The future of clinical neurology and psychiatry is intimately tied to that of molecular neural science.

Background Basics
- Reflex pathways
- Organelles
- Neurohormones
- Gated channels
- Matrix
- Gap junctions
- Positive feedback
- Phagocytosis
- Antagonistic control
- Resting membrane potential
- Exocytosis
- Equilibrium potential
- Bioelectricity

Neurons: Cellular and Network Properties

Organization of the Nervous System

Cells of the Nervous System
- Neurons Carry Electrical Signals
- Establishing Synapses Depends on Chemical Signals
- Glial Cells Provide Support for Neurons
- Can Stem Cells Repair Damaged Neurons?

Electrical Signals in Neurons
- The Nernst Equation Predicts Membrane Potential for a Single Ion
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- Postsynaptic Responses May Be Slow or Fast
- Neural Pathways May Involve Many Neurons
- Synaptic Activity Can Be Modified
- Long-Term Potentiation Alters Synapses
- Disorders of Synaptic Transmission Are Responsible for Many Diseases
In an eerie scene from a science fiction movie, white-coated technicians move quietly through a room filled with bubbling cylindrical fish tanks. As the camera zooms in on one tank, no fish can be seen darting through aquatic plants. The lone occupant of the tank is a gray mass with a convoluted surface like a walnut and a long tail that appears to be edged with beads. Floating off the beads are hundreds of fine fibers, waving softly as the oxygen bubbles weave through them. This is no sea creature... It is a brain and spinal cord, removed from its original owner and awaiting transplantation into another body. Can this be real? Is this scenario possible? Or is it just the creation of an imaginative movie screenwriter?

The brain is regarded as the seat of the soul, the mysterious source of those traits that we think of as setting humans apart from other animals. The brain and spinal cord are also integrating centers for homeostasis, movement, and many other body functions. They are the control center of the nervous system, a network of billions or trillions of nerve cells linked together in a highly organized manner to form the rapid control system of the body.

Nerve cells, or neurons, carry electrical signals rapidly and, in some cases, over long distances. They are uniquely shaped cells, and most have long, thin extensions, or processes, that can extend up to a meter in length. In most pathways, neurons release chemical signals, called neurotransmitters, into the extracellular fluid to communicate with neighboring cells. In a few pathways, neurons are linked by gap junctions, allowing electrical signals to pass directly from cell to cell.

Using electrical signals to release chemicals from a cell is not unique to neurons. For example, pancreatic beta cells generate an electrical signal to initiate exocytosis of insulin-containing storage vesicles. Single-celled protozoa and plants also employ electrical signaling mechanisms, in many cases using the same types of ion channels as vertebrates do.

Scientists sequencing ion channel proteins have found that many of these channel proteins have been highly conserved during evolution, indicating their fundamental importance.

Although electrical signaling is universal, sophisticated neural networks are unique to animal nervous systems. Reflex pathways in the nervous system do not necessarily follow a straight line from one neuron to the next. One neuron may influence multiple neurons, or many neurons may affect the function of a single neuron. The intricacy of neural networks and their neuronal components underlies the emergent properties of the nervous system. Emergent properties are complex processes, such as consciousness, intelligence, and emotion, that cannot be predicted from what we know about the properties of individual nerve cells and their specific connections. The search to explain emergent properties makes neuroscience one of the most active research areas in physiology today.

Neuroscience, like many other areas of science, has its own specialized language. In many instances, multiple terms describe a single structure or function, which potentially can lead to confusion. Table 8.1 lists some neuroscience terms used in this course, along with their common synonyms, which you may encounter in other publications.

### Synonyms in Neuroscience

<table>
<thead>
<tr>
<th>Term Used in This Book</th>
<th>Synonym(s)</th>
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<tbody>
<tr>
<td>Action potential</td>
<td>AP, spike, nerve impulse, conduction signal</td>
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<tr>
<td>Autonomic nervous system</td>
<td>Visceral nervous system</td>
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<tr>
<td>Axon</td>
<td>Nerve fiber</td>
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<tr>
<td>Axonal transport</td>
<td>Axoplasmic flow</td>
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<tr>
<td>Axon terminal</td>
<td>Synaptic knob, synaptic bouton, presynaptic terminal</td>
</tr>
<tr>
<td>Axoplasm</td>
<td>Cytoplasm of an axon</td>
</tr>
<tr>
<td>Cell body</td>
<td>Cell soma, nerve cell body</td>
</tr>
<tr>
<td>Cell membrane of an axon</td>
<td>Axolemma</td>
</tr>
<tr>
<td>Glial cells</td>
<td>Neuroglia, glia</td>
</tr>
<tr>
<td>Interneuron</td>
<td>Association neuron</td>
</tr>
<tr>
<td>Rough endoplasmic reticulum</td>
<td>Nissl substance, Nissl body</td>
</tr>
<tr>
<td>Sensory neuron</td>
<td>Afferent neuron, afferent</td>
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</table>
Neurons: Cellular and Network Properties

Organization of the Nervous System

The nervous system can be divided into two parts (Fig. 8.1). The central nervous system (CNS) consists of the brain and the spinal cord. The peripheral nervous system (PNS) consists of sensory (afferent) neurons and efferent neurons. Information flow through the nervous system follows the basic pattern of a reflex: stimulus → sensor → input signal → integrating center → output signal → target → response.

Sensory receptors throughout the body continuously monitor conditions in the internal and external environments. These sensors send information along sensory neurons to the CNS, which is the integrating center for neural reflexes. CNS neurons integrate information that arrives from the sensory division of the PNS and determine whether a response is needed.

If a response is needed, the CNS sends output signals that travel through efferent neurons to their targets, which are mostly muscles and glands. Efferent neurons subdivide into the somatic motor division, which controls skeletal muscles, and the autonomic division, which controls smooth and cardiac muscles, exocrine glands, some endocrine glands, and some types of adipose tissue. Terminology used to describe efferent neurons can be confusing. The expression motor neuron is sometimes used to refer to all efferent neurons. However, clinically, the term motor neuron (or motoneuron) is often used to describe somatic motor neurons that control skeletal muscles.

The autonomic division of the PNS is also called the visceral nervous system because it controls contraction and secretion in the various internal organs (viscera, internal organs). Autonomic neurons are further divided into sympathetic and parasympathetic branches which can be distinguished by their anatomical organization and by the chemicals they use to communicate with their target cells. Many internal organs receive innervation from both types of autonomic neurons, and it is common for the two divisions to exert antagonistic control over a single target.

In recent years, a third division of the nervous system has received considerable attention. The enteric nervous system is a network of neurons in the walls of the digestive tract. It is frequently controlled by the autonomic division of the nervous system, but it is also able to function autonomously as its own integrating center. You will learn more about the enteric nervous system when you study the digestive system.

It is important to note that the CNS can initiate activity without sensory input, such as when you decide to text a friend. Also, the CNS need not create any measurable output to the efferent divisions. For example, thinking and dreaming are complex higher-brain functions that can take place totally within the CNS.

RUNNING PROBLEM

Guillain-Barré syndrome is a relatively rare paralytic condition that strikes after a viral infection or an immunization. There is no cure, but usually the paralysis slowly disappears, and lost sensation slowly returns as the body repairs itself. In classic Guillain-Barré, patients can neither feel sensations nor move their muscles.

Q1: Which division(s) of the nervous system may be involved in Guillain-Barré syndrome (GBS)?

Concept Check

Answers: End of Chapter

1. Organize the following terms describing functional types of neurons into a map or outline: afferent, autonomic, brain, central, efferent, enteric, parasympathetic, peripheral, sensory, somatic motor, spinal, sympathetic.

Cells of the Nervous System

The nervous system is composed primarily of two cell types: neurons—the basic signaling units of the nervous system—and support cells known as glial cells (or glia or neuroglia).

Neurons Carry Electrical Signals

The neuron, or nerve cell, is the functional unit of the nervous system. (A functional unit is the smallest structure that can carry out the functions of a system.) Neurons are uniquely shaped cells with long processes that extend outward from the nerve cell body. These processes are usually classified as either dendrites, which receive incoming signals, or axons, which carry outgoing information. The shape, number, and length of axons and dendrites vary from one neuron to the next, but these structures are an essential feature that allows neurons to communicate with one another and with other cells. Neurons may be classified either structurally or functionally (Fig. 8.2).

Structurally, neurons are classified by the number of processes that originate from the cell body. The model neuron that is commonly used to teach how a neuron functions is multipolar, with many dendrites and branched axons (Fig. 8.2e). Multipolar neurons in the CNS look different from multipolar efferent neurons (Fig. 8.2d). In other structural neuron types, the axons and dendrites may be missing or modified. Pseudounipolar neurons have the cell body located off one side of one long process that is called the axon (Fig. 8.2a). (During development, the dendrites fused and became part of the axon.) Bipolar neurons
The Organization of the Nervous System

**THE NERVOUS SYSTEM**

- **The Peripheral Nervous System (PNS)**
  - Sensory division of the PNS sends information to the CNS through afferent (sensory) neurons.
  - Efferent division of the PNS takes information from the CNS to target cells via efferent neurons.

- **The Central Nervous System (CNS)**, which acts as the integrating center

The enteric nervous system can act autonomously or can be controlled by the CNS through the autonomic division of the PNS.

**CENTRAL NERVOUS SYSTEM**

Brain

Spinal cord

**Sensory receptors**

- Signal

**Sensory neurons (afferents)**

- Stimulate

**Spinal cord**

**Efferent neurons**

- Autonomic neurons
  - Sympathetic
  - Parasympathetic
- Somatic motor neurons
- Skeletal muscles

**Neurons of enteric nervous system**

- Stimulate

**Digestive tract**

**Tissue responses**

**KEY**

- Stimulus
- Sensor
- Input signal
- Integrating center
- Output signal
- Target
- Tissue response
### Fig. 8.2 ESSENTIALS

#### Neuron Anatomy

#### Functional Categories

<table>
<thead>
<tr>
<th>Sensory Neurons</th>
<th>Interneurons of CNS</th>
<th>Efferent Neurons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurons for somatic senses</td>
<td>Neurons for smell and vision</td>
<td>Neurons for smell and vision</td>
</tr>
<tr>
<td>Pseudounipolar</td>
<td>Bipolar</td>
<td>Anaxonic</td>
</tr>
<tr>
<td>Neurons for smell and vision</td>
<td>Bipolar neurons have two relatively equal fibers extending off the central cell body.</td>
<td>Anaxonic CNS interneurons have no apparent axon.</td>
</tr>
<tr>
<td>(a) Pseudounipolar neurons have a single process called the axon. During development, the dendrite fused with the axon.</td>
<td>(b) Bipolar neurons have two relatively equal fibers extending off the central cell body.</td>
<td>(c) Anaxonic CNS interneurons have no apparent axon.</td>
</tr>
<tr>
<td>(d) Multipolar CNS interneurons are highly branched but lack long extensions.</td>
<td>(e) A typical multipolar efferent neuron has five to seven dendrites, each branching four to six times. A single long axon may branch several times and end at enlarged axon terminals.</td>
<td></td>
</tr>
</tbody>
</table>

#### Structural Categories

<table>
<thead>
<tr>
<th>Pseudounipolar</th>
<th>Bipolar</th>
<th>Anaxonic</th>
<th>Multipolar</th>
</tr>
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</tbody>
</table>

#### (f) Parts of a Neuron

- Nucleus
- Axon hillock
- Axon (initial segment)
- Myelin sheath
- Postsynaptic neuron
- Postsynaptic axon terminal
- Synaptic cleft
- Postsynaptic dendrite
- Presynaptic axon terminal
- Synapse: The region where an axon terminal communicates with its postsynaptic target cell

**Integration**: Input signal -> Integration -> Output signal
have a single axon and single dendrite coming off the cell body (Fig. 8.2b). *Anaxonic* neurons lack an identifiable axon but have numerous branched dendrites (Fig. 8.2c).

Because physiology is concerned chiefly with function, however, we will classify neurons according to their functions: sensory (afferent) neurons, interneurons, and efferent (somatic motor and autonomic) neurons. Sensory neurons carry information about temperature, pressure, light, and other stimuli from sensory receptors to the CNS. Peripheral sensory neurons are pseudounipolar, with cell bodies located close to the CNS and very long processes that extend out to receptors in the limbs and internal organs. In these sensory neurons, the cell body is out of the direct path of signals passing along the axon (Fig. 8.2a). In contrast, sensory neurons in the nose and eye are much smaller bipolar neurons. Signals that begin at the dendrites travel through the cell body to the axon (Fig. 8.2b).

Neurons that lie entirely within the CNS are known as *interneurons* (short for *interconnecting neurons*). They come in a variety of forms but often have quite complex branching processes that allow them to communicate with many other neurons (Fig. 8.2c, d). Some interneurons are quite small compared to the model neuron.

Efferent neurons, both somatic motor and autonomic, are generally very similar to the neuron in Figure 8.2e. Efferent neurons have enlarged axon terminals. Many autonomic neurons also have enlarged regions along the axon called *varicosities*. Both axon terminals and varicosities store and release neurotransmitter.

The long axons of both afferent and efferent peripheral neurons are bundled together with connective tissue into cord-like fibers called *nerves* that extend from the CNS to the targets of the component neurons. Nerves that carry afferent signals only are called *sensory nerves*, and those that carry efferent signals only are called *motor nerves*. Nerves that carry signals in both directions are *mixed nerves*. Many nerves are large enough to be seen with the naked eye and have been given anatomical names. For example, the *phrenic nerve* runs from the spinal cord to the muscles of the diaphragm.

The Cell Body Is the Control Center The *cell body* (cell soma) of a neuron resembles a typical cell, with a nucleus and all organelles needed to direct cellular activity. An extensive cytoskeleton extends outward into the axon and dendrites. The position of the cell body varies in different types of neurons, but in most neurons the cell body is small, generally making up one-tenth or less of the total cell volume. Despite its small size, the cell body with its nucleus is essential to the well-being of the cell because it contains DNA that is the template for protein synthesis.

Dendrites Receive Incoming Signals Dendrites (*dendron*, tree) are thin, branched processes that receive incoming information from neighboring cells (Fig. 8.2f). Dendrites increase the surface area of a neuron, allowing it to communicate with multiple other neurons. The simplest neurons have only a single dendrite. At the other extreme, neurons in the brain may have multiple dendrites with incredibly complex branching (Fig. 8.2d). A dendrite’s surface area can be expanded even more by the presence of *dendritic spines* that vary from thin spikes to mushroom-shaped knobs (see Fig. 8.25).

The primary function of dendrites in the peripheral nervous system is to receive incoming information and transfer it to an integrating region within the neuron. Within the CNS, dendrite function is more complex. Dendritic spines can function as independent compartments, sending signals back and forth with other neurons in the brain. Many dendritic spines contain polyribosomes and can make their own proteins.

Dendritic spines can change their size and shape in response to input from neighboring cells. Changes in spine morphology are associated with learning and memory as well as with various pathologies, including genetic disorders that cause mental retardation and degenerative diseases such as Alzheimer’s disease. Because of these associations, dendritic spines are a hot topic in neuroscience research.

Axons Carry Outgoing Signals Most peripheral neurons have a single axon that originates from a specialized region of the cell body called the *axon hillock* (Fig. 8.2f). Axons vary in length from more than a meter to only a few micrometers. They often branch sparsely along their length, forming *collaterals* (*col*-, with + *lateral*, something on the side). In our model neuron, each collateral ends in a swelling called an *axon terminal*. The axon terminal contains mitochondria and membrane-bound vesicles filled with *neurocrine* molecules.

The primary function of an axon is to transmit outgoing electrical signals from the integrating center of the neuron to the end of the axon. At the distal end of the axon, the electrical signal is usually translated into a chemical message by secretion of a neurotransmitter, neuromodulator, or neurohormone. Neurons that secrete neurotransmitters and neuromodulators terminate near their target cells, which are usually other neurons, muscles, or glands.

**RUNNING PROBLEM**

In classic Guillain-Barré syndrome, the disease affects both sensory and somatic motor neurons. Dr. McKhann observed that although the Beijing children could not move their muscles, they could feel a pin prick.

**Q2**: Do you think the paralysis found in the Chinese children affected both sensory (afferent) and somatic motor neurons? Why or why not?
The role of motor proteins in axonal transport is similar to their role in muscle contraction and in the movement of chromosomes during cell division.

Fast axonal transport goes in two directions. Forward (or anterograde) transport moves synaptic and secretory vesicles and mitochondria from the cell body to the axon terminal. Backward (or retrograde) transport returns old cellular components from the axon terminal to the cell body for recycling. There is evidence that nerve growth factors and some viruses also reach the cell body by fast retrograde transport.

Establishing Synapses Depends on Chemical Signals

The region where an axon terminal meets its target cell is called a synapse (syn-, together + hapsis, to join). The neuron that delivers a signal to the synapse is known as the presynaptic cell, and the cell that receives the signal is called the postsynaptic cell (Fig. 8.2f). The narrow space between the two cells is called the synaptic cleft. Although illustrations make the synaptic cleft look like an empty gap, it is filled with extracellular matrix whose fibers hold the presynaptic and postsynaptic cells in position.

During embryonic development, how can more than 100 billion neurons in the brain find their correct targets and make synapses among more than 10 times that many glial cells? How can a somatic motor neuron in the spinal cord find the correct...
This “use it or lose it” scenario is most dramatically reflected by the fact that the infant brain is only about one-fourth the size of the adult brain. Further brain growth is due not to an increase in cell number but to an increase in size and number of axons, dendrites, and synapses. This development depends on electrical signaling between sensory pathways, interneurons, and efferent neurons.

Babies who are neglected or deprived of sensory input may experience delayed development (“failure to thrive”) because of the lack of nervous system stimulation. On the other hand, there is no evidence that extra stimulation in infancy enhances intellectual development, despite a popular movement to expose babies to art, music, and foreign languages before they can even walk. Once synapses form, they are not fixed for life. Variations in electrical activity can cause rearrangement of the synaptic connections, a process that continues throughout life. Maintaining synapses is one reason that older adults are urged to keep learning new skills and information.

Glial Cells Provide Support for Neurons

Glial cells (glia, glue) are the unsung heroes of the nervous system, outnumbering neurons by 10–50 to 1. For many years scientists thought that the primary function of glial cells was physical support, and that glial cells had little influence on information processing. That view has changed. Although glial cells do not participate directly in the transmission of electrical signals over long distances, they do communicate with and provide important biochemical support to neurons. The peripheral nervous system has two types of glial cells—Schwann cells and satellite cells—and the CNS has four types: oligodendrocytes, microglia, astrocytes, and ependymal cells (Fig. 8.5a).

Myelin-Forming Glia

Neural tissue secretes very little extracellular matrix, and glial cells provide structural stability to neurons by wrapping around them. Schwann cells in the PNS and oligodendrocytes in the CNS support and insulate axons by forming myelin, a substance composed of multiple concentric layers of phospholipid membrane (Fig. 8.5c). In addition to providing support, the myelin acts as insulation around axons and speeds up their signal transmission.

Myelin forms when the glial cells wrap around an axon, squeezing out the glial cytoplasm so that each wrap becomes two membrane layers (Fig. 8.5d). As an analogy, think of...
Neurons: Cellular and Network Properties

wrapping a deflated balloon tightly around a pencil. Some neurons have as many as 150 wraps (300 membrane layers) in the myelin sheath that surrounds their axons. Gap junctions connect the membrane layers and allow the flow of nutrients and information from layer to layer.

One difference between oligodendrocytes and Schwann cells is the number of axons each cell wraps around. In the CNS, one oligodendrocyte branches and forms myelin around portions of several axons (Fig. 8.5b). In the peripheral nervous system, one Schwann cell associates with one axon.

**Schwann Cells** A single axon may have as many as 500 different Schwann cells along its length. Each Schwann cell wraps around a 1–1.5 mm segment of the axon, leaving tiny gaps, called the nodes of Ranvier, between the myelin-insulated areas (Fig. 8.5c). At each node, a tiny section of axon membrane remains in direct contact with the extracellular fluid. The nodes play an important role in the transmission of electrical signals along the axon.

**Satellite Cells** The second type of PNS glial cell, the satellite cell, is a nonmyelinating Schwann cell (Fig. 8.5a). Satellite cells form supportive capsules around nerve cell bodies located in ganglia. A ganglion (cluster or knot) is a collection of nerve cell bodies found outside the CNS. Ganglia appear as knots or swellings along a nerve. (A cluster of nerve cell bodies inside the CNS, the equivalent of a peripheral ganglion, is called a nucleus (plural, nuclei).)

**Astrocytes** Astrocytes (astron, a star) are highly branched glial cells that by some estimates make up about half of all cells in the brain (Fig. 8.5a, b). They come in several subtypes and form a functional network by communicating with one another through gap junctions. Astrocytes have multiple roles. The terminals of some astrocyte processes are closely associated with synapses, where they take up and release chemicals. Astrocytes also provide neurons with substrates for ATP production, and they help maintain homeostasis in the CNS extracellular fluid by taking up K⁺ and water. Finally, the terminals of some astrocyte processes surround blood vessels and become part of the so-called blood-brain barrier that regulates the movement of materials between blood and extracellular fluid.

**Microglia** The glial cells known as microglia are specialized immune cells that reside permanently in the CNS (Fig. 8.5a, b). When activated, they remove damaged cells and foreign invaders. However, it now appears that microglia are not always helpful. Activated microglia sometimes release damaging reactive oxygen species (ROS) that form free radicals. The oxidative stress caused by ROS is believed to contribute to neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig’s disease).

**Ependymal Cells** The final class of glial cells is the ependymal cells, specialized cells that create a selectively permeable epithelial layer, the ependyma, that separates the fluid compartments of the CNS (Fig. 8.5a, b). The ependyma is one source of neural stem cells, immature cells that can differentiate into neurons and glial cells.

All glial cells communicate with neurons and with one another primarily through chemical signals. Glial-derived growth and trophic (nourishing) factors help maintain neurons and guide them during repair and development. Glial cells in turn respond to neurotransmitters and neuromodulators secreted by neurons. Glial cell function is an active area of neuroscience research, and scientists are still exploring the roles these important cells play in the nervous system.

**Can Stem Cells Repair Damaged Neurons?**

Neurons grow when we are young, but what happens when adult neurons are injured? The responses of mature neurons to injury are similar in many ways to the growth of neurons during development. Both processes rely on a combination of chemical and electrical signals.

When a neuron is damaged, if the cell body dies, the entire neuron dies. If the cell body is intact and only the axon is severed, the cell body and attached segment of axon survive (Fig. 8.6). The section of axon separated from the cell body usually degenerates slowly and dies because axons lack the cellular organelles to make essential proteins.

What are the cellular events that follow damage to a neuron? First, the axon cytoplasm leaks out at the injury site until membrane is recruited to seal the opening. The segment of axon still attached to the cell body swells as organelles and filaments brought in by axonal transport accumulate. Schwann cells near the injury site send chemical signals to the cell body to tell it that an injury has occurred.

In the distal segment of the axon, synaptic transmission ceases almost immediately. The axon, deprived of its protein source, slowly begins to collapse. The myelin sheath around the distal axon also begins to unravel. Scavenger microglia or...
Glial Cells

(a) Glial Cells and Their Functions

**Central Nervous System**
- Ependymal cells
- Astrocytes
- Microglia (modified immune cells)
- Oligodendrocytes

**Peripheral Nervous System**
- Schwann cells
- Satellite cells

- Myelin sheaths

**Functions**
- create Barriers between compartments
- Source of neural stem cells
- K⁺, water, neurotransmitters
- Neurotrophic factors
- Blood-brain barrier
- Substrates for ATP production
- act as Scavengers
- Neurotrophic factors
- Support cell bodies

(b) Glial Cells of the Central Nervous System
phagocytes ingest and clear away the debris. This process may take a month or longer.

If the severed axon belongs to a somatic motor neuron, death of the distal (distant) axon results in permanent paralysis of the skeletal muscles innervated by the neuron. (The term innervated means “controlled by a neuron.”) If the damaged neuron is a sensory neuron, the person may experience loss of sensation (numbness or tingling) in the region previously innervated by the neuron.

Under some conditions, axons in the peripheral nervous system can regenerate and re-establish their synaptic connections. Schwann cells secrete neurotrophic factors that keep the cell body alive and stimulate regrowth of the axon. The growing tip of a regenerating axon behaves much like the growth cone of a developing axon, following chemical signals in the extracellular matrix along its former path until the axon forms a new synapse with its target cell. Sometimes the loss of the distal axon is permanent, however, and the pathway is destroyed.

Regeneration of axons in the central nervous system is less likely to occur naturally. CNS glial cells tend to seal off and scar the damaged region, and damaged CNS cells secrete factors that inhibit axon regrowth. Many scientists are studying the mechanisms of axon growth and inhibition in the hopes of finding treatments that can restore function to victims of spinal cord injury and degenerative neurological disorders.

Scientists once believed that if a neuron died, it could never be replaced. The discovery of neural stem cells changed that view. During early development, an undifferentiated cell layer called neuroepithelium lines the lumen of the neural tube, a structure that will later become the brain and spinal cord. As development proceeds, some cells migrate out of the neuroepithelium and differentiate into neurons. Other cells bordering the lumen of the neural tube specialize into the epithelium of the ependyma. However, among the ependymal cells and in the subependymal layer, some neural stem cells remain unspecialized, waiting until they are called upon to replace damaged cells. Neural stem cells have also been found in other parts of the body, including the hippocampus of the brain and the enteric nervous system of the gut.

When neural stem cells receive the correct signals, they transform into neurons and glial cells. Scientists are working intensely to learn how to control this transformation, in the hope that stem cell transplants can reverse the loss of function that comes with degenerative neurological diseases. Most of these studies are being done with mice and rats, but in late 2006 a stem cell transplant into a human brain took place. The patient was a child suffering from Batten disease, a fatal lysosomal enzyme disorder similar to Tay-Sachs. Physicians hoped the transplanted neural stem cells would produce the missing enzymes and slow or stop progression of the disease. Within the year, another five patients with Batten disease also received transplants. Although the stem cells in this first trial did nothing to treat Batten disease, this trial did show that large numbers...
of stem cells can be transplanted into the brain without causing adverse effects. Scientists also hope to use neural stem cells to treat Parkinson’s disease, a degenerative condition in which dopamine-secreting neurons in the brain die.

**Electrical Signals in Neurons**

Nerve and muscle cells are described as *excitable tissues* because of their ability to propagate electrical signals rapidly in response to a stimulus. We now know that many other cell types generate electrical signals to initiate intracellular processes, but the ability of nerve and muscle cells to send a constant electrical signal over long distance is characteristic of electrical signaling in these tissues.

**The Nernst Equation Predicts Membrane Potential for a Single Ion**

Recall that all living cells have a resting membrane potential difference \( V_m \) that represents the separation of electrical charge across the cell membrane. Two factors influence the membrane potential:

1. **The uneven distribution of ions across the cell membrane.** Normally, sodium \(( \text{Na}^+ \)) , chloride \(( \text{Cl}^- \)) , and calcium \(( \text{Ca}^{2+} \)) are more concentrated in the extracellular fluid than in the cytosol. Potassium \(( \text{K}^+ \)) is more concentrated in the cytosol than in the extracellular fluid.

2. **Differing membrane permeability to those ions.** The resting cell membrane is much more permeable to \( \text{K}^+ \) than to \( \text{Na}^+ \) or \( \text{Ca}^{2+} \). This makes \( \text{K}^+ \) the major ion contributing to the resting membrane potential.

The Nernst equation describes the membrane potential that would result if the membrane were permeable to only one ion. For any given ion, this membrane potential is called the *equilibrium potential* of the ion \( E_{\text{ion}} \):

\[
E_{\text{ion}}(\text{in mV}) = \frac{61}{z} \log \left( \frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}} \right)
\]

where:

- 61 is 2.303 \( RT/F \) at 37 °C
- \( z \) is the electrical charge on the ion (+1 for \( \text{K}^+ \)), and \([\text{ion}]_{\text{out}}\) and \([\text{ion}]_{\text{in}}\) are the ion concentrations outside and inside the cell.

(\( R \) is the ideal gas constant, \( T \) is absolute temperature, and \( F \) is the Faraday constant. For additional information on these values, see Appendix B.)

When we use the estimated intracellular and extracellular concentrations for \( \text{K}^+ \) (see Tbl. 8.2) in the Nernst equation, the equation predicts a potassium equilibrium potential, or \( E_K \), of about −90 mV. However, an average value for the resting membrane potential of neurons is about −70 mV (inside the cell relative to outside), more positive than predicted by the potassium equilibrium potential. This means that other ions must be contributing to the membrane potential. Neurons at rest are slightly permeable to \( \text{Na}^+ \), and the leak of positive \( \text{Na}^+ \) into the cell makes the resting membrane potential slightly more positive than it would be if the cell were permeable only to \( \text{K}^+ \).
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Although this equation looks quite intimidating, it can be simplified into words to say: Resting membrane potential is determined by the combined contributions of the (concentration gradient × membrane permeability) for each ion.

If the membrane is not permeable to an ion, the permeability value for that ion is zero, and the ion drops out of the equation. For example, cells at rest normally are not permeable to Ca^{2+}, and therefore Ca^{2+} is not part of the GHK equation.

The GHK equation predicts resting membrane potentials based on given ion concentrations and membrane permeabilities. Notice that if permeabilities for Na^{+} and Cl\(^{-}\) are zero, the equation reverts back to the Nernst equation for K^{+}. The GHK equation explains how the cell’s slight permeability to Na\(^{+}\) makes the resting membrane potential more positive than the E\(_{K}\) determined with the Nernst equation. The GHK equation can also be used to predict what happens to membrane potential when ion concentrations or membrane permeabilities change.

### Ion Movement Creates Electrical Signals

The resting membrane potential of living cells is determined primarily by the K\(^{+}\) concentration gradient and the cell’s resting permeability to K\(^{+}\), Na\(^{+}\), and Cl\(^{-}\). A change in either the K\(^{+}\) concentration gradient or ion permeabilities changes the membrane potential. If you know numerical values for ion concentrations and permeabilities, you can use the GHK equation to calculate the new membrane potential.

In medicine you usually will not have numerical values, however, so it is important to be able to think conceptually about the relationship between ion concentrations, permeabilities, and membrane potential. For example, at rest, the cell membrane of a neuron is only slightly permeable to Na\(^{+}\). If the membrane suddenly increases its Na\(^{+}\) permeability, Na\(^{+}\) enters the cell, moving down its electrochemical gradient.

---

**Table 8.2**

<table>
<thead>
<tr>
<th>Ion</th>
<th>Extracellular Fluid (mM)</th>
<th>Intracellular Fluid (mM)</th>
<th>E(_{ion}) at 37 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>K(^{+})</td>
<td>5 mM (normal: 3.5–5)</td>
<td>150 mM</td>
<td>−90 mV</td>
</tr>
<tr>
<td>Na(^{+})</td>
<td>145 mM (normal: 135–145)</td>
<td>15 mM</td>
<td>+60 mV</td>
</tr>
<tr>
<td>Cl(^{-})</td>
<td>108 mM (normal: 100–108)</td>
<td>10 mM (normal: 5–15)</td>
<td>−63 mV</td>
</tr>
<tr>
<td>Ca(^{2+})</td>
<td>1 mM</td>
<td>0.0001 mM</td>
<td>See Concept Check question 7</td>
</tr>
</tbody>
</table>

**Concept Check**

7. Given the values in Table 8.2, use the Nernst equation to calculate the equilibrium potential for Ca\(^{2+}\). Express the concentrations as powers of 10 and use your knowledge of logarithms (Appendix B) to try the calculations without a calculator.

---

**The GHK Equation Predicts Membrane Potential Using Multiple Ions**

In living systems, several different ions contribute to the membrane potential of cells. The Goldman-Hodgkin-Katz (GHK) equation calculates the membrane potential that results from the contribution of all ions that can cross the membrane. The GHK equation includes membrane permeability values because the permeability of an ion influences its contribution to the membrane potential. If the membrane is not permeable to an ion, that ion does not affect the membrane potential.

For mammalian cells, we assume that Na\(^{+}\), K\(^{+}\), and Cl\(^{-}\) are the three ions that influence membrane potential in resting cells. Each ion’s contribution to the membrane potential is proportional to its ability to cross the membrane. The GHK equation for cells that are permeable to Na\(^{+}\), K\(^{+}\), and Cl\(^{-}\) is

\[
V_m = 61 \log \frac{P_{K}[K^+]_{\text{out}} + P_{Na}[Na^+]_{\text{out}} + P_{Cl}[Cl^-]_{\text{in}}}{P_{K}[K^+]_{\text{in}} + P_{Na}[Na^+]_{\text{in}} + P_{Cl}[Cl^-]_{\text{out}}}
\]

where:

- \(V_m\) is the resting membrane potential in mV at 37 °C.
- 61 is 2.303 \(RT/F\) at 37 °C.
- \(P\) is the relative permeability of the membrane to the ion shown in the subscript, and
- \([\text{ion}]_{\text{out}}\) and \([\text{ion}]_{\text{in}}\) are the ion concentrations outside and inside the cell.

---

Although this equation looks quite intimidating, it can be simplified into words to say: Resting membrane potential is determined by the combined contributions of the (concentration gradient × membrane permeability) for each ion.
The addition of positive Na\(^+\) to the intracellular fluid depolarizes the cell membrane and creates an electrical signal.

The movement of ions across the membrane can also hyperpolarize a cell. If the cell membrane suddenly becomes more permeable to K\(^+\), positive charge is lost from inside the cell, and the cell becomes more negative (hyperpolarizes). A cell may also hyperpolarize if negatively charged ions, such as Cl\(^-\), enter the cell from the extracellular fluid.

**Gated Channels Control the Ion Permeability of the Neuron**

How does a cell change its ion permeability? The simplest way is to open or close existing channels in the membrane. Neurons contain a variety of gated ion channels that alternate between open and closed states, depending on the intracellular and extracellular conditions. A slower method for changing membrane permeability is for the cell to insert new channels into the membrane or remove some existing channels.

Ion channels are usually named according to the primary ion(s) they allow to pass through them. There are four major types of selective ion channels in the neuron: (1) Na\(^+\) channels, (2) K\(^+\) channels, (3) Ca\(^{2+}\) channels, and (4) Cl\(^-\) channels. Other channels are less selective, such as the monovalent cation channels that allow both Na\(^+\) and K\(^+\) to pass.

The ease with which ions flow through a channel is called the channel’s **conductance** (G) \(\text{conductus, escort}\). Channel conductance varies with the gating state of the channel and with the channel protein isoform. Some ion channels, such as the K\(^+\) leak channels that are the major determinant of resting membrane potential, spend most of their time in an open state. Other channels have gates that open or close in response to particular stimuli. Most gated channels fall into one of three categories:

1. **Mechanically gated ion channels** are found in sensory neurons and open in response to physical forces such as pressure or stretch.
2. **Chemically gated ion channels** in most neurons respond to a variety of ligands, such as extracellular neurotransmitters and neuromodulators or intracellular signal molecules.
3. **Voltage-gated ion channels** respond to changes in the cell’s membrane potential. Voltage-gated Na\(^+\) and K\(^+\) channels play an important role in the initiation and conduction of electrical signals along the axon.

Not all voltage-gated channels behave in exactly the same way. The **threshold voltage** for channel opening varies from one channel type to another. For example, some channels we think of as leak channels are actually voltage-gated channels that remain open in the voltage range of the resting membrane potential.

The speed with which a gated channel opens and closes differs among different types of channels. Channel opening to allow ion flow is called channel **activation**. For example, Na\(^+\) channels and K\(^+\) channels of axons are both activated by cell depolarization. The Na\(^+\) channels open very rapidly, but the K\(^+\) channels are slower to open. The result is an initial flow of Na\(^+\) across the membrane, followed later by a flow of K\(^+\).

Many channels that open in response to depolarization close only when the cell repolarizes. The gating portion of the channel protein has an electrical charge that moves the gate between open and closed positions as membrane potential changes. This is like a spring-loaded door that opens when you push on it, then closes when you release it.

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**Concept Check**

Answers: End of Chapter

8. Would a cell with a resting membrane potential of −70 mV depolarize or hyperpolarize in the following cases? (You must consider both the concentration gradient and the electrical gradient of the ion to determine net ion movement.)

   (a) Cell becomes more permeable to Ca\(^{2+}\).
   (b) Cell becomes less permeable to K\(^+\).

9. Would the cell membrane depolarize or hyperpolarize if a small amount of Na\(^+\) leaked into the cell?

It is important to understand that a change in membrane potential from −70 mV to a positive value, such as +30 mV, **does not mean that the ion concentration gradients have reversed**! A significant change in membrane potential occurs with the movement of very few ions. For example, to change the membrane potential by 100 mV, only 1 of every 100,000 K\(^+\) must enter or leave the cell. This is such a tiny fraction of the total number of K\(^+\) in the cell that the intracellular concentration of K\(^+\) remains essentially unchanged even though the membrane potential has changed by 100 mV.

To appreciate how a tiny change can have a large effect, think of getting one grain of beach sand into your eye. There are so many grains of sand on the beach that the loss of one grain is not significant, just as the movement of one K\(^+\) across the cell membrane does not significantly alter the concentration of K\(^+\). However, the electrical signal created by moving a few K\(^+\) across the membrane has a significant effect on the cell’s membrane potential, just as getting that one grain of sand in your eye creates significant discomfort.
Mutant Channels

Ion channels are proteins, and like other proteins they may lose or change function if their amino acid sequence is altered. Channelopathies (pathos, suffering) are inherited diseases caused by mutations in ion channel proteins. The most common channelopathy is cystic fibrosis, which results from defects in chloride channel function. Because ion channels are so intimately linked to the electrical activity of cells, many channelopathies manifest themselves as disorders of the excitable tissues (nerve and muscle). One significant contribution of molecular biology to medicine was the discovery that what the medical community considers to be one disease can actually be a family of related diseases with different causes but similar symptoms. For example, the condition known as long Q-T syndrome (LQTS; named for changes in the electrocardiogram test) is a cardiac problem characterized by an irregular heartbeat (arrhythmia; a-, without), fainting, and sometimes sudden death. Scientists have identified eight different gene mutations in K⁺, Na⁺, or Ca²⁺ channels that result in various subtypes of LQTS. Other well-known channelopathies include some forms of epilepsy and malignant hyperthermia.

But some channels that open with a stimulus close even though the activating stimulus continues, a process known as inactivation. This is similar to doors with an automatic timed open-close mechanism. The door opens when you hit the button, then after a certain period of time, it closes itself, whether you are still standing in the doorway or not. An inactivated channel returns to its normal closed state shortly after the membrane repolarizes. The specific mechanisms underlying channel inactivation vary with different channel types.

Each major channel type has several to many subtypes with varying properties, and the list of subtypes grows longer each year. Within each subtype there may be multiple isoforms that express different opening and closing kinetics (kinetikos, moving) and associated proteins that modify channel properties. In addition, channel activity can be modulated by chemical factors that bind to the channel protein, such as phosphate groups.

Current Flow Obeys Ohm’s Law

When ion channels open, ions may move into or out of the cell. The flow of electrical charge carried by an ion is called the ion’s current, abbreviated $I_{\text{ion}}$. The direction of ion movement depends on the electrochemical (combined electrical and concentration) gradient of the ion. Potassium ions usually move out of the cell. Na⁺, Cl⁻, and Ca²⁺ usually flow into the cell. The net flow of ions across the membrane depolarizes or hyperpolarizes the cell, creating an electrical signal.

Current flow, whether across a membrane or inside a cell, obeys a rule known as Ohm’s Law. Ohm’s Law says that current flow (I) is directly proportional to the electrical potential difference (in volts, V) between two points and inversely proportional to the resistance (R) of the system to current flow: $I = \frac{V}{R}$ or $I = V/R$. In other words, as resistance increases, current flow decreases. (You will encounter a variant of Ohm’s Law when you study fluid flow in the cardiovascular and respiratory systems.)

Resistance in biological flow is the same as resistance in everyday life: it is a force that opposes flow. Electricity is a form of energy and, like other forms of energy, it dissipates as it encounters resistance. As an analogy, think of rolling a ball along the floor. A ball rolled across a smooth wood floor encounters less resistance than a ball rolled across a carpeted floor. If you throw both balls with the same amount of energy, the ball that encounters less resistance retains energy longer and travels farther along the floor.

In biological electricity, resistance to current flow comes from two sources: the resistance of the cell membrane ($R_m$) and the internal resistance of the cytoplasm ($R_i$). The phospholipid bilayer of the cell membrane is normally an excellent insulator, and a membrane with no open ion channels has very high resistance and low conductance. If ion channels open, ions (current) flow across the membrane if there is an electrochemical gradient for them. Opening ion channels therefore decreases the membrane resistance.

The internal resistance of most neurons is determined by the composition of the cytoplasm and is relatively constant. The membrane and internal resistances together determine how far current will flow through a cell before the energy is dissipated and the current dies. The combination of the two resistances is called the length constant for a given neuron.

Voltage changes across the membrane can be classified into two basic types of electrical signals: graded potentials and action potentials (see Table 8.3). Graded potentials are variable-strength signals that travel over short distances and lose strength as they travel through the cell. They are used for short-distance communication. If a depolarizing graded potential is strong enough when it reaches an integrating region within a neuron, the graded potential initiates an action potential. Action potentials are very brief, large depolarizations that travel for long distances through a neuron without losing strength. Their function is rapid signaling over long distances, such as from your toe to your brain.

Graded Potentials Reflect Stimulus Strength

Graded potentials in neurons are depolarizations or hyperpolarizations that occur in the dendrites and cell body or, less frequently, near the axon terminals. These changes in membrane...
Neurons: Cellular and Network Properties

Figure 8.7a shows a graded potential that begins when a stimulus opens monovalent cation channels on the cell body of a neuron. Sodium ions move into the neuron, bringing in electrical energy. The positive charge carried in by the $Na^+$ spreads as a wave of depolarization through the cytoplasm, just as a stone thrown into water creates ripples or waves that spread outward from the point of entry. The wave of depolarization that moves through the cell is known as local current flow. By convention, current in biological systems is the net movement of positive electrical charge.

The strength of the initial depolarization in a graded potential is determined by how much charge enters the cell, just as the size of waves caused by a stone tossed in water is determined by the size of the stone. If more $Na^+$ channels open, more $Na^+$ enters, and the graded potential has higher initial amplitude. The stronger the initial amplitude, the farther the graded potential can spread through the neuron before it dies out.

Why do graded potentials lose strength as they move through the cytoplasm? Two factors play a role:

- **Current leak.** The membrane of the neuron cell body has open leak channels that allow positive charge to leak out into the extracellular fluid. Some positive ions leak out of

---

### Concept Check

10. Match each ion’s movement with the type of graded potential it creates.

(a) $Na^+$ entry  
(b) $Cl^-$ entry  
(c) $K^+$ exit  
(d) $Ca^{2+}$ entry

1. depolarizing  
2. hyperpolarizing

Answers: End of Chapter

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### Table 8.3

<table>
<thead>
<tr>
<th></th>
<th>Graded Potential</th>
<th>Action Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of signal</strong></td>
<td>Input signal</td>
<td>Regenerating conduction signal</td>
</tr>
<tr>
<td><strong>Occurs where?</strong></td>
<td>Usually dendrites and cell body</td>
<td>Trigger zone through axon</td>
</tr>
<tr>
<td><strong>Types of gated ion channels involved</strong></td>
<td>Mechanically, chemically, or voltage-gated channels</td>
<td>Voltage-gated channels</td>
</tr>
<tr>
<td><strong>Ions involved</strong></td>
<td>Usually $Na^+$, $Cl^-$, $Ca^{2+}$</td>
<td>$Na^+$ and $K^+$</td>
</tr>
<tr>
<td><strong>Type of signal</strong></td>
<td>Depolarizing (e.g., $Na^+$ ) or hyperpolarizing (e.g., $Cl^-$)</td>
<td>Depolarizing</td>
</tr>
<tr>
<td><strong>Strength of signal</strong></td>
<td>Depends on initial stimulus; can be summed</td>
<td>All-or-none phenomenon; cannot be summed</td>
</tr>
<tr>
<td><strong>What initiates the signal?</strong></td>
<td>Entry of ions through gated channels</td>
<td>Above-threshold graded potential at the trigger zone opens ion channels</td>
</tr>
<tr>
<td><strong>Unique characteristics</strong></td>
<td>No minimum level required to initiate</td>
<td>Threshold stimulus required to initiate</td>
</tr>
<tr>
<td></td>
<td>Two signals coming close together in time will sum</td>
<td>Refractory period: two signals too close together in time cannot sum</td>
</tr>
<tr>
<td></td>
<td>Initial stimulus strength is indicated by frequency of a series of action potentials</td>
<td></td>
</tr>
</tbody>
</table>

---

Potential are called "graded" because their size, or amplitude (amplitudo, large), is directly proportional to the strength of the triggering event. A large stimulus causes a strong graded potential, and a small stimulus results in a weak graded potential.

In neurons of the CNS and the efferent division, graded potentials occur when chemical signals from other neurons open chemically gated ion channels, allowing ions to enter or leave the neuron. Mechanical stimuli (such as stretch) or chemical stimuli open ion channels in some sensory neurons. Graded potentials may also occur when an open channel closes, decreasing the movement of ions through the cell membrane. For example, if $K^+$ leak channels close, fewer $K^+$ leave the cell. The retention of $K^+$ depolarizes the cell.
At which point of the neuron will the graded potential be stronger, A or B? On the curve of the graph above, mark and label the approximate locations of A and B.

**Graded Potentials**

(a) Graded potentials decrease in strength as they spread out from the point of origin.

(b) Subthreshold Graded Potential

A graded potential starts above threshold (T) at its initiation point but decreases in strength as it travels through the cell body. At the trigger zone, it is below threshold and therefore does not initiate an action potential.

(c) Suprathreshold Graded Potential

A stronger stimulus at the same point on the cell body creates a graded potential that is still above threshold by the time it reaches the trigger zone, so an action potential results.
the cell across the membrane as the depolarization wave moves through the cytoplasm, diminishing the strength of the signal inside the cell.

2. **Cytoplasmic resistance.** The cytoplasm provides resistance to the flow of electricity, just as water creates resistance that diminishes the waves from the stone. The combination of current leak and cytoplasmic resistance means that the strength of the signal inside the cell decreases over distance.

Graded potentials that are strong enough eventually reach the region of the neuron known as the **trigger zone**. In efferent neurons and interneurons, the trigger zone is the **axon hillock** and the very first part of the axon, a region known as the **initial segment**. In sensory neurons, the trigger zone is immediately adjacent to the receptor, where the dendrites join the axon (see Fig. 8.2).

Graded potentials that are strong enough eventually reach the region of the neuron known as the **trigger zone**. In efferent neurons and interneurons, the trigger zone is the **axon hillock** and the very first part of the axon, a region known as the **initial segment**. In sensory neurons, the trigger zone is immediately adjacent to the receptor, where the dendrites join the axon (see Fig. 8.2).

**Concept Check**

11. Identify the trigger zones of the neurons illustrated in Figure 8.2, if possible.

The trigger zone is the integrating center of the neuron and contains a high concentration of voltage-gated Na⁺ channels in its membrane. If graded potentials reaching the trigger zone depolarize the membrane to the threshold voltage, voltage-gated Na⁺ channels open, and an action potential begins. If the depolarization does not reach threshold, the graded potential simply dies out as it moves into the axon.

Because depolarization makes a neuron more likely to fire an action potential, depolarizing graded potentials are considered to be excitatory. A hyperpolarizing graded potential moves the membrane potential farther from the threshold value and makes the neuron less likely to fire an action potential. Consequently, hyperpolarizing graded potentials are considered to be inhibitory.

Figure 8.7b shows a neuron with three recording electrodes placed at intervals along the cell body and trigger zone. A single stimulus triggers a *subthreshold* graded potential, one that is below threshold by the time it reaches the trigger zone. Although the cell is depolarized to −40 mV at the site where the graded potential begins, the current decreases as it travels through the cell body. As a result, the graded potential is below threshold by the time it reaches the trigger zone. (For the typical mammalian neuron, threshold is about −55 mV.) The stimulus is not strong enough to depolarize the cell to threshold at the trigger zone, and the graded potential dies out without triggering an action potential.

Figure 8.7c shows *suprathreshold* graded potential, one that is strong enough to cause an action potential. A stronger initial stimulus on the cell body initiates a stronger depolarization and current flow. Although this graded potential also diminishes with distance as it travels through the neuron, its higher initial strength ensures that it is above threshold at the trigger zone. In this example, the graded potential triggers an action potential. The ability of a neuron to respond to a stimulus and fire an action potential is called the cell’s **excitability**.

**Action Potentials Travel Long Distances**

Action potentials, also known as spikes, are electrical signals of uniform strength that travel from a neuron’s trigger zone to the end of its axon. In action potentials, ion channels in the axon membrane open sequentially as electrical current passes down the axon. Additional Na⁺ entering the cell reinforces the depolarization, which is why an action potential does not lose strength over distance the way a graded potential does. Instead, the action potential at the end of an axon is identical to the action potential that started at the trigger zone: a depolarization of about 100 mV amplitude. The high-speed movement of an action potential along the axon is called **conduction** of the action potential.

Action potentials are sometimes called all-or-none phenomena because they either occur as a maximal depolarization (if the stimulus reaches threshold) or do not occur at all (if the stimulus is below threshold). The strength of the graded potential that initiates an action potential has no influence on the amplitude of the action potential.

When we talk about action potentials, it is important to realize that there is no single action potential that moves through the cell. The action potential that occurs at the trigger zone is like the movement in the first domino of a series of dominos standing on end (Fig. 8.8a). As the first domino falls, it strikes the next, passing on its kinetic energy. As the second domino falls, it passes kinetic energy to the third domino, and so on. If you could take a snapshot of the line of falling dominos, you would see that as the first domino is coming to rest in the fallen position, the next one is almost down, the third one most of the way down, and so forth, until you reach the domino that has just been hit and is starting to fall.

In an action potential, a wave of electrical energy moves down the axon. Instead of getting weaker over distance, action potentials are replenished along the way so that they maintain constant amplitude. As the action potential passes from one part of the axon to the next, the membrane’s energy state is reflected in the membrane potential of each region. If we were to insert a series of recording electrodes along the length of an axon and start an action potential at the trigger zone, we would see a series of overlapping action potentials, each in a different part of the waveform, just like the dominos that are frozen in different positions (Fig. 8.8b).
of an action potential requires only a few types of ion channels: a voltage-gated $\text{Na}^+$ channel and a voltage-gated $\text{K}^+$ channel, plus some leak channels that help set the resting membrane potential. Action potentials begin when voltage-gated ion channels open, altering membrane permeability ($P$) to $\text{Na}^+$ and $\text{K}^+$. Figure 8.9 shows the voltage and ion permeability changes that take place in one section of membrane during an action potential.

Rising Phase of the Action Potential
The rising phase is due to a sudden temporary increase in the cell’s permeability to $\text{Na}^+$. An action potential begins when a graded potential reaching the trigger zone depolarizes the membrane to threshold ($-55 \text{ mV}$). As the cell depolarizes, voltage-gated $\text{Na}^+$ channels open, allowing for a rapid influx of $\text{Na}^+$ ions, which depolarizes the membrane.

**Fig. 8.8**

**Concept Check**

12. What is the difference between conductance and conduction in neurons?

**Answers:** End of Chapter
The Action Potential

Changes in ion permeability ($P_{ion}$) along the axon create ion flow and voltage changes.

Na$^+$ channels open, making the membrane much more permeable to Na$^+$. Because Na$^+$ is more concentrated outside the cell and because the negative membrane potential inside the cell attracts these positively charged ions, Na$^+$ flows into the cell. The addition of positive charge to the intracellular fluid depolarizes the cell membrane, making it progressively more positive (shown by the steep rising phase on the graph). In the top third of the rising phase, the inside of the cell has become more positive than the outside, and the membrane potential has reversed polarity. This reversal is represented on the graph by the overshoot, that portion of the action potential above 0 mV.

As soon as the cell membrane potential becomes positive, the electrical driving force moving Na$^+$ into the cell disappears. However, the Na$^+$ concentration gradient remains, so Na$^+$ continues to move into the cell. As long as Na$^+$ permeability remains high, the membrane potential moves toward the Na$^+$ equilibrium potential ($E_{Na}$) of +60 mV. (Recall that $E_{Na}$ is...
the membrane potential at which the movement of Na$^+$ into the cell down its concentration gradient is exactly opposed by the positive membrane potential. The action potential peaks at +30 mV, when Na$^+$ channels in the axon close and potassium channels open.

**Falling Phase of the Action Potential** The falling phase corresponds to an increase in K$^+$ permeability. Voltage-gated K$^+$ channels, like Na$^+$ channels, open in response to depolarization. The K$^+$ channel gates are much slower to open, however, and peak K$^+$ permeability occurs later than peak Na$^+$ permeability (Fig. 8.9, lower graph). By the time the K$^+$ channels finally open, the membrane potential of the cell has reached +30 mV because of Na$^+$ influx through faster-opening Na$^+$ channels.

When the Na$^+$ channels close at the peak of the action potential, the K$^+$ channels have just finished opening, making the membrane very permeable to K$^+$. At a positive membrane potential, the concentration and electrical gradients for K$^+$ favor movement of K$^+$ out of the cell. As K$^+$ moves out of the cell, the membrane potential rapidly becomes more negative, creating the falling phase of the action potential and sending the cell toward its resting potential.

When the falling membrane potential reaches −70 mV, the K$^+$ permeability has not returned to its resting state. Potassium continues to leave the cell through both voltage-gated and K$^+$ leak channels, and the membrane hyperpolarizes, approaching the E_K of −90 mV. This after-hyperpolarization is also called the undershoot.

Finally, the slow voltage-gated K$^+$ channels close, and some of the outward K$^+$ leak stops. Retention of K$^+$ and leak of Na$^+$ into the axon bring the membrane potential back to −70 mV, the value that reflects the cell’s resting permeability to K$^+$, Cl$^-$, and Na$^+$.

To summarize, the action potential is a change in membrane potential that occurs when voltage-gated ion channels in the membrane open, increasing the cell’s permeability first to Na$^+$ (which enters) and then to K$^+$ (which leaves). The influx (movement into the cell) of Na$^+$ depolarizes the cell. This depolarization is followed by K$^+$ efflux (movement out of the cell), which restores the cell to the resting membrane potential.

**One Action Potential Does Not Alter Ion Concentration Gradients**

As you just learned, an action potential results from ion movements across the neuron membrane. First Na$^+$ moves into the cell, and then K$^+$ moves out. However, it is important to understand that very few ions move across the membrane in a single action potential, so that the relative Na$^+$ and K$^+$ concentrations inside and outside the cell remain essentially unchanged. For example, only 1 in every 100,000 K$^+$ must leave the cell to shift the membrane potential from +30 to −70 mV, equivalent to the falling phase of the action potential. The tiny number of ions that cross the membrane during an action potential does not disrupt the Na$^+$ and K$^+$ concentration gradients.

Normally, the ions that do move into or out of the cell during action potentials are rapidly restored to their original compartments by Na$^+$-K$^+$-ATPase (also known as the Na$^+$-K$^+$ pump). The pump uses energy from ATP to exchange Na$^+$ that enters the cell for K$^+$ that leaked out of it. This exchange does not need to happen before the next action potential fires, however, because the ion concentration gradient was not significantly altered by one action potential! A neuron without a functional Na$^+$-K$^+$ pump could fire a thousand or more action potentials before a significant change in the ion gradients occurred.

**Concept Check**

13. If you put ouabain, an inhibitor of the Na$^+$-K$^+$ pump, on a neuron and then stimulate the neuron repeatedly, what do you expect to happen to action potentials generated by that neuron?

(a) They cease immediately.
(b) There is no immediate effect, but they diminish with repeated stimulation and eventually disappear.
(c) They get smaller immediately, then stabilize with smaller amplitude.
(d) Ouabain has no effect on action potentials.

**Axonal Na$^+$ Channels Have Two Gates**

One question that puzzled scientists for many years was how the voltage-gated Na$^+$ channels could close at the peak of the action potential, when the cell was depolarized. Why should these channels close when depolarization was the stimulus for Na$^+$ channel opening? After many years of study, they found the answer. These voltage-gated Na$^+$ channels have two gates to regulate ion movement rather than a single gate. The two gates, known as activation and inactivation gates, flip-flop back and forth to open and close the Na$^+$ channel.

When a neuron is at its resting membrane potential, the activation gate of the Na$^+$ channel closes and no Na$^+$ can move through the channel (Fig. 8.10a). The inactivation gate, an amino acid sequence behaving like a ball and chain on the cytoplasmic side of the channel, is open. When the cell membrane near the channel depolarizes, the activation gate swings open (Fig. 8.10b). This opens the channel and allows Na$^+$ to move into the cell down its electrochemical gradient (Fig. 8.10c).
The addition of positive charge further depolarizes the inside of the cell and starts a positive feedback loop (Fig. 8.11). More Na$^+$ channels open, and more Na$^+$ enters, further depolarizing the cell. As long as the cell remains depolarized, activation gates in Na$^+$ channels remain open.

Positive feedback loops require outside intervention to stop them. In axons, the inactivation gates in the Na$^+$ channels are the outside intervention that stops the escalating depolarization of the cell. Both activation and inactivation gates move in response to depolarization, but the inactivation gate delays its movement for 0.5 msec. During that delay, the Na$^+$ channel is open, allowing enough Na$^+$ influx to create the rising phase of the action potential. When the slower inactivation gate finally closes, Na$^+$ influx stops, and the action potential peaks (Fig. 8.10d).

While the neuron repolarizes during K$^+$ efflux, the Na$^+$ channel gates reset to their original positions so they can respond to the next depolarization (Fig. 8.10e). The double-gating mechanism found in axonal voltage-gated Na$^+$ channels allows electrical signals to be conducted in only one direction, as you will see in the next section.

### Concept Check

14. The pyrethrin insecticides, derived from chrysanthemums, disable inactivation gates of Na$^+$ channels so that the channels remain open. In neurons poisoned with pyrethrins, what happens to the membrane potential? Explain your answer.

15. When Na$^+$ channel gates are resetting, is the activation gate opening or closing? Is the inactivation gate opening or closing?

### Action Potentials Will Not Fire During the Absolute Refractory Period

The double gating of Na$^+$ channels plays a major role in the phenomenon known as the refractory period. The adjective refractory comes from a Latin word meaning “stubborn.” The “stubbornness” of the neuron refers to the fact that once an action potential has begun, a second action potential cannot be triggered for about 1–2 msec, no matter how large the stimulus. This delay, which represents the time required for the Na$^+$ channel gates to reset to their resting positions, is called the absolute refractory period (Fig. 8.11). Because of the absolute refractory period, a second action potential cannot occur before the first has finished. Consequently, action potentials moving from trigger zone to axon terminal cannot overlap and cannot travel backward.

A relative refractory period follows the absolute refractory period. During the relative refractory period, some but not
Repolarization enters the axon, and the initial segment of those stimuli can be added to Neurons: Cellular and Network Properties.

Rising phase
ACTION POTENTIAL
Falling phase Peak
Na\(^+\) enters cell
Na\(^+\) enters, causing more depolarization and opening more Na\(^+\) channels in the adjacent membrane.

Channels inactivated and cannot open again so soon. The channels in the adjacent membrane.

Entry is off channel gates.

Loss ec because channels open, allowing channel gates have reset to their original positions. In addition, during the relative refractory period, K\(^+\) channels are still open.

The Na\(^+\) channels that have not quite returned to their resting position can be reopened by a stronger-than-normal graded potential. In other words, the threshold value has temporarily moved closer to zero, which requires a stronger depolarization to reach it. Although Na\(^+\) enters through newly reopened Na\(^+\) channels, depolarization due to Na\(^+\) entry is offset by K\(^+\) loss through still-open K\(^+\) channels. As a result, any action potentials that fire during the relative refractory period will be of smaller amplitude than normal.

The refractory period is a key characteristic that distinguishes action potentials from graded potentials. If two stimuli reach the dendrites of a neuron within a short time, the successive graded potentials created by those stimuli can be added to one another. If, however, two suprathreshold graded potentials reach the action potential trigger zone within the absolute refractory period, the second graded potential has no effect because the Na\(^+\) channels are inactivated and cannot open again so soon.

Refractory periods limit the rate at which signals can be transmitted down a neuron. The absolute refractory period also ensures one-way travel of an action potential from cell body to axon terminal by preventing the action potential from traveling backward.

**Action Potentials Are Conducted**

A distinguishing characteristic of action potentials is that they can travel over long distances of a meter or more without losing energy. The action potential that reaches the end of an axon is identical to the action potential that started at the trigger zone. To see how this happens, we must examine the conduction of action potentials at the cellular level.

The depolarization of a section of an axon causes positive current to spread through the cytoplasm in all directions by local current flow (Fig. 8.13). Simultaneously, on the outside of the axon membrane, current flows back toward the depolarized section. The local current flow in the cytoplasm diminishes over distance as energy dissipates. Forward flow down the axon would eventually die out were it not for voltage-gated channels. The axon is well supplied with voltage-gated Na\(^+\) channels. Whenever a depolarization reaches those channels, they open, allowing more Na\(^+\) to enter the cell and reinforcing the depolarization—the positive feedback loop shown in Figure 8.11. Let’s see how this works when an action potential begins at the axon’s trigger zone.

First, a graded potential above threshold enters the trigger zone (Fig. 8.14 1). Its depolarization opens voltage-gated Na\(^+\) channels, Na\(^+\) enters the axon, and the initial segment of axon depolarizes 2. Positive charge from the depolarized trigger zone spreads by local current flow to adjacent sections of membrane 3, repelled by the Na\(^+\) that entered the cytoplasm and attracted by the negative charge of the resting membrane potential.

The flow of local current toward the axon terminal (to the right in Figure 8.14) begins conduction of the action potential. When the membrane distal to the trigger zone depolarizes from local current flow, its Na\(^+\) channels open, allowing Na\(^+\) into the cell 4. This starts the positive feedback loop: depolarization opens Na\(^+\) channels, Na\(^+\) enters, causing more depolarization and opening more Na\(^+\) channels in the adjacent membrane.
REFRACTORY PERIODS FOLLOWING AN ACTION POTENTIAL

A single channel shown during a phase means that the majority of channels are in this state.

During the absolute refractory period, no stimulus can trigger another action potential.

During the relative refractory period, only a larger-than-normal stimulus can initiate a new action potential.

Where more than one channel of a particular type is shown, the population is split between the states.
LOW CURRENT FLOW

When a section of axon depolarizes, positive charges move by local current flow into adjacent sections of the cytoplasm. On the extracellular surface, current flows toward the depolarized region.

The continuous entry of Na\(^+\) channels open along the axon means that the strength of the signal does not diminish as the action potential propagates itself. (Contrast this with graded potentials in Figure 8.7, in which Na\(^+\) enters only at the point of stimulus, resulting in a membrane potential change that loses strength over distance.)

As each segment of axon reaches the peak of the action potential, its Na\(^+\) channels inactivate. During the action potential's falling phase, K\(^+\) channels open, allowing K\(^+\) to leave the cytoplasm. Finally, the K\(^+\) channels close, and the membrane in that segment of axon returns to its resting potential.

Although positive charge from a depolarized segment of membrane may flow backward toward the trigger zone, depolarization in that direction has no effect on the axon. The section of axon that has just completed an action potential is in its absolute refractory period, with its Na\(^+\) channels inactivated. For this reason, the action potential cannot move backward.

What happens to current flow backward from the trigger zone into the cell body? Scientists used to believe that there were few voltage-gated ion channels in the cell body, so that retrograde current flow could be ignored. However, they now know that the cell body and dendrites do have voltage-gated ion channels and may respond to local current flow from the trigger zone. These retrograde signals are able to influence and modify the next signal that reaches the cell. For example, depolarization flowing backward from the axon could open voltage-gated channels in the dendrites, strengthening an externally initiated graded potential.

Larger Neurons Conduct Action Potentials Faster

Two key physical parameters influence the speed of action potential conduction in a mammalian neuron: (1) the diameter of the axon and (2) the resistance of the axon membrane to ion leakage out of the cell. The larger the diameter of the axon or the more leak-resistant the membrane, the faster an action potential will move.

To understand the relationship between diameter and conduction, think of a water pipe with water flowing through it. The water that touches the walls of the pipe encounters resistance due to friction between the flowing water molecules and the stationary walls. The water in the center of the pipe meets no direct resistance from the walls and therefore flows faster. In a large-diameter pipe, a smaller fraction of the water flowing through the pipe is in contact with the walls, making the total resistance lower.

In the same way, charges flowing inside an axon meet resistance from the membrane. Thus, the larger the diameter of the axon, the lower its resistance to ion flow. The connection between axon diameter and speed of conduction is especially evident in the giant axons that certain organisms, such as squid, earthworms, and fish, use for rapid escape responses. These giant axons may be up to 1 mm in diameter. Because of their large diameter, they can easily be punctured with electrodes (Fig. 8.15). As a result, these species have been very important in research on electrical signaling.

If you compare a cross section of a squid giant axon with a cross section of a mammalian nerve, you find that the mammalian nerve contains about 200 axons in the same cross-sectional area. Complex nervous systems pack more axons into a small nerve by using smaller-diameter axons wrapped in insulating membranes of myelin instead of large-diameter unmyelinated axons.

Conduction Is Faster in Myelinated Axons

The conduction of action potentials down an axon is faster in high-resistance axons, in which current leak out of the cell is minimized. The unmyelinated axon depicted in Figure 8.14 has low resistance to current leak because the entire axon membrane is in contact with the extracellular fluid and has ion channels through which current can leak.

In contrast, myelinated axons limit the amount of membrane in contact with the extracellular fluid. In these axons, small sections of bare membrane—the nodes of Ranvier—alternate with longer segments wrapped in multiple layers of membrane (the myelin sheath). The myelin sheath creates a high-resistance wall that prevents ion flow out of the cytoplasm. The myelin membranes are analogous to heavy coats of plastic surrounding electrical wires, as they increase the effective thickness of the axon membrane by as much as 100-fold.

Concept Check

16. If you place an electrode in the middle of an axon and artificially depolarize the cell above threshold, in which direction will an action potential travel: to the axon terminal, to the cell body, or to both? Explain your answer.
Local current flow from the active region causes new sections of the membrane to depolarize. The refractory period prevents backward conduction. Loss of K\^+ from the cytoplasm repolarizes the membrane.

A graded potential above threshold reaches the trigger zone. Voltage-gated Na\(^+\) channels open, and Na\(^+\) enters the axon. Positive charge flows into adjacent sections of the axon by local current flow. Local current flow from the active region causes new sections of the membrane to depolarize. The refractory period prevents backward conduction. Loss of K\(^+\) from the cytoplasm repolarizes the membrane.

**FIGURE QUESTION**
Match the segments of the neuron in the bottom frame with the corresponding phrase(s):

(a) proximal axon (blue)
(b) absolute refractory period (pink)
(c) active region (yellow)
(d) relative refractory period (purple)
(e) distal inactive region (blue)

1. rising phase of action potential
2. falling phase of action potential
3. after-hyperpolarization
4. resting potential
As an action potential passes down the axon from trigger zone to axon terminal, it passes through alternating regions of unmyelinated axon and nodes of Ranvier (Fig. 8.16a). The conduction process is similar to that described previously for the unmyelinated axon, except that it occurs only at the nodes in myelinated axons. Each node has a high concentration of voltage-gated Na⁺ channels, which open with depolarization and allow Na⁺ into the axon. Sodium ions entering at a node reinforce the depolarization and restore the amplitude of the action potential constant as it passes from node to node. The apparent jump of the action potential from node to node is called saltatory conduction, from the Latin word saltare, meaning “to leap.”

What makes conduction more rapid in myelinated axons? Part of the answer lies with the cable properties of neurons (see Biotechnology box). Also, channel opening slows conduction slightly. In unmyelinated axons, channels must open sequentially all the way down the axon membrane to maintain the amplitude of the action potential. One clever student compared this process to moving the cursor across a computer screen by repeatedly pressing the space bar.

In myelinated axons, however, only the nodes need Na⁺ channels because of the insulating properties of the myelin membrane. As the action potential passes along myelinated segments, conduction is not slowed by channel opening. In the student’s analogy, this is like zipping across the screen by using the Tab key.

Saltatory conduction thus is an effective alternative to large-diameter axons and allows rapid action potentials through small axons. A myelinated frog axon 10-μm in diameter conducts action potentials at the same speed as an unmyelinated 500-μm squid axon. A myelinated 8.6-μm mammalian neuron
Neurons: Cellular and Network Properties

conducts action potentials at 120 m/sec (432 km/hr or 268 miles per hour), while action potentials in a smaller, unmyelinated 1.5-µm pain fiber travel only 2 m/s (7.2 km/hr or 4.5 mph). In summary, action potentials travel through different axons at different rates, depending on the two parameters of axon diameter and myelination.

(a) Action potentials appear to jump from one node of Ranvier to the next. Only the nodes have voltage-gated Na⁺ channels.

(b) In demyelinating diseases, conduction slows when current leaks out of the previously insulated regions between the nodes.

Fig. 8.16

Concept Check

17. Place the following neurons in order of their speed of conduction, from fastest to slowest:
   (a) myelinated axon, diameter 20-µm
   (b) unmyelinated axon, diameter 20-µm
   (c) unmyelinated axon, diameter 200-µm

Q3: In GBS, what would you expect the results of a nerve conduction test to be?

Answers: End of Chapter

RUNNING PROBLEM

The classic form of Guillain-Barré syndrome found in Europe and North America is an illness in which the myelin that insulates axons is destroyed. One way that GBS, multiple sclerosis, and other demyelinating illnesses are diagnosed is through the use of a nerve conduction test. This test measures the combined strength of action potentials from many neurons and the rate at which these action potentials are conducted as they travel down axons.
In demyelinating diseases, the loss of myelin from vertebrate neurons can have devastating effects on neural signaling. In the central and peripheral nervous systems, the loss of myelin slows the conduction of action potentials. In addition, when current leaks out of the now-uninsulated regions of membrane between the channel-rich nodes of Ranvier, the depolarization that reaches a node may no longer be above threshold, and conduction may fail (Fig. 8.16b).

Multiple sclerosis is the most common and best-known demyelinating disease. It is characterized by a variety of neurological complaints, including fatigue, muscle weakness, difficulty walking, and loss of vision. Guillian-Barré syndrome, described in this chapter’s Running Problem, is also characterized by the destruction of myelin. At this time, we can treat some of the symptoms but not the causes of demyelinating diseases, which are mostly either inherited or autoimmune disorders. Currently, researchers are using recombinant DNA technology to study demyelinating disorders in mice.

Chemical Factors Alter Electrical Activity

A large variety of chemicals alter the conduction of action potentials by binding to Na\(^+\), K\(^+\), or Ca\(^{2+}\) channels in the neuron membrane. For example, some neurotoxins bind to and block Na\(^+\) channels. Local anesthetics such as procaine, which block sensation, function the same way. If Na\(^+\) channels are not functional, Na\(^+\) cannot enter the axon. A depolarization that begins at the trigger zone then cannot be replenished as it travels; it loses strength as it moves down the axon, much like a normal graded potential. If the wave of depolarization manages to reach the axon terminal, it may be too weak to release neurotransmitter. As a result, the message of the presynaptic neuron is not passed on to the postsynaptic cell, and electrical signaling fails.

Alterations in the extracellular fluid concentrations of K\(^+\) and Ca\(^{2+}\) are also associated with abnormal electrical activity in the nervous system. The relationship between extracellular fluid K\(^+\) levels and the conduction of action potentials is the most straightforward and easiest to understand, as well as one of the most clinically significant.

The concentration of K\(^+\) in the blood and interstitial fluid is the major determinant of the resting potential of all cells. If K\(^+\) concentration in the blood moves out of the normal range of 3.5–5 mmol/L, the result is a change in the resting membrane potential of cells (Fig. 8.17). This change is not important to most cells, but it can have serious consequences to the body as a whole because of the relationship between resting potential and the excitability of nervous and muscle tissue.

At normal K\(^+\) levels, subthreshold graded potentials do not trigger action potentials, and suprathreshold graded potentials do (Fig. 8.17a, b). An increase in blood K\(^+\) concentration—hyperkalemia (hyper-, above + kalium, potassium + -emia, in the blood)—shifts the resting membrane potential of a neuron...
Neurons Communicate at Synapses

Each synapse has two parts: (1) the axon terminal of the presynaptic cell and (2) the membrane of the postsynaptic cell (see Fig. 8.2f). In a neural reflex, information moves from presynaptic cell to postsynaptic cell. The postsynaptic cells may be neurons or non-neuronal cells. In most neuron-to-neuron synapses, the presynaptic axon terminals are next to either the dendrites or the cell body of the postsynaptic neuron.

In general, postsynaptic neurons with many dendrites also have many synapses. A moderate number of synapses is 10,000, but some cells in the brain are estimated to have 150,000 or more synapses on their dendrites! Synapses can also occur on the axon and even at the axon terminal of the postsynaptic cell. Synapses are classified as electrical or chemical depending on the type of signal that passes from the presynaptic cell to the postsynaptic one.

Electrical Synapses   Electrical synapses pass an electrical signal, or current, directly from the cytoplasm of one cell to another through the pores of gap junction proteins. Information can flow in both directions through most gap junctions, but in some current can flow in only one direction (a rectifying synapse).

Electrical synapses occur mainly in neurons of the CNS. They are also found in glial cells, in cardiac and smooth muscle, and in nonexcitable cells that use electrical signals, such as the pancreatic beta cell. The primary advantage of electrical synapses is rapid conduction of signals from cell to cell that synchronizes activity within a network of cells. Gap junctions also allow chemical signal molecules to diffuse between adjacent cells.

Chemical Synapses   The vast majority of synapses in the nervous system are chemical synapses, which use neurocrine molecules to carry information from one cell to the next. At chemical synapses, the electrical signal of the presynaptic cell is converted into a neurocrine signal that crosses the synaptic cleft and binds to a receptor on its target cell.

Neurons Secrete Chemical Signals

The number of molecules identified as neurocrine signals is large and growing daily. Neurocrine chemical composition is varied, and these molecules may function as neurotransmitters, neuromodulators, or neurohormones. Neurotransmitters and neuromodulators act as paracrine signals, with target cells located close to the neuron that secretes them. Neurohormones, in contrast, are secreted into the blood and distributed throughout the body.

The distinction between neurotransmitter and neuromodulator depends on the receptor to which the chemical is binding, as many neurocrines can act in both roles. Generally, if a molecule primarily acts at a synapse and elicits a rapid response, we call it a neurotransmitter, even if it can also act as a neuromodulator. Neuromodulators act at both synaptic and nonsynaptic sites and are slower acting. Some neuromodulators and neurotransmitters also act on the cell that secretes them, making them autocrine signals as well as paracrines.
Neurocrine Receptors  The neurocrine receptors found in chemical synapses can be divided into two categories: receptor-channels, which are ligand-gated ion channels, and G protein–coupled receptors (GPCR). Receptor-channels mediate rapid responses by altering ion flow across the membrane, so they are also called ionicotropic receptors. Some ionicotropic receptors are specific for a single ion, such as Cl⁻, but others are less specific, such as the nonspecific monovalent cation channel.

G protein–coupled receptors mediate slower responses because the signal must be transduced through a second messenger system. GPCRs for neuromodulators are described as metabotropic receptors. Some metabotropic GPCRs regulate the opening or closing of ion channels.

All neurotransmitters except nitric oxide bind to one or more receptor types. Each receptor type may have multiple subtypes, allowing one neurotransmitter to have different effects in different tissues. Receptor subtypes are distinguished by combinations of letter and number subscripts. For example, serotonin (5-HT) has at least 20 receptor subtypes that have been identified, including 5-HT₁A and 5-HT₁B.

The study of neurotransmitters and their receptors has been greatly simplified by two advances in molecular biology. The genes for many receptor subtypes have been cloned, allowing researchers to create mutant receptors and study their properties. In addition, researchers have discovered or synthesized a variety of agonist and antagonist molecules that mimic or inhibit neurotransmitter activity by binding to the receptors.

Neurotransmitters Are Highly Varied

The array of neurocrines in the body and their many receptor types is truly staggering (Table 8.4). Neurocrine molecules can be informally grouped into seven classes according to their structure: (1) acetylcholine, (2) amines, (3) amino acids, (4) peptides, (5) purines, (6) gases, and (7) lipids. CNS neurons release many different neurocrines, including some polypeptides known mostly for their hormonal activity, such as the hypothalamic releasing hormones and oxytocin and vasopressin. In contrast, the PNS secretes only three major neurocrines: the neurotransmitters acetylcholine and norepinephrine, and the neurohormone epinephrine. Some PNS neurons co-secrete additional neurocrines, such as ATP, which we will mention when they are functionally important.

Acetylcholine  Acetylcholine (ACh), in a chemical class by itself, is synthesized from choline and acetyl coenzyme A (acetyl CoA). Choline is a small molecule also found in membrane phospholipids. Acetyl CoA is the metabolic intermediate that links glycolysis to the citric acid cycle. The synthesis of ACh from these two precursors is a simple enzymatic reaction that takes place in the axon terminal.

Neurons that secrete ACh and receptors that bind ACh are described as cholinergic.

Cholinergic receptors come in two main subtypes: nicotinic, named because nicotine is an agonist, and muscarinic, for which muscarine, a compound found in some fungi, is an agonist. Cholinergic nicotinic receptors are receptor-channels found on skeletal muscle, in the autonomic division of the PNS, and in the CNS. Nicotinic receptors are monovalent cation channels through which both Na⁺ and K⁺ can pass. Sodium entry into cells exceeds K⁺ exit because the electrochemical gradient for Na⁺ is stronger. As a result, net Na⁺ entry depolarizes the postsynaptic cell and makes it more likely to fire an action potential.

Cholinergic muscarinic receptors come in five related subtypes. They are all G protein–coupled receptors linked to second messenger systems. The tissue response to activation of a muscarinic receptor varies with the receptor subtype. These receptors occur in the CNS and in the autonomic parasympathetic division of the PNS.

Amines  The amine neurotransmitters are all active in the CNS. Like the amine hormones, these neurotransmitters are derived from single amino acids. Serotonin, also called 5-hydroxytryptamine or 5-HT, is made from the amino acid tryptophan. Histamine, made from histidine, plays a role in allergic responses in addition to serving as a neurotransmitter. The amino acid tyrosine is converted to dopamine, norepinephrine, and epinephrine. Norepinephrine is the major neurotransmitter of the PNS autonomic sympathetic division. All three tyrosine-derived neurocrines can also function as neurohormones.

Neurons that secrete norepinephrine are called adrenergic neurons, or, more properly, noradrenergic neurons. The adjective adrenergic does not have the same obvious link to its neurotransmitter as cholinergic does to acetylcholine. Instead, the adjective derives from the British name for epinephrine, adrenaline. In the early part of the twentieth century, British researchers thought that sympathetic neurons secreted adrenaline (epinephrine), hence the modifier adrenergic. Although our understanding has changed, the name persists. Whenever you see reference to "adrenergic control" of a function, you must make the connection to a neuron secreting norepinephrine.

Adrenergic receptors are divided into two classes: α (alpha) and β (beta), with multiple subtypes of each. Like cholinergic muscarinic receptors, adrenergic receptors are linked to G proteins. The two subtypes of adrenergic receptors work through different second messenger pathways. The action of epinephrine on β-receptors in dog liver led E. W. Sutherland to the discovery of cyclic AMP and the concept of second messenger systems as transducers of extracellular messengers.
### Major Neurocrines*  
*This table does not include the numerous peptides that can act as neurocrines.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Receptor Type</th>
<th>Type</th>
<th>Receptor Location</th>
<th>Key Agonists, Antagonists, and Potentiators†</th>
</tr>
</thead>
</table>
| Acetylcholine (ACh)       | Cholinergic                |               | Skeletal muscles, autonomic neurons, CNS                                            | **Agonist:** nicotine  
|                           |                            |               | **Antagonists:** curare, α-bungarotoxin                                             |                                               |
| Nicotinic                 | ICR† (Na⁺, K⁺)             |               | Smooth and cardiac muscle, endocrine and exocrine glands, CNS                       | **Agonist:** muscarine  
|                           |                            |               | **Antagonist:** atropine                                                             |                                               |
| Muscarinic                | GPCR                       |               | Smooth and cardiac muscle, endocrine and exocrine glands, CNS                       |                                               |
| Amines                    |                             |               |                                                                                   |                                               |
| Norepinephrine (NE)       | Adrenergic (α, β)          | GPCR          | Smooth and cardiac muscle, glands, CNS                                              | **Agonists:** α-receptors: ergotamine, phentolamine  
|                           |                            |               |                                                                                   | **β-receptors:** propranolol                   |
| Dopamine (DA)             | Dopamine (D)               | GPCR          | CNS                                                                                | **Agonist:** bromocriptine  
|                           |                            |               |                                                                                   | **Antagonists:** antipsychotic drugs          |
| Serotonin (5-hydroxytryptamine, 5-HT) | Serotonergic (5-HT) | ICR (Na⁺, K⁺), GPCR | CNS                                                                 | **Agonist:** sumatriptan  
|                           |                            |               |                                                                                   | **Antagonist:** LSD                           |
| Histamine (H)             | GPCR                       |               | CNS                                                                                | **Antagonists:** ranitidine (Zantac®)  
|                           |                            |               |                                                                                   | **and cimetidine (Tagamet®)**                 |
| Amino acids               |                             |               |                                                                                   |                                               |
| Glutamate                 | Glutaminergic ionotropic (iGluR) |           |                                                                                   |                                               |
|                           | AMPA                        | ICR (Na⁺, K⁺) | CNS                                                                 | **Agonist:** quisqualate                      |
|                           | NMDA                        | ICR (Na⁺, K⁺, Ca²⁺) | CNS | **Potentiator:** serine |                                               |
| Glutaminergic metabotropic (mGluR) | GPCR |               | CNS                                                                 | **Potentiator:** glycine                      |
| GABA (γ-aminobutyric acid) | GABA                       | ICR (Cl⁻), GPCR | CNS                                                                 | **Antagonist:** picrotoxin  
|                           |                             |               |                                                                                   | **Potentiators:** alcohol, barbiturates       |
| Glycine                   | ICR (Cl⁻)                  |               | CNS                                                                 | **Antagonist:** strychnine                    |
| Purines                   |                             |               |                                                                                   |                                               |
| Adenosine                 | Purine (P)                 | GPCR          | CNS                                                                 |                                               |
| Gases                     |                             |               |                                                                                   |                                               |
| Nitric oxide (NO)         | None                       | N/A           | N/A                                                                                 |                                               |

†This list does not include many chemicals that are used as agonists and antagonists in physiological research.

‡ICR = ion channel-receptor; GPCR = G protein–coupled receptor; AMPA = α-amino-3-hydroxy-5-methyl-4 isoxazole propionic acid; NMDA = N-methyl-D-aspartate; LSD = lysergic acid diethylamine; N/A = not applicable.
Amino Acids Several amino acids function as neurotransmitters in the CNS. Glutamate is the primary excitatory neurotransmitter of the CNS, and aspartate is an excitatory neurotransmitter in selected regions of the brain. Excitatory neurotransmitters depolarize their target cells, usually by opening ion channels that allow flow of positive ions into the cell.

The main inhibitory neurotransmitter in the brain is gamma-aminobutyric acid (GABA). The primary inhibitory neurotransmitter of the spinal cord is the amino acid glycine. These inhibitory neurotransmitters hyperpolarize their target cells by opening Cl⁻ channels and allowing Cl⁻ to enter the cell.

Glutamate also acts as a neuromodulator. The action of glutamate at a particular synapse depends on which of its receptor types occurs on the target cell. Metabotropic glutaminergic receptors act through GPCRs. Two ionotropic glutamate receptors are receptor-channels.

AMPA receptors are ligand-gated monovalent cation channels similar to nicotinic acetylcholine channels. Glutamate binding opens the channel, and the cell depolarizes because of net Na⁺ influx. AMPA receptors are named for their agonist α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid.

NMDA receptors are named for the glutamate agonist N-methyl-D-aspartate. They are unusual for several reasons. First, they are nonselective cation channels that allow Na⁺, K⁺, and Ca²⁺ to pass through the channel. Second, channel opening requires both glutamate binding and a change in membrane potential. The NMDA receptor-channel’s action is described in the section on long-term potentiation later in this chapter.

Glycine and the amino acid D-serine potentiate, or enhance, the excitatory effects of glutamate at one type of glutamate receptor. D-serine is made and released by glial cells as well as neurons, which illustrates the role that glial cells can play in altering electrical communication.

Peptides The nervous system secretes a variety of peptides that act as neurotransmitters and neuromodulators in addition to functioning as neurohormones. These peptides include substance P, involved in some pain pathways, and the opioid peptides (enkephalins and endorphins) that mediate pain relief, or analgesia (an-, without + algos, pain). Peptides that function as both neurohormones and neurotransmitters include cholecystokinin (CCK), vasopressin, and atrial natriuretic peptide. Many peptide neurotransmitters are co-secreted with other neurotransmitters.

Gases One of the most interesting neurotransmitters is nitric oxide (NO), an unstable gas synthesized from oxygen and the amino acid arginine. Nitric oxide acting as a neurotransmitter diffuses freely into a target cell rather than binding to a membrane receptor. Once inside the target cell, nitric oxide binds to proteins. With a half-life of only 2–30 seconds, nitric oxide is elusive and difficult to study. It is also released from cells other than neurons and often acts as a paracrine.

Recent work suggests that carbon monoxide (CO) and hydrogen sulfide (H₂S), both known as toxic gases, are produced by the body in tiny amounts to serve as neurotransmitters.

Lipids Lipid neurocrines include several eicosanoids that are the endogenous ligands for cannabinoid receptors. The CB₁ cannabinoid receptor is found in the brain, and the CB₂ receptor is found on immune cells. The receptors were named for one of their exogenous ligands, Δ⁹-tetrahydrocannabinoid (THC), which comes from the plant Cannabis sativa, more
Some vesicles are “docked” at active zones along the membrane closest to the synaptic cleft, waiting for a signal to release their contents. Other vesicles act as a reserve pool, clustering close to the docking sites. Axon terminals also contain mitochondria to produce ATP for metabolism and transport. In this section we discuss general patterns of neurotransmitter synthesis, storage, release, and termination of action.

**Neurotransmitter Synthesis**

Neurotransmitter synthesis takes place both in the nerve cell body and in the axon terminal. Polypeptide neurotransmitters must be made in the cell body because axon terminals do not have the organelles needed for protein synthesis. Protein synthesis follows the usual pathway. The large propeptide that results is packaged into vesicles along with the enzymes needed to modify it. The vesicles then move from the cell body to the axon terminal by fast axonal transport. Inside the vesicle, the propeptide is broken down into smaller active peptides—a pattern similar to the preprohormone-prohormone-active hormone process in endocrine cells. For example, one propeptide contains the amino acid sequences for three active peptides that are co-secreted: ACTH, gamma(\(\gamma\))-lipotropin, and beta(\(\beta\))-endorphin.

Some vesicles are “docked” at active zones along the membrane closest to the synaptic cleft, waiting for a signal to release their contents. Other vesicles act as a reserve pool, clustering close to the docking sites. Axon terminals also contain mitochondria to produce ATP for metabolism and transport. In this section we discuss general patterns of neurotransmitter synthesis, storage, release, and termination of action.

**Neurotransmitters Are Released from Vesicles**

When we examine the axon terminal of a presynaptic cell with an electron microscope, we find many small synaptic vesicles filled with neurotransmitter that is released on demand (Fig. 8.18).

**BIO TECHNOLOGY**

**Of Snakes, Snails, Spiders, and Sushi**

What do snakes, marine snails, and spiders have to do with neurophysiology? They all provide neuroscientists with compounds for studying synaptic transmission, extracted from the neurotoxic venoms these creatures use to kill their prey. The Asian snake *Bungarus multicinctus* provides us with \(\alpha\)-bungarotoxin, a long-lasting poison that binds tightly to nicotinic acetylcholine receptors. The fish-hunting cone snail, *Conus geographus*, and the funnel web spider, *Agelenopsis aperta*, use toxins that block different types of voltage-gated Ca\(^{2+}\) channels. One of the most potent poisons known, however, comes from the Japanese puffer fish, a highly prized delicacy whose flesh is consumed as sushi. The puffer has tetrodotoxin (TTX) in its gonads. This neurotoxin blocks Na\(^+\) channels on axons and prevents the transmission of action potentials, so ingestion of only a tiny amount can be fatal. The Japanese chefs who prepare the puffer fish, or *fugu*, for consumption are carefully trained to avoid contaminating the fish’s flesh as they remove the toxic gonads. There’s always some risk involved in eating *fugu*, though—one reason that traditionally the youngest person at the table is the first to sample the dish.

**RUNNING PROBLEM**

Dr. McKhann then asked to see autopsy reports on some of the children who had died of their paralysis at Beijing Hospital. In the reports, pathologists noted that the patients had normal myelin but damaged axons. In some cases, the axon had been completely destroyed, leaving only a hollow shell of myelin.

**Q5:** Do the results of Dr. McKhann’s investigation suggest that the Chinese children had classic Guillain-Barré syndrome? Why or why not?
Smaller neurotransmitters, such as acetylcholine, amines, and purines, are synthesized and packaged into vesicles in the axon terminal. The enzymes needed for their synthesis are made in the cell body and released into the cytosol. The dissolved enzymes are then brought to axon terminals by slow axonal transport.

Neurotransmitter Release  Neurotransmitters in the axon terminal are stored in vesicles, so their release into the synaptic cleft takes place by exocytosis. From what we can tell, exocytosis in neurons is similar to exocytosis in other types of cells, but much faster. Neurotoxins that block neurotransmitter release, including tetanus and botulinum toxins, exert their action by inhibiting specific proteins of the cell’s exocytotic apparatus.

Figure 8.19a shows how neurotransmitters are released by exocytosis. When the depolarization of an action potential reaches the axon terminal, the change in membrane potential sets off a sequence of events 1. The axon terminal membrane has voltage-gated Ca$^{2+}$ channels that open in response to depolarization 2. Calcium ions are more concentrated in the extracellular fluid than in the cytosol, and so they move into the cell. Ca$^{2+}$ entering the cell binds to regulatory proteins and initiates exocytosis 3. The membrane of the synaptic vesicle fuses with the cell membrane, aided by multiple membrane proteins. The fused area opens, and neurotransmitter inside the synaptic vesicle moves into the synaptic cleft 4. The neurotransmitter molecules diffuse across the gap to bind with membrane receptors on the postsynaptic cell. When neurotransmitters bind to their receptors, a response is initiated in the postsynaptic cell 5. Each synaptic vesicle contains the same amount of neurotransmitter, so measuring the magnitude of the target cell response is an indication of how many vesicles released their content.

In the classic model of exocytosis, the membrane of the vesicle becomes part of the axon terminal membrane. To prevent a large increase in membrane surface area, the membrane is recycled by endocytosis of vesicles at regions away from the active sites (see Fig. 8.3). The recycled vesicles are then refilled with newly made neurotransmitter.

The transporters that concentrate neurotransmitter into vesicles are H$^+$-dependent antiporters. The vesicles use H$^+$-ATPases to concentrate H$^+$ inside the vesicle, then exchange the H$^+$ for the neurotransmitter. Recently, a second model of secretion has emerged. In this model, called the kiss-and-run pathway, synaptic vesicles fuse to the presynaptic membrane at a complex called the fusion pore. This fusion opens a small channel that is just large enough for neurotransmitter to pass through. Then, instead of opening the fused area wider and incorporating the vesicle membrane into the cell membrane, the vesicle pulls back from the fusion pore and returns to the pool of vesicles in the cytoplasm.

Termination of Neurotransmitter Activity  A key feature of neural signaling is its short duration, due to the rapid removal or inactivation of neurotransmitter in the synaptic cleft. Recall that ligand binding to a protein is reversible and goes to a state of equilibrium, with a constant ratio of unbound to bound ligand. If unbound neurotransmitter is removed from the synapse, the receptors release bound neurotransmitter, terminating its activity, to keep the ratio of unbound/bound transmitter constant.

Removal of unbound neurotransmitter from the synaptic cleft can be accomplished in various ways (Fig. 8.19b). Some neurotransmitter molecules simply diffuse away from the synapse, becoming separated from their receptors. Other neurotransmitters are inactivated by enzymes in the synaptic cleft. For example, acetylcholine (ACh) in the extracellular fluid is rapidly broken down into choline and acetyl CoA by the enzyme acetylcholinesterase (AChE) in the extracellular matrix and in the membrane of the postsynaptic cell (Fig. 8.20). Choline from degraded ACh is transported back into the presynaptic axon terminal on a Na$^+$-dependent cotransporter. Once back in the axon terminal, it can be used to make new acetylcholine.

Many neurotransmitters are removed from the extracellular fluid by transport either back into the presynaptic cell or into adjacent neurons or glial cells. For example, norepinephrine action is terminated when the intact neurotransmitter is transported back into the presynaptic axon terminal. Norepinephrine uptake uses a Na$^+$-dependent cotransporter. Once back in the axon terminal, norepinephrine is either transported back into...
Synaptic Communication

Cell-to-cell communication uses chemical and electrical signaling to coordinate function and maintain homeostasis.

(a) Neurotransmitter Release

1. An action potential depolarizes the axon terminal.
2. The depolarization opens voltage-gated Ca\(^{2+}\) channels, and Ca\(^{2+}\) enters the cell.
3. Calcium entry triggers exocytosis of synaptic vesicle contents.
4. Neurotransmitter diffuses across the synaptic cleft and binds with receptors on the postsynaptic cell.
5. Neurotransmitter binding initiates a response in the postsynaptic cell.

(b) Neurotransmitter Termination

Neurotransmitter action terminates when the chemicals are broken down, are taken up into cells, or diffuse away from the synapse.

1. Neurotransmitters can be returned to axon terminals for reuse or transported into glial cells.
2. Enzymes inactivate neurotransmitters.
3. Neurotransmitters can diffuse out of the synaptic cleft.
For example, let's consider how a sensory neuron tells the CNS the intensity of an incoming stimulus. An above-threshold graded potential reaching the trigger zone of the sensory neuron does not trigger just one action potential. Instead, even a small graded potential that is above threshold triggers a burst of action potentials (Fig. 8.21a). As graded potentials increase in strength (amplitude), they trigger more frequent action potentials (Fig. 8.21b).

Usually a burst of action potentials arriving at the axon terminal results in increased neurotransmitter release, as shown in Figure 8.21b. However, in some cases of sustained activity, neurotransmitter release may decrease over time because the axon cannot replenish its neurotransmitter supply rapidly enough.

Electrical signaling patterns in the CNS are more variable. Brain neurons show different electrical personalities by firing action potentials in a variety of patterns, sometimes spontaneously, without an external stimulus to bring them to threshold. For example, some neurons are tonically active, firing regular trains of action potentials (beating pacemakers). Other neurons exhibit bursting, bursts of action potentials rhythmically alternating with intervals of quiet (rhythmic pacemakers).

These different firing patterns in CNS neurons are created by ion channel variants that differ in their activation and inactivation voltages, opening and closing speeds, and sensitivity to neuromodulators. This variability makes brain neurons more dynamic and complicated than the simple somatic motor neuron we use as our model.
THE FREQUENCY OF ACTION POTENTIAL FIRING INDICATES THE STRENGTH OF A STIMULUS.

(a) Weak stimulus releases little neurotransmitter.

(b) Strong stimulus causes more action potentials and releases more neurotransmitter.

Fig. 8.21

Integration of Neural Information Transfer

Communication between neurons is not always a one-to-one event as we have been describing. Frequently, a single presynaptic neuron branches, and its collaterals synapse on multiple target neurons. This pattern is known as divergence (Fig. 8.22a). On the other hand, when a group of presynaptic neurons provide input to a smaller number of postsynaptic neurons, the pattern is known as convergence (Fig. 8.22b).

Combination of convergence and divergence in the CNS may result in one postsynaptic neuron with synapses from as many as 10,000 presynaptic neurons (Fig. 8.22c). For example, the Purkinje neurons of the CNS have highly branched dendrites so that they can receive information from many neurons (Fig. 8.22d).

In addition, we now know that the traditional view of chemical synapses as sites of one-way communication, with all messages moving from presynaptic cell to postsynaptic cell, is not always correct. In the brain, there are some synapses where cells on both sides of the synaptic cleft release neurotransmitters that act on the opposite cell. Perhaps more importantly, we have learned that many postsynaptic cells “talk back” to their presynaptic neurons by sending neuromodulators that bind to presynaptic receptors. Variations in synaptic activity play a major role in determining how communication takes place in the nervous system.

The ability of the nervous system to change activity at synapses is called synaptic plasticity (plasticus, that which may be molded). Short-term plasticity may enhance activity at the synapse (facilitation) or decrease it (depression). Sometimes changes at the synapse persist for significant periods of time (long-term depression or long-term potentiation). In the sections that follow we examine some of the ways that communication at synapses can be modified.

Postsynaptic Responses May Be Slow or Fast

A neurotransmitter combining with its receptor sets in motion a series of responses in the postsynaptic cell (Fig. 8.23). Neurotransmitters that bind to G protein–coupled receptors linked to second messenger systems initiate slow postsynaptic responses.
Divergence and Convergence

(a) In a **divergent pathway**, one presynaptic neuron branches to affect a larger number of postsynaptic neurons.

(b) In a **convergent pathway**, many presynaptic neurons provide input to influence a smaller number of postsynaptic neurons.

(c) The cell body of a somatic motor neuron is nearly covered with synapses providing input from other neurons.

(d) The highly branched dendrites of a Purkinje cell (neuron) demonstrate convergence of signals from many synapses onto a cell body.

**FIGURE QUESTION**
The pattern of divergence in (a) is similar to ___________ in a second messenger system.

Highly branched dendrites projecting into the gray matter of the cerebellum

Cell body of Purkinje cell

Light micrograph of Purkinje cells in cerebellum
Some second messengers act from the cytoplasmic side of the cell membrane to open or close ion channels. Changes in membrane potential resulting from these alterations in ion flow are called slow synaptic potentials because the response of the second messenger pathway takes longer than the direct opening or closing of a channel. In addition, the response itself lasts longer, usually seconds to minutes.

Slow postsynaptic responses are not limited to altering the open state of ion channels. Neurotransmitters acting on GPCRs may also modify existing cell proteins or regulate the production of new cell proteins. These types of slow response have been linked to the growth and development of neurons and to the mechanisms underlying long-term memory.

Fast synaptic responses are always associated with the opening of ion channels. In the simplest response, the neurotransmitter binds to and opens a receptor-channel on the postsynaptic cell, allowing ions to move between the postsynaptic cell and the extracellular fluid. The resulting change in

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**Fast and Slow Postsynaptic Responses**

Fast responses are mediated by ion channels.

Slow responses are mediated by G protein–coupled receptors.
membrane potential is called a fast synaptic potential because it begins quickly and lasts only a few milliseconds.

If the synaptic potential is depolarizing, it is called an excitatory postsynaptic potential (EPSP) because it makes the cell more likely to fire an action potential. If the synaptic potential is hyperpolarizing, it is called an inhibitory postsynaptic potential (IPSP) because hyperpolarization moves the membrane potential farther from threshold and makes the cell less likely to fire an action potential.

Neural Pathways May Involve Many Neurons

When two or more presynaptic neurons converge on the dendrites or cell body of a single postsynaptic cell, the response of the postsynaptic cell is determined by the summed input from the presynaptic neurons. If the stimuli all create subthreshold excitatory postsynaptic potentials (EPSPs), those EPSPs can sum to create a suprathreshold potential at the trigger zone.

The initiation of an action potential from several nearly simultaneous graded potentials is an example of spatial summation. The word spatial (spatium, space) refers to the fact that the graded potentials originate at different locations (spaces) on the neuron.

Figure 8.24a illustrates spatial summation when three presynaptic neurons releasing excitatory neurotransmitters ("excitatory neurons") converge on one postsynaptic neuron. Each neuron's EPSP is too weak to trigger an action potential by itself, but if the three presynaptic neurons fire simultaneously, the sum of the three EPSPs is suprathreshold and creates an action potential.

Postsynaptic inhibition may occur when a presynaptic neuron releases an inhibitory neurotransmitter onto a postsynaptic cell and alters its response. Figure 8.24b shows three neurons, two excitatory and one inhibitory, converging on a postsynaptic cell. The neurons fire, creating one inhibitory postsynaptic potential (IPSP) and two excitatory graded potentials that sum as they reach the trigger zone. The IPSP counteracts the two EPSPs, creating an integrated signal that is below threshold. As a result, no action potential leaves the trigger zone.

Summation of graded potentials does not always require input from more than one presynaptic neuron. Two subthreshold graded potentials from the same presynaptic neuron can be summed if they arrive at the trigger zone close enough together in time. Summation that occurs from graded potentials overlapping in time is called temporal summation (tempus, time). Let's see how this can happen.

Figure 8.24c shows recordings from an electrode placed in the trigger zone of a neuron. A stimulus (X1) starts a subthreshold graded potential on the cell body at the time marked on the x-axis. The graded potential reaches the trigger zone and depolarizes it, as shown on the graph (A1), but not enough to trigger an action potential. A second stimulus (X2) occurs later, and its subthreshold graded potential (A2) reaches the trigger zone sometime after the first. The interval between the two stimuli is so long that the two graded potentials do not overlap. Neither potential by itself is above threshold, so no action potential is triggered.

In Figure 8.24d, the two stimuli occur closer together in time. As a result, the two subthreshold graded potentials arrive at the trigger zone at almost the same time. The second graded potential adds its depolarization to that of the first, causing the trigger zone to depolarize to threshold.

In many situations, graded potentials in a neuron incorporate both temporal and spatial summation. The summation of graded potentials demonstrates a key property of neurons: postsynaptic integration. When multiple signals reach a neuron, postsynaptic integration creates a signal based on the relative strengths and durations of the signals. If the integrated signal is above threshold, the neuron fires an action potential. If the integrated signal is below threshold, the neuron does not fire.

Figure 8.25 shows the distribution of excitatory and inhibitory synapses on a three-dimensional reconstruction of dendritic spines of various shapes and sizes. The summed input from these synapses determines the activity of the postsynaptic neuron.

Concept Check

27. In Figure 8.24b, assume the postsynaptic neuron has a resting membrane potential of –70 mV and a threshold of –55 mV. If the inhibitory presynaptic neuron creates an IPSP of –55 mV, and the two excitatory presynaptic neurons have EPSPs of 10 and 12 mV, will the postsynaptic neuron fire an action potential?

28. In the graphs of Figure 8.24c and 8.24d, why doesn't the membrane potential change at the same time as the stimulus?

Synaptic Activity Can Be Modified

The examples of synaptic integration we just discussed all took place on the postsynaptic side of a synapse, but the activity of presynaptic cells can also be altered. When an inhibitory or excitatory neuron terminates on or close to an axon terminal of a presynaptic cell, its IPSP or EPSP can alter the action potential reaching the terminal and alter neurotransmitter release by the presynaptic cell.

If activity in an inhibitory neuron decreases neurotransmitter release, the modulation is called presynaptic inhibition (Fig. 8.26a). Presynaptic inhibition allows selective modulation of collaterals and their targets. One collateral can be inhibited while others remain unaffected. In presynaptic facilitation, input from an excitatory neuron increases neurotransmitter release by the presynaptic cell.

Presynaptic alteration of neurotransmitter release provides a more precise means of control than postsynaptic modulation. In postsynaptic modulation, if a neuron synapses on the dendrites and cell body of a neuron, the responsiveness of the entire postsynaptic neuron is altered. In that case, all target cells of the postsynaptic neuron are affected equally (Fig. 8.26b).
Summation

Spatial Summation
Spatial summation occurs when the currents from nearly simultaneous graded potentials combine.

(a) Summation of several subthreshold signals results in an action potential.

Three excitatory neurons fire. Their graded potentials separately are all below threshold.

Graded potentials arrive at trigger zone together and sum to create a suprathreshold signal.

An action potential is generated.

(b) Postsynaptic inhibition. An inhibitory presynaptic neuron prevents an action potential from firing.

Temporal Summation
Temporal summation occurs when two graded potentials from one presynaptic neuron occur close together in time.

(c) No summation. Two subthreshold graded potentials will not initiate an action potential if they are far apart in time.

(d) Summation causing action potential. If two subthreshold potentials arrive at the trigger zone within a short period of time, they may sum and initiate an action potential.
### PRESYNAPTIC AND POSTSYNAPTIC INHIBITION

**A** In **presynaptic inhibition**, an inhibitory neuron synapses on one collateral of the presynaptic neuron and selectively inhibits one target.

1. An excitatory neuron fires.
2. An action potential is generated.
3. An inhibitory neuron fires, blocking neurotransmitter release at one synapse.

**B** In **postsynaptic inhibition**, all targets of the postsynaptic neuron are inhibited equally.

1. One excitatory and one inhibitory presynaptic neuron fire.
2. Modified signal in postsynaptic neuron below threshold.
3. No action potential initiated at trigger zone.
4. No response in any target cell.
Synaptic activity can also be altered by changing the target (postsynaptic) cell’s responsiveness to neurotransmitter. This may be accomplished by changing the identity, affinity, or number of neurotransmitter receptors. Modulators can alter all of these parameters by influencing the synthesis of enzymes, membrane transporters, and receptors. Most neuromodulators act through second messenger systems that alter existing proteins, and their effects last much longer than do those of neurotransmitters. One signal molecule can act as either a neurotransmitter or a neuromodulator, depending upon its receptor (Fig. 8.23).

**Concept Check**

29. Why are axon terminals sometimes called “biological transducers”?

**Long-Term Potentiation Alters Synapses**

Two of the “hot topics” in neurobiology today are long-term potentiation (LTP) and long-term depression (LTD), processes in which activity at a synapse brings about sustained changes in the quality or quantity of synaptic connections. Many times changes in synaptic transmission, such as the facilitation and inhibition we just discussed, are of limited duration. However, if synaptic activity persists for longer periods, the neurons may adapt through LTP and LTD. Our understanding of LTP and LTD is changing rapidly, and the mechanisms may not be the same in different brain areas. The descriptions below reflect some of what we currently know about long-term adaptations of synaptic transmission.

A key element in long-term changes in the CNS is the amino acid glutamate, the main excitatory neurotransmitter in the CNS. As you learned previously, glutamate has two types of receptor-channels: AMPA receptors and NMDA receptors. The NMDA receptor has an unusual property. First, at resting membrane potentials, the NMDA channel is blocked by both a gate and a Mg$^{2+}$ ion. Glutamate binding opens the ligand-activated gate, but ions cannot flow past the Mg$^{2+}$. However, if the cell depolarizes, the Mg$^{2+}$ blocking the channel is expelled, and then ions flow through the channel. Thus, the NMDA channel opens only when the receptor is bound to glutamate and the cell is depolarized.

In long-term potentiation, when presynaptic neurons release glutamate, the neurotransmitter binds to both AMPA and NMDA receptors on the postsynaptic cell (Fig. 8.27). Binding to the AMPA receptor opens a cation channel, and net Na$^+$ entry depolarizes the cell (2). Simultaneously, glutamate binding to the NMDA receptor opens the channel gate, and Na$^+$ entry through AMPA channels depolarizes the postsynaptic cell (2). Depolarization ejects Mg$^{2+}$ from NMDA receptor-channel and opens channel (3). Ca$^{2+}$ enters cytoplasm through NMDA channel (4). Ca$^{2+}$ activates second messenger pathways (5). Paracrine from postsynaptic cell enhances glutamate release (6).
depolarization of the cell creates electrical repulsion that knocks the Mg\(^{2+}\) out of the NMDA channel. Once the NMDA channel is open, Ca\(^{2+}\) enters the cytosol.

The Ca\(^{2+}\) signal initiates second messenger pathways. As a result of these intracellular pathways, the postsynaptic cell becomes more sensitive to glutamate, possibly by inserting more glutamate receptors in the postsynaptic membrane (up-regulation). In addition the postsynaptic cell releases a paracrine that acts on the presynaptic cell to enhance glutamate release.

Long-term depression seems to have two components: a change in the number of postsynaptic receptors and a change in the isoforms of the receptor proteins. In the face of continued neurotransmitter release from presynaptic neurons, the postsynaptic neurons withdraw AMPA receptors from the cell membrane by endocytosis, a process similar to down-regulation of receptors in the endocrine system. In addition, different subunits are inserted into the AMPA receptors, changing current flow through the ion channels.

Researchers believe that long-term potentiation and depression are related to the neural processes for learning and memory, and to changes in the brain that occur with clinical depression and other mental illnesses. The clinical link makes LTP and LTD hot topics in neuroscience research.

**Concept Check**

30. Why would depolarization of the membrane drive Mg\(^{2+}\) from the channel into the extracellular fluid?

**Disorders of Synaptic Transmission Are Responsible for Many Diseases**

Synaptic transmission is the most vulnerable step in the process of signaling through the nervous system. It is the point at which many things go wrong, leading to disruption of normal function. Yet, at the same time, the receptors at synapses are exposed to the extracellular fluid, making them more accessible to drugs than intracellular receptors are. In recent years scientists have linked a variety of nervous system disorders to problems with synaptic transmission. These disorders include Parkinson's disease, schizophrenia, and depression. The best understood diseases of the synapse are those that involve the neuromuscular junction, such as myasthenia gravis. Diseases resulting from synaptic transmission problems within the CNS have proved more difficult to study because they are more difficult to isolate anatomically.

Drugs that act on synaptic activity, particularly synapses in the CNS, are the oldest known and most widely used of all pharmacological agents. Caffeine, nicotine, and alcohol are common drugs in many cultures. Some of the drugs we use to treat conditions such as schizophrenia, depression, anxiety, and epilepsy act by influencing events at the synapse. In many disorders arising in the CNS, we do not yet fully understand either the cause of the disorder or the drug's mechanism of action. This subject is one major area of pharmacological research, and new classes of drugs are being formulated and approved every year.

**RUNNING PROBLEM**

Dr. McKhann suspected that the disease afflicting the Chinese children—which he named acute motor axonal polyneuropathy (AMAN)—might be triggered by a bacterial infection. He also thought that the disease initiates its damage of axons at the neuromuscular junctions.

Q6: Based on information provided in this chapter, name other diseases involving altered synaptic transmission.

**Mysterious Paralysis**

In this running problem you learned about acute motor axonal polyneuropathy (AMAN), a baffling paralytic illness that physicians thought might be a new disease. Although its symptoms resemble those of classic Guillain-Barré syndrome, AMAN is not a demyelinating disease. It affects only motor neurons. However, in both classic GBS and AMAN, the body’s immune system makes antibodies against nervous system components. This similarity led experts eventually to conclude that AMAN is a subtype of GBS. The classic form of GBS has been renamed acute inflammatory demyelinating polyneuropathy, or AIDP. AIDP is more common in Europe and North America, while AMAN is the predominant form of GBS in China, Japan, and South America. A significant number of patients with AMAN develop their disease following a gastrointestinal illness caused by the bacterium *Campylobacter jejuni*, and experts suspect that antibodies to the bacterium also attack glycolipids called gangliosides in the axonal membrane. To learn more about the link between *Campylobacter* and GBS, see “*Campylobacter* Species and Guillain-Barré Syndrome,” *Clin Microbiol Rev* 11: 555–567, July 1998 (http://cmr.asm.org). Check your understanding of this running problem by comparing your answers to the information in the summary table below.
### Question 1
Which division(s) of the nervous system may be involved in Guillain-Barré syndrome (GBS)?

**Facts:** The nervous system is divided into the central nervous system (CNS) and the afferent (sensory) and efferent subdivisions of the peripheral nervous system. Efferent neurons are either somatic motor neurons, which control skeletal muscles, or autonomic neurons, which control glands and smooth and cardiac muscle.

**Integration and Analysis:** Patients with GBS can neither feel sensations nor move their muscles. This suggests a problem in both afferent and somatic motor neurons. However, it is also possible that there is a problem in the CNS integrating center. You do not have enough information to determine which division is affected.

### Question 2
Do you think the paralysis found in the Chinese children affected both sensory (afferent) and somatic motor neurons? Why or why not?

**Facts:** The Chinese children can feel a pin prick but cannot move their muscles.

**Integration and Analysis:** Sensory (afferent) function is normal if they can feel the pin prick. Paralysis of the muscles suggests a problem with somatic motor neurons, with the CNS centers controlling movement, or with the muscles themselves.

### Question 3
In GBS, what would you expect the results of a nerve conduction test to be?

**Facts:** Nerve conduction tests measure conduction speed and strength of conduction action potentials. In GBS, myelin around neurons is destroyed.

**Integration and Analysis:** Myelin insulates axons and increases speed. Without myelin, ions leak out of the axon. Thus, in GBS you would expect decreased conduction speed and decreased strength of action potentials.

### Question 4
Is the paralytic illness that affected the Chinese children a demyelinating condition? Why or why not?

**Facts:** Nerve conduction tests showed normal conduction speed but decreased strength of the summed action potentials.

**Integration and Analysis:** Myelin loss should decrease conduction speed as well as action potential strength. Therefore, this illness is probably not a demyelinating disease.

### Question 5
Do the results of Dr. McKhann’s investigation suggest that the Chinese children had classic Guillain-Barré syndrome? Why or why not?

**Facts:** Autopsy reports on children who died from the disease showed that the axons were damaged but the myelin was normal.

**Integration and Analysis:** Classic GBS is a demyelinating disease that affects both sensory and motor neurons. The Chinese children had normal sensory function, and nerve conduction tests and histological studies indicated normal myelin. Therefore, it was reasonable to conclude that the disease was not GBS.

### Question 6
Based on information provided in this chapter, name other diseases involving altered synaptic transmission.

**Facts:** Synaptic transmission can be altered by blocking neurotransmitter release from the presynaptic cell, by interfering with the action of neurotransmitter on the target cell, or by removing neurotransmitter from the synapse.

**Integration and Analysis:** Parkinson’s disease, depression, schizophrenia, and myasthenia gravis are related to problems with synaptic transmission.

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Chapter Summary

This chapter introduces the nervous system, one of the major control systems responsible for maintaining homeostasis. The divisions of the nervous system correlate with the steps in a reflex pathway. Sensory receptors monitor regulated variables and send input signals to the central nervous system through sensory (afferent) neurons. Output signals, both electrical and chemical, travel through the efferent divisions (somatic motor and autonomic) to their targets throughout the body. Information transfer and communication depend on electrical signals that pass along neurons, on molecular interactions between signal molecules and their receptors, and on signal transduction in the target cells.

1. The nervous system is a complex network of neurons that form the rapid control system of the body.
2. Emergent properties of the nervous system include consciousness, intelligence, and emotion.

Organization of the Nervous System

3. The nervous system is divided into the central nervous system (CNS), composed of the brain and spinal cord, and the peripheral nervous system (PNS). (Fig. 8.1)
4. The peripheral nervous system has sensory (afferent) neurons that bring information into the CNS, and efferent neurons that carry information away from the CNS to various parts of the body.
5. The efferent neurons include somatic motor neurons, which control skeletal muscles, and autonomic neurons, which control smooth and cardiac muscles, glands, and some adipose tissue.
6. Autonomic neurons are subdivided into sympathetic and parasympathetic branches.

Cells of the Nervous System

7. Neurons have a cell body with a nucleus and organelles to direct cellular activity, dendrites to receive incoming signals, and an axon to transmit electrical signals from the cell body to the axon terminal. (Fig. 8.2)
8. Interneurons are neurons that lie entirely within the CNS. (Fig. 8.2c,d)
9. Material is transported between the cell body and axon terminal by axonal transport. (Fig. 8.3)
10. The region where an axon terminal meets its target cell is called a synapse. The target cell is called the postsynaptic cell, and the neuron that releases the chemical signal is known as the presynaptic cell. The region between these two cells is the synaptic cleft. (Fig. 8.2f)
11. Developing neurons find their way to their targets by using chemical signals.
12. Glial cells provide physical support and communicate with neurons. Schwann cells and satellite cells are glial cells associated with the peripheral nervous system. Oligodendrocytes, astrocytes, microglia, and ependymal cells are glial cells found in the CNS. Microglia are modified immune cells that act as scavengers. (Fig. 8.5)
13. Schwann cells and oligodendrocytes form insulating myelin sheaths around neurons. The nodes of Ranvier are sections of uninsulated membrane occurring at intervals along the length of an axon. (Fig. 8.5c)
14. Neural stem cells that can develop into new neurons and glia are found in the ependymal layer as well as in other parts of the nervous system.

Electrical Signals in Neurons

15. The Nernst equation describes the membrane potential of a cell that is permeable to only one ion.
16. Membrane potential is influenced by the concentration gradients of ions across the membrane and by the permeability of the membrane to those ions.
17. The Goldman-Hodgkin-Katz (GHK) equation predicts membrane potential based on ion concentration gradients and membrane permeability for multiple ions.
18. The permeability of a cell to ions changes when ion channels in the membrane open and close. Movement of only a few ions significantly changes the membrane potential.
19. Gated ion channels in neurons open or close in response to chemical or mechanical signals or in response to depolarization of the cell membrane. Channels also close through inactivation.
20. Current flow (I) obeys Ohm’s Law: \( I = \frac{V}{R} \). Resistance to current flow comes from the cell membrane, which is a good insulator, and from the cytoplasm. Conductance (G) is the reciprocal of resistance: \( G = \frac{1}{R} \).
21. Graded potentials are depolarizations or hyperpolarizations whose strength is directly proportional to the strength of the triggering event. Graded potentials lose strength as they move through the cell. (Tbl. 8.3; Fig. 8.7)
22. The wave of depolarization that moves through a cell is known as the local current flow.
23. Action potentials are rapid electrical signals that travel undiminished in amplitude (strength) down the axon from the cell body to the axon terminals.
24. Action potentials begin in the trigger zone if a single graded potential or the sum of multiple graded potentials exceeds the threshold voltage. (Fig. 8.7c)
25. Depolarizing graded potentials make a neuron more likely to fire an action potential. Hyperpolarizing graded potentials make a neuron less likely to fire an action potential.
26. Action potentials are uniform, all-or-none depolarizations that can travel undiminished over long distances.
27. The rising phase of the action potential is due to increased \( \text{Na}^+ \) permeability. The falling phase of the action potential is due to increased \( \text{K}^+ \) permeability. (Fig. 8.9)
28. The voltage-gated \( \text{Na}^+ \) channels of the axon have a fast activation gate and a slower inactivation gate. (Fig. 8.10)
29. Very few ions cross the membrane during an action potential. The \( \text{Na}^+ - \text{K}^+ - \text{ATPase} \) eventually restores \( \text{Na}^+ \) and \( \text{K}^+ \) to their original compartments.
30. Once an action potential has begun, there is a brief period of time known as the absolute refractory period during which a second action potential cannot be triggered, no matter how large the stimulus. Because of this, action potentials cannot be summed. (Fig. 8.12)

31. During the relative refractory period, a higher-than-normal graded potential is required to trigger an action potential.

32. The myelin sheath around an axon speeds up conduction by increasing membrane resistance and decreasing current leakage. Larger-diameter axons conduct action potentials faster than smaller-diameter axons do.

33. The apparent jumping of action potentials from node to node is called saltatory conduction. (Fig. 8.16)

34. Changes in blood K⁺ concentration affect resting membrane potential and the conduction of action potentials. (Fig. 8.17)

**Cell-to-Cell Communication in the Nervous System**

35. In electrical synapses, an electrical signal passes directly from the cytoplasm of one cell to another through gap junctions. Chemical synapses use neurotransmitters to carry information from one cell to the next, with the neurotransmitters diffusing across the synaptic cleft to bind with receptors on target cells.

36. Neurotransmitters come in a variety of forms. Cholinergic neurons secrete acetylcholine. Adrenergic neurons secrete norepinephrine. Glutamate, GABA, serotonin, adenosine, and nitric oxide are other major neurotransmitters. (Tbl. 8.4)

37. Neurotransmitter receptors are either ligand-gated ion channels (ionotropic receptors) or G protein–coupled receptors (metabotropic receptors).

38. Neurotransmitters are synthesized in the cell body or in the axon terminal. They are stored in synaptic vesicles and are released by exocytosis when an action potential reaches the axon terminal. (Fig. 8.19a)

39. Neurotransmitter action is rapidly terminated by reuptake into cells, diffusion away from the synapse, or enzymatic breakdown. (Fig. 8.19b)

40. Information about the strength and duration of a stimulus is conveyed by the amount of neurotransmitter released. Increased frequency of action potentials releases more neurotransmitter. (Fig. 8.21)

**Integration of Neural Information Transfer**

41. When a presynaptic neuron synapses on a larger number of postsynaptic neurons, the pattern is known as divergence. When several presynaptic neurons provide input to a smaller number of postsynaptic neurons, the pattern is known as convergence. (Fig. 8.22)

42. Synaptic transmission can be modified in response to activity at the synapse, a process known as synaptic plasticity.

43. G protein–coupled receptors either create slow synaptic potentials or modify cell metabolism. Ion channels create fast synaptic potentials. (Fig. 8.23)

44. The summation of simultaneous graded potentials from different neurons is known as spatial summation. The summation of graded potentials that closely follow each other sequentially is called temporal summation. (Fig. 8.24)

45. Presynaptic modulation of an axon terminal allows selective modulation of collaterals and their targets. Postsynaptic modulation occurs when a modulatory neuron synapses on a postsynaptic cell body or dendrites. (Fig. 8.26)

46. Long-term potentiation and long-term depression are mechanisms by which neurons change the strength of their synaptic connections. (Fig. 8.27)

**Questions**

Level One Reviewing Facts and Terms

1. List the three functional classes of neurons, and explain how they differ structurally and functionally.

2. Somatic motor neurons control ________, and ________ neurons control smooth and cardiac muscles, glands, and some adipose tissue.

3. Autonomic neurons are classified as either ________ or ________ neurons.

4. Match each term with its description:

   (a) axon 1. process of a neuron that receives incoming signals
   (b) dendrite 2. sensory neuron, transmits information to CNS
   (c) afferent 3. long process that transmits signals to the target cell
   (d) efferent 4. region of neuron where action potential begins
   (e) trigger zone 5. neuron that transmits information from CNS to the rest of the body

5. Name the two primary cell types found in the nervous system.

6. Draw a typical neuron and label the cell body, axon, dendrites, nucleus, trigger zone, axon hillock, collaterals, and axon terminals. Draw mitochondria, rough endoplasmic reticulum, Golgi complex, and vesicles in the appropriate sections of the neuron.

7. Axonal transport refers to the

   (a) release of neurotransmitters into the synaptic cleft.
   (b) use of microtubules to send secretions from the cell body to the axon terminal.
   (c) movement of organelles and cytoplasm up and down the axon.
   (d) movement of the axon terminal to synapse with a new postsynaptic cell.
   (e) none of these

8. Match the numbers of the appropriate characteristics with the two types of potentials. Characteristics may apply to one or both types.

   (a) action potential 1. all-or-none
   (b) graded potential 2. can be summed
   (c) amplitude decreases with distance
   (d) exhibits a refractory period
   (e) amplitude depends on strength of stimulus
   (f) has no threshold
Neurons: Cellular and Network Properties

9. Match the glial cell(s) on the right to the functions on the left. There may be more than one correct answer for each function.

| (a) modified immune cells | 1. astrocytes |
| (b) help form the blood-brain barrier | 2. ependymal cells |
| (c) form myelin | 3. microglia |
| (d) separate CNS fluid compartments | 4. oligodendrocytes |
| (e) found in peripheral nervous system | 5. satellite cells |
| (f) found in ganglia | 6. Schwann cells |

10. List the four major types of ion channels found in neurons. Are they chemically gated, mechanically gated, or voltage-gated?

11. Arrange the following events in the proper sequence:
   (a) Efferent neuron reaches threshold and fires an action potential.
   (b) Afferent neuron reaches threshold and fires an action potential.
   (c) Effector organ responds by performing output.
   (d) Integrating center reaches decision about response.
   (e) Sensory organ detects change in the environment.

12. An action potential is (circle all correct answers)
   (a) a reversal of the Na⁺ and K⁺ concentrations inside and outside the neuron.
   (b) the same size and shape at the beginning and end of the axon.
   (c) initiated by inhibitory postsynaptic graded potentials.
   (d) transmitted to the distal end of a neuron and causes release of neurotransmitter.

13. Choose from the following ions to fill in the blanks correctly: Na⁺, K⁺, Ca²⁺, Cl⁻.
   (a) The resting cell membrane is more permeable to ______ than to ______. Although ______, contribute little to the resting membrane potential, they play a key role in generating electrical signals in excitable tissues.
   (b) The concentration of ______ is 12 times greater outside the cell than inside.
   (c) The concentration of ______ is 30 times greater inside the cell than outside.
   (d) An action potential occurs when ______ enter the cell.
   (e) The resting membrane potential is due to the high ______ permeability of the cell.

14. What is the myelin sheath?

15. List two factors that enhance conduction speed.

16. List three ways neurotransmitters are removed from the synapse.

17. Draw and label a graph of an action potential. Below the graph, draw the positioning of the K⁺ and Na⁺ channel gates during each phase.

Level Two Reviewing Concepts

18. Create a map showing the organization of the nervous system using the following terms, plus any terms you choose to add:

- afferent signals
- astrocyte
- autonomic division
- brain
- efferent neuron
- ependymal cell
- glands
- glial cells
- integration
- interneuron
- microglia
- muscles
- neuron
- neurotransmitter
- oligodendrocyte
- parasympathetic division
- peripheral division
- satellite cell
- Schwann cell
- sensory division
- somatic motor division
- spinal cord
- stimulus
- sympathetic division
- target

19. What causes the depolarization phase of an action potential? (Circle all that apply.)
   (a) K⁺ leaving the cell through voltage-gated channels
   (b) K⁺ being pumped into the cell by the Na⁺-K⁺-ATPase
   (c) Na⁺ being pumped into the cell by the Na⁺-K⁺-ATPase
   (d) Na⁺ entering the cell through voltage-gated channels
   (e) opening of the Na⁺ channel inactivation gate

20. Name any four neurotransmitters, their receptor(s), and tell whether the receptor is an ion channel or a GPCR.

21. Arrange the following terms to describe the sequence of events after a neurotransmitter binds to a receptor on a postsynaptic neuron. Terms may be used more than once or not at all.
   (a) action potential fires at axon hillock
   (b) trigger zone reaches threshold
   (c) cell depolarizes
   (d) exocytosis
   (e) graded potential occurs
   (f) ligand-gated ion channel opens
   (g) local current flow occurs
   (h) salutary conduction occurs
   (i) voltage-gated Ca²⁺ channels open
   (j) voltage-gated K⁺ channels open
   (k) voltage-gated Na⁺ channels open

22. Match the best term (hyperpolarize, depolarize, repolarize) to the following events. The cell in question has a resting membrane potential of −70 mV.
   (a) membrane potential changes from −70 mV to −50 mV
   (b) membrane potential changes from −70 mV to −90 mV
   (c) membrane potential changes from +20 mV to −60 mV
   (d) membrane potential changes from −80 mV to −70 mV

23. A neuron has a resting membrane potential of −70 mV. Will the neuron hyperpolarize or depolarize when each of the following events occurs? (More than one answer may apply; list all those that are correct.)
   (a) Na⁺ enters the cell
   (b) K⁺ leaves the cell
   (c) Cl⁻ enters the cell
   (d) Ca²⁺ enters the cell

24. Define, compare, and contrast the following concepts:
   (a) threshold, subthreshold, suprathreshold, all-or-none, overshoot, undershoot
   (b) graded potential, EPSP, IPSP
   (c) absolute refractory period, relative refractory period
   (d) afferent neuron, efferent neuron, interneuron
   (e) sensory neuron, somatic motor neuron, sympathetic neuron, autonomic neuron, parasympathetic neuron
   (f) fast synaptic potential, slow synaptic potential
   (g) temporal summation, spatial summation
   (h) convergence, divergence

25. If all action potentials within a given neuron are identical, how does the neuron transmit information about the strength and duration of the stimulus?

26. The presence of myelin allows an axon to
   (a) produce more frequent action potentials.
   (b) conduct impulses more rapidly.
   (c) produce action potentials of larger amplitude.
   (d) produce action potentials of longer duration.
Neurons: Cellular and Network Properties

Level Three Problem Solving

27. If human babies’ muscles and neurons are fully developed and functional at birth, why can’t they focus their eyes, sit up, or learn to crawl within hours of being born? (Hint: Muscle strength is not the problem.)

28. The voltage-gated Na+ channels of a neuron open when the neuron depolarizes. If depolarization opens the channels, what makes them close when the neuron is maximally depolarized?

29. One of the pills that Jim takes for high blood pressure caused his blood K+ level to decrease from 4.5 mM to 2.5 mM. What happens to the resting membrane potential of his liver cells? (Circle all that are correct.)
   (a) decreases (b) increases (c) does not change (d) becomes more negative (e) becomes less negative (f) fires an action potential (g) depolarizes (h) hyperpolarizes (i) repolarizes

30. Characterize each of the following stimuli as being mechanical, chemical, or thermal:
   (a) bath water at 106 °F (b) acetylcholine (c) a hint of perfume (d) epinephrine (e) lemon juice (f) a punch on the arm

31. An unmyelinated axon has a much greater requirement for ATP than a myelinated axon of the same diameter and length. Can you explain why?

Level Four Quantitative Problems

32. The GHK equation is sometimes abbreviated to exclude chloride, which plays a minimal role in membrane potential for most cells. In addition, because it is difficult to determine absolute membrane permeability values for Na+ and K+, the equation is revised to use the ratio of the two ion permeabilities, expressed as \( \alpha = \frac{P_{Na}}{P_K} \):

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

Thus, if you know the relative membrane permeabilities of the two ions and their intracellular (ICF) and extracellular (ECF) concentrations, you can predict the membrane potential for a cell.

(a) A resting cell has an alpha value of 0.025 and the following ion concentrations:
   \( Na^+: ICF = 5 \text{ mM}, ECF = 135 \text{ mM} \)
   \( K^+: ICF = 150 \text{ mM}, ECF = 4 \text{ mM} \)

What is the cell’s membrane potential?

(b) The Na+ permeability of the cell in (a) suddenly increases so that \( \alpha = 20 \). Now what is the cell’s membrane potential?

(c) Mrs. Nguyen has high blood pressure, and her physician puts her on a drug whose side effect decreases her plasma (ECF) K+ from 4 mM to 2.5 mM. Using the other values in (a), now what is the membrane potential?

(d) The physician prescribes a potassium supplement for Mrs. Nguyen, who decides that if two pills are good, four must be better. Her plasma (ECF) K+ now goes to 6 mM. What happens to the membrane potential?

33. In each of the following scenarios, will an action potential be produced? The postsynaptic neuron has a resting membrane potential of −70 mV.

(a) Fifteen neurons synapse on one postsynaptic neuron. At the trigger zone, 12 of the neurons produce EPSPs of 2 mV each, and the other three produce IPSPs of 3 mV each. The threshold for the postsynaptic cell is −50 mV.

(b) Fourteen neurons synapse on one postsynaptic neuron. At the trigger zone, 11 of the neurons produce EPSPs of 2 mV each, and the other three produce IPSPs of 3 mV each. The threshold for the postsynaptic cell is −60 mV.

(c) Fifteen neurons synapse on one postsynaptic neuron. At the trigger zone, 14 of the neurons produce EPSPs of 2 mV each, and the other one produces an IPSP of 9 mV. The threshold for the postsynaptic cell is −50 mV.

Answers

Answers to Concept Check Questions

1. Compare your answer to the map in Figure 8.1.
2. Neurons that secrete neurohormones terminate close to blood vessels so that the neurohormones can enter the circulation.
3. A neuron is a single nerve cell. A nerve is a bundle of axons from many neurons.
4. See Figure 8.2.

5. Myelin insulates axon membranes. Microglia are scavenger cells in the CNS. Ependymal cells form epithelial barriers between fluid compartments of the CNS.

6. Schwann cells are in the PNS, and each Schwann cell forms myelin around a small portion of one axon. Oligodendrocytes are in the CNS, and one oligodendrocyte forms myelin around axons of several neurons.

7. For Ca2+, the electrical charge \( z = +2 \); the ratio of ion concentrations is \( 1/0.0001 = 10,000 \text{ or } 10^4 \). Log of \( 10^4 \) is 4 (see Appendix B). Thus \( E_{\text{syn}} \text{ (in mV)} = (61 \times 4)/(+2) = 122 \text{ mV} \).
8. (a) depolarize (b) depolarize
9. depolarize
10. (a) 1, (b) 2, (c) 2, (d) 1
11. The trigger zone for the sensory neurons is close to where the dendrites converge. You cannot tell where the trigger zone is for the anaxonic neuron. For multipolar neurons, the trigger zone is at the junction of the cell body and the axon.
12. Conductance refers to the movement of ions across a cell membrane. Conduction is the rapid, undiminished movement of an electrical signal down the axon of a neuron.
13. (b)
14. The membrane potential depolarizes and remains depolarized.
15. During resetting, the activation gate is closing, and the inactivation gate is opening.
16. The action potential will go in both directions because the Na⁺ channels around the stimulation site have not been inactivated by a previous depolarization. See discussion of refractory periods.
17. (a), (c), (b)
18. Because different receptor subtypes work through different signal transduction pathways, targeting drugs to specific receptor subtypes decreases the likelihood of unwanted side effects.
19. Proteins are synthesized on the ribosomes of the rough endoplasmic reticulum; then the proteins are directed into the Golgi apparatus to be packaged into vesicles.
20. Mitochondria are the primary sites of ATP synthesis.
21. Mitochondria reach the axon terminal by fast axonal transport along microtubules.
22. The researchers concluded that some event between arrival of the action potential at the axon terminal and depolarization of the postsynaptic cell is dependent on extracellular Ca²⁺. We now know that this event is neurotransmitter release.

23. The exchange is secondary active transport because it uses energy stored in the H⁺ concentration gradient to concentrate neurotransmitter inside the vesicles.
24. SSRIs decrease reuptake of serotonin into the axon terminal, thereby increasing the time serotonin is active in the synapse.
25. Acetyl CoA is made from pyruvate, the end product of glycolysis, and CoA.
26. Neurotransmitter uptake is secondary active transport because it uses energy stored in the Na⁺ concentration gradient to concentrate neurotransmitter inside the axon terminal.
27. The postsynaptic neuron will fire an action potential, because the net effect would be a 17 mV depolarization to -70 - (-17) = -53 mV, which is just above the threshold of -55 mV.
28. The membrane potential does not change at the same time as the stimulus because the depolarization must travel from the point of the stimulus to the recording point.
29. Axon terminals convert (transduce) the electrical action potential signal into a chemical neurotransmitter signal.
30. Membrane depolarization makes the inside of the membrane more positive than the outside. Like charges repel one another, so the more positive membrane potential tends to repel Mg²⁺.

Answers to Figure Questions

Figure 8.7: The graded potential is stronger at B. On the graph, A is between 3 and 4, and B is about at 1.
Figure 8.14: (a) 4; (b) 2, 3; (c) 1; (d) 3; (e) 4
Figure 8.15: Area of 100 giant axons is 50.344 mm², \( r^2 = 16 \text{ mm} \), \( r = 4 \text{ mm} \), so diameter = 8 mm.
Figure 8.17: (a) -108 mV; (b) -85 mV
Figure 8.22: Amplification
Answers to Review Questions

Level One  Reviewing Facts and Terms

1. Sensory afferents carry messages from sensory receptors to CNS. Their cell bodies are located close to the CNS. Interneurons are completely contained within the CNS and are often extensively branched. Efferents carry signals from the CNS to effectors. They have short, branched dendrites and long axons.
2. Skeletal muscles; autonomic
3. Sympathetic or parasympathetic
4. (a) 3, (b) 1, (c) 2, (d) 5, (e) 4
5. Neurons and glial cells
6. See Figs. 8.2 and 8.3.
7. (c). Answer (b) is only partly correct because not all axonal transport uses microtubules and not all substances moved will be secreted.
8. (a) 1, 4; (b) 2, 3, 5, 6
9. (a) 3, (b) 1, (c) 4, 6; (d) 2, (e) 5, 6; (f) 5
10. Na\(^+\) channels (voltage-gated along axon; any type of gating on dendrites); voltage-gated K\(^+\) channels along axon; voltage-gated Ca\(^{2+}\) channels in axon terminal; chemically gated Cl\(^-\) channels
11. (e) – (b) – (d) – (a) – (c)
12. (b) and (d)
13. (a) K\(^+\), Na\(^+\), Na\(^+\), (b) Na\(^+\), (c) K\(^+\), (d) Na\(^+\), (e) K\(^+\)
14. Insulating membranes around neurons that prevent current leak
15. Larger axon diameter and the presence of myelin
16. Enzymatic degradation, reabsorption, and diffusion
17. See Figs. 8.9, 8.10, and 8.12.

Level Two  Reviewing Concepts

18. See Figs. 8.1 and 8.5.
19. (d)
20. See Tbl. 8.4.
21. (f) – (c) – (g) – (e) – (b) – (k) – (c) – (a) – (b) – (j) – (i) – (d)
22. (a) depolarize, (b) hyperpolarize, (c) repolarize, (d) depolarize
23. (a) depolarize, (b) hyperpolarize, (c) hyperpolarize, (d) depolarize
24. (a) Threshold signals trigger action potentials. Suprathreshold also trigger action potentials, but subthreshold do not unless summed. Action potentials are all-or-none events. Overshoot—portion of the action potential above 0 mV. Undershoot—after-hyperpolarization portion of the action potential. (b) Graded potentials may be depolarizing or hyperpolarizing. Graded potential in a postsynaptic cell is an EPSP if depolarizing and an IPSP if hyperpolarizing. (c) No stimulus can trigger another action potential during the summation—multiple stimuli arrive at the trigger zone close together in time. Spatial summation—multiple stimuli from different locations arrive simultaneously at the trigger zone. (b) Divergence—a single neuron branches and its collaterals synapse on multiple targets. Convergence—many presynaptic neurons provide input to a smaller number of postsynaptic neurons.
25. Strength is coded by the frequency of action potentials; duration is coded by the duration of a train of repeated action potentials.
26. (b)

Level Three  Problem Solving

27. All the necessary synapses have not yet been made between neurons or between neurons and effectors.
28. Inactivation gates also respond to depolarization, but they close more slowly than the activation gates open, allowing ions to flow for a short period of time.
29. (b), (d), and (h)
30. (a) thermal, (b) chemical, (c) chemical, (d) chemical, (e) chemical, (f) mechanical
31. Unmyelinated axons have many ion channels, so more ions cross during an action potential and must be returned to their original compartments by the Na\(^+\)-K\(^+\)-ATPase, using energy from ATP.

Level Four  Quantitative Problems

32. (a) –80 mV (b) +63 mV (c) –86 mV (d) –73 mV
33. (a) \((12 \times 2 \text{ mV} = 24) + (3 \times -3 \text{ mV} = -9) = \text{signal strength} = 15. V_m = -70 + 15 = -55. \text{Threshold is} -50, \text{so no action potential.} (V_m \text{ must be equal to or more positive than threshold.}) (b) Signal = +13. V_m = -57. Action potential will fire. (c) Signal = +19. V_m = -51. No action potential.

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The Central Nervous System