43.3 Connective Tissue

Learning Outcomes

1. *Describe the structure and function of connective tissue.*
2. *Identify the different kinds of connective tissue.*
3. *List the cells that make connective tissue.*

Connective tissues derive from embryonic mesoderm and occur in many different forms (table 43.2). We divide these various forms into two major classes: *connective tissue proper*, which further divides into loose and dense connective tissues, and **special connective tissues,** which include cartilage, bone, and blood.

At first glance, it may seem odd that such diverse tissues are in the same category. Yet all connective tissues share a common structural feature: They all have abundant extracellular material because their cells are spaced widely apart. This extracellular material is called the **matrix** of the tissue. In bone, the matrix contains crystals that make the bones hard; in blood, the matrix is plasma, the fluid portion of the blood. The matrix itself consists of protein fibers and **ground substance,** the fluid material between cells and fibers containing a diverse array of proteins and polysaccharrides.

Connective tissue proper may be either loose or dense

During the development of both loose and dense connective tissues, cells called fibroblasts produce and secrete the extracellular matrix. Loose connective tissue contains other cells as well, including mast cells and macrophages—cells of the immune system.

Loose connective tissue

Loose connective tissue consists of cells scattered within a matrix that contains a large amount of ground substance. This gelatinous material is strengthened by a loose scattering of protein fibers such as collagen, which supports the tissue by forming a meshwork (figure 43.3), elastin, which makes the tissue elastic, and reticulin, which helps support the network of collagen. The flavored gelatin of certain desserts consists primarily of extracellular material extracted from the loose connective tissues of animals.

Adipose cells, more commonly termed fat cells, are important for nutrient storage, and they also occur in loose connective tissue. In certain areas of the body, including under the skin, in bone marrow, and around the kidneys, these cells can develop in large groups, forming **adipose tissue** (figure 43.4).

Each adipose cell contains a droplet of triglycerides within a storage vesicle. When needed for energy, the adipose cell hydrolyzes its stored triglyceride and secretes fatty acids into the blood for oxidation by the cells of the muscles, liver, and other organs. Adipose cells cannot divide; the number of adipose cells in an adult is generally fixed. When a person gains weight, the cells become larger, and when weight is lost, the cells shrink.

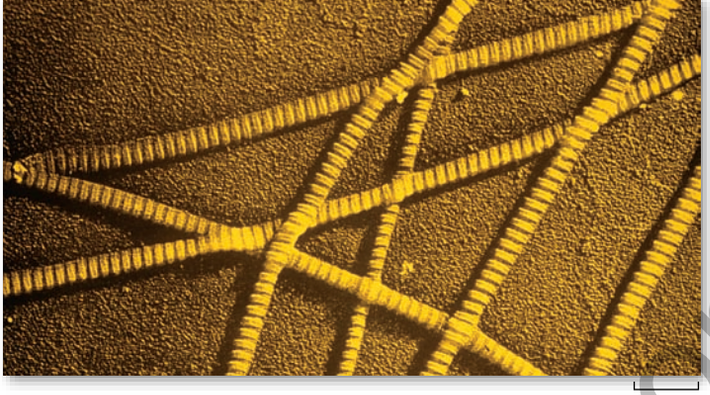


Figure 43.3 Collagen fibers. These fibers, shown under an electron microscope, are composed of many individual collagen strands and can be very strong under tension.

Dense connective tissue

Dense connective tissue, with less ground substance, contains tightly packed collagen fibers, making it stronger than loose connective tissue. It consists of two types: regular and irregular. The collagen fibers of *dense regular connective tissue* line up in parallel, like the strands of a rope. This is the structure of tendons, which bind muscle to bone, and ligaments, which bind bone to bone.

In contrast, the collagen fibers of *dense irregular connective tissue* have many different orientations. This type of connective tissue produces the tough coverings that package organs, such as the capsules of the kidneys and adrenal glands. It also covers muscle, nerves, and bones.

Special connective tissues have unique characteristics

The special connective tissues—cartilage, bone, and blood—each have unique cells and matrices that allow them to perform their specialized functions.

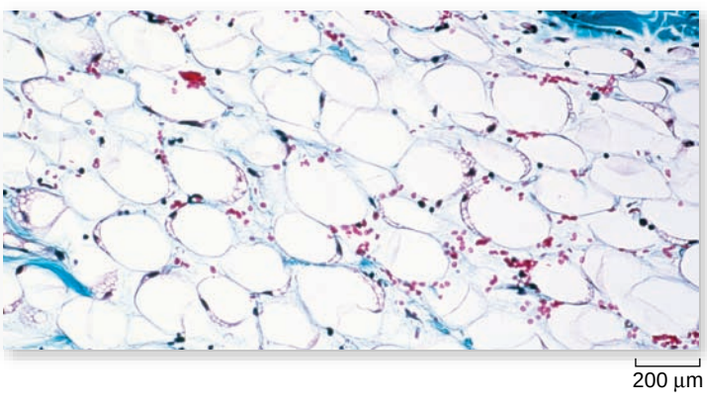
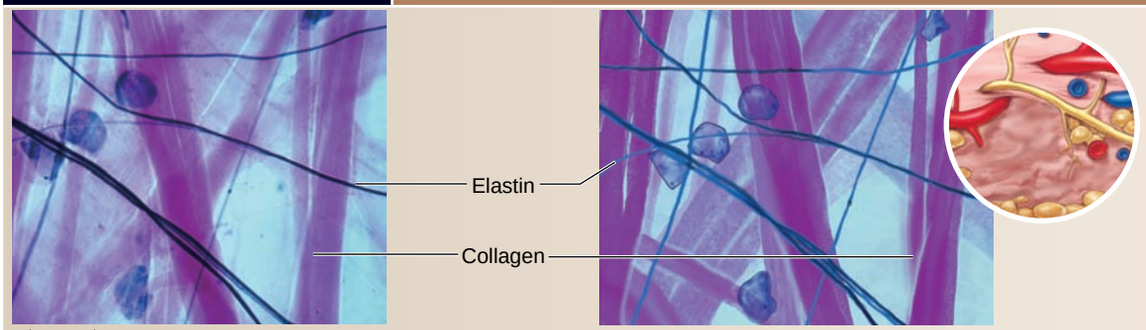
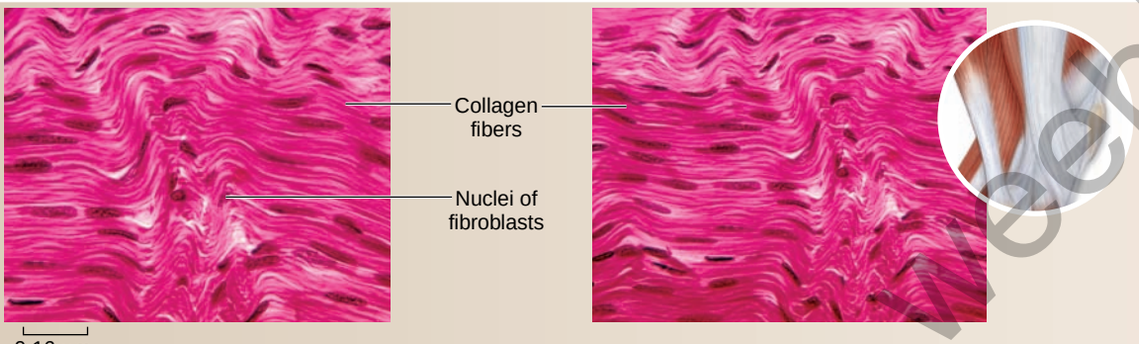


Figure 43.4 Adipose tissue. Fat is stored in globules of adipose tissue, a type of loose connective tissue. As a person gains or loses weight, the size of the fat globules increases or decreases. A person cannot decrease the number of fat cells by losing weight.

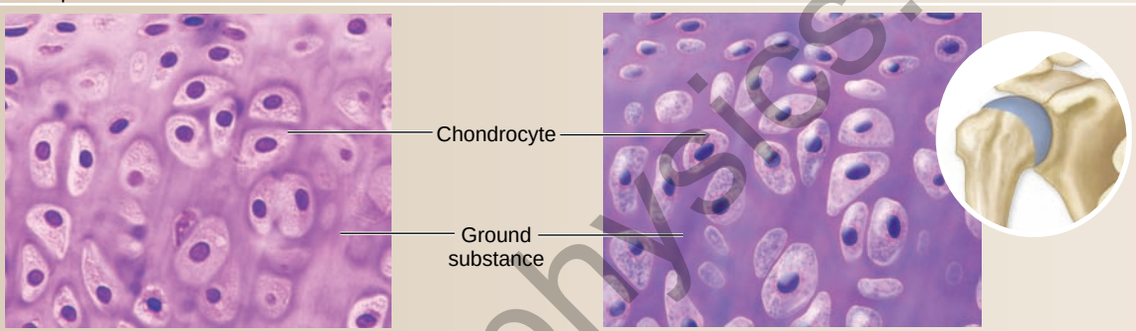
TABLE 43.2 Connective Tissue



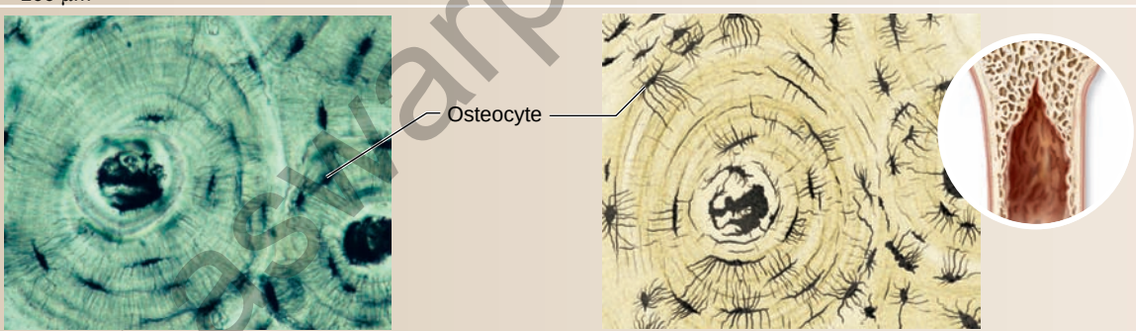
Loose Connective Tissue
Typical Location
Beneath skin; between organs
Function
Provides support, insulation, food storage, and nourishment for epithelium
Characteristic Cell Types
Fibroblasts, macrophages, mast cells, fat cells



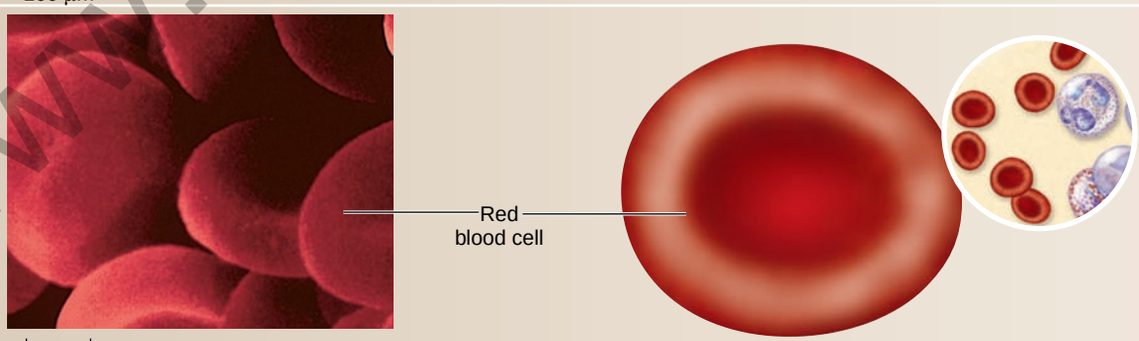
Dense Connective Tissue
Typical Location
Tendons; sheath around muscles; kidney; liver; dermis of skin
Function
Provides flexible, strong connections
Characteristic Cell Types
Fibroblasts



Cartilage
Typical Location
Spinal disks; knees and other joints; ear; nose; tracheal rings
Function
Provides flexible support, shock absorption, and reduction of friction on load-bearing surfaces
Characteristic Cell Types
Chondrocytes



Bone
Typical Location
Most of skeleton
Function
Protects internal organs; provides rigid support for muscle attachment
Characteristic Cell Types
Osteocytes



Blood
Typical Location
Circulatory system
Function
Functions as highway of immune system; carries nutrients and waste; and is the primary means of communication between organs
Characteristic Cell Types
Erythrocytes, leukocytes

Cartilage

Cartilage (see table 43.2) is a specialized connective tissue in which the ground substance forms from a characteristic type of glycoprotein, called *chondroitin*, and collagen fibers laid down along lines of stress in long, parallel arrays. The result is a firm and flexible tissue that does not stretch, is far tougher than loose or dense connective tissue, and has great tensile strength.

Cartilage makes up the entire skeletal system of the modern agnathans and cartilaginous fishes (see chapter 35). In most adult vertebrates, however, cartilage is restricted to the joint surfaces of bones that form freely movable joints and certain other locations. In humans, for example, the tip of the nose, the outer ear, the intervertebral disks of the backbone, the larynx, and a few other structures are composed of cartilage.

Chondrocytes, the cells of cartilage, live within spaces called **lacunae** within the cartilage ground substance. These cells remain alive even though there are no blood vessels within the cartilage matrix; they receive oxygen and nutrients by diffusion through the cartilage ground substance from surrounding blood vessels. This diffusion can only occur because the cartilage matrix is well hydrated and not calcified, as is bone.

Bone

Bone cells, or **osteocytes,** remain alive even though the extracellular matrix becomes hardened with crystals of calcium phosphate. Blood vessels travel through central canals into the bone, providing nutrients and removing wastes. Osteocytes extend cytoplasmic processes toward neighboring osteocytes through tiny canals, or *canaliculi*. Osteocytes communicate with the blood vessels in the central canal through this cytoplasmic network. Bone is described in more detail in chapter 47 along with muscle.

In the course of fetal development, the bones of vertebrate fins, arms, and legs, among other appendages, are first "modeled" in cartilage. The cartilage matrix then calcifies at particular locations, so that the chondrocytes are no longer able to obtain oxygen and nutrients by diffusion through the matrix. Living bone replaces the dying and degenerating cartilage.

Blood

We classify *blood* as a connective tissue because it contains abundant extracellular material, the fluid plasma. The cells of blood are *erythrocytes*, or red blood cells, and *leukocytes*, or white blood cells. Blood also contains platelets, or *thrombocytes*, which are fragments of a type of bone marrow cell. We discuss blood more fully in chapter 50.

All connective tissues have similarities

Although the descriptions of the types of connective tissue suggest numerous different functions for these tissues, they have some similarities. As mentioned, connective tissues originate as embryonic mesoderm, and they all contain abundant extracellular material called matrix; however, the extracellular matrix material is different in different types of connective tissue. Embedded within the extracellular matrix of each tissue type are varieties of cells, each with specialized functions.

Learning Outcomes Review 43.3

Connective tissues are characterized by abundant extracellular materials forming a matrix between loosely organized cells. Connective tissue proper is classified as either loose or dense. Special connective tissues have unique extracellular matrices between cells. The matrix of cartilage is composed of organic materials, whereas that of bones is calcium crystals. The matrix of blood is a fluid, the plasma.

- ***Why is blood considered connective tissue?***

43.4 Muscle Tissue

Learning Outcomes

1. *Identify the unique features of muscle cells.*
2. *Describe the three kinds of muscle and muscle cells.*

Muscles are the motors of the vertebrate body. The characteristic that makes muscle cells unique is the relative abundance and organization of actin and myosin filaments within them. Although these filaments form a fine network in all eukaryotic cells, where they contribute to movement of materials within the cell, they are far more abundant and organized in muscle cells, which are specialized for contraction.

Vertebrates possess three kinds of muscle: *smooth*, *skeletal*, and *cardiac* (table 43.3). Skeletal and cardiac muscles are also known as *striated muscles* because their cells appear to have transverse stripes when viewed in longitudinal section under the microscope. The contraction of each skeletal muscle is under voluntary control, whereas the contraction of cardiac and smooth muscles is generally involuntary.

Smooth muscle is found in most organs

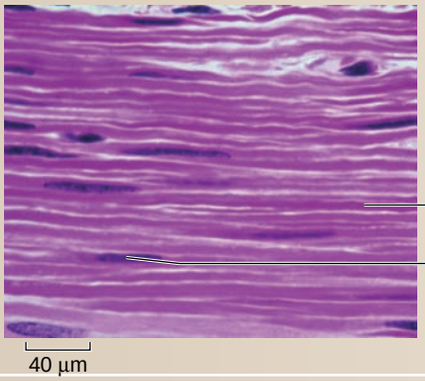
Smooth muscle was the earliest form of muscle to evolve, and it is found throughout most of the animal kingdom. In vertebrates, smooth muscle occurs in the organs of the internal environment, or *viscera*, and is also called *visceral muscle*. Smooth muscle tissue is arranged into sheets of long, spindle-shaped cells, each cell containing a single nucleus. In some tissues, the cells contract only when a nerve stimulates them—and then all of the cells in the sheet contract as a unit.

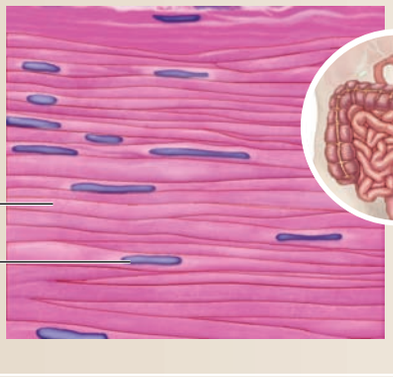
In vertebrates, muscles of this type line the walls of many blood vessels and make up the iris of the eye, which contracts in bright light. In other smooth muscle tissues, such as those in the wall of the digestive tract, the muscle cells themselves may spontaneously initiate electrical impulses, leading to a slow, steady contraction of the tissue. Here nerves regulate, rather than cause, the activity.

Skeletal muscle moves the body

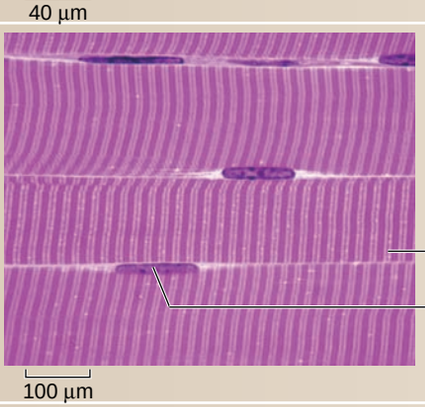
Skeletal muscles are usually attached to bones by tendons, so that their contraction causes the bones to move at their joints. A skeletal muscle is made up of numerous, very long muscle

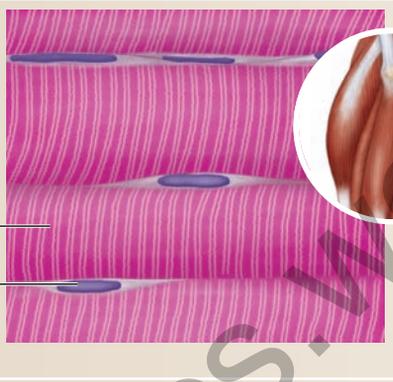
TABLE 43.3 Muscle Tissue



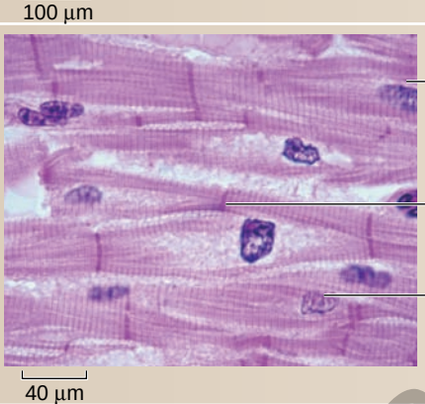


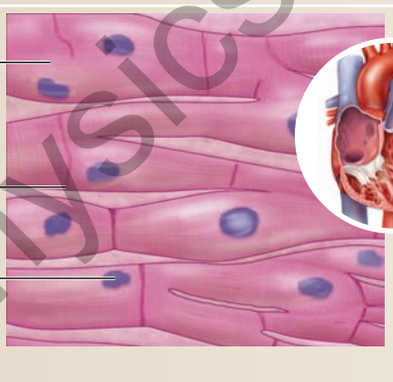
Smooth Muscle
Typical Location
Walls of blood vessels, stomach, and intestines
Function
Powers rhythmic, involuntary contractions commanded by the central nervous system
Characteristic Cell Types
Smooth muscle cells





Skeletal Muscle
Typical Location
Voluntary muscles
Function
Powers walking, lifting, talking, and all other voluntary movement
Characteristic Cell Types
Skeletal muscle cells





Cardiac Muscle
Typical Location
Walls of heart
Function
Highly interconnected cells; promotes rapid spread of signal initiating contraction
Characteristic Cell Types
Cardiac muscle cells

cells called **muscle fibers**, which have multiple nuclei. The fibers lie parallel to each other within the muscle and are connected to the tendons on the ends of the muscle. Each skeletal muscle fiber is stimulated to contract by a motor neuron.

The nervous system controls the overall strength of a skeletal muscle contraction by controlling the number of motor neurons that fire, and therefore the number of muscle fibers stimulated to contract. Each muscle fiber contracts by means of substructures called **myofibrils** containing highly ordered arrays of actin and myosin myofilaments. These filaments give the muscle fiber its striated appearance.

Skeletal muscle fibers are produced during development by the fusion of several cells, end to end. This embryological development explains why a mature muscle fiber contains many nuclei. The structure and function of skeletal muscle is explained in more detail in chapter 47.

The heart is composed of cardiac muscle

The hearts of vertebrates are made up of striated muscle cells arranged very differently from the fibers of skeletal muscle. Instead of having very long, multinucleate cells running the length of the muscle, **cardiac muscle** consists of smaller, interconnected cells, each with a single nucleus. The interconnections between adjacent cells appear under the microscope as dark lines called **intercalated disks.** In reality, these lines are regions where gap junctions link adjacent cells. As noted in chapter 4, gap junctions have openings that permit the movement of small substances and ions from one cell to another. These interconnections enable the cardiac muscle cells to form a single functioning unit.

Certain specialized cardiac muscle cells can generate electrical impulses spontaneously, but the nervous system usually

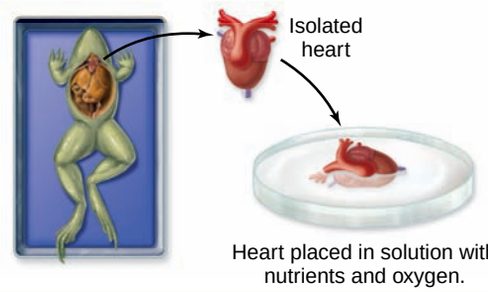
SCIENTIFIC THINKING

Question: *Is the heartbeat a function of the nervous system, or does it originate in the heart itself?*

Hypothesis: *Cells in the heart are capable of generating an action potential without stimulation by the nervous system.*

Prediction: *If the heartbeat is produced by cells in the heart, then an isolated heart should continue to beat.*

Test: *Remove a frog's heart and keep in a bath of nutrient solution and oxygen.*



Result: *The heart continues to contract with no connection to the nervous system.*

Conclusion: *The heartbeat is intrinsic to the heart.*

Further Experiments: *How would you integrate the conclusions from this experiment with the one described in figure 44.12?*

Figure 43.5 **The source of the heartbeat.**

regulates the rate of impulse activity (figure 43.5). The impulses generated by the specialized cell groups spread across the gap junctions from cell to cell, synchronizing the heart's contraction. Chapter 50 describes this process more fully.

Learning Outcomes Review 43.4

Muscles are the motors of the body; they are able to contract to change their length. Muscle tissue is of three types: smooth, skeletal, and cardiac. Smooth muscles provide a variety of visceral functions. Skeletal muscles enable the vertebrate body to move. Cardiac muscle forms a muscular pump, the heart.

- *Why is it important that cardiac muscle cells have gap junctions?*

43.5 *Nerve Tissue*

Learning Outcomes

1. *Describe the basic structure of neurons.*
2. *Distinguish between neurons and their supporting cells.*
3. *Identify the two divisions of the nervous system.*

The fourth major class of vertebrate tissue is nerve tissue (table 43.4). Its cells include neurons and their supporting cells, called neuroglia. Neurons are specialized to produce and conduct electrochemical events, or impulses.

Neurons sometimes extend long distances

Most **neurons** consist of three parts: a cell body, dendrites, and an axon. The *cell body* of a neuron contains the nucleus. *Dendrites* are thin, highly branched extensions that receive incoming stimulation and conduct electrical impulses to the cell body. The *axon* is a single extension of cytoplasm that conducts impulses away from the cell body. Axons and dendrites can be quite long. For example, the cell bodies of neurons that control the muscles in your feet lie in the spinal cord, and their axons may extend over a meter to your feet.

Neuroglia provide support for neurons

Neuroglia do not conduct electrical impulses, but instead support and insulate neurons and eliminate foreign materials in and around neurons. In many neurons, neuroglia cells associate with the axons and form an insulating covering, a *myelin sheath*, produced by successive wrapping of the membrane around the axon. Gaps in the myelin sheath, known as *nodes of Ranvier*, serve as sites for accelerating an impulse (see chapter 44).

Two divisions of the nervous system coordinate activity

The nervous system is divided into the **central nervous system (CNS),** which includes the brain and spinal cord, and the **peripheral nervous system (PNS),** which includes *nerves* and *ganglia*. Nerves consist of axons in the PNS that are bundled together in much the same way as wires are bundled together in a cable. Ganglia are collections of neuron cell bodies. The CNS generally has the role of integration and interpretation of input, such as input from the senses; the PNS communicates signals to and from the CNS to the rest of the body, such as to muscle cells or endocrine glands.

Learning Outcomes Review 43.5

Nerve tissue is composed of neurons and neuroglia. Neurons are specialized to receive and conduct electrical signals; they generally have a cell body with a nucleus, dendrites that receive incoming signals, and axons that conduct impulses away from the cell body. Neuroglia have support functions, including providing insulation to axons. The central nervous system (CNS) and peripheral nervous system (PNS) both contain neurons and neuroglia.

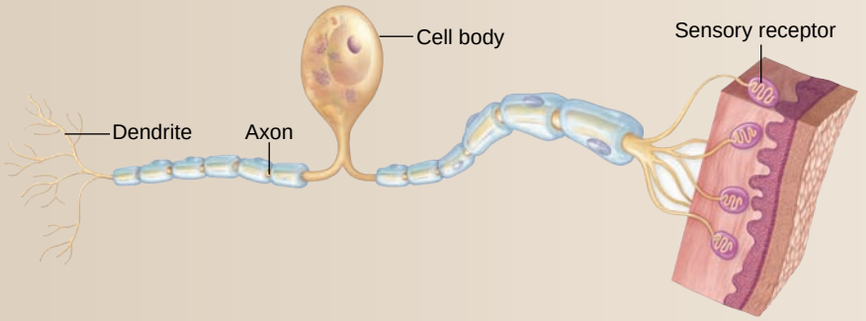
- *In chapter 4 you read that the surface-area-to-volume ratio limits cell size. How do neurons reach up to a meter in length in spite of this?*

43.6 *Overview of Vertebrate Organ Systems*

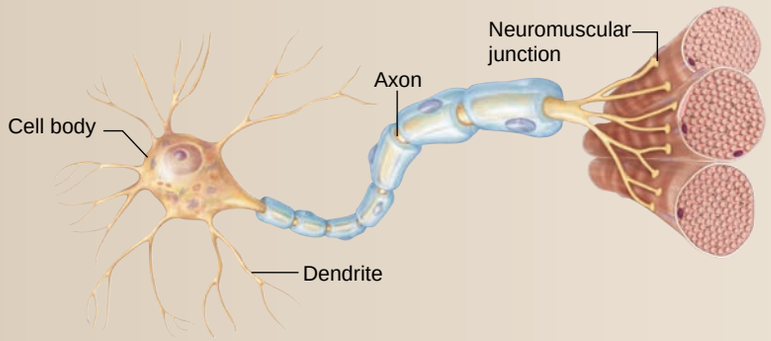
Learning Outcomes

1. *Identify the different organ systems in vertebrates.*
2. *Explain the functional organization of these systems.*

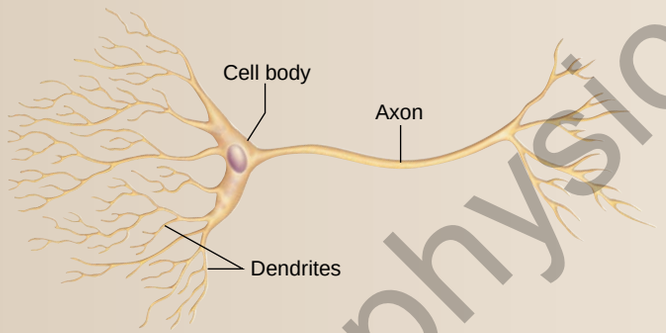
TABLE 43.4 Nerve Tissue



Sensory Neurons
Typical Location
Eyes; ears; surface of skin
Function
Receive information about the body's condition and external environment; send impulses from sensory receptors to central nervous system
Characteristic Cell Types
Rods and cones; muscle stretch receptors



Motor Neurons
Typical Location
Brain and spinal cord
Function
Stimulate muscles and glands; conduct impulses out of central nervous system toward muscles and glands
Characteristic Cell Types
Motor neurons



Interneurons
Typical Location
Brain and spinal cord
Function
Integrate information; conduct impulses between neurons within central nervous system
Characteristic Cell Types
Interneurons

In the chapters that follow, we look closely at the major organ systems of vertebrates (figure 43.6). In each chapter, you will be able to see the intimate relationship of structure and function. We approach the organ systems by placing them in the following functional groupings:

- Communication and integration
- Support and movement
- Regulation and maintenance
- Defense
- Reproduction and development

Communication and integration sense and respond to the environment

Two organ systems detect external and internal stimuli and coordinate the body's responses. The **nervous system,** which consists of the brain, spinal cord, nerves, and sensory organs, detects internal sensory feedback and external stimuli such as light, sound, and touch. This information is collected and integrated, and then the appropriate response is made.

The **sensory systems** are a subset of the nervous system we consider in a separate chapter. These include the organs and tissues that sense external stimuli, such as vision, hearing, smell, and so on.

Working in parallel with the nervous system, the **endocrine system** issues chemical signals that regulate and fine-tune the myriad chemical processes taking place in all other organ systems.

Skeletal support and movement are vital to all animals

The **musculoskeletal system** consists of two interrelated organ systems. Muscles are most obviously responsible for movement, but without something to pull on, a muscle is useless. The skeletal system is the rigid framework against which most muscles pull. Vertebrates have internal skeletons, but many other animals exhibit external skeletons (such as insects) or hydrostatic skeletons (earthworms). Together, these two organ systems enable animals to exhibit a wide array of finely controlled movements.

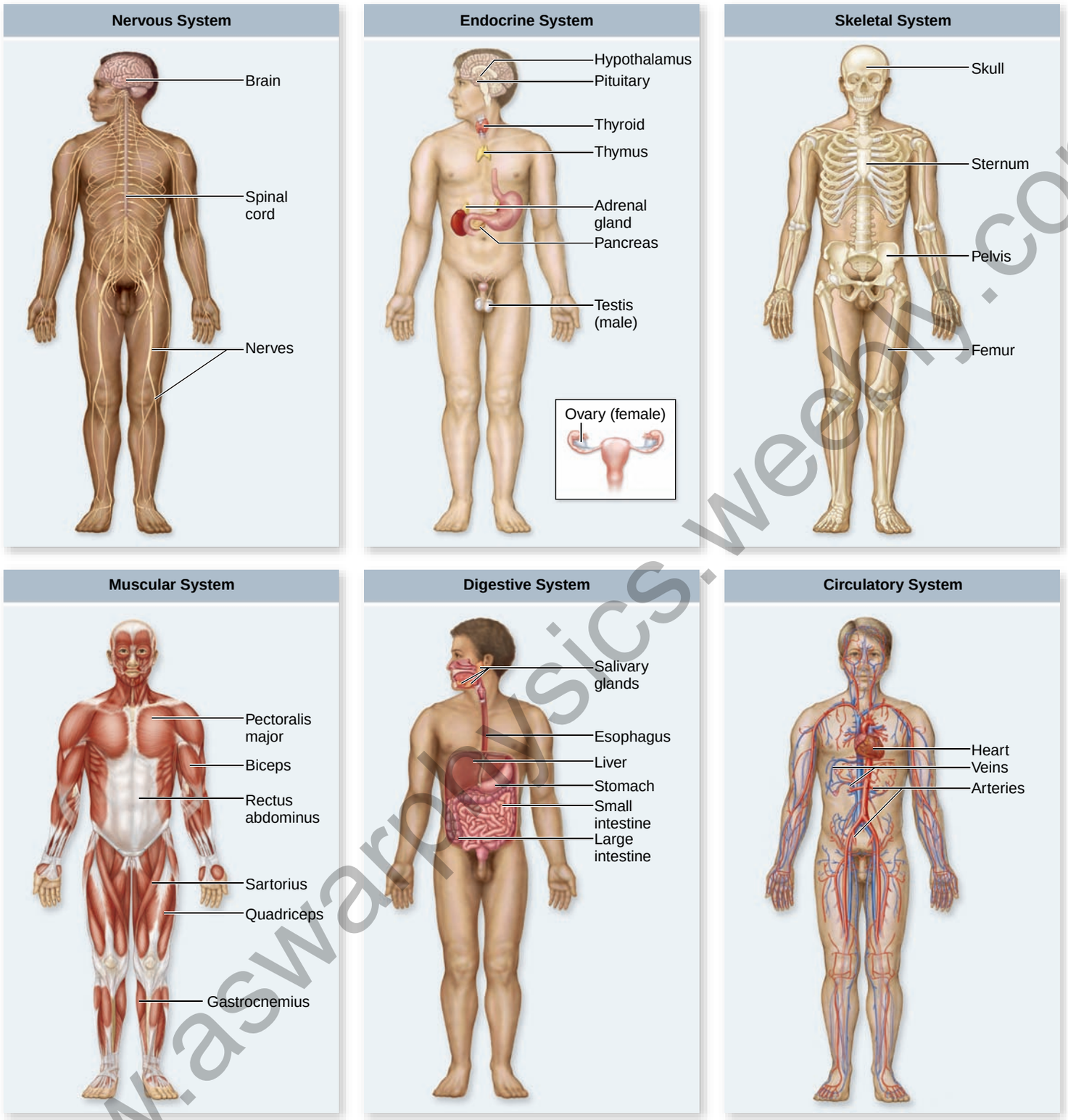
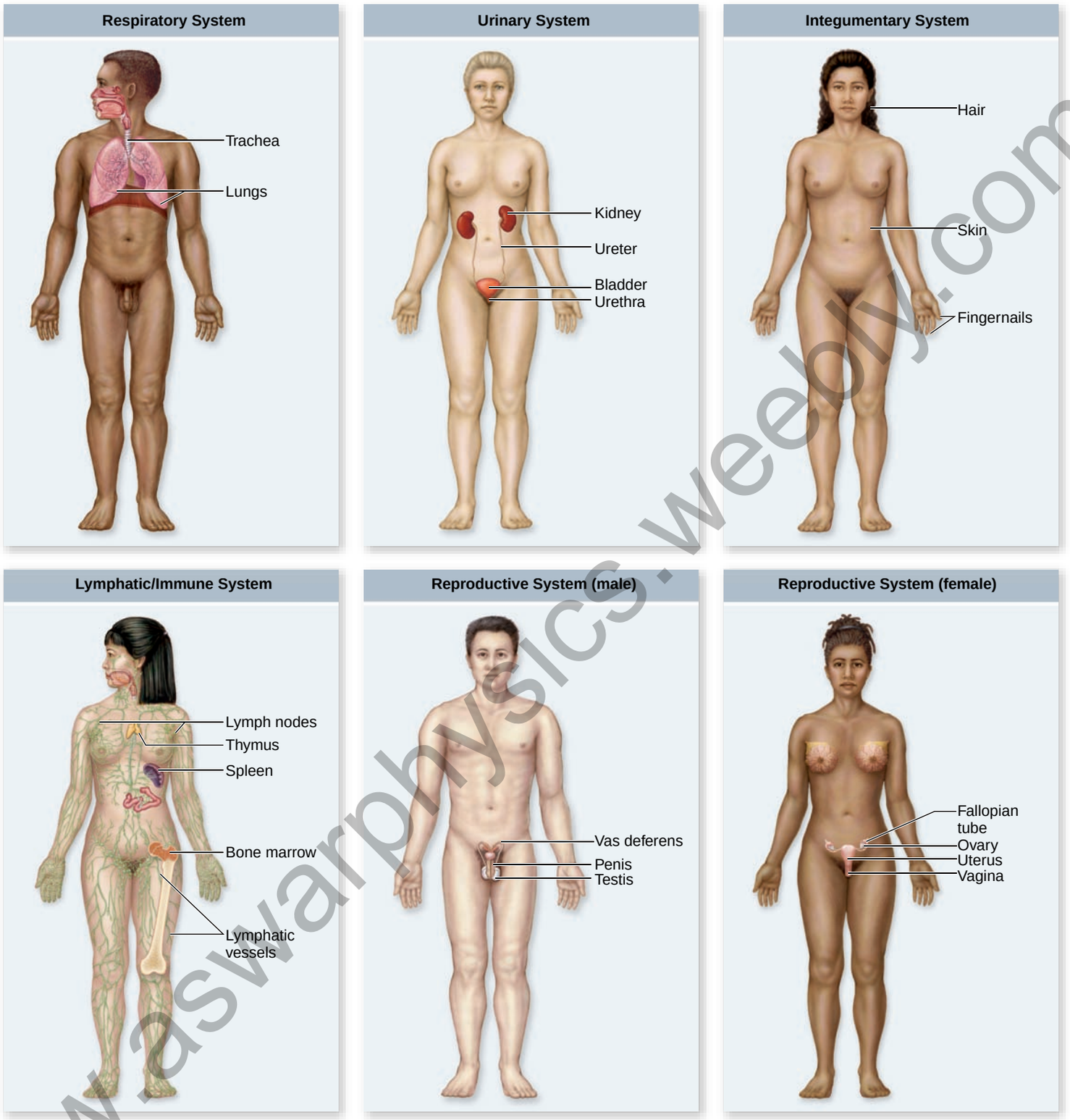


Figure 43.6 Vertebrate organ systems. Shown are the 11 principal organ systems of the human body, including both male and female reproductive systems.

Regulation and maintenance of the body's chemistry ensures continued life

The organ systems grouped under regulation and maintenance participate in nutrient acquisition, waste disposal, material distribution, and maintenance of the internal environment. The chapter on the **digestive system** describes how we eat, absorb nutrients, and eliminate solid wastes. The heart and vessels of the **circulatory system** pump and distribute blood, carrying nutrients and other substances throughout the body. The



body acquires oxygen and expels carbon dioxide via the **respiratory system.**

Finally, vertebrates tightly regulate the concentration of their body fluids. We explore these processes in the chapter on osmoregulation, which is largely carried out by the **urinary system.**

The body can defend itself from attackers and invaders

Every animal faces assault by bacteria, viruses, fungi, protists, and even other animals. The body's first line of defense

is the **integumentary system**—intact skin. Disease-causing agents that penetrate the first defense encounter a host of other protective **immune system** responses, including the production of antibodies and specialized cells that attack invading organisms.

Reproduction and development ensure continuity of species

The biological continuity of vertebrates is the province of the **reproductive system.** Male and female reproductive systems consist of organs where male and female gametes develop, as well as glands and tubes that nurture gametes and allow gametes of complementary sexes to come into contact with one another. The female reproductive system in many vertebrates also has systems for nurturing the developing embryo and fetus.

After gametes have fused to form a *zygote*, an elaborate process of cell division and development takes place to change this beginning diploid cell into a multicellular adult. This process is explored in the animal development chapter.

Learning Outcomes Review 43.6

Vertebrate organ systems include the nervous, endocrine, skeletal, muscular, digestive, circulatory, respiratory, urinary, integumentary, lymphatic/immune, and reproductive systems. These may be grouped functionally based on their roles in communication and integration, support and movement, regulation and maintenance, defense, and reproduction and development.

- ***Is there any overlap between the different organ systems?***

43.7 Homeostasis

Learning Outcomes

1. ***Explain homeostasis.***
2. ***Illustrate how negative feedback can limit a response.***
3. ***Illustrate how antagonistic effectors can maintain a system at a set point.***

As animals have evolved, specialization of body structures has increased. Each cell is a sophisticated machine, finely tuned to carry out a precise role within the body. Such specialization of cell function is possible only when extracellular conditions stay within narrow limits. Temperature, pH, the concentrations of glucose and oxygen, and many other factors must remain relatively constant for cells to function efficiently and interact properly with one another. The dynamic constancy of the internal environment is called *homeostasis.* The term *dynamic* is used because conditions are never constant, but fluctuate continuously within narrow limits. Homeostasis is essential for life, and most of the regulatory mechanisms of the vertebrate body are involved with maintaining homeostasis (figure 43.7).

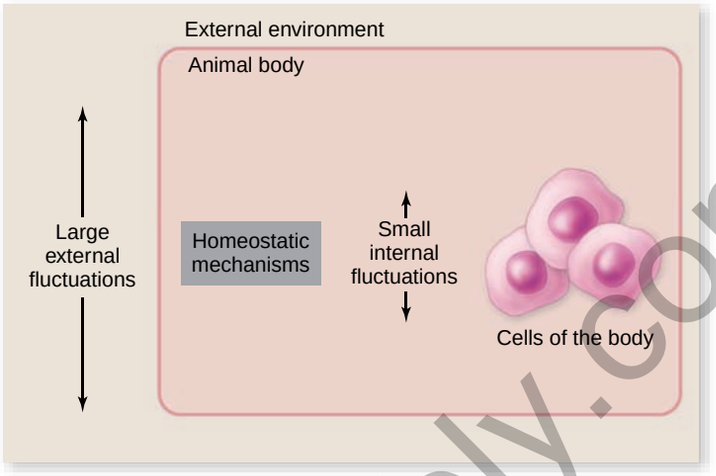


Figure 43.7 Homeostatic mechanisms help maintain stable internal conditions. Even though conditions outside of an animal's body may vary widely, the inside stays relatively constant due to many finely tuned control systems.

Negative feedback mechanisms keep values within a range

To maintain internal constancy, the vertebrate body uses a type of control system known as a **negative feedback.** In negative feedback, conditions within the body as well as outside it are detected by specialized sensors, which may be cells or membrane receptors. If conditions deviate too far from a set point, biochemical reactions are initiated to change conditions back toward the set point.

This *set point* is analogous to the temperature setting on a space heater. When room temperature drops, the change is detected by a temperature-sensing device inside the heater controls—the **sensor.** The thermostat on which you have indicated the set point for the heater contains a **comparator;** when the sensor information drops below the set point, the comparator closes an electrical circuit. The flow of electricity through the heater then produces more heat. Conversely, when the room temperature increases, the change causes the circuit to open, and heat is no longer produced. Figure 43.8 summarizes the negative feedback loop.

In a similar manner, the human body has set points for body temperature, blood glucose concentration, electrolyte (ion) concentration, the tension on a tendon, and so on. The integrating center is often a particular region of the brain or spinal cord, but in some cases, it can also be cells of endocrine glands. When a deviation in a condition occurs, a message is sent to increase or decrease the activity of particular target organs, termed *effectors.* Effectors are generally muscles or glands, and their actions can change the value of the condition in question back toward the set point value.

Mammals and birds are *endothermic;* they can maintain relatively constant body temperatures independent of the environmental temperature. In humans, when the blood temperature exceeds 37°C (98.6°F), neurons in a part of the brain called the **hypothalamus** detect the temperature change. Acting through the control of motor neurons, the hypothalamus responds by promoting the dissipation of heat through sweating, dilation of blood vessels in the skin, and other mechanisms. These responses tend to counteract the rise in body temperature.

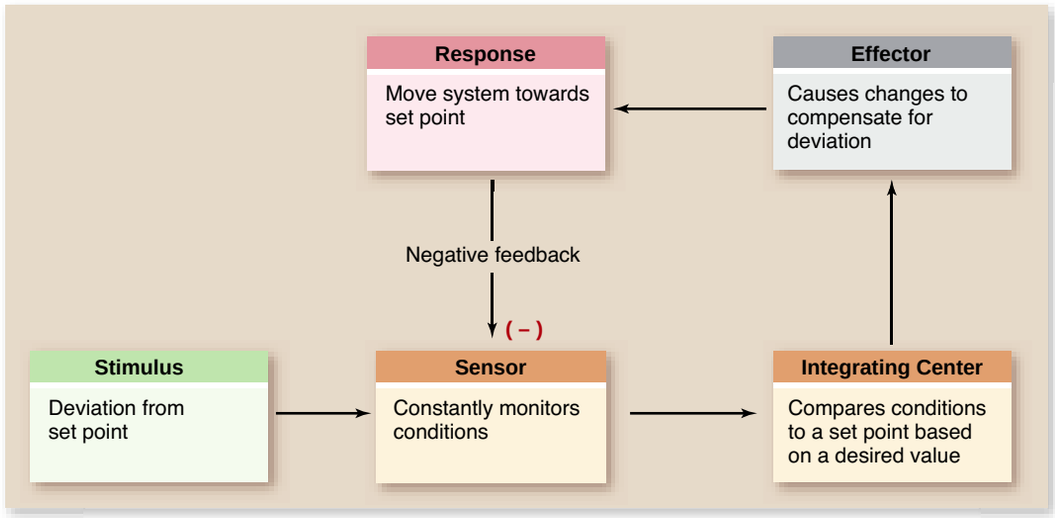


Figure 43.8 Generalized diagram of a negative feedback loop. Negative feedback loops maintain a state of homeostasis, or dynamic constancy of the internal environment. Changing conditions are detected by sensors, which feed information to an integrating center that compares conditions to a set point. Deviations from the set point lead to a response to bring internal conditions back to the set point. Negative feedback to the sensor terminates the response.

Antagonistic effectors act in opposite directions

The negative feedback mechanisms that maintain homeostasis often oppose each other to produce a finer degree of control. Most factors in the internal environment are controlled by several effectors, which often have antagonistic (opposing) actions. Control by antagonistic effectors is sometimes described as "push–pull," in which the increasing activity of one effector is accompanied by decreasing activity of an antagonistic effector. This affords a finer degree of control than could be achieved by simply switching one effector on and off.

To return to our earlier example, room temperature can be maintained by just turning the heater on and off, or turning an air conditioner on and off. A much more stable temperature is possible, however, if a thermostat controls both the air conditioner and heater. Then the heater turns on when the air conditioner shuts off, and vice versa (figure 43.9*a*).

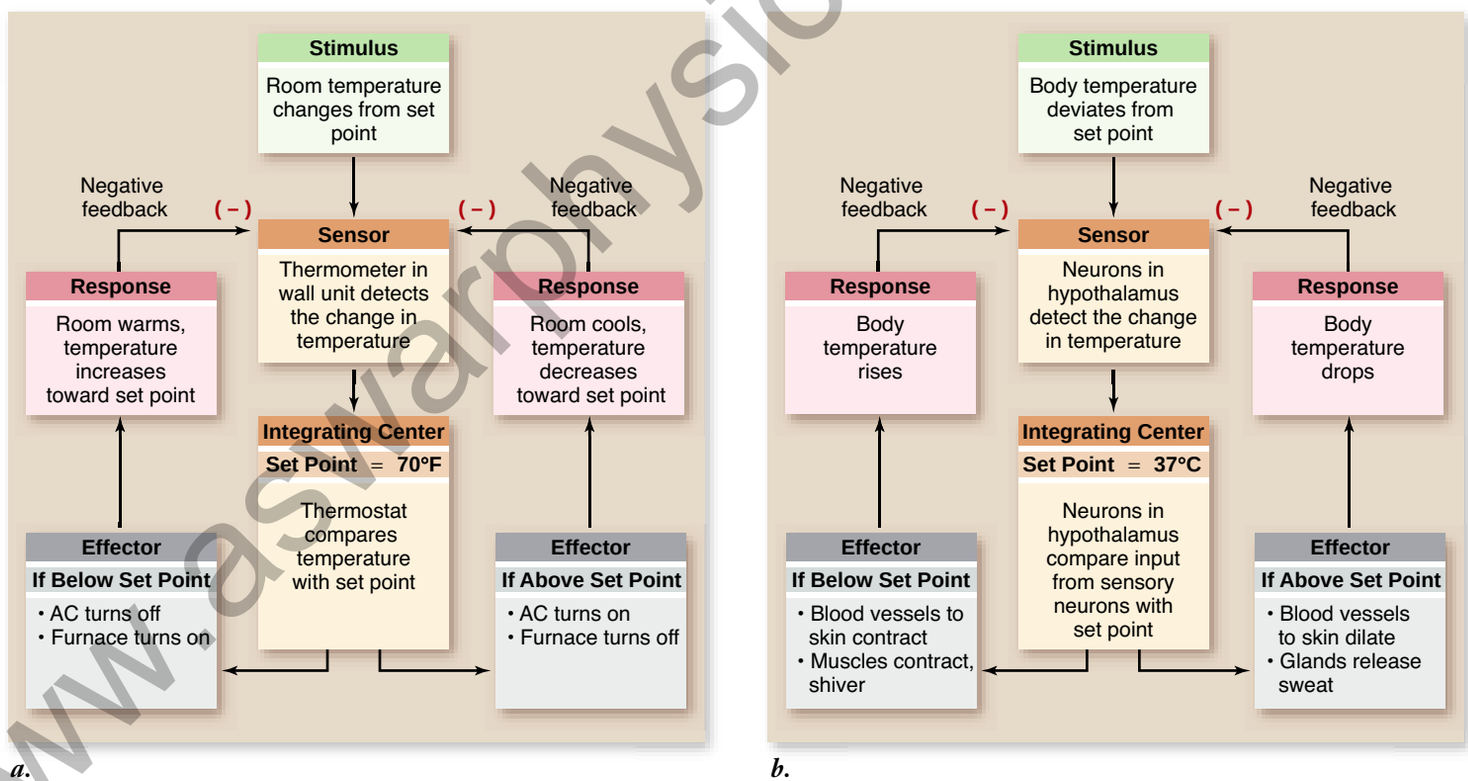


Figure 43.9 Room and body temperature are maintained by negative feedback and antagonistic effectors. ***a.*** If a thermostat senses a low temperature (as compared with a set point), the furnace turns on and the air conditioner turns off. If the temperature is too high, the air conditioner turns on and the furnace turns off. ***b.*** The hypothalamus of the brain detects an increase or decrease in body temperature. The comparator (also in the hypothalamus) then processes the information and activates effectors, such as surface blood vessels, sweat glands, and skeletal muscles. Negative feedback results in a reduction in the difference of the body's temperature compared with the set point. Consequently, the stimulation of the effectors by the comparator is also reduced.

Antagonistic effectors are similarly involved in the control of body temperature. When body temperature falls, the hypothalamus coordinates a different set of responses, such as constriction of blood vessels in the skin and initiation of shivering, muscle contractions that help produce heat. These responses raise body temperature and correct the initial challenge to homeostasis (figure 43.9*b*).

Positive feedback mechanisms enhance a change

In a few cases, the body uses *positive feedback* mechanisms, which push or accentuate a change further in the same direction. In a positive feedback loop, the effector drives the value of the controlled variable even farther from the set point. As a result, systems in which there is positive feedback are highly unstable, analogous to a spark that ignites an explosion. They do not help to maintain homeostasis.

Nevertheless, such systems are important components of some physiological mechanisms. For example, positive feedback occurs in blood clotting, in which one clotting factor activates another in a cascade that leads quickly to the formation of a clot. Positive feedback also plays a role in the contractions of the uterus during childbirth (figure 43.10). In this case, stretching of the uterus by the fetus stimulates contraction, and contraction causes further stretching; the cycle continues until the uterus expels the fetus.

In the body, most positive feedback systems act as part of some larger mechanism that maintains homeostasis. In the examples we have described, formation of a blood clot stops bleeding and therefore tends to keep blood volume constant, and expulsion of the fetus reduces the contractions of the uterus, stopping the cycle.

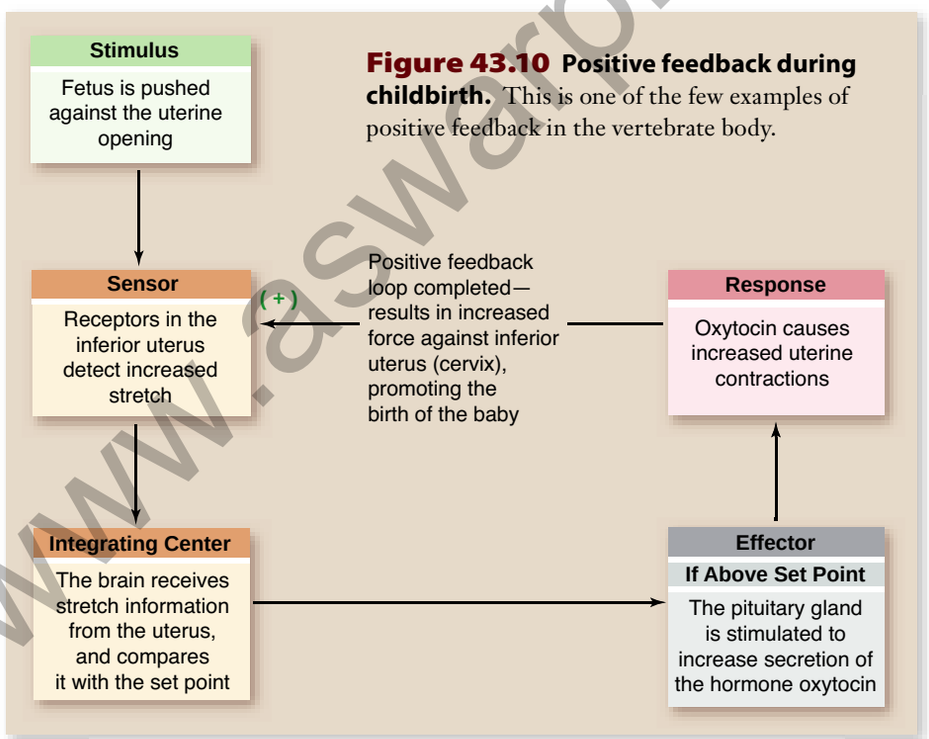


Figure 43.10 Positive feedback during childbirth. This is one of the few examples of positive feedback in the vertebrate body.

Learning Outcomes Review 43.7

Homeostasis can be thought of as the dynamic constancy of an organism's internal environment. Negative feedback mechanisms correct deviations from a set point for different internal variables, such as temperature, pH, and many others, helping to keep body conditions within a normal range. Effectors that act antagonistically to each other are more effective than effectors that act alone. Positive feedback mechanisms that accentuate changes are less common and have specialized functions, such as blood clotting and giving birth.

- ***Do antagonistic effectors and negative feedback function together?***

43.8 Regulating Body Temperature

Learning Outcomes

1. ***Explain Q_{10} and its significance.***
2. ***Define how organisms can be categorized with respect to temperature regulation.***
3. ***Describe mechanisms for temperature homeostasis.***

Temperature is one of the most important aspects of the environment that all organisms must contend with. This provides a good example to apply the principles of homeostatic regulation from the last section. As we will see, some organisms have a body temperature that conforms to the environment and others regulate their body temperature. First, let's consider why temperature is so important.

Q_{10} is a measure of temperature sensitivity

The rate of any chemical reaction is affected by temperature: The rate increases with increasing temperature, and it decreases with decreasing temperature. Reactions catalyzed by enzymes show the same kinetic effects, but the enzyme itself is also affected by temperature.

We can make this temperature dependence quantitative by examining the rate of a reaction at two different temperatures. The ratio between the rates of a reaction at two temperatures that differ by 10°C is called the **Q_{10}** for the enzyme:

$$Q_{10} = R_{T+10}/R_T$$

For most enzymes the Q_{10} value is around 2, which means for every 10°C increase in temperature, the rate of the reaction doubles. Obviously, this cannot continue forever since at high temperatures the enzyme's structure is affected and it can no longer be active.

The Q_{10} concept can also be applied to overall metabolism. The equation remains the same, but instead of the rate of a single reaction, the overall metabolic rate is used. When this has been measured, most organisms have a Q_{10} for metabolic rate around 2 to 3. This observation implies that the effect of temperature is mainly on the enzymes that make up metabolism.

In rare cases—for example, in some intertidal invertebrates—the Q_{10} is close to 1. Notice that this value means no change in metabolic rate with temperature. In the case of these intertidal invertebrates, they are exposed to large temperature fluctuations as they are alternately flooded with relatively cold water and exposed to direct sunlight and much higher air temperatures. These organisms have adapted to deal with these large temperature swings, probably through the evolution of different enzymes in a single metabolic pathway that have large differences in optimal temperature. This allows one enzyme to "make up" for others with decreased activity at a particular temperature.

Temperature is determined by internal and external factors

Body temperature appears simple, yet a large number of variables influence it. These variables include both internal and external factors, as well as behavior. As you may recall from chapter 6, the second law of thermodynamics indicates that no energy transaction is 100% efficient. Thus the reactions that make up metabolism are constantly producing heat as a result of this inefficiency. This heat must either be dissipated or can be used to raise body temperature.

Overall metabolic rate and body temperature are interrelated. Lower body temperatures do not allow high metabolic rates because of the temperature dependence of enzymes discussed earlier. Conversely, high metabolic rates may cause unacceptable heating of the body, requiring cooling.

Organisms therefore must deal with external and internal factors that relate body heat, metabolism, and the environment. The simplest model for temperature, more accurately body heat, is:

body heat = heat produced + (heat gained – heat lost)

we can simplify this further to:

body heat = heat produced + heat transferred

Notice that the heat transferred can be either positive or negative, that is, it can be used for both heating and cooling.

We recognize four mechanisms of heat transfer that are relevant to biological systems: radiation, conduction, convection, and evaporation (figure 43.11).

- **Radiation.** The transfer of heat by electromagnetic radiation, such as from the Sun, does not require direct contact. Heat is transferred from hotter bodies to colder bodies by radiation.

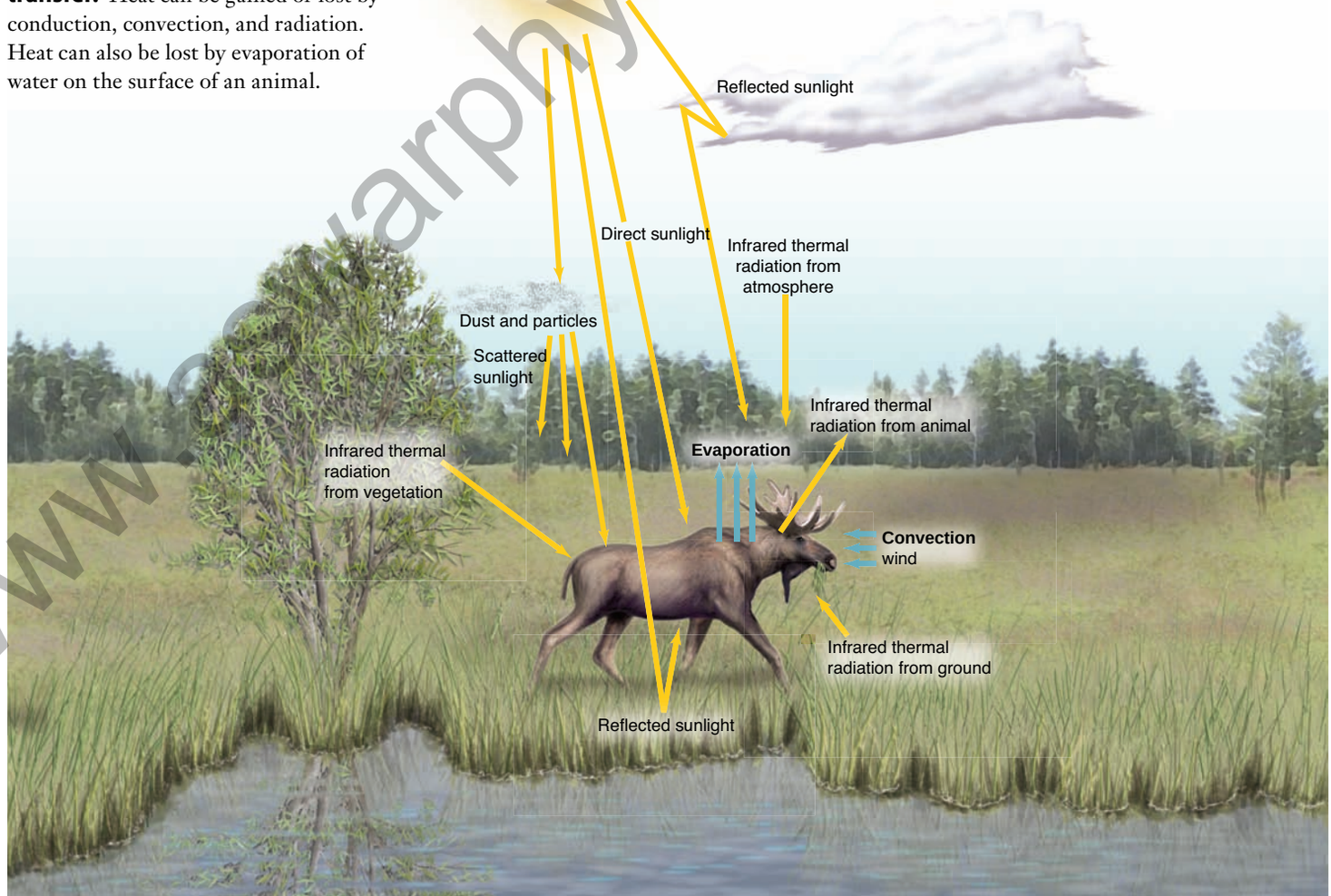


Figure 43.11 Methods of heat transfer. Heat can be gained or lost by conduction, convection, and radiation. Heat can also be lost by evaporation of water on the surface of an animal.

- **Conduction.** The direct transfer of heat between two objects is called conduction. It is literally a direct transfer of kinetic energy between the molecules of the two objects in contact. Energy is transferred from hotter objects to colder ones.
- **Convection.** Convection is the transfer of heat brought about by the movement of a gas or liquid. This movement may be externally caused (wind) or may be due to density differences related to heating and cooling—for example, heated air is less dense and rises; the same is true for water.
- **Evaporation.** All substances have a heat of vaporization, that is, the amount of energy needed to change them from a liquid to a gas phase. Water, as you saw in chapter 2, has a high heat of vaporization, and many animals use this attribute of water as a source of cooling.

Other factors

The overall rate of heat transfer by the methods just listed depends on a number of factors that influence these physical processes. These factors include surface area, temperature difference, and specific heat conduction. Taking these in order, the larger the surface area relative to overall mass, the greater the conduction of heat. Thus, small organisms have a relatively larger surface area for their mass, and they gain or lose heat more readily to the surroundings. This can be affected to a small extent by changing posture, and by extending or pulling in the limbs.

Temperature difference is also important; the greater the difference between ambient temperature and body temperature, the greater the heat transfer. The closer an animal's temperature is to the ambient temperature, the less heat is gained or lost.

Finally, an animal with high heat conductance tends to have a body temperature close to the ambient temperature. For animals that regulate temperature, surrounding the body with a substance with lower heat conductance has an advantage: It acts as insulation. Insulating substances includes such features as feathers, fur, and blubber. For animals that regulate body temperature through behavior, a high heat conductance can maximize heat transfer.

Organisms are classified based on heat source

For many years, physiologists classified animals according to whether they maintained a constant body temperature, or their body temperature fluctuated with environment. Animals that regulated their body temperature about a set point were called *homeotherms*, and those that allow their body temperature to conform to the environment were called *poikilotherms*.

Because homeotherms tended to maintain their body temperature above the ambient temperature, they were also colloquially called "warm-blooded"; poikilotherms were termed "cold-blooded." The problem with this terminology is that a poikilotherm in an environment with a stable temperature (for example, many deep-sea fish species) has a more constant body temperature than some homeotherms.

These limitations to the dichotomy based on temperature regulation led to another view based on how body heat is generated. Animals that use metabolism to generate body heat and maintain their temperatures above the ambient temperature are called *endotherms*. Animals with a relatively low metabolic rate that do not use metabolism to produce heat and have a body temperature that conforms to the ambient temperature are called *ectotherms*. Endotherms tend to have a lower thermal conductivity due to insulating mechanisms, and ectotherms tend to have high thermal conductivity and lack insulation.

These two terms represent ideal end points of a spectrum of physiology and adaptations. Many animals fall in between these extremes and can be considered *heterotherms*. It is a matter of judgment how a particular animal is classified if it exhibits characteristics of each group.

Ectotherms regulate temperature using behavior

Despite having low metabolic rates, ectotherms can regulate their temperature using behavior. Most invertebrates use behavior to adjust their temperature. Many butterflies, for example, must reach a certain body temperature before they can fly. In the cool of the morning, they orient their bodies so as to maximize their absorption of sunlight. Moths and many other insects use a shivering reflex to warm their thoracic flight muscles so that they may take flight (figure 43.12).

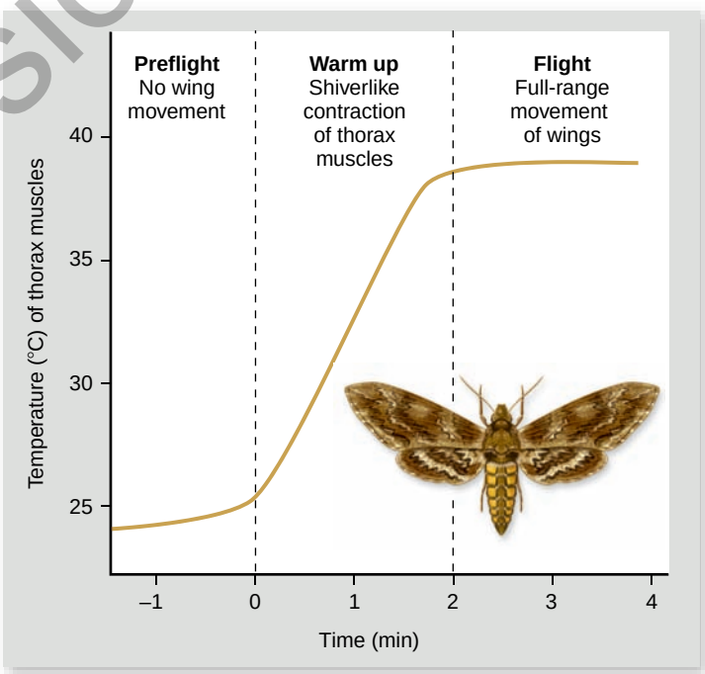


Figure 43.12 Thermoregulation in insects. Some insects, such as the sphinx moth, contract their thoracic muscles to warm up for flight.

Inquiry question

Why does muscle temperature stop warming after 2 min?

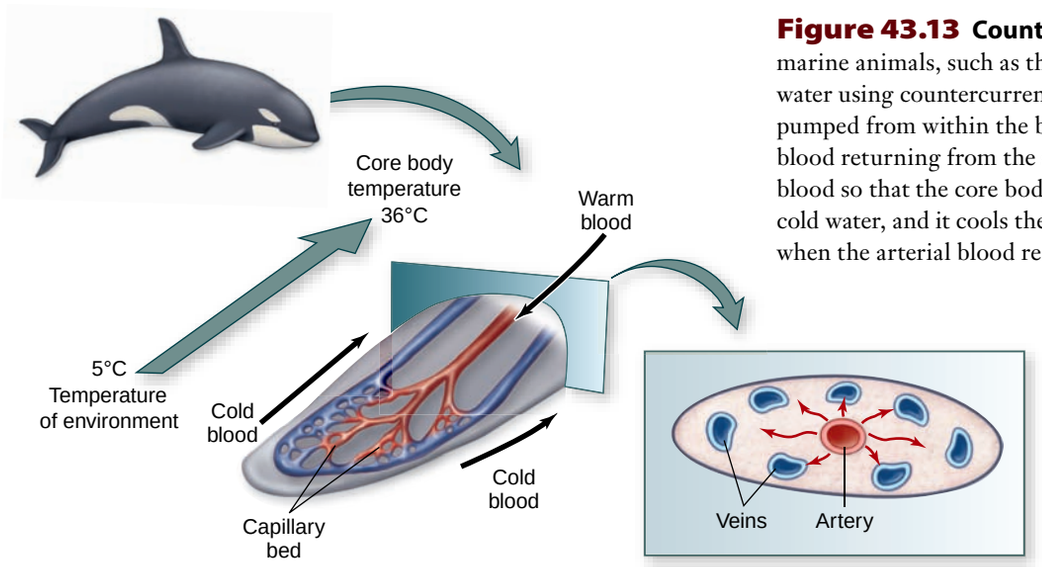


Figure 43.13 Countercurrent heat exchange. Many marine animals, such as this killer whale, limit heat loss in cold water using countercurrent heat exchange. The warm blood pumped from within the body in arteries loses heat to the cooler blood returning from the skin in veins. This warms the venous blood so that the core body temperature can remain constant in cold water, and it cools the arterial blood so that less heat is lost when the arterial blood reaches the tip of the extremity.

Vertebrates other than mammals and birds are also ectothermic, and their body temperatures are more or less dependent on the environmental temperature. This does not mean that these animals cannot maintain high and relatively constant body temperatures, but they must use behavior to do this. Many ectothermic vertebrates are able to maintain temperature homeostasis, that is, are homeothermic ectotherms.

For example, certain large fish, including tuna, swordfish, and some sharks, can maintain parts of their body at a significantly higher temperature than that of the water. They do so using *countercurrent heat exchange*. This circulatory adaptation allows the cooler blood in the veins to be warmed through radiation of heat from the warmer blood in the arteries located close to the veins. The arteries carry warmer blood from the center of the body (figure 43.13).

Reptiles attempt to maintain a constant body temperature through behavioral means—by placing themselves in varying locations of sunlight and shade. That's why you frequently see lizards basking in the sun. Some reptiles can maximize the effect of behavioral regulation by also controlling blood flow. The marine iguana can increase and decrease its heart rate and control the extent of dilation or contraction of blood vessels to regulate the amount of blood available for heat transfer by conduction. Increased heart rate and vasodilation allows them to maximize heating when on land, whereas decreased heart rate and vasoconstriction minimize cooling when diving for food.

In general, ectotherms have low metabolic rates, which has the advantage of correspondingly low intake of energy (food). It is estimated that a lizard (ectotherm) needs only 10% of the energy intake of a mouse (endotherm) of comparable size. The tradeoff is that ectotherms are not capable of sustained high-energy activity.

Endotherms create internal metabolic heat for conservation or dissipation

For endotherms, the generation of internal heat via high metabolic rate can be used to warm the organism if it is cold, but also represents a source of heat that must be dissipated at higher temperatures.

The simplest response that affects heat transfer is to control the amount of blood flow to the surface of the animal. Dilating blood vessels increases the amount of blood flowing to the surface, which in turn increases thermal heat exchange and dissipation of heat. In contrast, constriction of blood vessels decreases the amount of blood flowing to the surface and decreases thermal heat exchange, limiting the amount of heat lost due to conduction.

When ambient temperatures rise, many endotherms take advantage of evaporative cooling in the form of sweating or panting. Sweating is found in some mammals, including humans, and involves the active extrusion of water from sweat glands onto the surface of the body. As the water evaporates, it cools the skin, and this cooling can be transferred internally by capillaries near the surface of the skin. Panting is a similar adaptation used by some mammals and birds that takes advantage of respiratory surfaces for evaporative cooling. For evaporative cooling to be effective, the animal must be able to tolerate the loss of water.

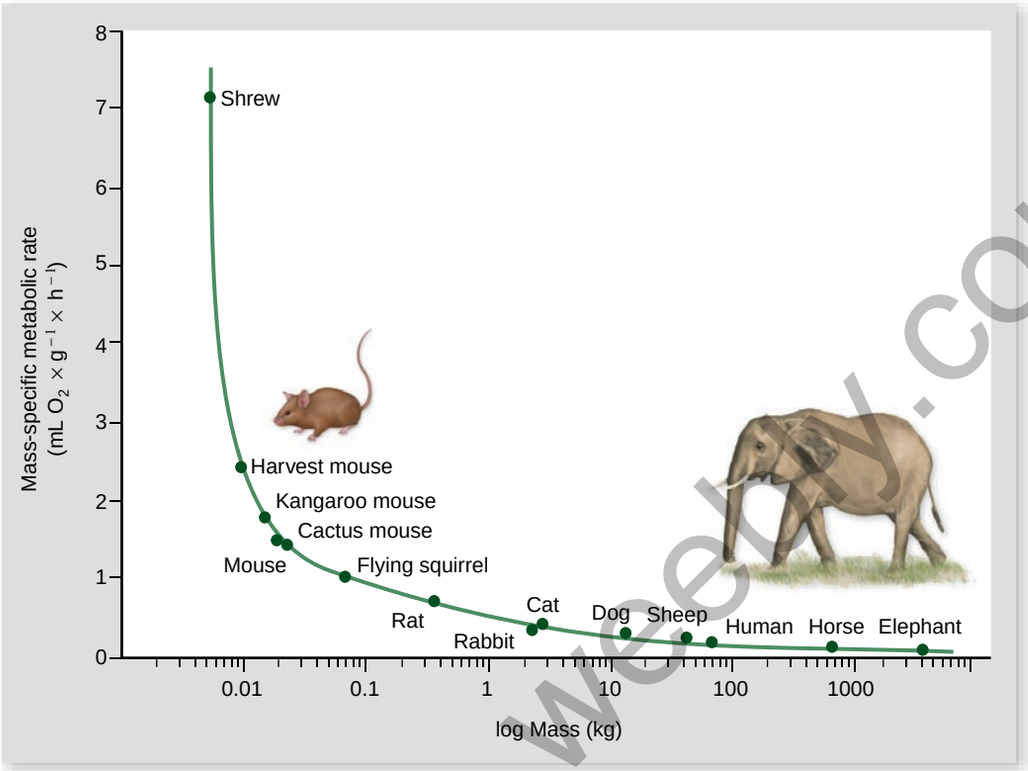
The advantage of endothermy is that it allows sustained high-energy activity. The tradeoff for endotherms is that the high metabolic rate has a corresponding cost in requiring relatively constant and high rates of energy intake (food).

Body size and insulation

Size is one important characteristic affecting animal physiology. Changes in body mass have a large effect on metabolic rate. Smaller animals consume much more energy per unit body mass than larger animals. This relationship is summarized in the "mouse to elephant" curve that shows the nonproportionality of metabolic rate versus size of mammals (figure 43.14).

For small animals with a high metabolic rate, surface area is also large relative to their volume. In a cold environment, this can be disastrous as they cannot produce enough internal heat to balance conductive loss through their large surface area.

Figure 43.14 Relationship between body mass and metabolic rate in mammals.
Smaller animals have a much higher metabolic rate per unit body mass relative to larger animals. In the figure, mass-specific metabolic rate (expressed as O_2 consumption per unit mass) is plotted against body mass. Note that the body mass axis is a logarithmic scale.



Inquiry question

What does this graph predict about the different challenges faced by smaller versus larger mammals in hot and cold environments?

Thus, small endotherms in cold environments require significant insulation to maintain their body temperature. The amount of insulation can also vary seasonally and geographically with thicker coats in the north and in winter.

Conversely, large animals in hot environments have the opposite problem: Although their metabolic rate is relatively low, they still produce a large amount of heat with much less relative surface area to dissipate this heat by conduction. Thus large endotherms in hot environments usually have little insulation and will use behavior to lose heat, such as elephants flapping their ears to increase convective heat loss.

Thermogenesis

When temperatures fall below a critical lower threshold, normal endothermic responses are not sufficient to warm an animal. In this case, the animal resorts to **thermogenesis,** or the use of normal energy metabolism to produce heat. Thermogenesis takes two forms: shivering and nonshivering thermogenesis.

In nonshivering thermogenesis, fat metabolism is altered to produce heat instead of ATP. Nonshivering thermogenesis takes place throughout the body, but in some mammals, special stores of fat called brown fat are utilized specifically for this purpose. This brown fat is stored in small deposits in the neck and between the shoulders. This fat is highly vascularized, allowing efficient transfer of heat away from the site of production.

Shivering thermogenesis uses muscles to generate heat without producing useful work. It occurs in some insects, such as the earlier example of a butterfly warming its flight muscles, and in endothermic vertebrates. Shivering involves the use of antagonistic muscles to produce little net generation of movement, but hydrolysis of ATP, generating heat.

Mammalian thermoregulation is controlled by the hypothalamus

Mammals that maintain a relatively constant core temperature need an overall control system (summarized in figure 43.15). The system functions much like the heating/cooling system in your house that has a thermostat connected to a furnace to produce heat and an air conditioner to remove heat. Such a system maintains the temperature of your house about a set point by alternately heating or cooling as necessary.

When the temperature of your blood exceeds 37°C (98.6°F), neurons in the hypothalamus detect the temperature change (see chapters 44 and 45). This leads to stimulation of the *heat-losing center* in the hypothalamus. Nerves from this area cause a dilation of peripheral blood vessels, bringing more blood to the surface to dissipate heat. Other nerves stimulate the production of sweat, leading to evaporative cooling. Production of hormones that stimulate metabolism is also inhibited.

When your temperature falls below 37°C, an antagonistic set of effects are produced by the hypothalamus. This is under control of the *heat-promoting center*, which has nerves that constrict blood vessels to reduce heat transfer, and inhibit sweating to prevent evaporative cooling. The adrenal medulla is stimulated to produce epinephrine, and the anterior pituitary to produce TSH, both of which stimulate metabolism. In the case of TSH, this is indirect as it stimulates the thyroid to produce thyroxin, which stimulates metabolism (see chapter 46). A

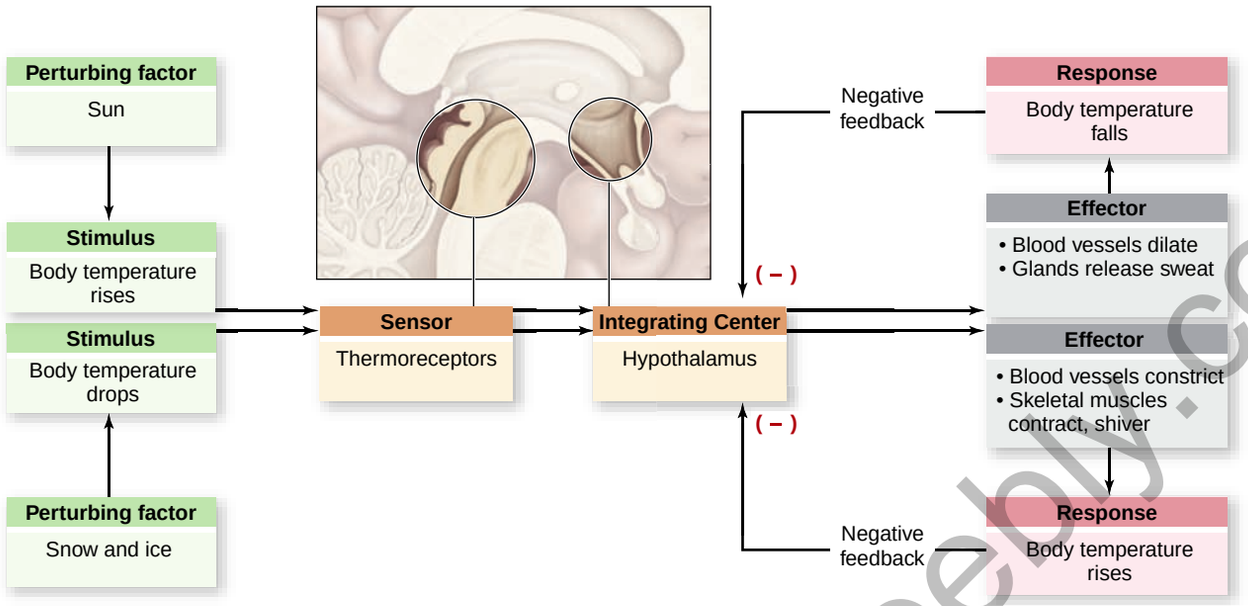


Figure 43.15 The control of body temperature by the hypothalamus. Central thermoreceptors in the brain and interior of the abdomen sense changes in core temperature. These thermoreceptors synapse with neurons on the hypothalamus, which acts as an integrating center. The hypothalamus then controls effectors such as blood vessels and sweat glands via sympathetic nerves. The hypothalamus also causes the release of hormones that stimulate the thyroid to produce thyroxin, which modulates metabolism.

combination of epinephrine and autonomic nerve stimulation of fat tissue can induce thermogenesis to produce more internal heat. Again, as temperature rises, negative feedback to the hypothalamus reduces the heat-producing response.

Fever

Substances that cause a rise in temperature are called **pyrogens,** and they produce the state we call **fever.** Fever is a result of resetting the body's normal set point to a higher temperature. A number of gram-negative bacteria have components in their cell walls called endotoxins that act as pyrogens. Substances produced by circulating white blood cells act as pyrogens as well. Pyrogens act on the hypothalamus to increase the set point.

The adaptive value of fever seems to be that increased temperature can inhibit the growth of bacteria. Evidence for this comes from the observation that some ectotherms respond to pyrogens as well. When desert iguanas were injected with pyrogen-producing bacteria, they spent more time in the sun, producing an elevated temperature: They induced fever behaviorally!

These observations have led to a reevaluation of fever as a state that should be treated medically. Fever is a normal response to infection, and treatment to reduce fever may be working against this natural defense system. Extremely high fevers, however, can be dangerous, inducing symptoms ranging from seizures to delirium.

Torpor

Endotherms can also reduce both metabolic rate and body temperature to produce a state of dormancy called *torpor.* Torpor allows an animal to reduce the need for food intake by reducing metabolism. Some birds, such as the hummingbird, allow their body temperature to drop as much as 25°C at night. This strategy is found in smaller endotherms; larger mammals have too large a mass to allow rapid cooling.

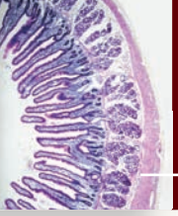
Hibernation is an extreme state in which deep torpor lasts for several weeks or even several months. In this case, the animal's temperature may drop as much as 20°C below its normal set point for an extended period of time. The animals that practice hibernation seem to be in the midrange of size; smaller endotherms quickly consume more energy than they can easily store, even by reducing their metabolic rate.

Very large mammals do not appear to hibernate. It was long thought that bears hibernate, but in reality their temperature is reduced only a few degrees. They instead undergo a prolonged winter sleep. With their large thermal mass and low rate of heat loss, they do not seem to require the additional energy savings of hibernation.

Learning Outcomes Review 43.8

The Q_{10} value of an enzyme indicates how its activity changes with a 10°C rise in temperature. The Q_{10} can also be applied to an organism's overall metabolism. Body heat is equal to heat produced plus heat transferred. Heat is transferred by conduction, convection, radiation, and evaporation. Organisms that generate heat and can maintain a temperature above ambient levels are called endotherms. Organisms that conform to their surroundings are called ectotherms. Both types can regulate temperature, but ectotherms mainly do so with behavior. Mammals maintain a consistent body temperature through regulation of metabolic rate by the hypothalamus. Two negative feedback loops act to raise or lower temperature as needed.

- ***Why are the terms "cold-blooded" and "warm-blooded" outmoded and inaccurate?***



Chapter Review

43.1 Organization of the Vertebrate Body (see figure 43.1)

Tissues are groups of cells of a single type and function.

Adult vertebrate primary tissues are epithelial, connective, muscle, and nerve tissues.

Organs and organ systems provide specialized function.

Organs consist of a group of different tissues that form a structural and functional unit. An organ system is a group of organs that collectively perform a function.

The general body plan of vertebrates is a tube within a tube, with internal support (see figure 43.2).

The tube of the digestive tract is surrounded by the skeleton and accessory organs and is enclosed in the integument.

Vertebrates have both dorsal and ventral body cavities.

The dorsal body cavity lies within the skull and vertebrae. The ventral body cavity, bounded by the rib cage and abdominal muscles, comprises the thoracic cavity and the abdominopelvic cavity.

The coelomic space of the abdominopelvic cavity is the peritoneal cavity; that surrounding the heart is the pericardial cavity; and those around the lungs are the pleural cavities.

43.2 Epithelial Tissue

Epithelium forms a barrier.

Epithelial cells are tightly bound together, forming a selective barrier. Epithelial cells are replaced constantly and can regenerate in wound healing. Epithelium has a basal surface attached to underlying connective tissues, and a free apical surface.

Epithelial types reflect their function.

Epithelium is divided into two general classes: simple (one cell layer) and stratified (multiple cells thick). These are further divided into squamous, cuboidal, and columnar based on the shape of cells (see table 43.1). Vertebrate glands form from invaginated epithelia.

43.3 Connective Tissue

Connective tissue proper may be either loose or dense.

Connective tissues contain various cells in an extracellular matrix of proteins and ground substance. Connective tissue proper is divided into loose connective tissue and dense connective tissue.

Special connective tissues have unique characteristics.

Special connective tissues, such as cartilage, rigid bone, and blood, have unique cells and matrices (see table 43.2). Cartilage is formed by chondrocytes and bone by osteocytes.

All connective tissues have similarities.

All connective tissues originate from mesoderm and contain a variety of cells within an extracellular matrix.

43.4 Muscle Tissue (see table 43.3)

Smooth muscle is found in most organs.

Involuntary smooth muscle occurs in the viscera and is composed of long, spindle-shaped cells with a single nucleus.

Skeletal muscle moves the body.

Voluntary skeletal or striated muscle is usually attached by tendons to bones, and the cells (fibers) have multiple nuclei and contain contractile myofibrils.

The heart is composed of cardiac muscle.

Cardiac muscle consists of striated muscle cells connected to each other by gap junctions that allow coordination.

43.5 Nerve Tissue (see table 43.4)

Neurons sometimes extend long distances.

Neurons have a cell body with a nucleus; dendrites, which receive impulses; and an axon, which transmits impulses away.

Neuroglia provide support for neurons.

Neuroglia help regulate the neuronal environment. Some types form the myelin sheaths that surround some axons.

Two divisions of the nervous system coordinate activity.

The central nervous system is the brain and spinal cord, and the peripheral nervous system contains nerves and ganglia.

43.6 Overview of Vertebrate Organ Systems (see figure 43.6)

Communication and integration sense and respond to the environment.

The three organ systems involved in communication and integration are the nervous, sensory, and endocrine systems.

Skeletal support and movement are vital to all animals.

The musculoskeletal system consists of muscles and the skeleton they act upon.

Regulation and maintenance of the body's chemistry ensures continued life.

The digestive, circulatory, respiratory, and urinary systems accomplish ingestion of nutrients and elimination of wastes.

The body can defend itself from attackers and invaders.

The integumentary system forms a barrier against attack; the immune system mounts a counterattack to foreign pathogens.

Reproduction and development ensure continuity of species.

All vertebrate species are capable of sexual reproduction.

43.7 Homeostasis

Homeostasis refers to the dynamic constancy of the internal environment and is essential for life.

Negative feedback mechanisms keep values within a range.

Negative feedback loops include a sensor, an integration center, and effectors that respond to deviations from a set point.

Antagonistic effectors act in opposite directions.

Negative feedback mechanisms often occur in antagonistic pairs that push and pull against each other.

Positive feedback mechanisms enhance a change.

In a positive feedback loop changes in one direction bring about further changes in the same direction.

43.8 Regulating Body Temperature

Q_{10} is a measure of temperature sensitivity.

Q_{10} is the ratio of reaction rates at two temperatures 10°C apart. For chemical reactions Q_{10} is about 2. Most organisms have a Q_{10} around 2 to 3, indicating temperature affects mainly enzymatic reactions.

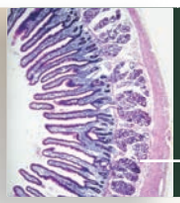
Temperature is determined by internal and external factors.
Internal factors include metabolic rate; external factors affect heat transfer. Heat is transferred through radiation, conduction, convection, and evaporation (see figure 43.11).

Organisms are classified based on heat source.
Endotherms have high metabolic rates and generate heat internally. Ectotherms have low metabolic rates and conform to ambient temperature.

Ectotherms regulate temperature using behavior.
Ectotherms move around in an environment to alter their temperature (see figures 43.12 and 43.13).

Endotherms create internal metabolic heat for conservation or dissipation.
Endotherms regulate temperature by changes in metabolic rate, blood flow, and sweating or panting. Thermogenesis occurs when temperature falls below a critical level.

Mammalian thermoregulation is controlled by the hypothalamus (see figure 43.15).
The hypothalamus acts through a heat-losing and heat-promoting center to keep the blood temperature near a set point. Fever is an increase in body temperature; torpor is a lowered metabolic state associated with dormancy.



Review Questions

UNDERSTAND

1. Which of the following cavities would contain your stomach?
   a. Peritoneal
   b. Pericardial
   c. Pleural
   d. Thoracic
2. Epithelial tissues do all of the following except
   a. form barriers or boundaries.
   b. absorb nutrients in the digestive tract.
   c. transmit information in the central nervous system.
   d. allow exchange of gases in the lung.
3. Ectotherms
   a. cannot regulate their body temperatures.
   b. regulate their internal temperature using metabolic energy.
   c. can regulate temperature using behavior.
   d. regulate temperature by dissipating but not generating heat.
4. Connective tissues include a diverse group of cells, yet they all share
   a. cuboidal shape.
   b. the ability to produce hormones.
   c. the ability to contract.
   d. the presence of an extracellular matrix.
5. Skeletal muscle cells differ from the "typical" mammalian cell in that they
   a. contain multiple nuclei.
   b. have mitochondria.
   c. have no plasma membrane.
   d. are not derived from embryonic tissue.
6. Examples of smooth muscle sites include
   a. the lining of blood vessels.
   b. the iris of the eye.
   c. the wall of the digestive tract.
   d. all of these.
7. The function of neuroglia is to
   a. carry messages from the PNS to the CNS.
   b. support and protect neurons.
   c. stimulate muscle contraction.
   d. store memories.
8. Skeletal muscle cells are
   a. large multinucleate cells that arise by growth.
   b. large multinucleate cells that arise by fusion of smaller cells.
   c. small cells connected by many gap junctions.
   d. large cells with a single nucleus.

APPLY

1. Connective tissues, although quite diverse in structure and location, do share a common theme; the connection between other types of tissues. Although all of the following seem to fit that criterion, one of the tissues listed is not a type of connective tissue. Which one?
   a. Blood
   b. Muscle
   c. Adipose
   d. Cartilage
2. What do all the organs of the body have in common?
   a. Each contains the same kinds of cells.
   b. Each is composed of several different kinds of tissue.
   c. Each is derived from ectoderm.
   d. Each can be considered part of the circulatory system.
3. Rheumatoid arthritis is an autoimmune disease that attacks the linings of joints within the body. The cells that line these joints, and whose destruction causes the symptoms of arthritis, are known as
   a. osteocytes.
   b. erythrocytes.
   c. chondrocytes.
   d. thrombocytes.
4. Suppose that an alien virus arrives on Earth. This virus causes damage to the nervous system by attacking the structures of neurons. Which of the following structures would be immune from attack?
   a. Axon
   b. Dendrite
   c. Neuroglia
   d. All of these would be attacked by the virus.
5. Homeostasis
   a. is a dynamic process.
   b. describes the maintenance of the internal environment of the body.
   c. is essential to life.
   d. is all of these.

6. Which of the following scenarios correctly describes positive feedback?
   a. If the temperature increases in your room, your furnace increases its output of warm air.
   b. If you drink too much water, you produce more urine.
   c. If the price of gasoline increases, drivers decrease the length of their trips.
   d. If you feel cold, you start to shiver.
7. The three types of muscle all share
   a. a structure that includes striations.
   b. a membrane that is electrically excitable.
   c. the ability to contract.
   d. the characteristic of self-excitation.

SYNTHESIZE

1. Suppose that you discover a new disease that affects nutrient absorption in the gut as well as causes problems with the skin. Is it possible that one disease could involve the same tissues? How could this occur?
2. Which organ systems are involved in regulation and maintenance? Why do you think they are linked in this way?
3. We have all experienced hunger pangs. Is hunger a positive or negative feedback stimulus? Describe the steps involved in the response to this stimulus.
4. Why is homeostasis described as a dynamic process? How does negative feedback function in this process? How can antagonistic effectors result in a constant level, and how does this relate to the idea of a dynamic process?

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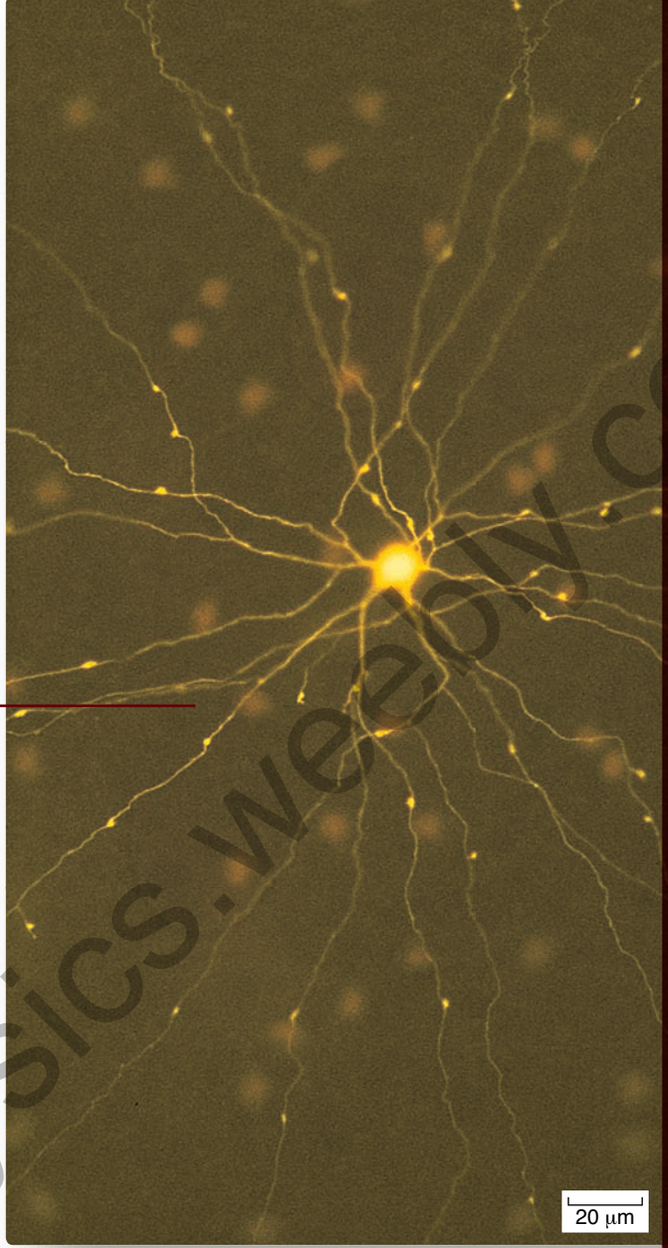
Chapter 44

The Nervous System



Chapter Outline

Introduction

All animals except sponges use a network of nerve cells to gather information about the body's condition and the external environment, to process and integrate that information, and to issue commands to the body's muscles and glands. As we saw in chapter 43, homeostasis of the animal's body is accomplished by negative feedback loops that maintain conditions within narrow limits. Negative feedback implies not only detection of appropriate stimuli but also communication of information to begin a response. The nervous system, composed of neurons, such as the one pictured here, is a fast communication system and a part of many feedback systems in the body.

44.1 Nervous System Organization

Learning Outcomes

1. *Distinguish the subdivisions of the vertebrate nervous system.*
2. *Identify the functional structure of neurons.*
3. *Name the different cell types in the nervous system.*

An animal must be able to respond to environmental stimuli. A fly escapes a flyswatter; the antennae of a crayfish detect food and the crayfish moves toward it. To accomplish these actions, animals must have *sensory receptors* that can detect the stimulus and *motor effectors* that can respond to it. In most invertebrate phyla and in all vertebrate classes, sensory receptors and motor effectors are linked by way of the nervous system.

The central nervous system is the "command center"

As described in chapter 43, the nervous system consists of neurons and supporting cells. Figure 44.1 shows the three types of neurons. In vertebrates, **sensory neurons** (or afferent neurons) carry impulses from sensory receptors to the *central nervous system (CNS)*, which is composed of the brain and spinal cord. **Motor neurons** (or efferent neurons) carry impulses from the CNS to effectors—muscles and glands. A third type of neuron is present in the nervous systems of most invertebrates and all vertebrates: **interneurons** (or association neurons). Interneurons are located in the brain and spinal cord of vertebrates, where they help provide more complex reflexes and higher associative functions, including learning and memory.

The peripheral nervous system collects information and carries out responses

Together, sensory and motor neurons constitute the *peripheral nervous system (PNS)* in vertebrates. Motor neurons that stimulate skeletal muscles to contract make up the **somatic nervous system;** those that regulate the activity of the smooth muscles, cardiac muscle, and glands compose the **autonomic nervous system.**

The autonomic nervous system is further broken down into the *sympathetic* and *parasympathetic* divisions. These divisions counterbalance each other in the regulation of many organ systems. Figure 44.2 illustrates the relationships among the different parts of the vertebrate nervous system.

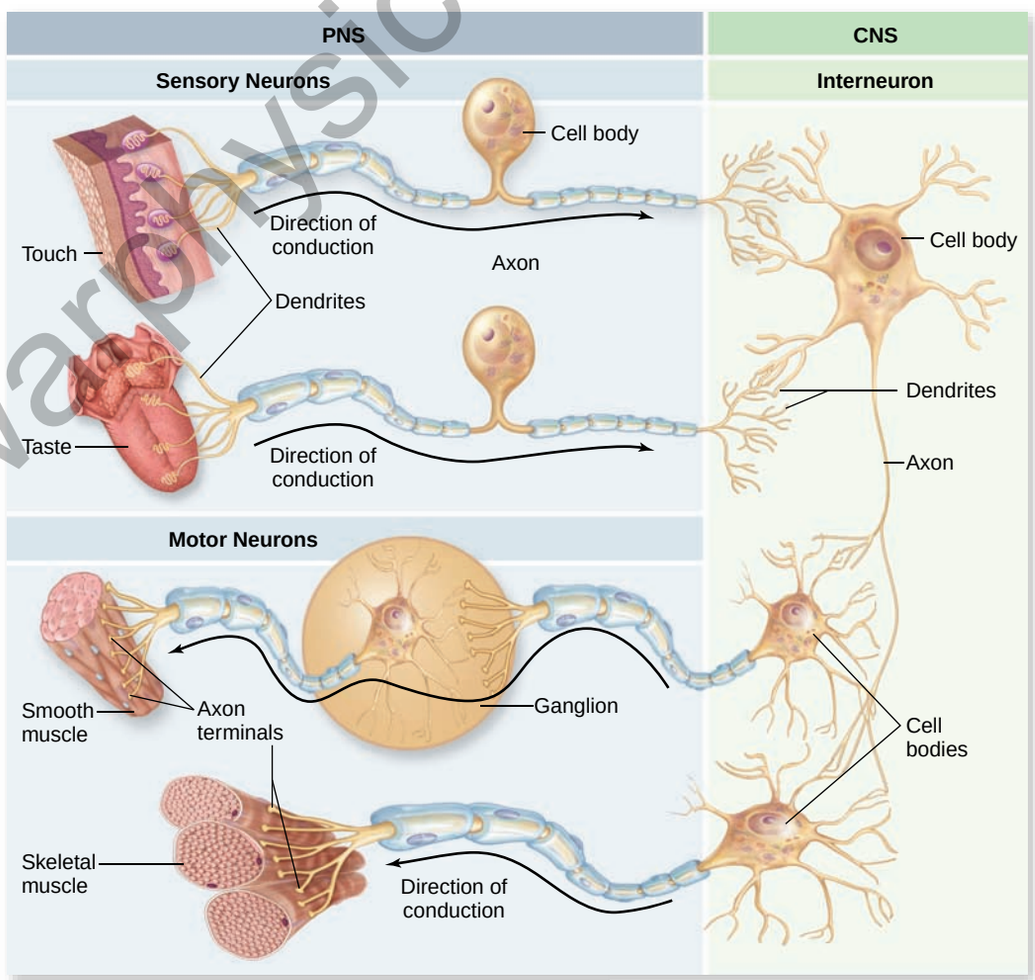


Figure 44.1 Three types of neurons. The brain and spinal cord form the central nervous system (CNS) of vertebrates, and sensory and motor neurons form the peripheral nervous system (PNS). Sensory neurons of the peripheral nervous system carry information about the environment to the CNS. Interneurons in the CNS provide links between sensory and motor neurons. Motor neurons of the PNS system carry impulses or "commands" to muscles and glands (effectors).

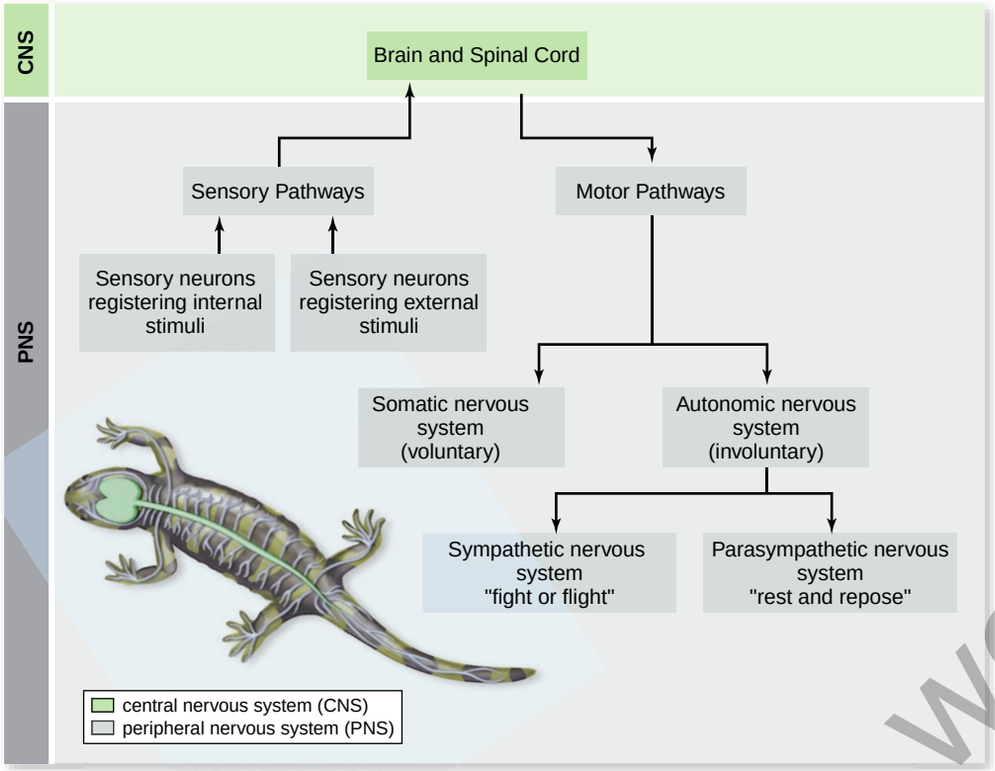


Figure 44.2 Divisions of the vertebrate nervous system. The major divisions are the central and peripheral nervous systems. The brain and spinal cord make up the central nervous system (CNS). The peripheral nervous system (PNS) includes everything outside the CNS and is divided into sensory and motor pathways. Sensory pathways can detect either external or internal stimuli. Motor pathways are divided into the somatic nervous system that activates voluntary muscles and the autonomic nervous system that activate involuntary muscles. The sympathetic and parasympathetic nervous systems are subsets of the autonomic nervous system that trigger opposing actions.

The structure of neurons supports their function

Despite their varied appearances, most neurons have the same functional architecture (figure 44.3). The **cell body** is an enlarged region containing the nucleus. Extending from the cell body are one or more cytoplasmic extensions called **dendrites.** Motor and association neurons possess a profusion of highly branched dendrites, enabling those cells to receive information from many different sources simultaneously. Some neurons have extensions from the dendrites called *dendritic spines* that increase the surface area available to receive stimuli.

The surface of the cell body integrates the information arriving at its dendrites. If the resulting membrane excitation is sufficient, it triggers the conduction of impulses away from the cell body along an **axon.** Each neuron has a single axon leaving its cell body, although an axon may also branch to stimulate a number of cells. An axon can be quite long: The axons controlling the muscles in a person's feet can be more than a meter long, and the axons that extend from the skull to the pelvis in a giraffe are about 3 m long.

Supporting cells include Schwann cells and oligodendrocytes

Neurons are supported both structurally and functionally by supporting cells, which are collectively called neuroglia. These cells are one-tenth as big and 10 times more numerous than neurons, and they serve a variety of functions, including supplying the neurons with nutrients, removing wastes from neurons, guiding axon migration, and providing immune functions.

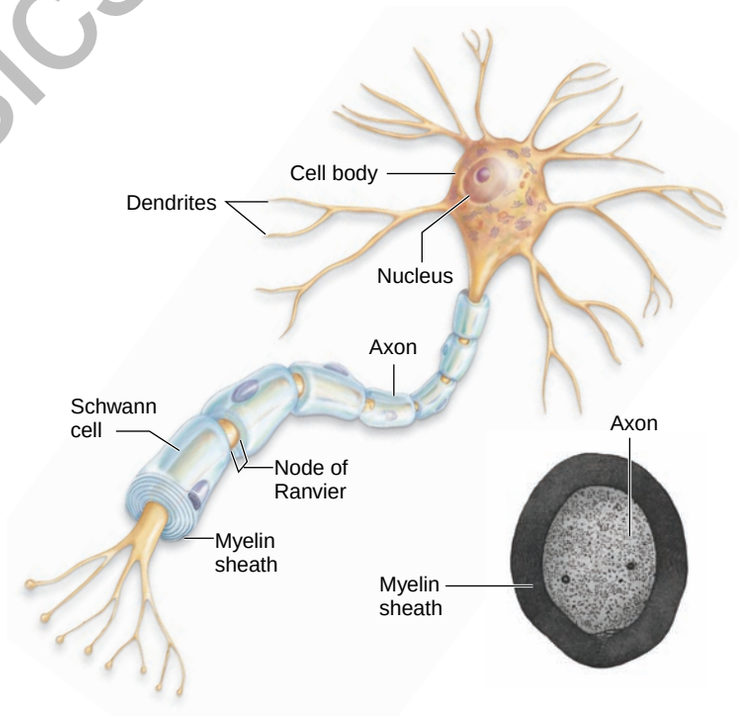


Figure 44.3 Structure of a typical vertebrate neuron. Extending from the cell body are many dendrites, which receive information and carry it to the cell body. A single axon transmits impulses away from the cell body. Many axons are encased by a myelin sheath, with multiple membrane layers that insulate the axon. Small gaps, called nodes of Ranvier, interrupt the sheath at regular intervals. Schwann cells form myelin sheaths in the PNS (as shown for this motor neuron); extensions of oligodendrocytes form myelin sheaths in the CNS.

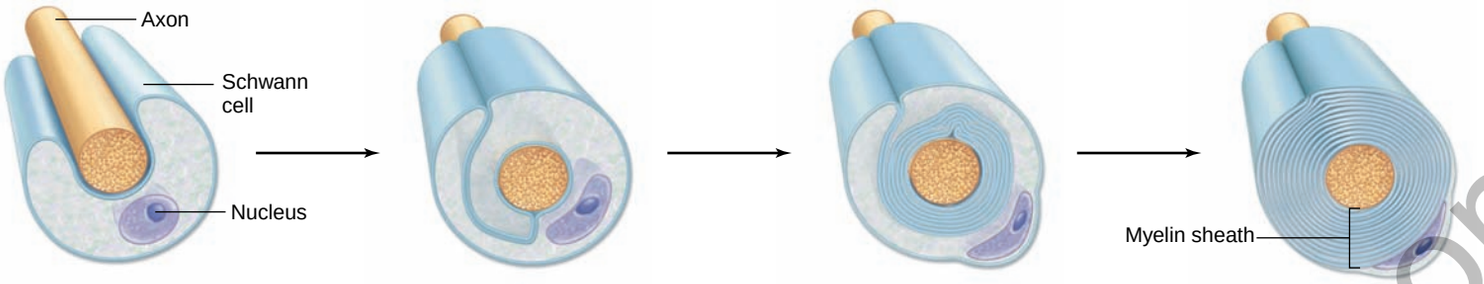


Figure 44.4 The formation of the myelin sheath around a peripheral axon. The myelin sheath forms by successive wrappings of Schwann cell membranes around the axon.

Two of the most important kinds of neuroglia in vertebrates are **Schwann cells** and **oligodendrocytes,** which produce **myelin sheaths** that surround the axons of many neurons. Schwann cells produce myelin in the PNS, and oligodendrocytes produce myelin in the CNS. During development, these cells wrap themselves around each axon several times to form the myelin sheath—an insulating covering consisting of multiple layers of compacted membrane (figure 44.4).

Axons that have myelin sheaths are said to be myelinated, and those that don't are unmyelinated. In the CNS, myelinated axons form the *white matter*; and the unmyelinated dendrites and cell bodies form the *gray matter*. In the PNS, myelinated axons are bundled together, much like wires in a cable, to form nerves.

Small gaps, known as **nodes of Ranvier** (see figure 44.3), interrupt the myelin sheath at intervals of 1 to 2 μm. We discuss the role of the myelin sheath in impulse conduction in the next section.

Learning Outcomes Review 44.1

The vertebrate nervous system consists of the central nervous system (CNS) and peripheral nervous system (PNS). The PNS comprises the somatic nervous system and autonomic nervous system; the latter has sympathetic and parasympathetic divisions. A neuron consists of a cell body, dendrites that receive information, and a single axon that sends signals. Neurons carry out nervous system functions; they are supported by a variety of neuroglia.

- ***Which division of the PNS is under conscious control?***

44.2 *The Mechanism of Nerve Impulse Transmission*

Learning Outcomes

1. ***Identify the ions involved in nerve impulse transmission and their relative concentrations inside and outside the neuron.***
2. ***Describe the production of the resting potential.***
3. ***Explain how the action of voltage-gated channels produces an action potential.***

Neuronal function depends on a changeable permeability to ions. Upon stimulation, electrical changes in the plasma membrane spread or propagate from one part of the cell to another. The architecture of the neuron provides the mechanisms for the generation and spread of these membrane electrical potentials.

The unique mechanisms of neurons primarily depend on the presence of specialized membrane transport proteins, where they are located, and how they are activated. First, we examine some of the basic electrical properties common to the plasma membranes of most animal cells, and then we look at how these properties operate in neurons.

An electrical difference exists across the plasma membrane

You first learned about membrane potential in chapter 5, where transport of ions across the cell membrane was discussed. Membrane potential is similar to the electrical potential difference that exists between the two poles of a flashlight or automobile battery. One pole is positive, and the other is negative. Similarly, a potential difference exists across every cell's plasma membrane. The side of the membrane exposed to the cytoplasm is the negative pole, and the side exposed to the extracellular fluid is the positive pole.

When a neuron is not being stimulated, it maintains a **resting potential.** A cell is very small, and so its membrane potential is very small. The resting membrane potential of many vertebrate neurons ranges from –40 to –90 millivolts (mV), or 0.04 to 0.09 volts (V). For the examples and figures in this chapter, we use an average resting membrane potential value of –70 mV. The minus sign indicates that the inside of the cell is negative with respect to the outside.

Contributors to membrane potential

The inside of the cell is more negatively charged in relation to the outside because of two factors:

1. The sodium–potassium pump, described in chapter 5, brings two potassium ions (K^+) into the cell for every three sodium ions (Na^+) it pumps out (figure 44.5). This helps establish and maintain concentration differences that result in high K^+ and low Na^+ concentrations inside the cell, and high Na^+ and low K^+ concentrations outside the cell.

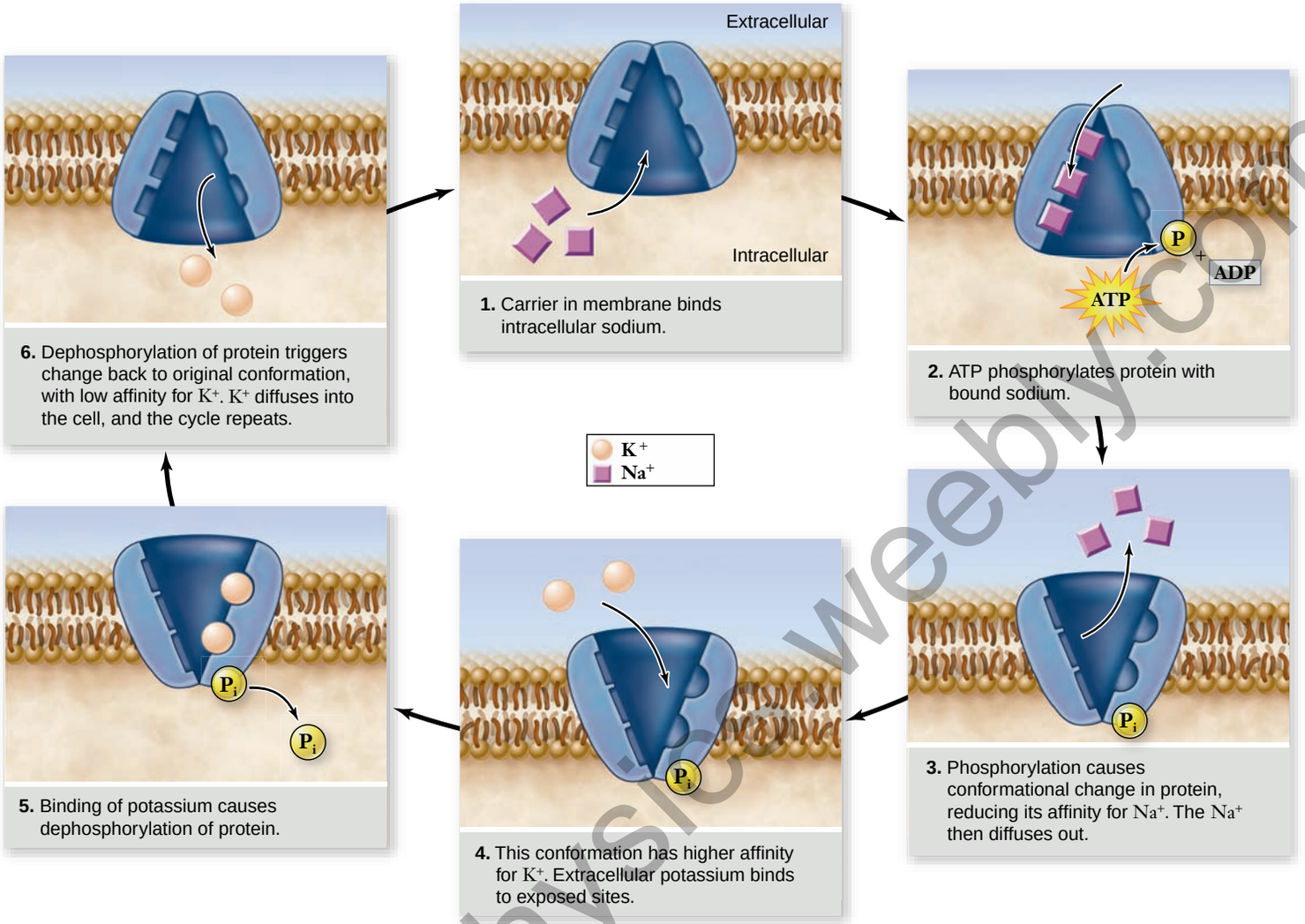


Figure 44.5 The sodium–potassium pump. This pump transports three Na^+ to the outside of the cell and simultaneously transports two K^+ to the inside of the cell. This is an active transport carrier requiring the (phosphorylating) energy of ATP.

2. **Ion channels** in the cell membrane are more numerous for K^+ than for Na^+ making the membrane more permeable for K^+. Ion channels are membrane proteins that form pores through the membrane, allowing diffusion of specific ions across the membrane. Because there are more ion channels for K^+, the membrane is more permeable to K^+ and it will diffuse out of the cell.

Two major forces act on ions in establishing the resting membrane potential: (1) The electrical potential produced by unequal distribution of charges across the membrane, and (2) the chemical force produced by unequal concentrations of ions across the membrane.

The resting potential: Balance between two forces

The resting potential arises due to the action of the sodium–potassium pump and the differential permeability of the membrane to Na^+ and K^+ due to ion channels. The pump moves three Na^+ outside for every two K^+ inside, which creates a small imbalance in cations outside the cell. This has only a minor effect; however, the concentration gradients created by the pump are significant. The concentration of K^+ is much higher inside the cell than outside, leading to diffusion of K^+ through open K^+ channels. Since the membrane is not permeable to the negative ions that could counterbalance this (mainly organic phosphates, amino acids, and proteins) it leads to a buildup of positive charge outside the membrane and negative charge inside the membrane. This electrical potential then is an attractive force pulling K^+ ions back inside the cell. The balance between the diffusional force and the electrical force leads to the **equilibrium potential** (table 44.1). By relating the work done by each type of force, we can derive a quantitative expression for this equilibrium potential called the Nernst equation. This assumes the action of a single ion, and for a positive ion with charge equal to +1, the Nernst equation is:

$$E_K = 58 \text{ mV} \log([K^+]_{out}/[K^+]m_{in})$$

The calculated equilibrium potential for K^+ is –90 mV (see table 44.1), close to the measured value of –70 mV. The calculated value for Na^+ is +60 mV, clearly not at all close to the measured value, but the leakage of a small amount of Na^+ back into the cell is responsible for lowering the equilibrium potential of K^+ to the –70 mV value observed. The resting membrane potential of a neuron

TABLE 44.1 The Ionic Composition of Cytoplasm and Extracellular Fluid (ECF)

Ion	Concentration in ECF (mM)	Concentration in Cytoplasm (mM)	Ratio (ECF:cytoplasm)	Equilibrium Potential (mV)
Na^+	150	15	10:1	+60
K^+	5	150	1:30	–90
Cl^-	110	7	15:1	–70

can be measured and viewed or graphed using a voltmeter and a pair of electrodes, one outside and one inside the cell (figure 44.6).

The uniqueness of neurons compared with other cells is not the production and maintenance of the resting membrane potential, but rather the sudden temporary disruptions to the resting membrane potential that occur in response to stimuli. Two types of changes can be observed: *graded potentials* and *action potentials*.

Graded potentials are small changes that can reinforce or negate each other

Graded potentials, small transient changes in membrane potential, are caused by the activation of a class of channel proteins called **gated ion channels.** Introduced in chapter 9, gated channels behave like a door that can open or close, unlike ion leakage channels that are always open. The structure of gated ion channels is such that they have alternative conformations that can be open, allowing the passage of ions, or closed, not allowing the passage of ions. Each gated channel is selective, that is, when open they allow diffusion of only one type of ion. Most gated channels are closed in the normal resting cell.

Chemically gated channels

In most neurons, gated ion channels in dendrites respond to the binding of signaling molecules (figure 44.7; see also figure 9.4*a*). These are referred to as *chemically gated*, or *ligand-gated*, *channels*. *Ligands* are chemical groups that attach to larger molecules to regulate or contribute to their function. When ligands temporarily bind to membrane receptor proteins or channels, they cause the shape of the protein to change, thus opening the ion channel. Hormones and neurotransmitters act as ligands, inducing opening of ligand-gated channels, and causing changes in plasma membrane permeability that lead to changes in membrane voltage.

Depolarization and hyperpolarization

Permeability changes are measurable as depolarizations or hyperpolarizations of the membrane potential. A **depolarization** makes the membrane potential less negative (more positive), whereas a **hyperpolarization** makes the membrane potential more negative. For example, a change in potential from –70 mV to –65 mV is a depolarization; a change from –70 mV to –75 mV is a hyperpolarization.

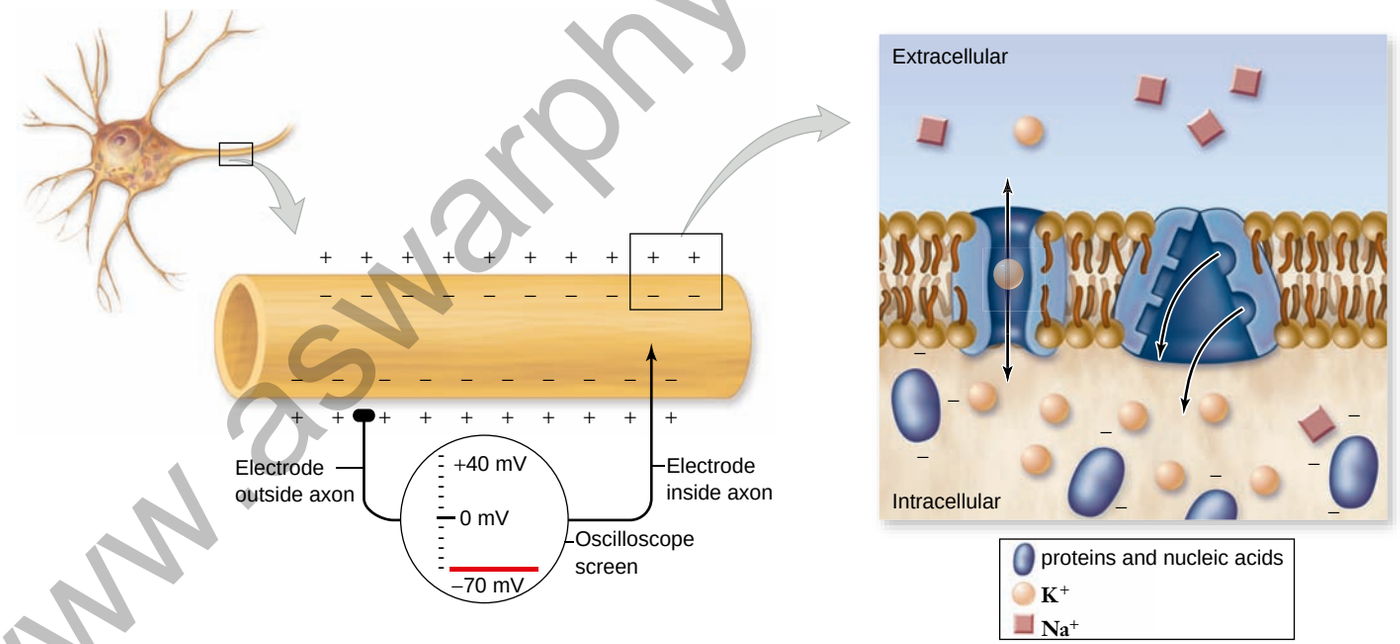


Figure 44.6 Establishment of the resting membrane potential. A voltmeter placed with one electrode inside an axon and the other outside the membrane. The electric potential inside is –70 mV relative to the outside of the membrane. K^+ diffuses out of the cell through ion channels because its concentration is higher inside than outside. Negatively charged proteins and nucleic acids inside the cell cannot leave the cell and attract cations from outside the cell, such as K^+. This balance of electrical and diffusional forces produces the resting potential. The sodium–potassium pump maintains cell equilibrium by counteracting the effects of Na^+ leakage into the cell and contributes to the resting potential by moving 3 Na^+ outside for every 2 K^+ moved inside.

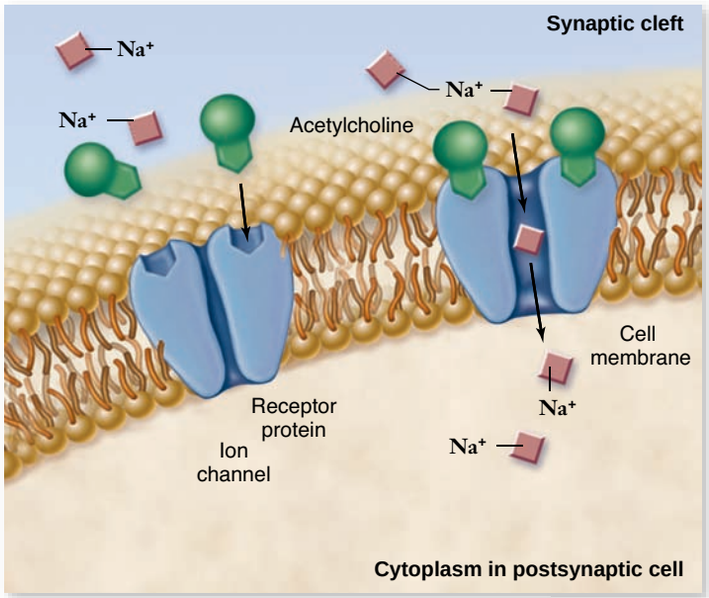


Figure 44.7 A chemically gated ion channel. The acetylcholine (ACh) receptor is a chemically gated channel that can bind the neurotransmitter ACh. Binding of ACh causes the channel to open allowing Na^+ ions to flow into the cell by diffusion.

These small changes in membrane potential result in *graded potentials* because their size depends on either the strength of the stimulus or the amount of ligand available to bind with their receptors. These potentials diminish in amplitude as they spread from their point of origin. Depolarizing or hyperpolarizing potentials can add together to amplify or reduce their effects, just as two waves can combine to make a bigger one when they meet in synchronization or can cancel each other out when a trough meets with a crest. The ability of graded potentials to combine is called **summation** (figure 44.8). We will return to this topic in the next section after we discuss the nature of action potentials.

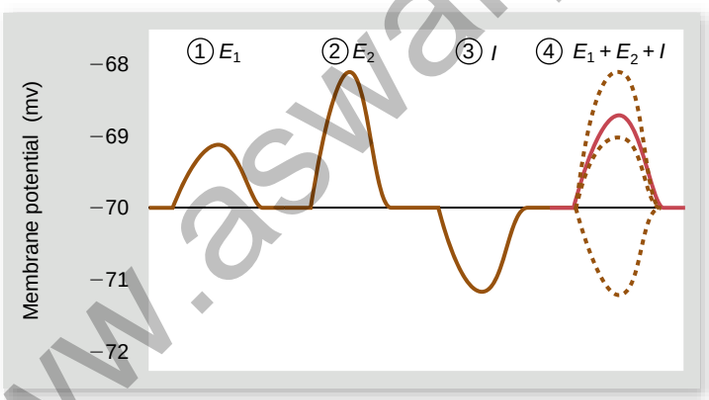


Figure 44.8 Graded potentials. Graded potentials are the summation of subthreshold potentials produced by the opening of different chemically gated channels. (1) A weak excitatory stimulus, E_1, elicits a smaller depolarization than (2) a stronger stimulus, E_2. (3) An inhibitory stimulus, I, produces a hyperpolarization. (4) If all three stimuli occur very close together, the resulting polarity change will be the sum of the three individual changes.

Action potentials result when depolarization reaches a threshold

When a particular level of depolarization is reached (about −55 mV in some mammalian axons), a nerve impulse, or action potential, is produced in the region where the axon arises from the cell body. The level of depolarization needed to produce an action potential is called the **threshold potential.** Depolarizations bring a neuron closer to the threshold, and hyperpolarizations move the neuron further from the threshold.

The action potential is caused by another class of ion channels: **voltage-gated ion channels.** These channels open and close in response to changes in membrane potential; the flow of ions controlled by these channels creates the action potential. Voltage-gated channels are found in neurons and in muscle cells. Two different channels are used to create an action potential in neurons: **voltage-gated Na^+ channels** and **voltage-gated K^+ channels.**

Sodium and potassium voltage-gated channels

The behavior of the voltage-gated Na^+ channel is more complex than that of the K^+ channel, so we will consider it first. The channel has two gates: an activation gate and an inactivation gate. In its resting state the activation gate is closed and the inactivation gate is open. When the threshold voltage is reached, the activation gate opens rapidly, leading to an influx of Na^+ ions due to both concentration and voltage gradients. After a short period the inactivation gate closes, stopping the influx of Na^+ ions and leaving the channel in a temporarily inactivated state. The channel is returned to its resting state by the activation gate closing and the inactivation gate opening. The result of this is a transient influx of Na^+ that depolarizes the membrane in response to a threshold voltage.

The K^+ channel has a single activation gate that is closed in the resting state. In response to a threshold voltage, it opens slowly. With the high concentration of K^+ inside the cell, and the membrane now far from the equilibrium potential, an efflux of K^+ begins. The positive charge now leaving the cell counteracts the effect of the Na^+ channel and repolarizes the membrane.

Tracing an action potential's changes

Let us now put all of this together and see how the changing flux of ions leads to an action potential. The action potential has three phases: a *rising phase*, a *falling phase*, and an *undershoot phase* (figure 44.9). When a threshold potential is reached, the rapid opening of the Na^+ channel causes an influx of Na^+ that shifts the membrane potential toward the equilibrium potential for Na (+60 mV). This appears as the rising phase on an oscilloscope. The membrane potential never quite reaches +60 mV because the inactivation gate of the Na^+ channel closes, terminating the rising phase. At the same time, the opening of the K^+ channel leads to K^+ diffusing out of the cell, repolarizing the membrane in the falling phase. The K^+ channels remain open longer than necessary to restore the resting potential, resulting in a slight undershoot. This entire sequence of events for a single action potential takes about a millisecond.

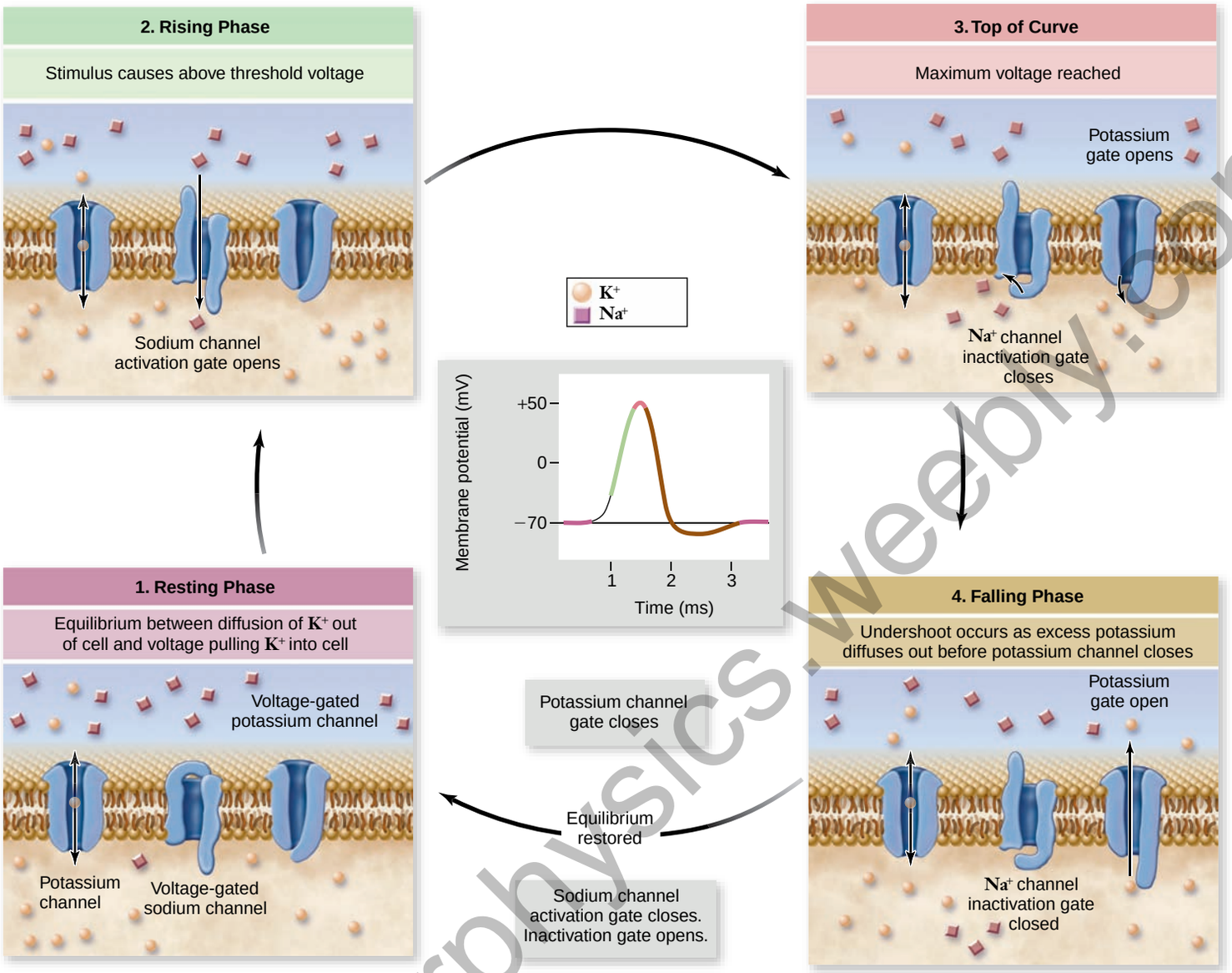


Figure 44.9 The action potential. (1) At resting membrane potential, voltage-gated ion channels are closed, but there is some diffusion of K^+. In response to a stimulus, the cell begins to depolarize, and once the threshold level is reached, an action potential is produced. (2) Rapid depolarization occurs (the rising portion of the spike) because voltage-gated sodium channel activation gates open, allowing Na^+ to diffuse into the axon. (3) At the top of the spike, Na^+ channel inactivation gates close, and voltage-gated potassium channels that were previously closed begin to open. (4) With the K^+ channels open, repolarization occurs because of the diffusion of K^+ out of the axon. An undershoot occurs before the membrane returns to its original resting potential.

The nature of action potentials

Action potentials are separate, all-or-none events. An action potential occurs if the threshold voltage is reached, but not while the membrane remains below threshold. Action potentials do not add together or interfere with one another, as graded potentials can. After Na^+ channels "fire" they remain in an inactivated state until the inactivation gate reopens, preventing any summing of effects. This is called the absolute refractory period when the membrane cannot be stimulated. There is also a relative refractory period during which stimulation produces action potentials of reduced amplitude.

The production of an action potential results entirely from the passive diffusion of ions. However, at the end of each action potential, the cytoplasm contains a little more Na^+ and a little less K^+ than it did at rest. Although the number of ions moved by a single action potential is tiny relative to the concentration gradients of Na^+ and K^+, eventually this would have an effect. The constant activity of the sodium–potassium pump compensates for these changes. Thus, although active transport is not required to produce action potentials, it is needed to maintain the ion gradients.

Action potentials are propagated along axons

The movement of an action potential through an axon is not generated by ions flowing from the base of the axon to the end.

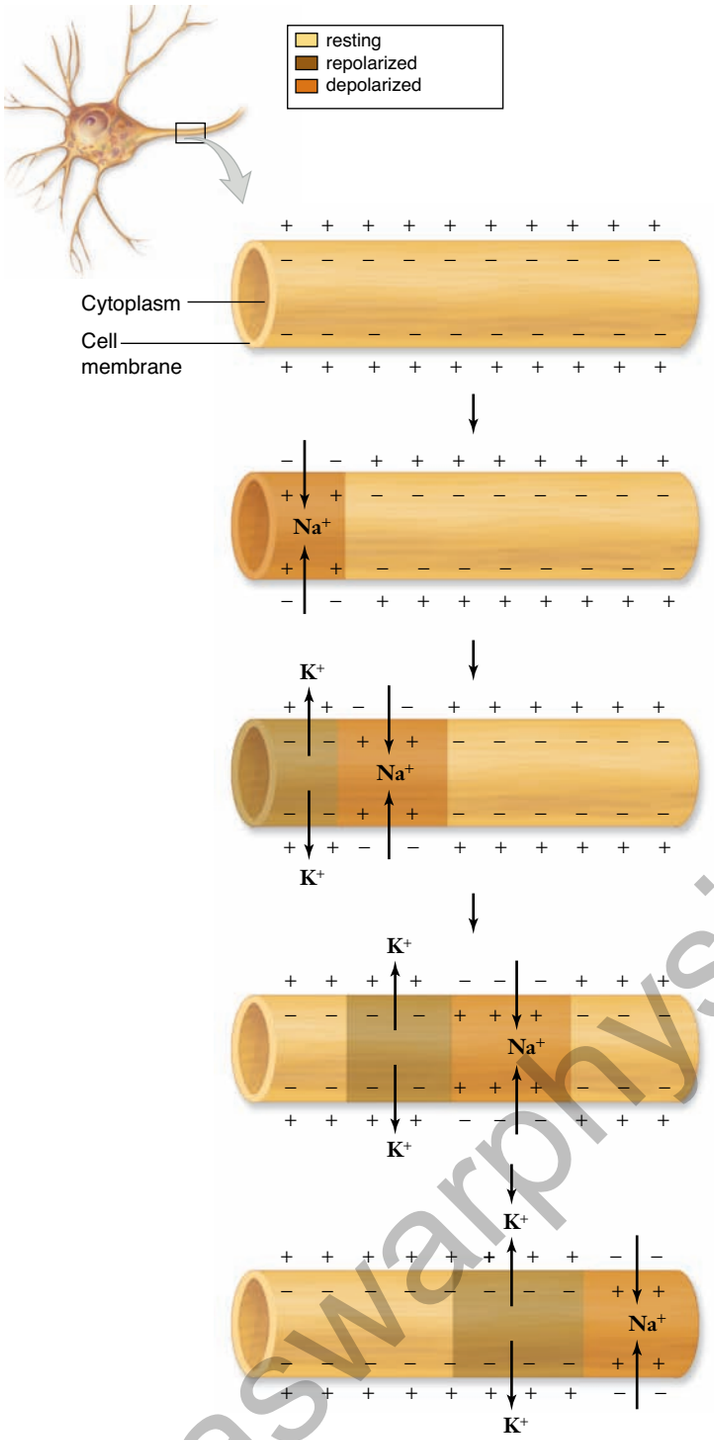


Figure 44.10 Propagation of an action potential in an unmyelinated axon. When one region produces an action potential and undergoes a reversal of polarity, it serves as a depolarization stimulus for the next region of the axon. In this way, action potentials regenerate along each small region of the unmyelinated axon membrane.

Instead an action potential originates at the base of the axon, and is then recreated in adjacent stretches of membrane along the axon.

Each action potential, during its rising phase, reflects a reversal in membrane polarity. The positive charges due to influx of Na^+ can depolarize the adjacent region of membrane to threshold, so that the next region produces its own action potential (figure 44.10). Meanwhile, the previous region of membrane repolarizes back to the resting membrane potential. The signal does not back up because the Na^+ channels that have just "fired" are still in an inactivated state and are refractory (resistant) to stimulation.

The propagation of an action potential is similar to people in a stadium performing the "wave": Individuals stay in place as they stand up (depolarize), raise their hands (peak of the action potential), and sit down again (repolarize). The wave travels around the stadium, but the people stay in place.

There are two ways to increase the velocity of nerve impulses

Action potentials are conducted without decreasing in amplitude, so the last action potential at the end of an axon is just as large as the first action potential. Animals have evolved two ways to increase the velocity of nerve impulses. The velocity of conduction is greater if the diameter of the axon is large or if the axon is myelinated (table 44.2).

Increasing the diameter of an axon increases the velocity of nerve impulses due to the electrical property of resistance. Electrical resistance is inversely proportional to cross-sectional area, which is a function of diameter, so larger diameter axons have less resistance to current flow. The positive charges carried by Na^+ flows farther in a larger diameter axon, leading to a higher than threshold voltage farther from the origin of Na^+ influx.

Larger diameter axons are found primarily in invertebrates. For example, in the squid, the escape response is controlled by a so-called giant axon. This large axon conducts nerve impulses faster than other smaller squid axons, allowing a rapid escape response. The squid giant axon was used by Alan Lloyd Hodgkin and Andrew Huxley in their pioneering studies of nerve transmission.

Myelinated axons conduct impulses more rapidly than unmyelinated axons because the action potentials in myelinated

TABLE 44.2 Conduction Velocities of Some Axons

	Axon Diameter (μm)	Myelin	Conduction Velocity (m/s)
Squid giant axon	500	No	25
Large motor axon to human leg muscle	20	Yes	120
Axon from human skin pressure receptor	10	Yes	50
Axon from human skin temperature receptor	5	Yes	20
Motor axon to human internal organ	1	No	2

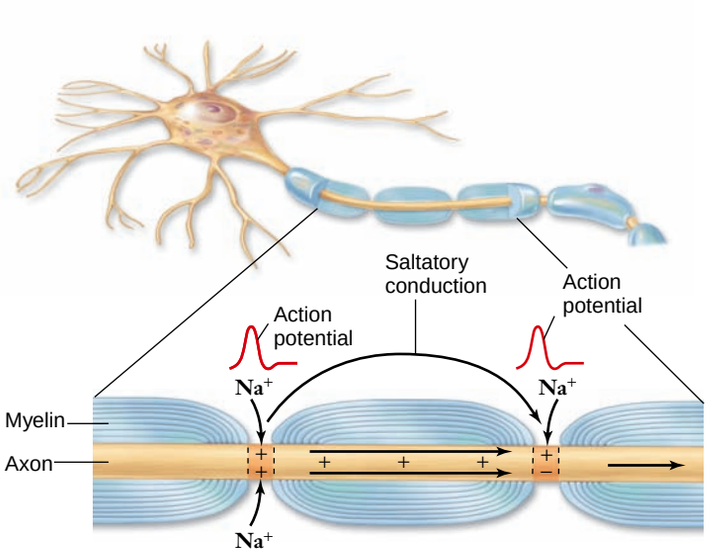


Figure 44.11 Saltatory conduction in a myelinated axon. Action potentials are only produced at the nodes of Ranvier in a myelinated axon. One node depolarizes the next node so that the action potentials can skip between nodes. As a result, saltatory ("jumping") conduction in a myelinated axon is more rapid than conduction in an unmyelinated axon.

axons are only produced at the nodes of Ranvier. One action potential still serves as the depolarization stimulus for the next, but the depolarization at one node spreads quickly beneath the insulating myelin to trigger opening of voltage-gated channels at the next node. The impulses therefore seem to jump from node to node (figure 44.11) in a process called **saltatory conduction** (Latin *saltare*, "to jump").

To see how saltatory conduction speeds impulse transmission, let's return for a moment to the stadium wave analogy to describe propagation of an action potential. The wave moves across the seats of a crowded stadium as fans seeing the people in the adjacent section stand up are triggered to stand up in turn. Because the wave skips sections of empty bleachers, it actually progresses around the stadium even faster with more empty sections. The wave doesn't have to "wait" for the missing people to stand, so it simply moves to the next populated section—just as the action potential jumps the nonconducting regions of myelin between exposed nodes.

Learning Outcomes Review 44.2

Neurons maintain high K^+ levels inside the cell, and high Na^+ levels outside the cell. Diffusion of K^+ to the outside leads to a resting potential of about –70 mV. Opening of ligand-gated channels can depolarize or hyperpolarize the membrane, causing a graded potential. Action potentials are triggered when membrane potential exceeds a threshold value. Voltage-gated Na^+ channels open, and depolarization occurs; subsequent opening of K^+ channels leads to repolarization.

- ***How can only positive ions result in depolarization and repolarization of the membrane during an action potential?***

44.3 Synapses: Where Neurons Communicate with Other Cells

Learning Outcomes

1. ***Distinguish between electrical and chemical synapses.***
2. ***List the different chemical neurotransmitters.***
3. ***Explain the effects of addictive drugs on the nervous system.***

An action potential passing down an axon eventually reaches the end of the axon and all of its branches. These branches may form junctions with the dendrites of other neurons, with muscle cells, or with gland cells. Such intercellular junctions are called **synapses.** The neuron whose axon transmits action potentials to the synapse is termed the *presynaptic cell*, and the cell receiving the signal on the other side of the synapse is the *postsynaptic cell.*

The two types of synapses are electrical and chemical

The nervous systems of animals have two basic types of synapses: electrical and chemical. **Electrical synapses** involve direct cytoplasmic connections formed by gap junctions between the pre- and postsynaptic neurons (see chapter 4; figure 4.27). Membrane potential changes, including action potentials, pass directly and rapidly from one cell to the other through the gap junctions. Electrical synapses are common in invertebrate nervous systems, but are rare in vertebrates.

The vast majority of vertebrate synapses are *chemical synapses* (figure 44.12). When synapses are viewed under a light microscope, the presynaptic and postsynaptic cells appear to touch, but when viewed with an electron microscope most have a **synaptic cleft,** a narrow space that separates these two cells (figure 44.13).

The end of the presynaptic axon is swollen and contains numerous **synaptic vesicles,** each packed with chemicals called *neurotransmitters.* When action potentials arrive at the end of the axon, they stimulate the opening of voltage-gated calcium (Ca^{2+}) channels, causing a rapid inward diffusion of Ca^{2+}. This influx of Ca^{2+} triggers a complex series of events that leads to the fusion of synaptic vesicles with the plasma membrane and the release of neurotransmitter by exocytosis (see chapter 5; figure 44.14).

The higher the frequency of action potentials in the presynaptic axon, the greater the number of vesicles that release their contents of neurotransmitters. The neurotransmitters diffuse to the other side of the cleft and bind to chemical- or ligand-gated receptor proteins in the membrane of the postsynaptic cell. The action of these receptors produces graded potentials in the postsynaptic membrane.

Neurotransmitters are chemical signals in an otherwise electrical system, requiring tight control over the duration of their action. Neurotransmitters must be rapidly removed from the synaptic cleft to allow new signals to be transmitted. This is accomplished by a variety of mechanisms, including enzymatic

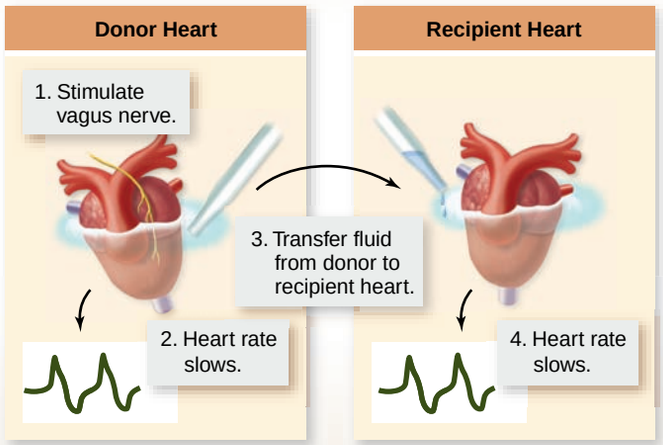
SCIENTIFIC THINKING

Question: *Is communication between neurons, and between neurons and muscle, chemical or electrical?*

Hypothesis: *Signaling between a neuron and heart muscle is chemical.*

Prediction: *Application of chemical solutes from one heart will affect the activity of another heart.*

Test: *Two frog hearts are placed in saline, one with vagus nerve attached, the other without. The vagus heart is stimulated, then fluid from around the vagus nerve is removed and applied to the other heart.*



Result: *Heart that was not stimulated by the vagus nerve slows as though it was stimulated.*

Conclusion: *The nerve released a chemical signal that slowed heart rate.*

Further Experiments: *How does this conclusion extend the experiment described in Fig 43.5?*

Figure 44.12 Synaptic signaling.

digestion in the synaptic cleft, reuptake of neurotransmitter molecules by the neuron, and uptake by glial cells.

Several different types of neurotransmitters have been identified, and they act in different ways. We next consider the action of a few of the important neurotransmitter chemicals.

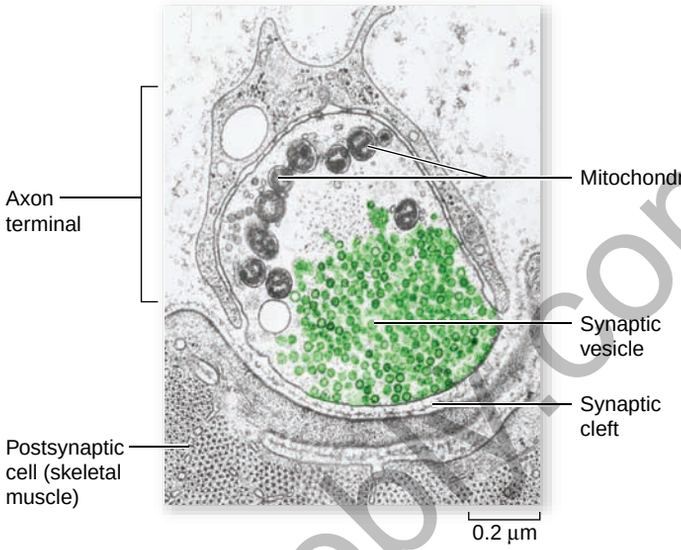


Figure 44.13 A synaptic cleft. An electron micrograph showing a neuromuscular synapse. Synaptic vesicles have been colored green.

Many different chemical compounds serve as neurotransmitters

No single chemical characteristic defines a neurotransmitter, although we can group certain types according to chemical similarities. Some, such as acetylcholine, have wide use in the nervous system, particularly where nerves connect with muscles. Other neurotransmitters are found only in very specific types of junctions, such as in the CNS.

Acetylcholine

Acetylcholine (ACh) is the neurotransmitter that crosses the synapse between a motor neuron and a muscle fiber. This synapse is called a **neuromuscular junction** (figures 44.14, 44.15).

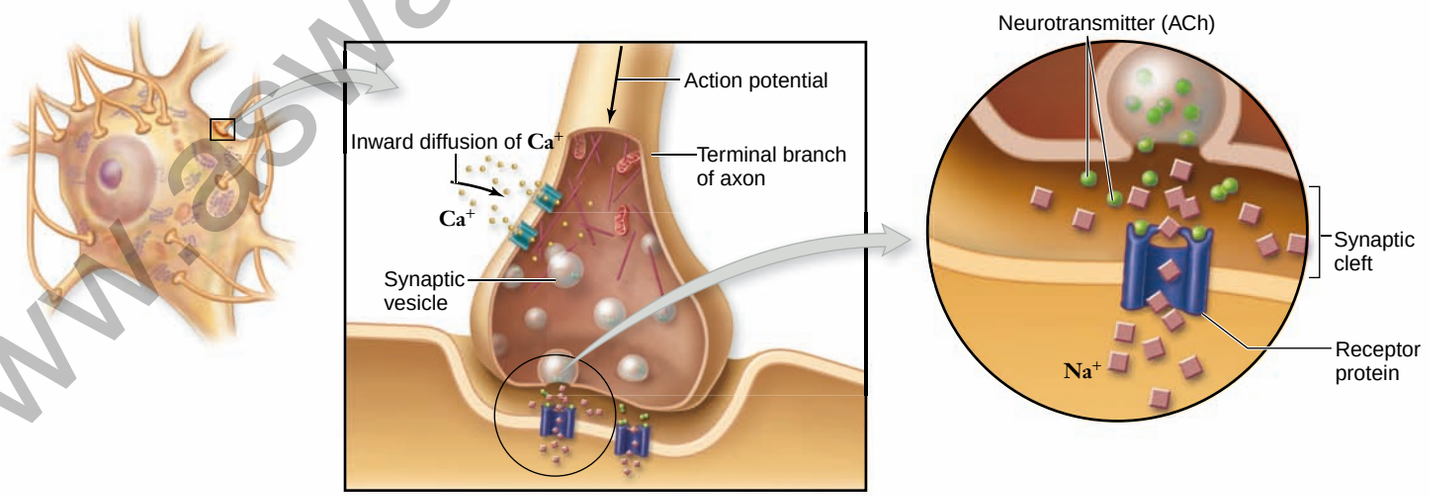


Figure 44.14 The release of neurotransmitter. Action potentials arriving at the end of an axon trigger inward diffusion of Ca^{2+}, which causes synaptic vesicles to fuse with the plasma membrane and release their neurotransmitters (acetylcholine [ACh] in this case). Neurotransmitter molecules diffuse across the synaptic gap and bind to ligand-gated receptors in the postsynaptic membrane.

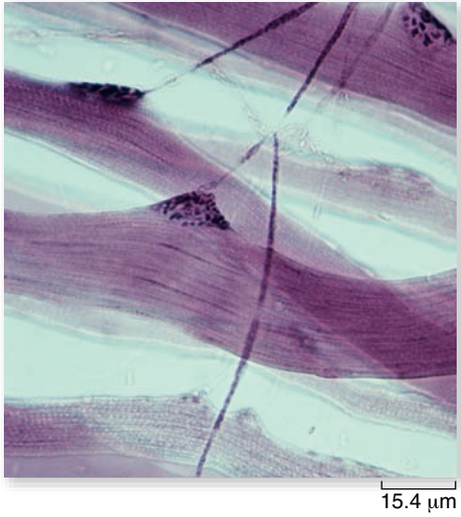


Figure 44.15 Neuromuscular junctions. A light micrograph shows axons branching to make contact with several individual muscle fibers.

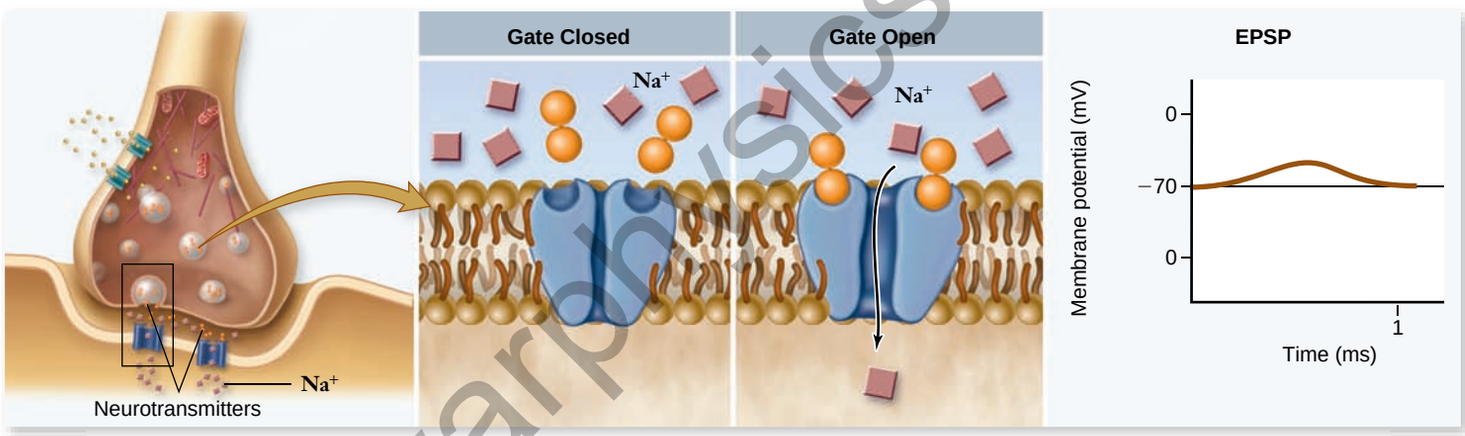
Acetylcholine binds to its receptor proteins in the postsynaptic membrane and causes ligand-gated ion channels within these proteins to open (see figure 44.7). As a result, that site on the postsynaptic membrane produces a depolarization (figure 44.16*a*) called an *excitatory postsynaptic potential (EPSP)*. The EPSP, if large enough, can open the voltage-gated channels for Na^+ and K^+ that are responsible for action potentials. Because the postsynaptic cell in this case is a skeletal muscle fiber, the action potentials it produces stimulate muscle contraction through mechanisms discussed in chapter 47.

For the muscle to relax, ACh must be eliminated from the synaptic cleft. *Acetylcholinesterase (AChE)*, an enzyme in the postsynaptic membrane, eliminates ACh. This enzyme, one of the fastest known, cleaves ACh into inactive fragments. Nerve gas and the agricultural insecticide parathion are potent inhibitors of AChE; in humans, they can produce severe spastic paralysis and even death if paralysis affects the respiratory muscles. Although ACh acts as a neurotransmitter between motor neurons and skeletal muscle cells, many neurons also use ACh as a neurotransmitter at their synapses with the dendrites or cell bodies of other neurons.

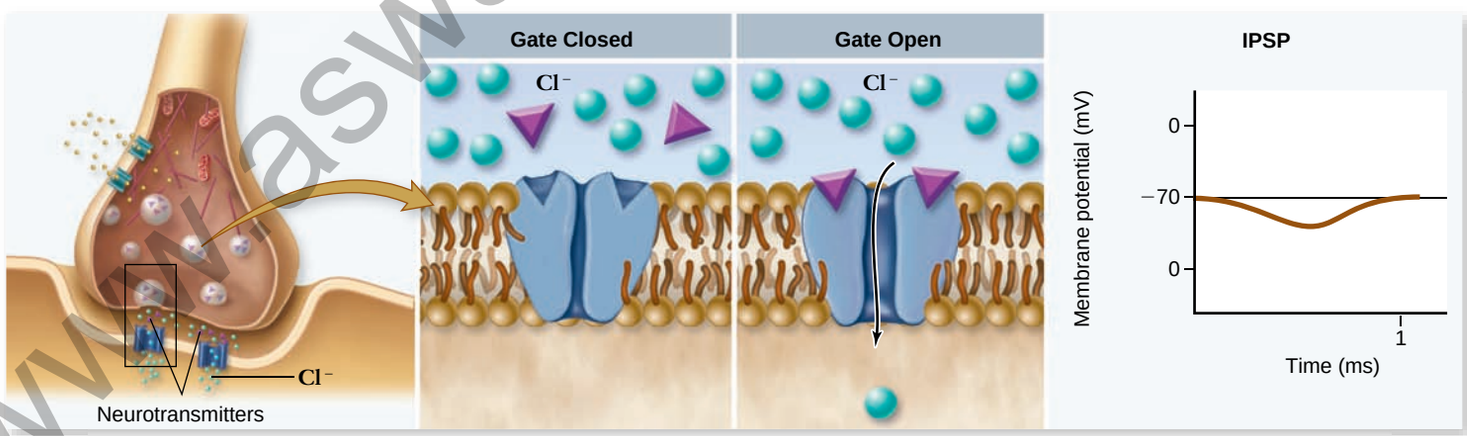
Amino acids

Glutamate is the major excitatory neurotransmitter in the vertebrate CNS. Excitatory neurotransmitters act to stimulate action potentials by producing EPSPs. Some neurons in the brains of people suffering from Huntington disease undergo changes that render them hypersensitive to glutamate, leading to neurodegeneration.

Glycine and γ-aminobutyric acid (GABA) are inhibitory neurotransmitters. These neurotransmitters cause the opening of ligand-gated channels for the chloride ion (Cl^-), which has a concentration gradient favoring its diffusion into the neuron. Because Cl^- is negatively charged, it makes the inside of the membrane



a.



b.

Figure 44.16 Different neurotransmitters can have different effects. ***a.*** An excitatory neurotransmitter promotes a depolarization, or excitatory postsynaptic potential (EPSP). ***b.*** An inhibitory neurotransmitter promotes a hyperpolarization, or inhibitory postsynaptic potential (IPSP).

even more negative than it is at rest—for example, from –70 mV to –85 mV (see figure 44.16*b*). This hyperpolarization is called an *inhibitory postsynaptic potential (IPSP)*, and it is very important for neural control of body movements and other brain functions. The drug diazepam (Valium) causes its sedative and other effects by enhancing the binding of GABA to its receptors, thereby increasing the effectiveness of GABA at the synapse.

Biogenic amines

The **biogenic amines** include the hormone epinephrine (adrenaline), together with the neurotransmitters dopamine, norepinephrine, and serotonin. Epinephrine, norepinephrine, and dopamine are derived from the amino acid tyrosine and are included in the subcategory of *catecholamines.* Serotonin is a biogenic amine derived from a different amino acid, tryptophan.

Epinephrine is released into the blood as a hormonal secretion, while **norepinephrine** is released at synapses of neurons in the sympathetic nervous system (discussed in detail later on). The effects of these neurotransmitters on target receptors are responsible for the "fight or flight" response—faster and stronger heartbeat, increased blood glucose concentration, and diversion of blood flow into the muscles and heart.

Dopamine is a very important neurotransmitter used in some areas of the brain controlling body movements and other functions. Degeneration of particular dopamine-releasing neurons produces the resting muscle tremors of Parkinson disease, and people with this condition are treated with L-dopa (an acronym for L–3,4–dihydroxyphenylalanine), a precursor from which dopamine can be produced. Additionally, studies suggest that excessive activity of dopamine-releasing neurons in other areas of the brain is associated with schizophrenia. As a result, drugs that block the production of dopamine, such as the dopamine antagonist chlorpromazine (Thorazine), sometimes help patients with schizophrenia.

Serotonin is a neurotransmitter involved in the regulation of sleep, and it is also implicated in various emotional states. Insufficient activity of neurons that release serotonin may be one cause of clinical depression. Antidepressant drugs, such as fluoxetine (Prozac), block the elimination of serotonin from the synaptic cleft; these drugs are termed *selective serotonin reuptake inhibitors*, or SSRIs.

Other neurotransmitters

Axons also release various polypeptides, called **neuropeptides,** at synapses. These neuropeptides may have a typical neurotransmitter function, or they may have more subtle, long-term action on the postsynaptic neurons. In the latter case, they are often called **neuromodulators.** A given axon generally releases only one kind of neurotransmitter, but many can release both a neurotransmitter and a neuromodulator.

Substance P is an important neuropeptide released at synapses in the CNS by sensory neurons activated by painful stimuli. The perception of pain, however, can vary depending on circumstances. An injured football player may not feel the full extent of his trauma, for example, until he is out of the game.

The intensity with which pain is perceived partly depends on the effects of neuropeptides called *enkephalins* and *endorphins.* **Enkephalins,** released by axons descending from the brain into the spinal cord, inhibit the passage of pain information back up to the brain. **Endorphins,** released by neurons in the brain stem, also block the perception of pain. Opium and its derivatives, morphine and heroin, have an analgesic (pain-reducing) effect because they are similar enough in chemical structure to bind to the receptors normally used by enkephalins and endorphins. For this reason, the enkephalins and the endorphins are referred to as *endogenous opiates.*

Nitric oxide (NO) is the first gas known to act as a regulatory molecule in the body. Because NO is a gas, it diffuses through membranes, so it cannot be stored in vesicles. It is produced as needed from the amino acid arginine. Nitric oxide diffuses out of the presynaptic axon and into neighboring cells by simply passing through the lipid portions of the plasma membranes.

In the PNS, nitric oxide is released by some neurons that innervate the gastrointestinal tract, penis, respiratory passages, and cerebral blood vessels. These autonomic neurons cause smooth-muscle relaxation in their target organs. This relaxation can produce the engorgement of the spongy tissue of the penis with blood, causing an erection. The drug sildenafil (Viagra) increases the release of NO in the penis, thus enabling and prolonging an erection. The brain releases nitric oxide as a neurotransmitter, where it appears to participate in the processes of learning and memory.

A postsynaptic neuron must integrate input from many synapses

Different types of input from a number of presynaptic neurons influence the activity of a postsynaptic neuron in the brain and spinal cord of vertebrates. For example, a single motor neuron in the spinal cord can have in excess of 50,000 synapses from presynaptic axons.

Each postsynaptic neuron may receive both excitatory and inhibitory synapses (figure 44.17). The EPSPs (depolarizations)

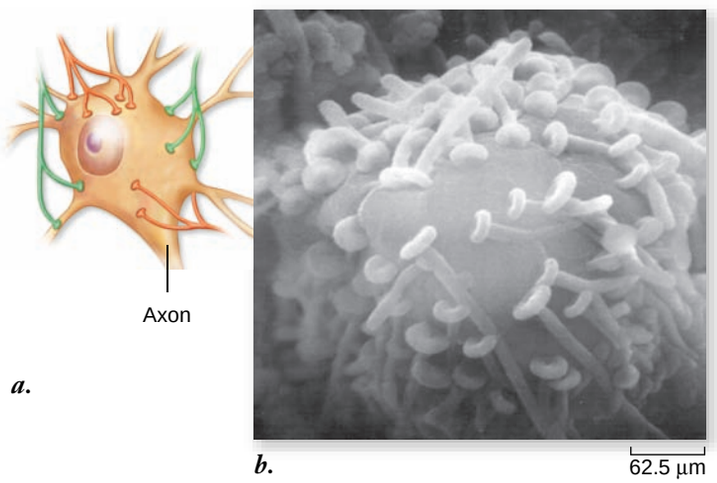


Figure 44.17 Integration of EPSPs and IPSPs takes place on the neuronal cell body. ***a.*** The synapses made by some axons are excitatory *(green);* the synapses made by other axons are inhibitory *(red).* The summed influence of all of these inputs determines whether the axonal membrane of the postsynaptic cell will be sufficiently depolarized to produce an action potential. ***b.*** Micrograph of a neuronal cell body with numerous synapses.

and IPSPs (hyperpolarizations) from these synapses interact with each other when they reach the cell body of the neuron. Small EPSPs add together to bring the membrane potential closer to the threshold, and IPSPs subtract from the depolarizing effect of the EPSPs, deterring the membrane potential from reaching threshold. This process is called *synaptic integration*.

Because of the all-or-none characteristic of an action potential, a postsynaptic neuron is like a switch that is either turned on or remains off. Information may be encoded in the pattern of firing over time, but each neuron can only fire or not fire when it receives a signal.

The events that determine whether a neuron fires may be extremely complex and involve many presynaptic neurons. There are two ways the membrane can reach the threshold voltage: by many different dendrites producing EPSPs that sum to the threshold voltage, or by one dendrite producing repeated EPSPs that sum to the threshold voltage. We call the first **spatial summation** and the second **temporal summation.**

In spatial summation, graded potentials due to dendrites from different presynaptic neurons that occur at the same time add together to produce an above-threshold voltage. All of this input does not need to be in the form of EPSPs, just so the potential produced by summing all of the EPSPs and IPSPs is greater than the threshold voltage. When the membrane at the base of the axon is depolarized above the threshold, it produces an action potential and a nerve impulse is sent down the axon.

In temporal summation, a single dendrite can produce sufficient depolarization to produce an action potential if it produces EPSPs that are close enough in time to sum to a depolarization that is greater than threshold. A typical EPSP can last for 15 ms, so for temporal summation to occur, the next impulse must arrive in less time. If enough EPSPs are produced to raise the membrane at the base of the axon above threshold, then an impulse will be sent.

The distinction between these two methods of summation is like filling a hole in the ground with soil: you can have many shovels that add soil to the hole until it is filled, or a single shovel that adds soil at a faster rate to fill the hole. When the hole is filled, the axon will fire.

Neurotransmitters play a role in drug addiction

When certain cells of the nervous system are exposed to a constant stimulus that produces a chemically mediated signal for a prolonged period, the cells may lose their ability to respond to that stimulus, a process called **habituation.** You are familiar with this loss of sensitivity—when you sit in a chair, for example, your awareness of the chair diminishes after a certain length of time.

Some nerve cells are particularly prone to this loss of sensitivity. If receptor proteins within synapses are exposed to high levels of neurotransmitter molecules for prolonged periods, the postsynaptic cell often responds by decreasing the number of receptor proteins in its membrane. This feedback is a normal function in all neurons, one of several mechanisms that have evolved to make the cell more efficient. In this case, the cell adjusts the number of receptors downward because plenty of stimulating neurotransmitter is available. In the case of artificial neurotransmitter effects produced by drugs, long-term drug use means that more of the drug is needed to obtain the same effect.

Cocaine

The drug cocaine causes abnormally large amounts of neurotransmitter to remain in the synapses for long periods. Cocaine affects neurons in the brain's "pleasure pathways" (the *limbic system*, described later). These cells use the neurotransmitter dopamine. Cocaine binds tightly to the transporter proteins on presynaptic membranes that normally remove dopamine from the synaptic cleft. Eventually the dopamine stays in the cleft, firing the receptors repeatedly. New signals add more and more dopamine, firing the pleasure pathway more and more often (figure 44.18).

Nicotine

Nicotine has been found to have no affinity for proteins on the presynaptic membrane, as cocaine does; instead, it binds directly to a specific receptor on postsynaptic neurons of the brain. Because nicotine does not normally occur in the brain, why should it have a receptor there?

Researchers have found that "nicotine receptors" are a class of receptors that normally bind the neurotransmitter acetylcholine. Nicotine evolved in tobacco plants as a secondary compound—it affects the CNS of herbivorous insects, and therefore helps to protect the plant. It is an "accident of nature" that nicotine is also able to bind to some human ACh receptors.

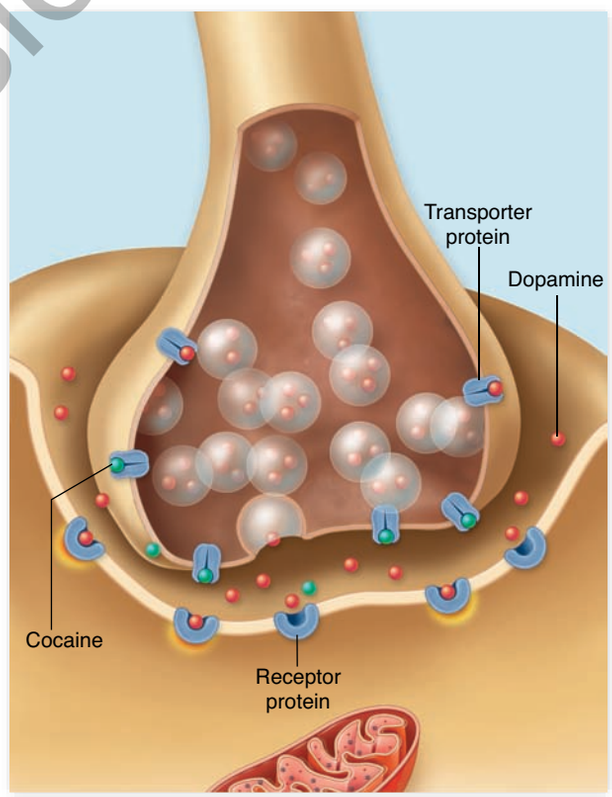


Figure 44.18 How cocaine alters events at the synapse.
When cocaine binds to the dopamine transporters, it prevents reuptake of dopamine so the neurotransmitter survives longer in the synapse and continues to stimulate the postsynaptic cell. Cocaine thus acts to intensify pleasurable sensations.

When neurobiologists compare the nerve cells in the brains of smokers with those of nonsmokers, they find changes in both the number of nicotine receptors and the levels of RNA used to make the receptors. The brain adjusts to prolonged, chronic exposure to nicotine by "turning down the volume" in two ways: (1) by making fewer receptor proteins to which nicotine can bind; and (2) by altering the pattern of activation of the nicotine receptors—that is, their sensitivity to stimulation by neurotransmitters.

Having summarized the physiology and chemistry of neurons and synapses, we turn now to the structure of the vertebrate nervous system, beginning with the CNS and then the PNS.

Learning Outcomes Review 44.3

Electrical synapses involve direct cytoplasmic connections between two neurons; chemical synapses involve chemicals that cross the synaptic cleft, which separates neurons. Neurotransmitters include acetylcholine, epinephrine, glycine, GABA, biogenic amines, substance P, and nitric oxide. Many addictive drugs bind to sites that normally bind neurotransmitters or to membrane transport proteins in synapses.

- ***Why is tobacco use such a difficult habit to overcome?***

44.4 The Central Nervous System: Brain and Spinal Cord

Learning Outcomes

1. ***Describe the organization of the brain in vertebrates.***
2. ***Describe characteristics of the human cerebrum.***
3. ***Explain how a simple reflex works.***

The complex nervous system of vertebrate animals has a long evolutionary history. In this section we describe the structures making up the CNS, namely the brain and the spinal cord. First, it is helpful to review the origin and development of the vertebrate nervous system.

As animals became more complex, so did their nervous systems

Among the noncoelomate invertebrates (see chapter 33), sponges are the only major phylum that lack nerves. The simplest nervous systems occur among cnidarians (figure 44.19),

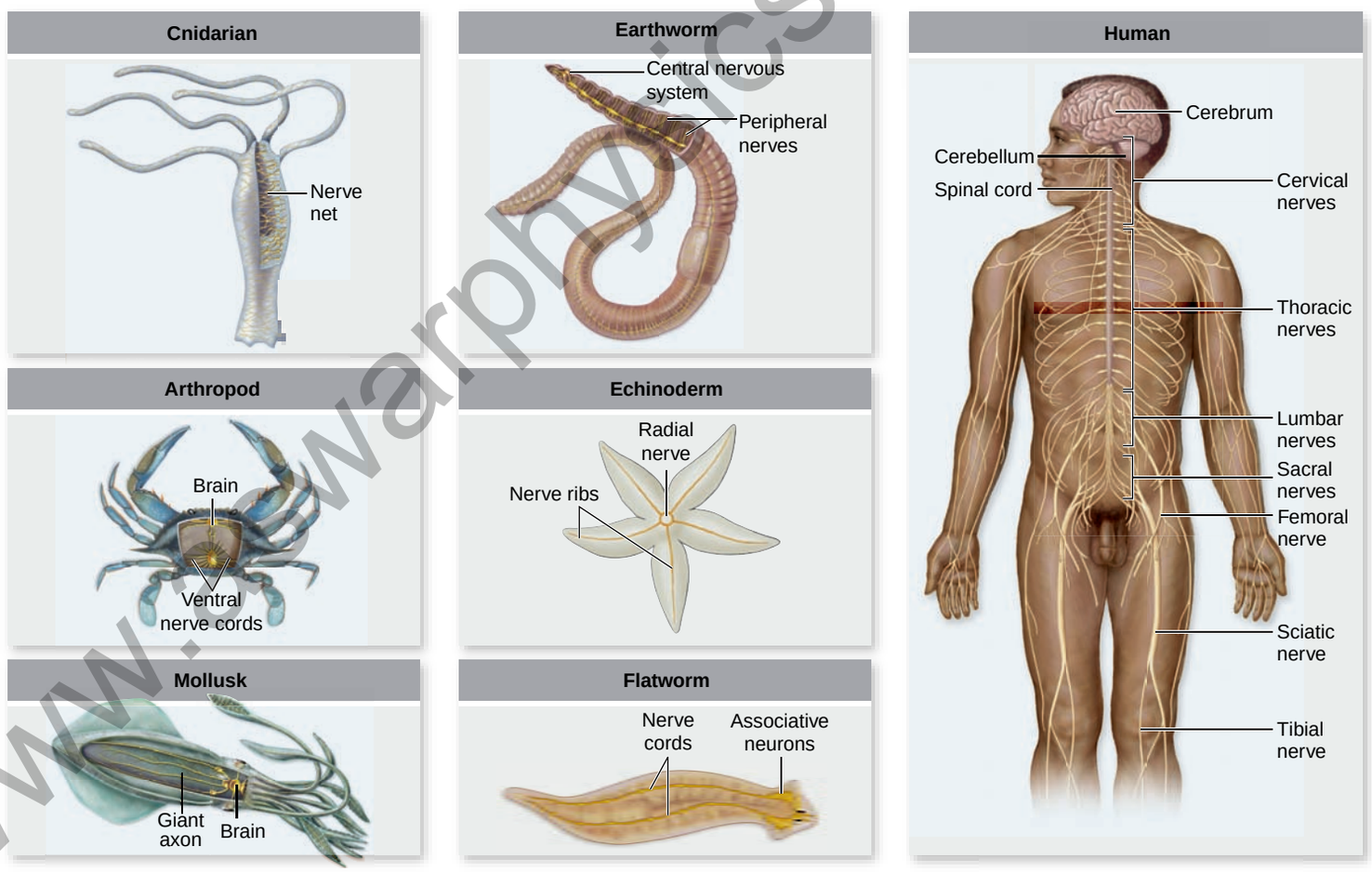


Figure 44.19 Diversity of nervous systems. Nervous systems in animals range from simple nerve nets to paired nerve cords with primitive brains to elaborate brains and sensory systems. Bilateral symmetry is correlated with the concentration of nervous tissue and sensory structures in the front end of the nerve cord. This evolutionary process is referred to as cephalization.

in which all neurons are similar and linked to one another in a web, or **nerve net.** There is no associative activity, no control of complex actions, and little coordination.

The simplest animals with associative activity in the nervous system are the free-living flatworms, phylum Platyhelminthes. Running down the bodies of these flatworms are two nerve cords, from which peripheral nerves extend outward to the muscles of the body. The two nerve cords converge at the front end of the body, forming an enlarged mass of nervous tissue that also contains interneurons with synapses connecting neurons to one another. This primitive "brain" is a rudimentary central nervous system and permits a far more complex control of muscular responses than is possible in cnidarians.

All of the subsequent evolutionary changes in nervous systems can be viewed as a series of elaborations on the characteristics already present in flatworms. For example, among coelomate invertebrates (see chapter 34), earthworms exhibit a central nervous system that is connected to all other parts of the body by peripheral nerves. And in arthropods, the central coordination of complex responses is increasingly localized in the front end of the nerve cord. As this region evolved, it came to contain a progressively larger number of interneurons and to develop tracts, which are major information highways within the brain.

Vertebrate brains have three basic divisions

Casts of the interior braincases of fossil agnathans, fishes that swam 500 MYA (see chapter 35), have revealed much about the early evolutionary stages of the vertebrate brain. Although small, these brains already had the three divisions that characterize the brains of all contemporary vertebrates:

1. the *hindbrain*, or rhombencephalon;
2. the *midbrain*, or mesencephalon; and
3. the *forebrain*, or prosencephalon (figure 44.20 and table 44.3).

The hindbrain in fishes

The hindbrain was the major component of these early brains, as it still is in fishes today. Composed of the **cerebellum, pons,** and **medulla oblongata,** the hindbrain may be considered an extension of the spinal cord devoted primarily to coordinating motor reflexes. Tracts containing large numbers of axons run like cables up and down the spinal cord to the hindbrain. The hindbrain, in turn, integrates the many sensory signals coming from the muscles and coordinates the pattern of motor responses.

Much of this coordination is carried on within a small extension of the hindbrain called the cerebellum ("little cerebrum"). In more advanced vertebrates, the cerebellum plays an increasingly important role as a coordinating center for movement and it is correspondingly larger than it is in the fishes. In all vertebrates, the cerebellum processes data on the current position and movement of each limb, the state of relaxation or contraction of the muscles involved, and the general position of the body and its relation to the outside world.

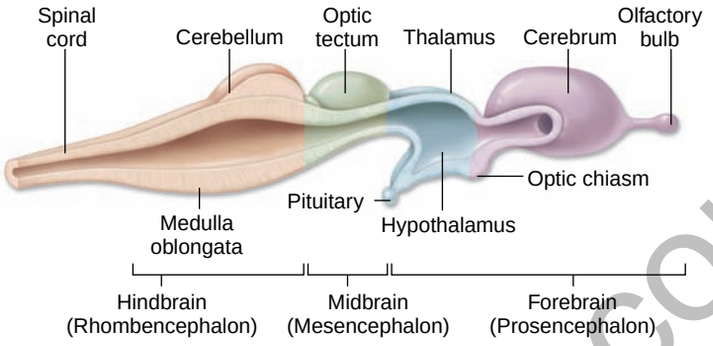


Figure 44.20 The basic organization of the vertebrate brain can be seen in the brains of primitive fishes. The brain is divided into three regions that are found in differing proportions in all vertebrates: the hindbrain, which is the largest portion of the brain in fishes; the midbrain, which in fishes is devoted primarily to processing visual information; and the forebrain, which is concerned mainly with olfaction (the sense of smell) in fishes. In terrestrial vertebrates, the forebrain plays a far more dominant role in neural processing than it does in fishes.

TABLE 44.3 Subdivisions of the Central Nervous System

Major Subdivision	Function
SPINAL CORD	Spinal reflexes; relays sensory and motor information
BRAIN	
Hindbrain (Rhombencephalon)	
Medulla oblongata	Sensory nuclei; reticular-activating system; autonomic functions
Pons	Reticular-activating system; autonomic functions
Cerebellum	Coordination of movements; balance
Midbrain (Mesencephalon)	Reflexes involving eyes and ears
Forebrain (Prosencephalon)	
Diencephalon	
Thalamus	Relay station for ascending sensory and descending motor tracts; autonomic functions
Hypothalamus	Autonomic functions; neuroendocrine control
Telencephalon (cerebrum)	
Basal ganglia	Motor control
Corpus callosum	Connects and relays information between the two hemispheres
Hippocampus (limbic system)	Memory; emotion
Cerebral cortex	Higher cognitive functions; integrates and interprets sensory information; organizes motor output

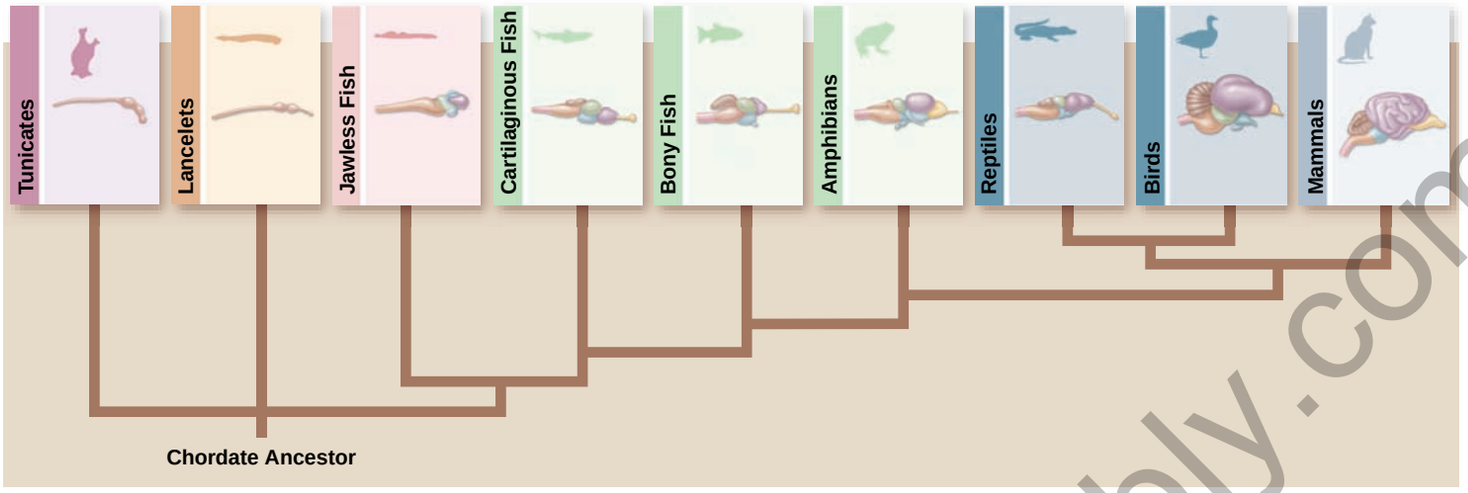


Figure 44.21 Evolution of the vertebrate brain. The relative sizes of different brain regions have changed as vertebrates have evolved. In sharks and other fishes, the hindbrain is predominant, and the rest of the brain serves primarily to process sensory information. In amphibians and reptiles, the forebrain is far larger, and it contains a larger cerebrum devoted to associative activity. In birds, which evolved from reptiles, the cerebrum is even more pronounced. In mammals, the cerebrum covers the optic tectum and is the largest portion of the brain. The dominance of the cerebrum is greatest in humans, in whom it envelops much of the rest of the brain.

The midbrain and forebrain of fishes

In fishes, the remainder of the brain is devoted to the reception and processing of sensory information. The midbrain is composed primarily of the *optic tectum*, which receives and processes visual information, whereas the forebrain is devoted to the processing of olfactory (smell) information.

The brains of fishes continue growing throughout their lives. This continued growth is in marked contrast to the brains of other classes of vertebrates, which generally complete their development by infancy. The human brain continues to develop through early childhood, but few new neurons are produced once development has ceased. One exception is the hippocampus, which has control over which experiences are filed away into long-term memory and which are forgotten. The extent of neurogenesis (production of new neurons) in adult brains is controversial, and one area of active current research.

The dominant forebrain in more recent vertebrates

Starting with the amphibians and continuing more prominently in the reptiles, processing of sensory information is increasingly centered in the forebrain. This pattern was the dominant evolutionary trend in the further development of the vertebrate brain (figure 44.21).

The forebrain in reptiles, amphibians, birds, and mammals is composed of two elements that have distinct functions. The *diencephalon* consists of the thalamus and hypothalamus. The **thalamus** is an integration and relay center between incoming sensory information and the cerebrum. The hypothalamus participates in basic drives and emotions and controls the secretions of the pituitary gland. The **telencephalon,** or "end brain," is located at the front of the forebrain and is devoted largely to associative activity. In mammals, the telencephalon is called the cerebrum. The telencephalon also includes structures we discuss later on when describing the human brain.

The expansion of the cerebrum

In examining the relationship between brain mass and body mass among the vertebrates, a remarkable difference is observed between fishes and reptiles on the one hand, and birds and mammals on the other. Mammals have brains that are particularly large relative to their body mass. This is especially true of porpoises and humans.

The increase in brain size in mammals largely reflects the great enlargement of the cerebrum, the dominant part of the mammalian brain. The **cerebrum** is the center for correlation, association, and learning in the mammalian brain. It receives sensory data from the thalamus and issues motor commands to the spinal cord via descending tracts of axons.

In vertebrates, the central nervous system is composed of the brain and the spinal cord (see table 44.3). These two structures are responsible for most of the information processing within the nervous system and they consist primarily of interneurons and neuroglia. Ascending tracts carry sensory information to the brain. Descending tracts carry impulses from the brain to the motor neurons and interneurons in the spinal cord that control the muscles of the body.

The human forebrain exhibits exceptional information-processing ability

The human cerebrum is so large that it appears to envelop the rest of the brain. It is split into right and left **cerebral hemispheres,** which are connected by a tract called the **corpus**

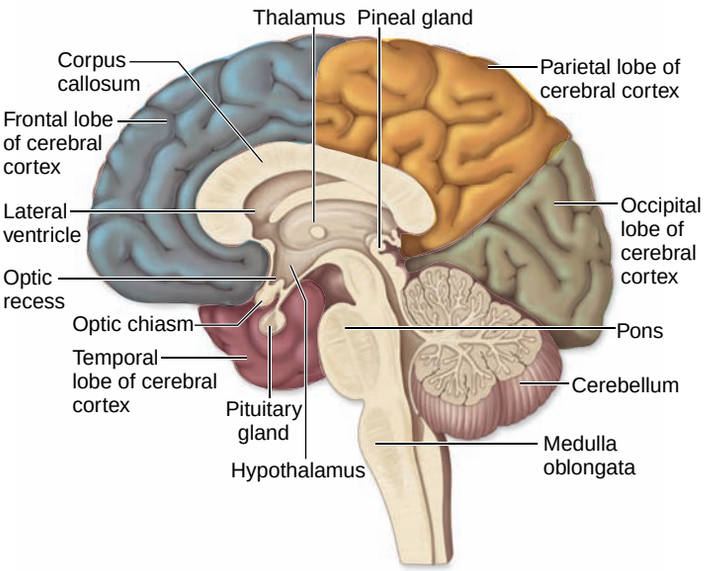


Figure 44.22 A section through the human brain. In this sagittal section showing one cerebral hemisphere, the corpus callosum, a fiber tract connecting the two cerebral hemispheres, can be clearly seen.

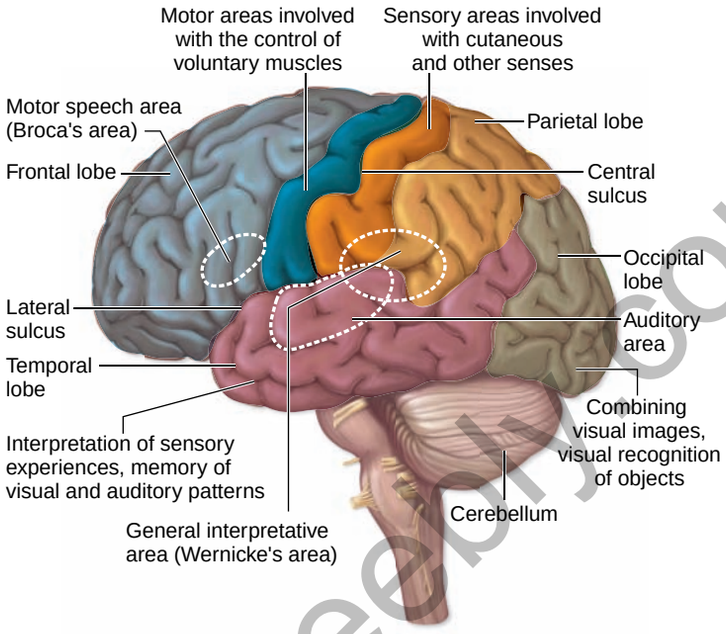


Figure 44.23 The cerebrum. This diagram shows the lobes of the cerebrum and indicates some of the known regions of specialization.

callosum (figure 44.22). The hemispheres are further divided into the *frontal*, *parietal*, *temporal*, and *occipital lobes*.

Each hemisphere primarily receives sensory input from the opposite, or contralateral, side of the body and exerts motor control primarily over that side. Therefore, a touch on the right hand is relayed primarily to the left hemisphere, which may then initiate movement of the right hand in response to the touch. Damage to one hemisphere due to a stroke often results in a loss of sensation and paralysis on the contralateral side of the body.

The cerebral cortex

Much of the neural activity of the cerebrum occurs within a layer of gray matter only a few millimeters thick on its outer surface. This layer, called the **cerebral cortex,** is densely packed with nerve cells. In humans, it contains over 10 billion nerve cells, amounting to roughly 10% of all the neurons in the brain. The surface of the cerebral cortex is highly convoluted; this is particularly true in the human brain, where the convolutions increase the surface area of the cortex threefold.

The activities of the cerebral cortex fall into one of three general categories: motor, sensory, and associative. Each of its regions correlates with a specific function (figure 44.23). The **primary motor cortex** lies along the *gyrus* (convolution) on the posterior border of the frontal lobe, just in front of the central *sulcus* (crease). Each point on the surface of the motor cortex is associated with the movement of a different part of the body (figure 44.24, right).

Just behind the central sulcus, on the anterior edge of the parietal lobe, lies the **primary somatosensory cortex.** Each point in this area receives input from sensory neurons serving skin and muscle senses in a particular part of the body (figure 44.24, left). Large areas of the primary motor cortex and primary somatosensory cortex are devoted to the fingers, lips, and tongue because of the need for manual dexterity and speech. The auditory cortex lies within the temporal lobe, and different regions of this cortex deal with different sound frequencies. The visual cortex lies on the occipital lobe, with different sites processing information from different positions on the retina, equivalent to particular points in the visual fields of the eyes.

The portion of the cerebral cortex that is not occupied by these motor and sensory cortices is referred to as the **association cortex.** The site of higher mental activities, the association cortex reaches its greatest extent in primates, especially humans, where it makes up 95% of the surface of the cerebral cortex.

Basal ganglia

Buried deep within the white matter of the cerebrum are several collections of cell bodies and dendrites that produce islands of gray matter. These aggregates of neuron cell bodies, which are collectively termed the *basal ganglia*, receive sensory information from ascending nerve tracts and motor commands from the cerebral cortex and cerebellum.

Outputs from the basal ganglia are sent down the spinal cord, where they participate in the control of body movements. Damage to specific regions of the basal ganglia can produce the resting tremor of muscles that is characteristic of Parkinson disease.

Thalamus and hypothalamus

The thalamus is a primary site of sensory integration in the brain. Visual, auditory, and somatosensory information is sent to the thalamus, where the sensory tracts synapse with association neurons. The sensory information is then relayed via the thalamus to the occipital, temporal, and parietal lobes of the cerebral cortex, respectively. The transfer of each of these types

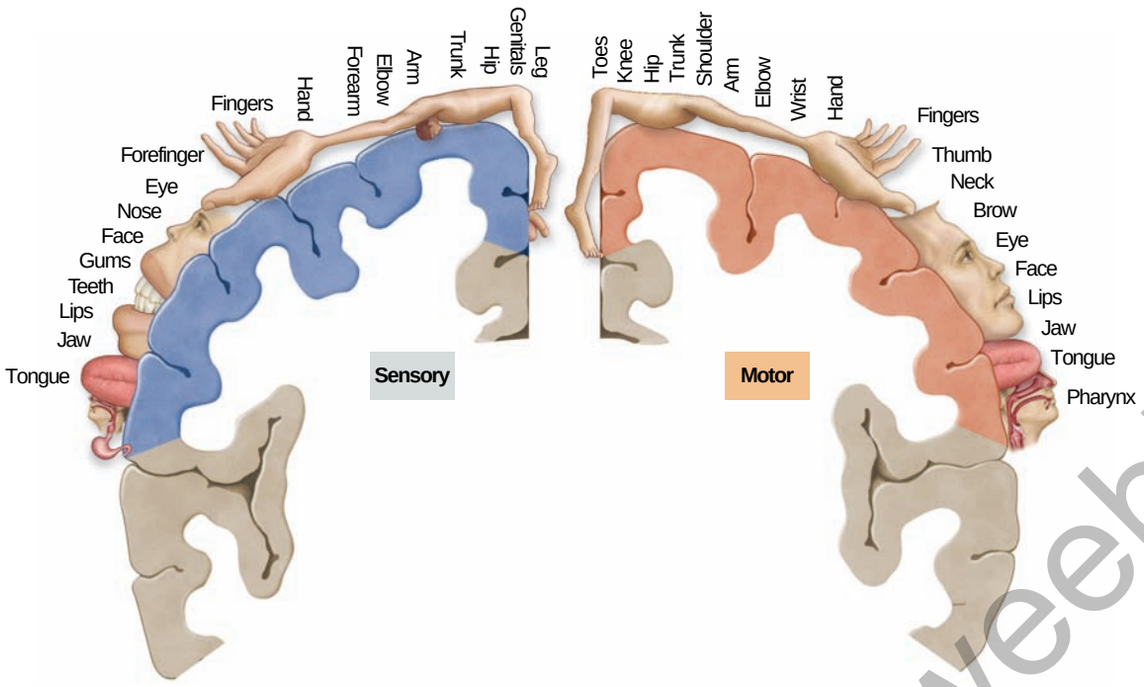


Figure 44.24 The primary somatosensory cortex (left) and the primary motor cortex (right). Each of these regions of the cerebral cortex is associated with a different region of the body, as indicated in this stylized map. The areas of the body are drawn in relative proportion to the amount of cortex dedicated to their sensation or control. For example, the hands have large areas of sensory and motor control, and the pharynx has a considerable area of motor control but little area devoted to the sensations of the pharynx.

of sensory information is handled by specific aggregations of neuron cell bodies within the thalamus.

The hypothalamus integrates the visceral activities. It helps regulate body temperature, hunger and satiety, thirst, and—along with the limbic system—various emotional states. The hypothalamus also controls the pituitary gland, which in turn regulates many of the other endocrine glands of the body. By means of its interconnections with the cerebral cortex and with control centers in the *brainstem* (a term used to refer collectively to the midbrain, pons, and medulla oblongata), the hypothalamus helps coordinate the neural and hormonal responses to many internal stimuli and emotions.

The *hippocampus* and **amygdala,** along with the hypothalamus, are the major components of the **limbic system**—an evolutionarily ancient group of linked structures deep within the cerebrum that are responsible for emotional responses, as described earlier. The hippocampus is also believed to be important in the formation and recall of memories.

Complex functions of the human brain may be controlled in specific areas

Although studying brain function is difficult, it has long fascinated researchers. The distinction between sleep and waking, the use and acquisition of language, spatial recognition, and memory are all areas of active research. Although far from understood, one generalization that emerged was the regionalization of function.

Sleep and arousal

The brainstem contains a diffuse collection of neurons referred to as the *reticular formation.* One part of this formation, the *reticular-activating system*, controls consciousness and alertness. All of the sensory pathways feed into this system, which monitors the information coming into the brain and identifies important stimuli. When the reticular-activating system has been stimulated to arousal, it increases the level of activity in many parts of the brain. Neural pathways from the reticular formation to the cortex and other brain regions are depressed by anesthetics and barbiturates.

The reticular-activating system controls both sleep and the waking state. It is easier to sleep in a dark room than in a lighted one because there are fewer visual stimuli to stimulate the reticular-activating system. In addition, activity in this system is reduced by serotonin, a neurotransmitter discussed earlier. Serotonin causes the level of brain activity to fall, bringing on sleep.

Brain state can be monitored by means of an electroencephalogram (EEG), a recording of electrical activity. Awake but relaxed individuals with eyes closed exhibit a brain pattern of large, slow waves termed *alpha waves.* In an alert individual with eyes open, the waves are more rapid *(beta waves)* and more desynchronized as sensory input is being received. *Theta waves* and *delta waves* are very slow waves seen during sleep. When an individual is in REM sleep—characterized by rapid eye movements with the eyes closed—the EEG is more like that of an awake, relaxed individual.

Language

Although the two cerebral hemispheres seem structurally similar, they are responsible for different activities. The most thoroughly investigated example of this lateralization of function is language.

The left hemisphere is the "dominant" hemisphere for language in 90% of right-handed people and nearly two-thirds of left-handed people. (By *dominant*, we mean it is the hemisphere in which most neural processing related to language is performed.) Different brain regions control language in the

Figure 44.25 Different brain regions control various language activities. This illustration shows how the brain reacts in human subjects asked to listen to a spoken word, to read that same word silently, to repeat the word out loud, and then to speak a word related to the first. Regions of white, red, and yellow show the greatest activity. Compare this with figure 44.24 to see how regions of the brain are mapped.

dominant hemisphere (figure 44.25). Wernicke's area, located in the parietal lobe between the primary auditory and visual areas, is important for language comprehension and the formulation of thoughts into speech (see figure 44.23). Broca's area, found near the part of the motor cortex controlling the face, is responsible for the generation of motor output needed for language communication.

Damage to these brain areas can cause language disorders known as *aphasias*. For example, if Wernicke's area is damaged, the person's speech is rapid and fluid but lacks meaning; words are tossed together as in a "word salad."

Spatial recognition

Whereas the dominant hemisphere for language is adept at sequential reasoning, like that needed to formulate a sentence, the nondominant hemisphere (the right hemisphere in most people) is adept at spatial reasoning, the type of reasoning needed to assemble a puzzle or draw a picture. It is also the hemisphere primarily involved in musical ability—a person with damage to Broca's speech area in the left hemisphere may not be able to speak but may retain the ability to sing.

Damage to the nondominant hemisphere may lead to an inability to appreciate spatial relationships and may impair musical activities such as singing. Even more specifically, damage to the inferior temporal cortex in that hemisphere eliminates the capacity to recall faces, a condition known as prosopagnosia. Reading, writing, and oral comprehension remain normal, and patients with this disability can still recognize acquaintances by their voices. The nondominant hemisphere is also important for the consolidation of memories of nonverbal experiences.

Memory and learning

One of the great mysteries of the brain is the basis of memory and learning. Memory appears dispersed across the brain. Specific cortical sites cannot be identified for particular memories because relatively extensive cortical damage does not selectively remove memories. Although memory is impaired if portions of the brain, particularly the temporal lobes, are removed, it is not lost entirely. Many memories persist in spite of the damage, and the ability to access them is gradually recovered with time.

Fundamental differences appear to exist between short-term and long-term memory. Short-term memory is transient, lasting only a few moments. Such memories can readily be erased by the application of an electrical shock, leaving previously stored long-term memories intact. This result suggests that short-term memories are stored in the form of a transient neural excitation. Long-term memory, in contrast, appears to involve structural changes in certain neural connections within the brain.

Two parts of the temporal lobes, the hippocampus and the amygdala, are involved in both short-term memory and its consolidation into long-term memory. Damage to these structures impairs the ability to process recent events into long-term memories.

Synaptic plasticity

Part of the basis of learning and memory are changes to the function of a synapse over time. Two examples of this synaptic plasticity are long-term potentiation (LTP), and long-term depression (LTD). The mechanism of LTP is complex and not completely understood. One well-studied form involves synapses that release the neurotransmitter glutamate, and have *N*-methyl-D-aspartic acid (NMDA) type of receptors. When either the same synapse is stimulated repeatedly, or neighboring synapses are stimulated, the postsynaptic membrane becomes significantly depolarized. This releases a block of the NMDA receptor by Mg^{2+} such that glutamate binding causes an influx of Ca^{2+} that stimulates a signal transduction pathway involving calcium/calmodulin-dependent protein kinase II. This pathway leads to the insertion of another receptor type, the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor, into the postsynaptic membrane, making the synapse more sensitive to future stimulation (figure 44.26).

If the stimulation of an NMDA receptor is less, and the postsynaptic membrane is less depolarized, LTD can result. In this case, a different Ca^{2+}-dependent signaling pathway results in the loss of AMPA receptors from the membrane. Taken together, these two mechanisms can make a synapse more or less sensitive to future stimulation.

Alzheimer disease: Degeneration of brain neurons

In the past, little was known about *Alzheimer disease*, a condition in which the memory and thought processes of the brain become dysfunctional. Scientists disagree about the biological nature of the disease and its cause. Two hypotheses have been proposed: One suggests that nerve cells in the brain are killed from the outside in, and the other that the cells are killed from the inside out.

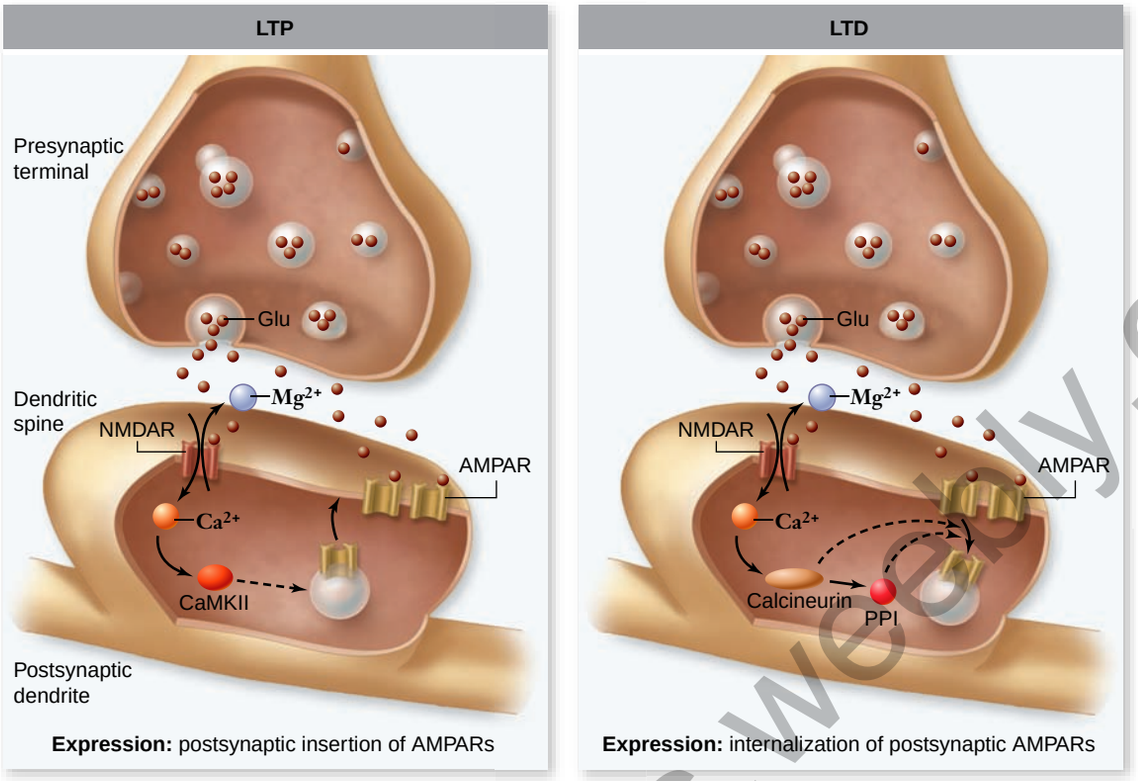


Figure 44.26 LTP and LTD modulate synaptic function. ***a.*** When a the postsynaptic membrane is significantly depolarized, when GABA binds to the *N*-methyl-D-aspartic acid receptor (NMDAR), the influx of Ca^{2+} leads to the insertion of α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptors (AMPAR). This potentiates the synapse for future stimulation. ***b.*** When the postsynaptic membrane does not have as large a depolarization, or there is less GABA, then GABA binding to NMDA receptor triggers a different pathway that results in removal of AMPA receptors. This depresses the synapse for future stimulation. CaMKII, calmodulin-dependent protein kinase 2.

In the first hypothesis, external proteins called β-amyloid exist in an abnormal form, which then forms aggregates, or plaques. The plaques begin to fill in the brain and then damage and kill nerve cells. However, these amyloid plaques have been found in autopsies of people who did not exhibit Alzheimer disease.

The second hypothesis maintains that the nerve cells are killed by an abnormal form of an internal protein called tau (τ), which normally functions to maintain protein transport microtubules. Abnormal forms of τ-protein assemble into helical segments that form tangles, which interfere with the normal functioning of the nerve cells. At this point, the association of tangles with actual neuronal death is stronger.

The spinal cord conveys messages and controls some responses directly

The spinal cord is a cable of neurons extending from the brain down through the backbone (figure 44.27). It is enclosed and protected by the vertebral column and layers of membranes called *meninges*, which also cover the brain. Inside the spinal cord are two zones.

The inner zone is gray matter and primarily consists of the cell bodies of interneurons, motor neurons, and neuroglia. The outer zone is white matter and contains cables of sensory axons in the dorsal columns and motor axons in the ventral columns. These nerve tracts may also contain the dendrites of other nerve cells. Messages from the body and the brain run up and down the spinal cord, the body's "information highway."

In addition to relaying messages, the spinal cord also functions in **reflexes,** the sudden, involuntary movement of muscles. A reflex produces a rapid motor response to a stimulus because the sensory neuron passes its information to a motor

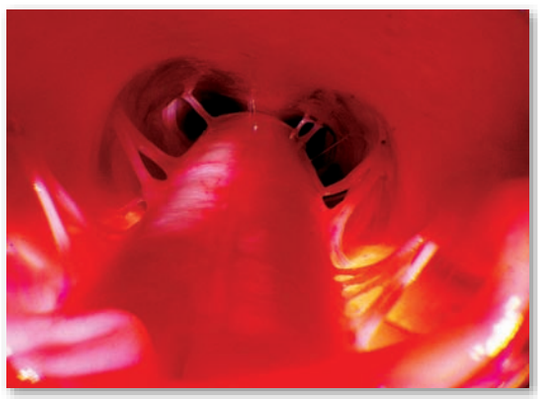
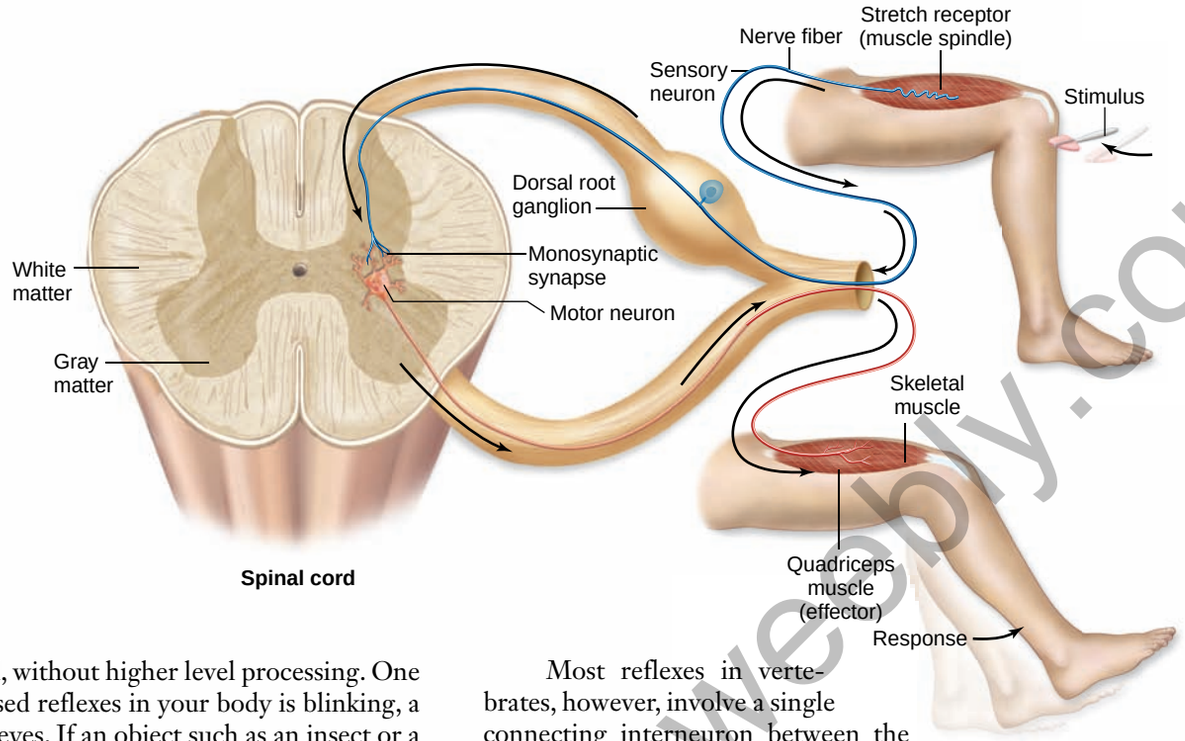


Figure 44.27 A view down the human spinal cord. Pairs of spinal nerves can be seen extending from the spinal cord. Along these nerves, as well as the cranial nerves that arise from the brain, the central nervous system communicates with the rest of the body.

Figure 44.28
The knee-jerk reflex.
This is the simplest reflex, involving only sensory and motor neurons.

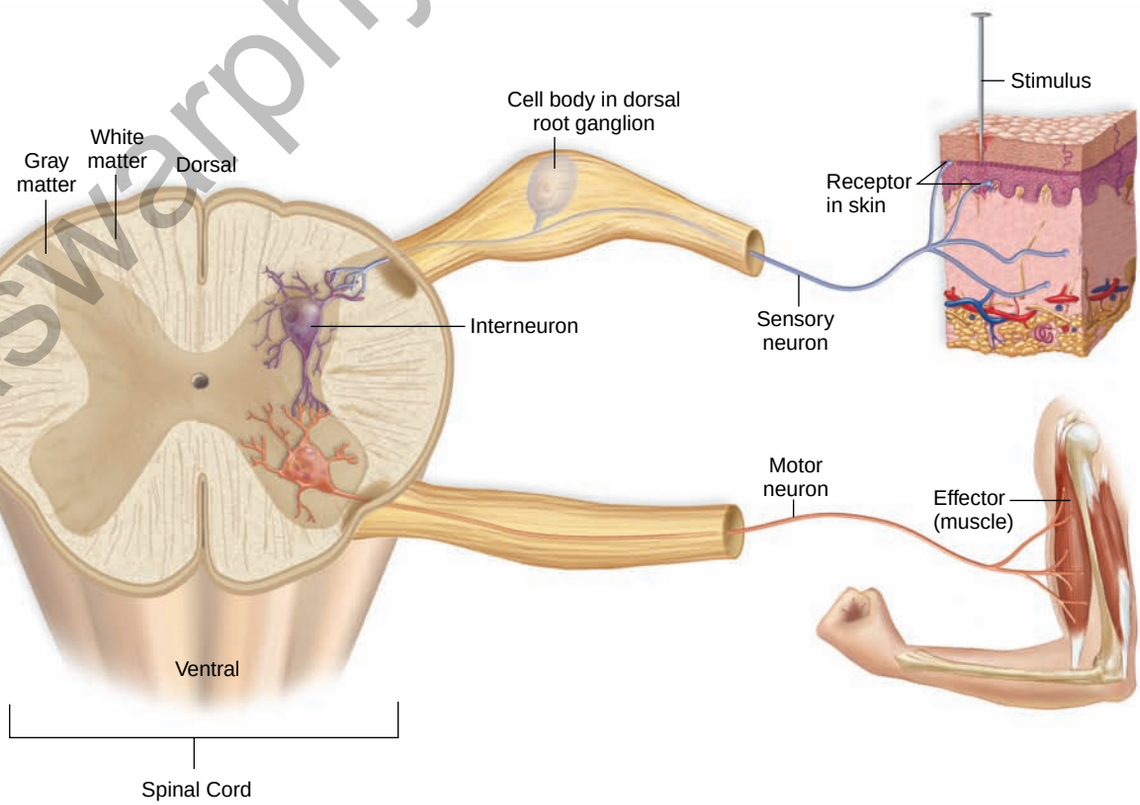


neuron in the spinal cord, without higher level processing. One of the most frequently used reflexes in your body is blinking, a reflex that protects your eyes. If an object such as an insect or a cloud of dust approaches your eye, the eyelid blinks before you realize what has happened. The reflex occurs before the cerebrum is aware the eye is in danger.

Because they pass information along only a few neurons, reflexes are very fast. A few reflexes, such as the knee-jerk reflex (figure 44.28), are monosynaptic reflex arcs. In these, the sensory nerve cell makes synaptic contact directly with a motor neuron in the spinal cord whose axon travels directly back to the muscle.

Most reflexes in vertebrates, however, involve a single connecting interneuron between the sensory neuron and the motor neuron (figure 44.29). The withdrawal of a hand from a hot stove or the blinking of an eye in response to a puff of air involves a relay of information from a sensory neuron through one or more interneurons to a motor neuron. The motor neuron then stimulates the appropriate muscle to contract. Notice that the sensory neuron may also connect to other interneurons to send signals to the brain. Although you jerked your hand away from the stove, you will still feel pain.

Figure 44.29
A cutaneous spinal reflex. This reflex is more complex than a knee-jerk reflex because it requires interneurons as well as sensory and motor neurons. Interneurons connect a sensory neuron with a motor neuron to cause muscle contraction as shown. Other interneurons inhibit motor neurons, allowing antagonistic muscles to relax.



Spinal cord regeneration

In the past, scientists tried to repair severed spinal cords by installing nerves from another part of the body to bridge the gap and act as guides for the spinal cord to regenerate. But most of these experiments failed. Although axons may regenerate through the implanted nerves, they cannot penetrate the spinal cord tissue once they leave the implant. Also, a factor that inhibits nerve growth is present in the spinal cord.

After discovering that fibroblast growth factor stimulates nerve growth, neurobiologists working with rats tried "gluing" the nerves on, from the implant to the spinal cord, with fibrin that had been mixed with the fibroblast growth factor. Three months later, rats with the nerve bridges began to show movement in their lower bodies. Dye tests indicated that the spinal cord nerves had regrown from both sides of the gap.

Many scientists are encouraged by the potential to use a similar treatment in human medicine. But most spinal cord injuries in humans do not involve a completely severed spinal cord; often, nerves are crushed, which results in different tissue damage. Also, even though the rats with nerve bridges did regain some ability to move, tests indicated that they were barely able to walk or stand.

Learning Outcomes Review 44.4

The vertebrate brain has three primary regions: the hindbrain, midbrain, and forebrain. The cerebrum, part of the forebrain, is composed of two cerebral hemispheres in which gray matter of the cerebral cortex overlays white matter and islands of gray matter (nuclei) called the basal ganglia. The spinal cord relays messages to and from the brain; a reflex occurs when the spinal cord processes sensory information directly and initiates a motor response.

- ***What is the advantage of having reflexes?***

44.5 *The Peripheral Nervous System: Sensory and Motor Neurons*

Learning Outcomes

1. ***Describe the organization of the peripheral nervous system.***
2. ***Explain the actions of sensory and somatic neurons.***
3. ***Distinguish between the somatic and autonomic nervous systems.***
4. ***Describe differences between the sympathetic and parasympathetic divisions of the autonomic nervous system.***

The PNS consists of nerves, the cablelike collections of axons (figure 44.30), and **ganglia** (singular, *ganglion*), aggregations of neuron cell bodies located outside the CNS. To review, the function of the PNS is to receive information from the environment, convey it to the CNS, and to carry responses to effectors such as muscle cells.

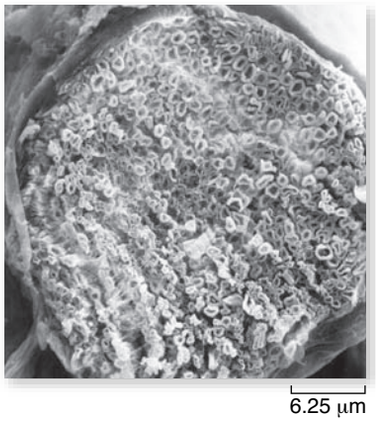


Figure 44.30 Nerves in the peripheral nervous system. Photomicrograph showing a cross section of a bullfrog nerve. The nerve is a bundle of axons bound together by connective tissue. Many myelinated axons are visible, each looking somewhat like a doughnut.

The PNS has somatic and autonomic systems

At the spinal cord, a spinal nerve separates into sensory and motor components. The axons of sensory neurons enter the dorsal surface of the spinal cord and form the **dorsal root** of the spinal nerve, whereas motor axons leave from the ventral surface of the spinal cord and form the **ventral root** of the spinal nerve. The cell bodies of sensory neurons are grouped together outside each level of the spinal cord in the **dorsal root ganglia.** The cell bodies of somatic motor neurons, on the other hand, are located within the spinal cord and so are not located in ganglia.

As mentioned earlier, somatic motor neurons stimulate skeletal muscles to contract, and autonomic motor neurons innervate involuntary effectors—smooth muscles, cardiac muscle, and glands. A comparison of the somatic and autonomic nervous systems is provided in table 44.4; we discuss each system in turn.

TABLE 44.4 Comparison of the Somatic and Autonomic Nervous Systems

Characteristic	Somatic	Autonomic
Effectors	Skeletal muscle	Cardiac muscle
		Smooth muscle Gastrointestinal tract Blood vessels Airways
		Exocrine glands
Effect on motor nerves	Excitation	Excitation or inhibition
Innervation of effector cells	Always single	Typically dual
Number of sequential neurons in path to effector	One	Two
Neurotransmitter	Acetylcholine	Acetylcholine, norepinephrine

The somatic nervous system controls movements

Somatic motor neurons stimulate the skeletal muscles of the body to contract in response to conscious commands and as part of reflexes that do not require conscious control. Voluntary control of skeletal muscles is achieved by activation of tracts of axons that descend from the cerebrum to the appropriate level of the spinal cord. Some of these descending axons stimulate spinal cord motor neurons directly, and others activate interneurons that in turn stimulate the spinal motor neurons.

When a particular muscle is stimulated to contract, however, its antagonist must be inhibited. In order to flex the arm, for example, the flexor muscles must be stimulated while the antagonistic extensor muscle is inhibited (see chapter 47). Descending motor axons produce this necessary inhibition by causing hyperpolarizations (IPSPs) of the spinal motor neurons that innervate the antagonistic muscles.

The autonomic nervous system controls involuntary functions through two divisions

The autonomic nervous system is composed of the *sympathetic* and *parasympathetic* divisions plus the medulla oblongata of the hindbrain, which coordinates this system. Although they differ, the sympathetic and parasympathetic divisions share several features. In both, the efferent motor pathway involves two neurons: The first has its cell body in the CNS and sends an axon to an autonomic ganglion; it is called *preganglionic neuron*. These neurons release acetylcholine at their synapses.

The second neuron has its cell body in the autonomic ganglion and sends its axon to synapse with a smooth muscle, cardiac muscle, or gland cell (figure 44.31). This second neuron is termed the *postganglionic neuron*. Those in the parasympathetic division release ACh, and those in the sympathetic division release norepinephrine.

The sympathetic division

In the sympathetic division, the preganglionic neurons originate in the thoracic and lumbar regions of the spinal cord (figure 44.32, left). Most of the axons from these neurons synapse in two parallel chains of ganglia immediately outside the spinal cord. These structures are usually called the *sympathetic chain* of ganglia. The sympathetic chain contains the cell bodies of postganglionic neurons, and it is the axons from these neurons that innervate the different visceral organs.

There are some exceptions to this general pattern, however. The axons of some preganglionic sympathetic neurons pass through the sympathetic chain without synapsing and, instead, terminate within the medulla of the adrenal gland (see chapter 46). In response to action potentials, the adrenal medulla cells secrete the hormone epinephrine (adrenaline). At the same time, norepinephrine is released at the synapses of the postganglionic neurons. As described earlier, both of these neurotransmitters prepare the body for action by heightening metabolism and blood flow.

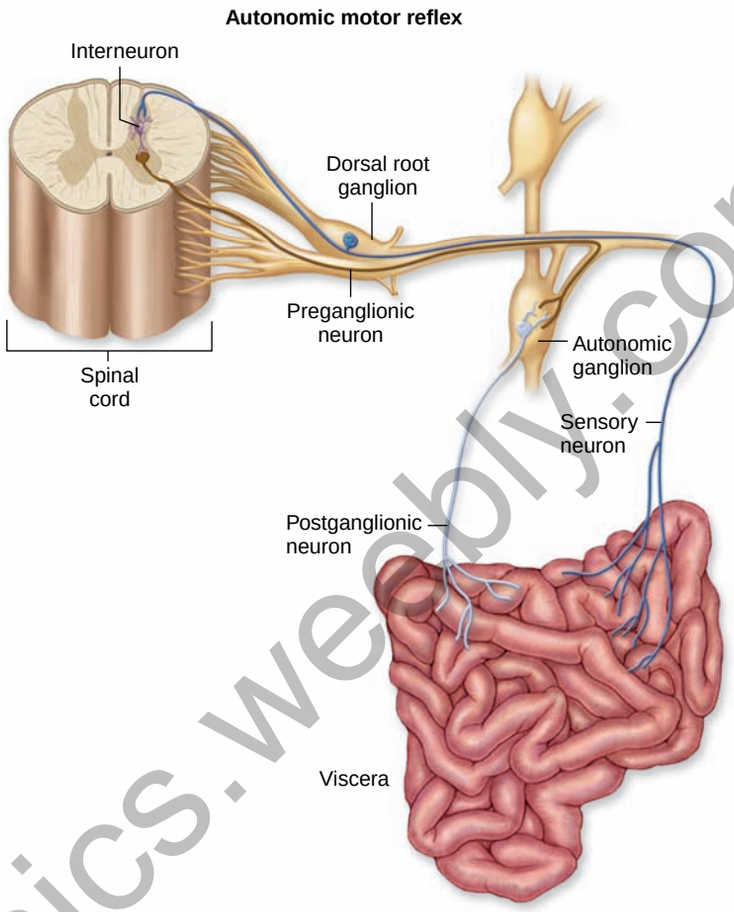


Figure 44.31 An autonomic neural path. There are two motor neurons in the efferent pathway. The first, or preganglionic neuron, exits the CNS and synapses at an autonomic ganglion. The second, or postganglionic neuron, exits the ganglion and regulates the visceral effectors (smooth muscle, cardiac muscle, or glands).

The parasympathetic division

The actions of the sympathetic division are antagonized by the parasympathetic division. Preganglionic parasympathetic neurons originate in the brain and sacral regions of the spinal cord (see figure 44.32, right). Because of this origin, there cannot be a chain of parasympathetic ganglia analogous to the sympathetic chain. Instead, the preganglionic axons, many of which travel in the vagus (tenth cranial) nerve, terminate in ganglia located near or even within the internal organs. The postganglionic neurons then regulate the internal organs by releasing ACh at their synapses. Parasympathetic nerve effects include a slowing of the heart, increased secretions and activities of digestive organs, and so on. Table 44.5 compares the actions of the sympathetic and parasympathetic divisions.

G proteins mediate cell responses to autonomic signals

You might wonder how release of ACh can slow the heart rate—an inhibitory effect—when it has excitatory effects elsewhere.

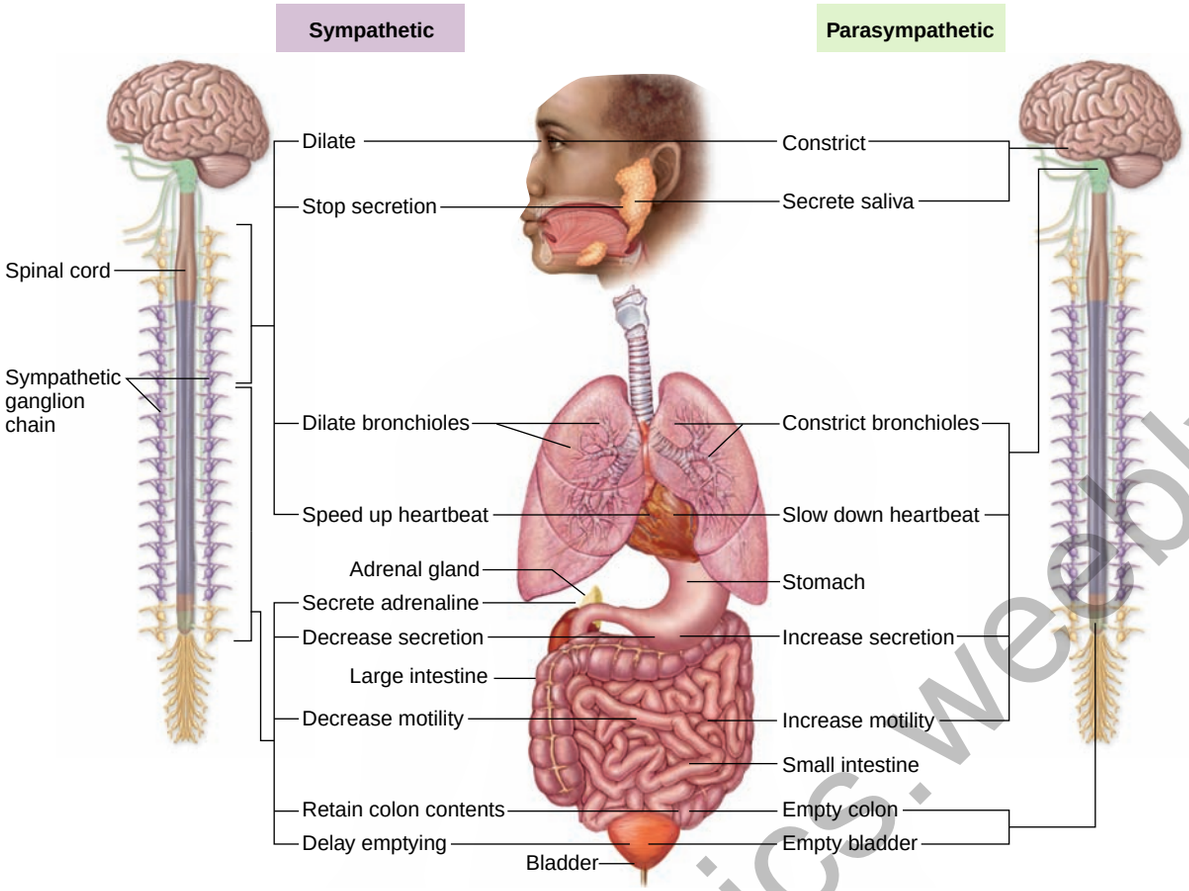


Figure 44.32
The sympathetic and parasympathetic divisions of the autonomic nervous system. The preganglionic neurons of the sympathetic division exit the thoracic and lumbar regions of the spinal cord, and those of the parasympathetic division exit the brain and sacral region of the spinal cord. The ganglia of the sympathetic division are located near the spinal cord; and those of the parasympathetic division are located near the organs they innervate. Most of the internal organs are innervated by both divisions.

TABLE 44.5 Autonomic Innervation of Target Tissues

Target Tissue	Sympathetic Stimulation	Parasympathetic Stimulation
Pupil of eye	Dilation	Constriction
Glands		
Salivary	Vasoconstriction; slight secretion	Vasodilation; copious secretion
Gastric	Inhibition of secretion	Stimulation of gastric activity
Liver	Stimulation of glucose secretion	Inhibition of glucose secretion
Sweat	Sweating	None
Gastrointestinal tract		
Sphincters	Increased tone	Decreased tone
Wall	Decreased tone	Increased motility
Gallbladder	Relaxation	Contraction
Urinary bladder		
Muscle	Relaxation	Contraction
Sphincter	Contraction	Relaxation
Heart muscle	Increased rate and strength	Decreased rate
Lungs	Dilation of bronchioles	Constriction of bronchioles
Blood vessels		
In muscles	Dilation	None
In skin	Constriction	None
In viscera	Constriction	Dilation

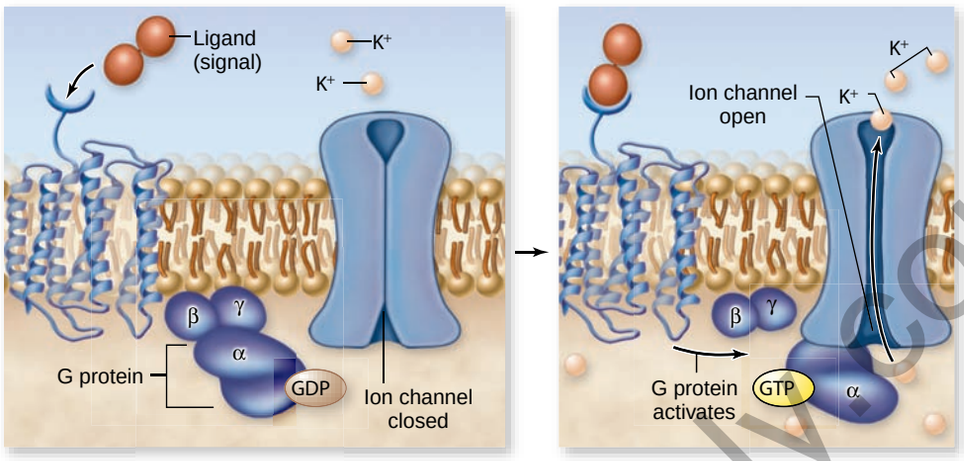


Figure 44.33 The parasympathetic effects of ACh require the action of G proteins. The binding of ACh to its receptor causes dissociation of a G protein complex, releasing some components of this complex to move within the membrane and bind to other proteins that form ion channels. Shown here are the effects of ACh on the heart, where the G protein components cause the opening of K+ channels. This leads to outward diffusion of potassium and hyperpolarization, slowing the heart rate.

The answer is simple, the cells involved in each case have different receptors for ACh that produce different effects. In the neuromuscular junction, the receptor for ACh is a ligand-gated Na^+ channel that when open allows an influx of Na^+ that depolarizes the membrane. In the case of the heart, the inhibitory effect on the pacemaker cells is produced because binding of ACh to a different receptor leads to K^+ channels opening, resulting in the outward diffusion of K^+, hyperpolarizing the membrane. The ACh receptor in the heart is a member of the class of receptors called G protein–coupled receptors.

In chapter 9, you learned that G protein–coupled receptors consist of a membrane receptor and effector protein that are coupled by the action of a G protein. The receptor is activated by binding to its ligand, in this case ACh, and the receptor activates a G protein that in turn activates an effector protein, in this case a K^+ channel (figure 44.33).

This kind of system can also lead to excitation in other organs if the G protein acts on different effector proteins. For example, the parasympathetic nerves that innervate the stomach can cause increased gastric secretions and contractions.

The sympathetic nerve effects also are mediated by the action of G protein–coupled receptors. Stimulation by norepinephrine from sympathetic nerve endings and epinephrine from the adrenal medulla requires G proteins to activate the target cells. We describe these interactions in more detail, together with hormone action, in chapter 46.

Learning Outcomes Review 44.5

The PNS comprises the somatic (voluntary) and autonomic (involuntary) nervous systems. A spinal nerve contains sensory neurons, which carry information from sense organs to the CNS, and motor neurons, which carry directives from the CNS to targets such as muscle cells. The sympathetic division of the autonomic nervous system activates the body for fight-or-flight responses; the parasympathetic division generally promotes relaxation and digestion.

- ***Why would having the sympathetic and parasympathetic divisions be more advantageous than having a single system?***

Chapter Review

44.1 Nervous System Organization

The three types of neurons in vertebrates are sensory neurons, motor neurons, and interneurons (see figure 44.1).

The central nervous system is the "command center."

The CNS consists of the brain and the spinal cord, where sensory input is integrated and responses originate.

The peripheral nervous system collects information and carries out responses.

The PNS comprises sensory neurons that carry impulses to the CNS and motor neurons that carry impulses from the CNS to effectors.

The somatic nervous system primarily acts on skeletal muscles; the autonomic nervous system is involuntary and consists of the antagonistic sympathetic and parasympathetic divisions.

The structure of neurons supports their function.

Neurons have a cell body, dendrites that receive information, and a long axon that conducts impulses away from the cell.

Supporting cells include Schwann cells and oligodendrocytes.

Neuroglia are supporting cells of the nervous system. Schwann cells (PNS) and oligodendrocytes (CNS) produce myelin sheaths that surround and insulate axons (see figure 44.3).

44.2 The Mechanism of Nerve Impulse Transmission

An electrical difference exists across the plasma membrane.

The sodium–potassium pump moves Na^+ outside the cell and K^+ into the cell. Leakage of K^+ also moves positive charge outside the cell. The membrane resting potential is typically –70 mV.

Graded potentials are small changes that can reinforce or negate each other.

Ligand-gated ion channels are responsible for graded potentials. Graded potentials can combine in an additive way (summation).

Action potentials result when depolarization reaches a threshold.

Action potentials are all-or-nothing events resulting from the rapid and sequential opening of votage-gated ion channels (see figure 44.9).

Action potentials are propagated along axons.

Influx of Na^+ during an action potential causes the adjacent region to depolarize, producing its own action potential (see figure 44.10).

There are two ways to increase the velocity of nerve impulses.

The speed of nerve impulses increases as the diameter of the axon increases. Saltatory conduction, in which impulses jump from node to node, also increases speed (see figure 44.11).

44.3 Synapses: Where Neurons Communicate with Other Cells

An action potential terminates at the end of the axon at the synapse—a gap between the axon and another cell.

The two types of synapses are electrical and chemical.

Electrical synapses consist of gap junctions; chemical synapses release neurotransmitters to cross the synapse (see figure 44.14).

Many different chemical compounds serve as neurotransmitters.

Neurotransmitter molecules include acetylcholine, amino acids, biogenic amines, neuropeptides, and a gas—nitric oxide.

A postsynaptic neuron must integrate input from many synapses.

Excitatory postsynaptic potentials (EPSPs) depolarize the membrane; inhibitory postsynaptic potentials (IPSPs) hyperpolarize it. The additive effect may or may not produce an action potential.

Neurotransmitters play a role in drug addiction.

Addictive drugs often act by mimicking a neurotransmitter or by interfering with neurotransmitter reuptake.

44.4 The Central Nervous System: Brain and Spinal Cord

As animals became more complex, so did their nervous systems.

The nervous system has evolved from a nerve net composed of linked nerves, to nerve cords with association nerves, and to the development of coordination centers (see figure 44.19).

Vertebrate brains have three basic divisions.

The vertebrate brain is divided into hindbrain, midbrain, and forebrain (see figure 44.20). The forebrain is divided further into the diencephalon and telencephalon. The telencephalon, called the cerebrum in mammals, is the center for association and learning.

The human forebrain exhibits exceptional information-processing ability.

The cerebrum is divided into right and left hemispheres (see figure 44.22), which are subdivided into frontal, parietal, temporal, and occipital lobes (see figure 44.23). The cerebrum contains the primary motor and somatosensory cortexes as well as the basal ganglia.

The limbic system consists of the hypothalamus, hippocampus, and amygdala, and it is responsible for emotional states.

Complex functions of the human brain may be controlled in specific areas.

The reticular activating system in the brainstem controls consciousness and alertness. Short-term memory may be stored as transient neural excitation; long-term memory involves changes in neural connections.

The spinal cord conveys messages and controls some responses directly.

Reflexes are the sudden, involuntary movement of muscles in response to a stimulus (see figures 44.28 and 44.29).

44.5 The Peripheral Nervous System: Sensory and Motor Neurons

The PNS has somatic and autonomic systems.

Sensory axons (inbound) form the dorsal root of the spinal nerve. The cell bodies are in the dorsal root ganglia.

Motor axons (outbound) form the ventral root of the spinal nerve. Cell bodies are located in the spinal cord.

The somatic nervous system controls movements.

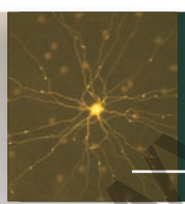
Somatic motor neurons stimulate skeletal muscles in response to conscious commands and involuntary reflexes.

The autonomic nervous system controls involuntary functions through two divisions.

Sympathetic neurons originate in the thoracic and lumbar regions of the spinal cord and synapse at an autonomic ganglion outside the spinal cord (see figure 44.31). Parasympathetic neurons originate in the brain and in sacral regions of the spinal cord and terminate in ganglia near or within internal organs (see figure 44.32 and table 44.5).

G proteins mediate cell responses to autonomic signals.

The binding of ACh activates a G protein that in turn activates a K^+ channel, allowing outflow of K^+ and hyperpolarization of the membrane and slowing heart rate.



Review Questions

UNDERSTAND

1. Which of the following best describes the electrical state of a neuron at rest?
   a. The inside of a neuron is more negatively charged than the outside.
   b. The outside of a neuron is more negatively charged than the inside.
   c. The inside and the outside of a neuron have the same electrical charge.
   d. Potassium ions leak into a neuron at rest.
2. The ____cannot be controlled by conscious thought.
   a. motor neurons
   b. somatic nervous system
   c. autonomic nervous system
   d. skeletal muscles

3. A fight-or-flight response in the body is controlled by the
   a. sympathetic division of the nervous system.
   b. parasympathetic division of the nervous system.
   c. release of acetylcholine from postganglionic neurons.
   d. somatic nervous system.
4. Inhibitory neurotransmitters
   a. hyperpolarize postsynaptic membranes.
   b. hyperpolarize presynaptic membranes.
   c. depolarize postsynaptic membranes.
   d. depolarize presynaptic membranes.
5. White matter is____, and gray matter is____.
   a. comprised of axons; comprised of cell bodies and dendrites
   b. myelinated; unmyelinated
   c. found in the CNS; also found in the CNS
   d. all of these are correct
6. During an action potential
   a. the rising phase is due to an influx of Na^+.
   b. the falling phase is due to an influx of K^+.
   c. the falling phase is due to an efflux of K^+.
   d. both a and c occur.
7. A functional reflex requires
   a. only a sensory neuron and a motor neuron.
   b. a sensory neuron, the thalamus, and a motor neuron.
   c. the cerebral cortex and a motor neuron.
   d. only the cerebral cortex and the thalamus.

APPLY

1. Imagine that you are doing an experiment on the movement of ions across neural membranes. Which of the following plays a role in determining the equilibrium concentration of ions across these membranes?
   a. Ion concentration gradients
   b. Ion pH gradients
   c. Ion electrical gradients
   d. Both a and c
2. The Na^+/K^+ ATPase pump is
   a. not required for action potential firing.
   b. important for long-term maintenance of resting potential.
   c. important only at the synapse.
   d. used to stimulate graded potentials.
3. Botox, a derivative of the botulinum toxin that causes food poisoning, inhibits the release of acetylcholine at the neuromuscular junction. How could this strange-sounding treatment produce desired cosmetic effects?
   a. By inhibiting the parasympathetic branch of the autonomic nervous system
   b. By inhibiting the sympathetic branch of the autonomic nervous system
   c. By causing paralysis of facial muscles, which decreases wrinkles in the face
   d. By causing facial muscles to contract, whereby the skin is stretched tighter, thereby reducing wrinkles
4. The following is a list of the components of a chemical synapse. A mutation in the structure of which of these would affect only the reception of the message, not its release or the response?
   a. Membrane proteins in the postsynaptic cell
   b. Proteins in the presynaptic cell
   c. Cytoplasmic proteins in the postsynaptic cell
   d. Both a and b
5. Suppose that you stick your finger with a sharp pin. The area affected is very small and only one pain receptor fires. However, it fires repeatedly at a rapid rate (it hurts!). This is an example of
   a. temporal summation.
   b. spatial summation.
   c. habituation.
   d. repolarization.
6. As you sit quietly reading this sentence, the part of the nervous system that is most active is the
   a. somatic nervous system.
   b. sympathetic nervous system.
   c. parasympathetic nervous system.
   d. none of these choices is correct.
7. G protein–coupled receptors are involved in the nervous system by
   a. controlling the release of neurotransmitters.
   b. controlling the opening and closing of Na+ channels during an action potential.
   c. controlling the opening and closing of K+ channels during an action potential.
   d. acting as receptors for neurotransmitters on postsynaptic cells.

SYNTHESIZE

1. Tetraethylammonium (TEA) is a drug that blocks voltage-gated K^+ channels. What effect would TEA have on the action potentials produced by a neuron? If TEA could be applied selectively to a presynaptic neuron that releases an excitatory neurotransmitter, how would it alter the synaptic effect of that neurotransmitter on the postsynaptic cell?
2. Describe the status of the Na^+ and K^+ channels at each of the following stages: rising, falling, and undershoot.
3. Describe the steps required to produce an excitatory postsynaptic potential (EPSP). How would these differ at an inhibitory synapse?
4. Your friend Karen loves caffeine. However, lately she has been complaining that she needs to drink more caffeinated beverages in order to get the same effect she used to. Excellent student of biology that you are, you tell her that this is to be expected. Why?

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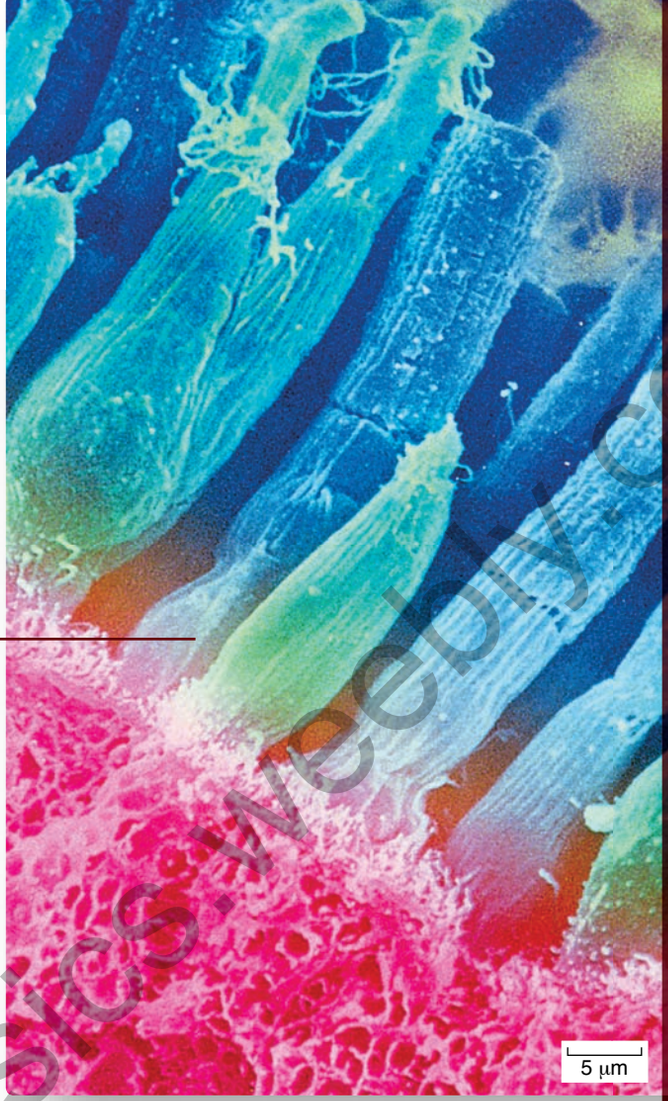
Chapter 45

Sensory Systems



Chapter Outline

Introduction

All input from sensory neurons to the central nervous system (CNS) arrives in the same form, as electrical signals. Sensory neurons receive input from a variety of different kinds of sense receptor cells, such as the rod and cone cells found in the vertebrate eye shown in the micrograph. Different sensory neurons lead to different brain regions and so are associated with the different senses. The intensity of the sensation depends on the frequency of action potentials conducted by the sensory neuron. The brain distinguishes a sunset, a symphony, and searing pain only in terms of the identity of the sensory neuron carrying the action potentials and the frequency of these impulses. Thus, if the auditory nerve is artificially stimulated, the brain perceives the stimulation as sound. But if the optic nerve is artificially stimulated in exactly the same manner and degree, the brain perceives a flash of light.

In this chapter, we examine sensory systems, primarily in vertebrates. We also compare some of these systems with their counterparts in invertebrates.

45.1 Overview of Sensory Receptors

Learning Outcomes

1. *List the three categories of vertebrate sensory receptors.*
2. *Explain how sensory information is conveyed from sensory neurons to the CNS.*
3. *Describe how gated ion channels work.*

When we think of sensory receptors, the senses of vision, hearing, taste, smell, and touch come to mind—the senses that provide information about our environment. Certainly this external information is crucial to the survival and success of animals, but sensory receptors also provide information about internal states, such as stretching of muscles, position of the body, and blood pressure. In this section, we take a general look at types of receptors and how they work.

Sensory receptors detect both external and internal stimuli

Exteroceptors are receptors that sense stimuli that arise in the external environment. Almost all of a vertebrate's exterior senses evolved in water before the invasion of land. Consequently, many senses of terrestrial vertebrates emphasize stimuli that travel well in water, using receptors that have been retained in the transition from sea to land. Mammalian hearing, for example, converts an airborne stimulus into a waterborne one, using receptors similar to those that originally evolved in the water.

A few vertebrate sensory systems that function well in the water, such as the electrical organs of fish, cannot function in the air and are not found among terrestrial vertebrates. In contrast, some land-dwellers have sensory systems that could not function in water, such as infrared heat detectors.

Interoceptors sense stimuli that arise from within the body. These internal receptors detect stimuli related to muscle length and tension, limb position, pain, blood chemistry, blood volume and pressure, and body temperature. Many of these receptors are simpler than those that monitor the external environment and are believed to bear a closer resemblance to primitive sensory receptors. In the rest of this chapter, we consider the different types of exteroceptors and interoreceptors according to the kind of stimulus each is specialized to detect.

Receptors can be grouped into three categories

Sensory receptors differ with respect to the nature of the environmental stimulus that best activates their sensory dendrites. Broadly speaking, we can recognize three classes of receptors:

1. **Mechanoreceptors** are stimulated by mechanical forces such as pressure. These include receptors for touch, hearing, and balance.
2. **Chemoreceptors** detect chemicals or chemical changes. The senses of smell and taste rely on chemoreceptors.
3. **Electromagnetic receptors** react to heat and light energy. The photoreceptors of the eyes that detect light are an example, as are the thermal receptors found in some reptiles.

The simplest sensory receptors are free nerve endings that respond to bending or stretching of the sensory neuron's membrane to changes in temperature or to chemicals such as oxygen in the extracellular fluid. Other sensory receptors are more complex, involving the association of the sensory neurons with specialized epithelial cells.

Sensory information is conveyed in a four-step process

Sensory information picked up by sensory neurons is conveyed to the CNS, where the impulses are perceived in a four-step process (figure 45.1):

1. *Stimulation.* A physical stimulus impinges on a sensory neuron or an associated, but separate, sensory receptor.
2. *Transduction.* The stimulus energy is transformed into graded potentials in the dendrites of the sensory neuron.
3. *Transmission.* Action potentials develop in the axon of the sensory neuron and are conducted to the CNS along an afferent nerve pathway.
4. *Interpretation.* The brain creates a sensory perception from the electrochemical events produced by afferent stimulation. We actually perceive the five senses with our brains, not with our sense organs.

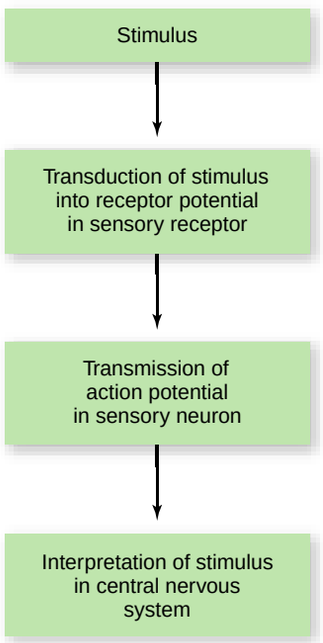


Figure 45.1 The path of sensory information. Sensory stimuli are transduced into receptor potentials, which can trigger sensory neuron action potentials that are conducted to the brain for interpretation.

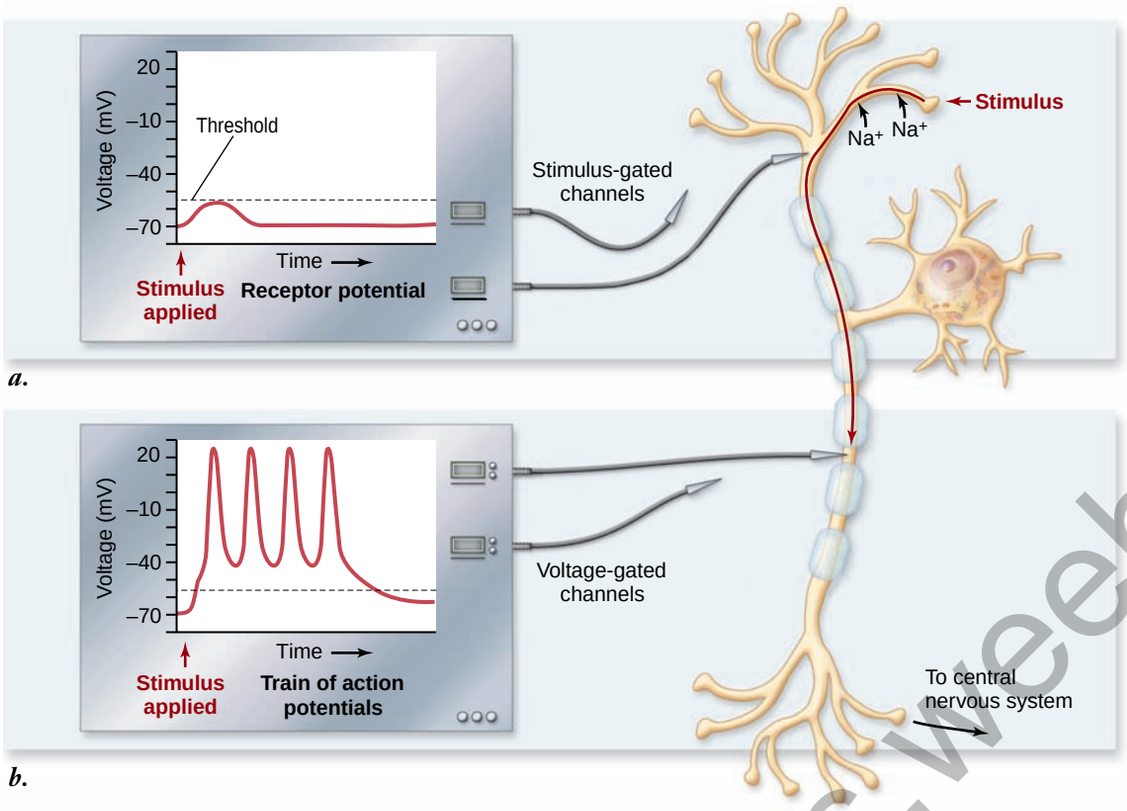


Figure 45.2 Events in sensory transduction. ***a.*** Depolarization of a free nerve ending leads to a receptor potential that spreads by local current flow to the axon. ***b.*** Action potentials are produced in the axon in response to a sufficiently large receptor potential.

Sensory transduction involves gated ion channels

Sensory cells respond to stimuli because they possess **stimulus-gated ion channels** in their membranes. The sensory stimulus causes these ion channels to open or close, depending on the sensory system involved. In most cases, the sensory stimulus produces a depolarization of the receptor cell, analogous to the excitatory postsynaptic potential (EPSP, described in chapter 44) produced in a postsynaptic cell in response to a neurotransmitter. A depolarization that occurs in a sensory receptor on stimulation is referred to as a *receptor potential* (figure 45.2*a*).

Like an EPSP, a receptor potential is a graded potential: The larger the sensory stimulus, the greater the degree of depolarization. Receptor potentials also decrease in size with distance from their source. This prevents small, irrelevant stimuli from reaching the cell body of the sensory neuron. If the receptor potential or the summation of receptor potentials is great enough to generate a threshold level of depolarization, an action potential is produced that propagates along the sensory axon into the CNS (figure 45.2*b*).

The greater the sensory stimulus, the greater the depolarization of the receptor potential and the higher the frequency of action potentials. (Remember that frequency of action potentials, not their summation, is responsible for conveying the intensity of the stimulus.)

Generally, a logarithmic relationship exists between stimulus intensity and action potential frequency—for example, a particular sensory stimulus that is 10 times greater than another sensory stimulus produces action potentials at twice the frequency of the other stimulus. This relationship allows the CNS to interpret the strength of a sensory stimulus based on the frequency of incoming signals.

Learning Outcomes Review 45.1

Sensory receptors include mechanoreceptors, chemoreceptors, and electromagnetic energy-detecting receptors. The four steps by which information is conveyed to the CNS are stimulation, transduction, transmission, and interpretation in the CNS. Gated ion channels open or close in response to stimuli, altering membrane potential; if this change exceeds a threshold, an action potential is generated.

- ***Why is the relationship between intensity of stimulus and frequency of action potentials said to be logarithmic?***

45.2 Mechanoreceptors: Touch and Pressure

Learning Outcomes

1. ***Explain how mechanoreceptors detect touch.***
2. ***Distinguish between nociceptors, thermoreceptors, proprioceptors, and baroreceptors.***

Although the receptors of the skin, called the cutaneous receptors, are classified as interoceptors, they in fact respond to stimuli at the border between the external and internal environments. These receptors serve as good examples of the specialization of receptor structure and function, responding to pain, heat, cold, touch, and pressure.

Pain receptors alert the body to damage or potential damage

A stimulus that causes or is about to cause tissue damage is perceived as pain. The receptors that transmit impulses perceived as pain are called **nociceptors,** so named because they can be sensitive to noxious substances as well as tissue damage. Although specific nociceptors exist, many hyperstimulated sensory receptors can also produce the perception of pain in the brain.

Most nociceptors consist of free nerve endings located throughout the body, especially near surfaces where damage is most likely to occur. Different nociceptors may respond to extremes in temperature, very intense mechanical stimulation such as a hard impact, or specific chemicals in the extracellular fluid, including some that are released by injured cells. The thresholds of these sensory cells vary; some nociceptors are sensitive only to actual tissue damage, but others respond before damage has occurred.

Transient receptor potential ion channels

One kind of tissue damage can be due to extremes of temperature, and in this case the molecular details of how a noxious stimulus can result in the sensation of pain are becoming clear. A class of ion channel protein found in nociceptors, the transient receptor potential (TRP) ion channel, can be stimulated by temperature to produce an inward flow of cations, primarily Na^+ and Ca^{2+}. This depolarizing current causes the sensory neuron to fire, leading to the release of glutamate and an EPSP in neurons in the spinal cord, ultimately producing the pain response.

TRP channels that respond to both hot and cold have been found. Differences have also been found in the sensitivity of TRP channels to the degree of temperature change, with some responding only to temperature changes that damage tissues and others that respond to milder changes. Thus, we can respond to the feelings of hot and cold as well as feel pain associated with extremes of hot and cold.

The first such TRP channel identified responds to the chemical capsaicin, found in chili peppers, as well as to heat. This explains the sensation of heat we feel when we eat chili peppers, as well as the associated pain! A cold-responsive TRP receptor also responds to the chemical menthol, explaining how this substance is perceived as "cold." Chemical stimulation of TRP channels can reduce the body's pain response by desensitizing the sensory neuron. This analgesic response is why menthol is found in cough drops.

Thermoreceptors detect changes in heat energy

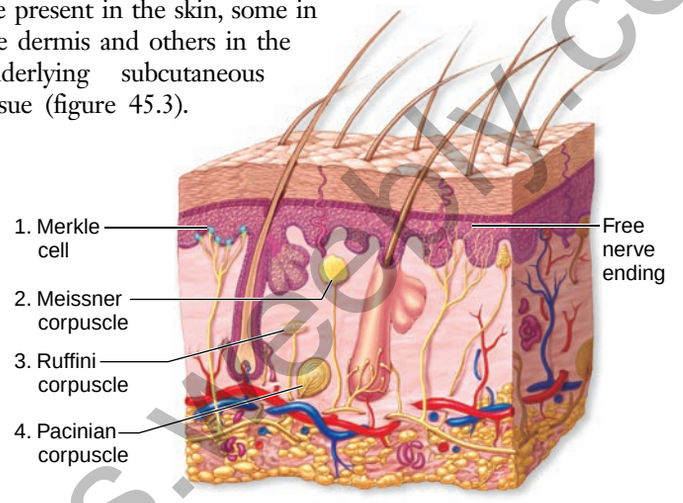
The skin contains two populations of **thermoreceptors,** which are naked dendritic endings of sensory neurons that are sensitive to changes in temperature. (Nociceptors are similar in that they consist of free nerve endings.) These thermoreceptors contain TRP ion channels that are responsive to hot and cold.

Cold receptors are stimulated by a fall in temperature and are inhibited by warming, whereas warm receptors are stimulated by a rise in temperature and inhibited by cooling. Cold receptors are located immediately below the epidermis; they are three to four times more numerous than are warm receptors. Warm receptors are typically located slightly deeper, in the dermis.

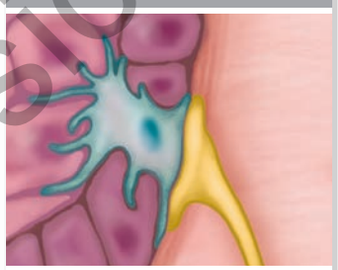
Thermoreceptors are also found within the hypothalamus of the brain, where they monitor the temperature of the circulating blood and thus provide the CNS with information on the body's internal (core) temperature. Information from the hypothalamic thermoreceptors alter metabolism and stimulate other responses to increase or decrease core temperature as needed.

Different receptors detect touch, depending on intensity

Several types of mechanoreceptors are present in the skin, some in the dermis and others in the underlying subcutaneous tissue (figure 45.3).



1. Merkle Cell

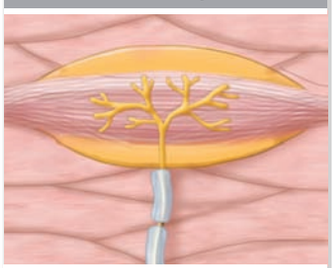


Tonic receptors located near the surface of the skin that are sensitive to touch pressure and duration.

2. Meissner Corpuscle

Phasic receptors sensitive to fine touch, concentrated in hairless skin.

3. Ruffini Corpuscle



Tonic receptors located near the surface of the skin that are sensitive to touch pressure and duration.

4. Pacinian Corpuscle

Pressure-sensitive phasic receptors deep below the skin in the subcutaneous tissue.

Figure 45.3 Sensory receptors in human skin.
Cutaneous receptors may be free nerve endings or sensory dendrites in association with other supporting structures.

These receptors contain sensory cells with ion channels that open in response to mechanical distortion of the membrane. They detect various forms of physical contact, known as the sense of touch.

Morphologically specialized receptors that respond to fine touch are most concentrated on areas such as the fingertips and face. They are used to localize cutaneous stimuli very precisely. These receptors can be either phasic (intermittently activated) or tonic (continuously activated). The phasic receptors include hair follicle receptors and Meissner corpuscles, which are present on surfaces that do not contain hair, such as the fingers, palms, and nipples.

The tonic receptors consist of Ruffini corpuscles in the dermis and touch dome endings (Merkel's disks) located near the surface of the skin. These receptors monitor the duration of a touch and the extent to which it is applied.

Deep below the skin in the subcutaneous tissue lie phasic, pressure-sensitive receptors called Pacinian corpuscles. Each of these receptors consists of the end of an afferent axon surrounded by a capsule of alternating layers of connective tissue cells and extracellular fluid. When sustained pressure is applied to the corpuscle, the elastic capsule absorbs much of the pressure, and the axon ceases to produce impulses. Pacinian corpuscles thus monitor only the onset and removal of pressure, as may occur repeatedly when something that vibrates is placed against the skin.

Muscle length and tension are monitored by proprioceptors

Buried within the skeletal muscles of all vertebrates except the bony fishes are **muscle spindles,** sensory stretch receptors that lie in parallel with the rest of the fibers in the muscle (figure 45.4). Each spindle consists of several thin muscle fibers wrapped together and innervated by a sensory neuron, which becomes activated when the muscle, and therefore the spindle, is stretched.

Muscle spindles, together with other receptors in tendons and joints, are known as **proprioceptors.** These sensory receptors provide information about the relative position or movement of the animal's body parts. The sensory neurons conduct action potentials into the spinal cord, where they synapse with somatic motor neurons that innervate the muscle. This pathway constitutes the muscle stretch reflex, including the knee-jerk reflex mentioned in chapter 44. When the muscle is briefly stretched by tapping the patellar ligament with a rubber mallet, the muscle spindle apparatus is also stretched. The spindle apparatus is embedded within the muscle, and, like the muscle fibers outside the spindle, is stretched along with the muscle. The result is the action potential that activates the somatic motor neurons and causes the leg to jerk.

When a muscle contracts, it exerts tension on the tendons attached to it. The **Golgi tendon organs,** another type of proprioceptor, monitor this tension. If it becomes too high, they elicit a reflex that inhibits the motor neurons innervating the muscle. This reflex helps ensure that muscles do not contract so strongly that they damage the tendons to which they are attached.

Baroreceptors detect blood pressure

Blood pressure is monitored at two main sites in the body. One is the carotid sinus, an enlargement of the left and right internal carotid arteries that supply blood to the brain. The other is the aortic arch, the portion of the aorta very close to its emergence from the heart. The walls of the blood vessels at both sites contain a highly branched network of afferent neurons called baroreceptors, which detect tension or stretch in the walls.

When the blood pressure decreases, the frequency of impulses produced by the baroreceptors decreases. The CNS responds to this reduced input by stimulating the sympathetic division of the autonomic nervous system, causing an increase in heart rate and vasoconstriction. Both effects help raise the blood pressure, thus maintaining homeostasis. A rise in blood pressure increases baroreceptor impulses, which conversely reduces sympathetic activity and stimulates the parasympathetic division, slowing the heart and lowering the blood pressure.

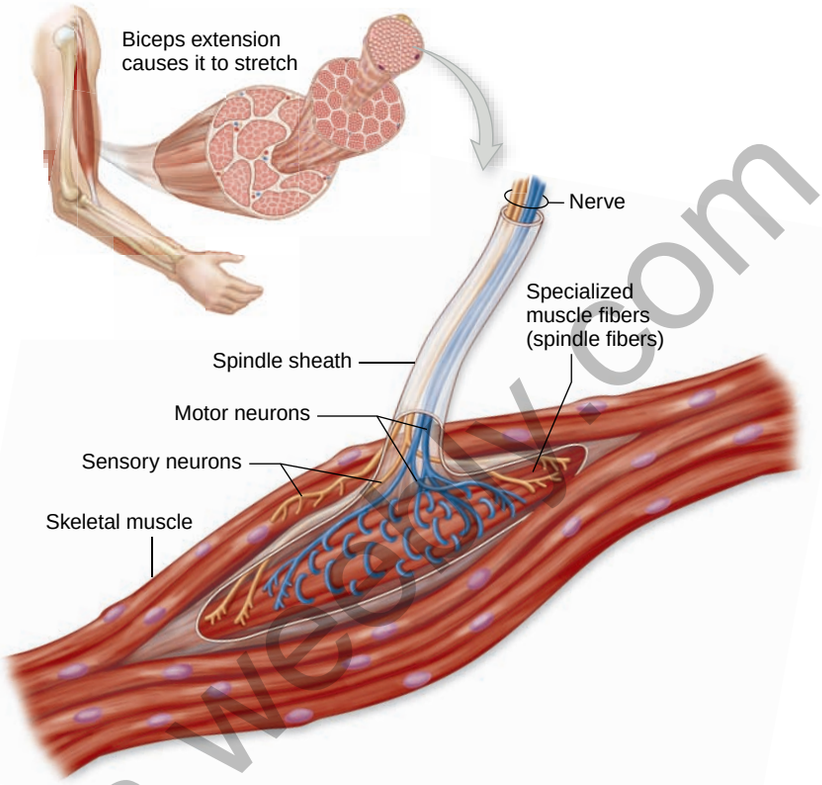


Figure 45.4 How a muscle spindle works. A muscle spindle is a stretch receptor embedded within skeletal muscle. Stretching of the muscle elongates the spindle fibers and stimulates the sensory dendritic endings wrapped around them. This causes the sensory neurons to send impulses to the CNS, where they synapse with interneurons and, in some cases, motor neurons.

Learning Outcomes Review 45.2

Mechanical distortion of the plasma membrane of mechanoreceptors produces nerve impulses. Nociceptors detect damage or potential damage to tissues and cause pain; thermoreceptors sense changes in heat energy; proprioceptors monitor muscle length; and baroreceptors monitor blood pressure within arteries.

- ***Why is it important to detect stretching of muscles?***

45.3 Hearing, Vibration, and Detection of Body Position

Learning Outcomes

1. *Explain how sound waves in the environment lead to production of action potentials in the inner ear.*
2. *Describe how hearing differs between aquatic and terrestrial animals.*
3. *Describe how body position and movement are detected by hearing-associated structures.*

Hearing, the detection of sound waves, actually works better in water than in air because water transmits pressure waves more efficiently. Despite this limitation, hearing is widely used by terrestrial vertebrates to monitor their environments, communicate with other members of their species, and detect possible sources of danger.

Sound is a result of vibration, or waves, traveling through a medium, such as water or air. Detection of sound waves is possible through the action of specialized mechanoreceptors that first evolved in aquatic organisms. The cells that are involved in the detection of sound are also evolutionarily related to the gravity-sensing systems discussed in the end of this section.

The lateral line system in fish detects low-frequency vibrations

In addition to hearing, the lateral line system in fish provides a sense of "distant touch," enabling them to sense objects that reflect pressure waves and low-frequency vibrations. This enables a fish to detect prey, for example, and to swim in synchrony with the rest of its school. It also enables a blind cave fish to sense its environment by monitoring changes in the patterns of water flow past the lateral line receptors.

The lateral line system is found in amphibian larvae, but is lost at metamorphosis and is not present in any terrestrial vertebrate. The sense provided by the lateral line system supplements the fish's sense of hearing, which is performed by the sensory structures in their ears.

The lateral line system consists of hair cells within a longitudinal canal in the fish's skin that extends along each side of the body and within several canals in the head (figure 45.5*a*). The hair cells' surface processes project into a gelatinous membrane called a cupula. The hair cells are innervated by sensory neurons that transmit impulses to the brain.

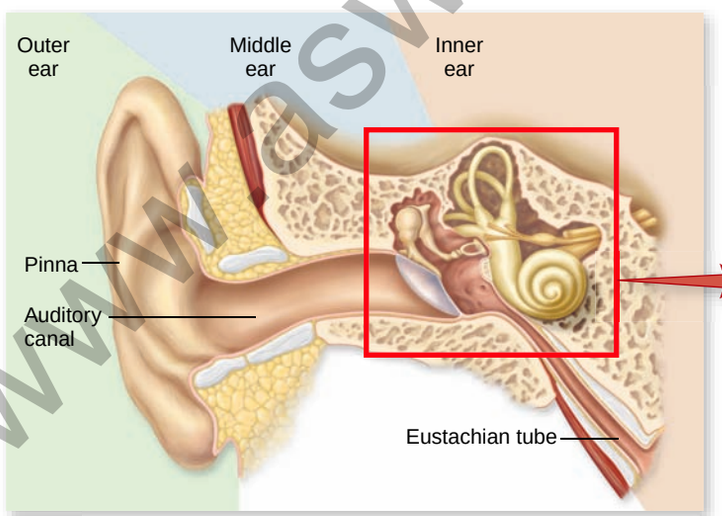
Hair cells have several hairlike processes, called stereocilia, and one longer process called a **kinocilium** (figure 45.5*b*). The stereocilia are actually microvilli containing actin fibers, and the kinocilium is a true cilium that contains microtubules. Vibrations carried through the fish's environment produce movements of the cupula, which cause the processes to bend. When the stereocilia bend in the direction of the kinocilium, the associated sensory neurons are stimulated and generate a receptor potential. As a result, the frequency of action potentials produced by the sensory neuron is increased. In contrast, if the stereocilia are bent in the opposite direction, then the activity of the sensory neuron is inhibited.

Ear structure is specialized to detect vibration

The structure of the ear allows pressure waves to be transduced into nerve impulses based on mechanosensory cells like those in the lateral line system. We will first consider the structure of the ear in fish, which is related to the lateral line system that senses pressure waves in water. Then we will consider how the structure of the ear of terrestrial vertebrates allows the sensing of pressure waves in air.

Hearing structures in fish

Sound waves travel through the body of a fish as easily as through the surrounding water because the fish's body is composed primarily of water. For sound to be detected, therefore, an object of different density is needed. In many fish, this function is served by the **otoliths,** literally "ear rocks," composed of calcium carbonate crystals. Otoliths are contained in the otolith organs of the membranous **labyrinth,** a system of fluid-filled chambers and tubes also present in other vertebrates. When



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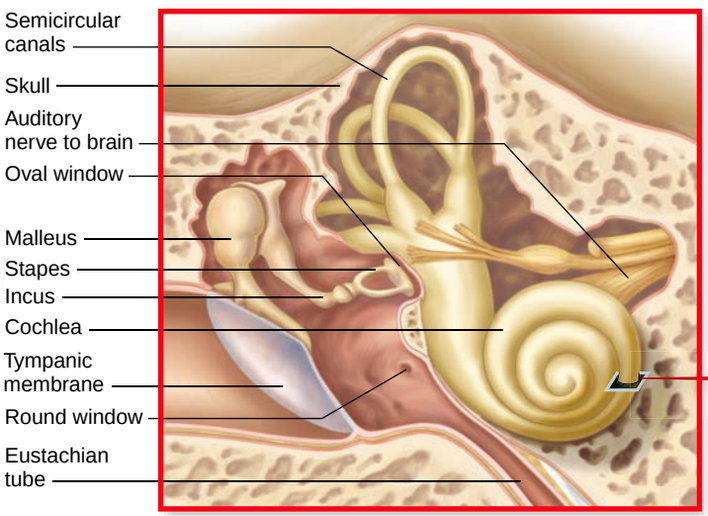

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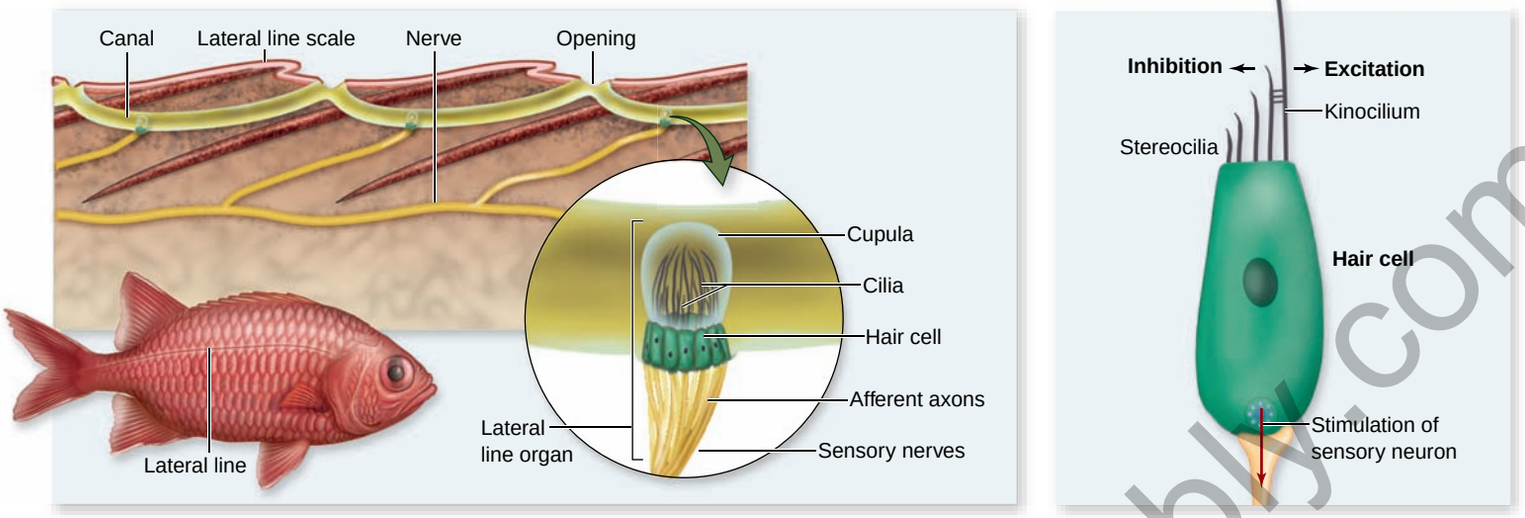


a. *b.*

Figure 45.5 The lateral line system. ***a.*** This system consists of canals running the length of the fish's body beneath the surface of the skin. Within these canals are sensory structures containing hair cells with cilia that project into a gelatinous cupula. Pressure waves traveling through the water in the canals deflect the cilia and depolarize the sensory neurons associated with the hair cells. ***b.*** Hair cells are mechanoreceptors with hairlike cilia that project into a gelatinous membrane. The hair cells of the lateral line system (and the membranous labyrinth of the vertebrate inner ear) have a number of smaller cilia called stereocilia and one larger kinocilium. When the cilia bend in the direction of the kinocilium, the hair cell releases a chemical transmitter that depolarizes the associated sensory neuron. Bending of the cilia in the opposite direction has an inhibitory effect.

Inquiry question

How would the lateral line system of a shark detect an injured and thrashing fish?

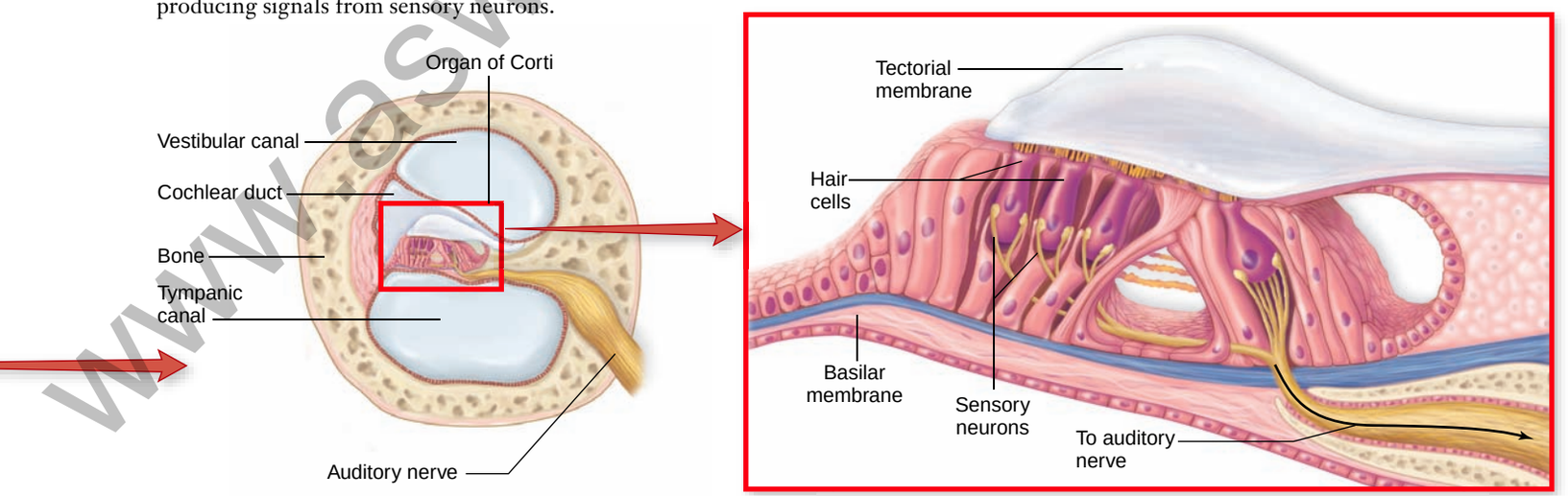
otoliths in fish vibrate against hair cells in the otolith organ, action potentials are produced. Hair cells are so-called because of the stereocilia that project from their surface.

Hearing structures of terrestrial vertebrates

In the ears of terrestrial vertebrates, vibrations in air may be channeled through an ear canal to the eardrum, or tympanic membrane. These structures are part of the **outer ear.** Vibrations of the tympanic membrane cause movement of one or more small bones that are located in a bony cavity known as the **middle ear**.

Amphibians and reptiles have a single middle ear bone, the **stapes** (stirrup), but mammals have two others: the **malleus** (hammer) and **incus** (anvil) (figure 45.6*a*, *b*). Where did these two additional bones come from?

Figure 45.6 Structure and function of the human ear. The structure of the human ear is shown in successive enlargements illustrating functional parts ***(a*** to ***d)***. Sound waves passing through the ear canal produce vibrations of the tympanic membrane, which causes movement of the middle-ear ossicles (the malleus, incus, and stapes) against an inner membrane (the oval window). This vibration creates pressure waves in the fluid in the vestibular and tympanic canals of the cochlea. These pressure waves cause cilia in hair cells to bend, producing signals from sensory neurons.



c. *d.*

The fossil record makes clear that the malleus and incus of modern mammals is derived from the two bones in the lower jaws of synapsid reptiles (figure 45.7). Through evolutionary time, these bones became progressively smaller and came to lie closer to the stapes. Eventually, in modern mammals, they became completely disconnected from the jawbone and moved within the middle ear itself.

The middle ear is connected to the throat by the Eustachian tube, also known as the auditory tube, which equalizes the air pressure between the middle ear and the external environment. The "ear popping" you may have experienced when flying in an airplane or driving on a mountain is caused by pressure equalization between the two sides of the eardrum.

The stapes vibrates against a flexible membrane, the oval window, which leads into the **inner ear.** Because the oval window is smaller in diameter than the tympanic membrane, vibrations against it produce more force per unit area, transmitted into the inner ear. The inner ear consists of the **cochlea,** a bony structure containing part of the membranous labyrinth called the cochlear duct. The cochlear duct is located in the center of the cochlea; the area above the cochlear duct is the vestibular canal, and the area below is the tympanic canal (figure 45.6*c*). All three chambers are filled with fluid. The oval window opens to the upper vestibular canal, so that when the stapes causes it to vibrate, it produces pressure waves of fluid. These pressure waves travel down to the tympanic canal, pushing another flexible membrane, the round window, that transmits the pressure back into the middle ear cavity.

Transduction occurs in the cochlea

As pressure waves are transmitted through the cochlea to the round window, they cause the cochlear duct to vibrate. The bottom of the cochlear duct, called the basilar membrane, is quite flexible and vibrates in response to these pressure waves. The surface of the basilar membrane contains sensory hair cells. The stereocilia from the hair cells project into an overhanging gelatinous membrane, the tectorial membrane. This sensory apparatus, consisting of the basilar membrane, hair cells with associated sensory neurons, and tectorial membrane, is known as the organ of Corti (figure 45.6*d*).

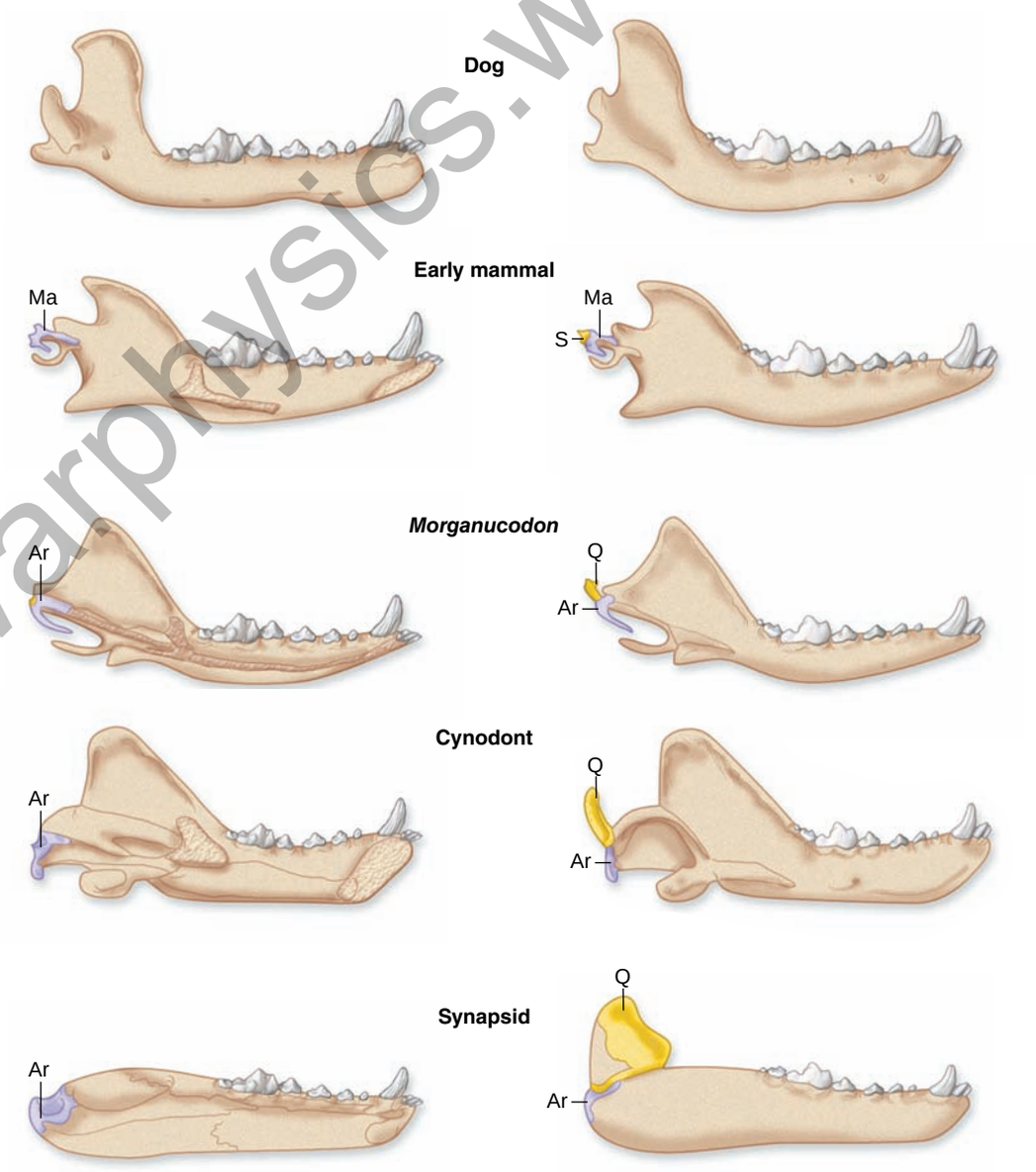


Figure 45.7 Evolution of the mammalian inner ear. Two of the bones in the inner ear of modern mammals, the stapes and malleus, are derived from the quadrate and articular bones, respectively, of their reptilian ancestors. The transition from an early ancestor of mammals, a synapsid, through several transition forms, to a modern dog is illustrated. Note how the bones become smaller and change position, ultimately disappearing from the lower jaw entirely in modern mammals (represented by the dog) and becoming parts of the inner ear. During embryology in modern mammals, these bones develop in association with the lower jaw bone before moving inward to the inner ear, providing further evidence of their evolutionary origin.

As the basilar membrane vibrates, the cilia of the hair cells bend in response to the movement of the basilar membrane relative to the tectorial membrane. The bending of these stereocilia in one direction depolarizes the hair cells. Bending in the opposite direction repolarizes or even hyperpolarizes the membrane. The hair cells, in turn, stimulate the production of action potentials in sensory neurons that project to the brain, where they are interpreted as sound.

Frequency localization in the cochlea

The basilar membrane of the cochlea consists of elastic fibers of varying length and stiffness, like the strings of a musical instrument, embedded in a gelatinous material. At the base of the cochlea (near the oval window), the fibers of the basilar membrane are short and stiff. At the far end of the cochlea (the apex), the fibers are 5 times longer and 100 times more flexible. Therefore, the resonant frequency of the basilar membrane is higher at the base than at the apex; the base responds to higher pitches, the apex to lower pitches.

When a wave of sound energy enters the cochlea from the oval window, it initiates an up-and-down motion that travels the length of the basilar membrane. However, this wave imparts most of its energy to that part of the basilar membrane with a resonant frequency near the frequency of the sound wave, resulting in a maximum deflection of the basilar membrane at that point (figure 45.8). As a result, the hair cell depolarization is greatest in that region, and the afferent axons from that region are stimulated more than those of other regions. When these action potentials arrive in the brain, they are interpreted as representing a sound of a particular frequency, or pitch.

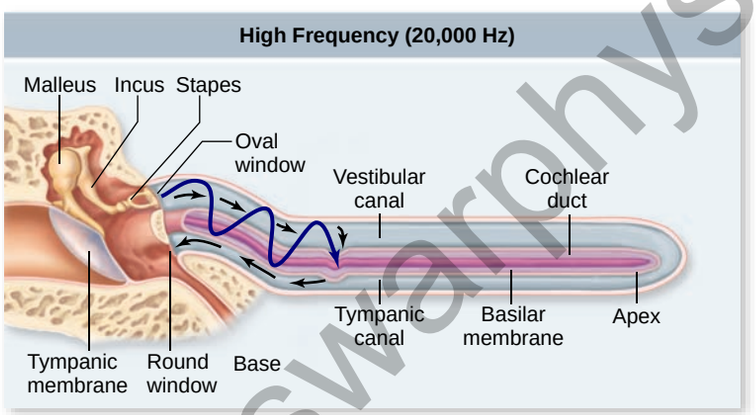
The range of terrestrial vertebrate hearing

The flexibility of the basilar membrane limits the frequency range of human hearing to between approximately 20 and 20,000 cycles per second (hertz, Hz) in children. Our ability to hear high-pitched sounds decays progressively throughout middle age. Other vertebrates can detect sounds at frequencies lower than 20 Hz and much higher than 20,000 Hz. Dogs, for example, can detect sounds at 40,000 Hz, enabling them to hear high-pitched dog whistles that seem silent to a human listener.

Hair cells are also innervated by efferent axons from the brain, and impulses in those axons can make hair cells less sensitive. This central control of receptor sensitivity can increase an individual's ability to concentrate on a particular auditory signal (for example, a single voice) in the midst of background noise, which is effectively "tuned out" by the efferent axons.

Some vertebrates have the ability to navigate by sound

Because terrestrial vertebrates have two ears located on opposite sides of the head, the information provided by hearing can be used to determine the direction of a sound source with some precision. Sound sources vary in strength, however, and sounds are weakened and reflected to varying degrees by the presence



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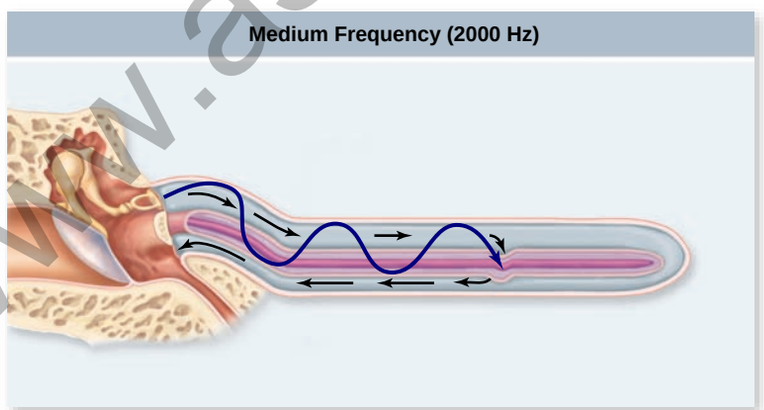

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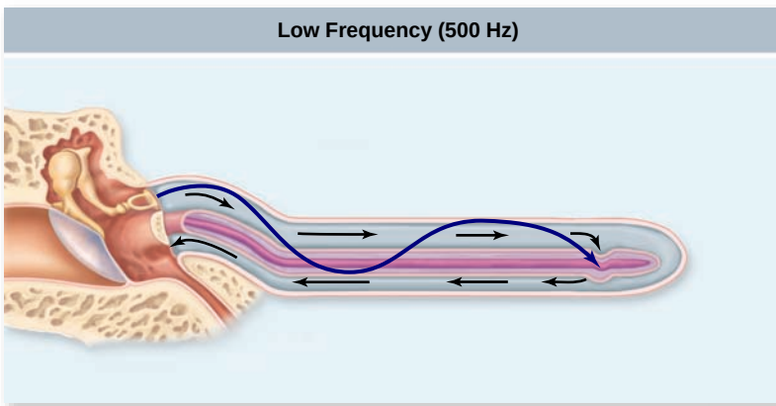


c.

Figure 45.8 Frequency localization in the cochlea. The cochlea is shown unwound, so that the length of the basilar membrane can be seen. The fibers within the basilar membrane vibrate in response to different frequencies of sound, related to the pitch of the sound. Thus, regions of the basilar membrane show maximum vibrations in response to different sound frequencies. ***a.*** Notice that high-frequency (pitch) sounds vibrate the basilar membrane more toward the base whereas medium frequencies ***(b)*** and low frequencies ***(c)*** cause vibrations more toward the apex.

of objects in the environment. For these reasons, auditory sensors do not provide a reliable measure of distance.

A few groups of mammals that live and obtain their food in dark environments have circumvented the limitations of darkness. A bat flying in a completely dark room easily avoids objects placed in its path—even a wire less than a millimeter in diameter. Shrews use a similar form of "lightless vision" beneath the ground, as do whales and dolphins beneath the sea. All of these mammals are able to perceive presence and distance of objects by sound.

These mammals emit sounds and then determine the time it takes these sounds to reach an object and return to the animal. This process is called **echolocation.** A bat, for example, produces clicks that last 2 to 3 ms and are repeated several hundred times per second. By calculating the time each click takes to hit an object and return, bats can calculate the location, direction of movement, and speed of objects in their environment. The human inventions sonar and radar are based on the same principles of echolocation.

The three-dimensional imaging achieved with such an auditory sonar system is quite sophisticated. Bats can track and intercept rapidly maneuvering aerial prey and can distinguish one type of insect from another.

Body position and movement are detected by systems associated with hearing systems

The evolutionary strategy of using internal calcium carbonate crystals as a way to detect vibration has also allowed the development of sensory organs that detect body position in space and movements such as acceleration.

Most invertebrates can orient themselves with respect to gravity due to a sensory structure called a **statocyst.** Statocysts generally consist of ciliated hair cells with the cilia embedded in a gelatinous membrane containing crystals of calcium carbonate. These stones, or statoliths, increase the mass of the gelatinous membrane so that it can bend the cilia when the animal's position changes. If the animal tilts to the right, for example, the statolith membrane bends the cilia on the right side and activates associated sensory neurons.

A similar structure is found in the membranous labyrinth of the inner ear of vertebrates. This labyrinth is surrounded by bone and perilymph, which is similar in ionic content to interstitial fluid. Inside, the chambers and tubes are filled with endolymph fluid, which is similar in ionic content to intracellular fluid. Though intricate, the entire structure is very small; in a human, it is about the size of a pea.

Structure of the labyrinth and semicircular canals

The receptors for gravity in most vertebrates consist of two chambers of the membranous labyrinth called the **utricle** and **saccule** (figure 45.9). Within these structures are hair cells with stereocilia and a kinocilium, similar to those in the lateral line system of fish. The hairlike processes are embedded within a gelatinous membrane, the otolith membrane, containing calcium carbonate crystals. Because the otolith organ is oriented differently in the utricle and saccule, the utricle is more sensitive to

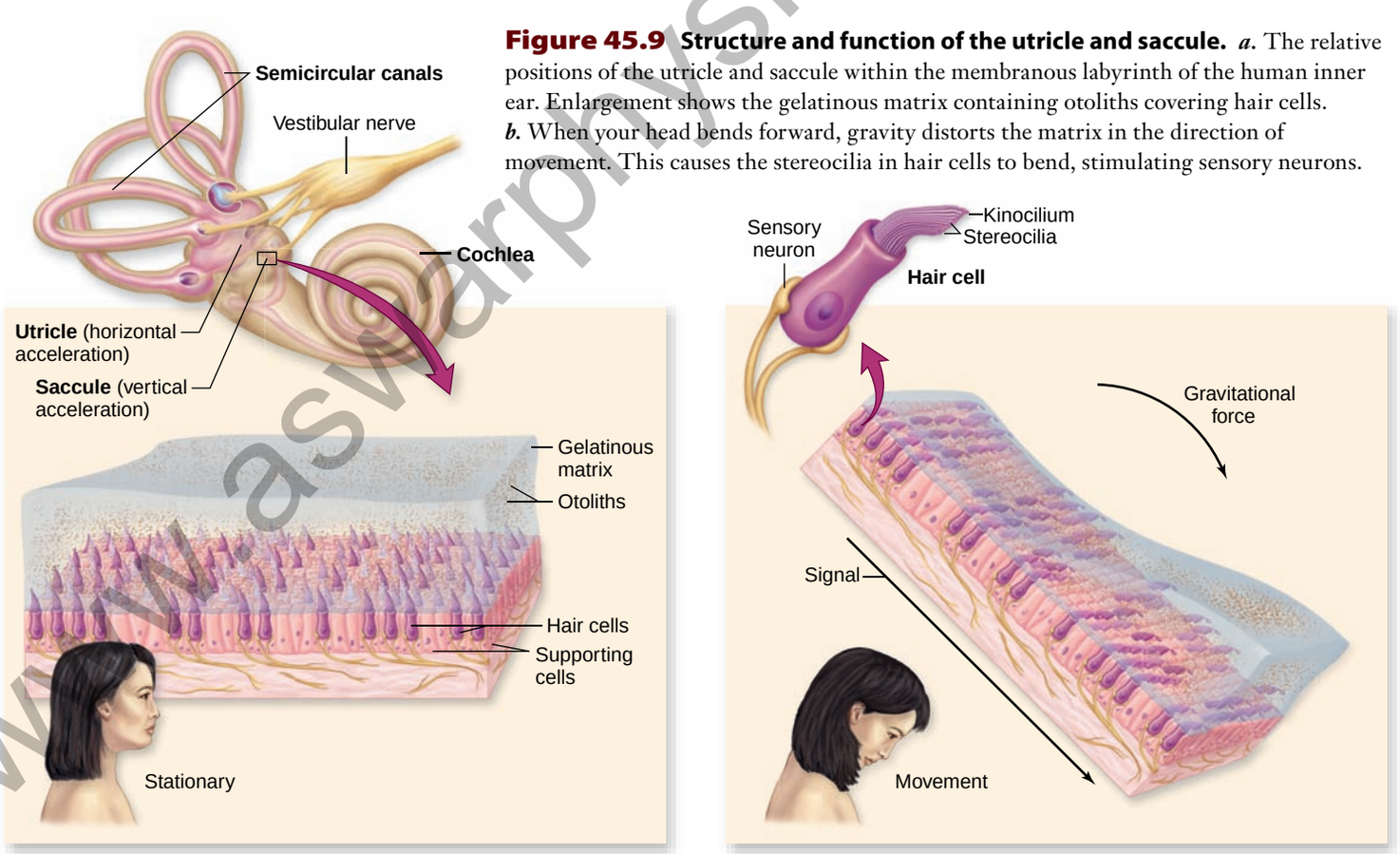


Figure 45.9 Structure and function of the utricle and saccule. ***a.*** The relative positions of the utricle and saccule within the membranous labyrinth of the human inner ear. Enlargement shows the gelatinous matrix containing otoliths covering hair cells. ***b.*** When your head bends forward, gravity distorts the matrix in the direction of movement. This causes the stereocilia in hair cells to bend, stimulating sensory neurons.

horizontal acceleration (as in a moving car) and the saccule to vertical acceleration (as in an elevator). In both cases, the acceleration causes the stereocilia to bend, and consequently produces action potentials in an associated sensory neuron.

The membranous labyrinth of the utricle and saccule is continuous with three **semicircular canals,** oriented in different planes so that angular acceleration in any direction can be detected (figure 45.10). At the ends of the canals are swollen chambers called ampullae, into which protrude the cilia of another group of hair cells. The tips of the cilia are embedded within a sail-like wedge of gelatinous material called a cupula (similar to the cupula of the fish lateral line system) that protrudes into the endolymph fluid of each semicircular canal.

Action of the vestibular apparatus

When the head rotates, the fluid inside the semicircular canals pushes against the cupula and causes the cilia to bend. This bending either depolarizes or hyperpolarizes the hair cells, depending on the direction in which the cilia are bent. This is similar to the way the lateral line system works in a fish: If the stereocilia are bent in the direction of the kinocilium, a receptor potential is produced, which stimulates the production of action potentials in associated sensory neurons.

The saccule, utricle, and semicircular canals are collectively referred to as the **vestibular apparatus.** The saccule and utricle provide a sense of linear acceleration, and the semicircular canals provide a sense of angular acceleration. The brain uses information that comes from the vestibular apparatus about the body's position to maintain balance and equilibrium.

Learning Outcomes Review 45.3

Sound waves cause middle-ear ossicles to vibrate; fluid in the inner ear is vibrated in turn, bending hair cells and causing action potentials. In terrestrial animals, sound waves in air must transition to the fluid in the inner ear. Hair cells in the vestibular apparatus of terrestrial vertebrates provide a sense of acceleration and balance.

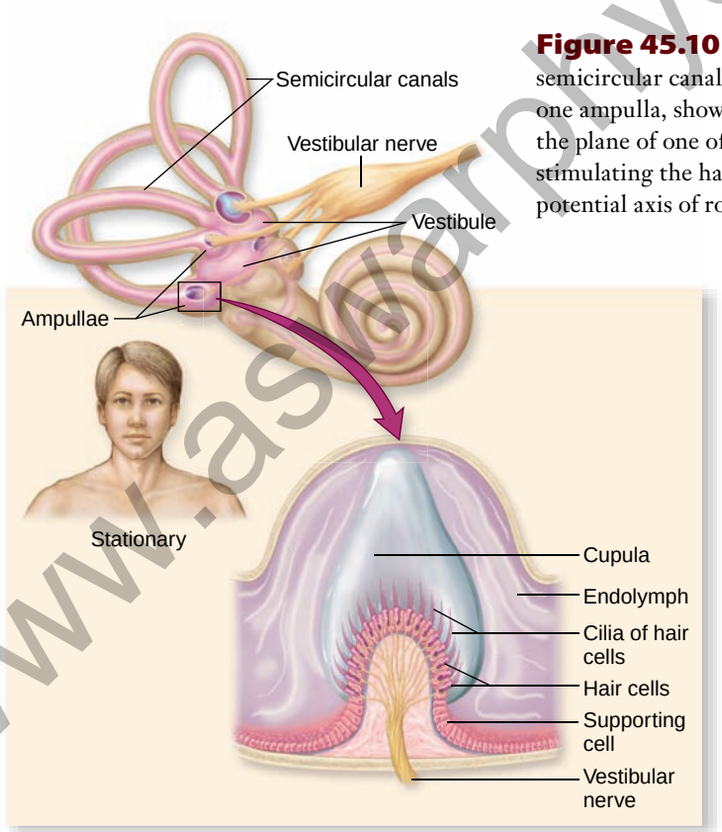
- ***Why is a lateral line system not useful to adult amphibians?***

45.4 Chemoreceptors: Taste, Smell, and pH

Learning Outcomes

1. ***List the five taste categories.***
2. ***Describe how taste buds and olfactory neurons function.***

Some sensory cells, called chemoreceptors, contain membrane proteins that can bind to particular chemicals or ligands in the extracellular fluid. In response to this chemical interaction, the membrane of the sensory neuron becomes depolarized and produces action potentials. Chemoreceptors are used in the senses of taste and smell and are also important in monitoring the chemical composition of the blood and cerebrospinal fluid.



a. *b.*

Figure 45.10 The structure of the semicircular canals. The position of the semicircular canals in relation to the rest of the inner ear. ***a.*** Enlargement of a section of one ampulla, showing how hair cell cilia insert into the cupula. ***b.*** Angular acceleration in the plane of one of the semicircular canals causes bending of the cupula, thereby stimulating the hair cells. Each inner ear contains three semicircular canals, one for each potential axis of rotation.

Taste detects and analyzes potential food

The perception of taste (gustation), like the perception of color, is a combination of physical and psychological factors. This is commonly broken down into five categories: sweet, sour, salty, bitter, and umami (perception of glutamate and other amino acids that give a hearty taste to many protein-rich foods such as meat, cheese, and broths). Taste buds—collections of chemosensitive epithelial cells associated with afferent neurons—mediate the sense of taste in vertebrates. In a fish, the taste buds are scattered over the surface of the body. These are the most sensitive vertebrate chemoreceptors known. They are particularly sensitive to amino acids; a catfish, for example, can distinguish between two different amino acids at a concentration of less than 100 parts per billion (1 g in 10,000 L of water)! The ability to taste the surrounding water is very important to bottom-feeding fish, enabling them to sense the presence of food in an often murky environment.

The taste buds of all terrestrial vertebrates occur in the epithelium of the tongue and oral cavity, within raised areas called papillae (figure 45.11). Taste buds are onion-shaped structures of between 50 and 100 taste cells; each cell has fingerlike projections called microvilli that poke through the top of the taste bud, called the taste pore (figure 45.11*c*). Chemicals from food dissolve in saliva and contact the taste cells through the taste pore.

Within a taste bud, the chemicals that produce salty and sour tastes act directly through ion channels. The prototypical salty taste is due to Na^+ ions, which diffuse through Na^+ channels into cells in receptor cells in the taste bud. This Na^+ influx depolarizes the membrane, causing the receptor cell to release neurotransmitter and activate a sensory neuron that sends an impulse to the brain. The cells that detect sour taste act in a similar fashion except that the ion detected is H^+. Sour tastes are associated with increased concentration of protons that can also depolarize the membrane when they diffuse through ion channels.

The mechanism of detection of sweet, bitter, and umami are indirect. In this case substances that fall into these categories can bind to G protein–coupled receptors (see chapter 9) specific for each category. The nature and distribution of these receptors is an area of active investigation, but recent data indicate that individual receptor cells in the taste bud express only one type of receptor. This leads to cells that have receptors for sweet, for bitter or for umami tastes. Activation of any of these G protein–coupled receptors then stimulates a single signaling pathway that leads the release of neurotransmitter from receptor cells to activate a sensory neuron and send an impulse to the brain. There they interact with other sensory neurons carrying information related to smell, described next. In this model, the different tastes are encoded to the brain based on which receptor cells are activated.

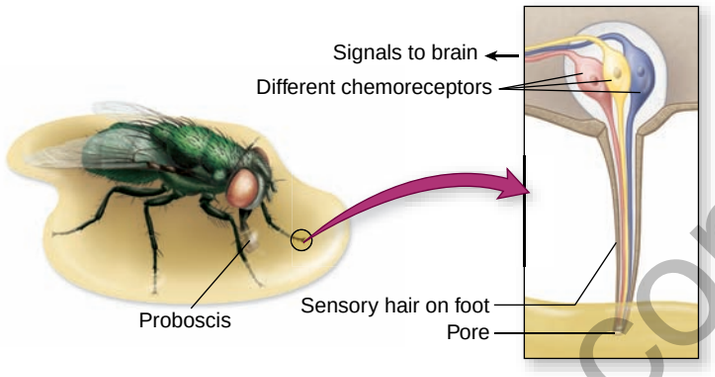


Figure 45.12 Many insects taste with their feet. In the blowfly shown here, chemoreceptors extend into the sensory hairs on the foot. Different chemoreceptors detect different types of food molecules. When the fly steps in a food substance, it can taste the different food molecules and extend its proboscis for feeding.

Like vertebrates, many arthropods also have taste chemoreceptors. For example, flies, because of their mode of searching for food, have taste receptors in sensory hairs located on their feet. The sensory hairs contain a variety of chemoreceptors that are able to detect sugars, salts, and other tastes by the integration of stimuli from these chemoreceptors (figure 45.12). If they step on potential food, their proboscis (the tubular feeding apparatus) extends to feed.

Smell can identify a vast number of complex molecules

In terrestrial vertebrates, the sense of smell (olfaction) involves chemoreceptors located in the upper portion of the

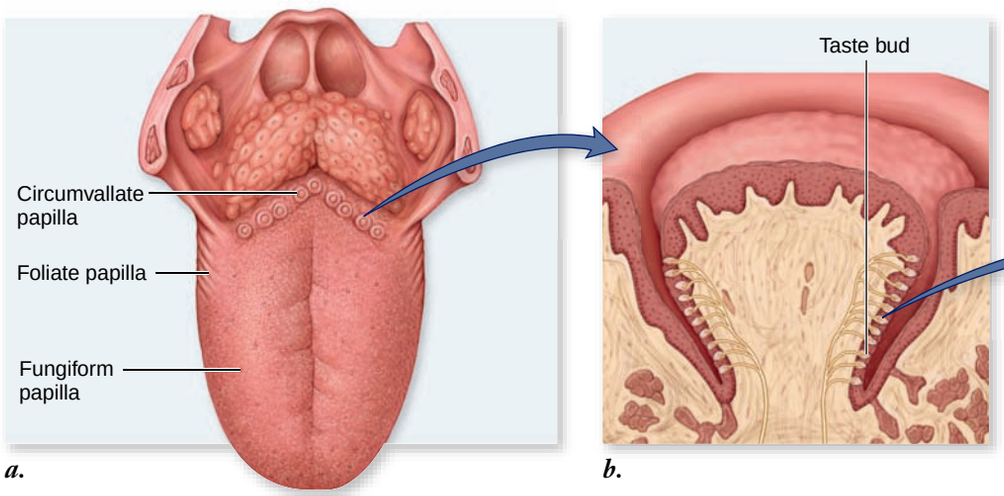


Figure 45.11 Taste. *a.* Human tongues have projections called papillae that bear taste buds. Different sorts of taste buds are located on different regions of the tongue. *b.* Groups of taste buds are embedded within a papilla. *c.* Individual taste buds are bulb-shaped collections of chemosensitive receptors that open out into the mouth through a pore. *d.* Photomicrograph of taste buds in papillae.

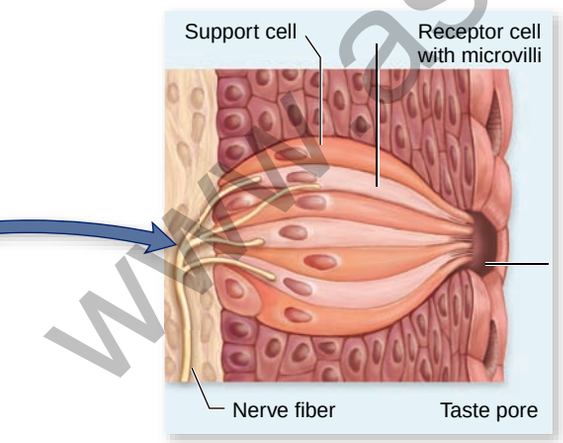
nasal passages (figure 45.13). These receptors, whose dendrites end in tassels of cilia, project into the nasal mucosa, and their axons project directly into the cerebral cortex. A terrestrial vertebrate uses its sense of smell in much the same way that a fish uses its sense of taste—to sample the chemical environment around it.

Because terrestrial vertebrates are surrounded by air, their sense of smell has become specialized to detect airborne particles—but these particles must first dissolve in extracellular fluid before they can activate the olfactory receptors. The sense of smell can be extremely acute in many mammals, so much so that a single odorant molecule may be all that is needed to excite a given receptor.

Although humans can detect only five modalities of taste, they can discern thousands of different smells. New research suggests that as many as a thousand different genes may code for different receptor proteins for smell. The particular set of olfactory neurons that respond to a given odor might serve as a "fingerprint" the brain can use to identify the odor.

Internal chemoreceptors detect pH and other characteristics

Sensory receptors within the body detect a variety of chemical characteristics of the blood or fluids derived from the blood, including cerebrospinal fluid. Included among these receptors are the **peripheral chemoreceptors** of the aortic and carotid bodies, which are sensitive primarily to plasma pH, and the **central chemoreceptors** in the medulla oblongata of the brain, which are sensitive to the pH of cerebrospinal fluid. When the breathing rate is too low, the concentration of plasma CO_2 increases, producing more carbonic acid and causing a fall in the blood pH. The carbon dioxide can also enter the cerebrospinal fluid and lower the pH, thereby stimulating the central chemoreceptors. This stimulation indirectly affects the respiratory control center of the brainstem, which increases the breathing rate. The aortic bodies can also respond to a lowering of blood oxygen concentrations, but this effect is normally not significant unless a person goes to a high altitude where the partial pressure of oxygen is lower.



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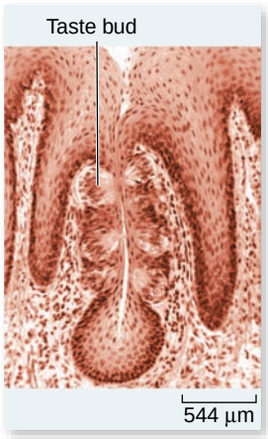

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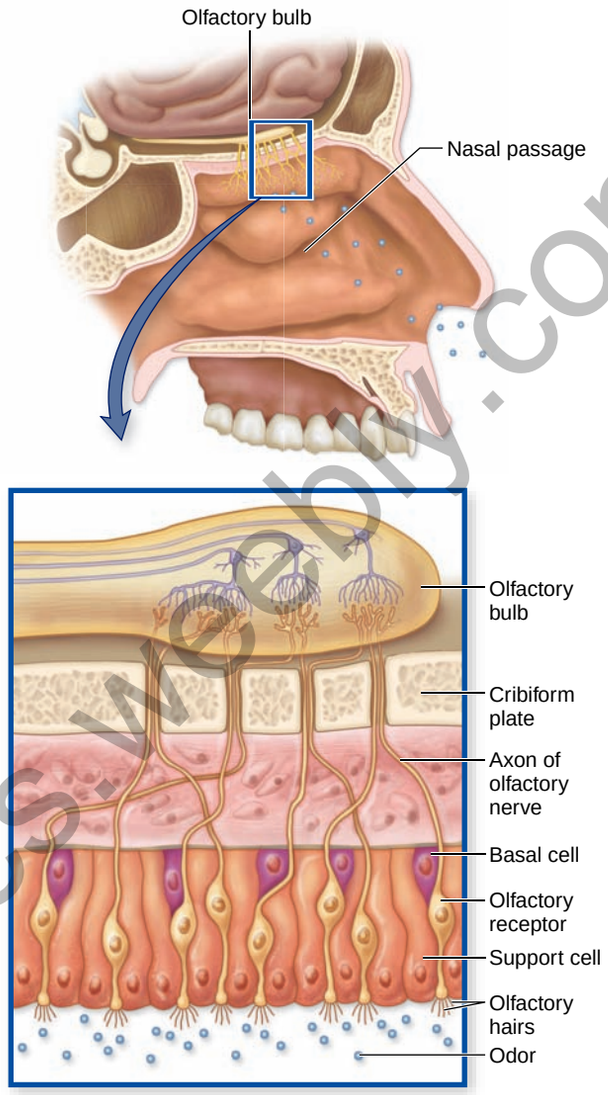


Figure 45.13 Smell. Humans detect smells by means of olfactory neurons (receptor cells) located in the lining of the nasal passages. The axons of these neurons transmit impulses directly to the brain via the olfactory nerve. Basal cells regenerate new olfactory neurons to replace dead or damaged cells. Olfactory neurons typically live about a month.

Inquiry question

In what ways do the senses of taste and smell share similarities? How are they different?

Learning Outcomes Review 45.4

The five tastes humans perceive are sweet, sour, salty, bitter, and umami (amino acids). Taste and smell chemoreceptors detect chemicals from outside the body; olfactory receptors can identify thousands of different odors. Internal chemoreceptors monitor acid–base balance within the body and help regulate breathing.

- ***What are the advantages of insects' having taste receptors on their feet?***

45.5 Vision

Learning Outcomes

1. *Compare invertebrate and vertebrate eyes.*
2. *Explain how a vertebrate eye focuses an image.*
3. *Describe how photoreceptors function.*

The ability to perceive objects at a distance is important to most animals. Predators locate their prey, and prey avoid their predators, based on the three long-distance senses of hearing, smell, and vision. Of these, vision can act most distantly; with the naked eye, humans can see stars thousands of light years away—and a single photon is sufficient to stimulate a cell of the retina to send an action potential.

Vision senses light and light changes at a distance

Vision begins with the capture of light energy by **photoreceptors.** Because light travels in a straight line and arrives virtually instantaneously regardless of distance, visual information can be used to determine both the direction and the distance of an object. Other stimuli, which spread out as they travel and move more slowly, provide much less precise information.

Invertebrate eyes

Many invertebrates have simple visual systems with photoreceptors clustered in an eyespot. Simple eyespots can be made sensitive to the direction of a light source by the addition of a pigment layer that shades one side of the eye. Flatworms have a screening pigmented layer on the inner and back sides of both eyespots, allowing stimulation of the photoreceptor cells only by light from the front of the animal (figure 45.14). The flatworm will turn and swim in the direction in which the photoreceptor cells are the least stimulated. Although an eyespot can perceive the direction of light, it cannot be used to construct a visual image.

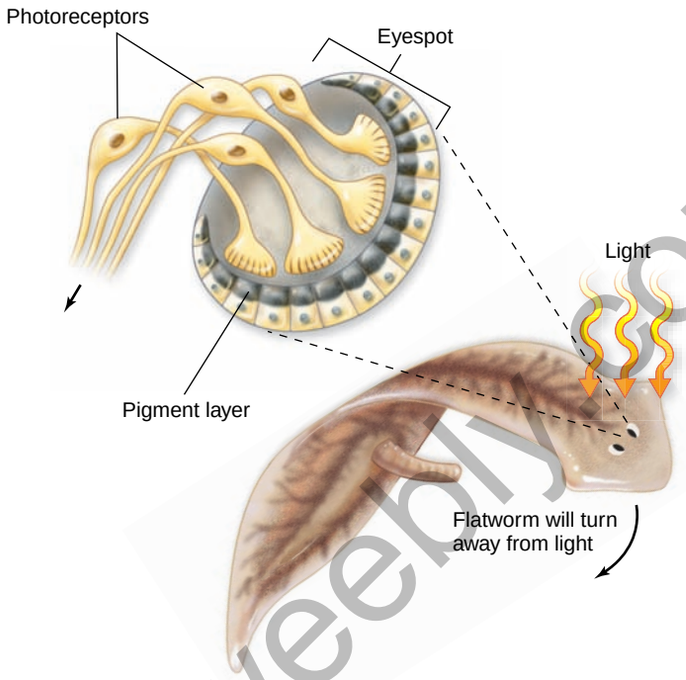


Figure 45.14 Simple eyespots in the flatworm. Eyespots can detect the direction of light because a pigmented layer on one side of the eyespot screens out light coming from the back of the animal. Light is thus detected more readily coming from the front of the animal; flatworms respond by turning away from the light.

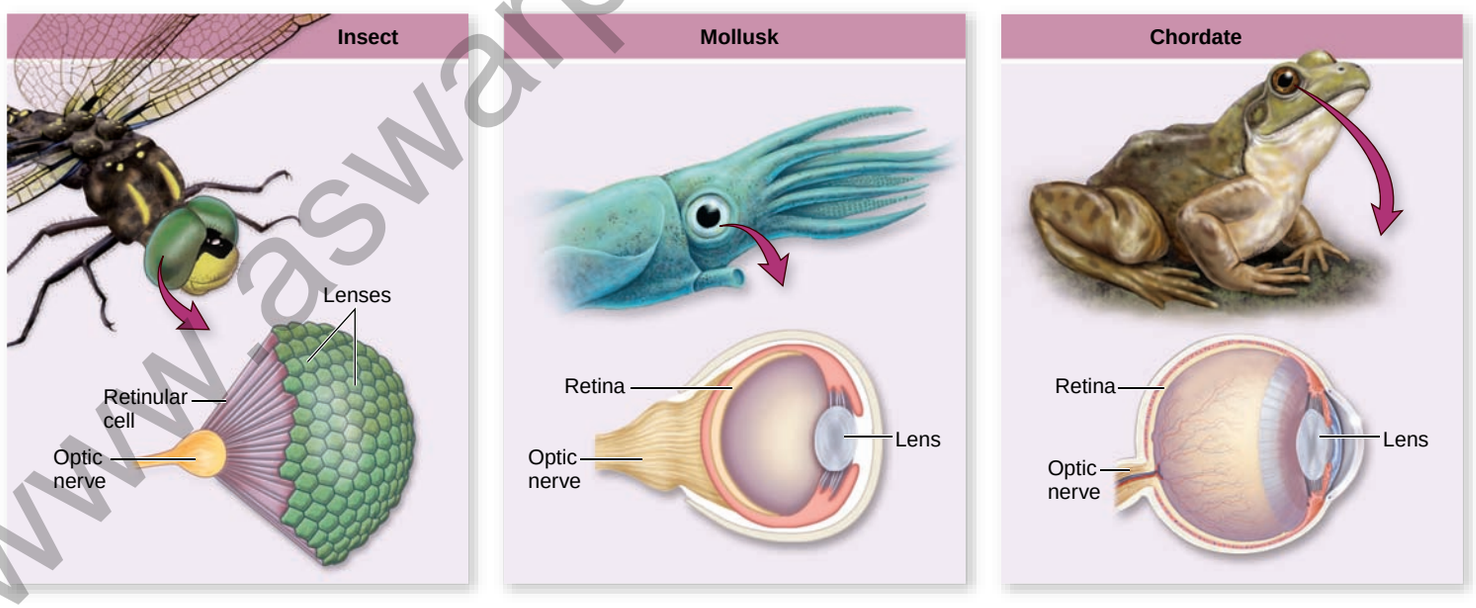


Figure 45.15 Eyes in three phyla of animals. Although they are superficially similar, these eyes differ greatly in structure from one another (see also figure 21.16 for a detailed comparison of mollusk and chordate eye structure). Each has evolved separately and, despite the apparent structural complexity, has done so from simpler structures.

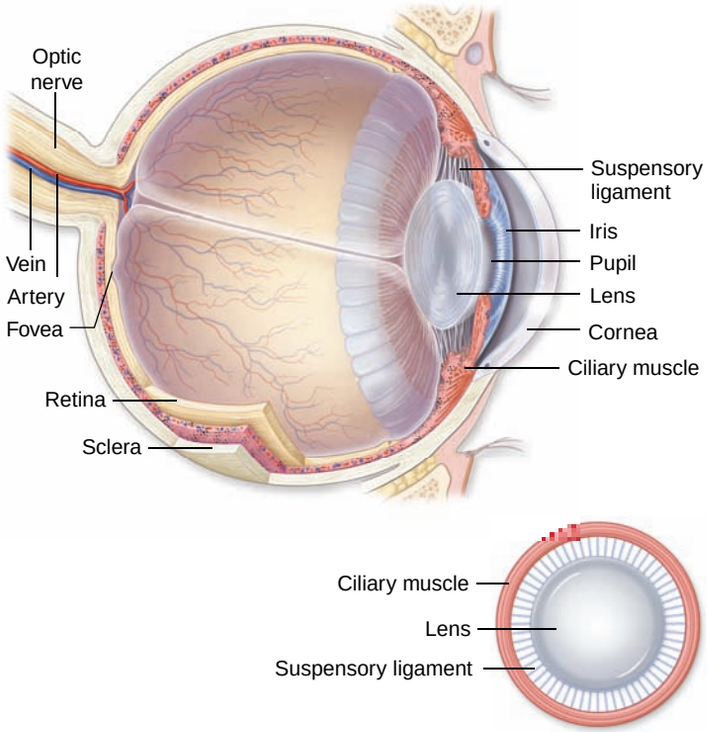


Figure 45.16 Structure of the human eye. The transparent cornea and lens focus light onto the retina at the back of the eye, which contains the photoreceptors (rods and cones). The center of each eye's visual field is focused on the fovea. Focusing is accomplished by contraction and relaxation of the ciliary muscle, which adjusts the curvature of the lens.

Inquiry question

How does the human eye differ from the eye of a mollusk, and how do these differences create a blind spot?

The members of four phyla—annelids, mollusks, arthropods, and chordates—have evolved well-developed, image-forming eyes. True image-forming eyes in these phyla, although strikingly similar in structure, are believed to have evolved independently, an example of convergent evolution (figure 45.15). Interestingly, the photoreceptors in all of these image-forming eyes use the same light-capturing molecule, suggesting that not many alternative molecules are able to play this role.

Structure of the vertebrate eye

The human eye is typical of the vertebrate eye (figure 45.16). The "white of the eye" is the **sclera,** formed of tough connective tissue. Light enters the eye through a transparent **cornea,** which begins to focus the light. Focusing occurs because light is refracted (bent) when it travels into a medium of different density. The colored portion of the eye is the **iris;** contraction of the iris muscles in bright light decreases the size of its opening, the pupil. Light passes through the pupil to the **lens,** a transparent structure that completes the focusing of the light onto the retina at the back of the eye. The lens is attached by the suspensory ligament to the ciliary muscles.

The shape of the lens is influenced by the amount of tension in the suspensory ligament, which surrounds the lens and attaches it to the circular ciliary muscle. When the ciliary muscle contracts, it puts slack in the suspensory ligament, and the lens becomes more rounded and bends light more strongly. This rounding is required for close vision. In distance vision, the ciliary muscles relax, moving away from the lens and tightening the suspensory ligament. The lens thus becomes more flattened and bends light less, keeping the image focused on the retina. People who are nearsighted or farsighted do not properly focus the image on the retina (figure 45.17). Interestingly,

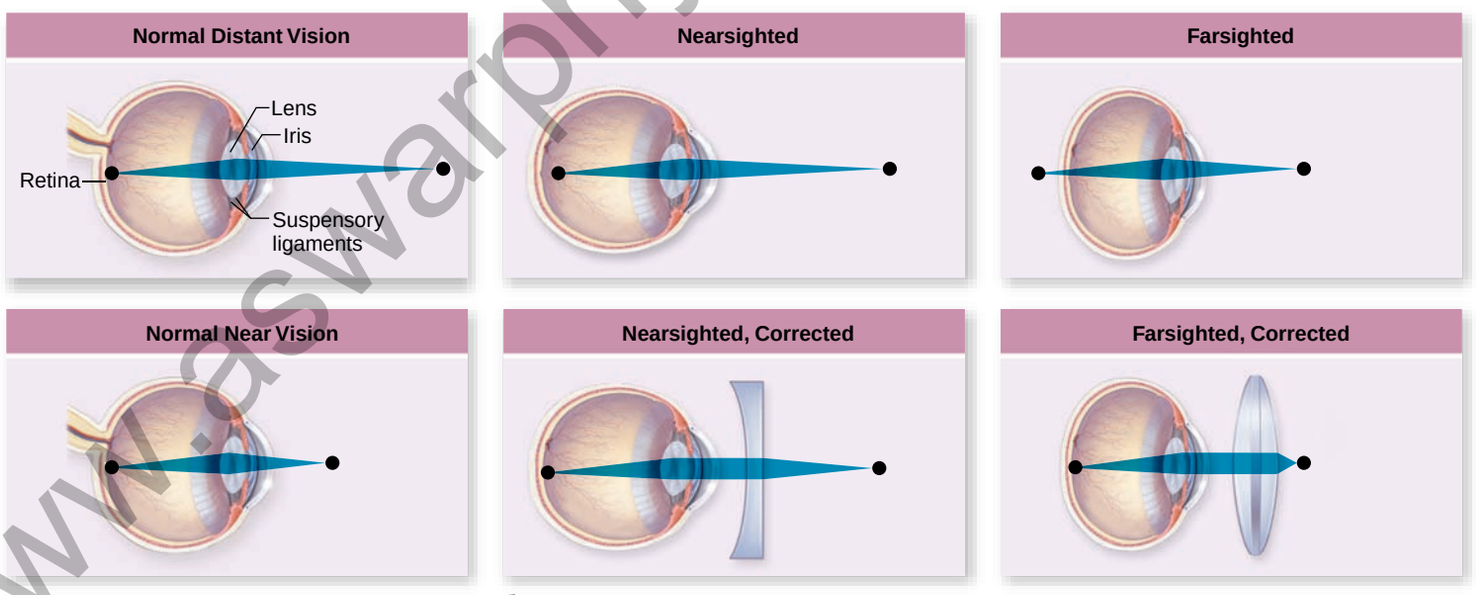


Figure 45.17 Focusing the human eye. ***a.*** In people with normal vision, the image remains focused on the retina in both near and far vision because of changes produced in the curvature of the lens. When a person with normal vision stands 20 feet or more from an object, the lens is in its least convex form, and the image is focused on the retina. ***b.*** In nearsighted people, the image comes to a focus in front of the retina, and the image thus appears blurred. ***c.*** In farsighted people, the focus of the image would be behind the retina because the distance from the lens to the retina is too short. Corrective lenses adjust the angle of the light as it enters the eye, focusing it on the retina.

the lens of an amphibian or a fish does not change shape; these animals instead focus images by moving their lens in and out, just as you would do to focus a camera.

Vertebrate photoreceptors are rod cells and cone cells

The vertebrate retina contains two kinds of photoreceptor cells, called rods and cones (figure 45.18). **Rods,** which get their name from the shape of their outer segment, are responsible for black-and-white vision when the illumination is dim. In contrast, **cones** are responsible for high visual acuity (sharpness) and color vision; cones have a cone-shaped outer segment. Humans have about 100 million rods and 3 million cones in each retina. Most of the cones are located in the central region of the retina known as the **fovea,** where the eye forms its sharpest image. Rods are almost completely absent from the fovea.

Structure of rods and cones

Rods and cones have the same basic cellular structure. An inner segment rich in mitochondria contains numerous vesicles filled with neurotransmitter molecules. It is connected by a narrow stalk to the outer segment, which is packed with hundreds of flattened disks stacked on top of one another. The light-capturing molecules, or photopigments, are located on the membranes of these disks (see figure 45.18).

In rods, the photopigment is called **rhodopsin.** It consists of the protein opsin bound to a molecule of *cis*-retinal, which is produced from vitamin A. Vitamin A is derived from carotene, a photosynthetic pigment in plants.

The photopigments of cones, called **photopsins,** are structurally very similar to rhodopsin. Humans have three kinds of cones, each of which possesses a photopsin consisting of *cis*-retinal bound to a protein with a slightly different amino acid sequence. These differences shift the absorption maximum, the region of the electromagnetic spectrum that is best absorbed by the pigment (figure 45.19). The absorption maximum of the *cis*-retinal in rhodopsin is 500 nanometers (nm); in contrast, the absorption maxima of the three kinds of cone photopsins are 420 nm (blue-absorbing), 530 nm (green-absorbing), and 560 nm (red-absorbing). These differences in the light-absorbing properties of the photopsins are responsible for the different color sensitivities of the three kinds of cones, which are often referred to as simply blue, green, and red cones.

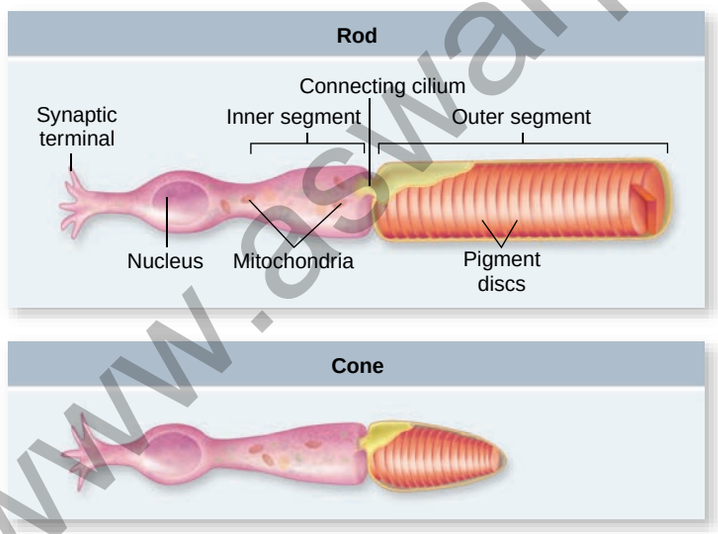


Figure 45.18 Rods and cones. The pigment-containing outer segment in each of these cells is separated from the rest of the cell by a partition through which there is only a narrow passage, the connecting cilium.

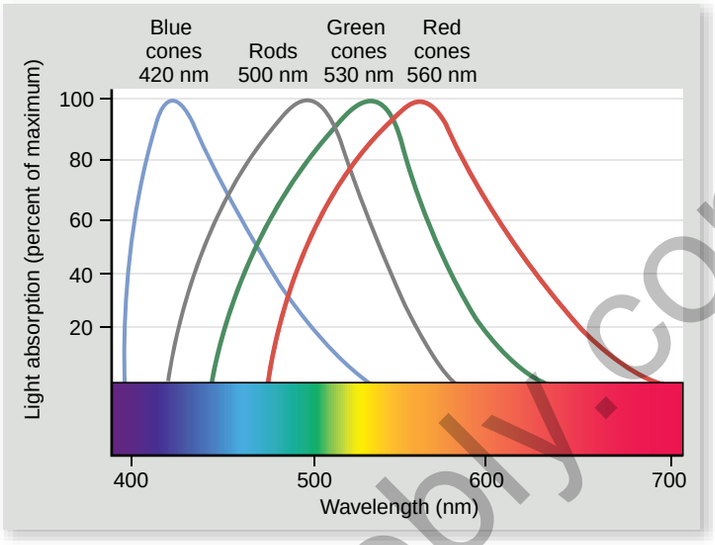


Figure 45.19 Color vision. The absorption maximum of *cis*-retinal in the rhodopsin of rods is 500 nm. However, the "blue cones" have their maximum light absorption at 420 nm; the "green cones" at 530 nm; and the "red cones" at 560 nm. The brain perceives all other colors from the combined activities of these three cones' systems.

The **retina,** the inside surface of the eye, is made up of three layers of cells (figure 45.20): The layer closest to the external surface of the eyeball consists of the rods and cones; the next layer contains **bipolar cells;** and the layer closest to the cavity of the eye is composed of **ganglion cells.** Thus, light must first pass through the ganglion cells and bipolar cells in order to reach the photoreceptors. The rods and cones synapse with the bipolar cells, and the bipolar cells synapse with the ganglion cells, which transmit impulses to the brain via the optic nerve. Ganglion cells are the only neurons of the retina capable of sending action potentials to the brain. The flow of sensory information in the retina is therefore opposite to the path of light through the retina.

Because the ganglion cells lie in the inner cavity of the eye, the optic nerve must intrude through the retina (see figure 45.16), creating a blind spot. You can see this blind spot yourself by holding a finger up in front of your face. Put a colored object on the finger tip, and then, with your left eye closed, focus on a point next to, but beyond, the fingertip. Now slowly move your finger to the right while keeping your eye focused on the distant point. At some point, you'll notice that you can no longer see the colored spot on your finger. The structure of the eye of mollusks avoids this problem by having the sensory neurons attach behind, rather than in front of, the retina (see figure 45.15).

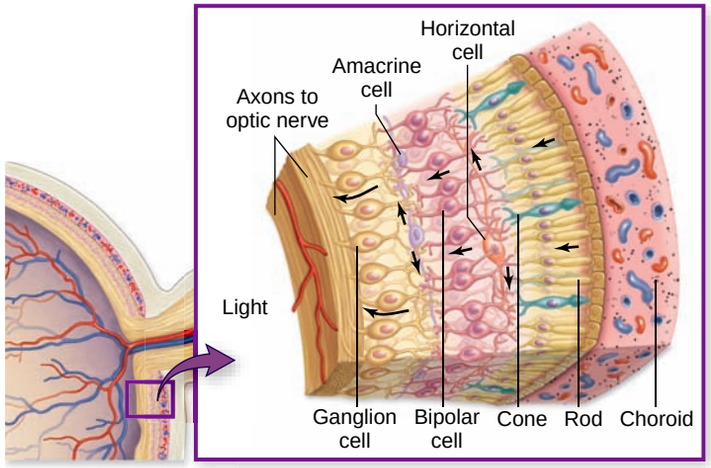


Figure 45.20 Structure of the retina. Note that the rods and cones are at the rear of the retina, not the front. Light passes through four other types of cells (ganglion, amacrine, bipolar, and horizontal) in the retina before it reaches the rods and cones. Once the photoreceptors are activated, they stimulate bipolar cells, which in turn stimulate ganglion cells. The flow of sensory information in the retina is thus opposite to the direction of light.

The retina contains two additional types of neurons called horizontal cells and amacrine cells. Stimulation of horizontal cells by photoreceptors at the center of a spot of light on the retina can inhibit the response of photoreceptors peripheral to the center. This lateral inhibition enhances contrast and sharpens the image.

Most vertebrates, particularly those that are diurnal (active during the day), have color vision, as do many insects and some other invertebrates. Indeed, honeybees—as well as some birds, lizards, and other vertebrates (figure 45.21)—can see light in the near-ultraviolet range, which is invisible to the human eye. Color vision requires the presence of more than one photopigment in different receptor cells, but not all animals with color vision have the three-cone system characteristic of humans and other primates. Fish, turtles, and birds, for example, have four or five kinds of cones; the "extra" cones enable these animals to see near-ultraviolet light and to distinguish shades of colors that we cannot detect. On the other hand, many mammals, for example, squirrels and dogs, have only two types of cones and thus have more limited ability to distinguish different colors.

Sensory transduction in photoreceptors

The transduction of light energy into nerve impulses follows a sequence that is the opposite of the usual way that sensory stimuli are detected. In the dark, the photoreceptor cells release an inhibitory neurotransmitter that hyperpolarizes the bipolar neurons. This prevents the bipolar neurons from releasing excitatory neurotransmitter to the ganglion cells that signal to the brain. In the presence of light, the photoreceptor cells stop releasing their inhibitory neurotransmitter, in effect, stimulating bipolar cells. The bipolar cells in turn stimulate the ganglion cells, which transmit action potentials to the brain.

The production of inhibitory neurotransmitter by photoreceptor cells is due to the presence of ligand-gated Na^+ channels. In the dark, many of these channels are open, allowing an influx of Na^+. This flow of Na^+ in the absence of light, called the dark current, depolarizes the membrane of photoreceptor cells. In this state, the cells produce inhibitory neurotransmitter that hyperpolarizes the membrane of bipolar cells. In the light, the Na^+ channels in the photoreceptor cell rapidly close, reducing the dark current and causing the photoreceptor to hyperpolarize. In this state, they no longer produce inhibitory neurotransmitter. In the absence of inhibition, the membrane of the bipolar cells is depolarized, causing them to release excitatory neurotransmitter to the ganglion cells.

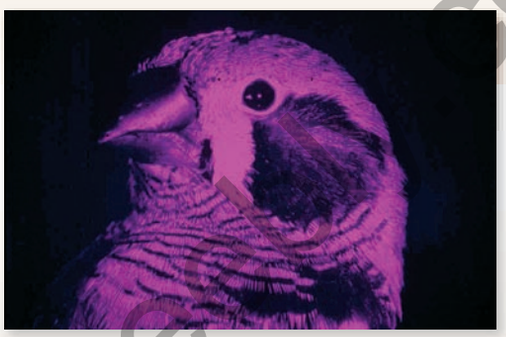
The control of the dark current depends on the ligand for the Na^+ channels in the photoreceptor cells: the nucleotide cyclic guanosine monophosphate (cGMP). In the dark, the level of cGMP is high, and the channels are open. The system is made sensitive to light by the nature and structure of the photopigments. Photopigments in the eye are actually G protein–coupled receptor proteins that are activated by absorbing light. When a photopigment absorbs light, *cis*-retinal isomerizes and dissociates from the receptor protein, opsin, in what is known as the bleaching reaction. As a result of this dissociation, the opsin receptor protein changes shape, activating its associated G protein. The activated G protein then activates its effector protein, the enzyme phosphodiesterase, which cleaves cGMP to GMP. The loss of cGMP causes the cGMP-gated Na^+

SCIENTIFIC THINKING

Hypothesis: *Birds can see light in the ultraviolet range.*

Prediction: *Birds will respond to individuals differently depending on how much ultraviolet is detected in their feathers.*

Test: *Zebra finch feathers reflect a moderate amount of ultraviolet light. Female zebra finches were exposed to different males, some of which were behind a filter that screened out UV light, whereas others were behind a control filter that let the UV pass through.*



Result and Conclusion: *Females preferred to spend time near the UV-positive males. Not only can female zebra finches see light in the UV range, but they prefer males with UV in the feathers.*

Further Experiments: *What are two hypotheses about why females prefer UV-positive males? How would you test these hypotheses?*

Figure 45.21 Ultraviolet vision in birds. Humans cannot distinguish colors in the near ultraviolet range, whereas many animals can. This photograph was taken with a special film that shows ultraviolet patterns on a zebra finch *(Taeniopygia guttata)* that are not detectable by humans.

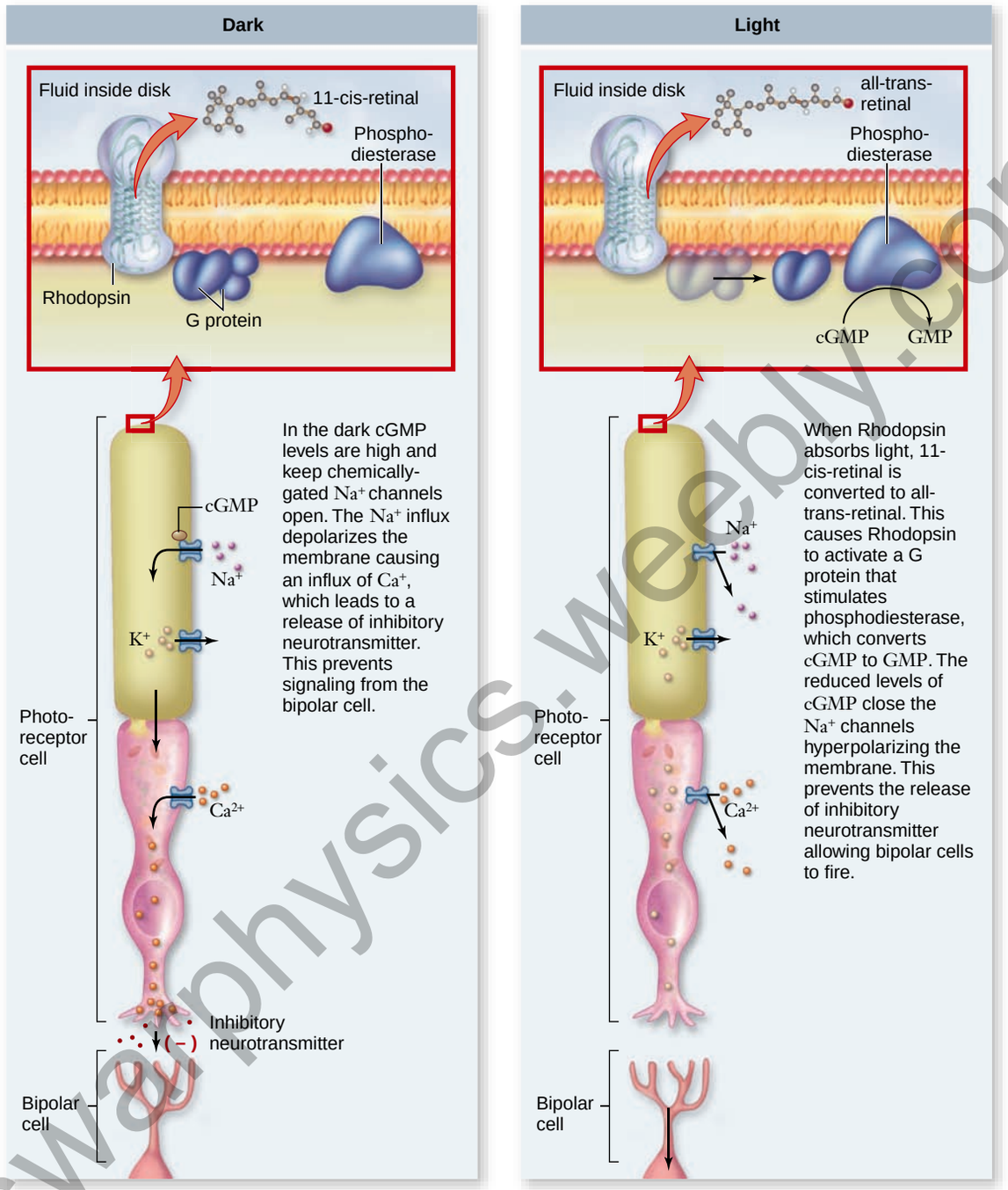


Figure 45.22 Signal transduction in the vertebrate eye. In the absence of light, cGMP keeps Na^+ channels open causing a Na^+ influx that leads to the release of inhibitory neurotransmitter. Light is absorbed by the retinal in rhodopsin, changing its structure. This causes rhodopsin to associate with a G protein. The activated G protein stimulates phosphodiesterase, which converts cGMP to GMP. Loss of cGMP closes Na^+ channels and prevents release of inhibitory neurotransmitter, which causes bipolar cells to stimulate ganglion cells.

channels to close, reducing the dark current (figure 45.22). Each opsin is associated with over 100 regulatory G proteins, which, when activated, release subunits that activate hundreds of molecules of the phosphodiesterase enzyme. Each enzyme molecule can convert thousands of cGMP to GMP, closing the Na^+ channels at a rate of about 1000 per second and inhibiting the dark current.

The absorption of a single photon of light can block the entry of more than a million Na^+, without changing K^+ permeability—the photoreceptor becomes hyperpolarized and releases less inhibitory neurotransmitter. Freed from inhibition, the bipolar cells activate the ganglion cells, which send impulses to the brain (figure 45.23).

Visual processing takes place in the cerebral cortex

Action potentials propagated along the axons of ganglion cells are relayed through structures called the **lateral geniculate nuclei** of the thalamus and projected to the occipital lobe of the cerebral cortex (see figure 45.23). There the brain interprets this information as light in a specific region of the eye's receptive field. The pattern of activity among the ganglion cells across the retina encodes a point-to-point map of the receptive field, allowing the retina and brain to image objects in visual space.

The frequency of impulses in each ganglion cell provides information about the light intensity at each point. At the same time,

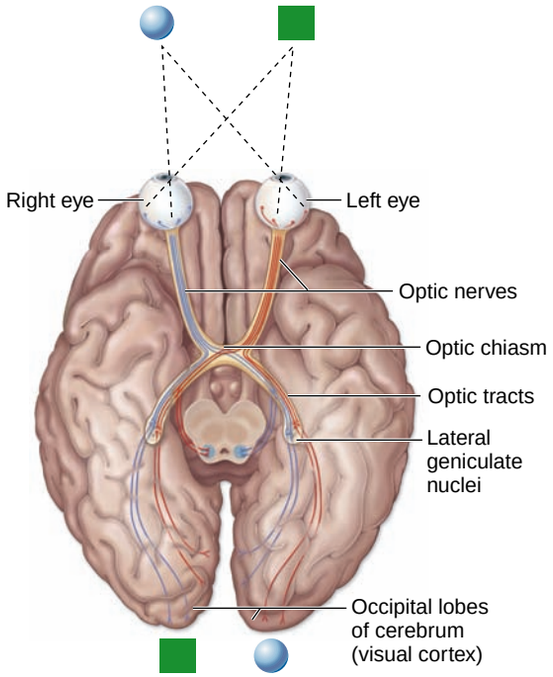


Figure 45.23 The pathway of visual information. Action potentials in the optic nerves are relayed from the retina to the lateral geniculate nuclei, and from there to the visual cortex of the occipital lobes. Note that half the optic nerves (the medial fibers arising from the inner portion of the retinas) cross to the other side at the optic chiasm, so that each hemisphere of the cerebrum receives input from both eyes.

the relative activity of ganglion cells connected (through bipolar cells) with the three types of cones provides color information.

Visual acuity

The relationship between receptors, bipolar cells, and ganglion cells varies in different parts of the retina. In the fovea, each cone makes a one-to-one connection with a bipolar cell, and each bipolar cell synapses with one ganglion cell. This point-to-point relationship is responsible for the high acuity of foveal vision.

Outside the fovea, many rods can converge on a single bipolar cell, and many bipolar cells can converge on a single ganglion cell. This convergence permits the summation of neural activity, making the area of the retina outside the fovea more sensitive to dim light than the fovea, but at the expense of acuity and color vision. This is why dim objects, such as faint stars at night, are best seen when you don't look directly at them. It has been said that we use the periphery of the eye as a detector, and the fovea as an inspector.

Color blindness can result from an inherited lack of one or more types of cones. People with normal color vision are trichromats; that is they have all three cones. Those with only two types of cones are dichromats. For example, people with red-green color blindness may lack red cones and have difficulty distinguishing red from green. Color blindness resulting from absence of one type of cone is a sex-linked recessive trait (see chapter 13), and therefore it is most often exhibited in males. Red-green color blindness can also result from a shift in the sensitivity curve of the absorption spectrum for one type of cone, resulting in the different cone types being stimulated by the same electromagnetic wavelengths and causing the individual to be unable to distinguish between red and green.

Binocular vision

Primates (including humans) and most predators have two eyes, one located on each side of the face. When both eyes are trained on the same object, the image that each eye sees is slightly different because the views have a slightly different angle. This slight displacement of the images (an effect called parallax) permits **binocular vision,** the ability to perceive three-dimensional images and to sense depth. Having eyes facing forward maximizes the field of overlap in which this stereoscopic vision occurs.

In contrast, prey animals generally have eyes located to the sides of the head, preventing binocular vision but enlarging the overall receptive field. It seems that natural selection has favored the detection of potential predators over depth perception in many prey species. The eyes of the American woodcock *(Scolopax minor)*, for example, are located at exactly opposite sides of the bird's skull so that it has a 360° field of view without turning its head.

Most birds have laterally placed eyes and, as an adaptation, have two foveas in each retina. One fovea provides sharp frontal vision, like the single fovea in the retina of mammals, and the other fovea provides sharper lateral vision.

Learning Outcomes Review 45.5

Many invertebrate groups have eyespots that detect light without forming images. Annelids, mollusks, arthropods, and chordates have independently evolved image-forming eyes. The vertebrate eye admits light through a pupil and then focuses it with an adjustable lens onto the retina, which contains photoreceptors. Photoreceptor rods and cones contain the photopigment *cis*-retinal, which indirectly activates bipolar neurons and then ganglion cells. The latter then transmit action potentials that ultimately reach the occipital lobe of the brain.

- ***Can an individual with red-green color blindness learn to distinguish these two colors? Why or why not?***

45.6 *The Diversity of Sensory Experiences*

Learning Outcomes

1. ***List examples of uncommon special senses.***
2. ***Explain how ampullae of Lorenzini work.***

Vision is the primary sense used by all vertebrates that live in a light-filled environment, but visible light is by no means the only part of the electromagnetic spectrum that vertebrates use to sense their environment.

Some snakes have receptors capable of sensing infrared radiation

Electromagnetic radiation with wavelengths longer than those of visible light is too low in energy to be detected by photoreceptors. Radiation from this infrared portion of the spectrum is what we normally think of as radiant heat.

Heat is an extremely poor environmental stimulus in water because water readily absorbs heat. Air, in contrast, has a low thermal capacity, so heat in air is a potentially useful stimulus. The only vertebrates known to have the ability to sense infrared radiation, however, are several types of snakes.

One type, the pit vipers, possess a pair of heat-detecting **pit organs** located on either side of the head between the eye and the nostril (figure 45.24). Each pit organ is composed of two chambers separated by a membrane. The infrared radiation falls on the membrane and warms it. Thermal receptors on the membrane are stimulated. The nature of these receptors is not known; they probably consist of temperature-sensitive neurons innervating the two chambers.

The paired pit organs appear to provide stereoscopic information, in much the same way that two eyes do. In fact, the nerves from the pits are connected to the optic tectum, the same part of the brain that controls vision; recent research suggests that information from the pits and from the eyes are overlain on each other, allowing snakes to combine visual and infrared thermal data. In fact, the pits are designed like a pinhole camera, and to some extent can focus a thermal image!

As a result, these exteroceptors are extraordinarily sensitive. Blind pit vipers can strike as accurately as a normal snake, and snakes deprived of their senses of sight and smell can accurately strike a target only 0.2° warmer than the background. Many pit vipers hunt endothermic prey at night, so the value of these capabilities is obvious.

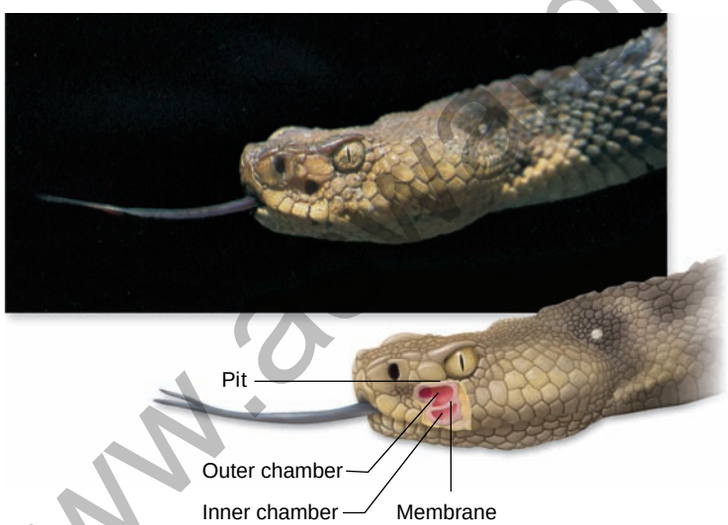


Figure 45.24 "Seeing" heat. The depression between the nostril and the eye of this rattlesnake opens into the pit organ. In the cutaway portion of the diagram, you can see that the organ is composed of two chambers separated by a membrane. Snakes known as pit vipers have the ability to sense infrared radiation (heat).

Some vertebrates can sense electrical currents

Although air does not readily conduct an electrical current, water is a good conductor. All aquatic animals generate electrical currents from contractions of their muscles. A number of different groups of fishes can detect these electrical currents. The so-called electrical fish even have the ability to produce electrical discharges from specialized electrical organs. Electrical fish use these weak discharges to locate their prey and mates and to construct a three-dimensional image of their environment, even in murky water.

The elasmobranchs (sharks, rays, and skates) have electroreceptors called the **ampullae of Lorenzini.** The receptor cells are located in sacs that open through jelly-filled canals to pores on the body surface. The jelly is a very good conductor, so a negative charge in the opening of the canal can depolarize the receptor at the base, causing the release of neurotransmitter and increased activity of sensory neurons. This allows sharks, for example, to detect the electrical fields generated by the muscle contractions of their prey. Although the ampullae of Lorenzini were lost in the evolution of teleost fish (most of the bony fish), electroreception reappeared in some groups of teleost fish that developed analogous sensory structures. Electroreceptors evolved yet another time, independently, in the duck-billed platypus, an egg-laying mammal. The receptors in its bill can detect the electrical currents created by the contracting muscles of shrimp and fish, enabling the mammal to detect its prey at night and in muddy water.

Some organisms detect magnetic fields

Eels, sharks, bees, and many birds appear to navigate along the magnetic field lines of the Earth. Even some bacteria use such forces to orient themselves.

Birds kept in dark cages, with no visual cues to guide them, peck and attempt to move in the direction in which they would normally migrate at the appropriate time of the year. They do not do so, however, if the cage is shielded from magnetic fields by steel. In addition, if the magnetic field of a blind cage is deflected 120° clockwise by an artificial magnet, a bird that normally orients to the north will orient toward the east-southeast. The nature of magnetic receptors in these vertebrates is the subject of much speculation, but the mechanism remains very poorly understood.

Learning Outcomes Review 45.6

Pit vipers can detect infrared radiation (heat). Many aquatic vertebrates can locate prey and perceive environmental contours by means of electroreceptors. The ampullae of Lorenzini, electroreceptors found in sharks and their relatives, contain a highly conductive jelly that triggers sensory neurons. Magnetic receptors may aid in bird migration.

- ***Would a heat-sensing organ be useful for hunting ectothermic prey?***

Chapter Review

45.1 Overview of Sensory Receptors

Sensory receptors detect both external and internal stimuli.

Exteroreceptors sense stimuli from the external environment, whereas interoreceptors sense stimuli from the internal environment.

Receptors can be grouped into three categories.

Receptors differ with respect to the environmental stimulus to which they respond: mechanoreceptors, chemoreceptors, and energy-detecting receptors.

Sensory information is conveyed in a four-step process.

Once detected, sensory information is conveyed in four steps: stimulation, transduction, transmission, and interpretation.

Sensory transduction involves gated ion channels.

Sensory transduction produces a graded receptor potential. A single potential or a sum of potentials may exceed a threshold to produce an action potential (see figure 45.2). A logarithmic relationship exists between stimulus intensity and action potential frequency.

45.2 Mechanoreceptors: Touch and Pressure

Pain receptors alert the body to damage or potential damage.

Nociceptors are free nerve endings located in the skin that respond to damaging stimuli, which is perceived as pain. Extreme temperatures can affect transient receptor potential (TRP) ion channels and cause depolarization by inflow of Na^+ and Ca^{2+}.

Thermoreceptors detect changes in heat energy.

Thermoreceptors are naked dendritic endings of sensory neurons that also contain TRP ion channels and respond to cold or heat.

Different receptors detect touch, depending on intensity.

Various receptors in the skin respond to mechanical distortion of the membrane to convey touch (see figure 45.3).

Muscle length and tension are monitored by proprioceptors.

Proprioceptors provide information about the relative position or movement of body parts and the degree of muscle stretching.

Baroreceptors detect blood pressure.

45.3 Hearing, Vibration, and Detection of Body Position

Hearing, the detection of sound or pressure waves, works best in water and provides directional information.

The lateral line system in fish detects low-frequency vibrations (see figure 45.5).

Ear structure is specialized to detect vibration.

The outer ear of terrestrial vertebrates channels sound to the eardrum (tympanic membrane) (see figure 45.6). Vibrations are transferred through middle ear bones to the oval window and into the cochlea, where the organ of Corti transduces them.

Transduction occurs in the cochlea.

The basilar membrane of the cochlea consists of fibers that respond to different frequencies of sound (see figure 45.8).

Some vertebrates have the ability to navigate by sound.

Echolocation allows bats, whales, and other species to navigate by sound.

Body position and movement are detected by systems associated with hearing systems.

Body position is detected by statocysts, ciliated hair cells embedded in a gelatinous matrix containing statoliths (see figure 45.9). Body movement is detected by hair cells located in the saccule and utricle (see figure 45.10).

45.4 Chemoreceptors: Taste, Smell, and pH

Taste detects and analyzes potential food.

Taste buds are collections of chemosensitive epithelial cells located on papillae (see figure 45.11). Tastes are broken down into five categories: sweet, sour, salty, bitter, and umami.

Smell can identify a vast number of complex molecules.

Smell, or olfaction, involves chemoreceptors located in the upper portion of the nasal passages (see figure 45.13). Their axons connect directly to the cerebral cortex.

Internal chemoreceptors detect pH and other characteristics.

Internal chemoreceptors of the aorta detect changes in blood pH, and central chemoreceptors in the medulla oblongata are sensitive to the pH of the cerebrospinal fluid.

45.5 Vision

Vision senses light and light changes at a distance.

Four phyla—annelids, mollusks, arthropods, and chordates—have independently evolved image-forming eyes (see figure 45.15).

In the vertebrate eye, light enters through the pupil, with intensity controlled by the iris. The lens, controlled by the ciliary muscle, focuses the light on the retina (see figure 45.16).

Vertebrate photoreceptors are rod cells and cone cells.

Rods detect black and white; cones are necessary for visual acuity and color vision (see figure 45.18).

In the retina, photoreceptors synapse with bipolar cells, which in turn synapse with ganglion cells; the ganglion cells send action potentials to the brain (see figure 45.20).

Visual processing takes place in the cerebral cortex (see figure 45.23).

In the fovea, a region of the retina responsible for high acuity, each cone cell is connected to a single bipolar cell/ganglion cell, unlike in areas outside the fovea.

Primates and most predators have binocular vision—images from each eye overlap to produce a three-dimensional image.

45.6 The Diversity of Sensory Experiences

Some snakes have receptors capable of sensing infrared radiation.

The pit organ of pit vipers detects heat.

Some vertebrates can sense electrical currents.

Electroreceptors in elasmobranchs and the duck-billed platypuses can detect electrical currents.

Some organisms detect magnetic fields.

Many organisms appear to navigate along magnetic field lines, but the mechanisms remains poorly understood.

Review Questions

UNDERSTAND

1. Which of these is not a method by which sensory receptors receive information about the internal or external environment?
   a. Changes in pressure
   b. Light or heat changes
   c. Changes in molecular concentration
   d. All of these are used by sensory receptors.
2. Which of the following correctly lists the steps of perception?
   a. Interpretation, stimulation, transduction, transmission
   b. Stimulation, transduction, transmission, interpretation
   c. Interpretation, transduction, stimulation, transmission
   d. Transduction, interpretation, stimulation, transmission
3. All sensory receptors are able to initiate nerve impulses by opening or closing
   a. voltage-gated ion channels.
   b. exteroceptors.
   c. interoceptors.
   d. stimulus-gated ion channels.
4. In the fairy tale, Sleeping Beauty fell asleep after pricking her finger. What kind of receptor responds to that kind of painful stimulus?
   a. Mechanoreceptor
   b. Nociceptor
   c. Thermoreceptor
   d. Touch receptor
5. The ear detects sound by the movement of
   a. the basilar membrane.
   b. the tectorial membrane.
   c. the Eustachian tube.
   d. fluid in the semicircular canals.
6. Hair cells in the vestibular apparatus of terrestrial vertebrates
   a. measure temperature changes within the body.
   b. sense sound in very low range of hearing.
   c. provide a sense of acceleration and balance.
   d. measure changes in blood pressure.
7. _____ is the photopigment contained within both rods and cones of the eye.
   a. Carotene
   b. *Cis*-retinal
   c. Photochrome
   d. Chlorophyll
8. Which of the following is not a method used by vertebrates to gather information about their environment?
   a. Infrared radiation
   b. Magnetic fields
   c. Electrical currents
   d. All of these are methods used for sensory reception.
9. The lobe of the brain that recognizes and interprets visual information is the
   a. occipital lobe.
   b. frontal lobe.
   c. parietal lobe.
   d. temporal lobe.

APPLY

1. What do the sensory systems of annelids, mollusks, arthropods, and chordates have in common?
   a. They all use the same stimuli for taste.
   b. They all use neurons to detect vibration.
   c. They all have image-forming eyes that evolved independently.
   d. They all use chemoreceptors in their skin to detect food.
2. Animals can more easily tell the direction of a visual signal than an auditory signal because
   a. light travels in straight lines.
   b. the wind provides too much background noise.
   c. sound travels faster underwater.
   d. eyes are more sensitive than ears.
3. The difference in the structure of the vertebrate and mollusk eyes
   a. results because mollusks live in water, causing images to be upside down.
   b. indicates that vertebrates have better vision than mollusks.
   c. reveals a disadvantage of vertebrate eye structure.
   d. makes color vision more efficient in vertebrates.
4. The ability of some insects, birds, and lizards to see ultraviolet light is
   a. a result of a common diet eaten by those species.
   b. an example of convergent evolution in cone cell sensitivity.
   c. the ancestral state inherited from flatworms.
   d. an adaptation for nocturnal activity.

SYNTHESIZE

1. When blood pH falls too low, a potentially fatal condition known as acidosis results. Among the variety of responses to this condition, the body changes the breathing rate. How does the body sense this change? How does the breathing rate change? How does this increase pH?
2. The function of the vertebrate eye is unusual compared with other processes found within the body. For example, the direction in which sensory information flows is actually opposite to path that light takes through the retina. Explain the sequence of events involved in the movement of light and information through the structures of the eye, and explain why they move in opposite directions. Consider, also, how this sequence of events compares to the functioning of the mollusk eye.
3. How would the otolith organs of an astronaut respond to zero gravity? Would the astronaut still have a subjective impression of motion? Would the semicircular canals detect angular acceleration equally well at zero gravity?

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Chapter 46

The Endocrine System

Chapter Outline

Introduction

Diabetes is a disease in which well-fed people appear to starve to death. The disease was known to Roman and Greek physicians, who described a "melting away of flesh" coupled with excessive urine production "like the opening of aqueducts." Until 1922, the diagnosis of diabetes in children was effectively a death sentence. In that year, Frederick Banting and Charles Best extracted the molecule insulin from the pancreas. Injections of insulin into the bloodstream dramatically reversed the symptoms of the disease. This served as an impressive confirmation of a new concept: that certain internal organs produced powerful regulatory chemicals that were distributed via the blood.

We now know that the tissues and organs of the vertebrate body cooperate to maintain homeostasis through the actions of many regulatory mechanisms. Two systems, however, are devoted exclusively to the regulation of the body organs: the nervous system and the endocrine system. Both release regulatory molecules that control the body organs by binding to receptor proteins on or in the cells of those organs. In this chapter, we examine the regulatory molecules of the endocrine system, the cells and glands that produce them, and how they function to regulate the body's activities.

46.1 Regulation of Body Processes by Chemical Messengers

Learning Outcomes

1. *Describe the role of hormones in regulating body processes.*
2. *Identify the different types of hormones.*
3. *Differentiate between lipophilic and hydrophilic hormones.*

There are four mechanisms of cell communication: direct contact, synaptic signaling, endocrine signaling, and paracrine signaling. Here we are concerned with signaling methods of communication; we begin with the three signaling mechanisms.

As discussed in chapter 44, the axons of neurons secrete chemical messengers called neurotransmitters into the synaptic cleft. These chemicals diffuse only a short distance to the postsynaptic membrane, where they bind to their receptor proteins and stimulate the postsynaptic cell. Synaptic transmission generally affects only the postsynaptic cell that receives the neurotransmitter.

A *hormone*, in contrast, is a regulatory chemical that is secreted into extracellular fluid and carried by the blood and can therefore act at a distance from its source. Organs that are specialized to secrete hormones are called *endocrine glands*, but some organs, such as the liver and the kidney, can produce hormones in addition to performing other functions. The organs and tissues that produce hormones are collectively called the **endocrine system.**

The blood carries hormones to every cell in the body, but only target cells with the appropriate receptor for a given hormone can respond to it. Hormone receptor proteins function in a similar manner to neurotransmitter receptors. The receptor proteins specifically bind the hormone and activate signal transduction pathways that produce a response to the hormone. The highly specific interaction between hormones and their receptors enable hormones to be active at remarkably small concentrations. It is not unusual to find hormones circulating in the blood at concentrations of 10^{-8} to 10^{-10} M. In addition to the chemical messengers released as neurotransmitters and as hormones, other molecules are released and act within an organ on nearby cells as local regulators. These chemicals are termed **paracrine regulators.** They act in a way similar to endocrine hormones, but they do not travel through the blood to reach their target. This allows cells of an organ to regulate one another.

Cells can also release signaling molecules that affect their own behavior, or autocrine signaling. This is common in the immune system, and is also seen in cancer cells that may release growth factors that stimulate their own growth.

Chemical communication is not limited to cells within an organism. *Pheromones* are chemicals released into the environment to communicate among individuals of a single species. These aid in communication between animals and may alter the behavior or physiology of the receiver, but are not involved in the normal metabolic regulation of an animal.

Figure 46.1 compares the different types of chemical messengers used for internal regulation.

Some molecules act as both circulating hormones and neurotransmitters

Blood delivery of hormones enables endocrine glands to coordinate the activity of large numbers of target cells distributed throughout the body, but that may not be the only role for these molecules. A molecule produced by an endocrine gland and used as a hormone may also be produced and used as a neurotransmitter by neurons. The hormone norepinephrine, for example, is secreted into the blood by the adrenal glands, but it is also released as a neurotransmitter by sympathetic nerve endings. Norepinephrine acts as a hormone to coordinate the activity of the heart, liver, and blood vessels during response to stress.

Neurons can also secrete a class of hormones called **neurohormones** that are carried by blood. The neurohormone antidiuretic hormone, for example, is secreted by neurons in the brain. Some specialized regions of the brain contain not only neurotransmitting neurons, but also clusters of neurons

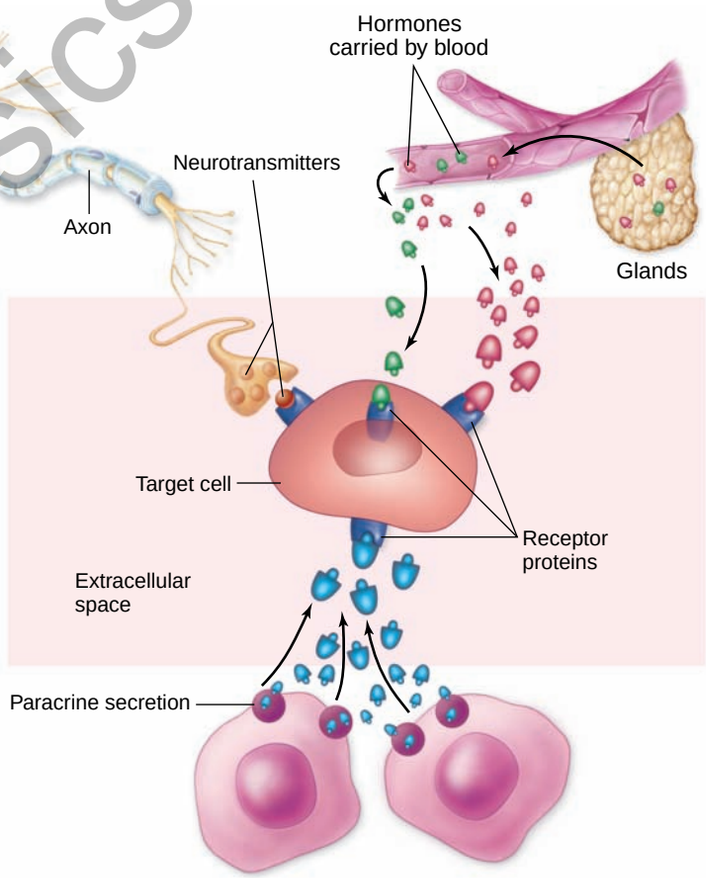


Figure 46.1 Different types of chemical messengers.
The functions of organs are influenced by neural, paracrine, and endocrine regulators. Each type of chemical regulator binds to specific receptor proteins on the surface or within the cells of target organs.

producing neurohormones. In this way, neurons can deliver chemical messages beyond the nervous system itself.

The secretory activity of many endocrine glands is controlled by the nervous system. As you will see, the hypothalamus controls the hormonal secretions of the anterior-pituitary gland, and produces the hormones of the posterior pituitary.

The secretion of a number of hormones, however, can be independent of neural control. For example, the release of insulin by the pancreas and aldosterone by the adrenal cortex is stimulated by increases in the blood concentrations of glucose and potassium (K^+), respectively.

Endocrine glands produce three chemical classes of hormones

The endocrine system (figure 46.2) includes all of the organs that secrete hormones—the thyroid gland, pituitary gland, adrenal glands, and so on (table 46.1). Cells in these organs secrete hormones into extracellular fluid, where it diffuses into surrounding blood capillaries. For this reason, hormones are referred to as endocrine secretions. In contrast, cells of some glands excrete their products into a duct to outside the body, or into the gut. For example, the pancreas excretes hydrolytic enzymes into the lumen of the small intestine. These glands are termed exocrine glands,.

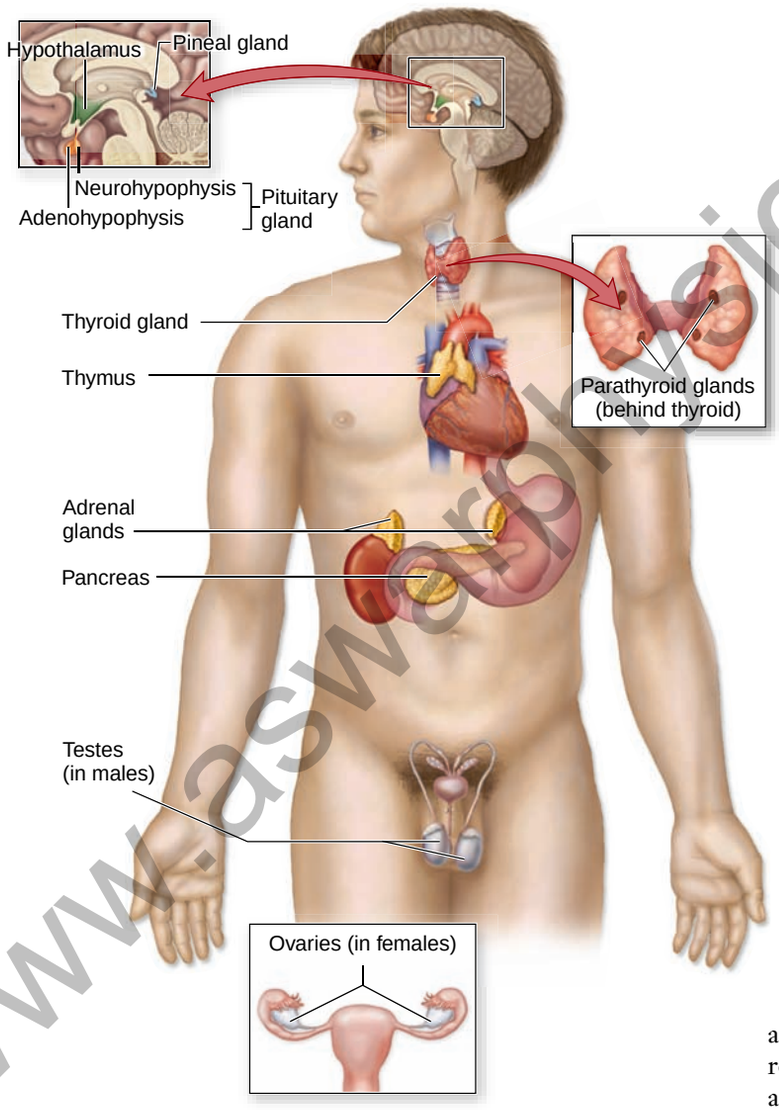


Figure 46.2 The human endocrine system. The major endocrine glands are shown, but many other organs secrete hormones in addition to their primary functions.

Molecules that function as hormones must exhibit two basic characteristics. First, they must be sufficiently complex to convey regulatory information to their targets. Simple molecules such as carbon dioxide, or ions such as Ca^{2+}, do not function as hormones. Second, hormones must be adequately stable to resist destruction prior to reaching their target cells. Three primary chemical categories of molecules meet these requirements.

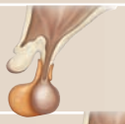
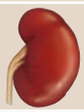
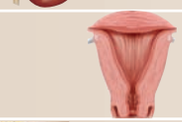
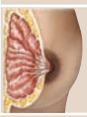
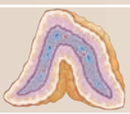
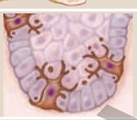
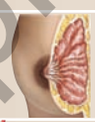
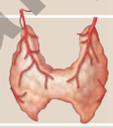
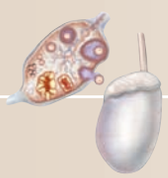
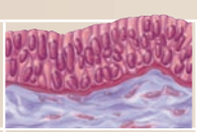
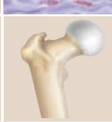
1. **Peptides and proteins** are composed of chains of amino acids. Some important examples of peptide hormones include antidiuretic hormone (9 amino acids), insulin (51 amino acids), and growth hormone (191 amino acids). These hormones are encoded in DNA and produced by the same cellular machinery responsible for transcription and translation of other peptide molecules. The most complex are glycoproteins composed of two peptide chains with attached carbohydrates. Examples include thyroid-stimulating hormone and luteinizing hormone.
2. **Amino acid derivatives** are hormones manufactured by enzymatic modification of specific amino acids; this group comprises the biogenic amines discussed in chapter 44. They include hormones secreted by the adrenal medulla (the inner portion of the adrenal gland), thyroid, and pineal glands. Those secreted by the adrenal medulla are derived from tyrosine. Known as **catecholamines,** they include epinephrine (adrenaline) and norepinephrine (noradrenaline). Other hormones derived from tyrosine are the **thyroid hormones,** secreted by the thyroid gland. The pineal gland secretes a different amine hormone, **melatonin,** derived from tryptophan.
3. **Steroids** are lipids manufactured by enzymatic modifications of cholesterol. They include the hormones testosterone, estradiol, progesterone, aldosterone, and cortisol. Steroid hormones can be subdivided into sex steroids, secreted by the testes, ovaries, placenta, and adrenal cortex, and corticosteroids (mineralocoricoids and cortisol), secreted only by the adrenal cortex.

Hormones can be categorized as lipophilic or hydrophilic

The manner in which hormones are transported and interact with their targets differs depending on their chemical nature. Hormones may be categorized as lipophilic (nonpolar), which are fat-soluble, or hydrophilic (polar), which are water-soluble. The lipophilic hormones include the steroid hormones and thyroid hormones. Most other hormones are hydrophilic.

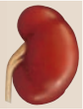
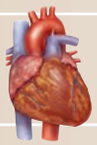
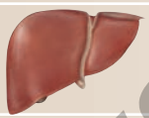
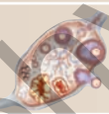
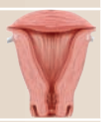
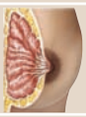
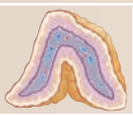
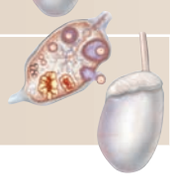
This distinction is important in understanding how these hormones regulate their target cells. Hydrophilic hormones are freely soluble in blood, but cannot pass through the membrane of

TABLE 46.1 Principal Mammalian Endocrine Glands and Their Hormones*

Endocrine Gland and Hormone	Target Tissue		Principal Actions	Chemical Nature
Hypothalamus				
Releasing hormones	Adenohypophysis		Activate release of adenohypophyseal hormones	Peptides
Inhibiting hormones	Adenohypophysis		Inhibit release of adenohypophyseal hormones	Peptides (except prolactin-inhibiting factor, which is dopamine)
Neurohypophysis (Posterior-pituitary gland)				
Antidiuretic hormone (ADH)	Kidneys		Conserves water by stimulating its reabsorption from urine	Peptide (9 amino acids)
Oxytocin (OT)	Uterus		Stimulates contraction	Peptide (9 amino acids)
	Mammary glands		Stimulates milk ejection	
Adenohypophysis (Anterior-pituitary gland)				
Adrenocorticotropic hormone (ACTH)	Adrenal cortex		Stimulates secretion of adrenal cortical hormones such as cortisol	Peptide (39 amino acids)
Melanocyte-stimulating hormone (MSH)	Skin		Stimulates color change in reptiles and amphibians; various functions in mammals	Peptide (two forms; 13 and 22 amino acids)
Growth hormone (GH)	Many organs		Stimulates growth by promoting bone growth, protein synthesis, and fat breakdown	Protein
Prolactin (PRL)	Mammary glands		Stimulates milk production	Protein
Thyroid-stimulating hormone (TSH)	Thyroid gland		Stimulates thyroxine secretion	Glycoprotein
Luteinizing hormone (LH)	Gonads		Stimulates ovulation and corpus luteum formation in females; stimulates secretion of testosterone in males	Glycoprotein
Follicle-stimulating hormone (FSH)	Gonads		Stimulates spermatogenesis in males; stimulates development of ovarian follicles in females	Glycoprotein
Thyroid Gland				
Thyroid hormones (thyroxine and triiodothyronine)	Most cells		Stimulates metabolic rate; essential to normal growth and development	Amino acid derivative (iodinated)
Calcitonin	Bone		Inhibits loss of calcium from bone	Peptide (32 amino acids)

*These are hormones released from endocrine glands. Hormones are released from organs that have additional, nonendocrine functions, such as the liver, kidney, and intestine.

TABLE 46.1 Principal Mammalian Endocrine Glands and Their Hormones, *continued*

Endocrine Gland and Hormone	Target Tissue		Principal Actions	Chemical Nature
Parathyroid Glands				
Parathyroid hormone (PTH)	Bone, kidneys, digestive tract		Raises blood calcium level by stimulating bone breakdown; stimulates calcium reabsorption in kidneys; activates vitamin D	Peptide (34 amino acids)
Adrenal Medulla				
Epinephrine (adrenaline) and norepinephrine (noradrenaline)	Smooth muscle, cardiac muscle, blood vessels		Initiates stress responses; raises heart rate, blood pressure, metabolic rate; dilates blood vessels; mobilizes fat; raises blood glucose level	Amino acid derivatives
Adrenal Cortex				
Glucocorticoids (e.g., cortisol)	Many organs		Adaptation to long-term stress; raises blood glucose level; mobilizes fat	Steroid
Mineralocorticoids (e.g., aldosterone)	Kidney tubules		Maintains proper balance of Na^+ and K^+ in blood	Steroid
Pancreas				
Insulin	Liver, skeletal muscles, adipose tissue		Lowers blood glucose level; stimulates glycogen, fat, protein synthesis	Peptide (51 amino acids)
Glucagon	Liver, adipose tissue		Raises blood glucose level; stimulates breakdown of glycogen in liver	Peptide (29 amino acids)
Ovary				
Estradiol	General		Stimulates development of female secondary sex characteristics	Steroid
	Female reproductive structures		Stimulates growth of sex organs at puberty and monthly preparation of uterus for pregnancy	
Progesterone	Uterus		Completes preparation for pregnancy	Steroid
	Mammary glands		Stimulates development	
Testis				
Testosterone	Many organs		Stimulates development of secondary sex characteristics in males and growth spurt at puberty	Steroid
	Male reproductive structures		Stimulates development of sex organs; stimulates spermatogenesis	
Pineal Gland				
Melatonin	Gonads, brain, pigment cells		Regulates biological rhythms	Amino acid derivative

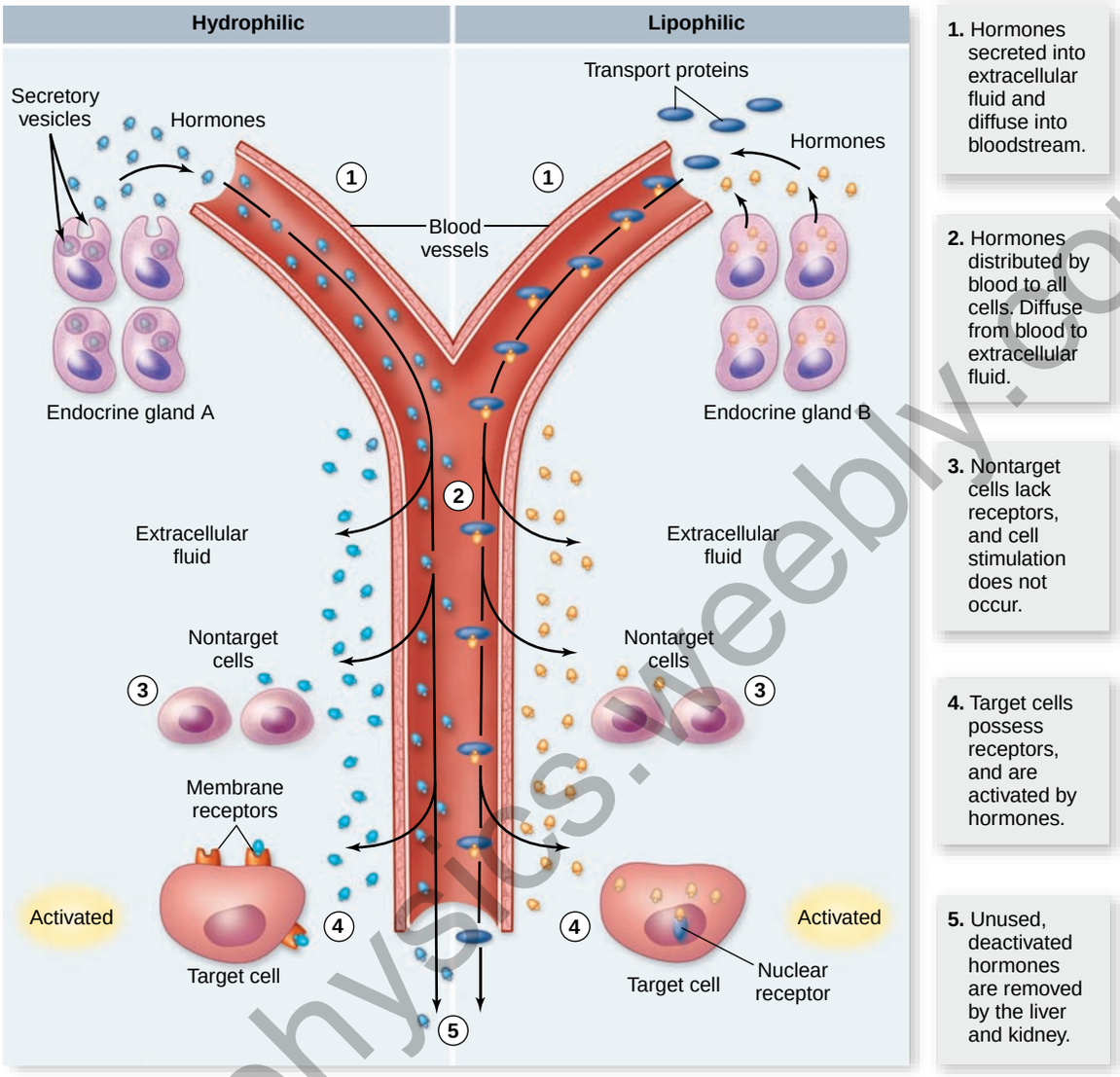


Figure 46.3 The life of hormones. Endocrine glands produce both hydrophilic and lipophilic hormones, which are transported to targets through the blood. Lipophilic hormones bind to transport proteins that make them soluble in blood. Target cells have membrane receptors for hydrophilic hormones, and intracellular receptors for lipophilic hormones. Hormones are eventually destroyed by their target cells or cleared from the blood by the liver or the kidney.

target cells. They must therefore activate their receptors from outside the cell membrane. In contrast, lipophilic hormones travel in the blood attached to transport proteins (figure 46.3). Their lipid solubility enables them to cross cell membranes and bind to intracellular receptors.

Both types of hormones are eventually destroyed or otherwise deactivated after their use, eventually being excreted in bile or urine. However, hydrophilic hormones are deactivated more rapidly than lipophilic hormones. Hydrophilic hormones tend to act over relatively brief periods of time (minutes to hours), whereas lipophilic hormones generally are active over prolonged periods, such as days to weeks.

Paracrine regulators exert powerful effects within tissues

Paracrine regulation occurs in most organs and among the cells of the immune system. **Growth factors,** proteins that promote growth and cell division in specific organs, are among the most important paracrine regulators. Growth factors play a critical role in regulating mitosis throughout life (see chapter 10). For example, *epidermal growth factor* activates mitosis of skin and development of connective tissue cells, whereas *nerve growth factor* stimulates the growth and survival of neurons. *Insulin-like growth factor* stimulates cell division in developing bone as well as protein synthesis in many other tissues. **Cytokines** (described in chapter 52) are growth factors specialized to control cell division and differentiation in the immune system, whereas **neurotropins** are growth factors that regulate the nervous system.

The importance of growth factor function is underscored by the observation that damage to the genes coding for growth factors or their receptors can lead to the unregulated cell division and development of tumors.

Paracrine regulation of blood vessels

The gas nitric oxide (NO), which can function as a neurotransmitter (see chapter 44), is also produced by the endothelium of blood vessels. In this context, it is a paracrine regulator because it diffuses to the smooth muscle layer of the blood vessel and promotes vasodilation. One of its major roles involves the control of blood pressure by dilating arteries. The endothelium of blood vessels is a rich source of paracrine regulators, including *endothelin*, which stimulates vasoconstriction, and *bradykinin*, which promotes vasodilation. Paracrine regulation supplements the regulation of blood vessels

by autonomic nerves, enabling vessels to respond to local conditions, such as increased pressure or reduced oxygen.

Prostaglandins

A particularly diverse group of paracrine regulators are the **prostaglandins.** A prostaglandin is a 20-carbon-long fatty acid that contains a five-membered carbon ring. This molecule is derived from the precursor molecule *arachidonic acid*, released from phospholipids in the cell membrane under hormonal or other stimulation. Prostaglandins are produced in almost every organ and participate in a variety of regulatory functions. Some prostaglandins are active in promoting smooth muscle contraction. Through this action, they regulate reproductive functions such as gamete transport, labor, and possibly ovulation. Excessive prostaglandin production may be involved in premature labor, endometriosis, or dysmenorrhea (painful menstrual cramps). They also participate in lung and kidney regulation through effects on smooth muscle.

In fish, prostaglandins have been found to function as both a hormone and a paracrine regulator. Prostaglandins produced in the fish's ovary during ovulation can travel to the brain to synchronize associated spawning behavior.

Prostaglandins are produced at locations of tissue damage, where they promote many aspects of inflammation, including swelling, pain, and fever. This effect of prostaglandins has been well studied. Drugs that inhibit prostaglandin synthesis, such as aspirin, help alleviate these symptoms.

Aspirin is the most widely used of the *nonsteroidal anti-inflammatory drugs (NSAIDs)*, a class of drugs that also includes indomethacin and ibuprofen. These drugs act to inhibit two related enzymes: cyclooxygenase-1 and 2 (COX-1 and COX-2). The anti-inflammatory effects are due to the inhibition of COX-2, which is necessary for the production of prostaglandins from arachidonic acid. This reduces inflammation and associated pain from the action of prostaglandins. Unfortunately, the inhibition of COX-1 produces unwanted side effects, including gastric bleeding and prolonged clotting time.

More recently developed pain relievers, called *COX-2 inhibitors*, selectively inhibit COX-2 but not COX-1. COX-2 inhibitors may be of potentially great benefit to arthritis sufferers and others who must use pain relievers regularly, but concerns have been raised that they may also affect other aspects of prostaglandin function in the cardiovascular system. Some COX-2 inhibitors were removed from the market when a greater risk of heart attack and stroke was detected. Some have remained in use, however, and others may be reintroduced upon FDA approval. Aside from the possibly lessened gastrointestinal side effects, COX-2 inhibitors are not more effective for pain than the older NSAIDs.

Learning Outcomes Review 46.1

Hormones coordinate the activity of specific target cells. The three chemical classes of endocrine hormones are peptides and proteins, amino acid derivatives, and steroids. Lipophilic hormones such as steroids can cross membranes, but need carriers in the blood; hydrophilic hormones move readily in the blood, but cannot cross membranes. Paracrine regulators act within the organ in which they are produced.

- ***How do hormones and neurotransmitters differ?***

46.2 Actions of Lipophilic Versus Hydrophilic Hormones

Learning Outcomes

1. ***Explain how steroid hormone receptors activate transcription.***
2. ***Explain how the signal carried by peptide hormones crosses the membrane.***
3. ***Describe the different types of membrane receptors.***

As mentioned previously, hormones can be divided into the lipophilic (lipid-soluble) and the hydrophilic (water-soluble). The receptors and actions of these two broad categories have notable differences, which we explore in this section.

Lipophilic hormones activate intracellular receptors

The lipophilic hormones include all of the steroid hormones and thyroid hormones (figure 46.4) as well as other lipophilic regulatory molecules including the retinoids, or vitamin A.

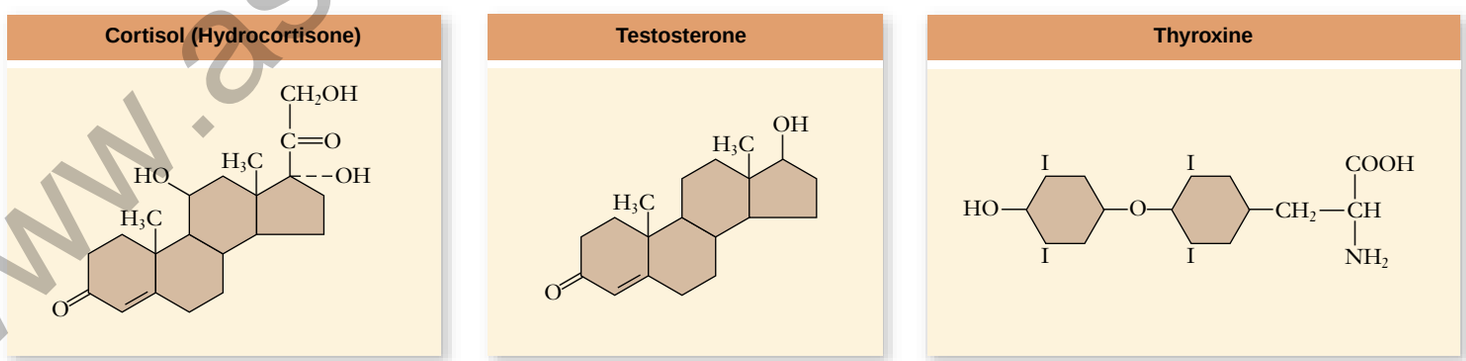


Figure 46.4 Chemical structures of lipophilic hormones. Steroid hormones are derived from cholesterol. The two steroid hormones shown, cortisol and testosterone, differ slightly in chemical structure yet have widely different effects on the body. The thyroid hormone, thyroxine, is formed by coupling iodine to the amino acid tyrosine.

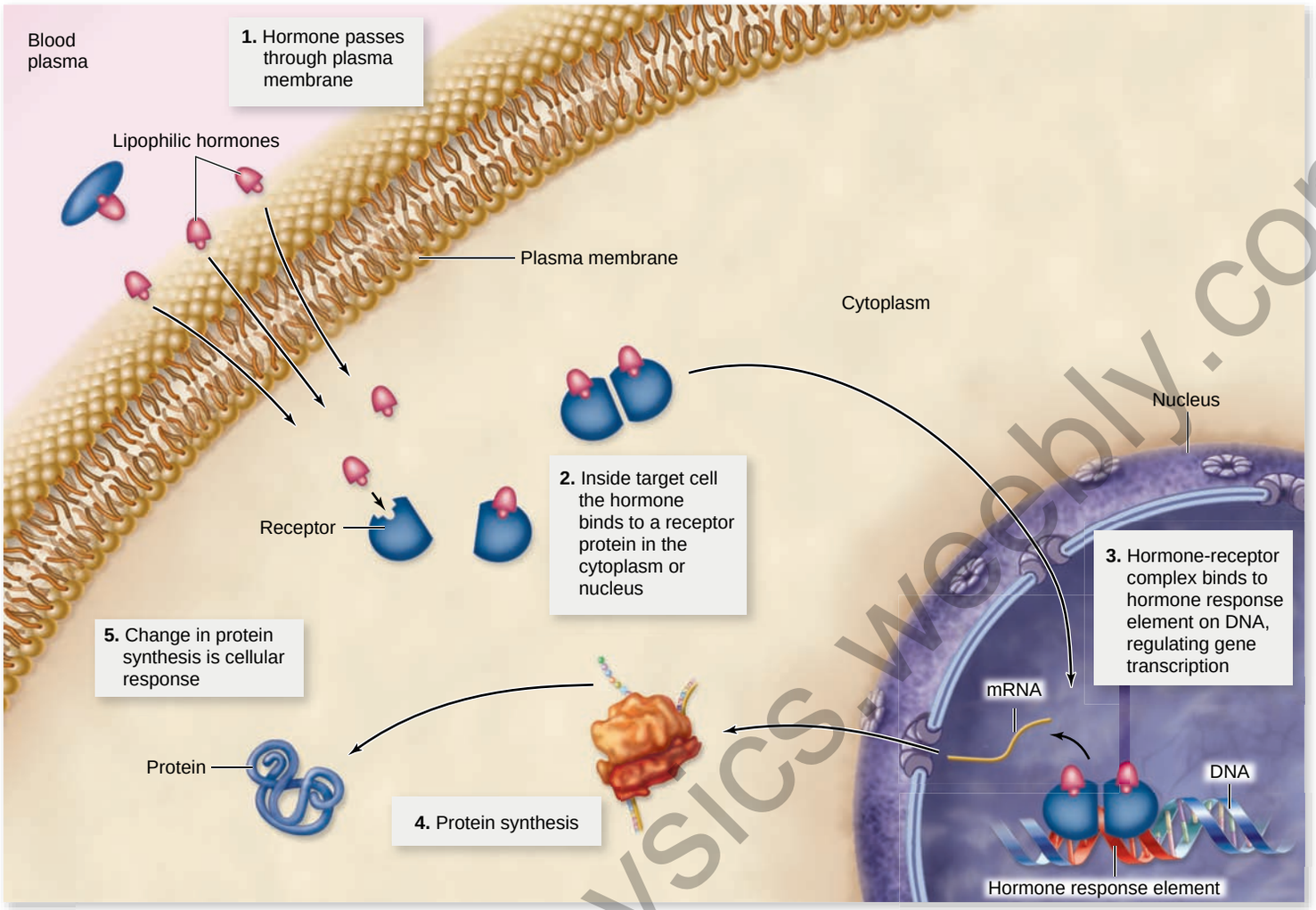


Figure 46.5 The mechanism of lipophilic hormone action. Lipophilic hormones diffuse through the plasma membrane of cells and bind to intracellular receptor proteins. The hormone-receptor complex then binds to specific regions of the DNA (hormone response elements), regulating the production of messenger RNA (mRNA). Most receptors for these hormones reside in the nucleus; if the hormone is one that binds to a receptor in the cytoplasm, the hormone-receptor complex moves together into the nucleus.

Lipophilic hormones can enter cells because the lipid portion of the plasma membrane does not present a barrier. Once inside the cell the lipophilic regulatory molecules all have a similar mechanism of action.

Transport and receptor binding

These hormones circulate bound to transport proteins (see figure 46.3), which make them soluble and prolong their survival in the blood. When the hormones arrive at their target cells, they dissociate from their transport proteins and pass through the plasma membrane of the cell (figure 46.5). The hormone then binds to an intracellular receptor protein.

Some steroid hormones bind to their receptors in the cytoplasm, and then move as a hormone-receptor complex into the nucleus. Other steroids and the thyroid hormones travel directly into the nucleus before encountering their receptor proteins. Whether the hormone finds its receptor in the nucleus or translocates with its receptor into the nucleus from the cytoplasm, the rest of the story is similar.

Activation of transcription in the nucleus

The hormone receptor, activated by binding to the hormone, is now also able to bind to specific regions of the DNA. These DNA regions, located in the promoters of specific genes, are known as **hormone response elements.** The binding of the hormone-receptor complex has a direct effect on the level of transcription at that site by activating, or in some cases deactivating, gene transcription. Receptors therefore function as *hormone-activated transcription factors* (see chapters 9 and 16).

The proteins that result from activation of these transcription factors often have activity that changes the metabolism of the target cell in a specific fashion; this change constitutes the cell's response to hormone stimulation. When estrogen binds to its receptor in liver cells of chickens, for example, it activates the cell to produce the protein vitellogenin, which is then transported to the ovary to form the yolk of eggs. In contrast, when thyroid hormone binds to its receptor in the anterior pituitary of humans, it inhibits the expression of the gene for thyrotropin, a mechanism of negative feedback (described later).

Because this activation and transcription process requires alterations in gene expression, it often takes several hours before the response to lipophilic hormone stimulation is apparent in target cells.

Hydrophilic hormones activate receptors on target cell membranes

Hormones that are too large or too polar to cross the plasma membranes of their target cells include all of the peptide, protein, and glycoprotein hormones, as well as the catecholamine hormones. These hormones bind to receptor proteins located on the outer surface of the plasma membrane. This binding must then activate the hormone response inside the cell, initiating the process of signal transduction. The cellular response is most often achieved through receptor-dependent activation of the powerful intracellular enzymes called *protein kinases*. As described in chapter 9, protein kinases are critical regulatory enzymes that activate or deactivate intracellular proteins by phosphorylation. By regulating protein kinases, hydrophilic hormone receptors exert a powerful influence over the broad range of intracellular functions.

Receptor kinases

For some hormones, such as insulin, the receptor itself is a kinase (figure 46.6), and it can directly phosphorylate intracellular proteins that alter cellular activity. In the case of insulin, this action results in the placement in the plasma membrane of glucose transport proteins that enable glucose to enter cells. Other peptide hormones, such as growth hormone, work through similar mechanisms, although the receptor itself is not a kinase. Instead, the hormone-bound receptor recruits and activates intracellular kinases, which then initiate the cellular response.

Second-messenger systems

Many hydrophilic hormones, such as epinephrine, work through second-messenger systems. A number of different molecules in the cell can serve as second messengers, as you saw in chapter 9. The interaction between the hormone and its receptor activates mechanisms in the plasma membrane that increase the concentration of the second messengers within the target cell cytoplasm.

In the early 1960s, Earl Sutherland showed that activation of the epinephrine receptor on liver cells increases intracellular cyclic adenosine monophosphate, or cyclic AMP (cAMP), which then serves as an intracellular second messenger. The

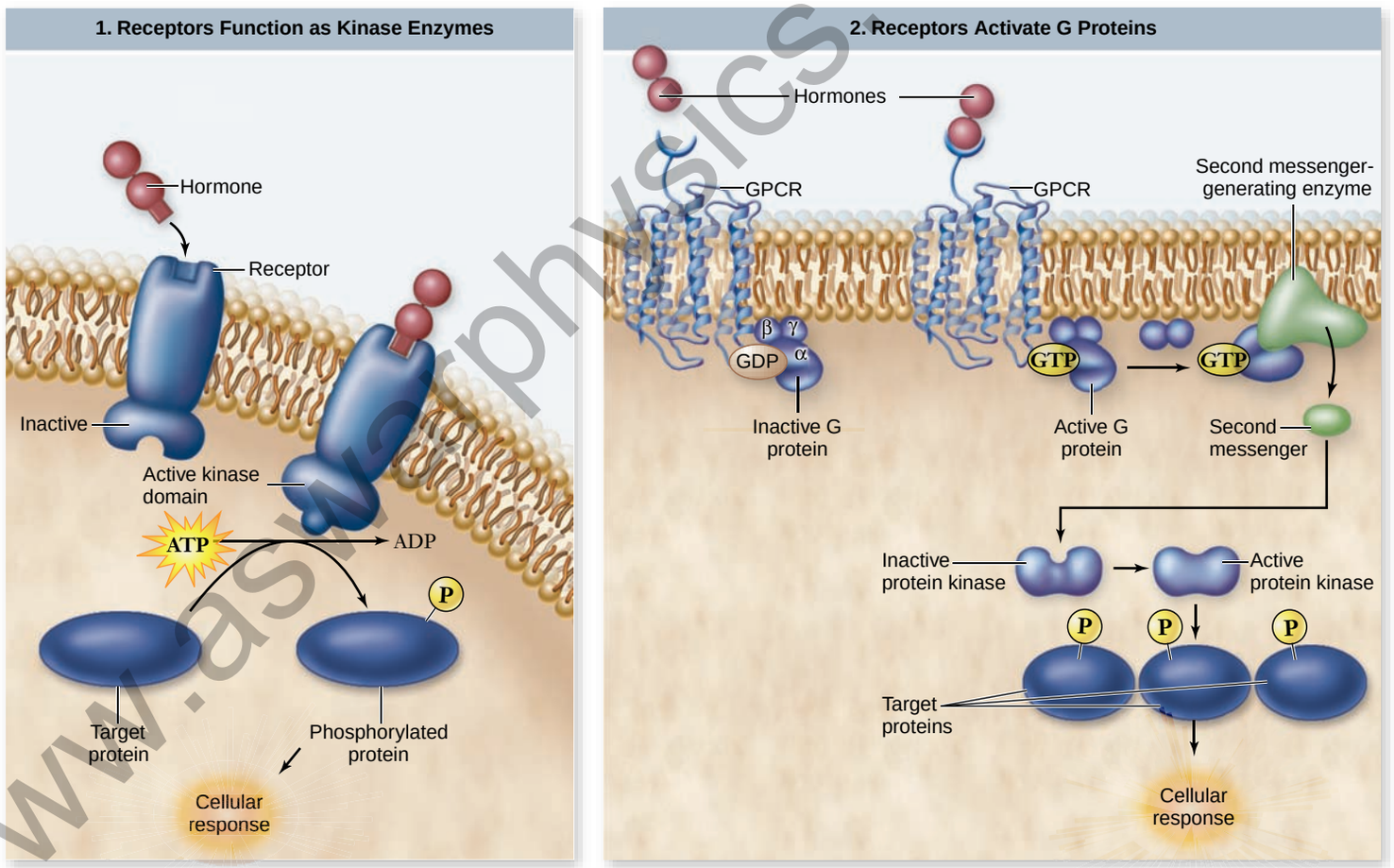


Figure 46.6 The action of hydrophilic hormones. Hydrophilic hormones cannot enter cells and must therefore work extracellularly via activation of transmembrane receptor proteins. (1) These receptors can function as kinase enzymes, activating phosphorylation of other proteins inside cells. (2) Alternatively, acting through intermediary G proteins, the hormone-bound receptor activates production of a second messenger. The second messenger activates protein kinases that phosphorylate and thereby activate other proteins. GPCR, G protein–coupled receptor.

cAMP second-messenger system was the first such system to be described. Since that time, another hormonally regulated second-messenger system has been described that generates two lipid messengers: **inositol triphosphate (IP_3)** and diacyl glycerol (DAG). These systems were described in chapter 9.

The action of G proteins

Receptors that activate second messengers do not manufacture the second messenger themselves. Rather, they are linked to a second-messenger-generating enzyme via membrane proteins called *G proteins* [that is, they are G protein–coupled receptors (GPCR); see chapter 9]. The binding of the hormone to its receptor causes the G protein to shuttle within the plasma membrane from the receptor to the second-messenger-generating enzyme (see figure 46.6). When the G protein activates the enzyme, the result is an increase in second-messenger molecules inside the cell.

In the case of epinephrine, the G protein activates an enzyme called *adenylyl cyclase*, which catalyzes the formation of the second messenger cAMP from ATP. The second messenger formed at the inner surface of the plasma membrane then diffuses within the cytoplasm, where it binds to and activates protein kinases.

The identities of the proteins that are subsequently phosphorylated by the protein kinases vary from one cell type to the next and include enzymes, membrane transport proteins, and transcription factors. This diversity provides hormones with distinct actions in different tissues. In liver cells, for example, cAMP-dependent protein kinases activate enzymes that convert glycogen into glucose. In contrast, cardiac muscle cells express a different set of cellular proteins such that a cAMP increase activates an increase in the rate and force of cardiac muscle contraction.

Activation versus inhibition

The cellular response to a hormone depends on the type of G protein activated by the hormone's receptor. Some receptors are linked to G proteins that activate second-messenger-producing enzymes, whereas other receptors are linked to G proteins that inhibit their second-messenger-generating enzyme. As a result, some hormones stimulate protein kinases in their target cells, and others inhibit their targets. Furthermore, a single hormone can have distinct actions in two different cell types if the receptors in those cells are linked to different G proteins.

Epinephrine receptors in the liver, for example, produce cAMP through the enzyme adenylyl cyclase, mentioned earlier. The cAMP they generate activates protein kinases that promote the production of glucose from glycogen. In smooth muscle, by contrast, epinephrine receptors can be linked through a different stimulatory G protein to the IP_3-generating enzyme phospholipase C. As a result, epinephrine stimulation of smooth muscle results in IP_3-regulated release of intracellular calcium, causing muscle contraction.

Duration of hydrophilic hormone effects

The binding of a hydrophilic hormone to its receptor is reversible and usually very brief; hormones soon dissociate from receptors or are rapidly deactivated by their target cells after binding. Additionally, target cells contain specific enzymes that rapidly deactivate second messengers and protein kinases. As a result, hydrophilic hormones are capable of stimulating immediate responses within cells, but often have a brief duration of action (minutes to hours).

Learning Outcomes Review 46.2

Steroids, which are lipophilic, pass through a target cell's membrane and bind to intracellular receptor proteins. The hormone-receptor complex then binds to the hormone response element of the promotor region of the target gene. Hydrophilic hormones such as peptides bind externally to membrane receptors that activate protein kinases directly or that operate through second-messenger systems such as cAMP or IP_3/DAG.

- ***How can a single hormone, such as epinephrine, have different effects in different tissues?***

46.3 The Pituitary and Hypothalamus: The Body's Control Centers

Learning Outcomes

1. ***Explain why the pituitary is considered a compound gland.***
2. ***Describe the connections between the hypothalamus, posterior pituitary, and anterior pituitary.***
3. ***Describe the roles of releasing and inhibiting hormones.***

The **pituitary gland,** also known as the **hypophysis,** hangs by a stalk from the hypothalamus at the base of the brain posterior to the optic chiasm. The hypothalamus is a part of the central nervous system (CNS) that has a major role in regulating body processes. Both these structures were described in chapter 44; here we discuss in detail how they work together to bring about homeostasis and changes in body processes.

The pituitary is a compound endocrine gland

A microscopic view reveals that the gland consists of two parts, one of which appears glandular and is called the **anterior pituitary,** or **adenohypophysis.** The other portion appears fibrous and is called the **posterior pituitary,** or **neurohypophysis.** These two portions of the pituitary gland have different embryonic origins, secrete different hormones, and are regulated by different control systems. These two regions are conserved in all vertebrate animals, suggesting an ancient and important function of each.

The posterior pituitary stores and releases two neurohormones

The posterior pituitary appears fibrous because it contains axons that originate in cell bodies within the hypothalamus and that extend along the stalk of the pituitary as a tract of fibers. This anatomical relationship results from the way the posterior pituitary is formed in embryonic development. As the floor of the third ventricle of the brain forms the hypothalamus, part of this neural tissue grows downward

to produce the posterior pituitary. The hypothalamus and posterior pituitary thus remain directly interconnected by a tract of axons.

Antidiuretic hormone

The endocrine role of the posterior pituitary first became evident in 1912, when a remarkable medical case was reported: A man who had been shot in the head developed the need to urinate every 30 minutes or so, 24 hours a day. The bullet had lodged in his posterior pituitary. Subsequent research demonstrated that removal of this portion of the pituitary produces the same symptoms.

In the early 1950s investigators isolated a peptide from the posterior pituitary, **antidiuretic hormone (ADH).** ADH stimulates water reabsorption by the kidneys (figure 46.7), and in doing so inhibits diuresis (urine production). When ADH is missing, as it was in the shooting victim, the kidneys do not reabsorb as much water, and excessive quantities of urine are produced. This is why the consumption of alcohol, which inhibits ADH secretion, leads to frequent urination. The role of ADH in kidney function is covered in chapter 51.

Oxytocin

The posterior pituitary also secretes **oxytocin,** a second peptide neurohormone that, like ADH, is composed of nine amino acids. In mammals, oxytocin stimulates the milk ejection reflex. During suckling, sensory receptors in the nipples send impulses to the hypothalamus, which triggers the release of oxytocin.

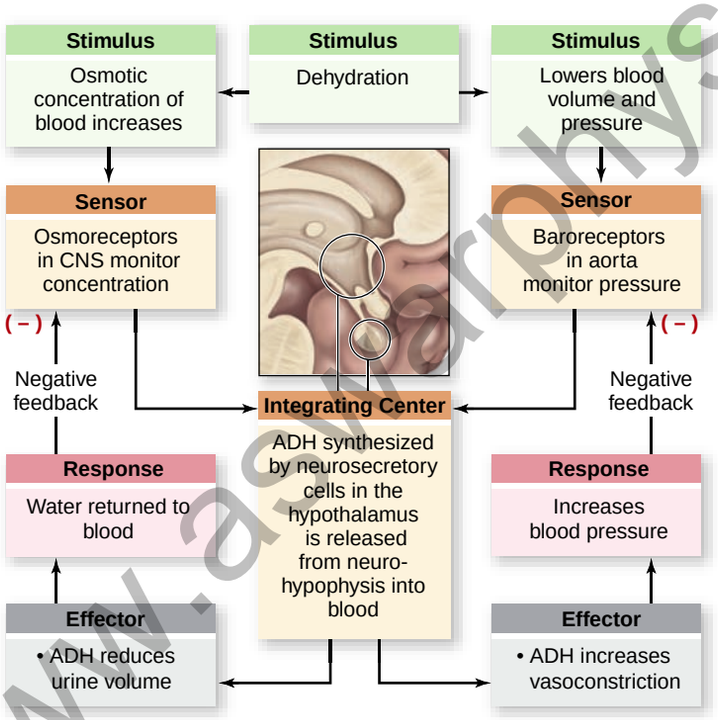


Figure 46.7 The effects of antidiuretic hormone (ADH). Dehydration increases the osmotic concentration of the blood and lowers blood pressure, stimulating the neurohypophysis to secrete ADH. ADH increases reabsorption of water by the kidneys and causes vasoconstriction, increasing blood pressure. Decreased blood osmolarity and increased blood pressure complete negative feedback loops to maintain homeostasis.

Oxytocin is also needed to stimulate uterine contractions in women during childbirth.

Oxytocin secretion continues after childbirth in a woman who is breast-feeding; as a result, the uterus of a nursing mother contracts and returns to its normal size after pregnancy more quickly than the uterus of a mother who does not breast-feed.

A related posterior pituitary neurohormone, *arginine vasotocin*, exerts similar effects in nonmammalian species. For example, in chickens and sea turtles, arginine vasotocin activates oviduct contraction during egg laying.

More recently, oxytocin has been identified as an important regulator of reproductive behavior. In both men and women, it is thought to be involved in promoting pair bonding (leading to its being called the "cuddle hormone") as well as regulating sexual responses, including arousal and orgasm. For these effects, it most likely functions in a paracrine fashion inside the CNS, much like a neurotransmitter.

Hypothalamic production of the neurohormones

ADH and oxytocin are actually produced by neuron cell bodies located in the hypothalamus. These two neurohormones are transported along the axon tract that runs from the hypothalamus to the posterior pituitary, where they are stored. In response to the appropriate stimulation—increased blood plasma osmolality in the case of ADH, the suckling of a baby in the case of oxytocin—the neurohormones are released by the posterior pituitary into the blood.

Because this reflex control involves both the nervous and the endocrine systems, ADH and oxytocin are said to be secreted by a **neuroendocrine reflex.**

The anterior pituitary produces seven hormones

The anterior pituitary, unlike the posterior pituitary, does not develop from growth of the brain; instead, it develops from a pouch of epithelial tissue that pinches off from the roof of the embryo's mouth. In spite of its proximity to the brain, it is not part of the nervous system.

Because it forms from epithelial tissue, the anterior pituitary is an independent endocrine gland. It produces at least seven essential hormones, many of which stimulate growth of their target organs, as well as production and secretion of other hormones from additional endocrine glands. Therefore, several hormones of the anterior pituitary are collectively termed *tropic hormones*, or *tropins*. Tropic hormones act on other endocrine glands to stimulate secretion of hormones produced by the target gland.

The hormones produced and secreted by different cell types in the anterior pituitary can be categorized into three structurally similar families: the *peptide hormones*, the *protein hormones*, and the *glycoprotein hormones*.

Peptide hormones

The **peptide hormones** of the anterior pituitary are cleaved from a single precursor protein, and therefore they share some common sequence. They are fewer than 40 amino acids in size.

1. **Adrenocorticotropic hormone** (**ACTH,** or *corticotropin*) stimulates the adrenal cortex to produce corticosteroid hormones, including cortisol (in humans)

and corticosterone (in many other vertebrates). These hormones regulate glucose homeostasis and are important in the response to stress.

2. **Melanocyte-stimulating hormone (MSH)** stimulates the synthesis and dispersion of melanin pigment, which darkens the epidermis of some fish, amphibians, and reptiles, and can control hair pigment color in mammals.

Protein hormones

The **protein hormones** each comprise a single chain of approximately 200 amino acids, and they share significant structural similarities.

1. **Growth hormone** (**GH,** or *somatotropin*) stimulates the growth of muscle, bone (indirectly), and other tissues, and it is also essential for proper metabolic regulation.
2. **Prolactin (PRL)** is best known for stimulating the mammary glands to produce milk in mammals; however, it has diverse effects on many other targets, including regulation of ion and water transport across epithelia, stimulation of a variety of organs that nourish young, and activation of parental behaviors.

Glycoprotein hormones

The largest and most complex hormones known, the *glycoprotein hormones* are dimers, containing alpha (α) and beta (β) subunits, each around 100 amino acids in size, with covalently linked sugar residues. The α subunit is common to all three hormones. The β subunit differs, endowing each hormone with a different target specificity.

1. **Thyroid-stimulating hormone** (**TSH,** or *thyrotropin*) stimulates the thyroid gland to produce the hormone thyroxine, which in turn regulates development and metabolism by acting on nuclear receptors.
2. **Luteinizing hormone (LH)** stimulates the production of estrogen and progesterone by the ovaries and is needed for ovulation in female reproductive cycles (see chapter 53). In males, it stimulates the testes to produce testosterone, which is needed for sperm production and for the development of male secondary sexual characteristics.
3. **Follicle-stimulating hormone (FSH)** is required for the development of ovarian follicles in females. In males, it is required for the development of sperm. FSH stimulates the conversion of testosterone into estrogen in females, and into dihydroxytestosterone in males. FSH and LH are collectively referred to as *gonadotropins*.

Hypothalamic neurohormones regulate the anterior pituitary

The anterior pituitary, unlike the posterior pituitary, is not derived from the brain and does not receive an axon tract from the hypothalamus. Nevertheless, the hypothalamus controls the production and secretion of its hormones. This control is itself exerted hormonally rather than by means of nerve axons.

Neurons in the hypothalamus secrete two types of neurohormones, **releasing hormones** and **inhibiting hormones,**

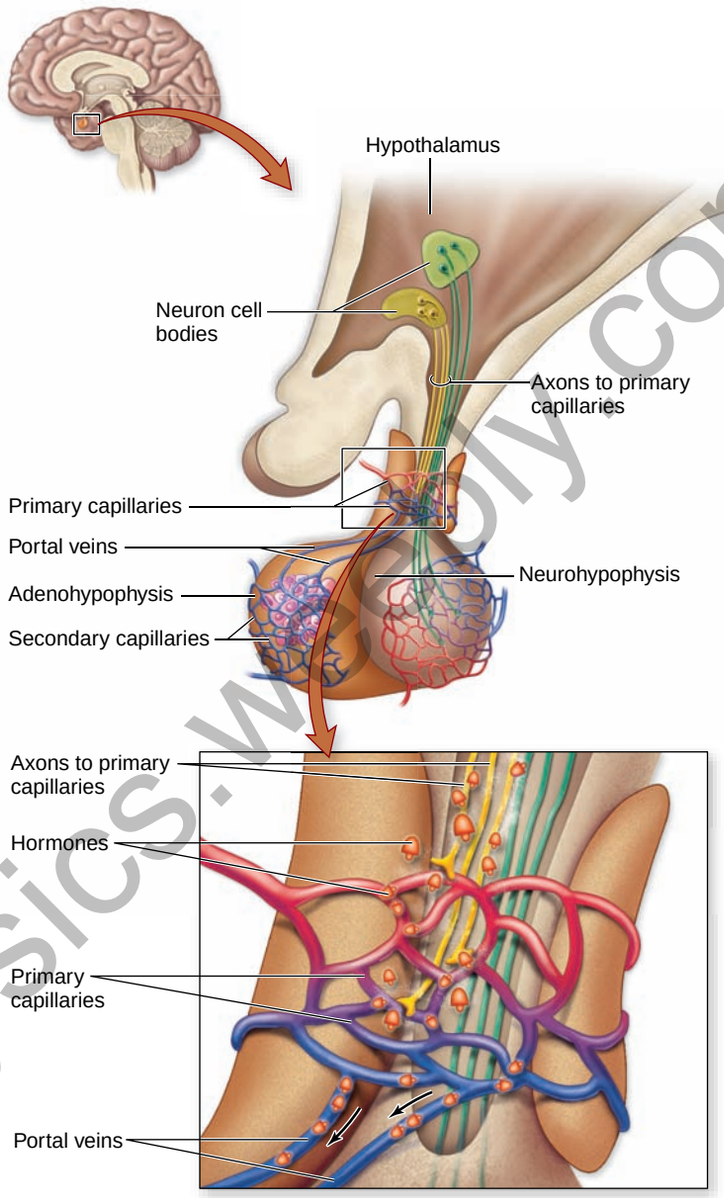


Figure 46.8 Hormonal control of the adenohypophysis by the hypothalamus. Neurons in the hypothalamus secrete hormones that are carried by portal blood vessels directly to the adenohypophysis, where they either stimulate or inhibit the secretion of hormones from the adenohypophysis.

that diffuse into blood capillaries at the base of the hypothalamus (figure 46.8). These capillaries drain into small veins that run within the stalk of the pituitary to a second bed of capillaries in the anterior pituitary. This unusual system of vessels is known as the *hypothalamohypophyseal portal system*. In a portal system, two capillary beds are linked by veins. In this case, the hormone enters the first capillary bed, and the vein delivers this to the second capillary bed where the hormone exits and enters the anterior pituitary.

Releasers

Each neurohormone released by the hypothalamus into the portal system regulates the secretion of a specific hormone in

the anterior pituitary. Releasing hormones are peptide neurohormones that stimulate release of other hormones; specifically, *thyrotropin-releasing hormone* (TRH) stimulates the release of TSH; *corticotropin-releasing hormone* (CRH) stimulates the release of ACTH; and *gonadotropin-releasing hormone* (GnRH) stimulates the release of FSH and LH. A releasing hormone for growth hormone, called *growth hormone-releasing hormone* (GHRH), has also been discovered, and TRH, oxytocin and vasoactive intestinal peptide all appear to act as releasing hormones for prolactin.

Inhibitors

The hypothalamus also secretes neurohormones that inhibit the release of certain anterior-pituitary hormones. To date, three such neurohormones have been discovered: *Somatostatin*, or *growth hormone-inhibiting hormone* (GHIH), which inhibits the secretion of GH; *prolactin-inhibiting factor* (PIF), which inhibits the secretion of prolactin and has been found to be the neurotransmitter dopamine; and *MSH-inhibiting hormone* (MIH), which inhibits the secretion of MSH.

Feedback from peripheral endocrine glands regulates anterior-pituitary hormones

Because hypothalamic hormones control the secretions of the anterior pituitary, and because the hormones of the anterior pituitary in turn control the secretions of other endocrine glands, it may seem that the hypothalamus is in charge of hormonal secretion for the whole body. This however, ignores a crucial aspect of endocrine control: The hypothalamus and the anterior pituitary are themselves partially controlled by the very hormones whose secretion they stimulate. In most cases, this control is inhibitory (figure 46.9). This type of control system is called *negative feedback*, and it acts to maintain relatively constant levels of the target cell hormone.

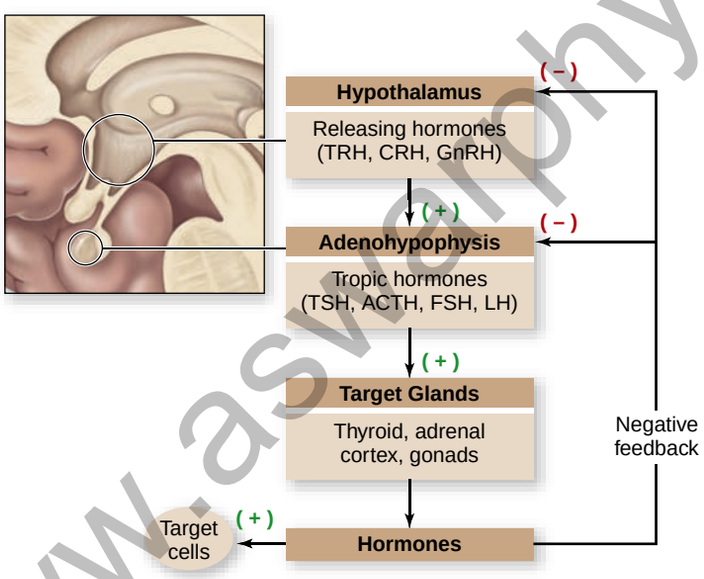


Figure 46.9 Negative feedback inhibition. The hormones secreted by some endocrine glands feed back to inhibit the secretion of hypothalamic releasing hormones and adenohypophysis tropic hormones. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; TRH, thyroid-releasing hormone; TSH, thyroid-stimulating hormone

An example of negative feedback: Thyroid gland control

To illustrate how important the negative feedback mechanism is, let's consider the hormonal control of the thyroid gland. The hypothalamus secretes TRH into the hypothalamohypophyseal portal system, which stimulates the anterior pituitary to secrete TSH. TSH in turn causes the thyroid gland to release **thyroxine.** Thyroxine and other thyroid hormones affect metabolic rate, as described in the following section.

Among thyroxine's many target organs are the hypothalamus and the anterior pituitary themselves. Thyroxine acts on these organs to inhibit their secretion of TRH and TSH, respectively. This negative feedback inhibition is essential for homeostasis because it keeps the thyroxine levels fairly constant.

The hormone thyroxine contains the element iodine; without iodine, the thyroid gland cannot produce thyroxine. Individuals living in iodine-poor areas (such as central prairies distant from seacoasts and the fish that are the natural source of iodine) lack sufficient iodine to manufacture thyroxine, so the hypothalamus and anterior pituitary receive far less negative feedback inhibition than is normal. This reduced inhibition results in elevated secretion of TRH and TSH.

High levels of TSH stimulate the thyroid gland, whose cells enlarge in a futile attempt to manufacture more thyroxine. Because they cannot without iodine, the thyroid gland keeps getting bigger and bigger—a condition known as a goiter (figure 46.10). Goiter size can be reduced by providing iodine in the diet. In most countries, goiter is prevented through the addition of iodine to table salt.

Figure 46.10 A woman with a goiter. This condition is caused by a lack of iodine in the diet. As a result, thyroxine secretion is low, so there is less negative feedback inhibition of TSH. The elevated TSH secretion, in turn, stimulates the thyroid to enlarge in an effort to produce additional thyroxine.

An example of positive feedback: Ovulation

Positive feedback in the control of the hypothalamus and anterior pituitary by the target glands is uncommon because positive feedback causes deviations from homeostasis. Positive feedback accentuates change, driving the change in the same direction. One example is the control of **ovulation,** the explosive release of a mature egg (an oocyte) from the ovary.

As the oocyte grows, follicle cells surrounding it produce increasing levels of the steroid hormone estrogen, resulting in a progressive rise in estrogen in the blood. Peak estrogen levels signal the hypothalamus that the oocyte is ready to be ovulated. Estrogen then exerts positive feedback on the hypothalamus and pituitary, resulting in a surge of LH from the anterior pituitary. This LH surge causes the follicle cells to rupture and release the oocyte to the oviduct, where it can potentially be fertilized. The positive feedback cycle is then terminated because the tissue remaining of the ovarian follicle forms the corpus luteum, which secretes progesterone and estrogen that feed back to inhibit secretion of FSH and LH. This process is discussed in more detail in chapter 53.

Hormones of the anterior pituitary work directly and indirectly

Early in the 20th century, experimental techniques were developed for surgical removal of the pituitary gland (a procedure called *hypophysectomy*). Hypophysectomized animals exhibited a number of deficits, including reduced growth and development, diminished metabolism, and failure of reproduction. These powerful and diverse effects earned the pituitary a reputation as the "master gland." Indeed, many of these are *direct effects*, resulting from anterior-pituitary hormones activating receptors in nonendocrine targets, such as liver, muscle, and bone. The tropic hormones produced by the anterior pituitary have *indirect effects*, however, through their ability to activate other endocrine glands, such as the thyroid, adrenal glands, and gonads. Of the seven anterior-pituitary hormones, growth hormone, prolactin, and MSH work primarily through direct effects, whereas the tropic hormones ACTH, TSH, LH, and FSH have endocrine glands as their exclusive targets.

Effects of growth hormone

The importance of the anterior pituitary is illustrated by a condition known as *gigantism*, characterized by excessive growth of the entire body or any of its parts. The tallest human being ever recorded, Robert Wadlow, had gigantism (figure 46.11). Born in 1928, he stood 8 feet 11 inches tall, weighed 485 pounds, and was still growing before he died from an infection at the age of 22.

We now know that gigantism is caused by the excessive secretion of GH in a growing child. By contrast, a deficiency in GH secretion during childhood results in **pituitary dwarfism**—a failure to achieve normal stature.

GH stimulates protein synthesis and growth of muscles and connective tissues; it also indirectly promotes the elongation of bones by stimulating cell division in the cartilaginous epiphyseal growth plates of bones (see chapter 47). Researchers found that this stimulation does not occur in the absence of blood plasma, suggesting that GH must work in concert with another hormone

Figure 46.11 The Alton giant. This photograph of Robert Wadlow of Alton, Illinois, taken on his 21st birthday, shows him at home with his father and mother and four siblings. Born normal size, he developed a growth-hormone-secreting pituitary tumor as a young child and never stopped growing during his 22 years of life, reaching a height of 8 ft 11 in.

to exert its effects on bone. We now know that GH stimulates the production of **insulin-like growth factors,** which liver and bone produce in response to stimulation by GH. The insulin-like growth factors then stimulate cell division in the epiphyseal growth plates, and thus the elongation of the bones.

Although GH exhibits its most dramatic effects on juvenile growth, it also functions in adults to regulate protein, lipid, and carbohydrate metabolism. Recently a peptide hormone named **ghrelin,** produced by the stomach between meals, was identified as a potent stimulator of GH release, establishing an important linkage between nutrient intake and GH production.

Because human skeletal growth plates transform from cartilage into bone at puberty, GH can no longer cause an increase in height in adults. Excessive GH secretion in an adult results in a form of gigantism called **acromegaly,** characterized by bone and soft tissue deformities such as a protruding jaw, elongated fingers, and thickening of skin and facial features. Our knowledge of the regulation of GH has led to the development of drugs that can control its secretion, for example through activation of somatostatin, or by mimicking ghrelin. As a result, gigantism is much less common today.

Animals that have been genetically engineered to express additional copies of the GH gene grow to larger than normal

size (see figure 17.16), making agricultural applications of GH manipulation an active area of investigation. Among other actions, GH has been found to increase milk yield in cows, promote weight gain in pigs, and increase the length of fish. The growth-promoting actions of GH thus appear to have been conserved throughout the vertebrates.

Other hormones of the anterior pituitary

Like growth hormone, prolactin acts on organs that are not endocrine glands. In contrast to GH, however, the actions of prolactin appear to be very diverse. In addition to stimulating production of milk in mammals, prolactin has been implicated in the regulation of tissues important in birds for the nourishment and incubation of young, such as the crop (which produces "crop milk," a nutritional fluid fed to chicks by regurgitation) and the brood patch (a vascular area on the abdomen of birds used to warm eggs).

In amphibians, prolactin promotes transformation of salamanders from terrestrial forms to aquatic breeding adults. Associated with these reproductive actions is an ability of prolactin to activate associated behaviors, such as parental care in mammals, broodiness in birds, and "water drive" in amphibians.

Prolactin also has varied effects on electrolyte balance through actions on the kidneys of mammals, the gills of fish, and the salt glands of marine birds. This variation suggests that although prolactin may have an ancient function in the regulation of salt and water movement across membranes, its actions have diversified with the appearance of new vertebrate species. The field of comparative endocrinology studies questions about hormone action across diverse species, with the objective of understanding the mechanisms of hormone evolution.

Unlike growth hormone and prolactin, the other adenohypophyseal hormones act on relatively few targets. TSH stimulates the thyroid gland, and ACTH stimulates the adrenal cortex. The gonadotropins, FSH and LH, act on the gonads. Although both FSH and LH act on the gonads, they each target different cells in the gonads of both females and males (see chapter 53). These hormones all share the common characteristic of activating target endocrine glands.

The final pituitary hormone, MSH regulates the activity of cells called melanophores, which contain the black pigment **melanin.** In response to MSH, melanin is dispersed throughout these cells, darkening the skin of reptiles, amphibians, or fish. In mammals, which lack melanophores but have similar cells called melanocytes, MSH can darken hair by increasing melanin deposition in the developing hair shaft.

Learning Outcomes Review 46.3

The posterior pituitary develops from neural tissue; the anterior pituitary develops from epithelial tissue. Axons from the hypothalamus extend into the posterior pituitary and produce neurohormones; these neurons also secrete factors that release or inhibit hormones of the anterior pituitary. Releasers stimulate secretion of hormones; TRH causes TSH release. Inhibitors suppress secretion; GHIH inhibits GH release.

- ***Could someone with a pituitary tumor causing gigantism be treated with GHIH? What outcome would you predict?***

46.4 The Major Peripheral Endocrine Glands

Learning Outcomes

1. ***Identify the major peripheral endocrine glands.***
2. ***Describe the components of Ca^{2+} homeostasis.***
3. ***Explain the action of pancreatic hormones on blood glucose.***

Although the pituitary produces an impressive array of hormones, many endocrine glands are found in other locations. Some of these may be controlled by tropic hormones of the pituitary, but others, such as the adrenal medulla and the pancreas, are independent of pituitary control. Several endocrine glands develop from derivatives of the primitive pharynx, which is the most anterior segment of the digestive tract (see chapter 48). These glands, which include the *thyroid* and *parathyroid* glands, produce hormones that regulate processes associated with nutrient uptake, such as carbohydrate, lipid, protein, and mineral metabolism.

The thyroid gland regulates basal metabolism and development

The thyroid gland varies in shape in different vertebrate species, but is always found in the neck area, anterior to the heart. In humans it is shaped like a bow tie and lies just below the Adam's apple in the front of the neck.

The thyroid gland secretes three hormones: primarily thyroxine, smaller amounts of triiodothyronine (collectively referred to as thyroid hormones), and calcitonin. As described earlier, thyroid hormones are unique in being the only molecules in the body containing iodine (thyroxine contains four iodine atoms, triiodothyronine contains three).

Thyroid-related disorders

Thyroid hormones work by binding to nuclear receptors located in most cells in the body, influencing the production and activity of a large number of cellular proteins. The importance of thyroid hormones first became apparent from studies of human thyroid disorders. Adults with hypothyroidism have low metabolism due to underproduction of thyroxine, including a reduced ability to utilize carbohydrates and fats. As a result, they are often fatigued, overweight, and feel cold. Hypothyroidism is particularly concerning in infants and children, where it impairs growth, brain development, and reproductive maturity. Fortunately, because thyroid hormones are small, simple molecules, people with hypothyroidism can take thyroxine orally as a pill.

People with hyperthyroidism, by contrast, often exhibit opposite symptoms: weight loss, nervousness, high metabolism, and overheating because of overproduction of thyroxine. Drugs are available that block thyroid hormone synthesis in the thyroid gland, but in some cases portions of the thyroid gland must be removed surgically or by radiation treatment.

Actions of thyroid hormones

Thyroid hormones regulate enzymes controlling carbohydrate and lipid metabolism in most cells, promoting the appropriate use of these fuels for maintaining the body's basal metabolic rate. Thyroid hormones often function cooperatively, or *synergistically*, with other hormones, promoting the activity of growth hormone, epinephrine, and reproductive steroids. Through these actions, thyroid hormones function to ensure that adequate cellular energy is available to support metabolically demanding activities.

In humans, which exhibit a relatively high metabolic rate at all times, thyroid hormones are maintained in the blood at constantly elevated levels. In contrast, in reptiles, amphibians, and fish, which undergo seasonal cycles of activity, thyroid hormone levels in the blood increase during periods of metabolic activation (such as growth, reproductive development, migration, or breeding) and diminish during periods of inactivity in cold months.

Some of the most dramatic effects of thyroid hormones are observed in their regulation of growth and development. In developing humans, for example, thyroid hormones promote growth of neurons and stimulate maturation of the CNS. Children born with hypothyroidism are stunted in their growth and suffer severe mental retardation, a condition called *cretinism*. Early detection through measurement of thyroid hormone levels allows this condition to be treated with thyroid hormone administration.

The most impressive demonstration of the importance of thyroid hormones in development is displayed in amphibians. Thyroid hormones direct the metamorphosis of tadpoles into frogs, a process that requires the transformation of an aquatic, herbivorous larva into a terrestrial, carnivorous juvenile (figure 46.12). If the thyroid gland is removed from a tadpole, it will not change into a frog. Conversely, if an immature tadpole is fed pieces of a thyroid gland, it will undergo premature metamorphosis and become a miniature frog. This illustrates the powerful actions thyroid hormones can elicit by regulating the expression of multiple genes.

Calcium homeostasis is regulated by several hormones

Calcium is a vital component of the vertebrate body both because of its being a structural component of bones and because of its role in ion-mediated processes such as muscle contraction. The thyroid and parathyroid glands act with vitamin D to regulate calcium homeostasis.

Calcitonin secretion by the thyroid

In addition to the thyroid hormones, the thyroid gland also secretes **calcitonin,** a peptide hormone that plays a role in maintaining proper levels of calcium (Ca^{2+}) in the blood. When the blood Ca^{2+} concentration rises too high, calcitonin stimulates the uptake of calcium into bones, thus lowering its

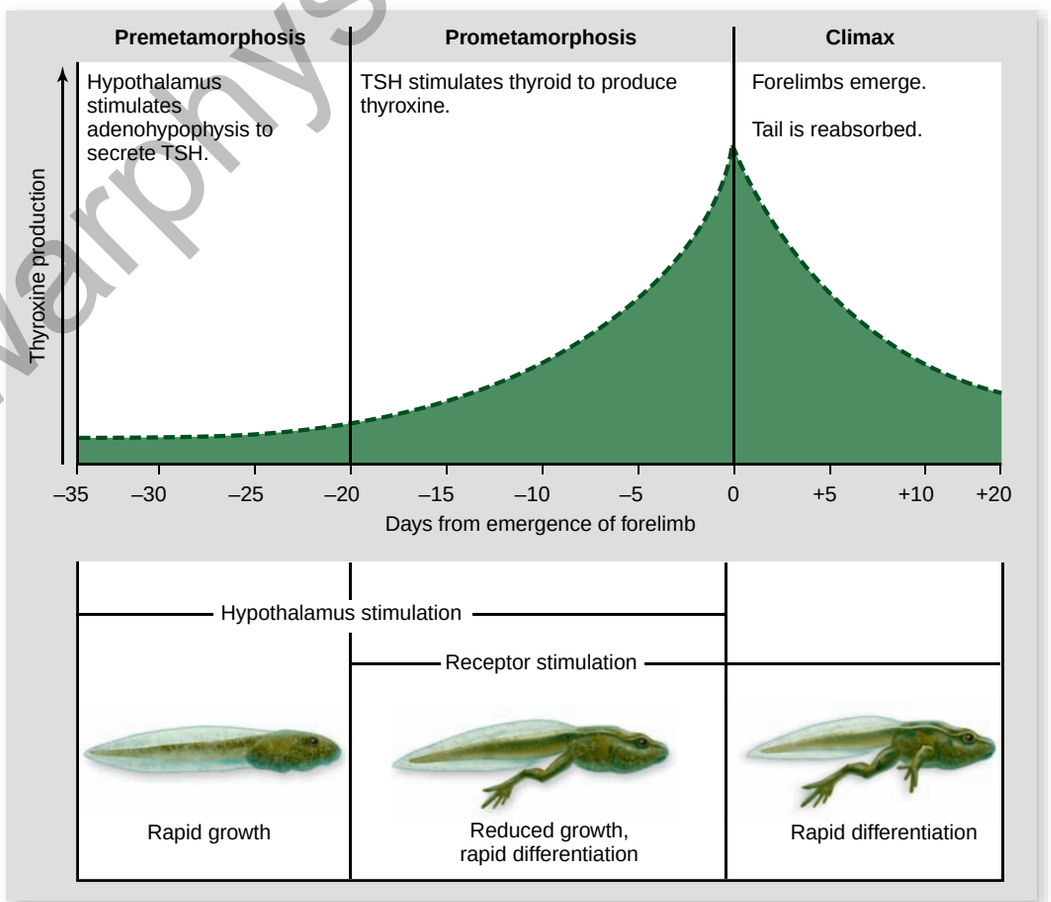


Figure 46.12 Thyroxine triggers metamorphosis in amphibians. In tadpoles at the premetamorphic stage, the hypothalamus stimulates the adenohypophysis to secrete TSH (thyroid-stimulating hormone). TSH then stimulates the thyroid gland to secrete thyroxine. Thyroxine binds to its receptor and initiates the changes in gene expression necessary for metamorphosis. As metamorphosis proceeds, thyroxine reaches its maximal level, after which the forelimbs begin to form and the tail is reabsorbed.

level in the blood. Although calcitonin may be important in the physiology of some vertebrates, it appears less important in the day-to-day regulation of Ca^{2+} levels in adult humans. It may, however, play an important role in bone remodeling in rapidly growing children.

Parathyroid hormone (PTH)

The parathyroid glands are four small glands attached to the thyroid. Because of their size, researchers ignored them until well into the 20th century. The first suggestion that these organs have an endocrine function came from experiments on dogs: If their parathyroid glands were removed, the Ca^{2+} concentration in the dogs' blood plummeted to less than half the normal value. The Ca^{2+} concentration returned to normal when an extract of parathyroid gland was administered. However, if too much of the extract was administered, the dogs' Ca^{2+} levels rose far above normal as the calcium phosphate crystals in their bones were dissolved. It was clear that the parathyroid glands produce a hormone that stimulates the release of calcium from bone.

The hormone produced by the parathyroid glands is a peptide called **parathyroid hormone (PTH).** PTH is synthesized and released in response to falling levels of Ca^{2+} in the blood. This decline cannot be allowed to continue uncorrected because a significant fall in the blood Ca^{2+} level can cause severe muscle spasms. A normal blood Ca^{2+} level is important for the functioning of muscles, including the heart, and for proper functioning of the nervous and endocrine systems.

PTH stimulates the osteoclasts (bone cells) in bone to dissolve the calcium phosphate crystals of the bone matrix and release Ca^{2+} into the blood (figure 46.13). PTH also stimulates the kidneys to reabsorb Ca^{2+} from the urine and leads to the activation of vitamin D, needed for the absorption of calcium from food in the intestine.

Vitamin D

Vitamin D is produced in the skin from a cholesterol derivative in response to ultraviolet light. It is called an essential vitamin because in temperate regions of the world a dietary source is needed to supplement the amount produced by the skin. (In the tropics, people generally receive enough exposure to sunlight to produce adequate vitamin D.) Diffusing into the blood from the skin, vitamin D is actually an inactive form of a hormone. In order to become activated, the molecule must gain two hydroxyl groups (—OH); one of these is added by an enzyme in the liver, the other by an enzyme in the kidneys.

The enzyme needed for this final step is stimulated by PTH, thereby producing the active form of vitamin D known as 1,25-dihydroxyvitamin D. This hormone stimulates the intestinal absorption of Ca^{2+} and thereby helps raise blood Ca^{2+} levels so that bone can become properly mineralized. A diet deficient in vitamin D thus leads to poor bone formation, a condition called rickets.

To ensure adequate amounts of this essential hormone, vitamin D is now added to commercially produced milk in the United States and some other countries. This is certainly a preferable alternative to the prior method of vitamin D administration, the dreaded dose of cod liver oil.

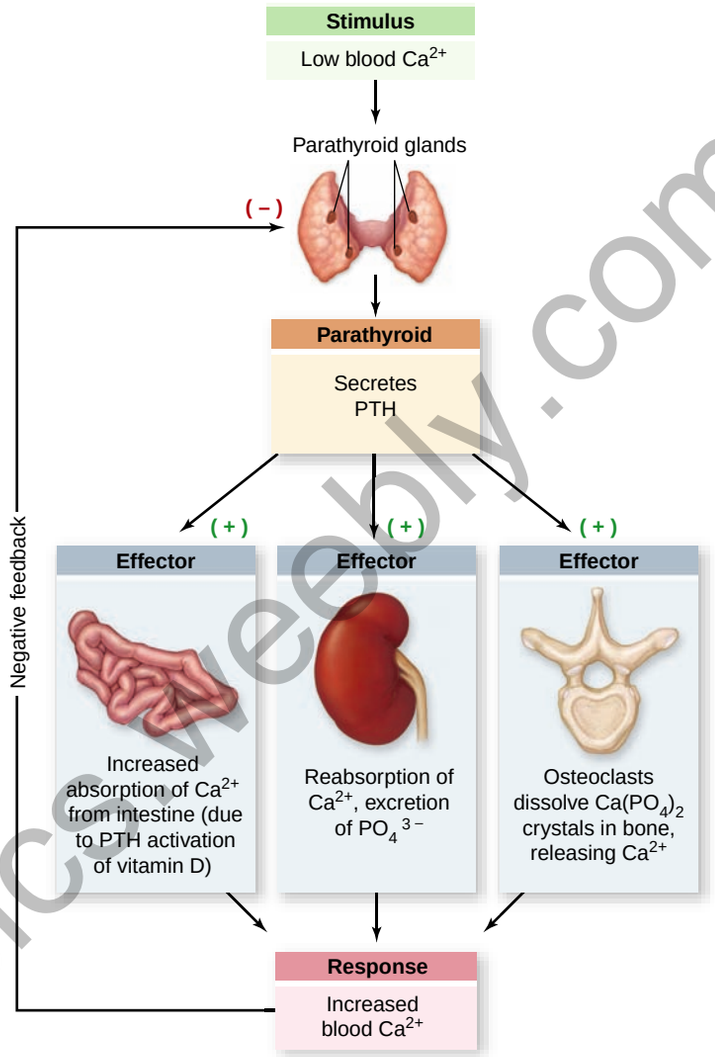


Figure 46.13 Regulation of blood Ca^{2+} levels by parathyroid hormone (PTH). When blood Ca^{2+} levels are low, PTH is released by the parathyroid glands. PTH directly stimulates the dissolution of bone and the reabsorption of Ca^{2+} by the kidneys. PTH indirectly promotes the intestinal absorption of Ca^{2+} by stimulating the production of the active form of vitamin D.

The adrenal gland releases both catecholamine and steroid hormones

The **adrenal glands** are located just above each kidney (figure 46.14). Each gland is composed of an inner portion, the *adrenal medulla*, and an outer layer, the *adrenal cortex*.

The adrenal medulla

The adrenal medulla receives neural input from axons of the sympathetic division of the autonomic nervous system, and it secretes the catecholamines epinephrine and norepinephrine in response to stimulation by these axons. The actions of these hormones trigger "alarm" responses similar to those elicited by the sympathetic division, helping to prepare the body for extreme efforts. Among the effects of these hormones are an increased heart rate, increased blood pressure, dilation of the bronchioles, elevation in blood glucose, reduced blood flow to the skin and digestive organs, and

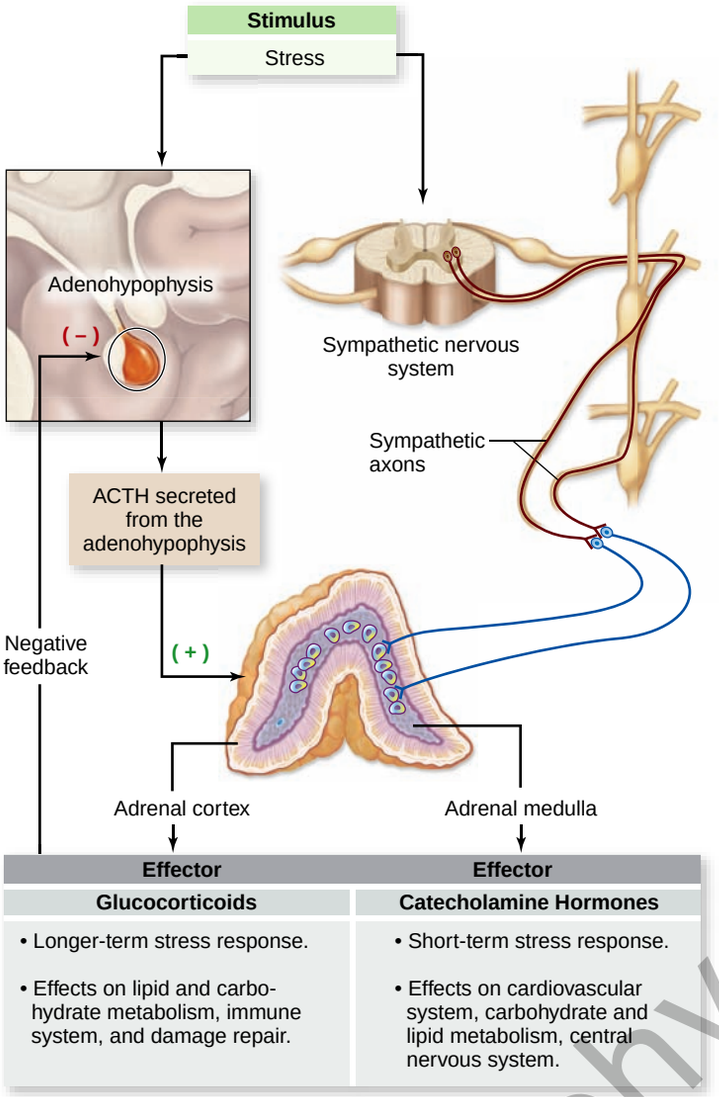


Figure 46.14 The adrenal glands. The adrenal medulla produces the catecholamines epinephrine and norepinephrine, which initiate a response to acute stress. The adrenal cortex produces steroid hormones, including the glucocorticoid cortisol. In response to stress, cortisol secretion increases glucose production and stimulates the immune response.

increased blood flow to the heart and muscles. The actions of epinephrine, released as a hormone, supplement those of neurotransmitters released by the sympathetic nervous system.

The adrenal cortex

The hormones from the adrenal cortex are all steroids and are referred to collectively as *corticosteroids*. *Cortisol* (also called hydrocortisone) and related steroids secreted by the adrenal cortex act on various cells in the body to maintain glucose homeostasis. In mammals, these hormones are referred to as glucocorticoids, and their secretion is primarily regulated by ACTH from the anterior pituitary.

The glucocorticoids stimulate the breakdown of muscle protein into amino acids, which are carried by the blood to the liver. They also stimulate the liver to produce the enzymes needed for gluconeogenesis, which can convert amino acids into glucose. Glucose synthesis from protein is particularly important during very long periods of fasting or exercise, when blood glucose levels might otherwise become dangerously low.

Whereas glucocorticoids are important in the daily regulation of glucose and protein, they, like the adrenal medulla hormones, are also secreted in large amounts in response to stress. It has been suggested that during stress they activate the production of glucose at the expense of protein and fat synthesis.

In addition to regulating glucose metabolism, the glucocorticoids modulate some aspects of the immune response. The physiological significance of this action is still unclear, and it may be apparent only when glucocorticoids are maintained at elevated levels for long periods of time (such as long-term stress). Glucocorticoids are used to suppress the immune system in persons with immune disorders (such as rheumatoid arthritis) and to prevent the immune system from rejecting organ and tissue transplants. Derivatives of cortisol, such as prednisone, have widespread medical use as anti-inflammatory agents.

Aldosterone, the other major corticosteroid, is classified as a mineralocorticoid because it helps regulate mineral balance. The secretion of aldosterone from the adrenal cortex is activated by angiotensin II, a product of the renin–angiotensin system described in chapter 51, as well as high blood K^+. Angiotensin II activates aldosterone secretion when blood pressure falls.

A primary action of aldosterone is to stimulate the kidneys to reabsorb Na^+ from the urine. (Blood levels of Na^+ decrease if Na^+ is not reabsorbed from the urine.) Sodium is the major extracellular solute; it is needed for the maintenance of normal blood volume and pressure, as well as for the generation of action potentials in neurons and muscles. Without aldosterone, the kidneys would lose excessive amounts of blood Na^+ in the urine.

Aldosterone-stimulated reabsorption of Na^+ also results in kidney excretion of K^+ in the urine. Aldosterone thus prevents K^+ from accumulating in the blood, which would lead to malfunctions in electrical signaling in nerves and muscles. Because of these essential functions performed by aldosterone, removal of the adrenal glands, or diseases that prevent aldosterone secretion, are invariably fatal without hormone therapy.

Pancreatic hormones are primary regulators of carbohydrate metabolism

The pancreas is located adjacent to the stomach and is connected to the duodenum of the small intestine by the pancreatic duct. It secretes bicarbonate ions and a variety of digestive enzymes into the small intestine through this duct (see chapter 48), and for a long time the pancreas was thought to be solely an exocrine gland.

Insulin

In 1869, however, a German medical student named Paul Langerhans described some unusual clusters of cells scattered throughout the pancreas; these clusters came to be called *islets of Langerhans*. They are now more commonly called pancreatic islets. Laboratory workers later observed that the surgical removal of the pancreas caused glucose to appear in the urine, the hallmark of the disease diabetes mellitus. This led to the discovery that the pancreas, specifically the islets of Langerhans, produced a hormone that prevents this disease.

That hormone is **insulin,** secreted by the beta (β) cells of the islets. Insulin was not isolated until 1922 when Banting and Best succeeded where many others had not. On January 11, 1922, they injected an extract purified from beef pancreas into a 13-year-old diabetic boy, whose weight had fallen to 65 pounds and who was not expected to survive. With that single injection, the glucose level in the boy's blood fell 25%. A more potent extract soon brought the level down to near normal. The doctors had achieved the first instance of successful insulin therapy.

Glucagon

The islets of Langerhans produce another hormone; the alpha (α) cells of the islets secrete **glucagon,** which acts antagonistically to insulin (figure 46.15). When a person eats carbohydrates, the blood glucose concentration rises. Blood glucose directly activates the secretion of insulin by the β cells and inhibits the secretion of glucagon by the α cells. Insulin promotes the cellular uptake of glucose into the liver, muscle, and fat cells. It also activates the storage of glucose as glycogen in liver and muscle or as fat in fat cells. Between meals, when the concentration of blood glucose falls, insulin secretion decreases, and glucagon secretion increases. Glucagon promotes the hydrolysis of stored glycogen in the liver and fat in adipose tissue. As a result, glucose and fatty acids are released into the blood and can be taken up by cells and used for energy.

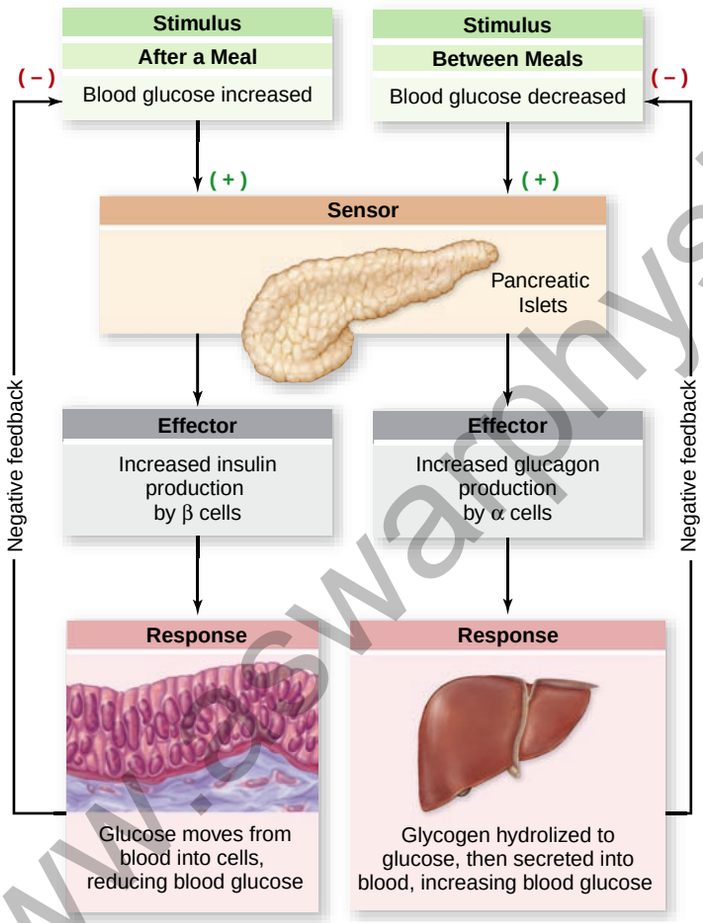


Figure 46.15 The antagonistic actions of insulin and glucagon on blood glucose. Insulin stimulates the cellular uptake of blood glucose into skeletal muscles, adipose cells, and the liver after a meal. Glucagon stimulates the hydrolysis of liver glycogen between meals, so that the liver can secrete glucose into the blood. These antagonistic effects help to maintain homeostasis of the blood glucose concentration.

Treatment of diabetes

Although many hormones favor the movement of glucose into cells, insulin is the only hormone that promotes movement of glucose from blood into cells. For this reason, disruptions in insulin signaling can have serious consequences. People with *type I*, or insulin-dependent, diabetes mellitus, lack the insulin-secreting β cells and consequently produce no insulin. Treatment for these patients consists of insulin injections. (Because insulin is a peptide hormone, it would be digested if taken orally and must instead be injected subcutaneously.)

In the past, only insulin extracted from the pancreas of pigs or cattle was available, but today people with insulin-dependent diabetes can inject themselves with human insulin produced by genetically engineered bacteria. Active research on the possibility of transplanting islets of Langerhans holds much promise of a lasting treatment for these patients.

Most diabetic patients, however, have *type II*, or noninsulin-dependent, diabetes mellitus. They generally have normal or even above-normal levels of insulin in their blood, but their cells have a reduced sensitivity to insulin. These people may not require insulin injections and can often control their diabetes through diet and exercise. It is estimated that over 90% of the cases of diabetes in North America are type II. Worldwide at least 171 million suffer from diabetes, and it is expected that this number will grow. Type II diabetes is especially common in developed countries, and it has been suggested that there is a linkage between type II diabetes and obesity.

Learning Outcomes Review 46.4

The major peripheral endocrine glands are the thyroid and parathyroid glands, the adrenal glands, and the pancreas. Calcium homeostasis results from the action of calcitonin, parathyroid hormone, and vitamin D. The adrenal glands produce stress hormones. Insulin and glucagon, antagonists from the pancreas, help maintain blood glucose at a normal level.

- ***Why does your body need two hormones to maintain blood sugar at a constant level?***

46.5 Other Hormones and Their Effects

Learning Outcomes

1. ***Characterize the role of sex steroids in development.***
2. ***List nonendrocrine sources of hormones.***
3. ***Identify the insect hormones involved in molting and metamorphosis.***

A variety of vertebrate and invertebrate processes are regulated by hormones and other chemical messengers, and in this section we review the most important ones.

Sex steroids regulate reproductive development

The ovaries and testes in vertebrates are important endocrine glands, producing the sex steroid hormones, including estrogens, progesterone, and testosterone (to be described in detail in chapter 53). Estrogen and progesterone are the primary "female" sex steroids, and testosterone and its immediate derivatives are the primary "male" sex steroids, or androgens. Both types of hormone can be found in both sexes, however.

During embryonic development, testosterone production in the male embryo is critical for the development of male sex organs. In mammals, sex steroids are responsible for the development of secondary sexual characteristics at puberty. These characteristics include breasts in females, body hair, and increased muscle mass in males. Because of this latter effect, some athletes have misused androgens to increase muscle mass. Use of steroids for this purpose has been condemned by virtually all major sports organizations, and it can cause liver disorders as well as a number of other serious side effects.

In females, sex steroids are especially important in maintaining the sexual cycle. Estrogen and progesterone produced in the ovaries are critical regulators of the menstrual and ovarian cycles. During pregnancy, estrogen production in the placenta maintains the uterine lining, which protects and nourishes the developing embryo.

Melatonin is crucial to circadian cycles

Another major endocrine gland is the pineal gland, located in the roof of the third ventricle of the brain in most vertebrates (see figure 44.22). It is about the size of a pea and is shaped like a pinecone, which gives it its name.

The pineal gland evolved from a medial light-sensitive eye (sometimes called a "third eye," although it could not form images) at the top of the skull in primitive vertebrates. This pineal eye is still present in primitive fish (cyclostomes) and some modern reptiles. In other vertebrates, however, the pineal gland is buried deep in the brain, and it functions as an endocrine gland by secreting the hormone melatonin.

Melatonin was named for its ability to cause blanching of the skin of lower vertebrates by reducing the dispersal of melanin granules. We now know, however, that it serves as an important timing signal delivered through the blood. Melatonin levels in the blood increase in darkness and fall during the daytime.

The secretion of melatonin is regulated by activity of the *suprachiasmatic nucleus* (*SCN*) of the hypothalamus. The SCN is known to function as the major biological clock in vertebrates, entraining (synchronizing) various body processes to a circadian rhythm—one that repeats every 24 hr. Through regulation by the SCN, the secretion of melatonin by the pineal gland is activated in the dark.

This daily cycling of melatonin release regulates sleep/wake and temperature cycles. Disruptions of these cycles, as occurs with jet lag or night shift work, can sometimes be minimized by melatonin administration. Melatonin also helps regulate reproductive cycles in some vertebrate species that have distinct breeding seasons.

Some hormones are not produced by endocrine glands

A variety of hormones are secreted by organs that are not exclusively endocrine glands. The thymus is the site of T cell production in many vertebrates and T cell maturation in mammals. It also secretes a number of hormones that function in the regulation of the immune system.

The right atrium of the heart secretes *atrial natriuretic hormone*, which stimulates the kidneys to excrete salt and water in the urine. This hormone acts antagonistically to aldosterone, which promotes salt and water retention.

The kidneys secrete *erythropoietin*, a hormone that stimulates the bone marrow to produce red blood cells. Other organs, such as the liver, stomach, and small intestine, also secrete hormones, and as mentioned earlier, the skin secretes vitamin D.

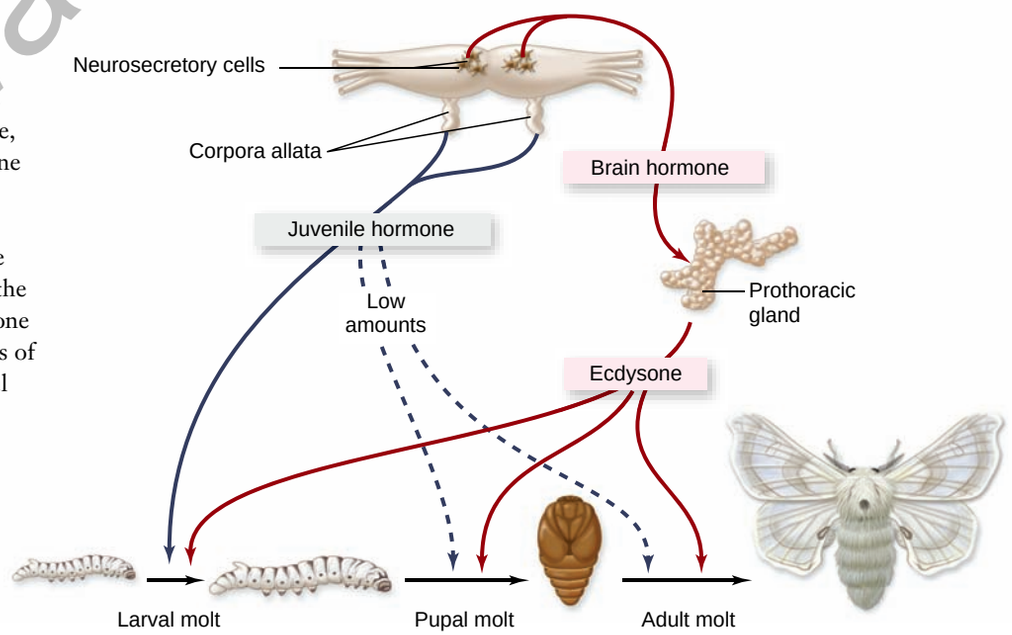


Figure 46.16 Hormonal control of metamorphosis in the silkworm moth, *Bombyx mori*. Molting hormone, ecdysone, controls when molting occurs. Brain hormone stimulates the prothoracic gland to produce ecdysone. Juvenile hormone determines the result of a particular molt. Juvenile hormone is produced by bodies near the brain called the corpora allata. High levels of juvenile hormone inhibit the formation of the pupa. Low levels of juvenile hormone are necessary for the pupal molt and metamorphosis.