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2 Neurons and Glia

Chapter Contents

Learning Objectives

2.1.1 Explain where neurons fit in with the other types of cells in the body.

2.1.2 Explain the cell theory and the neuron doctrine.

2.1.3 Describe the methods used to study neurons.

2.1.4 Explain what scientists have learned from having accurate estimates of the numbers of neurons in the brains of humans and other animals.

2.2.1 Describe the prototypical neuron and explain the roles of its parts.

2.2.2 Describe the ways by which neurons can be differentiated.

2.3.1 Explain the forces of diffusion and electrostatic pressure and how they are involved in the movement of ions across the cell membrane.

2.3.2 Explain how action potentials are initiated.

2.3.3 Explain how action potentials are propagated down the axons of neurons.

2.4.1 Describe the initial discovery of glia and the role initially assigned to them.

2.4.2 Explain the functions of the different types of glia.

The Black Mamba: A Potentially Deadly Encounter

The intact functioning of the nervous system depends on proper functioning of neurons. Neurons are specialized cells that communicate by generating electrical currents called action potentials. The generation of these action potentials depends on the flow of electrically charged molecules, called ions, back and forth from the outside to the inside of neurons. The two ions most implicated in the generation of action potentials are sodium and potassium. Interference with the flow of these ions can have drastic consequences for the functioning of the nervous system.

Poisons that attack the nervous system are known as neurotoxins. The ingestion of neurotoxins can seriously disrupt functioning of the nervous system and can ultimately lead to death. Neurotoxins can be synthetic chemicals, but they are also part of the self-defense mechanisms of many plants and animals. Fortunately, we tend to stay away from those. However, deadly encounters with such organisms do occur. For example, in the spring of 2008, a young man named Nathan Layton was on a safari-training course in South Africa. Some of the professors of the college he was attending captured a black mamba snake to use in a demonstration. Layton stood nearby as the snake was being transferred from container to container. The snake suddenly sprang upward and bit one of Layton's fingers. About 20 minutes later, Layton complained of blurred vision, slipped into a coma, and died.

The venom in the black mamba is composed of dendrotoxins. Dendrotoxins are a class of neurotoxins. These toxins block the flow of potassium out of neurons, resulting in muscle paralysis, disruption of heart muscle contraction, and respiratory failure.

INTRODUCTION

In this chapter, you will learn about the cells of the nervous system: neurons and glia. The brain contains billions of neurons and just about the same number of glia. Each one of these neurons can communicate with thousands of others, resulting in an extensive network of connectivity. Through communicating with each other, neurons permit us to sense our environment and appreciate music, good food, and works of art. This extensive network of connectivity is also responsible for the wide range of emotions that we experience and for encoding the information that results in our memories. You will also learn about glia, the other billions of cells that are crucial for the day-to-day maintenance and functioning of the nervous system, brain development, and communication between neurons.

2.1 Putting Neurons Into Context

Module Contents

Learning Objectives

2.1.1 Explain where neurons fit in with the other types of cells in the body.

2.1.2 Explain the cell theory and the neuron doctrine.

2.1.3 Describe the methods used to study neurons.

2.1.4 Explain what scientists have learned from having accurate estimates of the numbers of neurons in the brains of humans and other animals.

2.1.1 THE PLACE OF NEURONS WITHIN THE BODY

>> LO 2.1.1 Explain where neurons fit in with the other types of cells in the body.

Key Terms

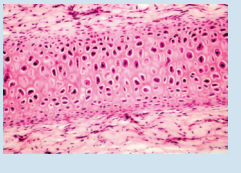
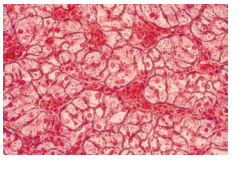
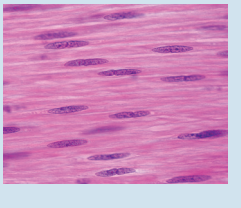
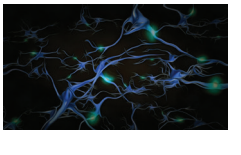
- **Nervous tissue:** Tissue that makes up the nervous system. It is composed of neurons and glia.
- **Central nervous system:** The division of the nervous system that includes the brain and the spinal cord.
- **Peripheral nervous system:** The nervous tissue that connects to the muscles and organs of the body.

The body is made up of four types of tissues: connective, epithelial, muscle, and nervous tissue. Connective tissue binds, separates, and connects other types of tissues. Connective tissue makes up the bones, blood, ligaments, and tendons of the body. Epithelial tissue forms the outer layer of the skin and lines the cavities of the body, such as the digestive and respiratory systems. Muscle tissue forms the muscles that move the body, make the heart beat, and move food through the digestive tract. Finally, **nervous tissue** makes up the nervous system, which includes the **central nervous system**, consisting of the brain and spinal cord, and the **peripheral nervous system**, consisting of the nervous tissue that connects to the muscles and organs of the body. (The divisions of the nervous system are discussed at length in Chapter 4.)

All tissues are composed of specific types of cells. For example, connective tissue includes bone cells called osteocytes and blood cells called hematocytes. Epithelial tissue includes skin cells called squamous cells, and the liver has cells called hepatocytes. Muscle tissue is composed of muscle cells called myocytes. Nervous tissue is composed of neurons and glia, which are the focus of prime interest to neuroscientists. Neurons communicate with other neurons, muscle, and organs and perform the major computational functions of the nervous system, whereas glia support neuronal function and clear debris, toxins, and bacteria from the brain. The types of tissue and the cells associated with them are listed in Table 2.1.

TABLE 2.1

The Tissues of the Body and an Example of the Cells of Which They Are Composed

TISSUE	FUNCTION	CELL
Connective tissue	Makes up the bones, blood, ligaments, and tendons of the body	 Bone (osteocytes)
Epithelial tissue	Makes up the outer layer of the skin and lines the cavities of the body, such as the digestive and respiratory systems	 Skin (squamous cells)
Muscle tissue	Makes up the muscles that move the body, make the heart beat, and move food through the digestive tract	 Muscle (myocytes)
Nervous tissue	Makes up the nervous system, which includes the brain, spinal cord, and nerves that connect to the muscles and organs of the body	 Nervous system (neurons)

Images (top to bottom): iStock.com/Dr_Microbe; iStock.com/tonaquatic; iStock.com/JOSE LUIS CALVO MARTIN & JOSE ENRIQUE GARCIA-MAURINO MUZQUIZ; iStock.com/bestdesigns

2.1.2 CELL THEORY AND THE NEURON DOCTRINE

>> LO 2.1.2 Explain the cell theory and the neuron doctrine.

Key Terms

- **Cell theory:** The idea that the cell is the basic functional unit of all living things.
- **Reticular theory:** The idea that the neurites (axons and dendrites) of neurons fuse with the neurites of other neurons in a neural net.
- **Neuron doctrine:** The idea that the cell theory is applicable to neurons.

The **cell theory**, proposed in 1838 by German physiologist Theodor Schwann (1810–1882), states that the cell is the basic functional unit of all living things. At the time, however, the cell theory did not seem to apply to neurons. With the use of increasingly more powerful microscopes, it was observed that neurons have several parts, but it was not known how these parts were linked to each other.

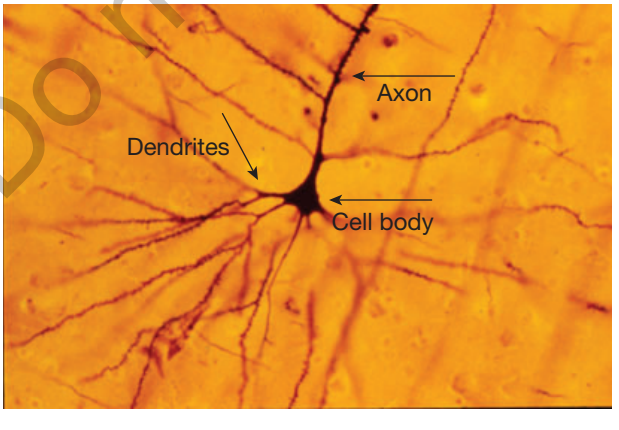
In the late 1800s, Camillo Golgi (1843–1946) invented a staining method that permitted researchers to clearly observe all the parts of neurons (cell body, axon, and dendrites) and how they relate to each other. This became known as the Golgi stain and involved immersing nervous tissue into a silver nitrate solution. Figure 2.1 shows a Golgi-stained neuron.

Despite researchers being able to study the structure of neurons, it still was not clear whether the cell theory applied to neurons. The neurites (axons and dendrites) of neurons seemed to fuse with the neurites of other neurons in a neural net. This idea, known as the **reticular theory**, was championed by Golgi and many others.

In 1888, Santiago Ramón y Cajal (1852–1934), highly skilled in drawing neurons (Figure 2.2), studied the neurons in the cerebellum of a chick using an improved version of the Golgi stain. He observed that the axons of neurons always led up to the dendrites of other neurons but that they were not continuous with them in that they did not touch. Ramón y Cajal concluded that, like other cells of the body, neurons are basic and independent functional units. This meant that the cell theory was also applicable to neurons. The idea that the cell theory applies to neurons is known as the **neuron doctrine**. Together, Golgi's and Ramón y Cajal's contributions earned them a shared Nobel prize in 1906. In the following decades, observations made through increasingly powerful microscopes supported the neuron doctrine.

FIGURE 2.1

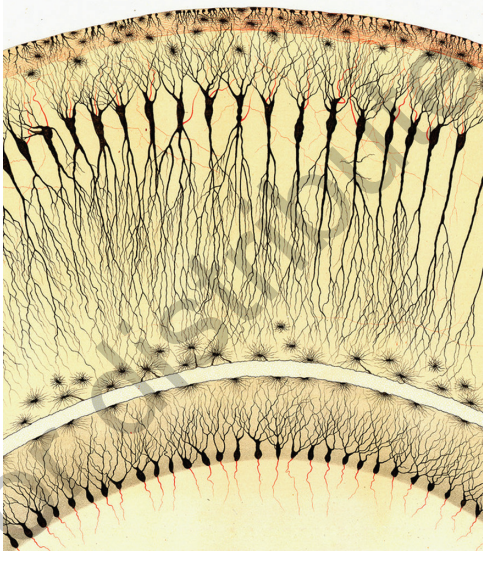
A Golgi-stained neuron.



Bob Jacobs, Laboratory of Quantitative Neuromorphology, Department of Psychology, Colorado College.

FIGURE 2.2

Santiago Ramón y Cajal's drawing of neurons in a rabbit's hippocampus (as you will learn later, the hippocampus is an area of the brain important for memory).



SCIENCE SOURCE

2.1.3 STUDYING NEURONS

>> LO 2.1.3 Describe the methods used to study neurons.

Key Terms

- **Histology:** The scientific study of cells and tissues.

- **Microscopy:** The field that uses microscopes to see objects that are not visible to the naked eye.
- **Microtome:** A laboratory instrument used to cut extremely thin sections of tissue.

Neuroscientists use several methods to study neurons. These include histology and microscopy. **Histology** is the scientific study of cells and tissues using special staining techniques combined with microscopy. **Microscopy** is the field that uses microscopes to see objects that are not visible to the naked eye.

To be able to clearly see neurons through a microscope, thin sections of brain tissue are cut, mounted on glass slides, and stained. However, the brain has the consistency of Jell-O. Therefore, sectioning it in its natural state is extremely difficult. To solve this problem, a method of fixing (hardening) the brain by soaking it in paraformaldehyde was devised. Extremely thin sections of the brain, micrometers thin (1 micrometer [μm] = 1 millionth of a meter), are made with the use of a **microtome**. Before being sectioned, the brain is frozen and sometimes embedded in a waxy substance. Figure 2.3a shows a technician using a microtome.

The sections of the brain are then mounted on microscope slides and treated with various types of stains. The Golgi stain, invented by Camillo Golgi, shown in Figure 2.1, is but one of these stains. You have already seen that the Golgi stain clearly shows the cell body, axon, and dendrites of neurons. The type of stain used depends on the types of cells and cell components a researcher is interested in studying. For example, a stain called cresyl violet is used to highlight the cell body (Figure 2.3b) but does not clearly identify axons and dendrites.

2.1.4 THE NUMBER OF NEURONS AND GLIA IN THE BRAIN

>> LO 2.1.4 Explain what scientists have learned from having accurate estimates of the numbers of neurons in the brains of humans and other animals.

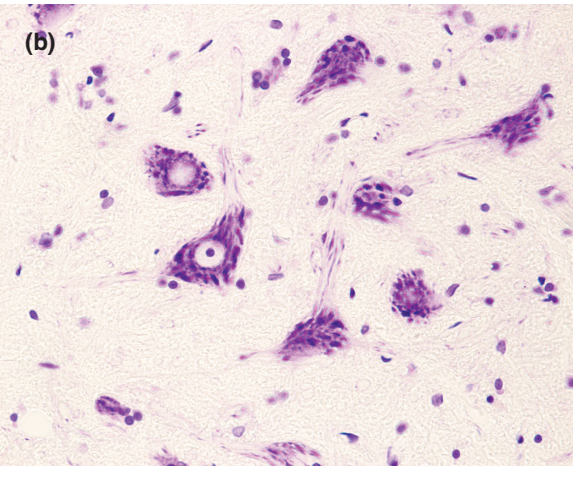
Key Term

- **Isotropic fractionation:** A method by which the number of cells in a brain area of interest can be estimated.

Various sources of information (including textbooks) state that the brain contains 100 billion neurons and 10 times as many glial cells (F. Doetsch, 2003; Kandel, Schwartz, & Jessell, 2000). However, recent research does not support these numbers. For example, using a method known as **isotropic fractionation**, neuroscientist Suzana Herculano-Houzel and colleagues found that the human brain contains, on average, 86.06 billion neurons and 84.61 billion glia (Azevedo et al., 2009; Herculano-Houzel, 2014). Isometric fractionation involves reducing brain areas of interest to a solution. The number of neurons and glia in an area of interest can then be estimated by the application of special stains that differentiate between them. Figure 2.4 shows a cross-section of a human brain with its distribution of neurons and glia, referred to as non-neuronal cells.

FIGURE 2.3

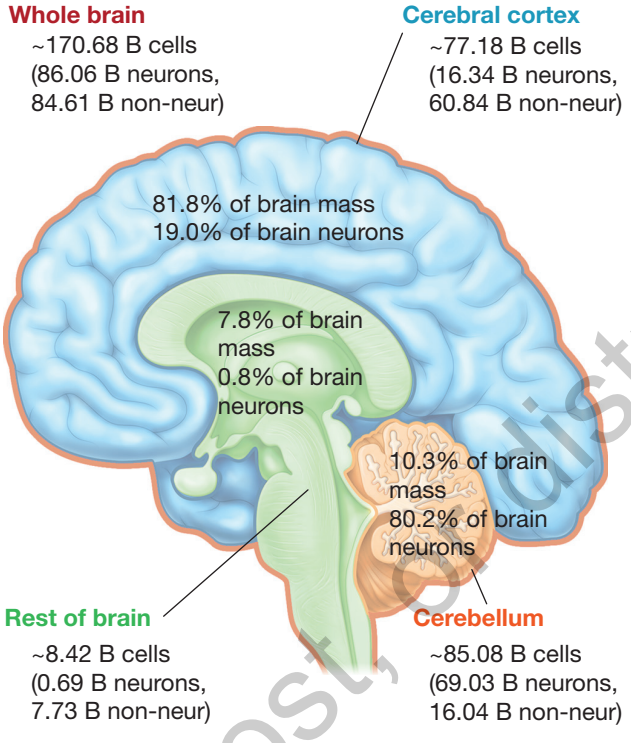
(a) A microtome being used to cut sections of a rodent brain. (b) A brain section stained with cresyl violet. Note the visibility of the cell nuclei compared with their axons and dendrites.



(a) age fotostock / Alamy Stock Photo; (b) Jose Luis Calvo/Science Source

FIGURE 2.4

Number of neurons and non-neuronal cells in the whole human brain and by brain area. B = billion; non-neur = non-neuronal cells, or glia.



Amanda Tomasikiewicz/Body Scientific Intl.

It is also widely believed that the differences in cognitive abilities across species of animals are related to brain size or to the number of neurons. However, recent studies show that these beliefs make no sense if humans are to be considered as the smartest animals. Compared to the brains of other species, the human brain neither is the largest nor does it contain the highest number of neurons. For example, elephants have a bigger and heavier brain (about 4.6 kilograms compared to about 1.5 kilograms for the human brain) with more neurons (about 258 billion) than humans have (about 86 billion). Rather, differences in intelligence between species may be related to the number of neurons located in the cerebral cortex. Elephants have significantly more neurons than humans but only about 5.93 billion are in the cerebral cortex. In contrast, the human cerebral cortex contains about 16 billion neurons (see Olkowicz et al., 2016, for a comparison in brain size, total number of neurons, and number of neurons concentrated in the cerebral cortex across birds and mammals).

IT'S A MYTH!

No New Neurons

The Myth

The adult brain is incapable of generating new neurons.

Where Does the Myth Come From?

The origin of this myth can be traced back to Santiago Ramón y Cajal, the father of the neuron doctrine. In

(Continued)

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his 1913 book *Degeneration and Regeneration of the Nervous System,* Ramón y Cajal stated that new neurons could not be generated after birth (Ramón y Cajal, DeFelipe, & Jones, 1991). He could not conceive how new neurons could be integrated into already well-established networks. Regarding the nervous system, he claimed that "everything may die and nothing may be regenerated." This dogma persisted in the minds of neuroscientists for many years, often in the face of contrary evidence. Even today, the "no new neurons" myth is still very much present in the general population.

Why Is the Myth Wrong?

It is true that neurons do not replicate through cell division. This is because they lack the molecular machinery needed to do so. However, in the 1960s, Joseph Altman discovered that neurogenesis (the generation of new neurons) occurs in postnatal guinea pigs, even though they are born with nearly adult-sized brains. He found that this occurred in the hippocampus, a brain structure known to be important for memory (Altman, 1962). Altman's findings were largely ignored, as often occurs when a new finding contradicts the prevailing view. Altman's report was followed by a series of findings that made neurogenesis more difficult to ignore. In the 1980s, Fernando Nottebohm and colleagues discovered neurogenesis in the brains of song birds (Alvarez-Buylla, Ling, & Nottebohm, 1992; Nottebohm, 1989). By the late 1990s, it was known that adult neurogenesis occurred in at least two brain areas: the hippocampus and the olfactory bulb. Several studies show that neurogenesis in the hippocampus is related to the formation of new memories (Hung, Hsiao, & Gean, 2014; Ko et al., 2009).

Today, the search for the functions of neurogenesis continues. For example, it was found that chronic stress, which can lead to major depression, inhibits neurogenesis in the hippocampus. In contrast, antidepressant drugs were found to increase neurogenesis (Anacker, 2014; Mahar, Bambico, Mechawar, & Nobrega, 2014; Ruiz et al., 2018). ●

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MODULE SUMMARY

The body is made up of many different types of tissues, each composed of specialized types of cells. The tissue of most interest to neuroscientists is nervous tissue. Nervous tissue is composed of two types of cells: neurons and glia. Neurons are responsible for the computational functions of the nervous system, which permit us to sense our environment, move around, experience emotions, and form memories. Glia support neuronal function and clear debris, toxins, and bacteria from the brain.

The cell theory states that the cell is the basic functional unit of all living things. It was once believed that neurons did not conform to the cell theory in that axons and dendrites of different neurons were thought to be continuous with each other in a neural net. This is known as the reticular theory. It was later discovered that the cell theory did apply to neurons. This is known as the neuron doctrine.

Neuroscientists study neurons using histological methods, in which they use special staining techniques, and microscopy. The human brain was once thought to contain 100 billion neurons and 10 times as many glia. However, recent studies show that the human brain contains about 86 billion neurons and approximately the same number of glia.

TEST YOURSELF

2.1.1 Describe how neurons and glia are but other types of cells in the body and explain what they are responsible for.

2.1.2 Explain the cell theory and the neuron doctrine.

2.1.3 Describe the methods used to study neurons.

2.1.4 How many neurons and glia are presently thought to be in the human brain? How does that differ from previous thinking? In what way is the number of neurons thought to account for the complexity of human behavior as compared to other species?

2.2 The Structure of Neurons

Module Contents

Learning Objectives

2.2.1 Describe the prototypical neuron and explain the roles of its parts.

2.2.2 Describe the ways by which neurons can be differentiated.

2.2.1 THE PROTOTYPICAL NEURON

>> LO 2.2.1 Describe the prototypical neuron and explain the roles of its parts.

Key Terms

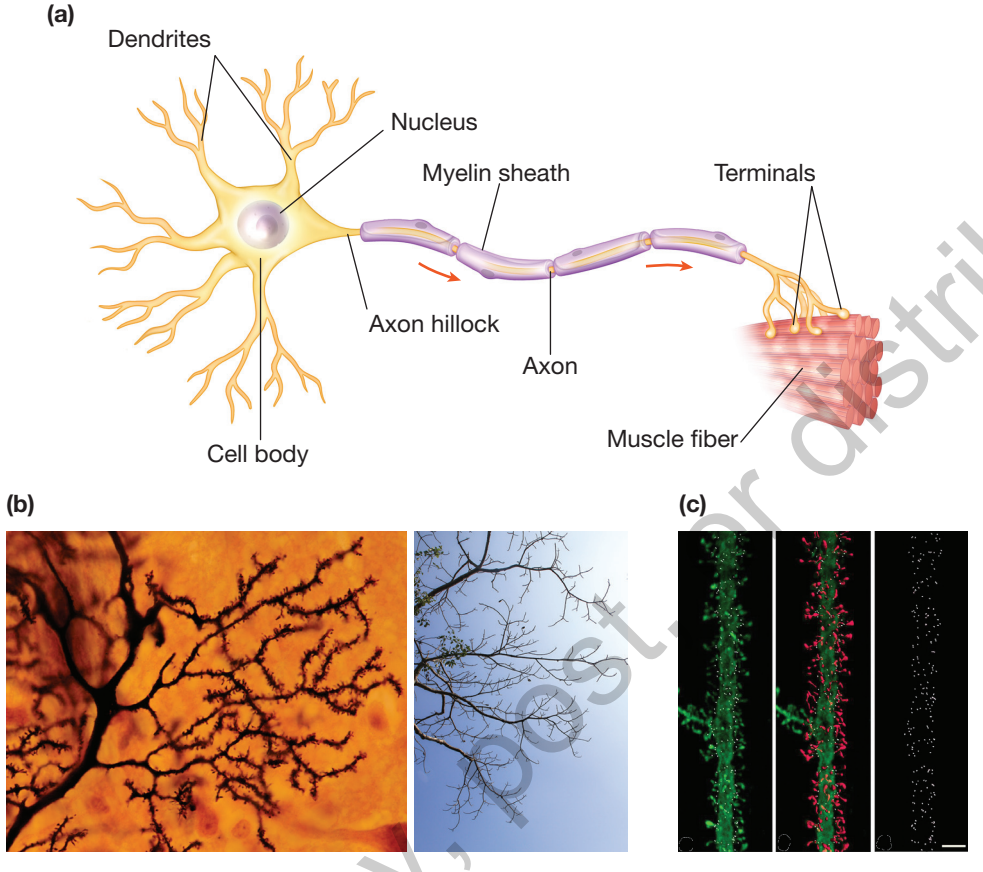
- **Action potential:** Also known as a nerve impulse; the conduction of an electrical charge within a neuron.
- **Neurotransmitter:** A chemical messenger released from neurons; used to communicate with other neurons and other types of cells in the body.
- **Soma:** Also called the cell body or perikaryon; contains the nucleus and organelles found in other cell types.
- **Nucleus:** The part of the cell that contains deoxyribonucleic acid (DNA), which codes for proteins.
- **Dendrite:** An outgrowth of the neuron at which connections between neurons are typically made.
- **Axon:** An outgrowth of neurons through which action potentials are conducted.
- **Axon hillock:** The point of contact between the soma and the beginning of the axon.
- **Axon terminal:** The part of the axon farthest from the cell body; stores and releases neurotransmitters.
- **Synaptic cleft:** The tiny gap that exists between neurons.
- **Ligand:** Neurotransmitters or other chemicals, such as drugs, that bind to neurotransmitter receptors.
- **Ligand-gated ion channels:** Channels that open in response to the binding of ligands to their receptors.
- **Synapse:** The site of communication between neurons or between neurons and other types of cells.
- **Presynaptic neuron:** The neuron that releases neurotransmitter molecules into the synaptic cleft.
- **Postsynaptic neuron:** The neuron located across the synaptic cleft.
- **Myelin sheath:** Fatty tissue that insulates axons.
- **Oligodendrocytes**: Myelin-producing glia in the central nervous system.
- **Schwann cells:** Myelin-producing glia in the peripheral nervous system.
- **Neuronal membrane:** The cellular membrane of neurons.
- **Cytoskeleton:** The collection of filaments and tubules that gives the cell its shape, rigidity, and ability to move.
- **Microtubules:** The largest of the cytoskeletal elements.
- **Actin filaments:** Also called microfilaments; the smallest of the cytoskeletal elements.
- **Intermediate filaments:** Also called neurofilaments; of intermediate size between microtubules and actin filaments.
- **Axoplasmic transport:** The transport of materials from one part of the cell to another via microtubules.

Figure 2.5a shows a prototypical neuron. As we explore their basic structures, keep in mind that neurons communicate through electrical impulses called **action potentials**, also known as nerve impulses, which are examined in depth later in the chapter. Action potentials result in the release of **neurotransmitters** onto specialized receptors situated on target cells. Target cells can be other neurons, muscle cells, or the cells of internal organs.

Neurotransmitters are chemical messengers that are released by neurons as well as being synthesized and stored within them. Many neurotransmitters are known to exist. Each neurotransmitter is associated with certain functions in both the central and

FIGURE 2.5

(a) A prototypical neuron. (b) Comparison between a photomicrograph of dendrites and a digital image of tree branches. (c) Images of a dendrite along with three-dimensional reconstruction of its spines (in red, center). The white dots represent the locations at which the spines insert into the dendrite (left and right).



(b) *left:* Jose Luis Calvo/Science Source; *right:* iStock.com/Siewwy84; (c) Morales, J., et al. (2014). Random Positions of Dendritic Spines in Human Cerebral Cortex. *Journal of Neuroscience 34*(30), 10078–10084. With permission from The Society for Neuroscience.

peripheral nervous systems. Neurotransmitters are discussed at length in Chapter 3.

The Structure of Neurons

The Soma (or Cell Body)

The **soma** is the part of the neuron that contains the **nucleus** of the neuron as well as many organelles, which are structures that carry out the cell's functions. The soma can measure anywhere from 5 μm to 100 μm in diameter, depending on the type of neuron. The nucleus contains deoxyribonucleic acid (DNA), which codes for proteins (see Chapter 1).

Dendrites

Dendrite is the Greek word for "tree." Dendrites are outgrowths of neurons at which connections between neurons are typically made. They have receptors to which neurotransmitters bind. Each type of neurotransmitter binds to its own type of receptor. As an analogy, think of receptors as keyholes and neurotransmitters as the keys that fit them. Through binding to these receptors, some neurotransmitters can trigger neurons to generate action potentials, whereas other neurotransmitters can prevent neurons from firing action potentials.

Dendrites have small outgrowths called dendritic spines. Figure 2.5c shows a three-dimensional reconstruction of a dendrite with its spines (Morales et al., 2014). Dendritic spines have neurotransmitter receptors. This increases the number of connections dendrites can make with other neurons. They undergo plastic changes in response to experience, which underscores their importance in learning and memory (see Chapter 5 for a discussion of neuroplasticity). Abnormalities in dendritic spines may be related to

developmental problems, such as the learning difficulties and cognitive deficits found in individuals with fragile X syndrome, a genetic disorder caused by an abnormality on the X chromosome (Comery et al., 1997; K. Han et al., 2015). Figure 2.5b compares a digital image of dendrites, taken through a microscope (photomicrograph), with an image of tree branches. Can you tell which is which?

The Axon

The **axon** joins the soma to the axon terminals, the parts of the axon farthest away from the soma. Action potentials are initiated at the **axon hillock**, which is the point of contact between the soma and the beginning of the axon. A bundle of axons in the central nervous system (situated in the brain and spinal cord) is called a tract. A bundle of axons in the peripheral nervous system (that connects to the muscles and internal organs) is referred to as a nerve.

Axons can be very long, up to 1.5 meters in length or more. The longest nerve in the human body is the sciatic nerve, which runs from the lower back to the foot. Have you ever heard of sciatica? It is a painful condition in which the sciatic nerve is pinched by a displaced disc in the lower vertebral column. People with sciatica can experience pain down the leg and sometimes all the way down to their toes.

Axon Terminals

Axon terminals (Figure 2.6) are situated at the end of the axon. They contain packets of neurotransmitters called synaptic vesicles. In response to action potentials reaching the axon terminals, calcium enters the terminal and synaptic vesicles bind to the neuronal membrane and release their contents of neurotransmitters into the tiny gap that exists between neurons, known as the **synaptic cleft**. The neurotransmitters then bind to receptors of the neuron across the synaptic cleft. These receptors are on channels that open in response to the binding of neurotransmitters. Neurotransmitters and other chemicals that bind to receptors are known as **ligands**. Because of this, these channels are known as **ligand-gated ion channels**.

The site of communication between neurons or between neurons and other types of cells is known as the **synapse**. Thus, the neuron releasing the neurotransmitters is referred to as the **presynaptic neuron**, whereas the neuron that receives the neurotransmitters, on the other side of the synaptic cleft, is referred to as the **postsynaptic neuron**. You will learn much more about this process in Chapter 3.

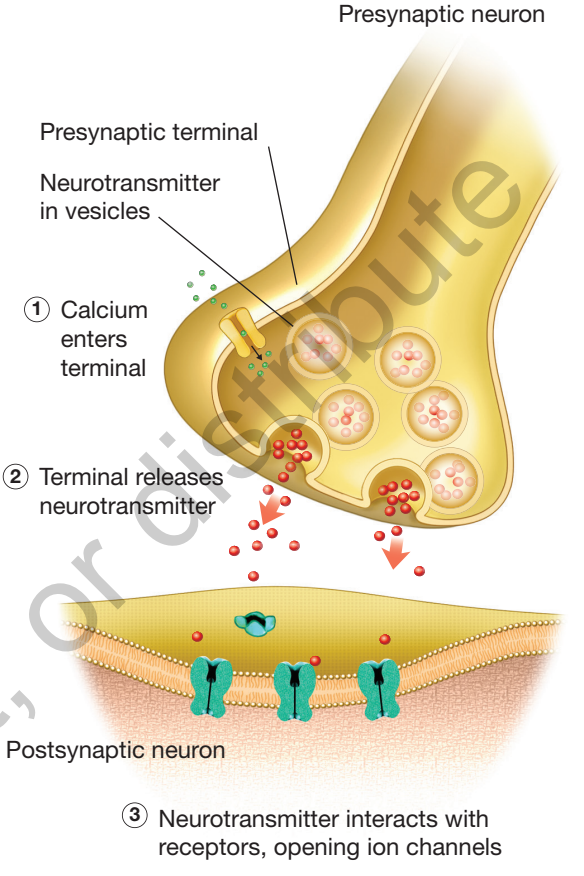
The Myelin Sheath

The **myelin sheath** is a fatty tissue that insulates axons. It contributes to how well neurons conduct action potentials. This is similar to the insulation of a power cord, without which current would not make it very far. The myelin sheath is not continuous through the entire length of the axon. There are frequent breaks in the sheath known as nodes of Ranvier, named after the French anatomist Louis-Antoine Ranvier (1835–1922). These breaks are about 1 μm in length and occur at intervals of about 1–2 μm. They are the sites at which action potentials are regenerated.

The myelin sheath is produced by glia. The myelin-producing glia in the central nervous system, which includes the brain and spinal cord, are called **oligodendrocytes**. In the peripheral nervous system, which controls your muscles and organs, the myelin-producing glia are called **Schwann cells**, named after Theodor Schwann, who, as you read earlier, proposed the cell theory. The process by which glial cells insulate axons is illustrated later in the chapter, in Figure 2.24.

FIGURE 2.6

A synapse.

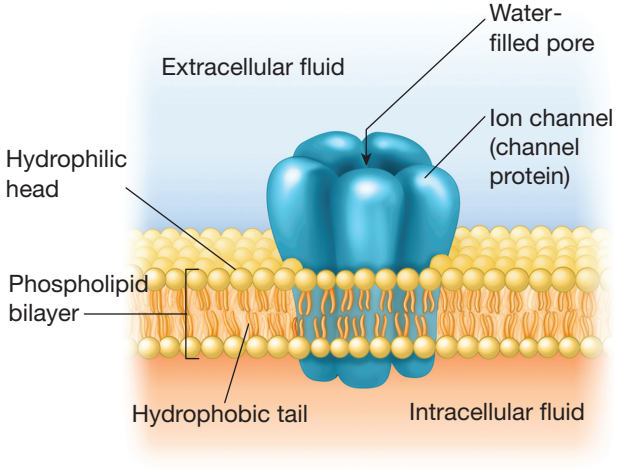


The Neuronal Membrane

The **neuronal membrane** (Figure 2.7) consists of a phospholipid bilayer, as the molecules that compose it form two layers. The term *phospholipid* is derived from two words: *phosphate* and *lipid* (*lipos* is Greek

FIGURE 2.7

The neuronal membrane with its phospholipid bilayer. Also shown, spanning the membrane, is an ion channel and a water-filled pore through which ions enter or exit the neuron.



Carolina Hrejsa/Body Scientific Intl.

for "fat"). The phospholipid molecules each have a head and a tail. The head of each molecule is hydrophilic, meaning water loving and that it readily interacts with water, whereas the tail of each molecule is hydrophobic, meaning water fearing and that it does not interact with water. Remember that oil and water do not mix.

The molecules are oriented so that the hydrophobic tail of each molecule faces the tail of another molecule. The hydrophilic heads of the molecules bathe in the extracellular and intracellular fluids. This arrangement keeps water and various particles either on the outside or on the inside of the neuron. Embedded within this membrane are proteins that form channels across the membrane, also seen in Figure 2.7. These channels are semipermeable and permit the movement of molecules in and out of the neuron. Channels come in many types, each type letting in or out of the cell certain molecules called ions, such as sodium or potassium, through a water-filled pore.

The Cytoskeleton

The word **cytoskeleton** literally means "skeleton of the cell." This is because it gives the cell its shape, rigidity, and ability to move. There are three types of cytoskeletal elements: microtubules, actin filaments, and intermediate filaments (Figure 2.8). **Microtubules** are the largest of the cytoskeletal elements. Microtubules are held together by tubulin-associated protein (TAU). **Actin filaments** (also called microfilaments) are the smallest of the cytoskeletal elements. They also run through axons and dendrites, but, in addition, they are fastened to the inside of the cell's membrane.

Intermediate filaments (also called neurofilaments) are of intermediate size between microtubules and actin filaments. They are present in dendrites but more numerous in axons. They are essential in preserving the axon's diameter and play an important role in maintaining the velocity of action potentials.

Axoplasmic Transport

The microtubules act as railroad tracks for the transport of materials from one part of the cell to another. This type of transport is called **axoplasmic transport**. Materials such as organelles, lipids, or proteins are transported in vesicles along microtubules by what look like little "legs." These "legs" are made of the proteins kinesin and dynein. In anterograde transport, kinesin carries materials from the soma toward the axon terminals. In retrograde transport, dynein carries materials from axon terminals to the soma (Figure 2.9).

Pathology of the cytoskeleton can lead to neuropsychiatric disorders. The most widely known of these disorders is Alzheimer's disease, in which people suffer progressively more severe memory loss and other cognitive problems. In Alzheimer's disease, the TAU

FIGURE 2.8

The cytoskeleton. Three different elements make up the cytoskeleton: actin filaments, intermediate filaments, and microtubules.

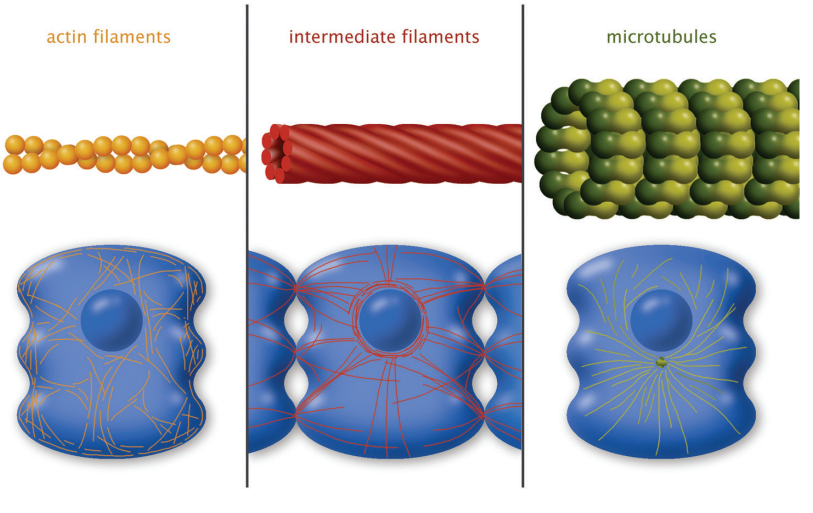


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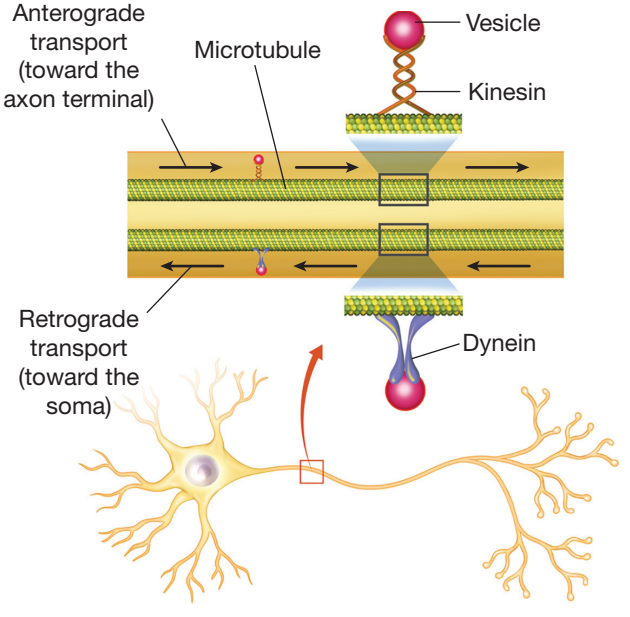
FIGURE 2.9

Axoplasmic transport.



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protein is hyperphosphorylated, meaning that it takes on additional phosphate groups. This change in structure of the TAU protein prevents it from binding with microtubules. This causes the microtubules to collapse into tangles known as neurofibrillary tangles and loose aggregates of TAU known as paired-helical filaments. Alzheimer's disease is discussed in Chapter 5.

2.2.2 THE DIVERSITY OF NEURONS

>> LO 2.2.2 Describe the ways by which neurons can be differentiated.

Key Terms

- **Sensory neuron:** A neuron that carries sensory information from the peripheral nervous system to the central nervous system.
- **Motor neuron:** A neuron that carries movement information from the central nervous system to the peripheral nervous system.
- **Interneuron:** A neuron that connects sensory neurons to motor neurons.
- **Bipolar neuron:** A neuron that has a single dendrite and axon, each exiting opposite sides of the soma.
- **Unipolar neuron:** A neuron with only one process that flows uninterrupted by the soma.
- **Multipolar neuron:** A neuron that has many dendrites sticking out of one side of the soma and an axon sticking out of the other side.
- **Pyramidal neuron:** A type of neuron that has the appearance of a pyramid.
- **Stellate cell:** A neuron in which the disposition of the dendrites gives it a star-shaped appearance.
- **Rosehip neuron:** A recently discovered type of neuron with unknown function that is found in humans but not in rodents.

Diverse types of neurons exist. Neurons can be differentiated by their function; their morphology; the architecture of their dendrites; and the type of neurotransmitters they synthesize, store, and release. Neurons also show considerable diversity across species.

Differences in Function

Functional differences between neurons are illustrated in the reflex arc (Figure 2.10). Movement is often produced involuntarily. For example, when the body makes contact with a painful stimulus, muscles contract automatically to move the affected part of the body away from the stimulus. This is known as a withdrawal reflex.

FIGURE 2.10

The reflex arc.

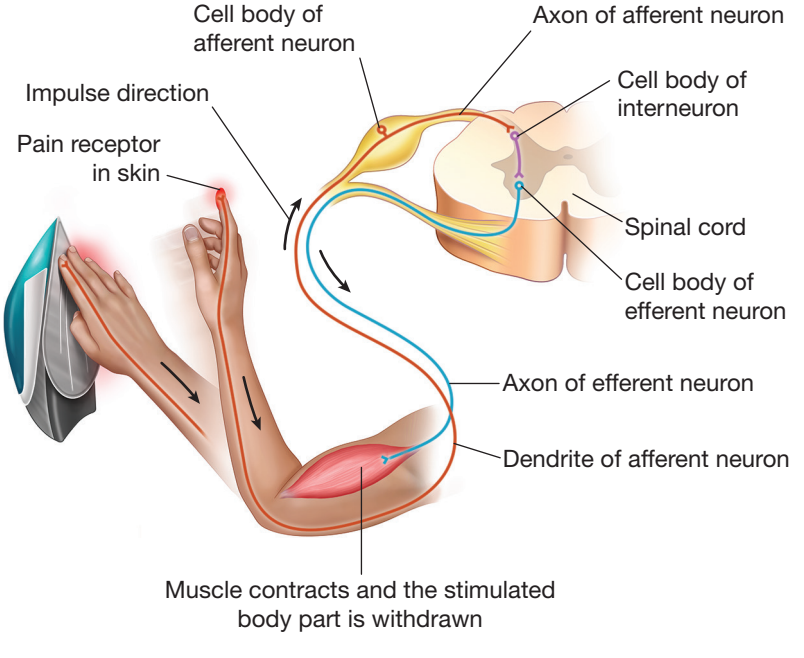

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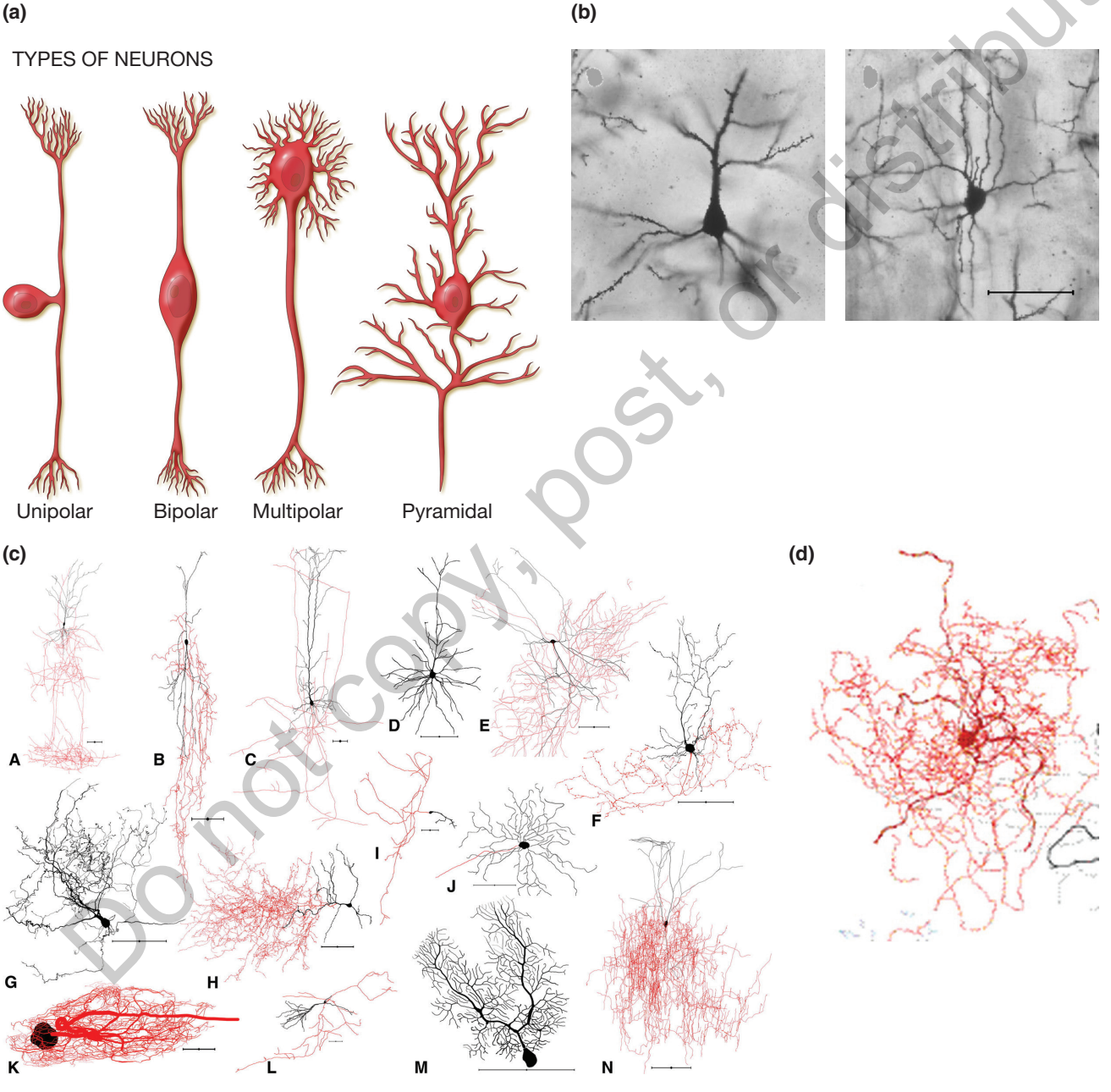
FIGURE 2.11

(a) Morphological variation in neurons, as described in the text. (b) Photomicrograph of a pyramidal cell (left) and a stellate cell (right). (c) Computer reconstructions of diverse neurons across species: (A) rat neocortex Martinotti cell, (B) rat neocortex bipolar cell, (C) rat neocortex pyramidal cell, (D) mouse neocortex pyramidal cell, (E) mouse hippocampus Schaffer collateral-associated neuron, (F) mouse cerebellum Golgi cell, (G) cat brainstem vertical cell, (H) rat olfactory bulb deep short-axon cell, (I) mouse neocortex Cajal-Retzius cell, (J) mouse retina ganglion cell, (K) spiny lobster stomatogastric ganglion motor neuron, (L) rat hippocampus granule cell, (M) mouse cerebellum Purkinje cell, and (N) rat neocortex interneuron. (d) Anatomical reconstruction of a rosehip neuron.



(a) Monica Schroeder/Science Source; (b) Parekh, R., & Ascoli, G. A. (2013). Neuronal morphology goes digital: a research hub for cellular and system neuroscience. *Neuron, 77*(6), 1017–38; (c) Parekh, R., & G.A. Ascoli. (2013). Neuronal morphology goes digital: a research hub for cellular and system neuroscience. *Neuron 77*(6), 1017–1038. With permission from Elsevier; (d) Boldog, E. et al. (2018). Transcriptomic and morphophysiological evidence for a specialized human cortical GABAergic cell type. *Nature Neuroscience 21*(9): 1185–1195. With permission from Springer Nature.

Unlike voluntary movement, reflexes do not require the brain for their execution. In a reflex arc (such as the one seen in Figure 2.10), three types of neurons, differentiated by their functions, are involved. These are sensory neurons, motor neurons, and interneurons. **Sensory neurons**, also known as afferent neurons (*afferent* means to carry information toward), bring information from sensory receptors, which are part of the peripheral nervous system, toward the brain and spinal cord, which constitute the central nervous system. **Motor neurons**, also known as efferent neurons (*efferent* means carrying information away from), carry information away from the brain and spinal cord to cause muscles to contract. To summarize, sensory neurons carry sensory information from the peripheral nervous system to the central nervous system, and motor neurons carry information from the central nervous system to the peripheral nervous system. **Interneurons** mediate the connections between sensory and motor neurons.

Morphological Variations

Variations in the morphology of neurons are illustrated in Figure 2.11a. **Bipolar neurons** have a single dendritic tree and axon each exiting from opposite sides of the soma. Think of the North and South Poles of Earth with a dendrite coming out of the north and an axon coming out of the south. Bipolar neurons are quite rare. They are found only in the auditory and visual systems. **Unipolar neurons** have a single process that flows uninterrupted by the soma. That is, the dendrite and the axon are continuous. Unipolar neurons have an axon that splits into two branches. One branch, the central branch, exits the cell body and enters the dorsal root of the spinal cord. The other branch, the peripheral branch, collects sensory information from the receptors in muscles, skin, and joints. These are typical of sensory neurons.

Multipolar neurons have many dendrites sticking out of one side of the soma and an axon sticking out of the other side. These are typical of motor neurons and interneurons. The prototypical neuron illustrated at the beginning of this chapter is a multipolar neuron.

Variations in Dendrite Architecture

Pyramidal neurons have a pyramid-shaped soma with a single dendrite arising from the top of the pyramid and several branching dendrites emanating from its base (right image in Figure 2.11a and left image in Figure 2.11b). **Stellate cells** are typically interneurons. They are called stellate cells because the disposition of their dendrites gives them a star-shaped appearance (right image in Figure 2.11b).

Variations in Neurotransmitter Type

Neurons can also be differentiated by the neurotransmitters they synthesize, store, and release. That is, different neurons synthesize, store, and release particular neurotransmitters. We discuss neurotransmitters and the mechanisms by which neurons use them to communicate in Chapter 3.

Diversity in Neurons Across Species

Figure 2.11c shows computer reconstructions of the diversity in neurons that exist across species (Parekh & Ascoli, 2013). The majority of neurons shown in Figure 2.11c are from rodents (rats and mice). New types of neurons continue to be discovered. For example, an entire new class of neurons was discovered in the neocortex, hippocampus, and olfactory bulb (Tripathy, Burton, Geramita, Gerkin, & Urban, 2015). More recently, a type of neuron called a **rosehip neuron** (so called because it looks like the fruit of a rose bush) was discovered in the neocortex of humans (Boldog et al., 2018) (Figure 2.11d). What is fascinating about these neurons is that they do not appear to exist in rodents. However, the exact functions of rosehip neurons are still a mystery to neuroscientists. This is important to know since rodents are the animals used most frequently for modeling behavior and cognition. As a result, a greater understanding of the neurobiological basis of human cognition, behavior, and psychological disorders might come from discovering neurons that are unique to humans.

MODULE SUMMARY

The soma (or cell body) is the part of the neuron that mostly resembles other cells. It contains the nucleus and various organelles. The nucleus codes for proteins. Neurons have an axon and many dendrites. Axons attach to the soma at the axon hillock and carry information in the form of action potentials. Action potentials travel down the axon until they reach the axon terminals, where they trigger the release of neurotransmitters into the synaptic cleft. The neurotransmitters released by neurons bind to receptors located on the dendrites of other neurons. Dendrites have small outgrowths known as dendritic spines, on which additional receptors are located. Dendritic spines greatly increase the connections a neuron can make with other neurons. Axons are insulated by a fatty tissue called the myelin sheath, which increases the conductivity. The myelin sheath is interrupted periodically at what are known as nodes of Ranvier.

The neuronal membrane keeps water and other soluble molecules from traveling in and out of the neuron. To enter or exit the neuron, ions pass through channels, selective to each ion. The shape, rigidity, and mobility of neurons are provided by the cytoskeleton, which is made up of three elements: microtubules, intermediate filaments, and actin filaments. Microtubules are also

used in axoplasmic transport. Anterograde transport is the transport of molecules from the soma toward the axon terminals, and retrograde transport is the transport of molecules from the axon terminals toward the soma. Alzheimer's disease may be due to pathology of the cytoskeleton.

Neurons can be differentiated by their function, as can be demonstrated in a reflex arc. For example, sensory neurons carry information from the body to the spinal cord, where they communicate with motor neurons through interneurons, which send electrical signals to the muscles. Neurons also come in a variety of shapes: unipolar, bipolar, and multipolar neurons; pyramidal cells; and stellate cells. Neurons also show diversity across species. Finally, neurons can be differentiated by the neurotransmitters they synthesize, store, and release.

TEST YOURSELF

2.2.1 On a sheet of paper, draw a prototypical neuron and label its parts. Describe the function of each part.

2.2.2 Describe the ways in which neurons can be differentiated.

2.3 The Action Potential

Module Contents

Learning Objectives

2.3.1 Explain the forces of diffusion and electrostatic pressure and how they are involved in the movement of ions across the cell membrane.
2.3.2 Explain how action potentials are initiated.
2.3.3 Explain how action potentials are propagated down the axons of neurons.

2.3.1 A LITTLE BIT OF CHEMISTRY

>> LO 2.3.1 Explain the forces of diffusion and electrostatic pressure and how they are involved in the movement of ions across the cell membrane.

Key Terms

- **Ion:** An electrically charged particle.
- **Diffusion:** The process by which molecules tend to move from an area of high concentration to an area of low concentration.
- **Electrostatic pressure:** The phenomenon by which ions that are of the same charge repel each other and ions that are of opposite charge attract each other.
- **Resting membrane potential:** The difference in charge between the inside and the outside of the neuron when not conducting action potentials.
- **Equilibrium potential:** The voltage across the membrane (V_m) at which the forces of electrostatic pressure and diffusion counteract each other.

As with any other cell, neurons bathe in fluid and are fluid filled. The fluid outside the neuron is called extracellular fluid; the fluid inside the neuron is referred to as intracellular fluid. **Ions**, which are electrically charged particles, float around inside these fluids. Some ions have a net positive electrical charge, whereas other ions have a net negative electrical charge. The charge of the ion is indicated by the appropriate superscript (+ or –). Ions with a net positive electrical charge are known as cations, whereas ions with a net negative electrical charge are known as anions. You need to know something about ions to understand how action potentials are initiated and propagated down the axon of a neuron.

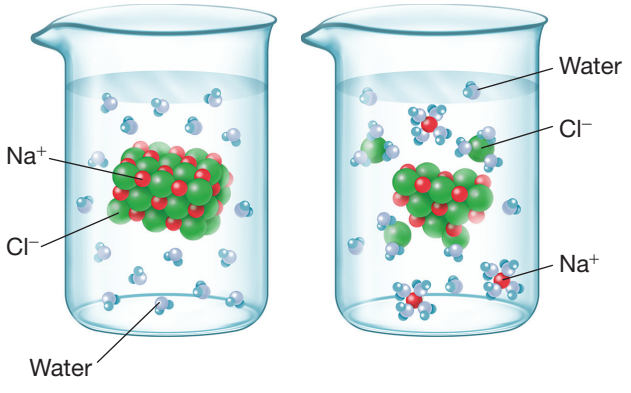
Ions result from dissolving molecules, such as sodium chloride (NaCl) (otherwise known as table salt) into water. As shown in Figure 2.12, when NaCl is dissolved in water, Na^+ and Cl^- are pulled apart, resulting in free Na^+ ions and Cl^- ions surrounded by water molecules. There are other types of ions within the extracellular and intracellular fluids, for example, potassium (K^+), calcium (Ca^{2+}), and hydrogen (H^+). For now, we will mostly focus our attention on only two of them, Na^+ and K^+.

Diffusion and Electrostatic Pressure: Two Forces of Nature in Action

When a neuron is not conducting an action potential, Na^+ is 10 times more concentrated in the extracellular fluid than it is in the intracellular fluid. In contrast, K^+ is 20 times more concentrated in the intracellular fluid than it is in the extracellular fluid. This difference in the concentration of ions between the outside and the

FIGURE 2.12

Table salt (NaCl) molecules dissolving in water, resulting in Na^+ and Cl^- ions surrounded by spheres of hydration.



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inside of the neuron (concentration gradient) sets up the condition for diffusion to occur. **Diffusion**, illustrated in Figure 2.13a, is the process by which solutes (substances dissolved in water) move from an area of high concentration to an area of low concentration. For example, when milk is poured into a cup of coffee, it is initially concentrated in one area. It then moves throughout the whole cup. The milk is said to move down its concentration gradient. That is, it moves from an area in which it is more concentrated to an area in which it is less concentrated.

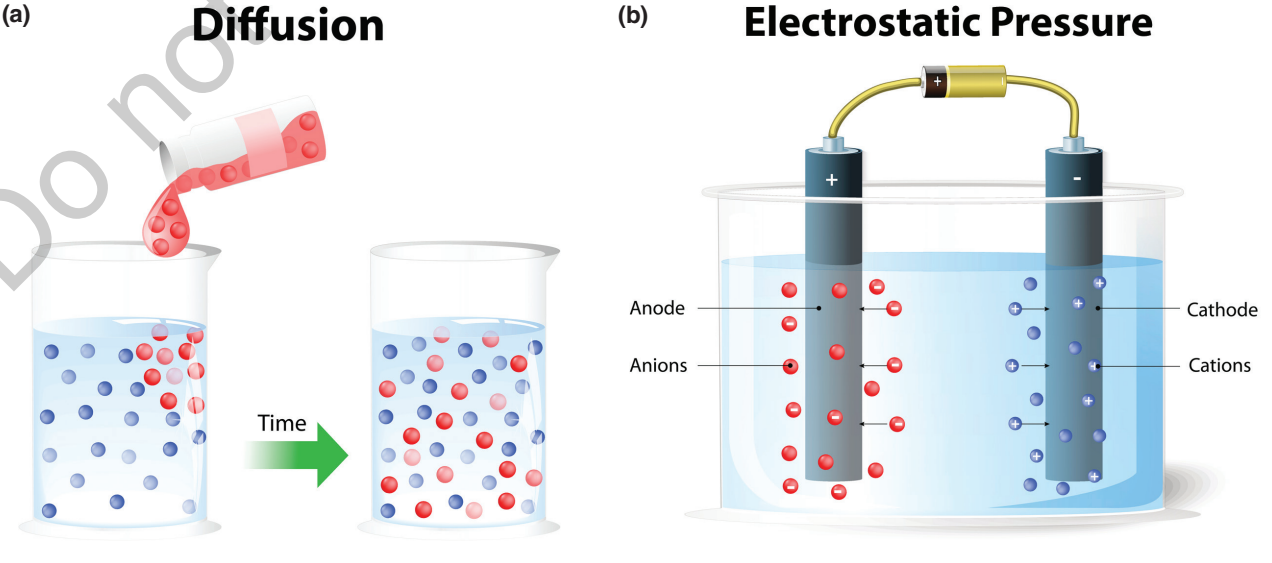
The inside of the neuron is electrically negative relative to the outside. This difference in electrical charge between the inside and the outside of the neuron sets up the condition for a second force—called **electrostatic pressure**, also known as the electrical force—to come into play. Electrostatic pressure creates the phenomenon by which ions that are of the same charge (+ + or – –) repel each other and ions that are of opposite charge (+ –) attract each other.

Cations and anions are also attracted to other sources of opposite electrical charge. For example, imagine that electrodes from the positive and negative poles of a battery are lowered into a beaker of water (Figure 2.13b). An electrode from the positive pole (anode) of the battery is lowered into the beaker on one side, and an electrode from the negative pole (cathode) of the battery is lowered into the beaker on the other side.

Imagine, also, that a permeable membrane was lowered into the beaker in between the two electrodes (the anode and the cathode). Now, imagine that channels permeable to Na^+ are inserted into the membrane. In which direction will the Na^+ ions flow? The answer is that they will flow from the side with the positive electrode to the side of the membrane with the negative electrode. There are two reasons for this. First, the Na^+ ions will flow down their concentration gradient, that is, from the area in which they are more concentrated to the area in which they are least concentrated, a case of diffusion. Second, because the Na^+ ions have a net positive electrical charge (anion), they will be drawn to the side of the membrane that was rendered electronegative

FIGURE 2.13

The forces of diffusion and electrostatic pressure. (a) In diffusion, solutes move from an area of high concentration to an area of lower concentration until the concentrations are balanced. (b) Electrostatic pressure causes ions with a net negative charge (anions) to be attracted to a positive electrical charge (anode) while ions with a net positive charge (cations) are attracted to a negative charge (cathode).



(a) iStock.com/ttsz; (b) iStock.com/ttsz

by the presence of the negative electrode. This is due to electrostatic pressure. This, of course, would also happen if channels permeable to K^+ were put in place. Ions with a net negative charge (cations), such as chloride (Cl^-), would move in the opposite direction.

The Resting Membrane Potential, Voltage, and Conductivity

The **resting membrane potential** refers to the difference in charge between the inside and the outside of the neuron when it is at rest, that is, when it is not generating action potentials. My favorite analogy for this is a car battery like the one illustrated in Figure 2.14a. A car battery, like any other battery, stores energy. You wouldn't know it just by looking at one. But you could hook up wires to the battery's positive and negative poles, marked, respectively, by a "+" and a "–," and then hook up both of these wires to a motor or anything else you want the battery to power.

The fact that one pole of the battery is marked with a "+" and the other is marked with a "–" means that there is a difference in electrical charge between the two poles. This difference in charge is measured in volts. For a standard car battery, the difference in charge between the negative and positive poles is about 12 volts (Figure 2.14a). If we used shoelaces to hook the poles of the battery to an engine, nothing would happen. This is because shoelaces have no conductivity. Conductivity is the ability of a material to conduct electricity.

The same goes for neurons. However, instead of a difference in charge between two poles, the difference in charge is across the membrane between the inside and the outside of the neuron (voltage across the membrane = V_m). The resting membrane potential, that is, the difference in charge between the inside and the outside of the neuron when it is not conducting action potentials is approximately –70 millivolts (mV) (Figure 2.14b).

What about conductivity? For the car battery, conductivity depends on how well current flows from its positive pole, through the engine, to the negative pole. We mentioned that shoelaces have no conductivity. Therefore, if you use shoelaces to hook up your car battery, you will not get anywhere. This is because the conductivity of shoelaces is "0." However, if you use electrical wires, the engine will start (provided the battery is not dead). This is because the conductivity of the cables is more than "0."

In neurons, conductivity depends on the number of ion channels that are open. Remember that channels are made of proteins that span the membrane. When many Na^+ channels are open, conductivity for Na^+ is high; when many channels are closed, conductivity for Na^+ is low. When conductivity for Na^+ is high, Na^+ ions flow freely into the neuron through diffusion.

The Equilibrium Potential

As mentioned earlier, K^+ is 20 times more concentrated inside the neuron than it is outside the neuron. This

FIGURE 2.14

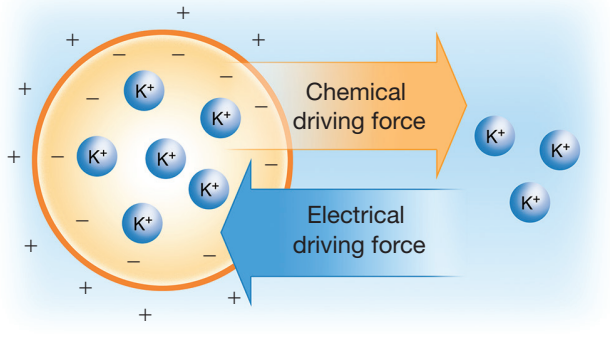
The voltage of a car battery versus that of a neuron at rest. (a) A voltmeter can be used to measure the voltage of a car battery. (b) To measure the voltage across the membrane of a neuron, two thin electrodes are used. One electrode records the electrical charge outside the neuron and the other records the charge inside the neuron. For a neuron at rest, this difference is –70 millivolts (mV).

(a) David Forster / Alamy Stock Photo; (b) Amanda Tomasikiewicz/Body Scientific Intl.

FIGURE 2.15

(a) The chemical driving force of diffusion and the electrical driving force of electrostatic pressure. (b) The equilibrium potential for several ions. The concentration of the ions inside and outside neurons is shown in micromoles per liter of water (a mole is a measure of the weight of molecules in chemistry; it is the molecular weight in grams).

(a)



(b)

ION	CONCENTRATION (mmol/L OF H_2O) INSIDE CELL	OUTSIDE CELL	EQUILIBRIUM POTENTIAL (mV)
Na+	15.0	150.0	+60
K+	150.0	7.5	–90
Cl–	9.0	125.0	–70

Resting membrane potential = –70 mV

(a) Carolina Hrejsa/Body Scientific Intl.

means that, when K^+ channels are open, K^+ will diffuse down its concentration gradient from the inside to the outside of the neuron (Figure 2.15a). However, as K^+ leaves the neuron, the inside of the neuron will become more electronegative relative to the outside of the neuron. This will eventually cause K^+ ions to be drawn back into the neuron due to electrostatic pressure. Remember! Opposites attract.

The V_m at which electrostatic pressure counteracts diffusion is known as the **equilibrium potential** (E_{ion}). For K^+ ions, the V_m at which this occurs is –90 mV or E_{K+} = –90 mV; for Na^+ ions, it is +60 mV (E_{Na+} = +60 mV). Every ion has its own equilibrium potential, as shown in Figure 2.15b. The maintenance of the resting membrane potential is highly dependent on E_{K+} as many K^+ channels are open when the neuron is at rest.

2.3.2 INITIATION OF ACTION POTENTIALS

>> LO 2.3.2 Explain how action potentials are initiated.

Key Terms

- **Depolarization:** To reduce polarity (i.e., to make less negative); the inside of the neuron becomes less electrically negative relative to the outside.
- **Activation threshold**: The minimal amount of depolarization that must occur for an

FIGURE 2.16

The phases of the action potential.

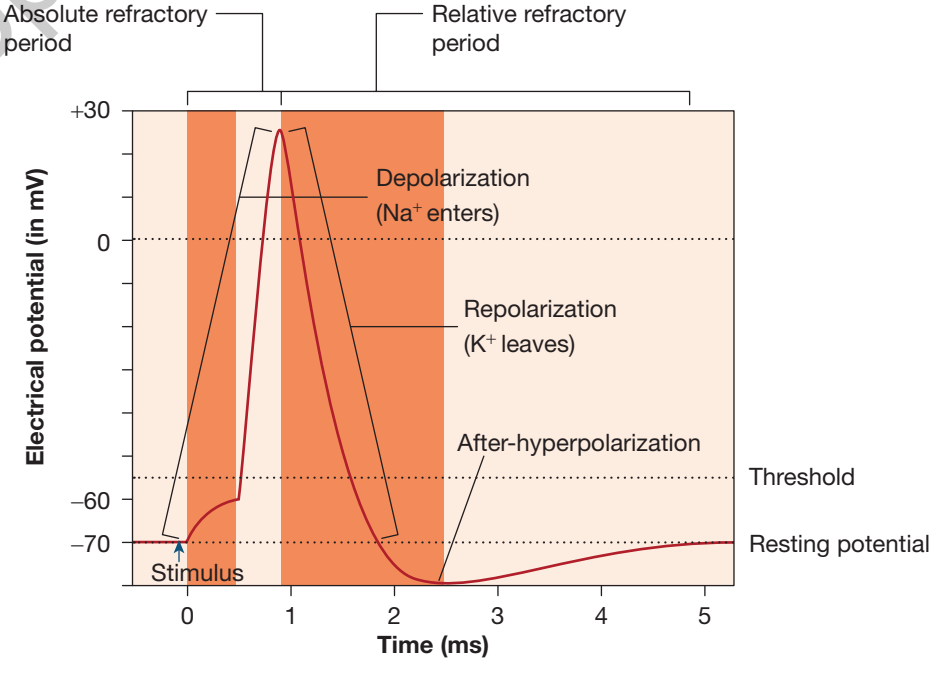
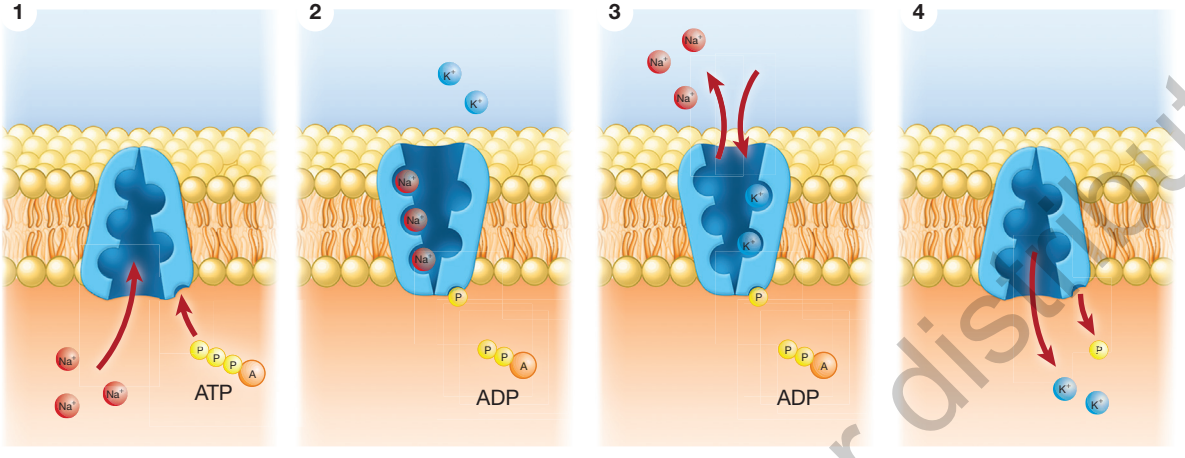


FIGURE 2.17

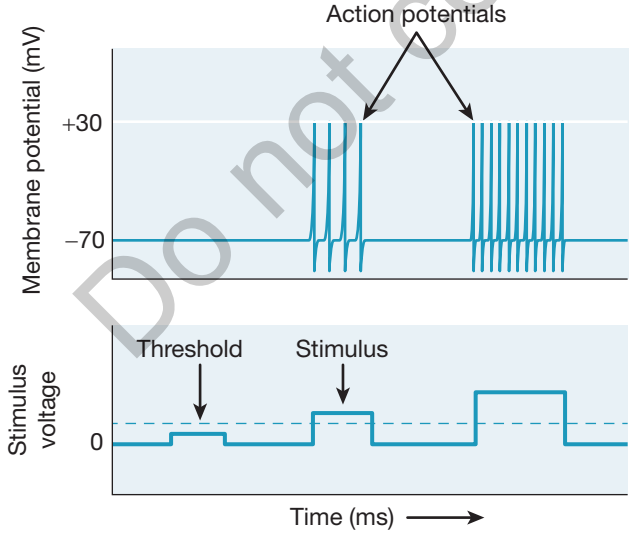
The sodium-potassium pump. (1) ATP powers the pump by giving up one of its phosphate molecules, becoming ADP. (2) Three Na^+ ions are sequestered by the pump. (3) The Na^+ ions are transferred out of the neuron and two K^+ ions are sequestered by the pump. (4) The K^+ ions are transferred to the inside of the neuron.



Carolina Hrejsa/Body Scientific Intl.

FIGURE 2.18

Current intensity and the frequency of action potentials. As stated in the all-or-none law, current intensity does not result in an action potential that reaches a higher voltage (+30 mV) once it has crossed the threshold. Instead, stimulus intensity is related to the frequency of action potentials.



Carolina Hrejsa/Body Scientific Intl.

action potential to be initiated, which is about −55 mV.

- **Absolute refractory period:** The voltage at which further depolarization of the neuron is impossible and another action potential cannot be initiated in that neuron.
- **Relative refractory period:** The period when initiation of another action potential is possible but is difficult to induce.
- **All-or-none law:** The fact that more stimulation than is necessary for the neuron to be depolarized to threshold will not result in a stronger action potential.

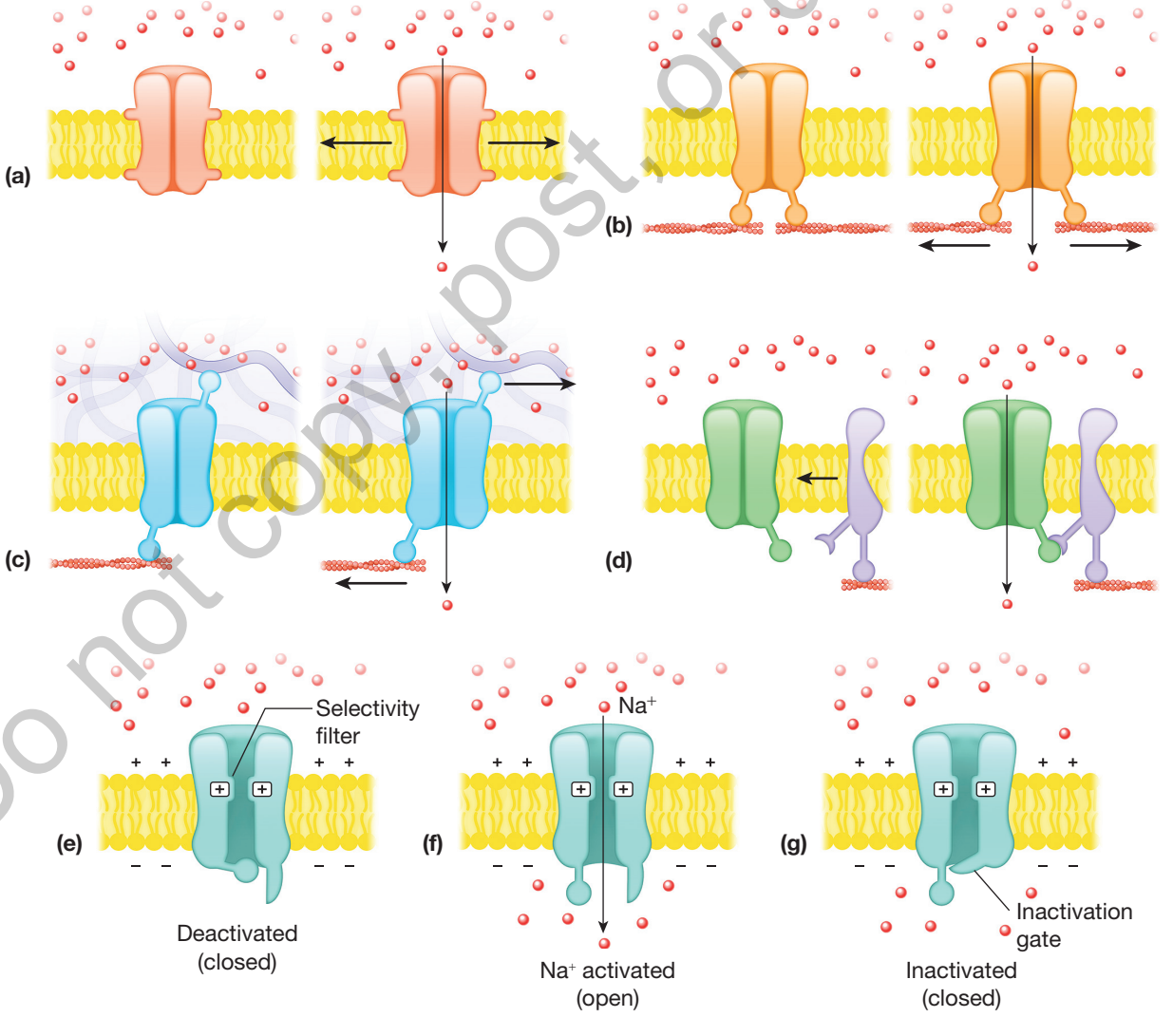
We are finally ready to put together all that you have learned so that you can understand how an action potential is generated. A stimulus such as pressure on the skin is felt because it causes Na^+ channels to open, resulting in action potentials moving up your arm, through your spinal cord, and to your brain. Action potentials are initiated because the opening of these channels increases conductivity for Na^+. Since Na^+ is more concentrated on the outside of the neuron, this causes Na^+ to flow down its concentration gradient and to enter the neuron by the force of diffusion. The entry of Na^+ into the neuron causes the membrane to undergo **depolarization**, which means that the inside of the neuron becomes less electrically negative relative to the outside. Depolarization of the membrane

causes other Na^+ channels to open. This is associated with the rising phase of the action potential (Figure 2.16). However, an action potential will be generated only if this depolarization crosses what is known as the **activation threshold**. The activation threshold, which refers to the minimal amount of depolarization that must occur for an action potential to be initiated, is about −55 mV.

Once the depolarization of the membrane crosses the activation threshold, it continues well past the point where $V_m = 0$ mV. This is referred to as the overshoot. When V_m reaches approximately +30 mV, K^+

FIGURE 2.19

Stretch-activated channels can be opened (a) by the stretch of the cell membrane itself, (b) by the displacement of cytoskeletal elements, or (c–d) by interacting with proteins inside and outside the neuron, which can sense deformation (modified from Del Valle et al., 2012). (e) A deactivated voltage-gated Na^+ channel. Ion channels have a selectivity filter, which makes them permeable only to certain ions (in this case, Na^+ ions). Voltage-gated channels also have voltage sensors (white rectangles with plus signs). (f) Depolarization of the membrane (for example, from resting membrane potential to the threshold) is detected by the voltage sensors, causing the channel to open, and Na^+ enters the neuron. (g) An inactivation gate then closes the channels until the channel is once again deactivated.



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channels open and K^+ ions flow down their concentration gradient to the outside of the neuron. At about the same time, Na^+ channels close and Na^+ can no longer enter the neuron. The outward movement of K^+ causes the voltage of the neuron to repolarize (to become more negative).

Because Na^+ channels are quickly inactivated after the initiation of an action potential, another action potential cannot be generated in the same neuron for a period of about 1 millisecond (ms). This is called the **absolute refractory period**. With the exit of K^+, voltage across the membrane of the neuron drops drastically, toward the resting membrane potential and beyond. This is the falling phase of the action potential, which is associated with repolarization.

The point at which voltage across the membrane is more negative than the resting membrane potential (–70 mV) is called undershoot, also known as after-hyperpolarization. During the period that covers repolarization and after-hyperpolarization, initiation of another action potential is possible, but it is difficult to induce. This is called the **relative refractory period**.

We are now confronted with a problem. There is a reversal of the concentration gradients for Na^+ and K^+. That is, there is now a greater concentration of K^+ ions on the outside of the neuron than there is on the inside of the neuron and a greater concentration of Na^+ ions on the inside than there is on the outside. The original concentration gradients must quickly be restored because the initiation of an action potential depends on the original ratios of Na^+ and K^+ ions with respect to the inside and the outside of the neuron. Restoration of the original concentration gradients is achieved by sodium-potassium pumps (Figure 2.17). Contrary to the forces of diffusion and electrostatic pressure, this is an active process that requires energy in the form of adenosine triphosphate (ATP), the energy currency of cells. For each molecule of ATP that is broken down into adenosine diphosphate (ADP), the sodium-potassium pump transfers three Na^+ ions out of the neuron and two K^+ ions back into the neuron.

Once the depolarization of the membrane crosses the activation threshold, all action potentials are of the same amplitude. That is, there is no such thing as a stronger or weaker action potential. Either a neuron fires an action potential or it does not. This is referred to as the **all-or-none law**. However, an intense stimulus, such as a punch on the arm versus a gentle stroke, will result in a higher frequency of action potentials. Therefore, the intensity of a stimulus is signaled not by the amplitude of action potentials but by their frequency (Figure 2.18).

You have learned how the entry of Na^+ through specialized channels triggers the initiation of action potentials. However, not much was said about the nature of these channels. As mentioned earlier, some channels open in response to mechanical deformations of the skin. These are known as stretch-gated or mechanosensitive channels, which mediate the sense of touch, discussed in Chapter 7. Others open or close in response to a change in voltage across the neuronal membrane. These are referred to as voltage-gated ion channels. These channels open or close in response to changes in voltage across the neuronal membrane. For example, you learned that Na^+ and K^+ channels open or close during the different phases of an action potential. These are referred to as voltage-gated Na^+ and voltage-gated K^+ channels. Other channels open through interacting with specific neurotransmitters. These are known as neurotransmitter-gated channels and are discussed in Chapter 3. Figure 2.19 illustrates how different types of stretch-activated and voltage-gated channels function.

2.3.3 PROPAGATION OF ACTION POTENTIALS

>> LO 2.3.3 Explain how action potentials are propagated down the axons of neurons.

Key Terms

- **Orthodromic conduction:** Movement of an action potential from the soma to the axon terminal.
- **Antidromic conduction:** Movement of an action potential toward the cell body.
- **Saltatory conduction:** Propagation of an action potential down an axon by jumping from one node of Ranvier to another.
- **Multiple sclerosis:** An autoimmune disease in which the myelin sheath is destroyed.

Figure 2.20 shows how an action potential is propagated down the axon of a neuron from the point of its initiation. As you already know, the entry of Na^+ ions through its channels causes the depolarization of the neuronal membrane. In addition, the Na^+ ions that have just entered the neuron diffuse down the axon away from the channel through which they entered. This causes the depolarization of the patch of membrane ahead of the channel, which triggers the opening of voltage-gated Na^+ channels. In this way, the action potential is continuously regenerated down the axon until it gets to the axon terminals. Depolarization of the axon terminal triggers the opening of voltage-gated Ca^{2+} channels. The entry of Ca^{2+} into the axon terminal triggers the release of a neurotransmitter into the synaptic cleft, which stimulates or inhibits

FIGURE 2.20

Propagation of an action potential. Following their entry into the neuron, Na^+ ions diffuse in both directions within the axon. This is followed by the exit of K^+ ions and the diffusion of Na^+ down the axon, depolarizing the patch of membrane ahead of where it initially entered, which in turn causes voltage-gated Na^+ channels to open. Another action potential is thus initiated.

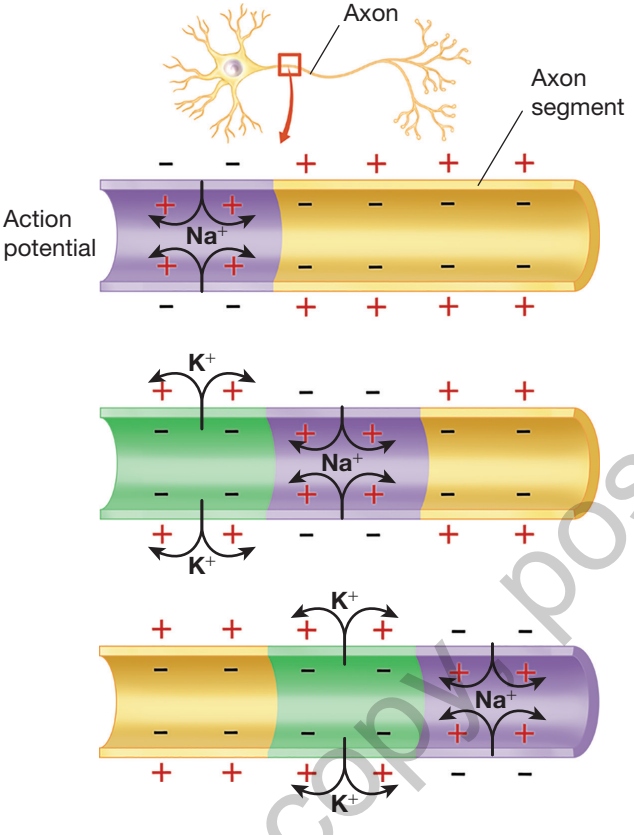

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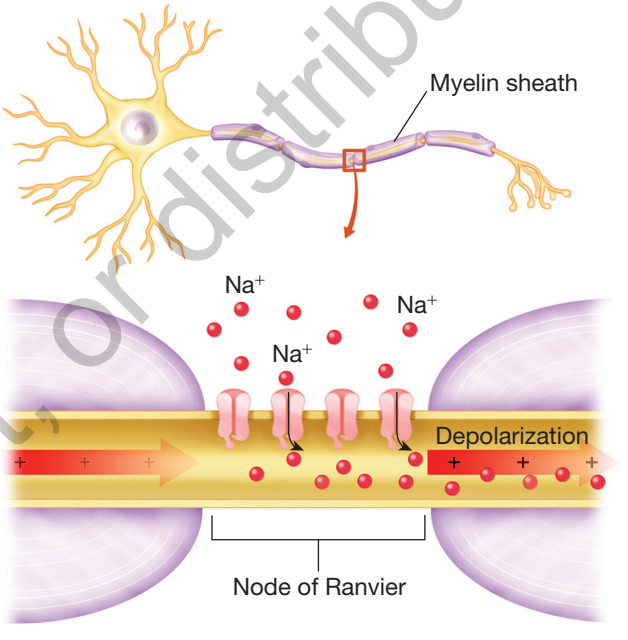
FIGURE 2.21

Saltatory conduction. The myelin sheath is not continuous throughout the axon. It is interrupted by the nodes of Ranvier. Many voltage-gated Na^+ channels are present at the nodes of Ranvier, which permits the regeneration of action potentials. The depolarization of the membrane by the entry of Na^+ ions quickly spreads through the insulated part of the axon to again be regenerated at the following node.



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the neuron or any other target cell the neuron is communicating with, a process discussed in Chapter 3.

Action potentials move through the axon in only one direction, from soma to the axon terminals. This is known as **orthodromic conduction**. Although Na^+ ions diffuse in both directions after entering the neuron, the patch of membrane before the point of entry is still in the absolute refractory period, during which no new action potential can be generated. **Antidromic conduction** refers to an action potential moving in the opposite direction, toward the cell body. However, this does not normally occur in neurons and can be achieved only in the laboratory.

The propagation of an action potential is facilitated by the myelin sheath, which insulates axons. One often-cited analogy for the insulation of axons provided by myelin is that of tape around a leaky garden hose. Without myelin, much of the current, flowing down the axon, escapes through the membrane, like water escapes through holes in a leaky garden hose. A break in the myelin sheath occurs at regular intervals called nodes of Ranvier, as mentioned earlier. At these intervals, a concentration of Na^+ channels can be found, where the action potential is regenerated. Depolarization of the membrane speeds down the covered part of the axon until the next node, to again be regenerated, a process called **saltatory conduction**, illustrated in Figure 2.21. In a devastating disease called **multiple sclerosis**, the myelin sheath is recognized as being foreign by the immune system and is progressively destroyed.

MODULE SUMMARY

The neuronal membrane is a phospholipid bilayer that keeps water and other molecules either on the outside or the inside of the neuron. The neuronal membrane has proteins that form channels that let specific ions in and out of the neuron. Two forces are at play in the exchange of ions across the neuronal membrane: diffusion and electrostatic pressure. The neuron at rest maintains a certain voltage (–70 mV). This voltage is called the resting membrane potential. Voltage is the difference in charge between the inside and the outside of the neuron.

Neurons communicate through generating electrical current in what are known as action potentials. Action potentials result from the movement of Na^+ and K^+ in and out of neurons. When channels selective for Na^+ open, Na^+ diffuses into the neuron due to its higher concentration on the outside relative to the inside of the neuron. This causes the membrane of the neuron to depolarize. This change in voltage causes Na^+ channels to close and K^+ channels to open. This causes K^+ to diffuse out of the neuron due to its higher concentration on the inside of the neuron relative to the outside, resulting in the repolarization of the neuron. This is followed by a period of hyperpolarization when the membrane voltage is below that of the resting membrane potential. The restoration of the initial relative concentrations of Na^+ and K^+ on the outside and inside of the neuron is performed by sodium-potassium pumps. Once a neuron reaches the threshold of voltage change during the depolarization of its membrane, it will generate an action potential. Every action potential is of equal intensity. This is known as the all-or-none law. The absolute refractory period refers to a period of 1 ms during which a new action potential cannot be generated. During the relative refractory period, which covers the periods of repolarization and after-hyperpolarization, a new action potential can be generated but is more difficult to induce.

Channels can be opened in a variety of ways. They can be stretch activated, voltage gated, or neurotransmitter gated. Depolarization of the axon terminals triggers the opening of voltage-gated Ca^{2+} channels. The entry of Ca^{2+} into the axon terminals triggers the release of neurotransmitters. These neurotransmitters then bind to specialized receptors on the postsynaptic neuron. Action potentials can travel only in the direction of the soma to the axon terminals. This is known as orthodromic conduction. Conduction in the opposite direction, from axon terminals to the soma, is known as antidromic conduction and can be achieved only in the laboratory. Myelin—the fatty tissue produced by oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system—speeds up the conduction of nerve impulses through saltatory conduction. Multiple sclerosis is an autoimmune disease in which the myelin sheath that surrounds axons is destroyed.

TEST YOURSELF

2.3.1 What are the forces of diffusion and hydrostatic pressure?

2.3.2 Explain how an action potential is generated, and then name and describe each phase of an action potential.

2.3.3 Describe and explain how action potentials are propagated down the axon of a neuron. Make sure to include the role played by the myelin sheath.

2.4 Glia

Module Contents

Learning Objectives

2.4.1 Describe the initial discovery of glia and the role initially assigned to them.

2.4.2 Explain the functions of the different types of glia.

2.4.1 PUTTING GLIA INTO CONTEXT

>> LO 2.4.1 Describe the initial discovery of glia and the role initially assigned to them.

Key Terms

- ***Nervenkitt*:** German word for "nerve cement"; used by Rudolf Virchow to describe the role of glia.
- **Migration:** The process during which young neurons make their way to the superficial layers of the cortex.

So far you have learned about neurons and how they transmit information in the form of action potentials. However, as mentioned at the beginning of the chapter,

neurons are not the only cells in the nervous system. The brain, with its approximately 86 billion neurons, contains just about as many glia (Azevedo et al., 2009).

The term *glia* was coined in 1858 by biologist Rudolf Virchow (1821–1902). *Glia* is Greek for "glue." Virchow chose this term for the non-neuronal cells of the nervous system because of his belief that they acted as "nerve cement" (German, ***nervenkitt***), lying between neurons and holding them together.

Today, we know that glia play many roles in the functioning of the nervous system. For example, depending on their type, they can clean up damaged tissue, cover axons with myelin, participate in neurotransmission, associate themselves with blood vessels to isolate the brain from potential toxins, and guide the **migration** of neurons to their proper brain area during development. The diversity of glia was first recognized in the 1920s.

2.4.2 THE FUNCTIONS OF GLIA

>> LO 2.4.2 Explain the functions of the different types of glia.

Key Terms

- **Phagocytosis:** The engulfing of particles by the membrane of a cell.
- **Apoptosis:** Organized cell death that results from cellular injury.
- **Phosphatidylserine:** A chemical marker that appears on dying cells, marking them for engulfment by microglia.
- **Lysosome:** An organelle that contains digestive enzymes.
- **Neuroplasticity:** The brain's ability to change with experience.

Microglia

Microglia are small in size, as their name suggests. They are activated when damage to nervous tissue occurs. For example, they play an important role in cleaning up damaged tissue and cell debris following a stroke, through the process of **phagocytosis** (*phago-* comes from the Greek word *phagein*, meaning "to devour") (Figure 2.22). A stroke occurs when an artery that brings blood up into the brain is clogged or ruptured. This causes some neurons to die by **apoptosis**, which is a form of organized cell death, because of a lack of oxygen and nutrients carried by the blood.

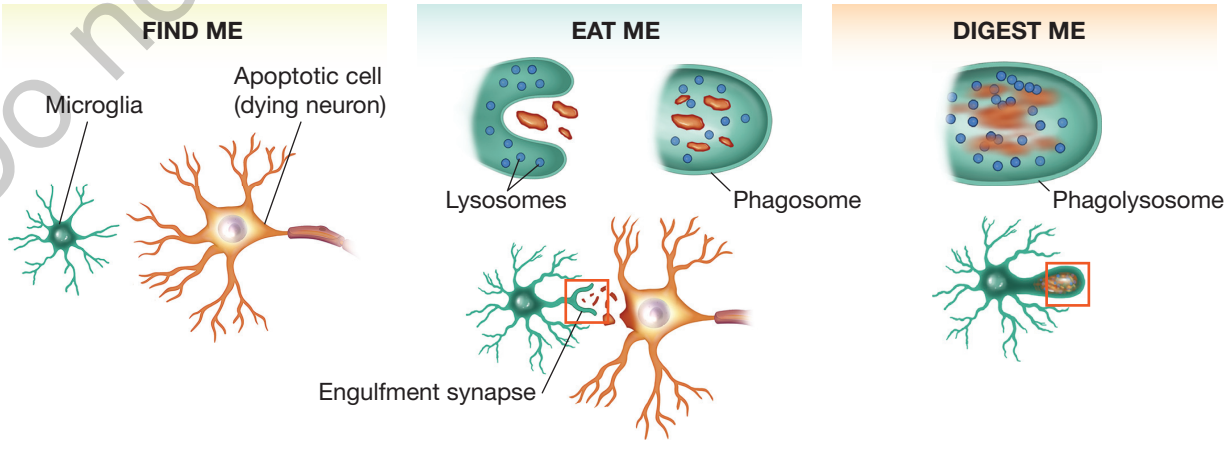
As a cell dies, it sends a chemical signal, which permits microglia to find it. This has been referred to as the "find me" phase. Another marker, consisting of a phospholipid (**phosphatidylserine**) that appears on the apoptotic cell surface, triggers the microglia to engulf the apoptotic cell. This has been referred to as the "eat me" phase. **Lysosomes**, which contain digestive enzymes, are drawn toward the apoptotic cell now sequestered in a vacuole (compartment) called a phagosome. The apoptotic cell is then digested within a phagolysosome, which is a phagosome that contains a lysosome. This has been referred to as the "digest me" phase (Brown & Neher, 2014; Ravichandran, 2010; Sierra, Abiega, Shahraz, & Neumann, 2013).

Macroglia

Macroglia are subdivided into many types. These are typically larger cells. Some of them are found

FIGURE 2.22

The three phases of phagocytosis: find me, eat me, and digest me.



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exclusively in the central nervous system and others in the peripheral nervous system. These include astrocytes, radial glia, oligodendrocytes, and Schwann cells.

Astrocytes. Astrocytes clear increasing levels of K^+ from the extracellular fluid due to nearby neurotransmission (remember that K^+ leaves the neuron during action potentials). This action is made possible due to the high permeability of astrocytes to K^+ ions. The K^+ that flowed inside the astrocyte is then spread out to more distant areas. This process is referred to as K^+ spatial buffering (Kofuji & Newman, 2004). Astrocytes were also found to play an important role in cleansing the brain of bacteria, cellular debris, and toxins (Iliff et al., 2012). In addition, astrocytes are an important part of the blood-brain barrier (discussed in Chapter 4), which keeps potentially dangerous molecules from entering the brain.

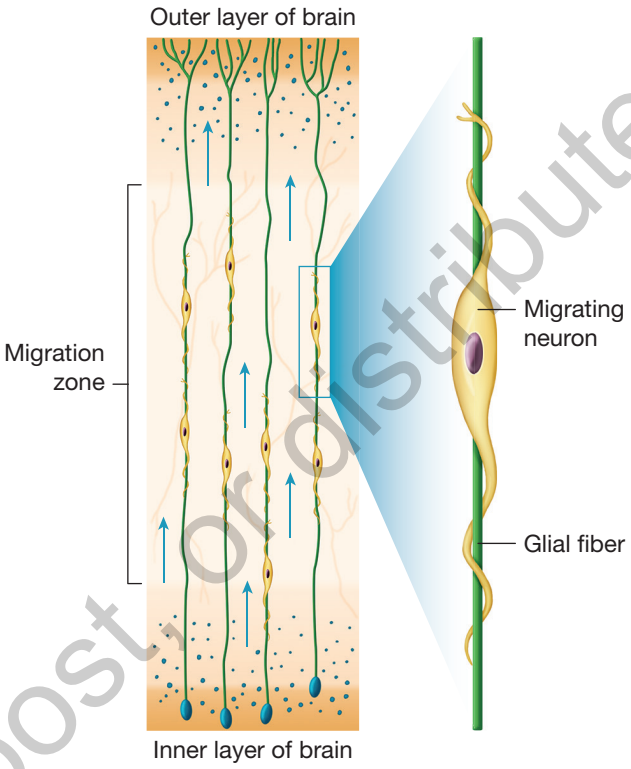
We also know that astrocytes play an active role in neurotransmission and neuroplasticity. **Neuroplasticity** refers to the brain's ability to change with experience, such as during learning (a topic covered in detail in Chapter 12). An example of neuroplasticity is the strengthening of highly active synapses between neurons. Astrocytes can sense the release of neurotransmitters at active synapses, leading them to increase their intracellular levels of Ca^{2+}. This increase in Ca^{2+} levels causes astrocytes to release a neurotransmitter (also known as gliotransmitter) into the synapse, which in turn increases the amount of neurotransmitter released by the presynaptic neuron (N. J. Allen, 2014; Santello, Cali, & Bezzi, 2012).

Radial Glia. Radial glia play a crucial role during development of the central nervous system, more precisely during neuron migration, the process during which young neurons make their way to the superficial layers of the cortex (Rakic, 1972; Zheng & Yuan, 2008). Radial glia act as scaffolds for newly created neurons to follow. Figure 2.23 shows a young neuron climbing up the appendage of a radial glia The role played by radial glia in neurodevelopment is discussed further in Chapter 5.

Oligodendrocytes and Schwann Cells. Oligodendrocytes produce and wrap the axons of neurons with myelin, which insulates axons in the central nervous system. The myelination process begins when an oligodendrocyte extends an appendage to an axon. Cytoplasm flows from the oligodendrocyte toward the axon to produce the myelin lamellae (Figure 2.24). Schwann cells are the glia that produce myelin for neurons of the peripheral nervous system. The process by which Schwann cells myelinate neurons in the peripheral nervous system differs from that of oligodendrocytes in the central nervous system. For example, a Schwann cell can myelinate only a single axon, whereas a single oligodendrocyte can myelinate up to 60 different axons.

FIGURE 2.23

Radial glia serve as scaffolds for migrating newly created neurons to the superficial layers of the cortex.



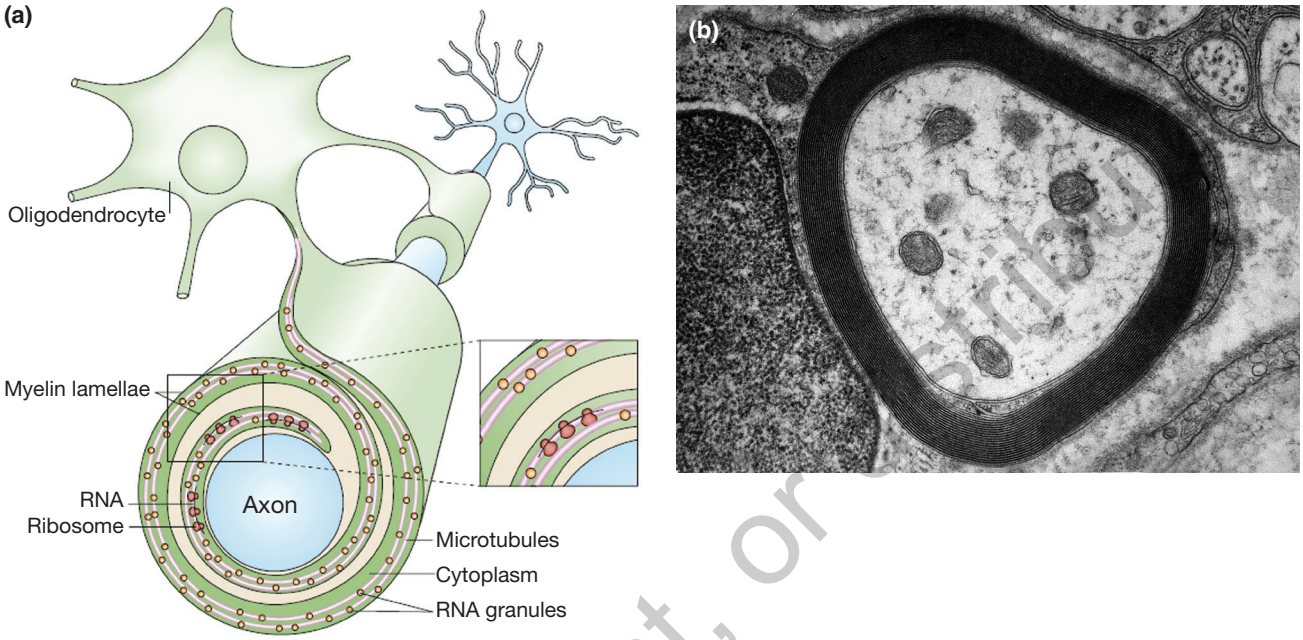
Adapted from illustration by Lydia Kibiuk, © 1995.

MODULE SUMMARY

Glia is the Greek word for "glue." The term was coined by Rudolf Virchow to reflect his belief that glia acted as nerve cement that kept neurons together. In the 1920s, it was discovered that neurons come in many different types: microglia, astrocytes, and oligodendrocytes and Schwann cells. We now know that the role of glia is much more extensive than previously thought. Microglia clean up dead tissue and cellular debris through the process of phagocytosis. Astrocytes regulate the chemical environment of neurons and participate in the strengthening of synapses between neurons. Radial glia guide the migration of neurons to the superficial layers of the cortex during development. Oligodendrocytes and Schwann cells produce the myelin that insulates the axons of neurons in the central nervous system and peripheral nervous system, respectively.

FIGURE 2.24

Oligodendrocytes and the myelin sheath. (a) An oligodendrocyte projects its appendages onto the axon of a neuron. Cytoplasm is excreted by the oligodendrocyte, producing the myelin lamellae. (b) Cross-section of an axon showing its myelin sheath.



(a) Sherman, D. and P. Brophy. (2005). Mechanisms of axon ensheathment and myelin growth. *Nature Reviews Neuroscience 6*(9): 683–690. With permission from Springer Nature; (b) Scott Camazine / Alamy Stock Photo

TEST YOURSELF

2.4.1 Describe the roles initially assigned to glia.

2.4.2 Explain the functions of the different types of glia.

APPLICATIONS

Optogenetics

Neuroscientists have been manipulating the flow of action potentials in neurons for decades. This has traditionally been done through the electrical stimulation of neurons or the use of drugs that can increase or decrease the flow of ions in and out of neurons.

Although these methods have proved to be extremely useful, neither can be used to target restricted sets of neurons. This kind of specificity has been achieved through optogenetics. Optogenetics is a method in which pulses of light are used to control the flow of action potentials within specific populations of neurons.

It has been known since the 1960s that certain microorganisms such as some algae and bacteria produce light-responsive proteins, called opsins, that regulate the electric charge across the membranes

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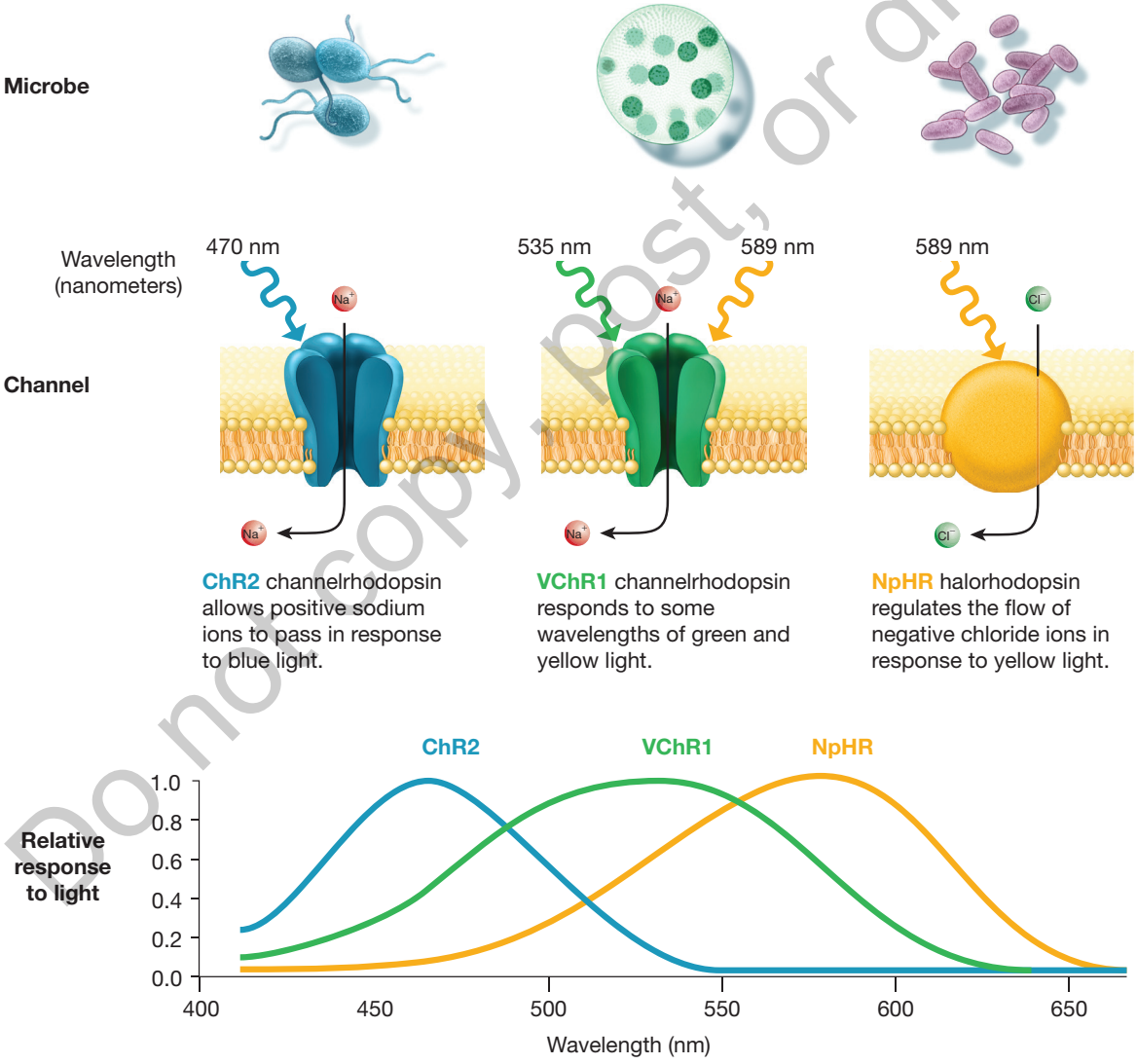
of their cells. In the early 2000s, researchers found that the algae *Chlamydomonas* and *Volvox carteri* have light-activated sodium channels, now known as channelrhodopsin-2 (ChR2) and channelrhodopsin-1 (VChR1), respectively. It was also found that the bacterium *Natronomonas pharaonis* has light-activated chloride pumps (similar to sodium-potassium pumps). These chloride pumps are activated through the opsin called halorhodopsin (NpHR).

Action potentials are generated through the depolarization created by the flow of sodium ions into a neuron. In contrast, the flow of chloride ions into a neuron causes it to hyperpolarize, making it less likely

FIGURE 2.25

Top: Some of the microorganisms from which opsins are obtained. Middle: Different opsins are sensitive to different wavelengths of light, resulting in the opening of sodium (Na^+) channels or the activation of chloride (Cl^-) pumps. Bottom: The relative response of each of the opsins to different wavelengths of light.



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to generate action potentials. The stage was set to figure out a way to use this knowledge to turn neurons on and off at will.

How Did They Do It?

Researchers identified the sequence of genes that produces light-activated channels. The next step was to figure out a way to incorporate these channels into the neurons of living animals. Neuroscientist Karl Deisseroth at Stanford University achieved this with the use of transfection. Transfection is a method by which genetic material from one organism can be incorporated into the cells of another organism. To do this, the gene responsible for light-activated channels is spliced into the genes of a harmless virus, known as a viral vector. The virus is then injected into the neurons of an animal, which will now produce its own light-activated channels.

As illustrated in Figure 2.25, each channel is mostly activated with lights of a different wavelength. When activated, ChR2 and VChR1 channels increase the flow of sodium ions into neurons, leading to their depolarization. NpHR-activated pumps increase the flow of chloride ions into the neuron, leading to their hyperpolarization. Once the genes coding for the light-activated channels and pumps are expressed, light of different wavelengths can be delivered to the brain with a fiber-optic cable.