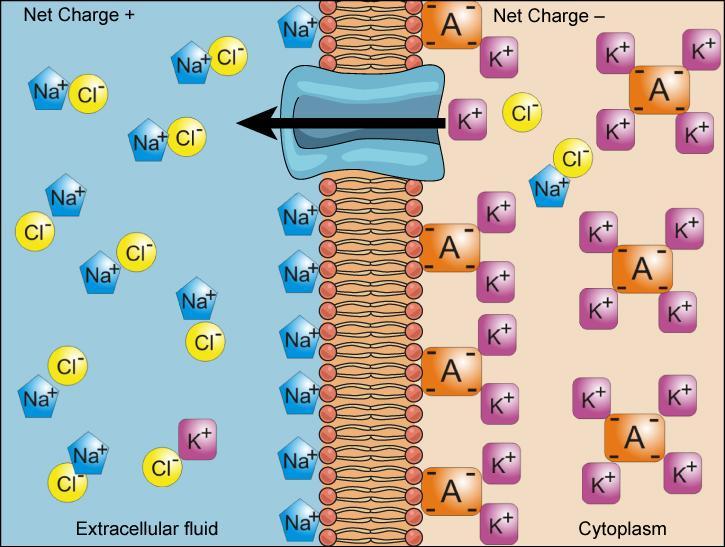
Chapter 8: The Electrochemical Gradient

# Electrochemical Gradient

We have discussed simple concentration gradients (link to previous chapter)—a substance's differential concentrations across space or a membrane—but in living systems, gradients are more complex. Because ions move into and out of cells and because cells contain proteins that do not move across the membrane and are mostly negatively charged, there is also an electrical gradient, a difference of charge, across the plasma membrane. The interior of living cells is electrically negative in comparison to the extracellular fluid due to ion concentration variations on either side of the membrane, the difference in charge/voltage across the plasma membrane is called the **membrane potential**. For example, cells have higher intracellular concentrations of potassium (K+) and lower intracellular concentrations of sodium (Na+) than the extracellular fluid. Thus, in a living cell, the concentration gradient of Na+ tends to drive it into the cell, and its electrical gradient (a positive ion) also drives it inward to the negatively charged interior. However, the situation is more complex for other ions, such as potassium. The electrical gradient of K+, a positive ion, also drives it into the cell, but the concentration gradient of K+ drives K+ out of the cell (Figure 8-1). We call the combined concentration gradient and electrical charge that affects an ion its **electrochemical gradient**.

In summary, ions including Na+ and K+ will still have a concentration gradient and the direction of passive transport will not be changed due to the fact that there is also an electrochemical gradient; rather, the force behind it would be slowed if a positively charged ion were being passively transported to the extracellular side of the membrane.

Figure 8-1 illustrates a membrane bilayer with a potassium channel embedded in it. The cytoplasm has a high concentration of potassium associated with a negatively charged molecule (such as a protein). The extracellular fluid has a high concentration of sodium associated with chlorine ions.If the channel embedded in the membrane is a sodium channel, then the concentration gradient moves the sodium inside the cell passively from high concentration outside the cell toward the lower concentration inside. The speed of movement within that channel is fast because the positive sodium ion is moving toward the negative charge inside of the cell,the positive ion is pulled toward the negative intracellular location. But if the channel is a potassium channel, then the potassium ions would move down their concentration gradient to outside the cell slowly because it is a positive ion moving toward the outside of the cell which has an overall positive charge. In this case, the positive ion is repelled by the positive extracellular environment.



**Figure 8-1: The Electrochemical Gradient.** Electrochemical gradients arise from the combined effects of concentration gradients and electrical gradients. Structures labeled A represent proteins.

All functions performed by the nervous system—from a simple motor reflex to more advanced functions such as making a memory or a decision—require neurons to communicate with one another. While humans use words and body language to communicate, neurons use electrical and chemical signals. Just like a person in a committee, one neuron usually receives and synthesizes messages from multiple other neurons before "making the decision" to send the message on to other neurons.

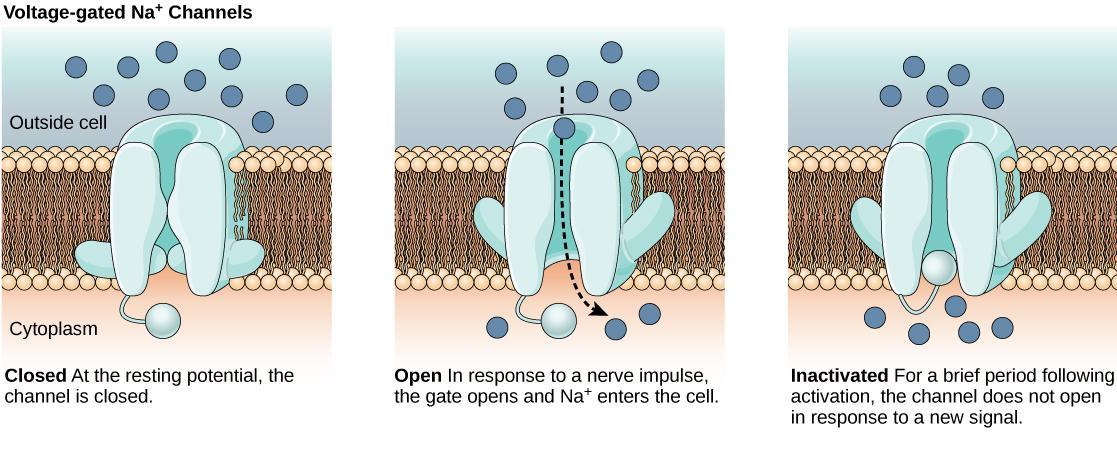
# Nerve Impulse Transmission within a Neuron

For the nervous system to function, neurons must be able to send and receive signals. These signals are possible because each neuron has a charged cellular membrane, also termed the membrane potential (a voltage difference between the inside and the outside), and the charge of this membrane can change in response to chemicals called **neurotransmitters** that are released from other neurons and environmental stimuli. To understand how neurons communicate, one must first understand the basis of the baseline or 'resting' membrane potential.

## Neuronal Charged Membranes

The lipid bilayer that surrounds a neuron is impermeable to charged molecules or ions. Ions must pass through special proteins called ion channels that span the membrane to enter or exit the neuron. Ion channels have different configurations: open, closed, and inactive, as illustrated in Figure 8-2. Some ion channels need to be activated to open and allow ions to pass into or out of the cell. These ion channels are sensitive to the environment and can change their shape accordingly. Ion channels that change their structure in response to differences in voltage, or changes in membrane potential are called **voltage-gated ion channels**. Voltage-gated ion channels regulate the relative concentrations of different ions inside and outside the cell.

In figure 8-2, the first image shows a closed voltage-gated sodium channel when the cell is at resting membrane potential. In response to a nerve impulse, the channel opens, allowing sodium to enter the cell. After the impulse, the channel enters an inactive state. The channel closes by a different mechanism and, for a brief period, does not reopen in response to a new nerve impulse.



**Figure 8-2: Voltage gated ion channels.** Voltage-gated ion channels open in response to changes in membrane voltage. After activation, they become inactivated for a brief period and will no longer open in response to a signal.

## Resting Membrane Potential

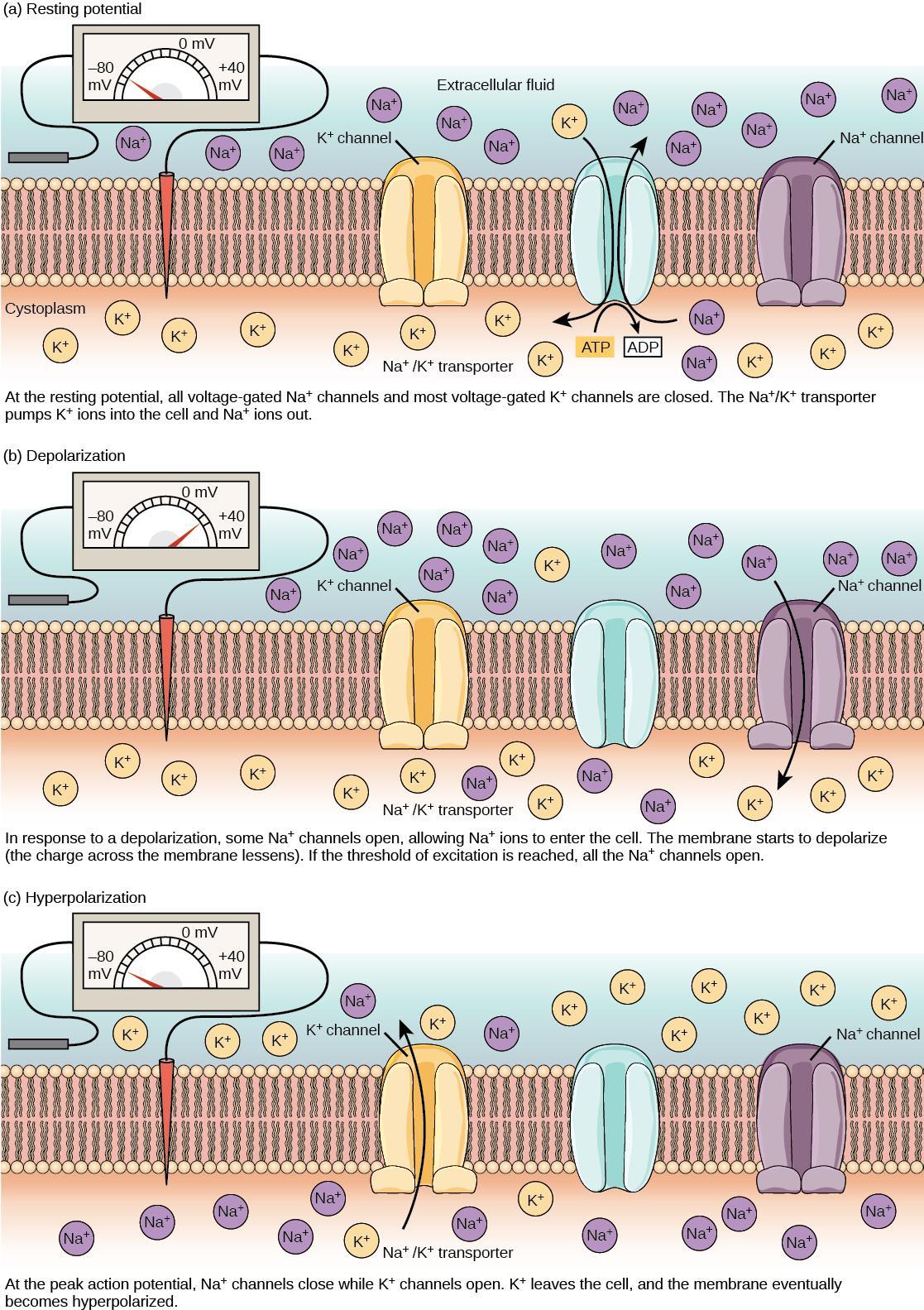
A resting neuron has a negatively charged cytoplasm. The interior of the cell is approximately 70 millivolts more negative than the outside (−70 mV, note that this number varies by neuron type and by species). The negative charge within the cell is created by the increased permeability of the cell membrane to potassium ion movement than the sodium ion movement. In neurons, potassium ions are maintained at high concentrations within the cell, while sodium ions are at high concentrations outside of the cell. The cell possesses potassium and sodium leakage channels that allow the two cations to diffuse down their concentration gradient. However, neurons have far more potassium leakage channels than sodium leakage channels. Therefore, potassium diffuses out of the cell at a much faster rate than sodium leaks inside. Because more cations are leaving the cell than are entering, this causes the interior of the cell to be negatively charged relative to the outside of the cell. This difference in voltage is the resting membrane potential (Figure 8-3). Therefore, the negative resting membrane potential is created and maintained by increasing the concentration of cations outside the cell (in the extracellular fluid) relative to inside the cell (in the cytoplasm). Alternatively, if the membrane were equally permeable to all ions and there was no way to pump ions against their concentration gradient, each type of ion would flow across the membrane, and the system would reach equilibrium (0 mV). Because ions cannot simply cross the membrane at will, there are different concentrations of several ions inside and outside the cell, as shown in the table below.

The actions of the sodium-potassium pump help to maintain the resting potential, once established. Recall that the sodium-potassium pump transports two K+ ions into the cell while removing three Na+ ions per ATP consumed (See Chapter 7). As more cations are expelled from the cell than taken in, the inside of the cell becomes more negatively charged relative to the extracellular fluid.

As stated above, the sodium-potassium pump moves sodium and potassium ions against the concentration gradient. This results in a higher concentration of sodium outside the cell (extracellular space), and a higher concentration of potassium inside the cell (cytoplasm). Other ions also have unequal concentrations of ions inside of the cell (cytoplasm) and outside the cell (extracellular space) (Table 8-1). For example, chloride ions (Cl–) tend to accumulate outside of the cell, rather than the inside. And, calcium ions (Ca2+) typically have a higher concentration outside the cell than inside. The difference in ions facilitates cell processes like transport of molecules like glucose into the epithelial cells of the small intestine, or the sending of a signal through a nerve cell. Interestingly, organelles such as the lysosome and ER have a unique ion environment maintained by its organelle membrane that is different from what is in the cytoplasm, which also helps the organelle in its specialized function.

**Table 8-1: Ion Concentration Inside and Outside the Plasma membrane of Neurons.**

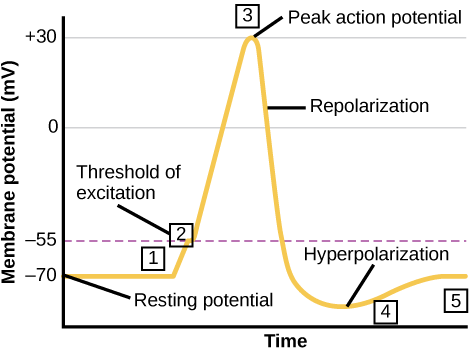
**Ion Concentration Inside and Outside the Plasma membrane of Neurons. 
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**Figure 8-3: Polarization of the plasma membrane.** The (a) resting membrane potential is a result of different concentrations of Na+ and K+ ions inside and outside the cell. A nerve impulse causes Na+ to enter the cell, resulting in (b) depolarization. At the peak action potential, K+ channels open, and the cell becomes (c) hyperpolarized.

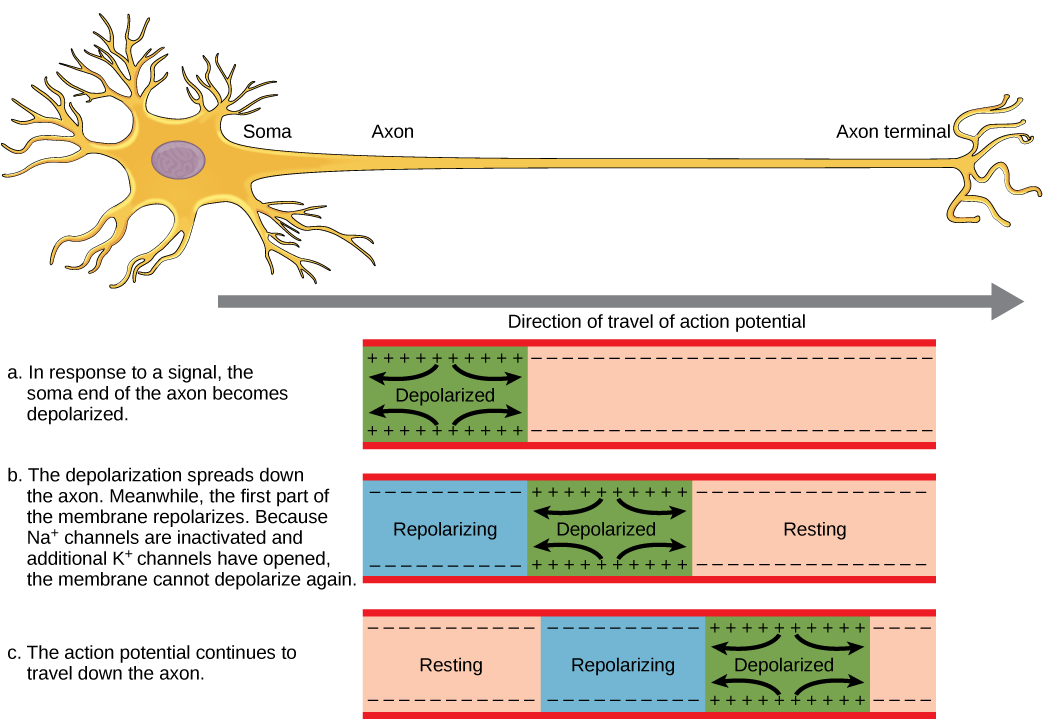
## Action Potential

A neuron can receive input from other neurons and, if this input is strong enough, send the signal to downstream neurons. A chemical called a neurotransmitter carries the transmission of a signal *between* neurons. A brief reversal of the resting membrane potential called an action potential carries the transmission of an electrical signal *within* a neuron (from dendrite to axon terminal). When neurotransmitter molecules bind to receptors located on a neuron's dendrites, ligand-gated ion channels open. This is when the chemical signal (neurotransmitter) is converted to an electrical signal. At excitatory synapses, the opening of ion channels allows positive ions to enter the neuron. It results in depolarization of the membrane and a decrease in the difference in voltage between the inside and outside of the neuron. A stimulus from a sensory cell or another neuron depolarizes the target neuron to its threshold of excitation (-55 mV). Na+ channels in the axon hillock open, allowing positive ions to enter the cell (Figure 8-4 and Figure 8-5). Once the sodium channels open, the neuron completely depolarizes to a membrane potential of about +40 mV. Action potentials are considered an "all-or-nothing" event, in that, once it has reached the threshold potential, the neuron always completely depolarizes (reaches +40 mV). Once depolarization is complete, the cell must now "reset" its membrane voltage back to the resting potential. This means the Na+ channels close and cannot be reopened for a short time. This begins the neuron's refractory period, in which it cannot produce another action potential because its sodium channels will not open. At the same time, voltage-gated K+ channels open, allowing K+ to leave the cell. As K+ ions leave the cell, the membrane potential once again becomes negative. The diffusion of K+ out of the cell hyperpolarizes the cell, in that the membrane potential becomes more negative than the cell's normal resting potential. At this point, the sodium channels will return to their resting state, meaning they are ready to open again if the membrane potential again exceeds the threshold potential. Eventually, the extra K+ ions diffuse into the cell through the potassium leakage channels, bringing the cell from its hyperpolarized state, back to its resting membrane potential.Figure 8-4 illustrates the membrane potential in millivolts versus time. The membrane remains at the resting potential of -70 millivolts until a nerve impulse occurs in step 1. Ligand-gated sodium channels open, and the potential begins to rapidly climb past the threshold of excitation of -55 millivolts, at which point signals voltage-gated sodium channels open. At the peak action potential, the potential begins to drop as voltage-gated potassium channels open and sodium channels close rapidly. As a result, the membrane repolarizes past the resting membrane potential and becomes hyperpolarized. The membrane potential then gradually returns to normal.



**Figure 8-4: Action Potential.** The formation of an action potential in five steps: (1) A stimulus from a sensory cell or another neuron causes the target cell to depolarize toward the threshold potential by causing ligand-gated Na+ channels to open. (2) If the threshold of excitation is reached, this causes voltage-gated Na+ channels open, and the membrane depolarizes. (3) At the peak action potential, voltage-gated K+ channels open and K+ begins to leave the cell. At the same time, Na+ channels close. (4) The membrane becomes hyperpolarized as K+ ions continue to leave the cell. The hyperpolarized membrane is in a refractory period and cannot fire. (5) The K+ channels close, and the Na+/K+ transporter restores the resting potential.

The action potential travels from the soma down the axon to the axon terminal. The initiation of the action potential occurs when a signal from the soma causes the soma-end of the axon membrane to depolarize. The depolarization spreads down the axon (Figure 8-5).



**Figure 8-5: Spreading of the action potential.** The action potential is conducted down the axon as the axon membrane depolarizes, then repolarizes.

Meanwhile, the membrane at the start of the axon repolarizes. Because potassium channels are open and the sodium channels are inactivated, the membrane cannot depolarize again until the membrane potential reaches a point where the sodium channels are active. The action potential continues to spread down the axon in this way.

**Myelin and the Propagation of the Action Potential**

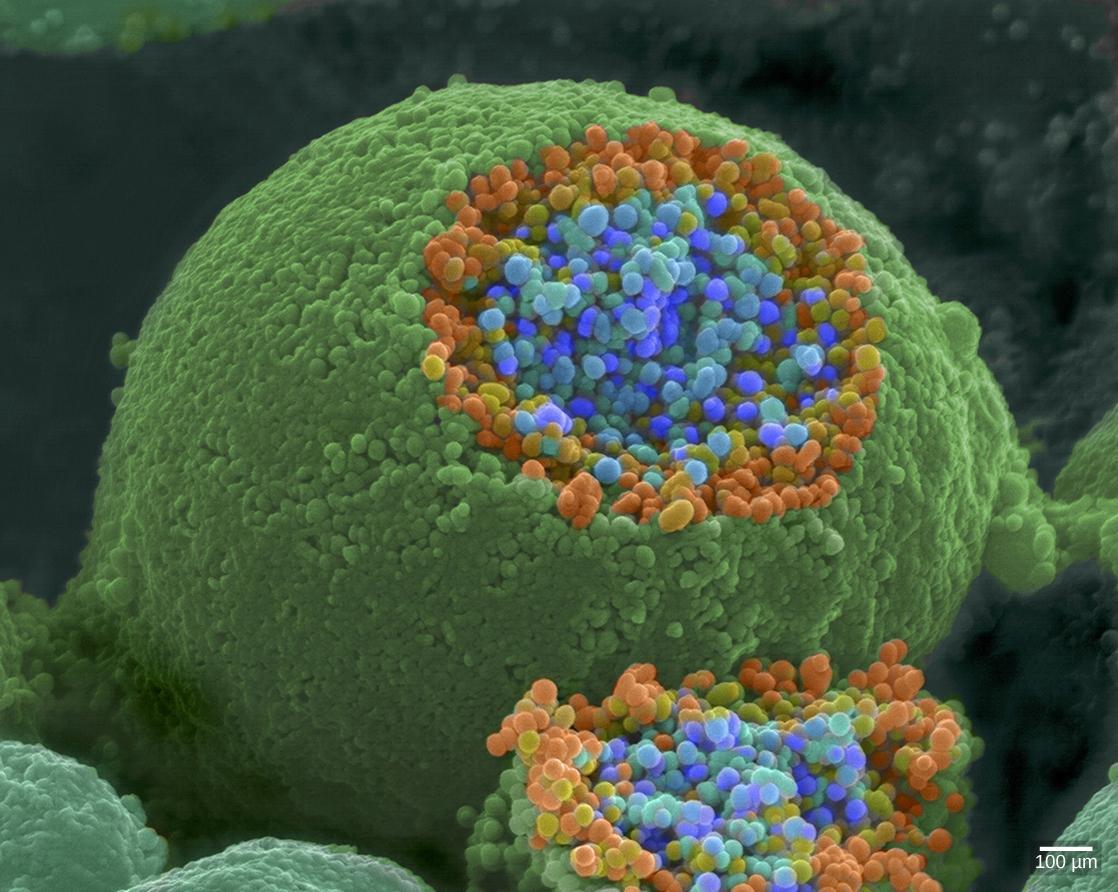
For an action potential to communicate information to another neuron, it must travel along the axon and reach the axon terminals where it can initiate neurotransmitter release. The speed of conduction of an action potential along an axon is influenced by both the diameter of the axon and the axon's resistance to the current leak. Myelin are types of neuronal cells that wrap axons and act as an insulator that prevents current from leaving the axon; this increases the speed of action potential conduction. In demyelinating diseases like multiple sclerosis, action potential conduction slows because of current leaks from previously insulated axon areas.

**Synaptic Transmission**

Transmission from one neuron to another occurs in the synapse. Synapses usually form between axon terminals and dendritic spines, but this is not universally true. There are also axon-to-axon, dendrite-to-dendrite, and axon-to-cell body synapses. The neuron transmitting the signal is called the presynaptic neuron, and the neuron receiving the signal is called the postsynaptic neuron. Note that these designations are relative to a particular synapse. Most neurons are both presynaptic and/or postsynaptic, depending on location in the neural pathway. There are two types of synapses: chemical and electrical.

**Chemical Synapse**

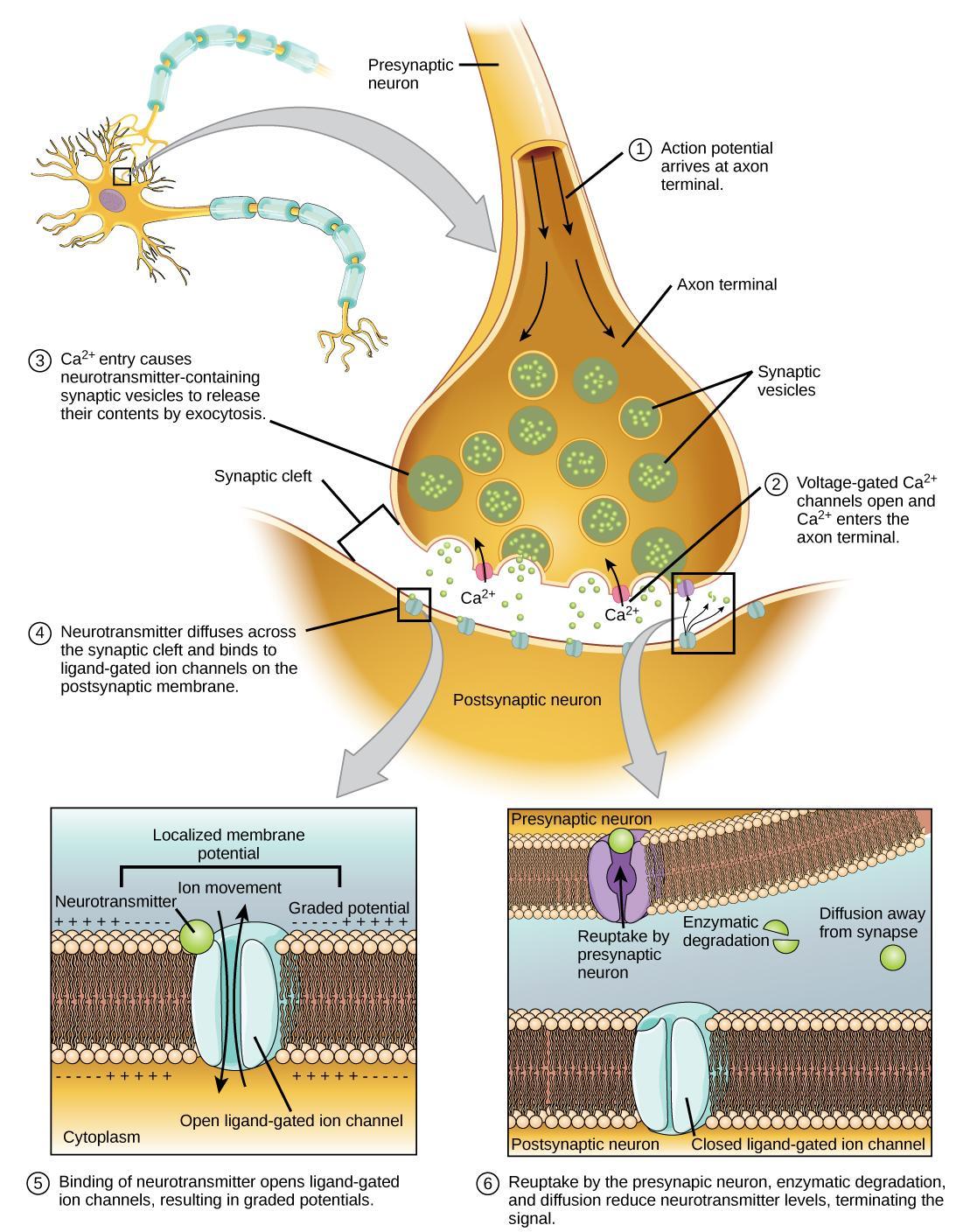
When an action potential reaches the axon terminal, it depolarizes the membrane and opens voltage-gated Na+ channels. Na+ ions enter the cell, further depolarizing the presynaptic membrane. This depolarization causes voltage-gated Ca2+ channels to open. Calcium ions entering the cell initiate a signaling cascade that causes small membrane-bound vesicles, called synaptic vesicles, containing neurotransmitter molecules to fuse with the presynaptic membrane. Synaptic vesicles are shown in Figure 8-6, which is an image from a scanning electron microscope. The axon terminal is spherical. A section is sliced off, revealing small blue and orange vesicles just inside.



**Figure 8-6: Synaptic Vesicles.** This pseudo colored image, taken with a scanning electron microscope, shows an axon terminal broken open to reveal synaptic vesicles (blue and orange) inside the neuron.

The fusion of a vesicle with the presynaptic membrane causes neurotransmitters to be released into the synaptic cleft. The **synaptic cleft** is the extracellular space between the presynaptic and postsynaptic membranes (Figure 8-7). The neurotransmitter diffuses across the synaptic cleft and binds to receptor proteins on the postsynaptic membrane. In this way, the electrical signal (change in voltage) from the presynaptic neuron is converted to a chemical signal (release of neurotransmitter) in the synaptic cleft.

Figure 8-7 shows a narrow axon of a presynaptic cell widening into a bulb-like axon terminal. A narrow synaptic cleft separates the axon terminal of the presynaptic cell from the postsynaptic cell. In step 1, an action potential arrives at the axon terminal (electrical signal). In step 2, the action potential causes voltage-gated calcium channels in the axon terminal to open, allowing calcium to enter. In step 3, calcium influx causes neurotransmitter-containing synaptic vesicles to fuse with the plasma membrane. Contents of the vesicles are released into the synaptic cleft by exocytosis (chemical signal). In step 4, neurotransmitter diffuses across the synaptic cleft and binds ligand-gated ion channels on the postsynaptic membrane, causing the channels to open (See Chapter 8). In step 5, the open channels cause ion movement into or out of the cell, resulting in a localized change in membrane potential (electrical signal). In step 6, reuptake by the presynaptic neuron, enzymatic degradation, and diffusion reduce neurotransmitter levels, terminating the signal.



**Figure 8-7: Synapse communication.** Communication at chemical synapses requires the release of neurotransmitters. When the presynaptic membrane is depolarized, voltage-gated Ca2+ channels open and allow Ca2+ to enter the cell. The calcium entry causes synaptic vesicles to fuse with the membrane and release neurotransmitter molecules into the synaptic cleft. The neurotransmitter diffuses across the synaptic cleft and binds to ligand-gated ion channels in the postsynaptic membrane, resulting in a localized depolarization or hyperpolarization of the postsynaptic neuron.

The binding of a specific neurotransmitter causes particular ion channels, in this case, ligand-gated channels, on the postsynaptic membrane to open. Neurotransmitters can either have excitatory or inhibitory effects on the postsynaptic membrane, as detailed in the table below. For example, the release of acetylcholine at the synapse between a nerve and muscle (called the neuromuscular junction) by a presynaptic neuron causes postsynaptic Na+ channels to open. Na+ enters the postsynaptic cell and causes the postsynaptic membrane to depolarize. This depolarization is called an excitatory postsynaptic potential (EPSP) and makes the postsynaptic neuron more likely to fire an action potential. The release of neurotransmitter at inhibitory synapses causes inhibitory postsynaptic potentials (IPSPs), hyperpolarization of the presynaptic membrane. For example, the release of the neurotransmitter GABA (gamma-aminobutyric acid) from a presynaptic neuron, it binds to and opens Cl- channels. Cl- ions enter the cell and hyperpolarize the membrane, making the neuron less likely to fire an action potential.

Once neurotransmission has occurred, the neurotransmitter must be removed from the synaptic cleft so the postsynaptic membrane can "reset" and be ready to receive another signal. Removal of the neurotransmitters occurs in three ways: the neurotransmitter can diffuse away from the synaptic cleft, enzymes can degrade it in the synaptic cleft, or it can be recycled (sometimes called reuptake) by transporter proteins in the presynaptic neuron. Several drugs act at this step of neurotransmission. For example, some Alzheimer's medications work by inhibiting acetylcholinesterase, the enzyme that degrades acetylcholine. This inhibition of the enzyme essentially increases neurotransmission at synapses that release acetylcholine. Once released, the acetylcholine stays in the cleft longer and can continually bind and unbind to postsynaptic receptors.

**Electrical Synapse**

While electrical synapses are fewer in number than chemical synapses, they are found in all nervous systems and play important and unique roles. The mode of neurotransmission in electrical synapses is quite different from that in chemical synapses. In an electrical synapse, the presynaptic and postsynaptic membranes are very close together and physically connected by channel proteins forming gap junctions (see Chapter 6). Gap junctions allow current to pass directly from one cell to the next. In addition to the ions that carry this current, other molecules, such as ATP, can diffuse through the large gap junction pores.

There are key differences between chemical and electrical synapses. Because chemical synapses depend on the release of neurotransmitter molecules from synaptic vesicles to pass on their signal, there is an approximately one-millisecond delay between when the axon potential reaches the presynaptic terminal and when the neurotransmitter leads to the opening of postsynaptic ion channels. Additionally, this signaling is unidirectional. Signaling in electrical synapses, in contrast, is virtually instantaneous (which is important for synapses involved in key reflexes), and some electrical synapses are bidirectional. Electrical synapses are also more reliable as they are less likely to be blocked, and they are important for synchronizing the electrical activity of a group of neurons. For example, recent research suggests electrical synapses in the thalamus regulate slow-wave sleep, and disruption of these synapses can cause seizures.

## Summary

Neurons have charged membranes because there are different concentrations of ions inside and outside of the cell. Voltage-gated ion channels control the movement of ions into and out of a neuron. When the depolarization of the neuronal membrane to at least the threshold of excitation, an action potential fires. The action potential propagates along a myelinated axon to the axon terminals. In a chemical synapse, the action potential causes the release of neurotransmitter molecules into the synaptic cleft. Through binding to postsynaptic receptors, the neurotransmitter can cause excitatory or inhibitory postsynaptic potentials by depolarizing or hyperpolarizing, respectively, the postsynaptic membrane. In electrical synapses, the action potential communicates directly to the postsynaptic cell through gap junctions, which are large channel proteins that connect the pre-and postsynaptic membranes. Synapses are not static structures and can be strengthened and weakened.