIs increase the duration for which serotonin functions at brain synapses without affecting the activities of the other biogenic amines. SSRIs include fluoxetine (Prozac®), paroxetine (Paxil®), and sertraline (Zoloft®).

Disease in Section 10.1). Many patients with Parkinson’s disease benefit from taking the drug L-dopa because it is a precursor of dopamine (Figure 7.36). For a limited period of time, taking L-dopa boosts dopamine production in affected brain areas.
The drug *lysergic acid diethylamine* (*LSD*) is an agonist of a specific type of serotonin receptor called the 5-HT\textsubscript{2A} receptor. Activation of these receptors by LSD results in powerful hallucinations.

**Purines**

The *purines*, which include adenosine and its triphosphate, diphosphate, and monophosphate derivatives (ATP, ADP, and AMP), are named for the purine ring that comprises adenine (see Figure 7.34). The purines function as neurotransmitters in both the CNS and the PNS. Once they are released, purines bind to *purinergic receptors* in the postsynaptic membrane. Some purinergic receptors are ionotropic, and others are metabotropic. Adenosine plays a role in inducing sleep by binding to purinergic receptors and inhibiting certain neurons of the reticular activating system of the brain that participate in arousal (see Section 8.3).

**Gases**

Two gases can function as neurotransmitters: nitric oxide and carbon monoxide (see Figure 7.34).

The simple gas *nitric oxide* (*NO*) is an important neurotransmitter that has widespread effects throughout the body. The enzyme *nitric oxide synthase* (NOS) catalyzes the formation of NO from the amino acid arginine. Unlike all previously identified neurotransmitters, NO is not synthesized in advance and packaged into synaptic vesicles. Instead, it is formed on demand and acts immediately. Its action is brief because NO is a highly reactive free radical that exists for less than 10 seconds before it combines with oxygen and water to form inactive nitrates and nitrites.

Studies have shown that blockage of NO signaling pathways in the hippocampus of the brain prevents long-term potentiation. This suggests that NO may play a role in learning and memory. NO is also released by certain autonomic neurons of the PNS. For example, parasympathetic neurons that innervate the erectile tissue of the penis release NO as a neurotransmitter. The NO in turn causes relaxation of smooth muscle in the walls of the arterioles supplying the penis. This results in penile erection. The drug *sildenafil* (Viagra\textsuperscript{®}) alleviates erectile dysfunction (impotence) by enhancing the effect of NO.

Some neurons of the brain release extremely small quantities of the gas *carbon monoxide* (CO) as a neurotransmitter. As with nitric oxide, CO is not synthesized in advance or packaged into synaptic vesicles. Instead, it is formed on demand and acts very quickly.

**Endocannabinoids**

Lipids known as the *endocannabinoids* can function as neurotransmitters. Examples of endocannabinoids are the fatty acids anandamide (see Figure 7.34) and 2-arachidonylglycerol. These neurotransmitters are formed from the breakdown of lipids in the plasma membrane and then released from the neuron that produces them. The endocannabinoids bind to *cannabinoid receptors*, which are present throughout the brain.

Research suggests that endocannabinoids play roles in learning and memory, regulation of motor activity, pain processing, and appetite stimulation. \(\Delta^1\)-*tetrahydrocannabinol* (*THC*), the active ingredient of marijuana, binds to and activates specific cannabinoid receptors called CB1 receptors. This causes the euphoria, relaxation, analgesic effects, altered perception, and increased appetite that is associated with smoking marijuana.

**Neuropeptides**

Neurotransmitters consisting of 3 to 40 amino acids linked by peptide bonds are called *neuropeptides* (noor-o-PEP-tids) (see Figure 7.34). They are numerous and widespread in both the CNS and the PNS. Neuropeptides are formed in the neuron cell body, packaged into vesicles, and transported to axon terminals. Virtually all receptors for neuropeptides are metabotropic. Besides their role as neurotransmitters, many neuropeptides serve as hormones that regulate physiological responses elsewhere in the body.

Scientists discovered that certain brain neurons have plasma membrane receptors for opiate drugs such as morphine and heroin. The quest to find the naturally occurring substances that use these receptors brought to light the first neuropeptides: two molecules, each a chain of five amino acids, named *enkephalins* (en-KEF-a-llins). Their potent analgesic (pain-relieving) effect is 200 times stronger than that of morphine. Other so-called *opioid peptides* include the *endorphins* (en-DOR-fins) and *dynorphins* (di-NOR-fins). It is thought that opioid peptides are the body's natural painkillers. Acupuncture may produce analgesia (loss of pain sensation) by increasing the release of opioids. These neuropeptides have also been linked to improved memory and learning; feelings of pleasure or euphoria; control of body temperature; regulation of hormones that affect the onset of puberty, sexual drive, and reproduction; and mental illnesses such as depression and schizophrenia.

Another neuropeptide, *substance P*, is released by neurons that transmit pain-related input from peripheral pain receptors into the central nervous system, enhancing the perception of pain. Enkephalin and endorphin suppress the release of substance P, thus decreasing the number of action potentials being relayed to the brain for pain sensations. Substance P has also been shown to counter the effects of certain nerve-damaging chemicals, prompting speculation that it might prove useful as a treatment for nerve degeneration.

Table 7.4 provides brief descriptions of these neuropeptides as well as others that will be discussed in later chapters.

**Checkpoint**

17. Which neurotransmitters are excitatory and which are inhibitory? How do they exert their effects?

18. In what ways is nitric oxide different from all previously identified neurotransmitters?
The CNS contains billions of neurons organized into complicated networks called neural circuits, functional groups of neurons that process specific types of information. In a simple series circuit, a presynaptic neuron stimulates a single postsynaptic neuron. The second neuron then stimulates another, and so on. However, most neural circuits are far more complex.

A single presynaptic neuron may synapse with several postsynaptic neurons. Such an arrangement, called divergence, permits one presynaptic neuron to influence several postsynaptic neurons (or several muscle fibers or gland cells) at the same time. In a diverging circuit, the action potential from a single presynaptic neuron causes the stimulation of increasing numbers of cells along the circuit (Figure 7.37a). For example, a small number of neurons in the brain that govern a particular body movement stimulate a much larger number of neurons in the spinal cord. Sensory signals are also arranged in diverging circuits, allowing sensory input to be relayed to several regions of the brain. This arrangement amplifies the signal.

In another arrangement, called convergence, several presynaptic neurons synapse with a single postsynaptic neuron. This arrangement permits more effective stimulation or inhibition of the postsynaptic neuron. In a converging circuit (Figure 7.37b), the postsynaptic neuron receives action potentials from several different sources. For example, a single motor neuron that synapses with skeletal muscle fibers at neuromuscular junctions receives input from several pathways that originate in different brain regions.

Some circuits are constructed so that once the presynaptic cell is stimulated, it will cause the postsynaptic cell to transmit a series of action potentials. One such circuit is called a reverberating circuit (Figure 7.37c). In this pattern, the incoming action potential stimulates the first neuron, which stimulates the second, which stimulates the third, and so on. Branches from later neurons synapse with earlier ones. This arrangement sends action potentials back through the circuit again and again. The output signal may last from a few seconds to many hours, depending on the number of synapses and the arrangement of neurons in the circuit. Inhibitory neurons may turn off a...
Chapter 7 The Nervous System and Neuronal Excitability

Figure 7.37 Examples of neural circuits.

A neural circuit is a functional group of neurons that processes a specific kind of information.

(a) Diverging circuit  (b) Converging circuit  (c) Reverberating circuit  (d) Parallel after-discharge circuit

A motor neuron in the spinal cord typically receives input from neurons that originate in several different regions of the brain. Is this an example of convergence or divergence?

A fourth type of circuit is the parallel after-discharge circuit (Figure 7.37d). In this circuit, a single presynaptic cell stimulates a group of neurons, each of which synapses with a common postsynaptic cell. A differing number of synapses between the first and last neurons imposes varying synaptic delays, so that the last neuron exhibits multiple EPSPs or IPSPs. If the input is excitatory, the postsynaptic neuron can then send out a stream of action potentials in quick succession. Parallel after-discharge circuits may be involved in precise activities such as mathematical calculations.

Checkpoint
19. What is a neural circuit?
20. What are the functions of diverging, converging, reverberating, and parallel after-discharge circuits?

CHAPTER REVIEW AND RESOURCE SUMMARY

Review

7.1 OVERVIEW OF THE NERVOUS SYSTEM
1. The nervous system is organized into two main subdivisions: the central nervous system (CNS) and the peripheral nervous system (PNS).
2. The CNS consists of the brain and spinal cord.
3. The PNS consists of all nervous tissue outside the CNS; it includes nerves and sensory receptors.
4. The PNS is divided into an afferent division and an efferent division. The afferent division conveys sensory input into the CNS and the efferent division conveys motor output from the CNS to effectors (muscles and glands).
5. The efferent division of the PNS is further subdivided into a somatic nervous system (conveys motor output from the CNS to skeletal muscles only) and an autonomic nervous system (conveys motor output from the CNS to smooth muscle, cardiac muscle, and glands).
6. The nervous system helps maintain homeostasis and integrates all body activities by sensing changes (sensory function), by analyzing them and making decisions for appropriate responses (integrative function), and by reacting to them (motor function).

Resources

Overview: The Nervous System: Overview
Overview: Nerve Animation: Structure and Function of the Nervous System
Figure 7.5 Neuroglia Exercise: Paint a Neuron
### 7.2 NERVOUS TISSUE

1. Nervous tissue consists of neurons (nerve cells) and neuroglia.
2. Most neurons have three parts. The dendrites are the main receiving or input region. The cell body functions as the control center and can also serve as an input region. The output part typically is a single axon, which propagates action potentials toward another neuron, a muscle fiber, or a gland cell.
3. Slow axonal transport and fast axonal transport are systems for conveying materials to and from the cell body and axon terminals.
4. Neurons are functionally classified as sensory (afferent) neurons, motor (efferent) neurons, and interneurons. Sensory neurons carry sensory information into the CNS. Motor neurons carry information out of the CNS to effectors (muscles and glands). Interneurons are located within the CNS between sensory and motor neurons.
5. Neuroglia support, nurture, and protect neurons and maintain the interstitial fluid that bathes them. Neuroglia in the CNS include astrocytes, oligodendrocytes, microglia, and ependymal cells. Neuroglia in the PNS include Schwann cells.
6. Two types of neuroglia produce myelin sheaths: Oligodendrocytes myelinate axons in the CNS, and Schwann cells myelinate axons in the PNS.
7. A damaged axon in the PNS may undergo repair if the cell body is intact and if Schwann cells are functional.
8. White matter consists of aggregates of myelinated axons; gray matter contains cell bodies, dendrites, unmyelinated axons, and neuroglia.

### 7.3 ELECTRICAL SIGNALS IN NEURONS

1. Neurons communicate with one another using graded potentials, which are used for short-distance communication only, and action potentials, which allow communication over long distances.
2. The electrical signals produced by neurons rely on four kinds of ion channels: leak channels, ligand-gated channels, mechanically-gated channels, and voltage-gated channels.
3. A resting membrane potential exists across the plasma membrane of excitable cells that are not stimulated (at rest). The resting membrane potential exists because of a small buildup of negative ions in the cytosol along the inside surface of the membrane and an equal buildup of positive ions in the extracellular fluid along the outside surface of the membrane.
4. A typical value for the resting membrane potential of a neuron is $-70 \text{ mV}$. A cell that exhibits a membrane potential is polarized.
5. The resting membrane potential is determined by two major factors: (1) unequal distribution of ions in the ECF and cytosol and (2) differences in membrane permeability to various ions.
6. A graded potential is a small deviation from the resting membrane potential that occurs because ligand-gated or mechanically-gated channels open or close. A hyperpolarizing graded potential makes the membrane more polarized (inside more negative); a depolarizing graded potential makes the membrane less polarized (inside less negative).
7. The amplitude of a graded potential varies, depending on the strength of the stimulus.
8. According to the all-or-none principle, if a stimulus is strong enough to generate an action potential, the action potential generated is of a constant size. A stronger stimulus does not generate a larger action potential. Instead, the greater the stimulus strength above threshold, the greater the frequency of the action potentials.
9. During an action potential, voltage-gated Na$^+$ and K$^+$ channels open and close in sequence. This results first in depolarization, the reversal of membrane polarization (from $-70 \text{ mV}$ to $+30 \text{ mV}$). Then repolarization, the recovery of the resting membrane potential (from $+30 \text{ mV}$ to $-70 \text{ mV}$), occurs.
10. During the first part of the refractory period, another action potential cannot be generated at all (absolute refractory period); a little later, one can be triggered only by a larger-than-normal stimulus (relative refractory period).
11. Because an action potential travels from point to point along the membrane without getting smaller, it is useful for long-distance communication.
12. Action potential propagation in which the action potential “leaps” from one node of Ranvier to the next along a myelinated axon is saltatory conduction. Saltatory conduction is faster than continuous conduction.
13. Large-diameter, myelinated axons conduct action potentials at higher speeds than do small-diameter, unmyelinated axons.
14. The intensity of a stimulus is encoded in the frequency of action potentials and in the number of sensory neurons that are recruited.
Chapter 7 The Nervous System and Neuronal Excitability

7.4 SIGNAL TRANSMISSION AT SYNAPSES
1. A synapse is the functional junction between one neuron and another or between a neuron and an effector such as a muscle or a gland. The two types of synapses are electrical and chemical.
2. A chemical synapse produces one-way information transfer—from a presynaptic neuron to a postsynaptic neuron.
3. When a neurotransmitter is released by a presynaptic neuron, it binds to neurotransmitter receptors in the postsynaptic membrane and causes a postsynaptic potential (a type of graded potential).
4. An excitatory neurotransmitter depolarizes the postsynaptic neuron’s membrane, bringing the membrane potential closer to threshold. A depolarizing postsynaptic potential is called an excitatory postsynaptic potential (EPSP).
5. An inhibitory neurotransmitter hyperpolarizes the membrane of the postsynaptic neuron, moving it farther from threshold. A hyperpolarizing postsynaptic potential is called an inhibitory postsynaptic potential (IPSP).
6. There are two major types of neurotransmitter receptors: ionotropic receptors and metabotropic receptors. An ionotropic receptor contains a neurotransmitter binding site and an ion channel. A metabotropic receptor contains a neurotransmitter binding site and is coupled to a separate ion channel by a G protein.
7. Neurotransmitter is removed from the synaptic cleft in three ways: diffusion, enzymatic degradation, and uptake by cells (neurons and neuroglia).
8. Postsynaptic potentials can summate. Summation may be spatial or temporal.
9. The postsynaptic neuron is an integrator. It receives excitatory and inhibitory signals, integrates them, and then responds accordingly.
10. During presynaptic modulation, the amount of neurotransmitter released by a presynaptic neuron is altered by another neuron. Examples of presynaptic modulation include presynaptic facilitation and presynaptic inhibition.

7.5 NEUROTRANSMITTERS
1. Both excitatory and inhibitory neurotransmitters are present in the CNS and the PNS. A given neurotransmitter may be excitatory in some locations and inhibitory in others.
2. Neurotransmitters can be divided into two classes based on size: (1) small-molecule neurotransmitters (acetylcholine, amino acids, biogenic amines, purines, gases, and endocannabinoids) and (2) neuropeptides, which are composed of 3 to 40 amino acids linked by peptide bonds.

7.6 NEURAL CIRCUITS
1. Neurons in the central nervous system are organized into networks called neural circuits.
2. Neural circuits include simple series, diverging, converging, reverberating, and parallel after-discharge circuits.

SELF-QUIZ QUESTIONS
Fill in the blanks in the following statements.

1. A collection of cell bodies located in the peripheral nervous system is referred to as a(n) _____________.
2. The separation of positive and negative charge observed across the membrane of an excitable cell when it is not stimulated can be measured as a voltage and is called the cell’s _____________.
3. Channels that are opened in response to pressure are known as ____________ gated channels.
4. In order for an action potential to be generated, the stimulus applied must be sufficient to meet the neuron’s _____________.
5. Receptors that contain the binding site and ion channel on the same protein and produce fast responses in the postsynaptic cell are called ____________ receptors.
6. ____________ summation occurs when several action potentials from a single source arrive at a postsynaptic neuron in rapid succession.

Are the following statements true or false? If the statement is false, find and fix the mistake to make the statement true.

7. The entire cytosol inside the cell contains a negative charge while all of the extracellular fluid contains a positive charge.
8. In a hypothetical cell containing only K⁺, changing permeability to K⁺ will result in a change in the ion’s equilibrium potential.
9. In order to determine a cell’s membrane potential, you must use the Goldman-Hodgkin-Katz equation.
10. Delivering a stimulus that is subthreshold will result in the production of an action potential with a small amplitude.
Choose the one best answer to the following questions.

11. All neural circuits are arranged in simple series containing a presynaptic neuron that stimulates a single postsynaptic neuron and so on.

12. Neurotransmitters can be removed from the synaptic cleft through enzymatic degradation and by reuptake by the presynaptic neuron.

13. Which of the following are components of the peripheral nervous system? Choose all that apply.
   1. Sensory receptors
   2. Spinal cord
   3. Sympathetic nervous system
   4. Brain
   5. Afferent neurons
   a. 1, 2, 3, 5  
   b. 1, 3, 5  
   c. 3, 5  
   d. 2, 3, 5

14. In a hypothetical cell containing only Na⁺ in the intracellular and extracellular fluid, what would happen to the cell's membrane potential if all leak channels were open AND the concentration of Na⁺ in the extracellular fluid was increased?
   a. The membrane potential would become more positive.
   b. The membrane potential would become more negative.
   c. This cannot be determined without knowing the concentration of K⁺.
   d. No change in potential would be observed.

15. In order to use the Goldman-Hodgkin-Katz equation to calculate a cell's membrane potential, which of the following parameters/values would you need to know?
   a. Ion permeabilities
   b. Neuron diameter
   c. Thickness of the plasma membrane
   d. Whether the neuron is myelinated or not

16. Which of the following classifies as a graded potential? Select all that apply.
   1. Excitatory postsynaptic potential
   2. Action potential
   3. End plate potential
   4. Receptor potential
   5. Inhibitory postsynaptic potential
   a. 1, 2, 3, 4, 5  
   b. 1, 2  
   c. 1, 3, 4, 5  
   d. 3, 4

17. Which of the following conditions must be met before another action potential can be generated in a neuron?
   a. Voltage-gated K⁺ channels must all be closed.
   b. Resting membrane potential must be reestablished.
   c. Activation gates of the voltage-gated Na⁺ channels must be reset.
   d. A and C
   e. A, B, and C

18. All of the following factors will affect the conduction velocity of a neuron EXCEPT:
   a. Myelination of the axon.
   b. Intensity of a threshold stimulus delivered to the axon hillock of a neuron.
   c. Axonal diameter.
   d. All of the above would affect conduction velocity in a neuron.

19. Why would a forceful needle prick result in a stronger perception of pain than a light needle prick when administered to the same finger, in the same area?
   a. The action potential delivered by the neurons stimulated due to the forceful needle prick are higher in amplitude.
   b. There is an increase in the frequency of action potentials delivered by the neurons associated with the forceful needle prick.
   c. The conduction velocity in the neurons stimulated by the forceful needle prick is slower.
   d. Fewer neurons are stimulated by a more forceful needle prick than by the light needle prick.

20. Put the following events associated with synaptic transmission between a presynaptic neuron and a postsynaptic neuron in the correct sequential order.
   1. An action potential is generated by the axon hillock of the postsynaptic neuron.
   2. Neurotransmitters are released and diffuse across the synaptic cleft and bind to their receptors.
   3. An action potential arrives at an axon terminal bulb.
   4. Opening Na⁺ channels results in a postsynaptic potential.
   5. Synaptic vesicles merge with the axon terminal membrane and exocytosis of neurotransmitter occurs.
   6. Voltage-gated Ca²⁺ channels are triggered to open.
   a. 3, 6, 5, 2, 1  
   b. 1, 4, 3, 6, 2  
   c. 1, 6, 5, 2, 4, 3  
   d. 3, 6, 4, 5, 2, 1

21. How is it possible for a neurotransmitter to cause an excitatory postsynaptic potential (EPSP) in one neuron and an inhibitory postsynaptic potential (IPSP) in another neuron?
   a. The two neurons receiving the neurotransmitter from the presynaptic neuron are of different sizes.
   b. A higher concentration of neurotransmitter is released on to the neuron that produces the EPSP while a much lower concentration is released on to the neuron that produces the IPSP.
   c. Upon release, the neurotransmitter will change its chemical nature to induce either an IPSP or an EPSP.
   d. The two postsynaptic neurons contain different receptors that bind to the same neurotransmitter.

22. Which of the following neurotransmitters is NOT classified as a biogenic amine?
   a. Epinephrine  
   b. Dopamine  
   c. Serotonin  
   d. Acetylcholine

23. Activating a single neuron in the motor cortex leads to a greater number of neurons being stimulated before the final signal reaches an even large number of muscle fibers to produce a movement. This is an example of what type of circuit?
   a. Converging  
   b. Diverging  
   c. Reverb erating  
   d. Parallel-after discharge

24. Which of the following are functions of an astrocyte? Select all that apply.
   1. Secrete chemicals that maintain the blood-brain barrier
   2. Guide neurons during embryological development
   3. Aid in the production of cerebrospinal fluid
   4. Maintain a chemical environment for proper neuronal function
   5. Form and maintain the myelin sheath in the central nervous system
   a. 1, 2, 3, 4, 5  
   b. 2, 4, 5  
   c. 1, 2, 4  
   d. 2, 3, 4

For each of the following, match the correct term with the proper definition/function

25. Match each of the following neuron functions with its appropriate structure.
   a. Receives signals from other neurons or from stimuli in the environment
Chapter 7 The Nervous System and Neuronal Excitability

26. Match each of the phases of an action potential with the type of ion and direction of movement observed. All options may be used only once and some options might not be used at all.

a. Depolarization
   1. Voltage-gated Na\(^+\) channels open, resulting in an influx of Na\(^+\).

b. Repolarization
   2. Voltage-gated K\(^+\) channels open, resulting in an efflux of K\(^+\).

c. After-hyperpolarization
   3. Voltage-gated K\(^+\) channels are slow to close, resulting in extra K\(^+\) leakage.

   4. Voltage-gated Na\(^+\) channels open, resulting in an efflux of Na\(^+\) ions.

   5. Voltage-gated K\(^+\) channels open, resulting in an influx of K\(^+\) ions.

CRITICAL THINKING QUESTIONS

1. Birth control pills often cause a problem with K\(^+\) concentration in the extracellular fluid. These pills often result in a condition known as hyperkalemia, an increased concentration of K\(^+\) in the extracellular fluid. Why should this condition be of concern?

2. You are walking around your house and neglect to notice the thumbtack located in front of you. As you walk toward your room, you step on the thumbtack and immediately withdraw your foot. Discuss the pathways involved in the perception of your initial sensation as well as your response. What parts of the nervous system were responsible for facilitating the transmission of this information?

3. Dr. Salazar, a prestigious taxonomist, has just discovered a new species of frog. In order to learn more about the nervous system of this species, Dr. Salazar sacrifices one organism (luckily he discovered a large population) and extracts a few neurons from the sciatic nerve of its leg. Dr. Salazar runs several tests on this neuron and compares his results to the well-documented data on the unmyelinated sciatic nerve of the bullfrog. Dr. Salazar concludes that the conduction velocity of the neurons in the new species is ten times faster than that of the conduction velocity of the bullfrog neurons. What must be different in the neurons of the new species compared to the neurons of the bullfrog? Explain your answer.

ANSWERS TO FIGURE QUESTIONS

7.1 The afferent division of the PNS conveys sensory input into the CNS from sensory receptors in the periphery.

7.2 Dendrites receive input; the cell body functions as the control center and can receive input; the axon sends output in the form of action potentials to another neuron or effector cell by releasing a neurotransmitter at its synaptic end bulbs.

7.3 Anterograde transport moves organelles and synaptic vesicles from the cell body to the axon terminals.

7.4 Interneurons are responsible for integration.

7.5 Microglia function as phagocytes in the central nervous system.

7.6 The myelin sheath electrically insulates the axon of a neuron and increases the speed of conduction of action potentials.

7.7 Myelin makes white matter look white.

7.8 Perception primarily occurs in the cerebral cortex.

7.9 A touch on the arm activates mechanically-gated channels.

7.10 No; only a tiny fraction of all of the charges in the ECF and cytosol must be separated across the plasma membrane in order to establish the normal resting membrane potential.

7.11 K\(^+\) ions have the greatest influence on the resting membrane potential of a neuron because neurons at rest are most permeable to K\(^+\) ions.

7.12 When an inside-negative membrane potential exists, the K\(^+\) electrical gradient favors movement of K\(^+\) ions from the ECF into the cytosol because the K\(^+\) ions are attracted to the negative charges along the inside surface of the plasma membrane and are repelled by the positive charges along the outside surface of the plasma membrane.

7.13 When an inside-positive membrane potential exists, the Na\(^+\) electrical gradient favors movement of Na\(^+\) ions from the cytosol into the ECF because the Na\(^+\) ions are attracted to the negative charges along the outside surface of the plasma membrane and are repelled by the positive charges along the inside surface of the plasma membrane.

7.14 More Na\(^+\) would leak into the cell and less K\(^+\) ions would leak out of the cell, which would make the resting membrane more inside-positive.

7.15 A change in membrane potential from −70 to −60 mV is a depolarizing graded potential since the membrane potential is inside less negative than at rest. A change in membrane potential from −70 to −80 mV is a hyperpolarizing graded potential since the membrane potential is inside more negative than at rest.

7.16 Ligand-gated channels and mechanically-gated channels can be present in the dendrites of sensory neurons, and ligand-gated...
7.17 A stronger stimulus opens more mechanically-gated channels or ligand-gated channels than a weaker stimulus.

7.18 Local current flow refers to the passive movement of charges from one region of membrane to adjacent regions of membrane due to difference in membrane potential in these regions.

7.19 As a graded potential spreads along the plasma membrane, it gradually dies out because its charges are lost across the membrane through leak channels.

7.20 Since individual graded potentials undergo decremental conduction, they would die out as they spread through the dendrites and cell body if summation did not occur and an action potential would not be generated at the trigger zone of the axon.

7.21 Voltage-gated Na⁺ channels are open during the depolarizing phase, and voltage-gated K⁺ channels are open during the repolarizing phase.

7.22 An action potential will not occur in response to a hyperpolarizing graded potential because a hyperpolarizing graded potential causes the membrane potential to become inside more negative and, therefore, farther away from threshold (~55 mV).

7.23 Yes, because the leak channels would still allow K⁺ to exit more rapidly than Na⁺ could enter the axon.

7.24 Local current flow is unable to depolarize an adjacent region of axon membrane in a backward direction because any region of membrane that has just undergone an action potential is temporarily in the absolute refractory period and cannot produce another action potential.

7.25 An action potential is not decremental. Instead, it propagates (keeps its strength as it spreads along the membrane) because when Na⁺ ions flow into the neuron they cause voltage-gated Na⁺ channels in adjacent segments of membrane to open and a positive feedback system is created.

7.26 The diameter of an axon and the presence or absence of a myelin sheath determine the speed of propagation of an action potential.

7.27 At a synapse between neurons, the presynaptic neuron sends the signal and the postsynaptic neuron receives the message.

7.28 In some electrical synapses (gap junctions), ions may flow equally well in either direction, so either neuron may be the presynaptic one. At a chemical synapse, one neuron releases neurotransmitter and the other neuron has receptors that bind this chemical. Thus, the signal can proceed in only one direction.

7.29 At some excitatory synapses, ACh binds to ionotropic receptors that contain cation channels that open and subsequently generate EPSPs in the postsynaptic cell. At some inhibitory synapses, ACh binds to metabotropic receptors coupled to G proteins that open K⁺ channels, resulting in the formation of IPSPs in the postsynaptic cell.

7.30 Reuptake of a neurotransmitter means that the neurotransmitter is transported back into the neuron that originally released it. Uptake of a neurotransmitter means that the neurotransmitter is transported into another cell and not into the neuron that originally released it.

7.31 This is an example of spatial summation since the summation results from the buildup of neurotransmitter released simultaneously by several presynaptic end bulbs.

7.32 Since ~60 mV is below threshold, an action potential will not occur in the postsynaptic neuron.

7.33 An axoaxonic synapse is typically associated with presynaptic inhibition or presynaptic facilitation.

7.34 Norepinephrine, epinephrine, dopamine, and serotonin are classified as biogenic amines because they are derived from amino acids that have been chemically modified.

7.35 The choline is transported back into the synaptic end bulb, where it is used to synthesize another ACh molecule. The acetate diffuses out of the synaptic cleft into the blood.

7.36 The catecholamine that has the lowest concentration in the brain is epinephrine.

7.37 A motor neuron receiving input from several other neurons is an example of convergence.