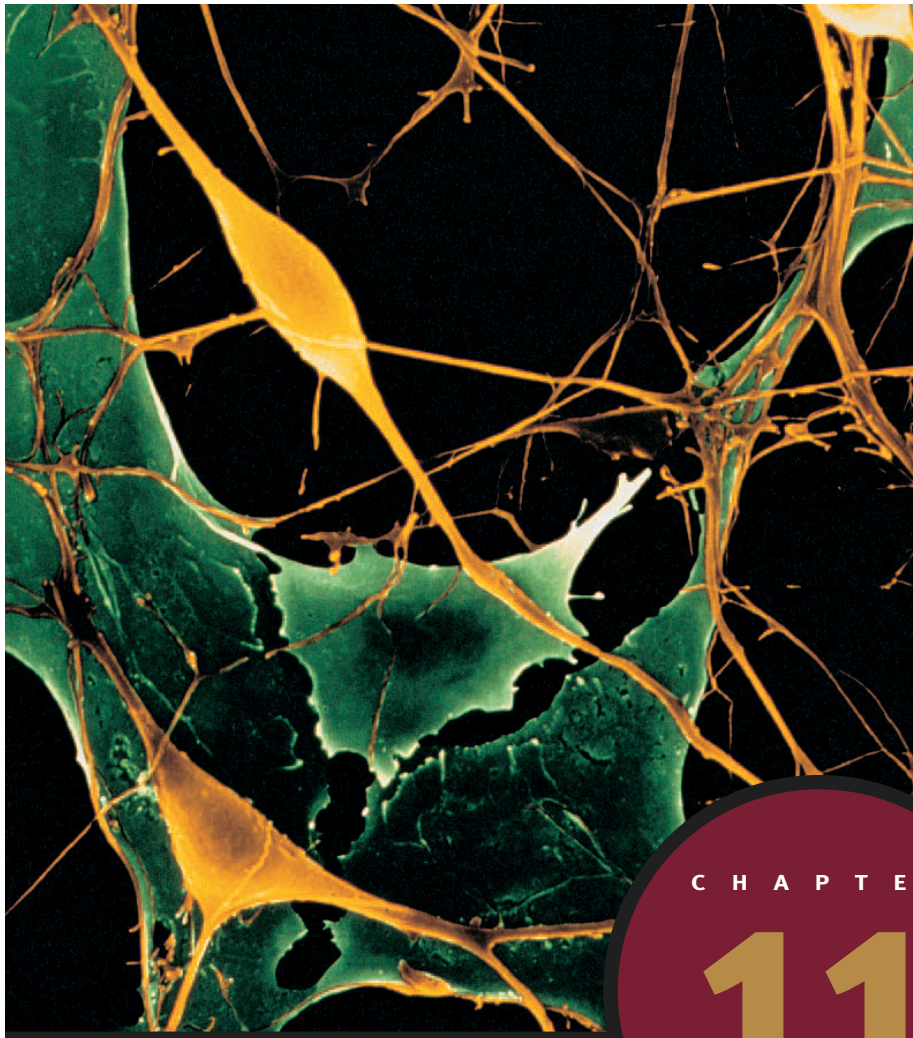




Light photomicrograph of pyramid-shaped neurons (green) growing on a fibrous network (yellow) in the central nervous system.

C H A P T E R

11

Functional Organization of Nervous Tissue

The nervous system is made up of the brain, spinal cord, nerves, and sensory receptors. It's responsible for sensory perceptions, mental activities, and stimulating muscle movements and the secretions of many glands. For example, as a hungry person prepares to drink a cup of hot soup, he smells the aroma and anticipates the taste of the soup. Feeling the warmth of the cup in his hands, he carefully raises the cup to his lips and takes a sip. The soup is so hot that he burns his tongue. Quickly, he jerks the cup away from his lips and gasps in pain. None of these sensations, thoughts, emotions, and movements would be possible without the nervous system.

This chapter explains the *functions of the nervous system* (364), *divisions of the nervous system* (364), *cells of the nervous system* (366), *organization of nervous tissue* (371), *electric signals* (371), *the synapse* (384), and *neuronal pathways and circuits* (393).

Functions of the Nervous System

Objective

- List the major functions of the nervous system.

The nervous system is involved in some way in most body functions. Some of the major functions of the nervous system are:

1. **Sensory input.** Sensory receptors monitor numerous external and internal stimuli, such as touch, temperature, taste, smell, sound, blood pressure, pH of body fluids, and body position.
2. **Integration.** The brain and spinal cord are the major organs for processing sensory input and initiating responses. The input may produce an immediate response, may be stored as memory, or may be ignored.
3. **Homeostasis.** The regulatory and coordinating activities of the nervous system are necessary for maintaining homeostasis. The trillions of cells in the human body do not function independently of each other but must work together to maintain homeostasis. For example, heart cells must contract at a rate that ensures adequate delivery of blood, skeletal muscles of respiration must contract at a rate that ensures oxygenation of blood, and kidney cells must regulate blood volume and remove waste products. The nervous system can stimulate or inhibit the activities of these and other structures to help maintain homeostasis.
4. **Mental activity.** The brain is the center of mental activities, including consciousness, thinking, memory, and emotions.
5. **Control of muscles and glands.** Skeletal muscles normally contract only when stimulated by the nervous system, and the nervous system controls the major movements of the body through the control of skeletal muscle. Some smooth muscle, such as in the walls of blood vessels, contracts only when stimulated by the nervous system or hormones (see chapter 18). Cardiac muscle and some smooth muscle, such as in the wall of the stomach, contract autorhythmically. That is, no external stimulation is necessary for contraction to occur. Although the nervous system does not initiate contraction in these muscles, it can cause the contractions to occur more rapidly or slowly. Finally, the nervous system controls the secretions from many glands, such as sweat glands, salivary glands, and glands of the digestive system.

- 1. List and give examples of the general functions of the nervous system.

Divisions of the Nervous System

Objective

- List the divisions of the nervous system, and describe the characteristics of each.

Humans have only one nervous system, even though some of its subdivisions are referred to as separate systems (figure 11.1). Thus the central nervous system and the peripheral nervous system are subdivisions of the nervous system, instead of separate organ systems as their names suggest. The **central nervous system**

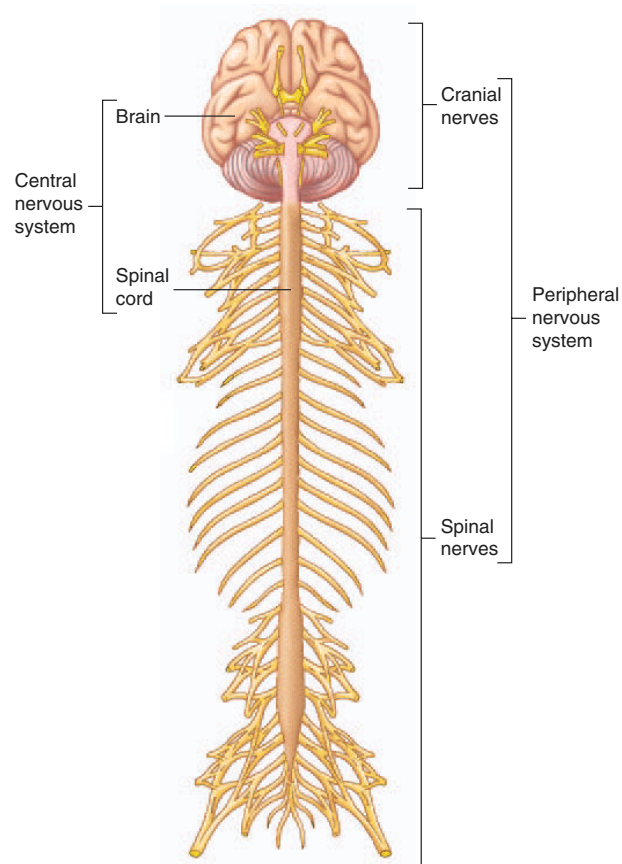


Figure 11.1 The Nervous System

The CNS consists of the brain and spinal cord. The PNS consists of cranial nerves, which arise from the brain, and spinal nerves, which arise from the spinal cord. The nerves, which are shown cut in the illustration, actually extend throughout the body.

(CNS) consists of the brain and the spinal cord. The brain is located within the skull, and the spinal cord is located within the vertebral canal, formed by the vertebrae (see chapter 7). The brain and spinal cord are continuous with each other at the foramen magnum.

The **peripheral nervous system (PNS)** is external to the CNS. It consists of sensory receptors, nerves, ganglia, and plexuses. **Sensory receptors** are the endings of nerve cells or separate, specialized cells that detect temperature, pain, touch, pressure, light, sound, odors, and other stimuli. Sensory receptors are located in the skin, muscles, joints, internal organs, and specialized sensory organs such as the eyes and ears. A **nerve** is a bundle of axons and their sheaths that connects the CNS to sensory receptors, muscles, and glands. Twelve pairs of **cranial nerves** originate from the brain, and 31 pairs of **spinal nerves** originate from the spinal cord (see figure 11.1). A **ganglion** (gang'glē-on; pl., ganglia, gang'glē-ä; knot) is a collection of neuron cell bodies located outside the CNS. A **plexus** (plek'sus; braid) is an extensive network of axons and, in some cases, also neuron cell bodies, located outside the CNS.

The PNS can be divided into two subcategories. The **sensory**, or **afferent, division** transmits electric signals, called **action potentials**, from the sensory receptors to the CNS. The cell bodies of sensory neurons are located in ganglia near the spinal cord (figure 11.2a) or near the origin of certain cranial nerves. The **motor**, or **efferent, division** transmits action potentials from the CNS to effector organs, such as muscles and glands.

The motor division is divided into the **somatic nervous system** and the **autonomic nervous system (ANS)**. The somatic nervous system transmits action potentials from the CNS to skeletal muscles (figure 11.2b). Skeletal muscles are voluntarily controlled through the somatic nervous system. The cell bodies of somatic motor neurons are located within the CNS, and their axons extend through nerves to form synapses with skeletal muscle cells. A **synapse** is the junction of a nerve cell with another cell. The neuromuscular junction, the synapse between a neuron and skeletal muscle cell, is discussed in detail in chapter 9. Nerve cells can also form synapses with other nerve cells, smooth muscle cells, cardiac muscle cells, and gland cells.

The ANS transmits action potentials from the CNS to smooth muscle, cardiac muscle, and certain glands. Subconscious, or involuntary, control of smooth muscle, cardiac muscle, and glands occurs through the ANS. The ANS has two sets of neurons that exist in a series between the CNS and the effector organs (figure 11.2c). Cell bodies of the first neurons are within the CNS and send their axons to autonomic ganglia, where neuron cell bodies of the second neurons are located. Synapses exist between the first and second neurons within the autonomic ganglia, and the axons of the second neurons extend from the autonomic ganglia to the effector organs.

The ANS is subdivided into the sympathetic and the parasympathetic divisions and the enteric nervous system. In general, the **sympathetic division** prepares the body for physical activity, whereas the **parasympathetic division** regulates resting or vegetative functions, such as digesting food or emptying the urinary bladder. The **enteric nervous system** consists of plexuses within the wall of the digestive tract (see figure 24.4). Although the enteric nervous system is capable of controlling the digestive tract independently of the CNS, it's considered part of the ANS because of the parasympathetic and sympathetic neurons that contribute to the plexuses. See chapters 16 and 24 for details on the enteric nervous system.

The sensory division of the PNS functions to detect stimuli and transmit information in the form of action potentials to the CNS (figure 11.3). The CNS is the major site for processing information, initiating responses, and integrating mental processes. It's much like a highly sophisticated computer with the ability to receive input, process and store information, and generate responses. The motor division of the PNS conducts action potentials from the CNS to muscles and glands.

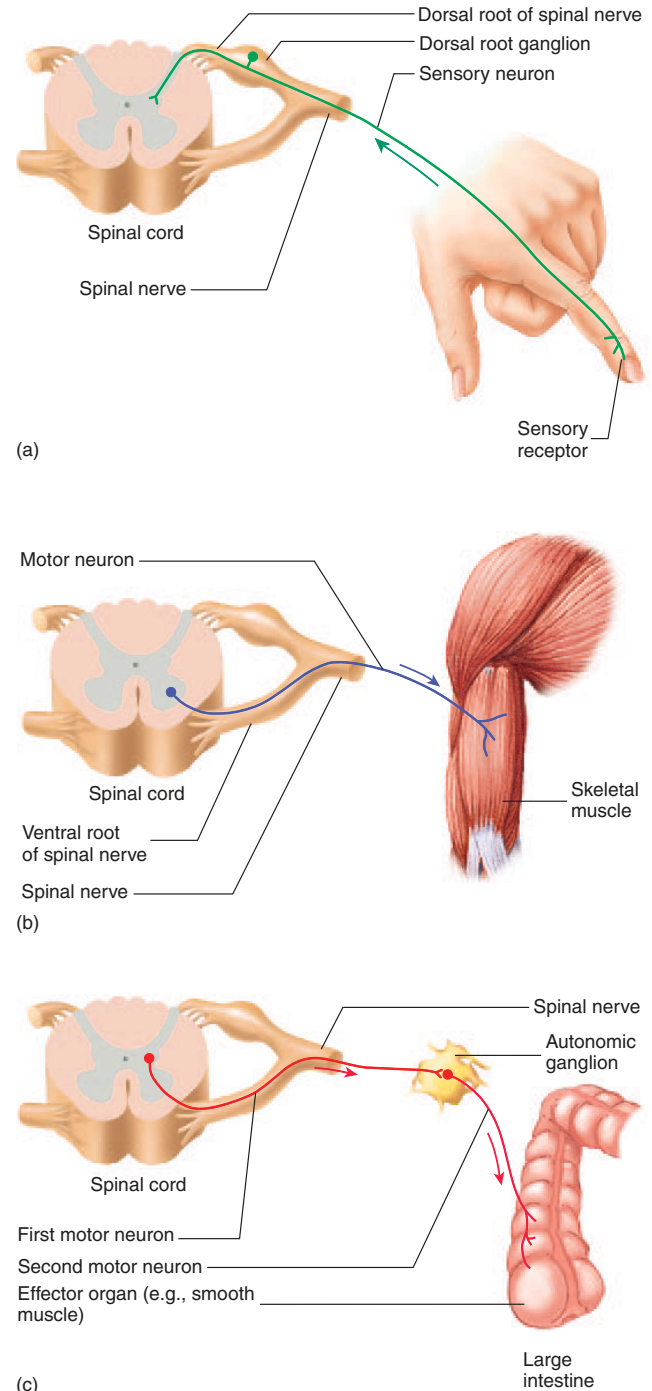


Figure 11.2 Divisions of the Peripheral Nervous System

(a) **Sensory division.** A neuron with its cell body in a dorsal root ganglion. (b) **Somatic nervous system.** The neuron extends from the CNS to skeletal muscle. (c) **Autonomic nervous system.** Two neurons are in series between the CNS and the effector cells (smooth muscle or glands). The first neuron has its cell body in the CNS, and the second neuron has its cell body in an autonomic ganglion.

2. Define the CNS and the PNS.
3. What is a sensory receptor, nerve, ganglion, and plexus?
4. Based on the direction they transmit action potentials, what are the two subcategories of the PNS?
5. Based on the structures they supply, what are the two subcategories of the motor division?

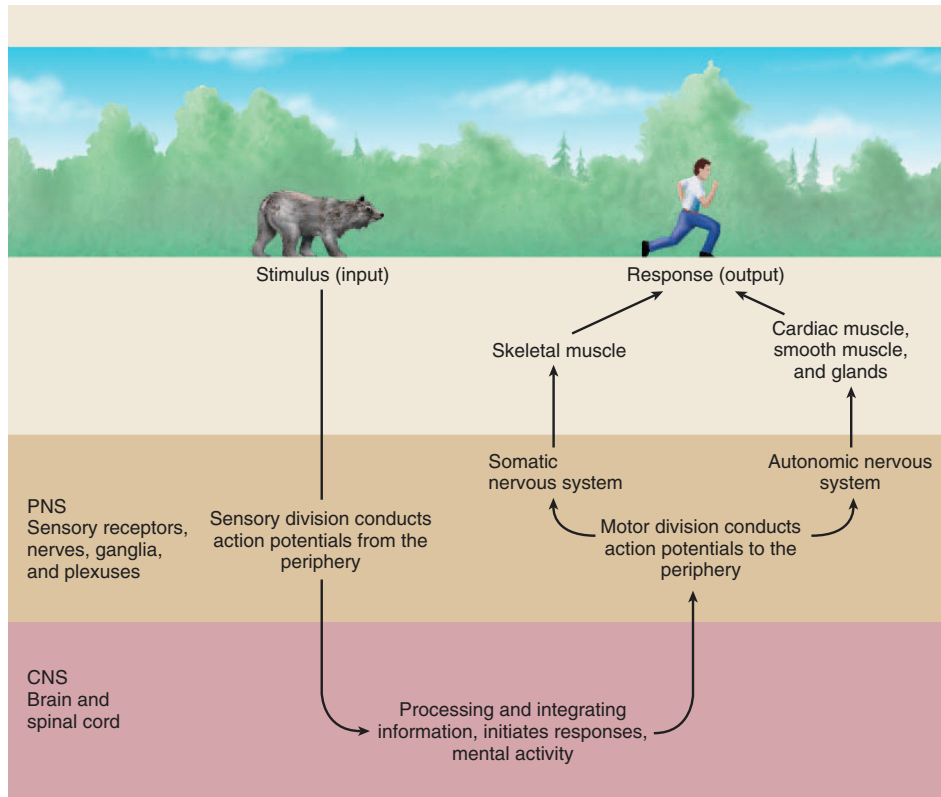


Figure 11.3 Organization of the Nervous System

The sensory division of the peripheral nervous system (PNS) detects stimuli and conducts action potentials to the central nervous system (CNS). The CNS interprets incoming action potentials and initiates action potentials that are conducted through the motor division to produce a response. The motor division is divided into the *somatic nervous system* and the *autonomic nervous system*.

6. Where are the cell bodies of sensory, somatic motor, and autonomic neurons located? What is a synapse?
7. What are the subcategories of the ANS?
8. Compare the general functions of the CNS and the PNS.

Cells of the Nervous System

Objectives

- Describe the structure of neurons and the different types of neurons.
- Describe the different types of neuroglia cells.
- Compare the structure and function of myelinated and unmyelinated axons.

The nervous system is made up of neurons and nonneural cells. Neurons receive stimuli and conduct action potentials. Non-neural cells are called **neuroglia** (noo-rog'lē-ă; nerve glue), or **glial** (glī'äl) **cells**, and they support and protect neurons and perform other functions.

Neurons

Neurons, or **nerve cells**, receive stimuli and transmit action potentials to other neurons or to effector organs. They are organized to form complex networks that perform the functions of the nervous system. Each neuron consists of a cell body and two types of processes (figure 11.4). The cell body is called the **neuron cell body**, or **soma** (sō'mă; body), and the processes are called **dendrites** (den'dritz) and **axons** (ak'sonz). Dendrite means tree and refers to the branching organization of dendrites. Axon means axis and refers to the straight alignment and uniform diameter of most axons. Axons are also referred to as **nerve fibers**.

Neuron Cell Body

Each neuron cell body contains a single relatively large and centrally located nucleus with a prominent nucleolus. Extensive rough endoplasmic reticulum and Golgi apparatuses surround the nucleus, and a moderate number of mitochondria and other organelles are also present. Randomly arranged lipid droplets and melanin pigments accumulate in the cytoplasm of some neuron

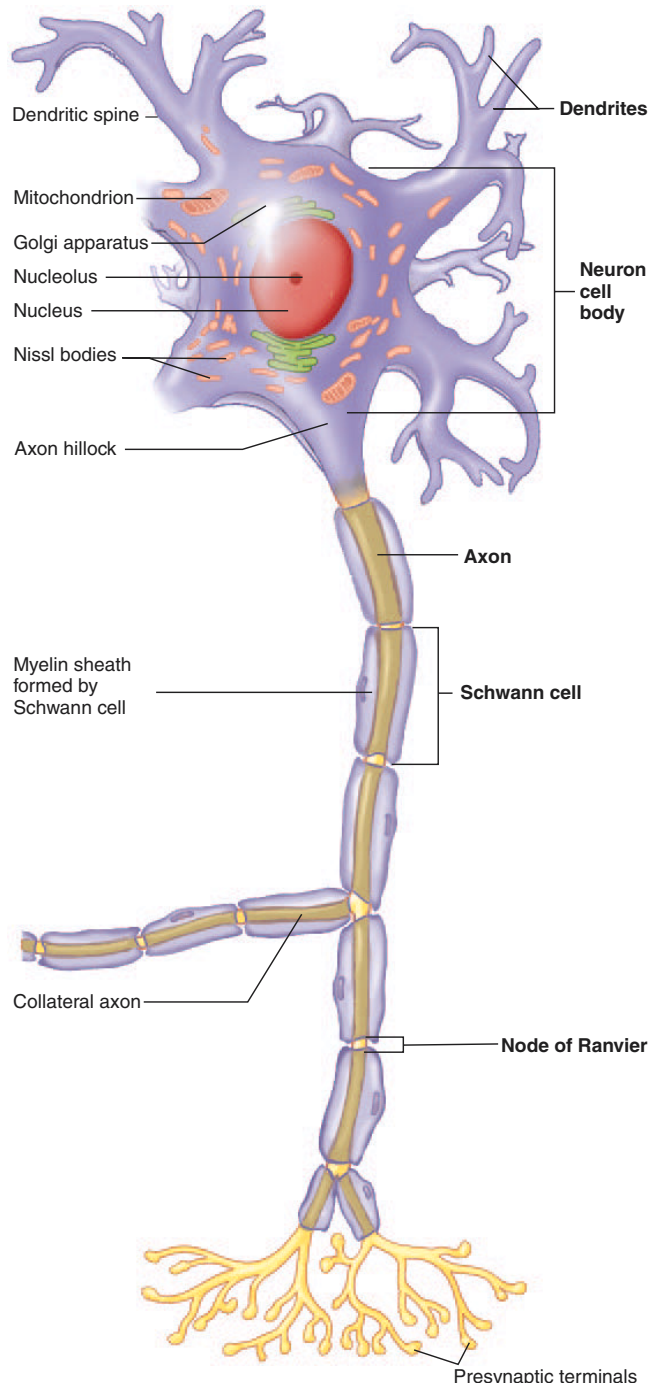


Figure 11.4 Neuron

Structural features of a neuron include a cell body and two types of cell processes: dendrites and an axon.

cell bodies. The lipid droplets and melanin pigments increase as humans age, but their functional significance is unknown. Large numbers of intermediate filaments (neurofilaments) and microtubules form bundles that course through the cytoplasm in all directions. The neurofilaments separate areas of rough endoplasmic reticulum called **chromatophilic** (krō-mă-tō-fil'ik) **substance**, or **Nissl** (nis'l) **bodies**. The presence of organelles such as rough endoplasmic reticulum indicates that the neuron cell body is the primary site of protein synthesis within neurons.

PREDICT 1

Predict the effect on the part of a severed axon that's no longer connected to its neuron cell body. Explain your prediction.

Dendrites

Dendrites are short, often highly branched cytoplasmic extensions that are tapered from their bases at the neuron cell body to their tips (see figure 11.4). Many dendrite surfaces have small extensions called **dendritic spines**, where axons of other neurons form synapses with the dendrites. Dendrites are the input part of the neuron. When stimulated, they generate small electric currents that are conducted to the neuron cell body.

Axons

In most neurons, a single axon arises from a cone-shaped area of the neuron cell body called the **axon hillock**. The beginning of the axon is called the **initial segment**. An axon can remain as a single structure or can branch to form collateral axons or side branches (see figure 11.4). Each axon has a constant diameter, but it can vary in length from a few millimeters to more than 1 meter. The cytoplasm of the axon is sometimes called **axoplasm**, and its plasma membrane is called the **axolemma** (*lemma* is Greek, meaning husk or sheath). Axons terminate by branching to form small extensions with enlarged ends called **presynaptic terminals**, or **terminal boutons** (boo-tonz'; buttons). Numerous small vesicles containing neurotransmitters are present in the presynaptic terminals. **Neurotransmitters** are chemicals released from the presynaptic terminal that cross the synapse to stimulate or inhibit the postsynaptic cell. Functionally, action potentials are generated at the **trigger zone**, which consists of the axon hillock and the part of the axon nearest to the cell body. Action potentials are conducted along the axon to the presynaptic terminal, where they stimulate the release of neurotransmitters.

Axon transport mechanisms can move cytoskeletal proteins (see chapter 3), organelles such as mitochondria, and vesicles containing neurohormones to be secreted (see chapter 17) down the axon to the presynaptic terminals. In addition, damaged organelles, recycled plasma membrane, and substances taken in by endocytosis can be transported up the axon to the neuron cell body. The movement of materials within the axon is necessary for its normal function, but it also provides a way for infectious agents and harmful substances to be transported from the periphery to the CNS. For example, rabies and herpes viruses enter the axon endings of damaged skin and are transported to the CNS.

- 9. Compare the functions of neuroglia and neurons.
- 10. Describe and give the function of a neuron cell body, dendrite, and axon.
- 11. Define trigger zone and neurotransmitter.

Types of Neurons

Neurons are classified according to their function or structure. The functional classification is based on the direction in which action potentials are conducted. **Sensory**, or **afferent**, **neurons** conduct action potentials toward the CNS, and **motor**, or **efferent**, **neurons** conduct action potentials away from the CNS toward muscles or glands. **Interneurons**, or **association neurons**, conduct action potentials from one neuron to another within the CNS.

The structural classification scheme is based on the number of processes that extend from the neuron cell body. The three major categories of neurons are multipolar, bipolar, and unipolar.

Multipolar neurons have many dendrites and a single axon. The dendrites vary in number and in their degree of branching (figure 11.5a). Most of the neurons within the CNS and motor neurons are multipolar.

Bipolar neurons have two processes: a dendrite and an axon (figure 11.5b). The dendrite often is specialized to receive the stimulus, and the axon conducts action potentials to the CNS. Bipolar neurons are located in some sensory organs, such as in the retina of the eye and in the nasal cavity.

Unipolar neurons have a single process extending from the cell body (figure 11.5c). This process divides into two branches a short distance from the cell body. One branch extends to the CNS, and the other branch extends to the periphery and has dendritelike sensory receptors. The two branches function as a single axon. The sensory receptors respond to stimuli resulting in the production of

action potentials that are transmitted to the CNS. According to a functional definition of a dendrite, the branch of a unipolar neuron that extends from the periphery to the neuron cell body could be classified as a dendrite because it conducts action potentials toward the neuron cell body. This branch is usually referred to as an axon, however, for two reasons: it cannot be distinguished from an axon on the basis of its structure, and it conducts action potentials in the same fashion as an axon.

- 12. Describe the three types of neurons based on their function.
- 13. Describe the three types of neurons based on their structure, and give an example of where each type is found.

Neuroglia of the CNS

Neuroglia are far more numerous than neurons and account for more than half the brain's weight. They are the major supporting cells in the CNS, participate in the formation of a permeability barrier between the blood and the neurons, phagocytize foreign substances, produce cerebrospinal fluid, and form myelin sheaths around axons. There are four types of CNS neuroglial cells and each has unique structural and functional characteristics.

Astrocytes

Astrocytes (as'trō-sitz, *aster* is Greek, meaning star) are neuroglia that are star-shaped because of cytoplasmic processes that extend from the cell body. These extensions widen and spread out to form foot processes which cover the surfaces of blood vessels (figure 11.6), neurons, and the pia mater. (The pia mater is a membrane covering the outside of the brain and spinal cord.) Astrocytes have an extensive cytoskeleton of microfilaments (see chapter 3) that enables them to form a supporting framework for blood vessels and neurons.

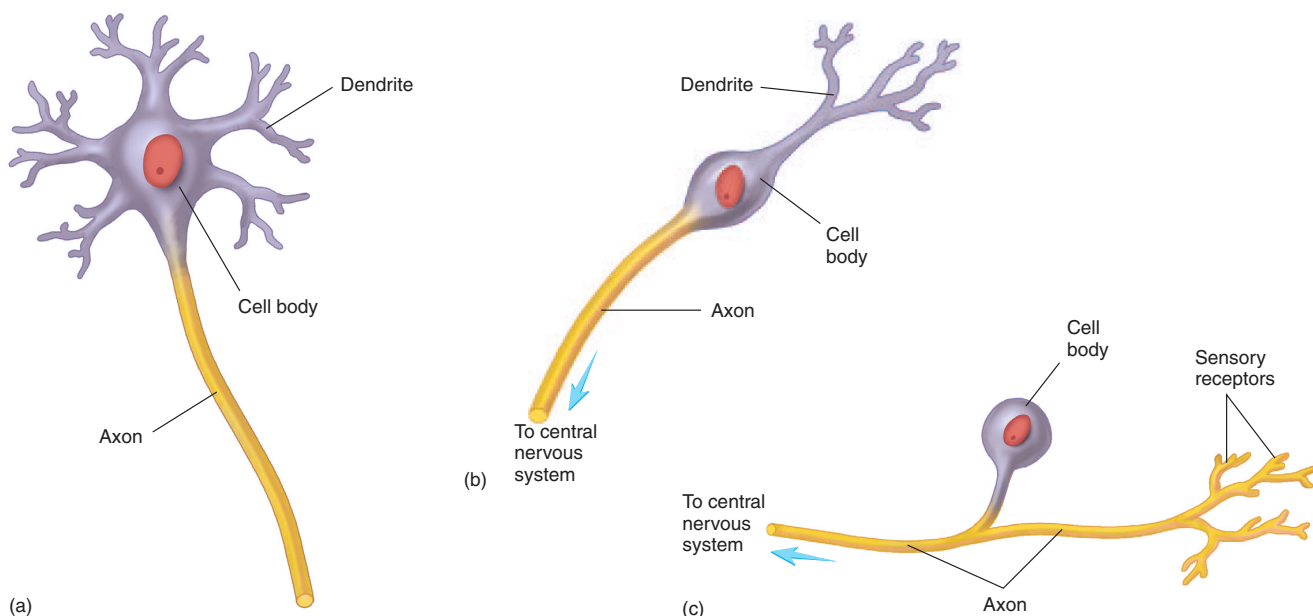


Figure 11.5 Types of Neurons

(a) A multipolar neuron has many dendrites and one axon. (b) A bipolar neuron has a dendrite and an axon. (c) A unipolar neuron has an axon and no dendrites.

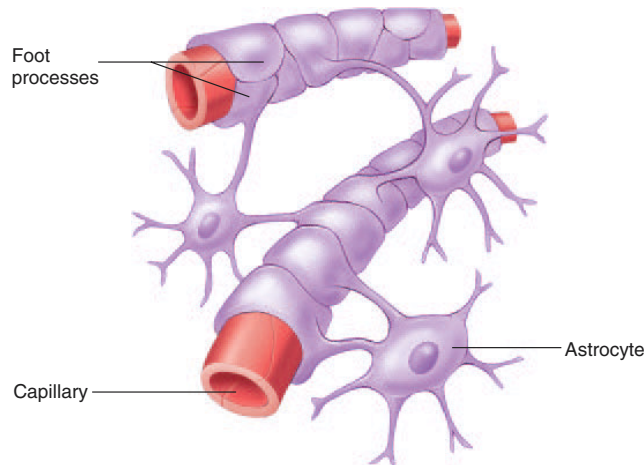


Figure 11.6 Astrocytes

Astrocyte processes form feet that cover the surfaces of neurons and blood vessels. The astrocytes provide structural support and play a role in regulating what substances from the blood reach the neurons.

Astrocytes play a role in regulating the extracellular composition of brain fluid. They release chemicals that promote the formation of tight junctions (see chapter 4) between the endothelial cells of capillaries. The endothelial cells with their tight junctions form the **blood–brain barrier**, which determines what substances can pass from the blood into the nervous tissue of the brain and spinal cord. The blood–brain barrier protects neurons from toxic substances in the blood, allows the exchange of nutrients and waste products between neurons and the blood, and prevents fluctuations in the composition of the blood from affecting the functions of the brain. Astrocytes also help to control the composition of interstitial fluid by regulating the concentration of ions and gases and by absorbing and recycling neurotransmitters.

Ependymal Cells

Ependymal (ep-en'di-mäl) cells line the ventricles (cavities) of the brain and the central canal of the spinal cord (figure 11.7a). Specialized ependymal cells and blood vessels form the **choroid plexuses** (ko'royd plek'süs-ez) (figure 11.7b), which are located within certain regions of the ventricles. The choroid plexuses secrete the cerebrospinal fluid that circulates through the ventricles of the brain (see chapter 13). The free surface of the ependymal cells frequently has patches of cilia that assist in moving cerebrospinal fluid through the cavities of the brain. Ependymal cells also have long processes (not illustrated) at their basal surfaces that extend deep into the brain and the spinal cord and seem, in some cases, to have astrocytelike functions.

Microglia

Microglia (mī-krog'lē-ă) are specialized macrophages in the CNS that become mobile and phagocytic in response to inflammation, and they phagocytize necrotic tissue, microorganisms, and foreign substances that invade the CNS (figure 11.8).

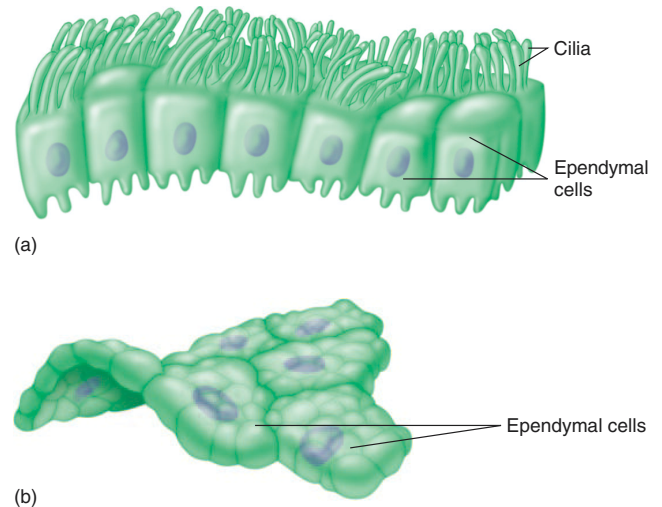


Figure 11.7 Ependymal Cells

(a) Ciliated ependymal cells lining the ventricles of the brain and the central canal of the spinal cord help to move cerebrospinal fluid. (b) Ependymal cells on the surface of the choroid plexus secrete cerebrospinal fluid.

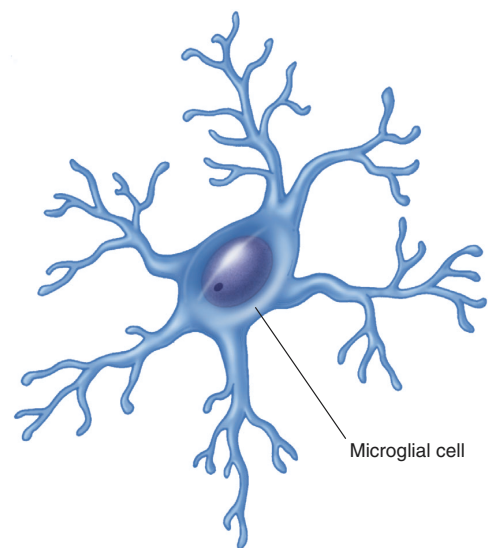


Figure 11.8 Microglia

Microglia within the CNS are similar to macrophages.

Microglia and Brain Damage

Numerous microglia migrate to areas damaged by infection, trauma, or stroke and perform phagocytosis. A pathologist can identify these damaged areas in the CNS during an autopsy because large numbers of microglia are found in them.



Oligodendrocytes

Oligodendrocytes (ol'i-gō-den'drō-sītz) have cytoplasmic extensions that can surround axons. If the cytoplasmic extensions wrap many times around the axons, they form **myelin** (mī'ě-lin) **sheaths**. A single oligodendrocyte can form myelin sheaths around portions of several axons (figure 11.9).

Neuroglia of the PNS

Schwann cells, or **neurolemmocytes** (noor-ō-lem'mō-sītz), are neuroglial cells in the PNS that wrap around axons. If the Schwann cell wraps many times around an axon, it forms a myelin sheath. Unlike oligodendrocytes, however, each Schwann cell forms a myelin sheath around a portion of only one axon (figure 11.10).

Satellite cells surround neuron cell bodies in ganglia, provide support, and can provide nutrients to the neuron cell bodies (figure 11.11).

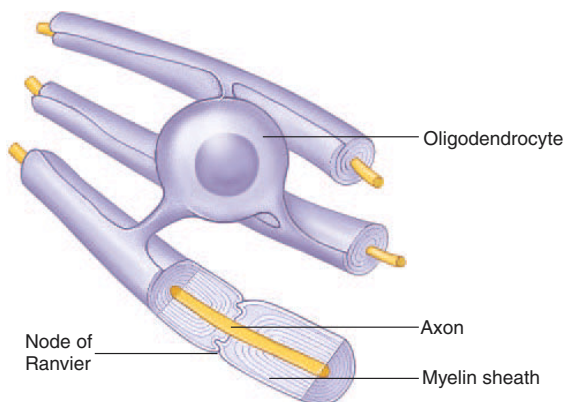


Figure 11.9 Oligodendrocyte

Extensions from the oligodendrocyte form the myelin sheaths of axons within the CNS.

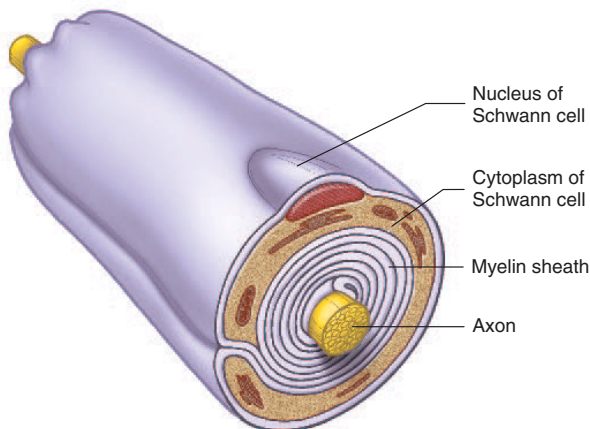


Figure 11.10 Schwann Cell

Extension from the Schwann cell forms the myelin sheath of an axon within the PNS.

Myelinated and Unmyelinated Axons

Cytoplasmic extensions of the oligodendrocytes in the CNS and of the Schwann cells in the PNS surround axons to form either myelinated or unmyelinated axons. Myelin protects and electrically insulates axons from one another. In addition, action potentials travel along myelinated axons more rapidly than along unmyelinated axons (see “Propagation of Action Potentials” on p. 382).

In **myelinated axons**, the extensions from oligodendrocytes or Schwann cells repeatedly wrap around a segment of an axon to form a series of tightly wrapped membranes rich in phospholipids with little cytoplasm sandwiched between the membrane layers (figure 11.12a). The tightly wrapped membranes constitute the myelin sheath and give myelinated axons a white appearance because of the high lipid concentration. The myelin sheath is not continuous but is interrupted every 0.3–1.5 mm. At these locations, there are slight constrictions where the myelin sheaths of adjacent cells dip toward the axon but don't cover it, leaving a bare area 2–3 μm in length. These interruptions in the myelin sheath are the **nodes of Ranvier** (ron'vĕ-ă), and the myelin covered areas between the nodes are called the **internodes**.

Unmyelinated axons rest in invaginations of the oligodendrocytes or the Schwann cells (figure 11.12b). The cell's plasma membrane surrounds each axon, but does not wrap around them many times. Thus each axon is surrounded by a series of cells, and each cell can simultaneously surround more than one unmyelinated axon.

14. Which type of neuroglia supports neurons and blood vessels and promotes the formation of the blood–brain barrier? What is the blood–brain barrier, and what is its function?
15. Name the different kinds of neuroglia responsible for the following functions: produces cerebrospinal fluid, phagocytosis, produces myelin sheaths in the CNS, produces myelin sheaths in the PNS, supports neuron cell bodies in the PNS.
16. Define myelin sheath, node of Ranvier, and internode. How are myelinated and unmyelinated axons different from each other?

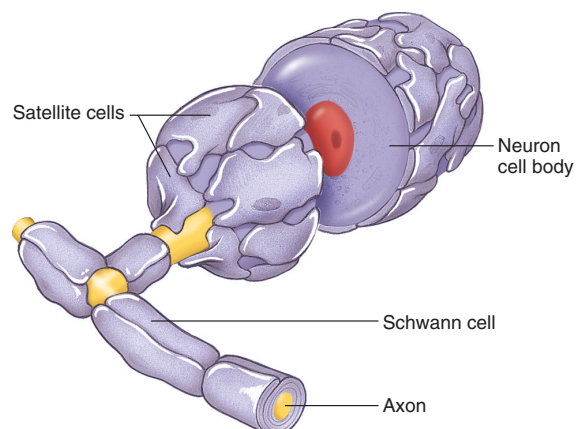


Figure 11.11 Satellite Cells

Neuron cell bodies within ganglia are surrounded by satellite cells.

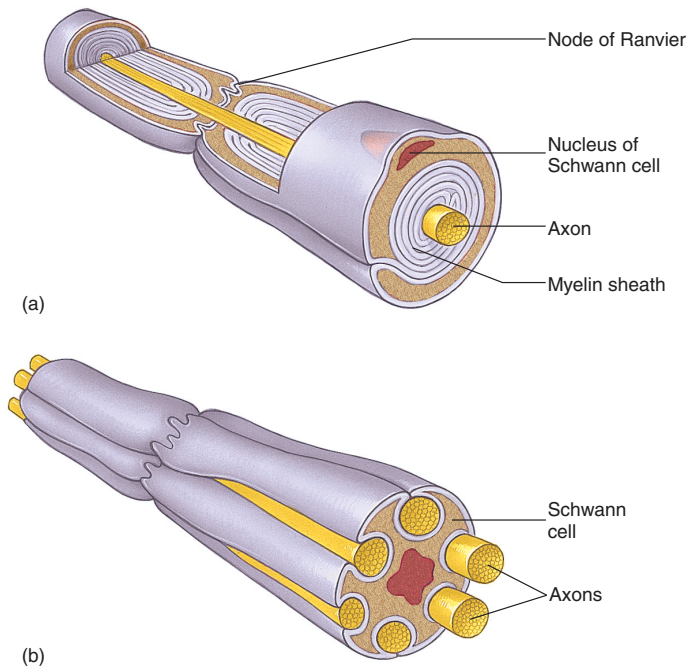


Figure 11.12 Comparison of Myelinated and Unmyelinated Axons

(a) Myelinated axon with two Schwann cells forming the myelin sheath around a single axon. Each Schwann cell surrounds part of one axon. (b) Unmyelinated axons with two Schwann cells surrounding several axons in parallel formation. Each Schwann cell surrounds part of several axons.

Organization of Nervous Tissue

Objective

- Describe the organization of nervous tissue in the CNS and the PNS.

Nervous tissue is organized so that axons form bundles, and neuron cell bodies and their relatively short dendrites are grouped together. Bundles of parallel axons with their associated myelin sheaths are whitish in color, which accounts for their name, **white matter**. Collections of neuron cell bodies and unmyelinated axons are more gray in color and are called **gray matter**.

The axons that make up the white matter of the CNS form **nerve tracts**, which propagate action potentials from one area in the CNS to another. The gray matter of the CNS performs integrative functions or acts as relay areas in which axons synapse with the cell bodies of neurons. The central area of the spinal cord is gray matter, and the outer surface of much of the brain consists of gray matter called **cortex**. Within the brain are other collections of gray matter called **nuclei**.

In the PNS, bundles of axons form nerves, which conduct action potentials to and from the CNS. Most nerves contain myelinated axons, but some consist of unmyelinated axons. Collections of neuron cell bodies in the PNS are called ganglia.

17. What is white and gray matter?

18. Define and state the location of nerve tracts, nerves, brain cortex, nuclei, and ganglia.

Electric Signals

Objectives

- State the concentration differences that exist between intracellular fluid and extracellular fluid, and explain how they occur.
- Describe how the resting membrane potential is established and how it can be changed.
- Explain the production of action potentials and their propagation along axons.

Like computers, humans depend on electric signals to communicate and process information. The electric signals produced by cells are called **action potentials**. They are an important means by which cells transfer information from one part of the body to another. For example, stimuli such as light, sound, and pressure act on specialized sensory cells in the eye, ear, and skin to produce action potentials, which are conducted from these cells to the spinal cord and brain. Action potentials originating within the brain and spinal cord are conducted to muscles and certain glands to regulate their activities.

The ability to perceive our environment, perform complex mental activities, and act depends upon action potentials. For example, interpreting the action potentials received from sensory cells results in the sensations of sight, hearing, and touch. Complex mental activities, such as conscious thought, memory, and emotions, result from action potentials. The contraction of muscles and the secretion of certain glands occur in response to action potentials generated in them.

A basic knowledge of the electrical properties of cells is necessary for understanding many of the normal functions and pathologies of the body. These properties result from the ionic concentration differences across the plasma membrane and from the permeability characteristics of the plasma membrane.

Concentration Differences Across the Plasma Membrane

Table 11.1 lists the concentration differences for positively charged ions (cations) and negatively charged ions (anions) between the intracellular and extracellular fluids. The concentration of sodium ions (Na^+) and chloride ions (Cl^-) is much greater outside the cell than inside. The concentration of potassium ions (K^+) and negatively charged molecules, such as proteins and other molecules containing phosphate, is much greater inside the cell than outside. Note that a steep concentration gradient (see chapter 3) exists for Na^+ from outside the cell to the inside. Also, a steep concentration gradient exists for K^+ from the inside to the outside of the cell.

Differences in intracellular and extracellular concentrations of ions result primarily from (1) the sodium–potassium exchange pump and (2) the permeability characteristics of the plasma membrane.

Table 11.1 Representative Concentrations of the Principal Cations and Anions in Extracellular and Intracellular Fluids of Vertebrates

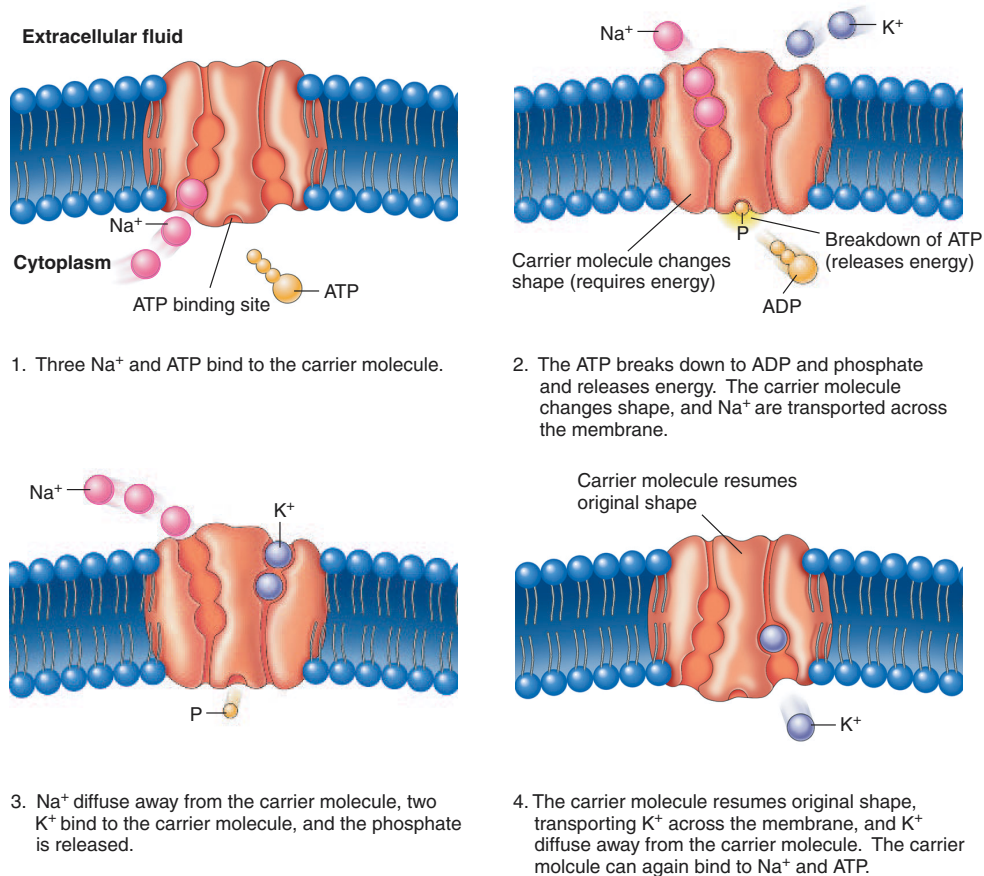
Ions	Intracellular Fluid (mEq/L)	Extracellular Fluid (mEq/L)
Cations (Positive)		
Potassium (K^+)	148	5
Sodium (Na^+)	10	142
Calcium (Ca^{2+})	<1	5
Others	41	3
TOTAL	200	155
Anions (Negative)		
Proteins	56	16
Chloride (Cl^-)	4	103
Others	140	36
TOTAL	200	155

The Sodium–Potassium Exchange Pump

The differences in K^+ and Na^+ concentrations across the plasma membrane are maintained primarily by the action of the **sodium–potassium exchange pump** (figure 11.13). Through active transport, the sodium–potassium exchange pump moves K^+ and Na^+ through the plasma membrane against their concentration gradients. K^+ is transported into the cell, increasing the concentration of K^+ inside the cell, and Na^+ is transported out of the cell, increasing the concentration of Na^+ outside the cell. Approximately three Na^+ are transported out of the cell and two K^+ are transported into the cell for each ATP molecule used.

Permeability Characteristics of the Plasma Membrane

As noted in chapter 3, the plasma membrane is selectively permeable, thus allowing some, but not all, substances to pass through it. Negatively charged proteins are synthesized inside the cell, and because of their large size and their solubility characteristics, they cannot readily diffuse across the plasma membrane (figure 11.14). Negatively charged Cl^- are repelled by the negatively charged proteins and other negatively charged ions inside the cell. Cl^- diffuse through the plasma membrane and accumulate outside it, resulting in a higher concentration of Cl^- outside of the cell than inside.



Process Figure 11.13 The Sodium–Potassium Exchange Pump

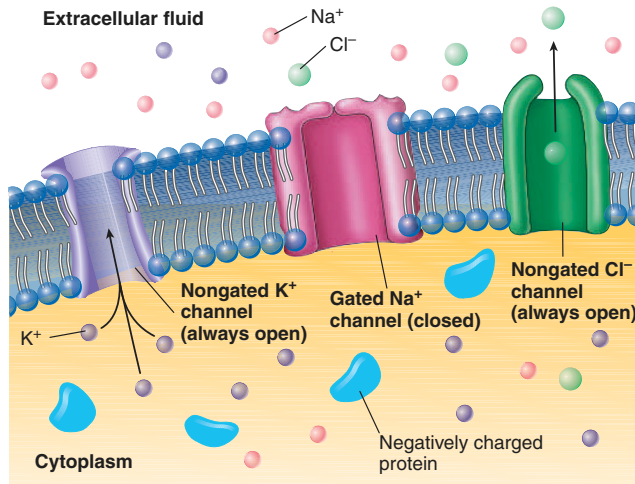


Figure 11.14 Membrane Permeability and Ion Channels

The permeability of the membrane to K^+ and Cl^- is greater than its permeability to Na^+ because some nongated K^+ and Cl^- channels are open, whereas most gated Na^+ channels are closed. The membrane is not permeable to the negatively charged proteins inside of the cell because they are too large to pass through membrane channels.

Ions pass through the plasma membrane through ion channels. The two major types of ion channels are nongated and gated ion channels.

Nongated Ion Channels

Nongated ion channels, or **leak channels**, are always open and are responsible for the permeability of the plasma membrane to ions when the plasma membrane is unstimulated, or at rest (see figure 11.14). Each ion channel is specific for one type of ion, although the specificity is not absolute. The number of each type of nongated ion channels in the plasma membrane determines the permeability characteristics of the resting plasma membrane to different types of ions. The plasma membrane is more permeable to K^+ and Cl^- and much less permeable to Na^+ because there are many more K^+ and Cl^- nongated ion channels than Na^+ nongated ion channels in the plasma membrane.

Gated Ion Channels

Gated ion channels open and close in response to stimuli. By opening and closing, these channels can change the permeability characteristics of the plasma membrane. The major types of gated ion channels are:

1. **Ligand-gated ion channels.** A **ligand** is a molecule that binds to a receptor. A **receptor** is a protein or glycoprotein that has a **receptor site** to which a ligand can bind. Most receptors are located in the plasma membrane. **Ligand-gated ion channels** open or close in response to a ligand binding to a receptor. For example, the neurotransmitter

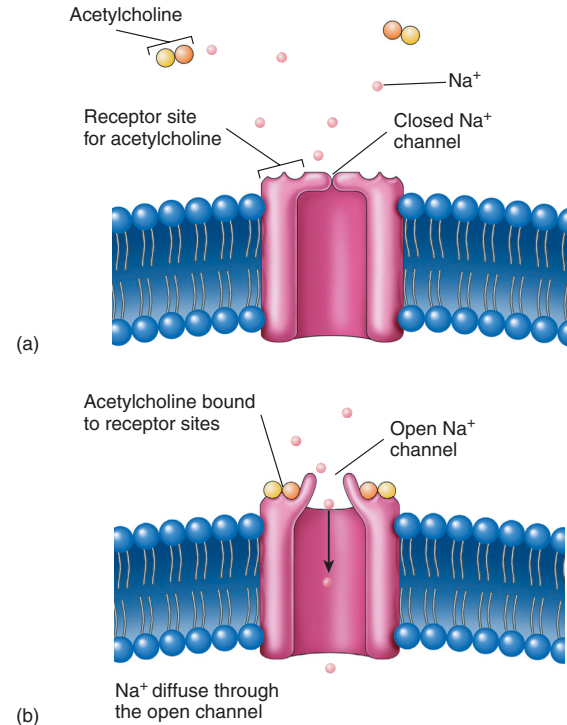


Figure 11.15 Ligand-Gated Ion Channel

(a) The Na^+ channel has receptor sites for the ligand, acetylcholine. When the receptor sites are not occupied by acetylcholine, the Na^+ channel remains closed. (b) When two acetylcholine molecules bind to their receptor sites on the Na^+ channel, the channel opens to allow Na^+ to diffuse through the channel into the cell.

acetylcholine released from the presynaptic terminal of a neuron is a ligand that can bind to a ligand-gated Na^+ channel in the membrane of a muscle cell. As a result, the Na^+ channel opens, allowing Na^+ to enter the cell (figure 11.15). Ligand-gated ion channels exist for Na^+ , K^+ , Ca^{2+} , and Cl^- , and these channels are common in tissues such as nervous and muscle tissues, as well as glands.

2. **Voltage-gated ion channels.** These channels open and close in response to small voltage changes across the plasma membrane. In an unstimulated cell, the inside of the plasma membrane is negatively charged relative to the outside. This charge difference can be measured in units called **millivolts** (mV; 1 mV = 1/1000 V). When a cell is stimulated, the charge difference changes, and that causes voltage-gated ion channels to open or close. Voltage-gated channels specific for Na^+ and K^+ are most numerous in electrically excitable tissues, but voltage-gated Ca^{2+} channels are also important, especially in smooth muscle and cardiac muscle cells (see chapters 9 and 20).

3. *Other-gated ion channels.* Gated ion channels that respond to stimuli other than ligands or voltage changes are present in specialized electrically excitable tissues. Examples include touch receptors, which respond to mechanical stimulation of the skin, and temperature receptors, which respond to temperature changes in the skin.

- 19. Describe the concentration differences for Na^+ and K^+ that exist across the plasma membrane.
- 20. In what direction, into or out of cells, does the sodium–potassium exchange pump move Na^+ and K^+ ?
- 21. Define nongated and gated ion channels. How are they responsible for the permeability characteristics of a resting versus a stimulated plasma membrane?
- 22. Define ligand, receptor, and receptor site.
- 23. What kinds of stimuli cause gated ion channels to open or close?

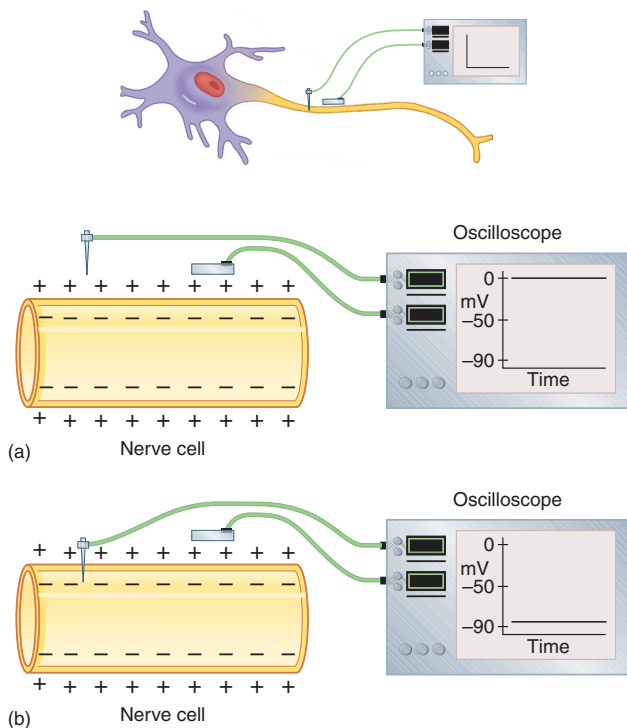


Figure 11.16 Measuring the Resting Membrane Potential

(a) Both recording (needle) and reference (block) electrodes are outside of the cell, and no potential difference (0 mV) is recorded. (b) The recording electrode is inside the cell, the reference electrode is outside, and a potential difference of about -85 mV is recorded, with the inside of the plasma membrane negative with respect to the outside of the membrane.

The Resting Membrane Potential

Although unequal concentrations of ions exist in the intracellular and extracellular fluids, these fluids are nearly electrically neutral. That is, both intracellular and extracellular fluids have nearly equal numbers of positively and negatively charged ions. However, an unequal distribution of charge exists between the immediate inside and the immediate outside of the plasma membrane. This electric charge difference across the plasma membrane, called a **potential difference**, can be measured between the inside and outside of essentially all cells. By placing the tip of one microelectrode inside a cell and another outside it, and by connecting the electrodes by wires to an appropriate measuring device such as a voltmeter or an oscilloscope, the potential difference can be measured (figure 11.16). The potential difference across the plasma membranes of skeletal muscle fibers and nerve cells is -70 to -90 mV. The potential difference is reported as a negative number, because the inside of the plasma membrane is negative compared to the outside. In an unstimulated, or resting, cell, the potential difference across the plasma membrane is called the **resting membrane potential**.

Establishing the Resting Membrane Potential

The resting membrane potential results from the permeability characteristics of the resting plasma membrane and the difference in concentration of ions between the intracellular and the extracellular fluids. The plasma membrane is somewhat permeable to K^+ because of nongated K^+ channels. Positively charged K^+ can therefore diffuse down their concentration gradient from inside to just outside the cell. Negatively charged proteins and other molecules cannot diffuse through the plasma membrane with the K^+ . As K^+ diffuse out of the cell, the loss of positive charges makes the inside of the plasma membrane more negative. Because opposite charges attract, the K^+ are attracted back toward the cell. K^+ accumulate just outside of the plasma membrane, making the outside of the plasma membrane positive relative to the inside. Thus, the tendency for K^+ to diffuse from a higher concentration inside the cell to a lower concentration outside the cell is opposed by the charge difference that develops across the plasma membrane. The resting membrane potential is in equilibrium because the K^+ concentration gradient, which causes K^+ to diffuse out of the cell, is equal to the potential difference across the plasma membrane, which opposes that movement (figure 11.17).

PREDICT 2

Given that tissue A has significantly more nongated K^+ channels than tissue B, which tissue has the larger resting membrane potential?

Other ions, such as Na^+ , Cl^- , and Ca^{2+} , do have some small influence on the resting membrane potential, but the major influence is from K^+ . Because the resting plasma membrane is 50–100 times less permeable to Na^+ than to K^+ , very few Na^+ can diffuse from the outside to the inside of the resting cell. The resting plasma membrane is not very permeable to Ca^{2+} either. The plasma membrane is relatively permeable to Cl^- , but these negatively charged ions are repelled by the negative charge inside the cell.

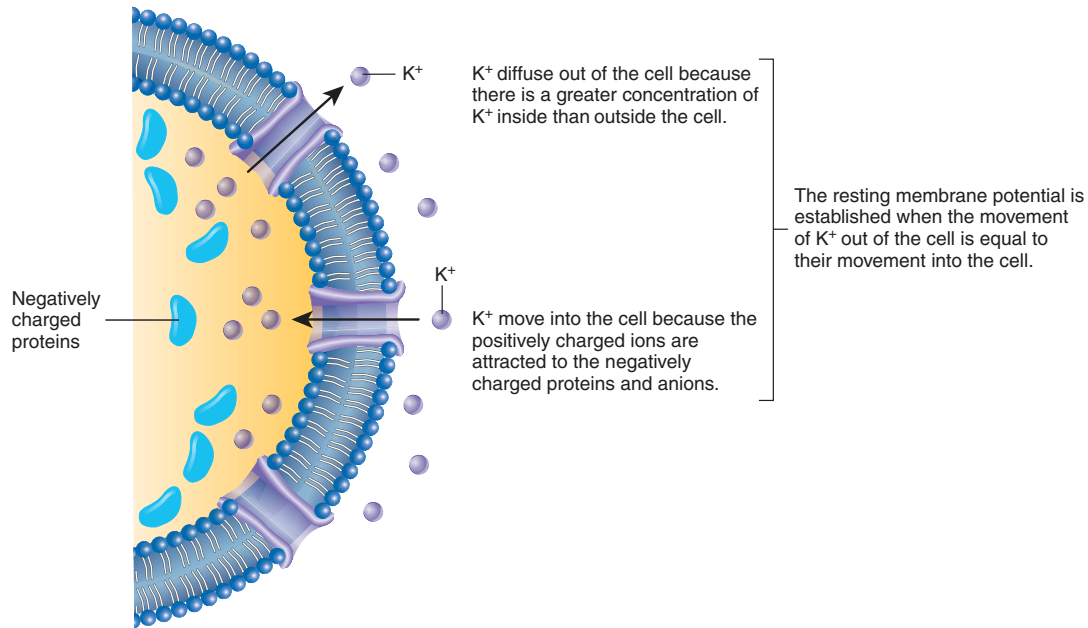


Figure 11.17 Potassium Ions and the Resting Membrane Potential

The resting membrane potential is proportional to the tendency for K⁺ to diffuse out of the cell and not to the actual rate of flow for K⁺. At equilibrium, very few of these ions pass through the plasma membrane because their movement out of the cell is opposed by the negative charge inside the cell. Still, some Na⁺ and K⁺ diffuse continuously across the plasma membrane, although at a low rate. The large concentration gradients for Na⁺ and K⁺ would eventually disappear without the continuous activity of the sodium–potassium exchange pump.

As already noted, the function of the sodium–potassium exchange pump is to maintain the normal concentration gradients for Na⁺ and K⁺ across the plasma membrane. The pump is also responsible for a small portion of the resting membrane potential, usually less than 15 mV, because it transports approximately three Na⁺ out of the cell and two K⁺ into the cell for each ATP molecule used (see figure 11.13). The outside of the plasma membrane becomes more positively charged than the inside, because more positively charged ions are pumped out of the cell than are pumped into it.

The characteristics responsible for a resting membrane potential are summarized in table 11.2.

Changing the Resting Membrane Potential

The resting membrane potential can be changed by alterations in the K⁺ concentration gradient, changes in membrane permeability to K⁺ and Na⁺, and changes in extracellular Ca²⁺ concentrations.

Table 11.2 Characteristics Responsible for the Resting Membrane Potential

1. The number of charged molecules and ions inside and outside the cell is nearly equal.
2. The concentration of K⁺ is higher inside than outside the cell, and the concentration of Na⁺ is higher outside than inside the cell.
3. The plasma membrane is 50–100 times more permeable to K⁺ than to other positively charged ions such as Na⁺.
4. The plasma membrane is impermeable to large intracellular negatively charged molecules such as proteins.
5. K⁺ tend to diffuse across the plasma membrane from the inside to the outside of the cell.
6. Because negatively charged molecules cannot follow the positively charged K⁺, a small negative charge develops just inside the plasma membrane.
7. The negative charge inside the cell attracts positively charged K⁺. When the negative charge inside the cell is great enough to prevent additional K⁺ from diffusing out of the cell through the plasma membrane, an equilibrium is established.
8. The charge difference across the plasma membrane at equilibrium is reflected as a difference in potential, which is measured in millivolts (mV).
9. The resting membrane potential is proportional to the potential for K⁺ to diffuse out of the cell but not to the actual rate of flow for K⁺.
10. At equilibrium there is very little movement of K⁺ or other ions across the plasma membrane.

1. **K^+ concentration gradient.** The concentration of K^+ is higher inside than outside cells. An increase in the extracellular concentration of K^+ decreases this concentration difference and thus decreases the K^+ concentration gradient. As a consequence, the tendency for K^+ to diffuse out of the cell decreases, and a smaller negative charge inside the cell is required to oppose the diffusion of K^+ out of the cell. At this new equilibrium, the charge difference across the plasma membrane is decreased, which means the resting membrane potential is less negative (figure 11.18a). This change is called **depolarization** (dē-pō'lār-i-zā'shūn), or **hypopolarization** (hī'pō-pō-lār-i-zā'shūn), of the resting membrane potential. That is, the potential difference across the plasma membrane becomes smaller, or less polar.

A decrease in the extracellular concentration of K^+ increases the concentration difference between the inside and the outside of cells and thus increases the K^+ concentration gradient. As a result, the tendency for K^+ to diffuse out of the cell increases and a greater negative charge inside the cell is required to resist that diffusion. Thus the resting membrane potential becomes more negative (figure 11.18b), a change called **hyperpolarization** (hī'per-pō'lār-i-zā'shūn). That is, the potential difference across the plasma membrane becomes greater, or more polar.

P R E D I C T 3

Does the resting membrane potential increase or decrease when the intracellular concentration of K^+ is increased by the injection of a solution of potassium succinate into the cell? Explain.

2. **K^+ membrane permeability.** Although nongated K^+ channels allow some K^+ to diffuse across the plasma membrane, the resting membrane is not freely permeable to K^+ . If gated K^+ channels open, membrane permeability to K^+ increases, and more K^+ diffuse out of the cell. The increased tendency for K^+ to diffuse out of the cell is opposed by a greater negative charge that develops inside the plasma membrane (hyperpolarization).

3. **Na^+ membrane permeability.** In an unstimulated cell, the membrane is not very permeable to Na^+ because there are few nongated Na^+ channels. Changes in the concentration of Na^+ on either side of the plasma membrane don't influence the resting membrane potential very much because of this low permeability. If gated Na^+ channels open, the permeability of the membrane to Na^+ increases (see figure 11.15). Na^+ then diffuses into the cell because the concentration gradient for Na^+ is from the outside to the inside of the cell. As Na^+ diffuses into the cell, the inside of the plasma membrane becomes more positive, resulting in depolarization.
4. **Extracellular Ca^{2+} concentrations.** Voltage-gated Na^+ channels are sensitive to changes in the extracellular concentration of Ca^{2+} . Ca^{2+} in the extracellular fluid are attracted to plasma membrane proteins with negatively charged groups exposed to the extracellular fluid. If the extracellular concentration of Ca^{2+} decreases, these ions diffuse away from plasma membrane proteins, including the voltage-gated Na^+ channels, causing the channels to open. If the extracellular concentration of Ca^{2+} increases, these ions bind to the voltage-gated Na^+ channels, causing them to close. At the Ca^{2+} concentrations normally found in the extracellular fluid, only a small percentage of the voltage-gated Na^+ channels are open at any single moment in an unstimulated cell.

P R E D I C T 4

Predict the effect of a decrease in the extracellular concentration of Ca^{2+} on the resting membrane potential.

Local Potentials

A stimulus applied at one location on the plasma membrane of a cell normally causes a change in the resting membrane potential called a **local potential**, which is confined to a small region of the plasma membrane. Local potentials can result from (1) ligands binding to their receptors, (2) changes in the charge across the plasma membrane, (3) mechanical stimulation, (4) temperature changes, or (5) spontaneous changes in membrane permeability.

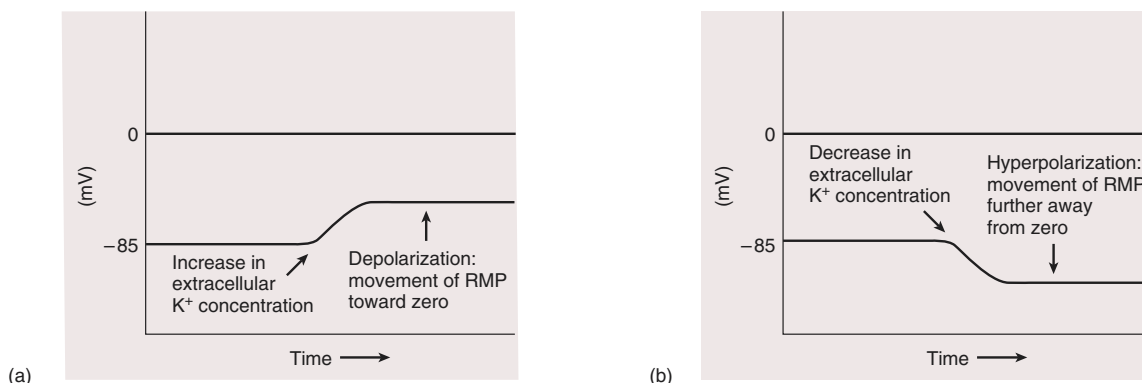


Figure 11.18 Changes in the Resting Membrane Potential Caused by Changes in Extracellular K^+ Concentration

(a) Elevated extracellular K^+ concentration causes depolarization. (b) Decreased extracellular K^+ concentration causes hyperpolarization.

Changes in membrane permeability to Na^+ , K^+ , or other ions can produce a local potential, which can be a depolarization or hyperpolarization. For example, if a stimulus causes gated Na^+ channels to open, the diffusion of a few Na^+ into cells results in depolarization. On the other hand, if a stimulus causes gated K^+ channels to open, the diffusion of a few K^+ out of the cell results in hyperpolarization.

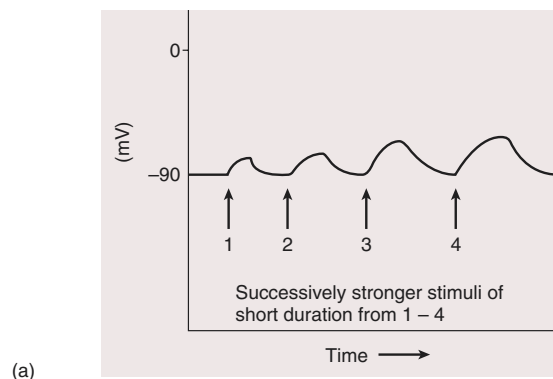
Local potentials are called **graded** because the magnitude of the potential change can vary from small to large depending on the stimulus strength or frequency. For example, a weak stimulus can cause a few gated Na^+ channels to open. A few Na^+ diffuse into the cell, cause a small depolarization, and produce a small local potential. A stronger stimulus can cause a greater number of gated Na^+ channels to open. A greater number of Na^+ diffusing into the cell causes a larger depolarization and produces a larger local potential (figure 11.19a).

Local potentials can **summate** (sŭm-āt'), or add onto each other (figure 11.19b). For example, if a second stimulus is applied before the local potential produced by the first stimulus has re-

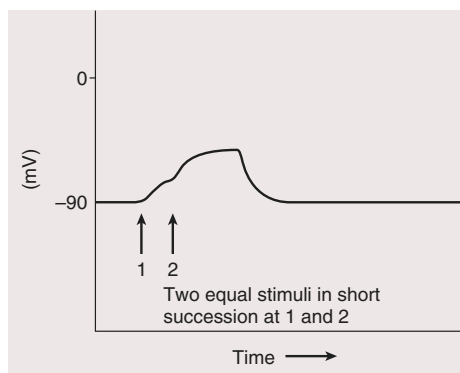
turned to the resting membrane potential, a larger depolarization results than would result from a single stimulus. The first stimulus causes gated Na^+ channels to open, and the second stimulus causes additional Na^+ channels to open. As a result, more Na^+ diffuse into the cell, producing a larger local potential.

Local potentials spread, or are conducted, over the plasma membrane in a decremental fashion. That is, they rapidly decrease in magnitude as they spread over the surface of the plasma membrane. It's much like a teacher talking to a large class. At the front of the class the teacher's voice can be easily heard, but the farther away a student sits, the more difficult it is to hear. Normally a local potential cannot be detected more than a few millimeters from the site of stimulation. As a consequence, a local potential cannot transfer information over long distances from one part of the body to another.

Local potentials are important because of their effect on the generation of action potentials. The characteristics of local potentials are summarized in table 11.3.



(a)



(b)

Figure 11.19 Local Potentials

(a) Local potentials are proportional to the stimulus strength. A weak stimulus applied briefly causes a small depolarization, which quickly returns to the resting membrane potential (1). Progressively stronger stimuli result in larger depolarizations (2 to 4). (b) A stimulus applied to a cell causes a small depolarization. When a second stimulus is applied before the depolarization disappears, the depolarization caused by the second stimulus is added to the depolarization caused by the first to result in a larger depolarization.

- 24. Define the resting membrane potential. Is the outside of the plasma membrane positively or negatively charged relative to the inside?
- 25. Explain the role of K^+ and the sodium–potassium exchange pump in establishing the resting membrane potential.
- 26. Define the terms depolarization and hyperpolarization. How do alterations in the K^+ concentration gradient, changes in membrane permeability to K^+ or Na^+ , and changes in extracellular Ca^{2+} concentration affect depolarization and hyperpolarization?
- 27. Define a local potential. What does it mean to say a local potential is graded, can summate, and spreads in a decremental fashion?

PREDICT 5

Given two cells that are identical in all ways except that the extracellular concentration of Na^+ is less for cell A than for cell B, how would the magnitude of the local potential in cell A differ from that in cell B if stimuli of identical strength were applied to each?

Table 11.3 Characteristics of Local Potentials

- | | |
|----|---|
| 1. | A stimulus causes increased permeability of the membrane to Na^+ , K^+ , or Cl^- . |
| 2. | Increased permeability of the membrane to Na^+ results in depolarization. Increased permeability of the membrane to K^+ or Cl^- results in hyperpolarization. |
| 3. | Local potentials are graded; that is, the size of the local potential is proportional to the strength of the stimulus. Local potentials can also summate. Thus, a local potential produced in response to several stimuli is larger than one produced in response to a single stimulus. |
| 4. | Local potentials are conducted in a decremental fashion, meaning that their magnitude decreases as they spread over the plasma membrane. Local potentials cannot be measured a few millimeters from the point of stimulation. |
| 5. | A depolarizing local potential can cause an action potential. |

Action Potentials

When a local potential causes depolarization of the plasma membrane to a level called **threshold**, a series of permeability changes occurs that results in an **action potential** (figure 11.20). An action potential is a large change in the membrane potential that propagates, without changing its magnitude, over long distances along the plasma membrane. Thus, action potentials can transfer information from one part of the body to another. It generally takes 1–2 milliseconds (ms) (1 ms = 0.001 s) for an action potential to occur. The characteristics of action potentials are summarized in table 11.4.

The generation of action potentials is dependent on local potentials. Depolarizing local potentials may generate an action potential, whereas hyperpolarizing local potentials do not. In addition, the magnitude of the local potential affects the likelihood of generating an action potential. A larger depolarizing local potential is more likely to produce an action potential than is a smaller one.

Action potentials occur according to the **all-or-none principle**. If a stimulus produces a depolarizing local potential that is large enough to reach threshold, all the permeability changes responsible for an action potential proceed without stopping and are constant in magnitude (the “all” part). If a stimulus is so weak that the depolarizing local potential does not reach threshold, few of the permeability changes occur. The membrane potential returns to its resting level after a brief period without producing an action potential (the “none” part). An action potential can be compared to the flash system of a camera. When the shutter is triggered (reaches threshold), the camera flashes (an action potential is produced), and each flash is the same brightness (magnitude; the “all” part) as previous flashes. If the shutter is depressed, but not triggered, no flash results (the “none” part).

The action potential has a **depolarization phase**, in which the membrane potential moves away from the resting membrane potential and becomes more positive, and a **repolarization phase**,

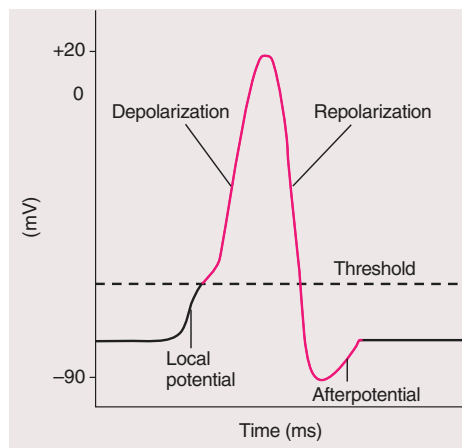


Figure 11.20 The Action Potential

The action potential consists of a depolarization phase and a repolarization phase, often followed by a short period of hyperpolarization called the afterpotential.

Table 11.4 Characteristics of the Action Potential

1. Action potentials are produced when a local potential reaches threshold.
2. Action potentials are all-or-none.
3. Depolarization is a result of increased membrane permeability to Na^+ and movement of Na^+ into the cell. Activation gates of the voltage-gated Na^+ channels open.
4. Repolarization is a result of decreased membrane permeability to Na^+ and increased membrane permeability to K^+ , which stops Na^+ movement into the cell and increased K^+ movement out of the cell. The inactivation gates of the voltage-gated Na^+ channels close, and the voltage-gated K^+ channels open.
5. No action potential is produced by a stimulus, no matter how strong, during the absolute refractory period. During the relative refractory period a stronger-than-threshold stimulus can produce an action potential.
6. Action potentials are propagated, and for a given axon or muscle fiber the magnitude of the action potential is constant.
7. Stimulus strength determines the frequency of action potentials.

in which the membrane potential returns toward the resting membrane state and becomes more negative. After the repolarization phase, the plasma membrane may be slightly hyperpolarized for a short period called the **afterpotential** (see figure 11.20).

Depolarization Phase

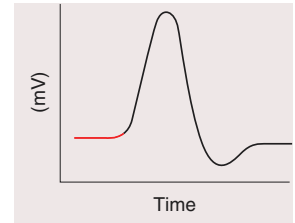
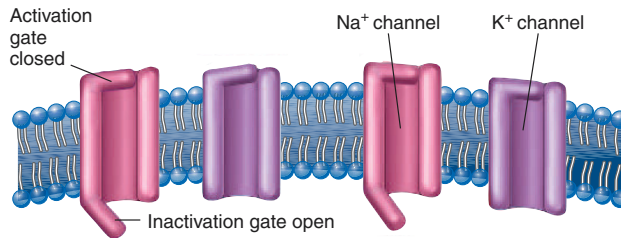
The change in charge across the plasma membrane caused by a local potential causes increasing numbers of voltage-gated Na^+ channels to open for a brief time. As soon as a threshold depolarization is reached, many voltage-gated Na^+ channels begin to open. Na^+ diffuse into the cell, and the resulting depolarization causes additional voltage-gated Na^+ channels to open. As a consequence, more Na^+ diffuse into the cell, causing a greater depolarization of the membrane, which, in turn, causes still more voltage-gated Na^+ channels to open. This is an example of a positive-feedback cycle, and it continues until most of the voltage-gated Na^+ channels in the plasma membrane are open.

Each voltage-gated Na^+ channel has two voltage-sensitive gates, called **activation** and **inactivation gates**. When the plasma membrane is at rest, the activation gates of the voltage-gated Na^+ channel are closed, and the inactivation gates are open (figure 11.21 1). Because the activation gates are closed, Na^+ cannot diffuse through the channels. When the local potential reaches threshold, the change in the membrane potential causes many of the activation gates to open, and Na^+ can diffuse through the Na^+ channels into the cell.

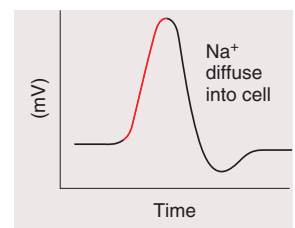
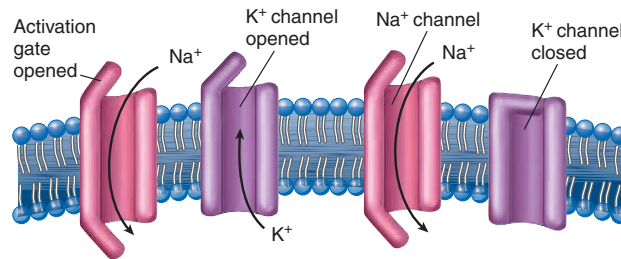
When the plasma membrane is at rest, voltage-gated K^+ channels, which have one gate, are closed (see figure 11.21 1). When the local potential reaches threshold, the voltage-gated K^+ channels begin to open at the same time as the voltage-gated Na^+ channels, but they open more slowly (figure 11.21 2). Only a small number of voltage-gated K^+ channels are open compared to the

1. Resting membrane potential.

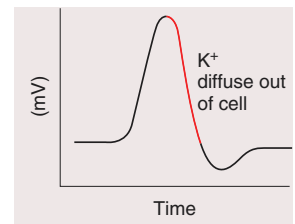
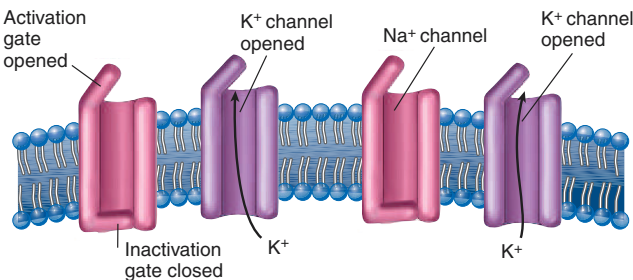
Voltage-gated Na^+ channels (pink) are closed (the activation gates are closed and the inactivation gates are open). Voltage-gated K^+ channels (purple) are closed.



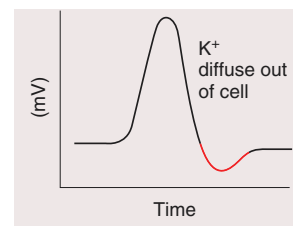
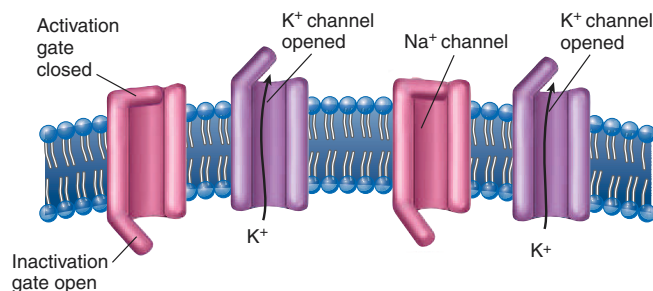
2. Depolarization. Voltage-gated Na^+ channels open because the activation gates open. Voltage-gated K^+ channels start to open. Depolarization results because the inward diffusion of Na^+ is much greater than the outward diffusion of K^+ .



3. Repolarization. Voltage-gated Na^+ channels are closed because the inactivation gates close. Voltage-gated K^+ channels are now open. Na^+ diffusion into the cell stops and K^+ diffuse out of the cell, causing repolarization.

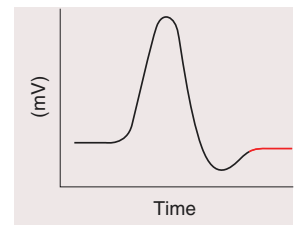
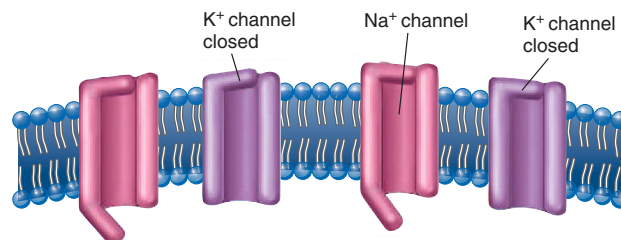


4. End of repolarization and afterpotential. Voltage-gated Na^+ channels are closed. Closure of the activation gates and opening of the inactivation gates reestablish the resting condition for Na^+ channels (see step 1). Diffusion of K^+ through voltage-gated channels produces the afterpotential.



5. Resting membrane potential.

The resting membrane potential is reestablished after the voltage-gated K^+ channels close.



Process Figure 11.21 Voltage-Gated Ion Channels and the Action Potential

Step 1 illustrates the status of voltage-gated Na^+ and K^+ channels in a resting cell. Steps 2–5 show how the channels open and close to produce an action potential. Next to each step, a graph shows in red the membrane potential resulting from the condition of the ion channels.

number of voltage-gated Na^+ channels because the voltage-gated K^+ channels open slowly. Depolarization occurs because more Na^+ diffuse into the cell than K^+ diffuse out of it.

PREDICT 6

Predict the effect of a reduced extracellular concentration of Na^+ on the magnitude of the action potential in an electrically excitable cell.

Repolarization Phase

As the membrane potential approaches its maximum depolarization, the change in the potential difference across the plasma membrane causes the inactivation gates in the voltage-gated Na^+ channels to begin closing, and the permeability of the plasma membrane to Na^+ decreases. During the repolarization phase, the voltage-gated K^+ channels, which started to open along with the voltage-gated Na^+ channels, continue to open (figure 11.21 3). Consequently, the permeability of the plasma membrane to Na^+ decreases, and the permeability to K^+ increases. The decreased diffusion of Na^+ into the cell and the increased diffusion of K^+ out of the cell causes repolarization.

At the end of repolarization, the decrease in membrane potential causes the activation gates in the voltage-gated Na^+ channels to close and the inactivation gates to open. Although this change doesn't affect the diffusion of Na^+ , it does return the voltage-gated Na^+ channels to their resting state (figure 11.21 4).

Afterpotential

In many cells, a period of hyperpolarization, or afterpotential, exists following each action potential. The afterpotential exists because the voltage-gated K^+ channels remain open for a short time (see figure 11.21 4). The increased K^+ permeability that develops during the repolarization phase of the action potential lasts slightly longer than the time required to bring the membrane potential back to its resting level. As the voltage-gated K^+ channels close, the original resting membrane potential is reestablished (figure 11.21 5).

During an action potential, a small number of Na^+ diffuse into the cell and a small number of K^+ diffuse out of the cell. The sodium–potassium exchange pump functions to restore normal resting ion concentrations by transporting these ions in the opposite direction of their movement during the action potential. That is, Na^+ are pumped out of the cell and K^+ are pumped into the cell. The sodium–potassium exchange pump is too slow to have an effect on either the depolarization or repolarization phase of individual action potentials. As long as the Na^+ and K^+ concentrations remain unchanged across the plasma membrane, all the action potentials produced by a cell are identical. They all take the same amount of time, and they all exhibit the same magnitude.

Refractory Period

Once an action potential is produced at a given point on the plasma membrane, the sensitivity of that area to further stimulation decreases for a time called the **refractory** (rē-frak'tōr-ē) **period**. The first part of the refractory period, during which complete insensitivity exists to another stimulus, is called the **absolute refractory period**. It occurs from the beginning of the action poten-

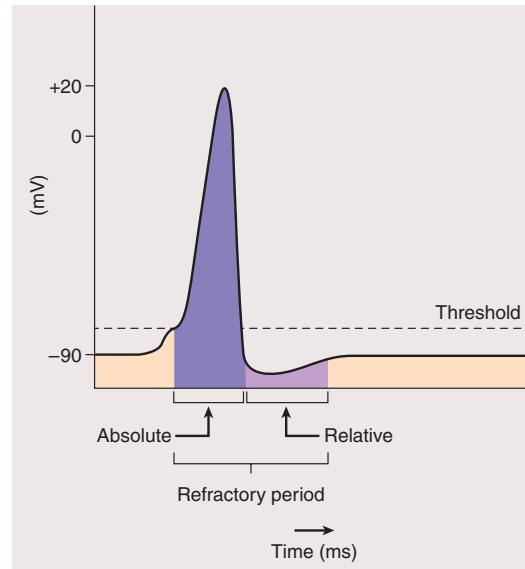


Figure 11.22 Refractory Period

The absolute and relative refractory periods of an action potential. In some cells the absolute refractory period may end during the repolarization phase of the action potential.

tial until near the end of repolarization (figure 11.22). At the beginning of the action potential, depolarization occurs when the activation gates in the voltage-gated Na^+ channel open. At this time, the inactivation gates in the voltage-gated Na^+ channels are already open (see figure 11.21 2). Depolarization ends as the inactivation gates close (see figure 11.21 3). As long as the inactivation gates are closed, further depolarization cannot occur. When the inactivation gates open and the activation gates close near the end of repolarization (see figure 11.21 4), it once again is possible to stimulate the production of another action potential.

The existence of the absolute refractory period guarantees that once an action potential is begun, both the depolarization and the repolarization phases will be completed, or nearly completed, before another action potential can begin, and that a strong stimulus cannot lead to prolonged depolarization of the plasma membrane. The absolute refractory period has important consequences for the rate at which action potentials can be generated and for the propagation of action potentials (see following sections).

The second part of the refractory period, called the **relative refractory period**, follows the absolute refractory period. A stronger-than-threshold stimulus can initiate another action potential during the relative refractory period. Thus, after the absolute refractory period, but before the relative refractory period is completed, a sufficiently strong stimulus can produce another action potential. During the relative refractory period, the membrane is more permeable to K^+ because many voltage-gated K^+ channels are open (see figure 11.21 4). The relative refractory period ends when the voltage-gated K^+ channels close (see figure 11.21 5).

Clinical Focus Examples of Abnormal Membrane Potentials

Several important conditions provide examples of the physiology of membrane potentials and the consequence of abnormal ones. **Hypokalemia** (hī-pō-ka-lē'mē-ă) is a lower-than-normal concentration of K^+ in the blood or extracellular fluid. Figure 11.18b shows that reduced extracellular K^+ concentrations cause hyperpolarization of the resting membrane potential. Thus, a greater-than-normal stimulus is required to depolarize the membrane to its threshold level and to initiate action potentials in neurons, skeletal muscle, and cardiac muscle. Symptoms of hypokalemia include

muscular weakness, an abnormal electrocardiogram, and sluggish reflexes. These symptoms are consistent with the effect of a reduced extracellular K^+ concentration. The symptoms result from the reduced sensitivity of the excitable tissues to stimulation. The several causes of hypokalemia include potassium depletion during starvation, alkalosis, and certain kidney diseases.

Hypocalcemia (hī-pō-kal-sē'mē-ă) is a lower-than-normal concentration of Ca^{2+} in blood or extracellular fluid. Symptoms of hypocalcemia include nervousness and uncontrolled contraction of skeletal muscles,

called **tetany** (tet'ă-nē). The symptoms are due to an increased membrane permeability to Na^+ that results because low blood levels of Ca^{2+} cause voltage-gated Na^+ channels in the membrane to open. Na^+ diffuse into the cell, causing depolarization of the plasma membrane to threshold, and initiating action potentials. The tendency for action potentials to occur spontaneously in nervous tissue and muscles accounts for the listed symptoms. A lack of dietary calcium, a lack of vitamin D, or a reduced secretion rate of a parathyroid gland hormone are examples of conditions that cause hypocalcemia.

28. Define an action potential. How do depolarizing and hyperpolarizing local potentials affect the likelihood of generating an action potential?
29. Explain the “all” and the “none” parts of the all-or-none principle of action potentials.
30. What are the depolarization and repolarization phases of an action potential? Explain how changes in membrane permeability and the movement of Na^+ and K^+ cause each phase. What happens when the activation gates in the voltage-gated Na^+ channels open and the inactivation gates close?
31. Describe the afterpotential and its cause.
32. What are the absolute and relative refractory periods? Relate them to the depolarization and repolarization phases of the action potential.

PREDICT 7

Does a prolonged threshold stimulus or a prolonged stronger-than-threshold stimulus produce the most action potentials? Explain.

Action Potential Frequency

The **action potential frequency** is the number of action potentials produced per unit of time in response to a stimulus. Action potential frequency is directly proportional to stimulus strength and to the size of the local potential. A **subthreshold stimulus** is any stimulus not strong enough to produce a local potential that reaches threshold. Therefore, no action potential is produced (figure 11.23). A **threshold stimulus** produces a local potential that's just strong enough to reach threshold and cause the production of a single action potential. A **maximal stimulus** is just strong enough to produce a maximum frequency of action potentials. A **submaximal stimulus** includes all stimuli between threshold and the maximal stimulus strength. For submaximal stimuli, the action potential frequency increases in proportion to the strength of the stimulus because the size of the local potential increases with

stimulus strength. A **supramaximal stimulus** is any stimulus stronger than a maximal stimulus. These stimuli cannot produce a greater frequency of action potentials than a maximal stimulus.

The duration of the absolute refractory period determines the maximum frequency of action potentials generated in an excitable cell. During the absolute refractory period, a second stimulus, no matter how strong, cannot stimulate an additional action potential. As soon as the absolute refractory period ends, however, it's possible for a second stimulus to cause the production of an action potential.

PREDICT 8

If the duration of the absolute refractory period of a nerve cell is 1 millisecond (ms), how many action potentials are generated by a maximal stimulus in one second?

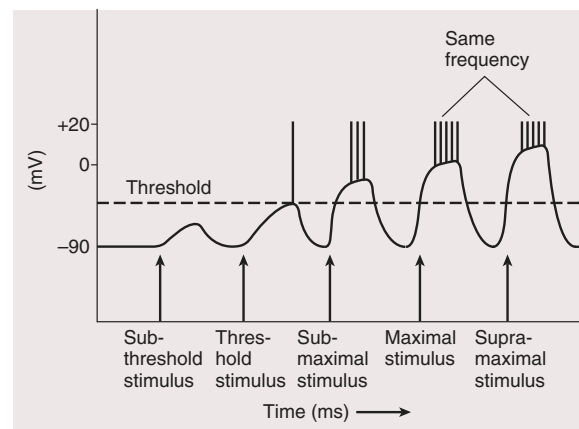


Figure 11.23 Stimuli, Local Potentials, and Action Potentials

Relationship among stimulus strength, local potential, and action potential frequency. Each stimulus in this figure is stronger than the previous one.

The frequency of action potentials provides information about the strength of a stimulus. For example, a weak pain stimulus generates a low frequency of action potentials, whereas a stronger pain stimulus generates a higher frequency of action potentials. The ability to interpret a stimulus as mildly painful versus very painful depends, in part, on the frequency of action potentials generated by individual pain receptors. Communication regarding the strength of stimuli cannot depend on the magnitude of action potentials because, according to the all-or-none principle, the magnitudes are always the same. The magnitude of action potentials produced by weak or strong pain stimuli is the same.

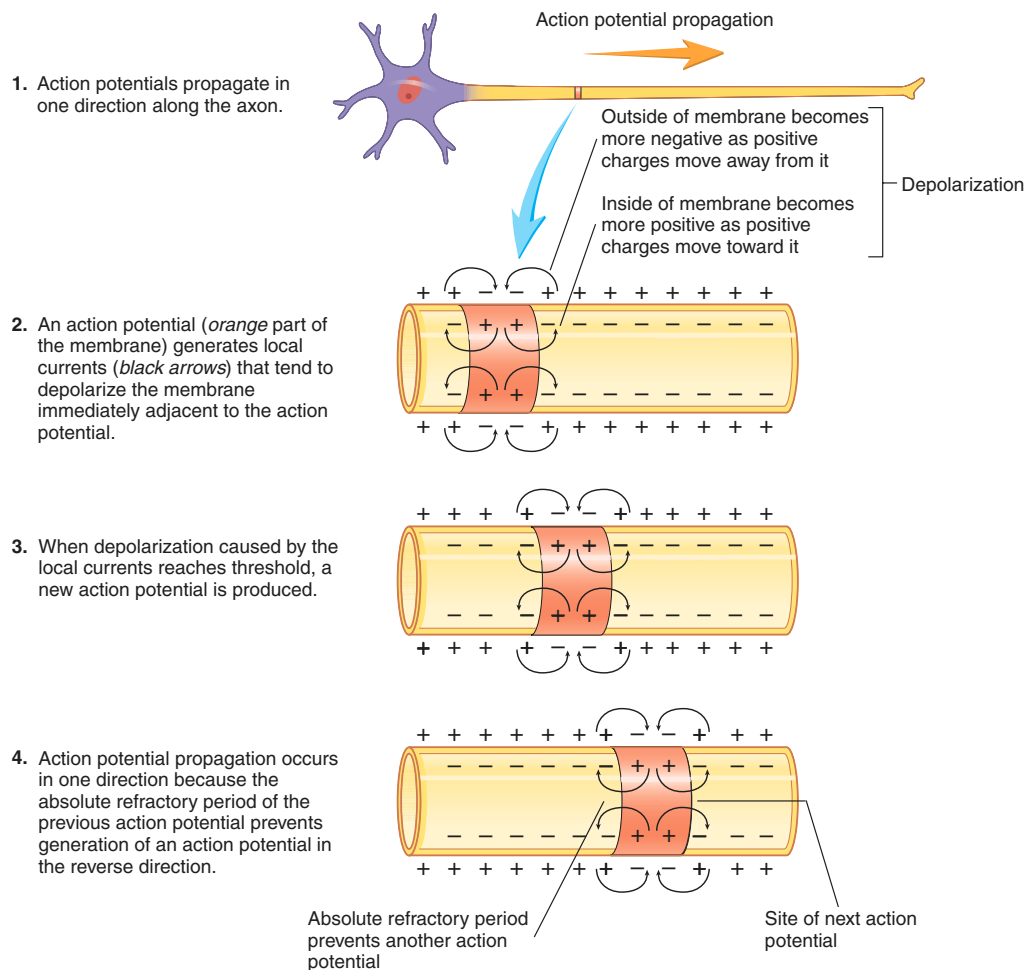
The ability to stimulate muscle or gland cells also depends on action potential frequency. A low frequency of action potentials produces a weaker muscle contraction or less secretion than does a higher frequency. For example, a low frequency of action potentials in a muscle results in incomplete tetanus and a high frequency in complete tetanus (see chapter 9).

In addition to the frequency of action potentials, how long the action potentials are produced provides important information. For example, a pain stimulus of 1 second is interpreted differently from the same stimulus applied for 30 seconds.

- 33. Define action potential frequency. What two factors determine action potential frequency?
- 34. Define a subthreshold, threshold, maximal, submaximal, and supramaximal stimulus. What determines the maximum frequency of action potential generation?

Propagation of Action Potentials

An action potential occurs in a very small area of the plasma membrane and does not affect the entire membrane at one time. Action potentials can, however, **propagate** or spread across the plasma membrane because an action potential produced at one location in the plasma membrane can stimulate the production of an action potential at an adjacent area of the plasma membrane. Note that an action potential doesn't actually move along an axon. Rather, an action potential at one location stimulates the production of another action potential at an adjacent location which, in turn, stimulates the production of another, and so on. It's like a long row of toppling dominos in which each domino knocks down the next one. Each domino falls, but no one domino actually travels the length of the row.



Process Figure 11.24 Action Potential Propagation in an Unmyelinated Axon

In a neuron, action potentials are normally produced at the trigger zone and propagate in one direction along the axon (figure 11.24 1). The location at which the next action potential is generated is different for unmyelinated and myelinated axons. In an unmyelinated axon, the next action potential is generated immediately adjacent to the previous action potential. When an action potential is produced, the inside of the membrane becomes more positive than the outside (figure 11.24 2). On the outside of the membrane, positively charged ions from the adjacent area are attracted to the negative charges at the site of the action potential. On the inside of the plasma membrane, positively charged ions at the site of the action potential are attracted to the adjacent negatively charged part of the membrane. The movement of positively charged ions is called a **local current**. As a result of the local current, the part of the membrane immediately adjacent to the action potential depolarizes. That is, the outside of the membrane immediately adjacent to the action potential becomes more negative because of the loss of positive charges and the inside becomes more positive because of the gain of positive charges. When the depolarization reaches threshold, an action potential is produced (figure 11.24 3).

If an action potential is initiated at one end of an axon, it is propagated in one direction down the axon. The absolute refractory period ensures one-way propagation of an action potential because it prevents the local current from stimulating the production of an action potential in the reverse direction (figure 11.24 4).

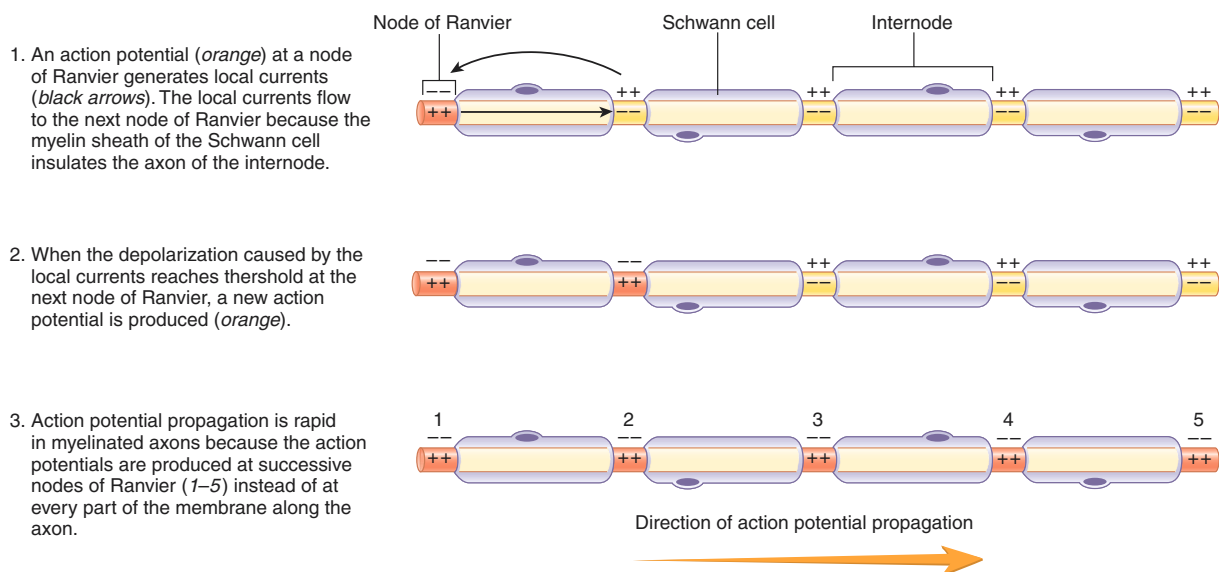
In a myelinated axon, an action potential is conducted from one node of Ranvier to another in a process called **saltatory conduction** (*saltare* is Latin, meaning to leap). An action potential at one node of Ranvier generates local currents that flow toward the next node of Ranvier (figure 11.25 1). The lipids within the membranes of the myelin sheath act as a layer of insulation, forcing the local currents to flow from one node of Ranvier to the next. The local current depolarizes the membrane at the next node of Ranvier, producing an action potential (figure 11.25 2).

The speed of action potential conduction along an axon depends on the myelination of the axon. Action potentials are conducted more rapidly in myelinated than unmyelinated axons because they are formed quickly at each successive node of Ranvier (figure 11.25 3) instead of being propagated more slowly through every part of the axon's membrane as in unmyelinated axons (see figure 11.24). Action potential conduction in a myelinated fiber is like a grasshopper jumping, whereas in an unmyelinated axon it's like a grasshopper walking. The grasshopper (action potential) moves more rapidly by jumping. The generation of action potentials at nodes of Ranvier occurs so rapidly that as many as 30 successive nodes of Ranvier are simultaneously in some phase of an action potential.

In addition to myelination, the diameter of axons affects the speed of action potential conduction. Large-diameter axons conduct action potentials more rapidly than small-diameter axons because large-diameter axons provide less resistance to action potential propagation.

Nerve fibers (axons) are classified according to their size and myelination. It's not surprising that the structure of nerve fibers reflects their functions. Type A fibers are large-diameter, myelinated axons that conduct action potentials at 15–120 m/s. Motor neurons supplying skeletal muscles and most sensory neurons have type A fibers. Rapid response to the external environment is possible because of the rapid input of sensory information to the CNS and rapid output of action potentials to skeletal muscles.

Type B fibers are medium-diameter, lightly myelinated axons that conduct action potentials at 3–15 m/s, and type C fibers are small-diameter, unmyelinated axons that conduct action potentials at 2 m/s or less. Type B and C fibers are primarily part of the ANS, which stimulates internal organs, such as the stomach, intestines, and heart. The responses necessary to maintain internal homeostasis such as digestion need not be as rapid as responses to the external environment.



Process Figure 11.25 Saltatory Conduction: Action Potential Propagation in a Myelinated Axon

- 35. What is a local current? How do local currents cause the propagation of action potentials in unmyelinated axons?
- 36. What prevents an action potential from reversing its direction of propagation?
- 37. Describe saltatory conduction of an action potential.
- 38. Compare the speed of action potential conduction in (a) myelinated and unmyelinated axons, and (b) large-diameter and small-diameter axons.
- 39. Compare the functions of type A nerve fibers to type B and C nerve fibers.

Importance of Myelin Sheaths

Myelin sheaths begin to form late in fetal development. The process continues rapidly until the end of the first year after birth and continues more slowly thereafter. The development of myelin sheaths is associated with the infant's continuing development of more rapid and better coordinated responses.

The importance of myelinated fibers is dramatically illustrated in diseases in which the myelin sheath is gradually destroyed. Action potential transmission is slowed, resulting in impaired control of skeletal and smooth muscles. In severe cases, complete blockage of action potential transmission can occur. Multiple sclerosis and some cases of diabetes mellitus are examples of diseases that result in myelin sheath destruction.

The Synapse

Objectives

- Describe the different kinds of synapses and how they work.
- Describe the production of excitatory and inhibitory postsynaptic potentials in a synapse.
- Explain the role of spatial and temporal summation in the generation of action potentials.

Just as the fire from one lit torch can light another torch, action potentials in one cell can stimulate action potentials in another cell, thereby allowing communication between the cells. For example, if your finger touches a hot pan, the heat is a stimulus that produces action potentials in sensory nerve fibers. The action potentials are propagated along the sensory fibers from the finger toward the CNS. For the CNS to get this information, the action potentials of the sensory neurons must produce action potentials in CNS neurons. After the CNS has received the information, it produces a response. One response is the contraction of the appropriate skeletal muscles causing the finger to move away from the hot pan. CNS action potentials cause motor neurons to produce action potentials that are then transmitted by the motor neurons toward skeletal muscles. The action potentials of the motor neuron produce skeletal muscle action potentials, which are the stimuli that cause muscle fibers to contract (see chapter 9).

The **synapse** (sin'aps), which is a junction between two cells, is the site where action potentials in one cell can cause the production of action potentials in another cell. The cell that carries action

potentials toward a synapse is called the **presynaptic cell**, and the cell that carries action potentials away from the synapse is called the **postsynaptic cell**. There are two types of synapses: electrical and chemical.

Electrical Synapses

Electrical synapses are gap junctions (see chapter 4) that allow a local current to flow between adjacent cells (figure 11.26). At these gap junctions, the membranes of adjacent cells are separated by a 2 nm gap that is spanned by tubular proteins called **connexons**. The movement of ions through the connexons can generate a local current. Thus, an action potential in one cell produces a local current that generates an action potential in the adjacent cell almost as if the two cells had the same membrane. Electrical synapses are found in cardiac muscle and in many types of smooth muscle. Coordinated contractions of these muscle cells occur when action potentials in one cell propagate to adjacent cells because of electrical synapses (see chapters 9 and 20).

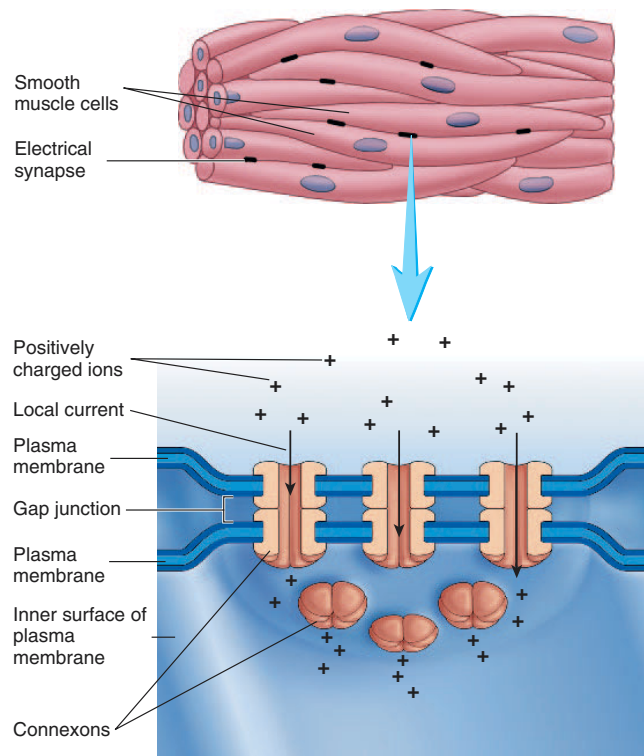


Figure 11.26 Electrical Synapse

Electrical synapses are gap junctions in which the plasma membranes of two cells come close together and are joined by connexons. An action potential in one cell can generate local currents (positively charged ions) that flow through the connexons to stimulate an action potential in the other cell.

Clinical Focus Nervous Tissue Response to Injury

When a nerve is cut, either healing or permanent interruption of the neural pathways occurs. The final outcome depends on the severity of the injury and on its treatment.

Several degenerative changes result when a nerve is cut (figure A). Within about 3–5 days, the axons in the part of the nerve distal to the cut break into irregular segments and degenerate. This occurs because the neuron cell body produces the substances essential to maintain the axon and these substances have no way of reaching parts of the axon distal to the point of damage. Eventually the distal part of the axon completely degenerates. At the same time the axons are degenerating, the myelin part of the Schwann cells around them also degenerates, and macrophages invade the area to phagocytize the myelin. The Schwann cells then enlarge, undergo mitosis, and finally form a column of cells along the re-

gions once occupied by the axons. The columns of Schwann cells are essential for the growth of new axons. If the ends of the regenerating axons encounter a Schwann cell column, their rate of growth increases, and reinnervation of peripheral structures is likely. If the ends of the axons do not encounter the columns, they fail to reinnervate the peripheral structures.

The end of each regenerating axon forms several axonal sprouts. It normally takes about 2 weeks for the axonal sprouts to enter the Schwann cell columns. Only one of the sprouts from each severed neuron forms an axon, however. The other branches degenerate. After the axons grow through the Schwann cell columns, new myelin sheaths are formed, and the neurons reinnervate the structures they previously supplied.

Treatment strategies that increase the probability of reinnervation include bringing the ends of the severed nerve close to-

gether surgically. In some cases in which sections of nerves are destroyed as a result of trauma, nerve transplants are performed to replace damaged segments. The transplanted nerve eventually degenerates, but it does provide Schwann cell columns through which axons can grow.

Regeneration of damaged nerve tracts within the CNS is very limited and is poor in comparison to regeneration of nerves in the PNS. In part, the difference may result from the oligodendrocytes, which exist only in the CNS. Each oligodendrocyte has several processes, each of which forms part of a myelin sheath. The cell bodies of the oligodendrocytes are a short distance from the axons they ensheath, and fewer oligodendrocytes are present than Schwann cells. Consequently, when the myelin degenerates following damage, no column of cells remains in the CNS to act as a guide for the growing axons.

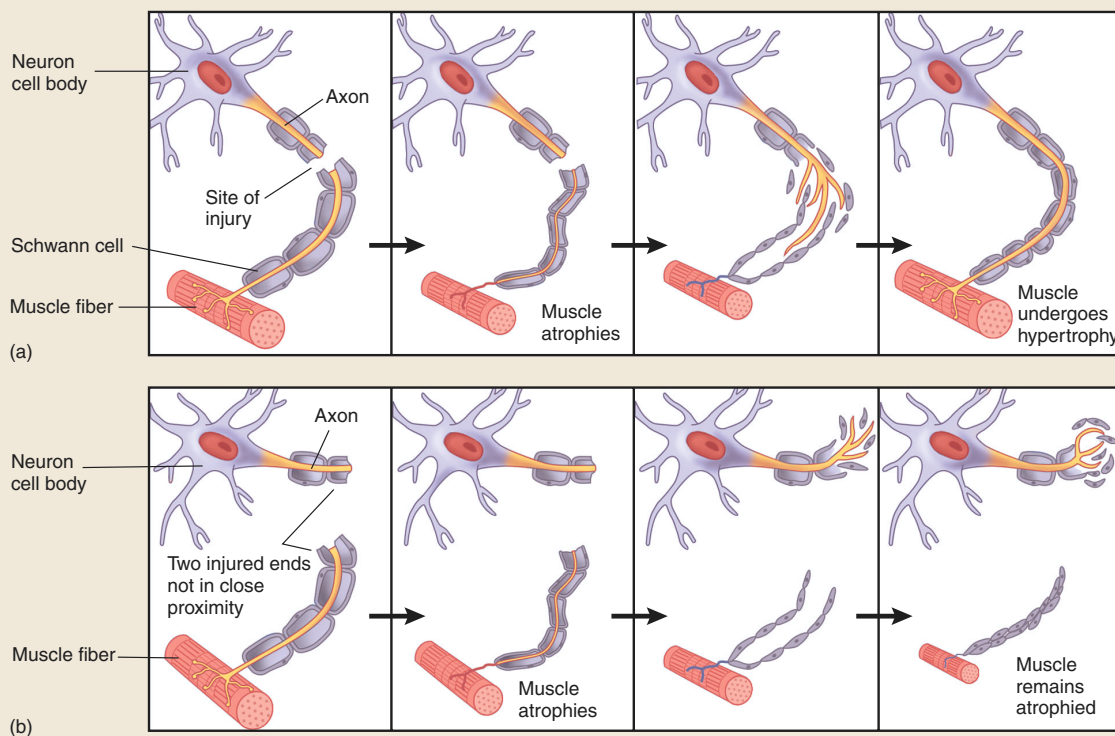


Figure A Changes That Occur in an Injured Nerve Fiber

(a) When the two ends of the injured nerve fiber are aligned in close proximity, healing and regeneration of the axon are likely to occur. Without stimulation from the nerve, the muscle is paralyzed and atrophies (shrinks in size). After reinnervation the muscle can become functional and hypertrophy (increase in size). (b) When the two ends of the injured nerve fiber are not aligned in close proximity, regeneration is unlikely to occur. Without innervation from the nerve, muscle function is completely lost, and the muscle remains atrophied.

40. What is an electrical synapse? Describe its operation. In what kinds of tissue are electrical synapses found?

Chemical Synapses

The essential components of a **chemical synapse** are the presynaptic terminal, the synaptic cleft, and the postsynaptic membrane (figure 11.27). The **presynaptic terminal** is formed from the end of an axon, and the space separating the axon ending and the cell with which it synapses is the **synaptic cleft**. The membrane of the postsynaptic cell opposed to the presynaptic terminal is the **postsynaptic membrane**. Postsynaptic cells are typically other neurons, muscle cells, or gland cells.

Neurotransmitter Release

In chemical synapses, action potentials don't directly pass from the presynaptic terminal to the postsynaptic membrane. Instead, the action potentials in the presynaptic terminal cause the release of neurotransmitters from the terminal.

Presynaptic terminals are specialized to produce and release neurotransmitters. The major cytoplasmic organelles within presynaptic terminals are mitochondria and numerous membrane-bounded **synaptic vesicles**, which contain neurotransmitters such as acetylcholine (see figure 11.27). Each action potential arriving at the presynaptic terminal initiates a series of specific events that results in the release of neurotransmitters. In response to an action potential, voltage-gated Ca^{2+} channels open, and Ca^{2+} diffuse into the presynaptic terminal. These ions cause synaptic vesicles to fuse with the presynaptic membrane and release their neurotransmitters by exocytosis into the synaptic cleft.

Aging of the Heart

Experiments in rats indicate that the number of voltage-gated Ca^{2+} channels in the presynaptic terminals of neurons that stimulate the heart decreases with age. Consequently, movement of Ca^{2+} into the presynaptic terminals decreases, causing a reduced release of neurotransmitters. The decreased amounts of neurotransmitter result in less stimulation of the heart and may explain the lower ability of the aged heart to pump faster and harder during exercise.

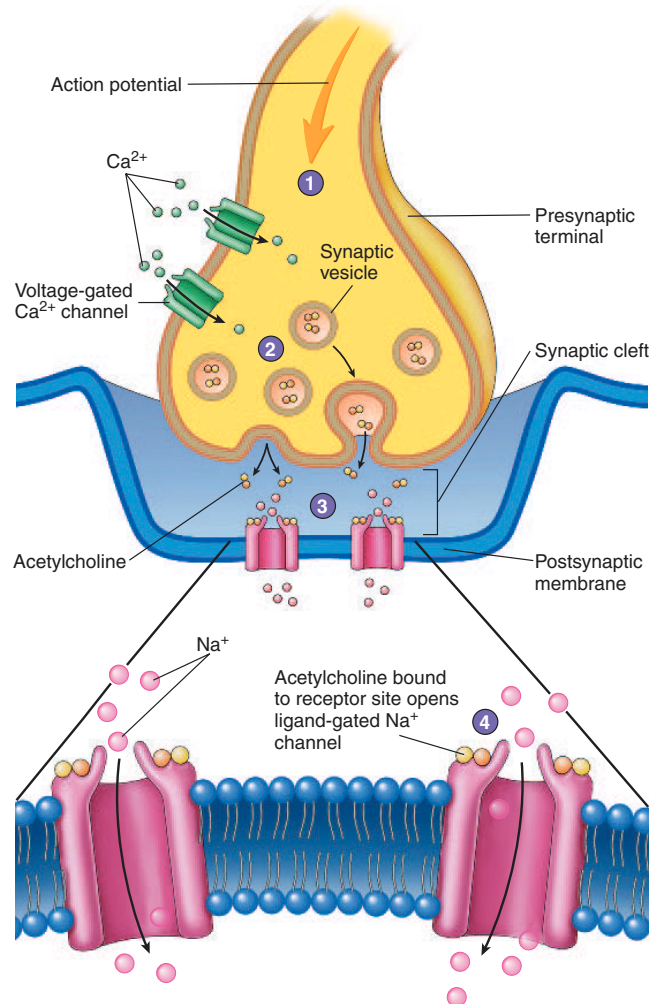
Once neurotransmitters are released from the presynaptic terminal, they diffuse rapidly across the synaptic cleft, which is about 20 nm wide, and bind in a reversible fashion to specific receptors in the postsynaptic membrane (see figure 11.27). Depending on the receptor type, this binding produces a depolarization or hyperpolarization of the postsynaptic membrane. For example, the binding of acetylcholine to ligand-gated Na^+ channels causes them to open, allowing the diffusion of Na^+ into the postsynaptic cell. If the resulting depolarization reaches threshold, an action potential is produced.

PREDICT 9

Is an action potential transmitted fastest between cells connected by electrical or chemical synapses? Explain.

Neurotransmitter Removal

The interaction between a neurotransmitter and a receptor represents an equilibrium.



1. Action potentials arriving at the presynaptic terminal cause voltage-gated Ca^{2+} channels to open.
2. Ca^{2+} diffuse into the cell and causes synaptic vesicles to release acetylcholine, a neurotransmitter molecule.
3. Acetylcholine diffuses from the presynaptic terminal across the synaptic cleft.
4. Acetylcholine molecules combine with their receptor sites and cause ligand-gated Na^+ channels to open. Na^+ diffuse into the cell and causes depolarization. If depolarization reaches threshold, an action potential is produced in the postsynaptic cell.

Process Figure 11.27 Chemical Synapse

A chemical synapse consists of the end of a neuron (presynaptic terminal), a small space (synaptic cleft), and the postsynaptic membrane of another neuron or an effector cell such as a muscle or gland cell.



When the neurotransmitter concentration in the synaptic cleft is high, many of the receptor molecules have neurotransmitter molecules bound to them, and when the neurotransmitter concentration declines, the neurotransmitter molecules diffuse away from the receptor molecules.

Neurotransmitters have short-term effects on postsynaptic membranes because the neurotransmitter is rapidly destroyed or removed from the synaptic cleft. For example, in the neuromuscular junction (see chapter 9), the neurotransmitter acetylcholine is broken down by the enzyme **acetylcholinesterase** (as'e-til-kō-lin-es'ter-ās) to acetic acid and choline. Choline is then transported back into the presynaptic terminal and is used to resynthesize acetylcholine (figure 11.28a). Acetic acid diffuses out of the synaptic cleft and can be absorbed and used by a variety of cells as a source of energy (see chapter 25).

When the neurotransmitter norepinephrine is released into the synaptic cleft, most of it is actively transported back into the presynaptic terminal, where most of it is repackaged into synaptic vesicles for reuse (figure 11.28b). The enzyme **monoamine oxidase (MAO)** (mon-ō-am'in ok'si-dās) inactivates some of the norepinephrine.

Diffusion of neurotransmitter molecules away from the synapse and into the extracellular fluid also limits the length of time the neurotransmitter molecules remain bound to their recep-

tors. Norepinephrine in the circulation is taken up primarily by liver and kidney cells, where the enzymes monoamine oxidase and **catechol-O-methyltransferase** (kat'ē-kol-ō-meth-il-trans'fer-ās) convert it into inactive metabolites.

41. Name three ways to stop the effect of a neurotransmitter on the postsynaptic membrane. Give an example of each way.

How Amphetamines Work

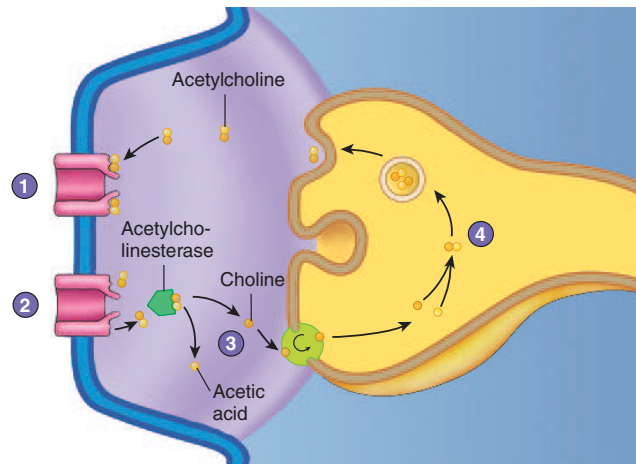
Amphetamines are known to increase the release of norepinephrine from presynaptic terminals, block the reuptake of norepinephrine from the synaptic cleft by presynaptic terminals, and inhibit the action of monoamine oxidase. The resulting increased stimulatory effects within the CNS produce a state of increased alertness and wakefulness.

Receptor Molecules in Synapses

Receptor molecules in synapses are membrane-bound, ligand-activated receptors with highly specific receptor sites. Consequently,

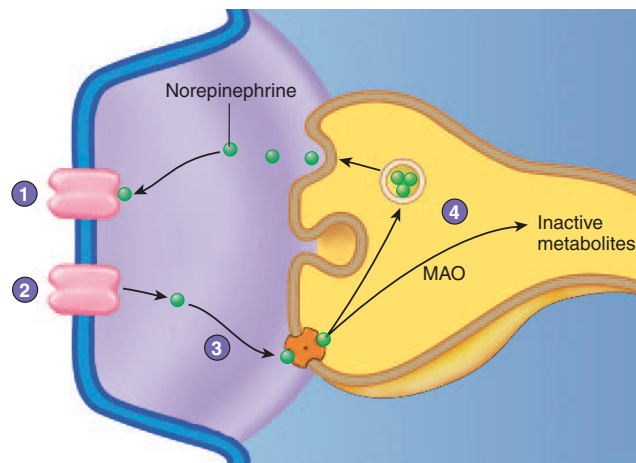
1. Acetylcholine molecules bind to their receptors.
2. Acetylcholine molecules unbind from their receptors.
3. Acetylcholinesterase splits acetylcholine into choline and acetic acid, which prevents acetylcholine from again binding to its receptors. Choline is taken up by the presynaptic terminal.
4. Choline is used to make new acetylcholine molecules that are packaged into synaptic vesicles.

(a)



1. Norepinephrine binds to its receptor.
2. Norepinephrine unbinds from its receptor.
3. Norepinephrine is taken up by the presynaptic terminal, which prevents norepinephrine from again binding to its receptor.
4. Norepinephrine is repackaged into synaptic vesicles or is broken down by monoamine oxidase (MAO).

(b)



Process Figure 11.28 Removal of Neurotransmitter from the Synaptic Cleft

(a) In some synapses, neurotransmitters are broken down by enzymes and recycled into the presynaptic terminal. (b) In some synapses, neurotransmitters are taken up whole into the presynaptic terminal.

only neurotransmitter molecules or very closely related substances normally bind to their receptors. For example, acetylcholine binds to acetylcholine receptors, but not norepinephrine receptors, whereas norepinephrine binds to norepinephrine receptors, but not to acetylcholine receptors. Any given cell does not have all possible receptors. Therefore, a neurotransmitter affects only the cells with receptors for that neurotransmitter.

A neurotransmitter can stimulate some cells but inhibit others. More than one type of receptor molecule exists for some neurotransmitters. Different cells respond differently to a neurotransmitter when these cells have different receptors. For example, norepinephrine can bind to one type of norepinephrine receptor to cause depolarization in one synapse and to another type of norepinephrine receptor to cause hyperpolarization in another synapse. Thus, norepinephrine is either stimulatory or inhibitory, depending on the type of norepinephrine receptor to which it binds and on the effect that receptor has on the permeability of the postsynaptic membrane.

Although neurotransmitter receptors are in greater concentrations on postsynaptic membranes, some receptors exist on presynaptic membranes. For example, norepinephrine released from the presynaptic membrane binds to receptors on both the presynaptic and postsynaptic membranes. Its binding to the receptors of the presynaptic membrane decreases the release of additional synaptic vesicles. Norepinephrine can therefore modify its own release by binding to presynaptic receptors. A high frequency of presynaptic action potentials results in the release of fewer synaptic vesicles in response to later action potentials.

Neurotransmitters and Neuromodulators

Several substances have been identified as neurotransmitters, and others are suspected neurotransmitters. It was once thought that each neuron contains only one type of neurotransmitter; however, it's now known that some neurons can secrete more than one type. If a neuron does produce more than one neurotransmitter, it secretes all of them from each of its presynaptic terminals. The physiologic significance of presynaptic terminals that secrete more than one type of neurotransmitter has not been clearly established.

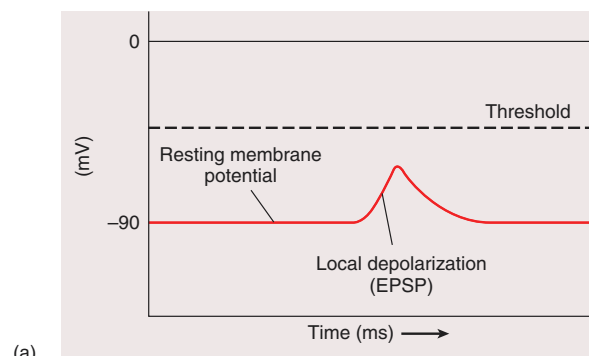
Neuromodulators are substances released from neurons that can presynaptically or postsynaptically influence the likelihood that an action potential in the presynaptic terminal will result in the production of an action potential in the postsynaptic cell. For example, a neuromodulator that decreases the release of an excitatory neurotransmitter from a presynaptic terminal decreases the likelihood of action potential production in the postsynaptic cell. A list of neurotransmitters and neuromodulators is presented in table 11.5.

Preventing Stroke Damage

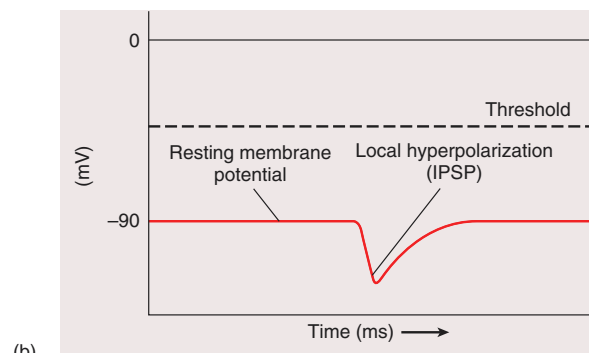
Glutamate (gloo'tă-mă) is an important excitatory neurotransmitter in the brain and spinal cord. During a stroke, oxygen-deprived presynaptic neurons release large amounts of glutamate. Glutamate binds to postsynaptic neurons and stimulates them to release **nitric oxide (NO)**, which in high concentrations can be toxic to cells. The NO diffuses from the postsynaptic neurons and causes damage to surrounding cells. It's possible that stroke damage may be reduced by drugs, not yet developed, that block glutamate receptors or inhibit the production of NO.

Excitatory and Inhibitory Postsynaptic Potentials

The combination of neurotransmitters with their specific receptors causes either depolarization or hyperpolarization of the postsynaptic membrane. When depolarization occurs, the response is stimulatory, and the local depolarization is an **excitatory postsynaptic potential (EPSP)** (figure 11.29a). EPSPs are important because the depolarization might reach threshold, thereby producing an action potential and a response from the cell. Neurons releasing neurotransmitter substances that cause EPSPs are **excitatory neurons**. In general, an EPSP occurs because of an increase in the permeability of the membrane to Na^+ . For example, glutamate in the brain and acetylcholine in skeletal muscle can bind to their receptors, causing Na^+ channels to open. Because the concentration gradient is large for Na^+ and because the negative charge inside the cell attracts the positively charged Na^+ , they diffuse into the cell and cause depolarization. If depolarization reaches threshold, an action potential is produced.



(a)



(b)

Figure 11.29 Postsynaptic Potentials

(a) Excitatory postsynaptic potential (EPSP) is closer to threshold.

(b) Inhibitory postsynaptic potential (IPSP) is farther from threshold.

Table 11.5 Substances That Are Neurotransmitters or Neuromodulators (or both)

Substance	Location	Effect	Clinical Example
Acetylcholine	Many nuclei scattered throughout the brain and spinal cord. Nerve tracts from the nuclei extend to many areas of the brain and spinal cord. Also found in the neuromuscular junction of skeletal muscle and many ANS synapses.	Excitatory or inhibitory	Alzheimer's disease (a type of senile dementia) is associated with a decrease in acetylcholine-secreting neurons. Myasthenia gravis (weakness of skeletal muscles) results from a reduction in acetylcholine receptors.
Monoamines			
Norepinephrine	A small number of small-sized nuclei in the brainstem. Nerve tracts extend from the nuclei to many areas of the brain and spinal cord. Also in some ANS synapses.	Excitatory or inhibitory	Cocaine and amphetamines increase the release and block the reuptake of norepinephrine, resulting in overstimulation of postsynaptic neurons.
Serotonin	A small number of small-sized nuclei in the brainstem. Nerve tracts extend from the nuclei to many areas of the brain and spinal cord.	Generally inhibitory	Involved with mood, anxiety, and sleep induction. Levels of serotonin are elevated in schizophrenia (delusions, hallucinations, and withdrawal).
Dopamine	Confined to a small number of nuclei and nerve tracts. Distribution is more restricted than that of norepinephrine or serotonin. Also found in some ANS synapses.	Generally excitatory	Parkinson's disease (depression of voluntary motor control) results from destruction of dopamine-secreting neurons. Drugs used to increase dopamine production induce vomiting and schizophrenia.
Histamine	Hypothalamus, with nerve tracts to many parts of the brain and spinal cord.	Generally inhibitory	No clear indication of histamine-associated pathologies. Histamine apparently is involved with arousal from sleep, pituitary hormone secretion, control of cerebral circulation, and thermoregulation.
Amino Acids			
Gamma-aminobutyric acid (GABA)	GABA-secreting neurons mostly control activities in their own area and are not usually involved with transmission from one part of the CNS to another. Most neurons of the CNS have GABA receptors.	Majority of postsynaptic inhibition in the brain; some presynaptic inhibition in the spinal cord	Drugs that increase GABA function have been used to treat epilepsy (excessive discharge of neurons).
Glycine	Spinal cord and brain. Like GABA, glycine predominantly produces local effects.	Most postsynaptic inhibition in the spinal cord	Glycine receptors are inhibited by the poison strychnine. Strychnine increases the excitability of certain neurons by blocking their inhibition. Strychnine poisoning results in powerful muscle contractions and convulsions. Tetanus of respiratory muscles can cause death.
Glutamate and aspartate	Widespread in the brain and spinal cord, especially in nerve tracts that ascend or descend the spinal cord or in tracts that project from one part of the brain to another.	Excitatory	Drugs that block glutamate or aspartate are under development. These drugs might prevent seizures and neural degeneration from overexcitation.

continued

Table 11.5 *continued*

Substance	Location	Effect	Clinical Example
Nitric Oxide	Brain, spinal cord, adrenal gland, intramural plexus, nerves to penis.	Excitatory	Blocking nitric oxide production may prevent stroke damage. Stimulating nitric oxide release is used to treat impotence.
Neuropeptides			
Endorphins and enkephalins	Widely distributed in the CNS and PNS.	Generally inhibitory	The opiates morphine and heroin bind to endorphin and enkephalin receptors on presynaptic neurons and reduce pain by blocking the release of a neurotransmitter, such as substance P.
Substance P	Spinal cord, brain, and sensory neurons associated with pain.	Generally excitatory	Substance P is a neurotransmitter in pain transmission pathways. Blocking the release of substance P by morphine reduces pain.

How Local Anesthetics Work

Awareness of pain can only occur if action potentials generated by sensory neurons stimulate the production of action potentials in CNS neurons. Local anesthetics, such as procaine (Novocain), act at their site of application to prevent pain sensations. They do so by blocking voltage-gated Na^+ channels, which prevents the propagation of action potentials along sensory neurons. Consequently, neurotransmitters are not released from the presynaptic terminals of the sensory neurons and EPSPs are not produced in CNS neurons.

When the combination of a neurotransmitter with its receptor results in hyperpolarization of the postsynaptic membrane, the response is inhibitory, and the local hyperpolarization is an **inhibitory postsynaptic potential (IPSP)** (figure 11.29b). IPSPs are important because they decrease the likelihood of producing action potentials by moving the membrane potential farther from threshold. Neurons releasing neurotransmitter substances that cause IPSPs are **inhibitory neurons**. The IPSP is the result of an increase in the permeability of the plasma membrane to Cl^- or K^+ . For example, in the spinal cord, glycine binds to its receptors, directly causing Cl^- channels to open. Because Cl^- are more concentrated outside the cell than inside, when the permeability of the membrane to Cl^- increases, they diffuse into the cell, causing the inside of the cell to become more negative and resulting in hyperpolarization. Acetylcholine can bind to its receptors in the heart, causing G protein-mediated opening of K^+ channels (see chapter 3). The concentration of K^+ is greater inside the cell than outside, and increased permeability of the membrane to K^+ results in diffusion of K^+ out of the cell. Consequently, the outside of the cell becomes more positive than the inside, resulting in hyperpolarization.

Presynaptic Inhibition and Facilitation

Many of the synapses of the CNS are **axoaxonic synapses**, meaning that the axon of one neuron synapses with the presynaptic terminal (axon) of another (figure 11.30). The axoaxonic synapse doesn't initiate an action potential in the presynaptic terminal. When an action potential reaches the presynaptic terminal, however, neuromodulators released in the axoaxonic synapse can alter the amount of neurotransmitter released from the presynaptic terminal.

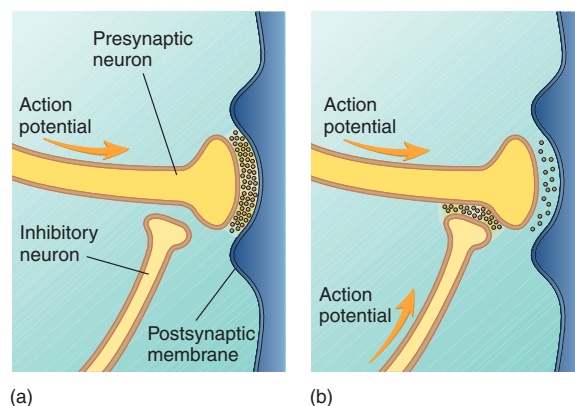


Figure 11.30 Presynaptic Inhibition at an Axoaxonic Synapse

(a) The inhibitory neuron of the axoaxonic synapse is inactive and has no effect on the release of neurotransmitter from the presynaptic terminal. (b) Release of a neuromodulator from the inhibitory neuron of the axoaxonic synapse reduces the amount of neurotransmitter released from the presynaptic terminal.

In **presynaptic inhibition**, there is a reduction in the amount of neurotransmitter released from the presynaptic terminal. For example, sensory neurons for pain can release neurotransmitters from their presynaptic terminals and stimulate the postsynaptic membranes of neurons in the brain or spinal cord. Awareness of pain occurs only if action potentials are produced in the postsynaptic membranes of the CNS neurons. Enkephalins and endorphins released from inhibitory neurons of axoaxonic synapses can reduce or eliminate pain sensations by inhibiting the release of neurotransmitter from the presynaptic terminals of sensory neurons (see figure 11.30). Enkephalins and endorphins can block voltage-gated Ca^{2+} channels. Consequently, when action potentials reach the presynaptic terminal, the influx of Ca^{2+} ions that normally stimulate neurotransmitter release is blocked.

In **presynaptic facilitation**, the amount of neurotransmitter released from the presynaptic terminal increases. For example, in some synapses, the release of neurotransmitter from the presynaptic terminal causes the release of yet more neurotransmitter. Glutamate released from a presynaptic neuron can bind to receptors on the postsynaptic membrane and stimulate the production of nitric oxide by the postsynaptic neuron. The nitric oxide diffuses out of the postsynaptic neuron, crosses the synaptic cleft, diffuses into the presynaptic neuron, and stimulates the release of additional glutamate from the presynaptic neuron.

- 42. What are the three parts of a chemical synapse?
- 43. Describe the release of a neurotransmitter in a chemical synapse.
- 44. State three ways to stop the effect of a neurotransmitter on the postsynaptic membrane. Give an example of each way.
- 45. Why does a given type of neurotransmitter affect only certain types of cells? How can a neurotransmitter stimulate one type of cell but inhibit another type?
- 46. What is a neuromodulator?
- 47. Define and explain the production of EPSPs and IPSPs. Why are they important?
- 48. What is presynaptic inhibition and facilitation?

Spatial and Temporal Summation

Depolarizations produced in postsynaptic membranes are local depolarizations. Within the CNS and in many PNS synapses, a single presynaptic action potential does not cause a local depolarization in the postsynaptic membrane sufficient to reach threshold and produce an action potential. Instead, many presynaptic action potentials causes many local potentials in the postsynaptic neuron. The local potentials combine in a process called **summation** at the trigger zone of the postsynaptic neuron, which is the normal site of action potential generation for most neurons. If summation results in a local potential that exceeds threshold at the trigger zone, an action potential is produced. Action potentials are readily produced at the trigger zone because the concentration of voltage-gated Na^+ channels is approximately seven times greater there than at the rest of the cell body.

Two types of summation, called spatial summation and temporal summation, are possible. The simplest type of **spatial summation** occurs when two action potentials arrive simultaneously at

two different presynaptic terminals that synapse with the same postsynaptic neuron. In the postsynaptic neuron, each action potential causes a local depolarization that undergoes summation at the trigger zone. If the summated depolarization reaches threshold, an action potential is produced (figure 11.31a).

Temporal summation results when two or more action potentials arrive in very close succession at a single presynaptic terminal. The first action potential causes a local depolarization in the postsynaptic membrane that remains for a few milliseconds before it disappears, although its magnitude decreases through time. Temporal summation results when another action potential initiates another local depolarization before the local depolarization caused by the previous action potential repolarizes to its resting value (see figure 11.19b). Subsequent action potentials cause local depolarizations that summate with previous local depolarizations. If the summated local depolarization reaches threshold at the trigger zone, an action potential is produced in the postsynaptic neuron (figure 11.31b).

P R E D I C T 10

Excitatory neurons A and B both synapse with neuron C. Neuron A releases a neurotransmitter, and neuron B releases the same type and amount of neurotransmitter plus a neuromodulator that produces EPSPs in neuron C. Action potentials produced in neuron A alone can result in action potential production in neuron C. Action potentials produced in neuron B alone also can cause action potential production in neuron C. Which results in more action potentials in neuron C, stimulation by only neuron A or stimulation by only neuron B? Explain.

Excitatory and inhibitory neurons can synapse with the same postsynaptic neuron. Spatial summation of EPSPs and IPSPs occurs in the postsynaptic neuron, and whether a postsynaptic action potential is initiated or not depends on which type of local potential has the greatest influence on the postsynaptic membrane potential (figure 11.31c). If the EPSPs (local depolarizations) cancel the IPSPs (local hyperpolarizations) and summate to threshold, an action potential is produced. If the IPSPs prevent the EPSPs from summing to threshold, no action potential is produced.

The synapse is an essential structure for the process of integration carried out by the CNS. For example, action potentials propagated along axons from sensory organs to the CNS can produce a sensation, or they can be ignored. To produce a sensation, action potentials must be transmitted across synapses as they travel through the CNS to the cerebral cortex, where information is interpreted. Stimuli that do not result in action potential transmission across synapses are ignored because information never reaches the cerebral cortex. The brain can ignore large amounts of sensory information as a result of complex integration.

- 49. Define spatial and temporal summation. In what part of the neuron does summation take place?
- 50. How do EPSPs and IPSPs affect the likelihood that summation will result in an action potential?

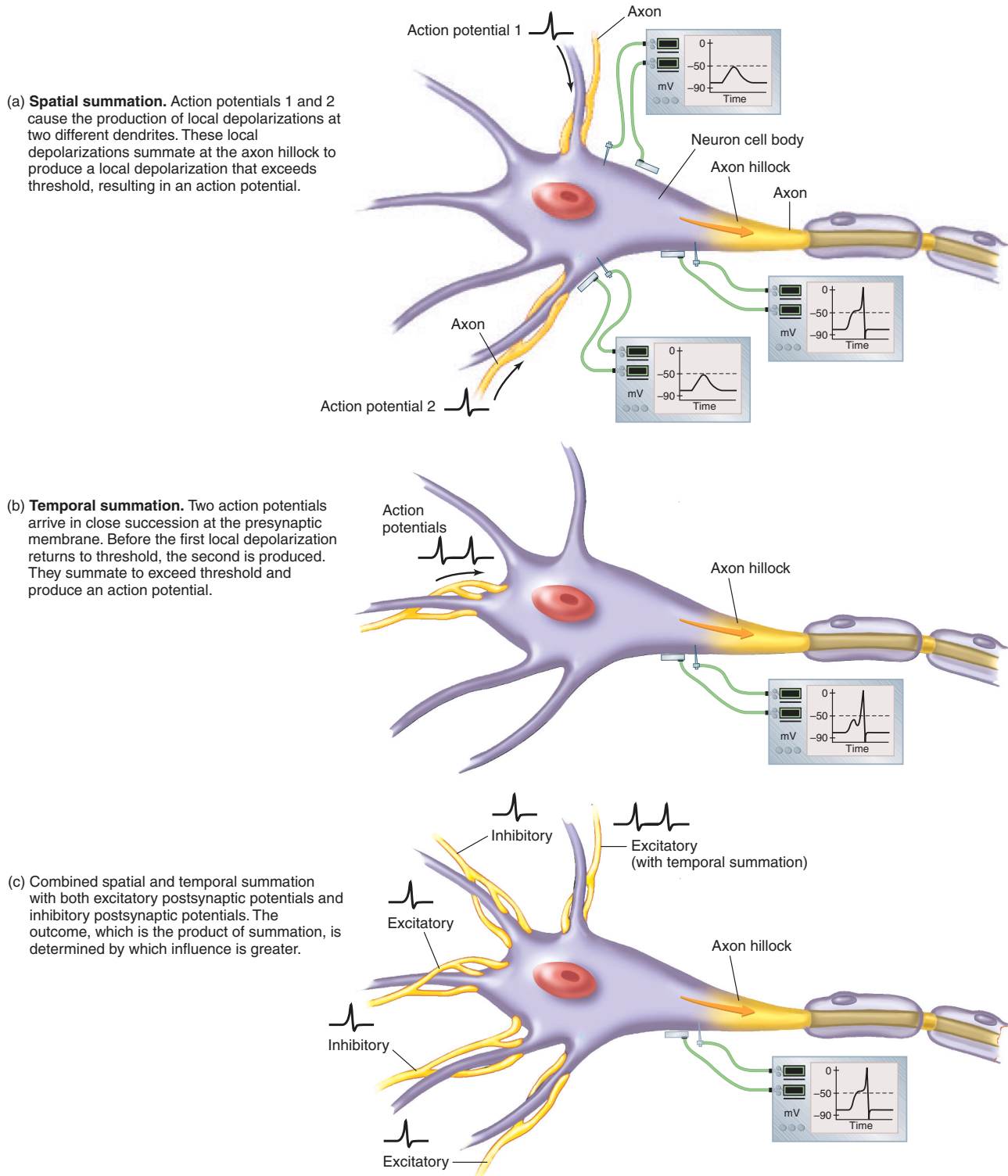


Figure 11.31 Summation

Neuronal Pathways and Circuits

Objective

- Describe convergent pathways, divergent pathways, and oscillating circuits.

The organization of neurons within the CNS varies from relatively simple to extremely complex patterns. The axon of a neuron can branch repeatedly to form synapses with many other neurons, and hundreds or even thousands of axons can synapse with the cell body and dendrites of a single neuron. Although their complexity varies, three basic patterns can be recognized: convergent pathways, divergent pathways, and oscillating circuits.

In **convergent pathways** many neurons converge and synapse with a smaller number of neurons (figure 11.32a). The simplest convergent pathway occurs when two presynaptic neu-

rons synapse with a single postsynaptic neuron, the activity of which is influenced by spatial summation. If action potentials in one presynaptic neuron cause a subthreshold depolarization in the postsynaptic neuron, no postsynaptic action potential occurs. That subthreshold depolarization, however, facilitates the response to action potentials from other presynaptic neurons. Also, if some presynaptic neurons are inhibitory and others are excitatory, the response of the postsynaptic neuron depends on the summation of both the EPSPs and the IPSPs.

In **divergent pathways**, a smaller number of presynaptic neurons synapse with a larger number of postsynaptic neurons to allow information transmitted in one neuronal pathway to diverge into two or more pathways. The simplest divergent pathway occurs when a single presynaptic neuron branches to synapse with two postsynaptic neurons (figure 11.32b).

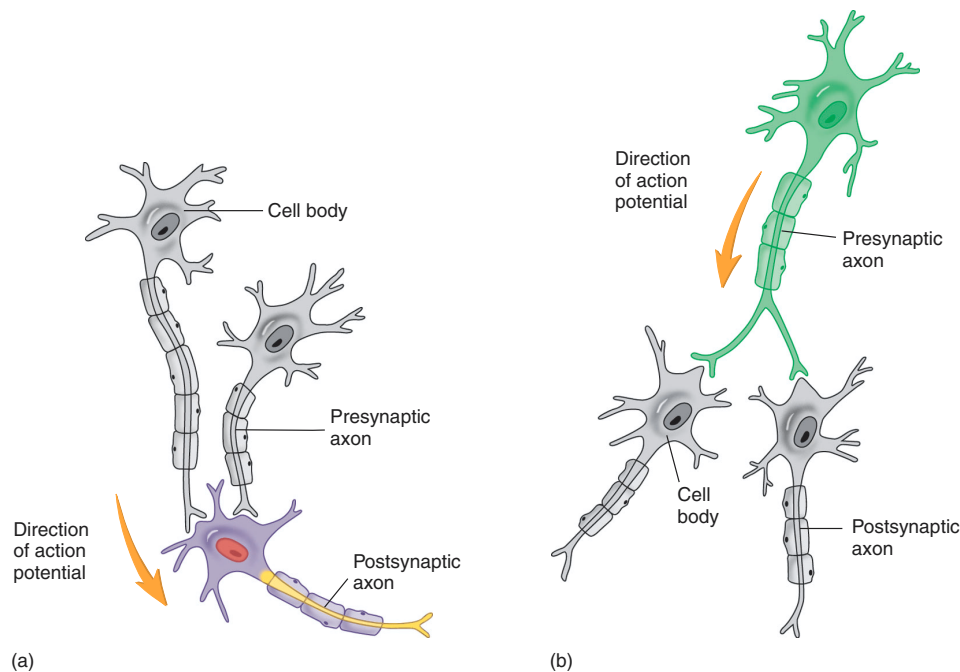


Figure 11.32 Convergent and Divergent Pathways

(a) General model of a convergent pathway, showing two neurons converging on one neuron. (b) General model of a divergent pathway, showing one neuron diverging onto two neurons.

Oscillating circuits have neurons arranged in a circular fashion, which allows action potentials entering the circuit to cause a neuron farther along in the circuit to produce an action potential more than once (figure 11.33). This response is called **afterdischarge**, and its effect is to prolong the response to a stimulus. Oscillating circuits are similar to positive-feedback systems. Once an oscillating circuit is stimulated, it continues to discharge until the synapses involved become fatigued or until they are inhibited by other neurons. Figure 11.33a illustrates a simple circuit in which a collateral axon stimulates its own cell body; figure 11.33b shows a more complex circuit. Oscillating circuits play a role in neuronal circuits that are periodically active. Respiration

may be controlled by an oscillating circuit that controls inspiration and another that controls expiration.

Neurons that spontaneously produce action potentials are common in the CNS and may activate oscillating circuits, which remain active awhile. The cycle of wakefulness and sleep may involve circuits of this type. Spontaneously active neurons are also capable of influencing the activity of other circuit types. The complex functions carried out by the CNS are affected by the numerous circuits operating together and influencing the activity of one another.

53. Diagram a convergent pathway, a divergent pathway, and an oscillating circuit, and describe what is accomplished in each.

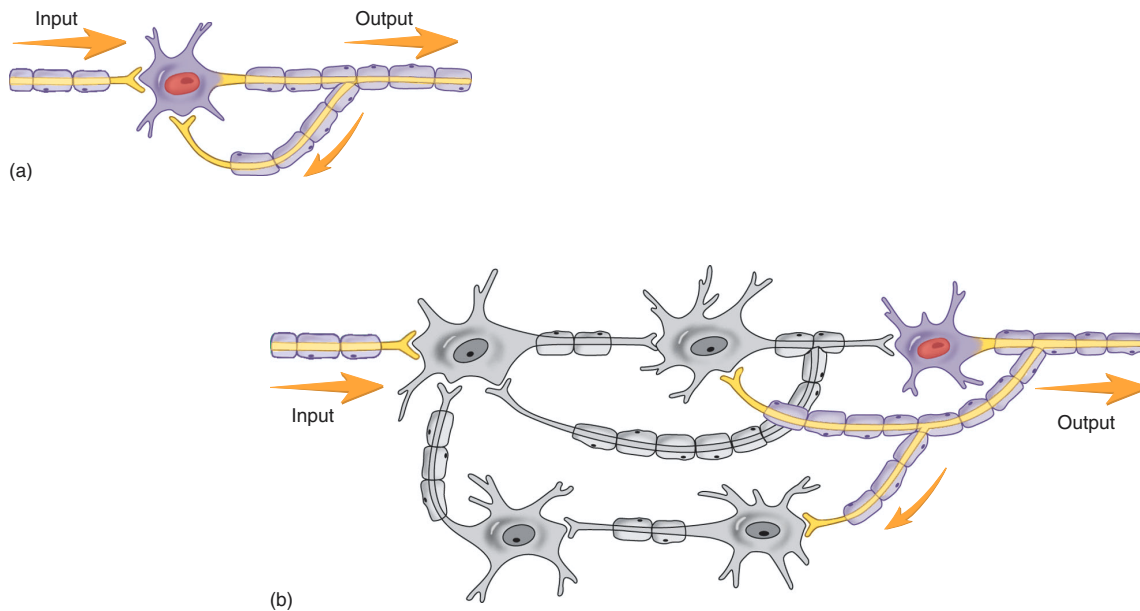


Figure 11.33 Oscillating Circuits

(a) A single neuron stimulates itself. (b) A more complex oscillating circuit in which the input neuron is stimulated by two other neurons.

S U M M A R Y

Functions of the Nervous System (p. 364)

The nervous system detects external and internal stimuli (sensory input), processes and responds to sensory input (integration), maintains homeostasis by regulating other systems, is the center for mental activities, and controls body movements through skeletal muscles.

Divisions of the Nervous System (p. 364)

- The nervous system has two anatomic divisions.
 - The central nervous system (CNS) consists of the brain and spinal cord and is encased in bone.
 - The peripheral nervous system (PNS), the nervous tissue outside of the CNS, consists of sensory receptors, nerves, ganglia, and plexuses.
- The PNS has two divisions.
 - The sensory division transmits action potentials to the CNS and usually consists of single neurons that have their cell bodies in ganglia.
 - The motor division carries action potentials away from the CNS in cranial or spinal nerves.
- The motor division has two subdivisions.
 - The somatic nervous system innervates skeletal muscle and is mostly under voluntary control. It consists of single neurons that have their cell bodies located within the CNS.
 - The autonomic nervous system (ANS) innervates cardiac muscle, smooth muscle, and glands. It has two sets of neurons between the CNS and effector organs. The first set has its cell bodies within the CNS, and the second set has its cell bodies within autonomic ganglia.
 - The ANS is subdivided into the sympathetic division, which prepares the body for activity, the parasympathetic division, which regulates resting functions, and the enteric nervous system, which controls the digestive system.
- The anatomic divisions perform different functions.
 - The PNS detects stimuli and transmits information to and receives information from the CNS.

- The CNS processes, integrates, stores, and responds to information from the PNS.

Cells of the Nervous System (p. 366)

Neurons

1. Neurons receive stimuli and transmit action potentials.
2. Neurons have three components.
 - The cell body is the primary site of protein synthesis.
 - Dendrites are short, branched cytoplasmic extensions of the cell body that usually conduct electric signals toward the cell body.
 - An axon is a cytoplasmic extension of the cell body that transmits action potentials to other cells.

Types of Neurons

1. Multipolar neurons have several dendrites and a single axon. Interneurons and motor neurons are multipolar.
2. Bipolar neurons have a single axon and dendrite and are found as components of sensory organs.
3. Unipolar neurons have a single axon. Most sensory neurons are unipolar.

Neuroglia of the CNS

1. Neuroglia are nonneural cells that support and aid the neurons of the CNS and PNS.
2. Astrocytes provide structural support for neurons and blood vessels. The endothelium of blood vessels forms the blood–brain barrier, which regulates the movement of substances between the blood and the CNS. Astrocytes influence the functioning of the blood–brain barrier and process substances that pass through it.
3. Ependymal cells line the ventricles and the central canal of the spinal cord. Some are specialized to produce cerebrospinal fluid.
4. Microglia are macrophages that phagocytize microorganisms, foreign substances, or necrotic tissue.
5. An oligodendrocyte forms myelin sheaths around the axons of several CNS neurons.

Neuroglia of the PNS

1. A Schwann cell forms a myelin sheath around part of the axon of a PNS neuron.
2. Satellite cells support and nourish neuron cell bodies within ganglia.

Myelinated and Unmyelinated Axons

1. Myelinated axons are wrapped by several layers of plasma membrane from oligodendrocytes (CNS) or Schwann cells (PNS). Spaces between the wrappings are the nodes of Ranvier. Myelinated axons conduct action potentials rapidly.
2. Unmyelinated axons rest in invaginations of oligodendrocytes (CNS) or Schwann cells (PNS). They conduct action potentials slowly.

Organization of Nervous Tissue (p. 371)

1. Nervous tissue can be grouped into white and gray matter.
 - White matter consists of myelinated axons and functions to propagate action potentials.
 - Gray matter consists of collections of neuron cell bodies or unmyelinated axons. Axons synapse with neuron cell bodies, which is functionally the site of integration in the nervous system.
2. White matter forms nerve tracts in the CNS and nerves in the PNS. Gray matter forms cortex and nuclei in the CNS and ganglia in the PNS.

Electric Signals (p. 371)

Electrical properties of cells result from the ionic concentration differences across the plasma membrane and from the permeability characteristics of the plasma membrane.

Concentration Differences Across the Plasma Membrane

1. The sodium–potassium exchange pump moves ions by active transport. K^+ is moved into the cell, and Na^+ is moved out of it.
2. The concentration of K^+ and negatively charged proteins and other molecules is higher inside, and the concentrations of Na^+ and Cl^- are higher outside the cell.
3. Negatively charged proteins and other negatively charged ions are synthesized inside the cell and cannot diffuse out of it, and they repel negatively charged Cl^- .
4. The permeability of the plasma membrane to ions is determined by nongated and gated ion channels.
 - Nongated K^+ channels are more numerous than nongated Na^+ channels, thus the plasma membrane is more permeable to K^+ than to Na^+ when at rest.
 - Gated ion channels in the plasma membrane include ligand-gated ion channels, voltage-gated ion channels, and other-gated ion channels.

The Resting Membrane Potential

1. The resting membrane potential is a charge difference across the plasma membrane when the cell is in an unstimulated condition. The inside of the cell is negatively charged compared to the outside of the cell.
2. The resting membrane potential is due mainly to the tendency of positively charged K^+ to diffuse out of the cell, which is opposed by the negative charge that develops inside the plasma membrane. At equilibrium, the tendency of positive charges to diffuse out of the cell is opposed by the negative charge inside the cell, and few ions actually diffuse through the plasma membrane.
3. Depolarization is a decrease in the resting membrane potential and can result from a decrease in the K^+ concentration gradient, a decrease in membrane permeability to K^+ , an increase in membrane permeability to Na^+ , or a decrease in extracellular Ca^{2+} concentration.
4. Hyperpolarization is an increase in the resting membrane potential that can result from an increase in the K^+ concentration gradient, an increase in membrane permeability to K^+ , a decrease in membrane permeability to Na^+ , or an increase in extracellular Ca^{2+} concentration.

Local Potentials

1. A local potential is a small change in the resting membrane potential that is confined to a small area of the plasma membrane.
2. An increase in membrane permeability to Na^+ can cause local depolarization, and an increase in membrane permeability to K^+ can result in local hyperpolarization.
3. A local potential is termed *graded* because a stronger stimulus produces a greater potential change than a weaker stimulus.
4. Local potentials can summate, or add together.
5. A local potential decreases in magnitude as the distance from the stimulation increases.

Action Potentials

1. An action potential is a larger change in the resting membrane potential that spreads over the entire surface of the cell.
2. Threshold is the membrane potential at which a local potential depolarizes the plasma membrane sufficiently to produce an action potential.
3. Action potentials occur in an all-or-none fashion. If the action potential occurs at all, it's of the same magnitude, no matter how strong the stimulus.
4. Depolarization occurs as the inside of the membrane becomes more positive because Na^+ diffuse into the cell through voltage-gated ion channels. Repolarization is a return of the membrane potential toward the resting membrane potential because voltage-gated Na^+ channels close and Na^+ diffusion into the cell slows to resting levels and because voltage-gated K^+ channels continue to open and K^+ diffuse out of the cell.

Refractory Period

1. The absolute refractory period is the time during an action potential when a second stimulus, no matter how strong, cannot initiate another action potential.
2. The relative refractory period follows the absolute refractory period and is the time during which a stronger-than-threshold stimulus can evoke another action potential.

Action Potential Frequency

1. The strength of stimuli affects the frequency of action potentials.
 - A subthreshold stimulus produces only a local potential.
 - A threshold stimulus causes a local potential that reaches threshold and results in a single action potential.
 - A submaximal stimulus is greater than a threshold stimulus and weaker than a maximal stimulus. The action potential frequency increases as the strength of the submaximal stimulus increases.
 - A maximal or a supramaximal stimulus produces a maximum frequency of action potentials.
2. A low frequency of action potentials represents a weaker stimulus than a high frequency.

Propagation of Action Potentials

1. An action potential generates local currents, which stimulate voltage-gated Na^+ channels in adjacent regions of the plasma membrane to open, producing a new action potential.
2. In an unmyelinated axon, action potentials are generated immediately adjacent to previous action potentials.
3. In a myelinated axon, action potentials are generated at successive nodes of Ranvier, which are separated from each other by Schwann cells.
4. Reversal of the direction of action potential propagation is prevented by the absolute refractory period.
5. Action potentials propagate most rapidly in myelinated, large-diameter axons.

The Synapse (p. 384)

Electrical Synapses

1. Electrical synapses are gap junctions in which tubular proteins called connexons allow local currents to move between cells.
2. At an electrical synapse, an action potential in one cell generates a local current that causes an action potential in an adjacent cell.

Chemical Synapses

1. Anatomically, a chemical synapse has three components.
 - The enlarged ends of the axon are the presynaptic terminals containing synaptic vesicles.

- The postsynaptic membranes contain receptors for the neurotransmitter.
 - The synaptic cleft, a space, separates the presynaptic and postsynaptic membranes.
2. An action potential arriving at the presynaptic terminal causes the release of a neurotransmitter, which diffuses across the synaptic cleft and binds to the receptors of the postsynaptic membrane.
 3. The effect of the neurotransmitter on the postsynaptic membrane can be stopped in several ways.
 - The neurotransmitter is broken down by an enzyme.
 - The neurotransmitter is taken up by the presynaptic terminal.
 - The neurotransmitter diffuses out of the synaptic cleft.
 4. Neurotransmitters are specific for their receptors. A neurotransmitter can be stimulatory in one synapse and inhibitory in another, depending on the type of receptor present.
 5. Neuromodulators influence the likelihood that an action potential in a presynaptic terminal will result in an action potential in a postsynaptic cell.
 6. Depolarization of the postsynaptic membrane caused by an increase in membrane permeability to Na^+ is an excitatory postsynaptic potential (EPSP).
 7. Hyperpolarization of the postsynaptic membrane caused by an increase in membrane permeability to K^+ is an inhibitory postsynaptic potential (IPSP).
 8. Presynaptic inhibition decreases neurotransmitter release. Presynaptic facilitation increases neurotransmitter release.

Spatial and Temporal Summation

1. Presynaptic action potentials through neurotransmitters produce local potentials in postsynaptic neurons. The local potential can summate to produce an action potential at the trigger zone.
2. Spatial summation occurs when two or more presynaptic terminals simultaneously stimulate a postsynaptic neuron.
3. Temporal summation occurs when two or more action potentials arrive in succession at a single presynaptic terminal.
4. Inhibitory and excitatory presynaptic neurons can converge on a postsynaptic neuron. The activity of the postsynaptic neuron is determined by the integration of the EPSPs and IPSPs produced in the postsynaptic neuron.

Neuronal Pathways and Circuits (p. 393)

1. Convergent pathways have many neurons synapsing with a few neurons.
2. Divergent pathways have a few neurons synapsing with many neurons.
3. Oscillating circuits have collateral branches of postsynaptic neurons synapsing with presynaptic neurons.

REVIEW AND COMPREHENSION

1. The peripheral nervous system includes the
 - a. somatic nervous system.
 - b. brain.
 - c. spinal cord.
 - d. nuclei.
 - e. all of the above.
2. The part of the nervous system that controls smooth muscle, cardiac muscle, and glands is the
 - a. somatic nervous system.
 - b. autonomic nervous system.
 - c. skeletal division.
 - d. sensory division.
3. Neurons have cytoplasmic extensions that connect one neuron to another neuron. Given these structures:
 1. axon
 2. dendrite
 3. dendritic spine
 4. presynaptic terminal

Choose the arrangement that lists the structures in the order they are found between two neurons.

 - a. 1,4,2,3
 - b. 1,4,3,2
 - c. 4,1,2,3
 - d. 4,1,3,2
 - e. 4,3,2,1

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4. A neuron with many short dendrites and a single long axon is a _____ neuron.
 - a. multipolar
 - b. unipolar
 - c. bipolar
5. Motor neurons and interneurons are _____ neurons.
 - a. unipolar
 - b. bipolar
 - c. multipolar
 - d. afferent
6. Cells found in the choroid plexuses that secrete cerebrospinal fluid are
 - a. astrocytes.
 - b. microglia.
 - c. ependymal cells.
 - d. oligodendrocytes.
 - e. Schwann cells.
7. Neuroglia that are phagocytic within the central nervous system are
 - a. oligodendrocytes.
 - b. microglia.
 - c. ependymal cells.
 - d. astrocytes.
 - e. Schwann cells.
8. Unmyelinated axons within nerves may have which of these associated with them?
 - a. Schwann cells
 - b. nodes of Ranvier
 - c. oligodendrocytes
 - d. all of the above
9. Action potentials are conducted more rapidly
 - a. in small-diameter axons than in large-diameter axons.
 - b. in unmyelinated axons than in myelinated axons.
 - c. along axons that have nodes of Ranvier.
 - d. all of the above.
10. Clusters of nerve cell bodies within the peripheral nervous system are
 - a. ganglia.
 - b. fascicles.
 - c. nuclei.
 - d. laminae.
11. Gray matter contains primarily
 - a. myelinated fibers.
 - b. neuron cell bodies.
 - c. Schwann cells.
 - d. oligodendrocytes.
12. Concerning concentration difference across the plasma membrane, there are
 - a. more K^+ and Na^+ outside the cell than inside.
 - b. more K^+ and Na^+ inside the cell than outside.
 - c. more K^+ outside the cell than inside and more Na^+ inside the cell than outside.
 - d. more K^+ inside the cell than outside and more Na^+ outside the cell than inside.
13. Compared to the inside of the resting plasma membrane, the outside surface of the membrane is
 - a. positively charged.
 - b. electrically neutral.
 - c. negatively charged.
 - d. continuously reversing so that it is positive one second and negative the next.
 - e. negatively charged whenever the sodium-potassium pump is operating.
14. Nongated ion channels
 - a. open in response to small voltage changes.
 - b. open when a ligand binds to its receptor.
 - c. are responsible for the ion permeability of the resting plasma membrane.
 - d. allow substances to move into the cell but not out.
 - e. all of the above.
15. The resting membrane potential results when the tendency for _____ to diffuse out of the cell is balanced by their attraction to opposite charges inside the cell.
 - a. Na^+
 - b. K^+
 - c. Cl^-
 - d. negatively charged proteins
16. If the permeability of the plasma membrane to K^+ increases, resting membrane potential _____. This is called _____.
 - a. increases, hyperpolarization
 - b. increases, depolarization
 - c. decreases, hyperpolarization
 - d. decreases, depolarization
17. Decreasing the extracellular concentration of K^+ affects the resting membrane potential by causing
 - a. hyperpolarization.
 - b. depolarization.
 - c. no change.
18. Which of these terms are correctly matched with their definition or description?
 - a. depolarization: membrane potential becomes more negative
 - b. hyperpolarization: membrane potential becomes more negative
 - c. hypopolarization: membrane potential becomes more negative
19. Which of these statements about ion movement through the plasma membrane is true?
 - a. Movement of Na^+ out of the cell requires energy (ATP).
 - b. When Ca^{2+} binds to proteins in ion channels, the diffusion of Na^+ into the cell is inhibited.
 - c. There are specific ion channels that regulate the diffusion of Na^+ through the plasma membrane.
 - d. All of the above.
20. The *major* function of the sodium–potassium exchange pump is to
 - a. pump Na^+ into and K^+ out of the cell.
 - b. generate the resting membrane potential.
 - c. maintain the concentration gradients of Na^+ and K^+ across the plasma membrane.
 - d. oppose any tendency of the cell to undergo hyperpolarization.
21. Local potentials
 - a. spread over the plasma membrane in decremental fashion.
 - b. are not propagated for long distances.
 - c. are graded.
 - d. can summate.
 - e. all of the above.
22. During the depolarization phase of an action potential, the permeability of the membrane
 - a. to K^+ is greatly increased.
 - b. to Na^+ is greatly increased.
 - c. to Ca^{2+} is greatly increased.
 - d. is unchanged.
23. During repolarization of the plasma membrane,
 - a. Na^+ diffuse into the cell.
 - b. Na^+ diffuse out of the cell.
 - c. K^+ diffuse into the cell.
 - d. K^+ diffuse out of the cell.

24. The absolute refractory period
 - a. limits how many action potentials can be produced during a given period of time.
 - b. prevents an action potential from starting another action potential at the same point on the plasma membrane.
 - c. is the period of time when a strong stimulus can initiate a second action potential.
 - d. both a and b.
 - e. all of the above.
25. A subthreshold stimulus
 - a. produces an afterpotential.
 - b. produces a local potential.
 - c. causes an all-or-none response.
 - d. produces more action potentials than a submaximal stimulus.
26. Neurotransmitter substances are stored in vesicles that are located in specialized portions of the
 - a. neuron cell body.
 - b. axon.
 - c. dendrite.
 - d. postsynaptic membrane.
27. In a chemical synapse,
 - a. action potentials in the presynaptic terminal cause voltage-gated Ca^{2+} channels to open.
 - b. neurotransmitters can cause ligand-gated Na^{+} channels to open.
 - c. neurotransmitters can be broken down by enzymes.
 - d. neurotransmitters can be taken up by the presynaptic terminal.
 - e. all of the above.
28. An inhibitory presynaptic neuron can affect a postsynaptic neuron by
 - a. producing an IPSP in the postsynaptic neuron.
 - b. hyperpolarizing the plasma membrane of the postsynaptic neuron.
 - c. causing K^{+} to diffuse out of the postsynaptic neuron.
 - d. causing Cl^{-} to diffuse into the postsynaptic neuron.
 - e. all of the above.
29. Summation
 - a. is caused by combining two or more local potentials.
 - b. occurs at the trigger zone of the postsynaptic neuron.
 - c. results in an action potential if it reaches the threshold potential.
 - d. can occur when two action potentials arrive in close succession at a single presynaptic terminal.
 - e. all of the above.
30. In convergent pathways,
 - a. the response of the postsynaptic neuron depends on the summation of EPSPs and IPSPs.
 - b. a smaller number of presynaptic neurons synapse with a larger number of postsynaptic neurons.
 - c. information transmitted in one neuronal pathway can go into two or more pathways.
 - d. all of the above.

Answers in Appendix F

C R I T I C A L T H I N K I N G

1. Predict the consequence of a reduced intracellular K^{+} concentration on the resting membrane potential.
2. A child eats a whole bottle of salt (NaCl) tablets. What effect would this have on action potentials?
3. Lithium ions reduce the permeability of plasma membranes to sodium ions. Predict the effect lithium ions in the extracellular fluid would have on the response of a neuron to stimuli.
4. Some smooth muscle has the ability to contract spontaneously. That is, it contracts without any external stimulation. Propose an explanation for the ability of smooth muscle to contract spontaneously based on what you know about membrane potentials. Assume that an action potential in a smooth muscle cell causes it to contract.
5. Assume that you have two nerve fibers of the same diameter, but one is myelinated and the other is unmyelinated. Along which type of fiber is the conduction of an action potential most energy efficient? (*Hint: ATP*)
6. Explain the consequences when an inhibitory neuromodulator is released from a presynaptic terminal and a stimulatory neurotransmitter is released from another presynaptic terminal, both of which synapse with the same neuron.
7. With aging, the speed of action potential propagation and synaptic transmission decreases. List possible explanations.
8. Students in a veterinary school were given the following hypothetical problem. A dog ingests organophosphate poison, and the students are responsible for saving the animal's life. Organophosphate poisons bind to and inhibit acetylcholinesterase. Several substances they could inject include the following: acetylcholine, curare (which blocks acetylcholine receptors), and potassium chloride. If you were a student in the class, what would you do to save the animal?
9. Strychnine blocks receptor sites for inhibitory neurotransmitter substances in the CNS. Explain how strychnine could produce tetany in skeletal muscles.

Answers in Appendix G

A N S W E R S T O P R E D I C T Q U E S T I O N S

1. When the axon of a neuron is severed, the proximal portion of the axon remains attached to the neuron cell body. The distal portion is detached, however, and has no way to replenish the enzymes and other proteins essential to its survival. Because the DNA in the nucleus provides the information that determines the structure of proteins by directing mRNA synthesis, the distal portion of the axon has no source of new proteins. Consequently, it degenerates and dies. On the other hand, the proximal portion of the axon is still attached to the nucleus and therefore has a source of new proteins. It remains alive and, in many cases, grows to replace the severed distal axon.
2. Tissue A has the larger resting membrane potential. There's a greater tendency for K^{+} to diffuse out of the cell because it has significantly more nongated K^{+} channels. As a result, a greater negative charge develops on the inside of the plasma membrane, resulting in a larger resting membrane potential.
3. If the intracellular concentration of K^{+} is increased, the concentration gradient from the inside to the outside of the plasma membrane increases. This situation is similar to decreasing the extracellular concentration of K^{+} . The greater concentration gradient for K^{+} increases their tendency to diffuse out of the cell

across the plasma membrane. A greater negative charge then develops inside the cell (hyperpolarization).

4. Ca^{2+} binds to gating proteins that regulate the voltage-gated Na^+ channels. Low concentrations of Ca^{2+} cause the voltage-gated Na^+ channels to open, and high concentrations of Ca^{2+} cause the voltage-gated Na^+ channels to close. If the extracellular concentration of Ca^{2+} decreases, the resting membrane potential depolarizes because voltage-gated Na^+ channels open and Na^+ diffuses into the cell.
5. When the cells are stimulated, there is an increase in the permeability of their plasma membranes to Na^+ . These ions diffuse into the cells down their concentration gradients and cause depolarization of the plasma membranes. If the concentration gradient for Na^+ is reduced, the tendency for Na^+ to diffuse into the cell decreases. In cell A, with the reduced Na^+ concentration gradient, the local depolarization is of a smaller magnitude than in cell B because fewer ions are able to diffuse into the cell in response to the stimulus.
6. If the extracellular concentration of Na^+ decreases, the magnitude of the action potential is reduced. The smaller extracellular concentration of Na^+ reduces the tendency for Na^+ to diffuse into the cell when the Na^+ channels are open during an action potential. Consequently, the inside of the plasma membrane doesn't become as positive as it does in cells with a high extracellular concentration of Na^+ . Even though the magnitude of action potentials is reduced when the extracellular Na^+ concentration is reduced, all of the actions potentials are the same magnitude (all-or-none principle).
7. A prolonged stronger-than-threshold stimulus produces more action potentials than a prolonged threshold stimulus of the same duration. A prolonged stronger-than-threshold stimulus can stimulate more action potentials because the permeability of the membrane to Na^+ is increased. A very strong stimulus can even stimulate action potentials during the relative refractory period, whereas a prolonged threshold stimulus stimulates a low frequency of action potentials. Thus, when a prolonged stronger-than-threshold stimulus is applied, less time elapses between the production of one action potential and the next, resulting in the production of a greater number of action potentials.
8. If the duration of the absolute refractory period is 1 ms, that means action potentials can be generated no faster than every millisecond. The maximal frequency of action potentials is 1000 per second because there is 1000 milliseconds in a second.
9. Action potentials are transmitted fastest by electrical synapses because the local currents can quickly flow through the connexons. In contrast, chemical synapses are slower because the synaptic vesicles must be stimulated to release neurotransmitter, which diffuses across the synaptic cleft. The neurotransmitter must stimulate ligand-gated Na^+ channels to open. The resulting movement of Na^+ into the cell can produce an action potential. All of these events take time.
10. Temporal summation resulting from stimulation by neuron B produces more action potentials in the postsynaptic neuron than temporal summation resulting from stimulation by neuron A. The neuromodulator from neuron B produces EPSPs, which depolarize the membrane potential of neuron C, bringing the membrane potential closer to threshold. A smaller amount of neurotransmitter is therefore required to produce an action potential. Although neuron A and B release the same amount and type of neurotransmitter, the neuromodulator makes the neurotransmitter from neuron B more effective, resulting in more action potentials.

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