Chapter 48
Neurons, Synapses, and Signaling

Lecture Outline

Overview: Lines of Communication

- **Neurons** are nerve cells that transfer information within the body.
- Communication by neurons is based on two distinct types of signals: long-distance electrical signals and short-distance chemical signals.
  - The specialized structure of neurons allows them to use pulses of electrical current to receive, transmit, and regulate the long-distance flow of information within the body.
  - To transfer information between cells, neurons use a chemical signal that acts over very short distances.
- Neurons transmit sensory information, control heart rate, coordinate hand and eye movements, record memories, and generate dreams.
- Information is transmitted within neurons as an electrical signal, consisting of the movement of charged ions.
- The identity of the information being transmitted is encoded by the connections made by the active neuron.
- Interpreting signals in the nervous system involves sorting a complex set of neuronal paths and connections.
  - In complex animals, this higher-order processing is carried out in groups of neurons organized into a **brain** or into simpler clusters called **ganglia**.

Concept 48.1 Neuron organization and structure reflect function in information transfer

Nervous systems consist of circuits of neurons and supporting cells.

- There are three stages in the processing of information by nervous systems: sensory input, integration, and motor output.
- **Sensory neurons** transmit information from sensors that detect external stimuli (light, sound, heat, touch, smell, and taste) and internal conditions (blood pressure, blood CO$_2$ level, and muscle tension).
- This information is sent to processing centers in the brain or in ganglia, which integrate the sensory input, interpreting it in context.
- The vast majority of neurons in the brain are **interneurons**, which form local connecting neurons in the brain.
- Neurons extend out of processing centers and trigger muscle or gland activity.
For example, motor neurons transmit signals to muscle cells, causing them to contract.

In many animals, the neurons that carry out integration are organized in a central nervous system (CNS), which includes a brain and longitudinal nerve cord.

Neurons that bring information into and out of the CNS make up the peripheral nervous system (PNS).

When bundled together, these neurons form nerves.

Networks of neurons with intricate connections form nervous systems.

The neuron is the structural and functional unit of the nervous system.

Most of a neuron’s organelles, including its nucleus, are located in the cell body.

Two types of extensions arise from the cell body: numerous dendrites and a single axon.

- Dendrites are highly branched extensions that receive signals from other neurons.
- The single axon is a longer extension that transmits signals to neurons or effector cells.
- The axon joins the cell body at the axon hillock, where signals that travel down the axon are generated.

Each branched end of an axon transmits information to another cell at a junction called a synapse.

- Each axon branch ends in a synaptic terminal.

At most synapses, information is passed from the transmitting neuron (the presynaptic cell) to the receiving cell (the postsynaptic cell) by means of chemical messengers called neurotransmitters.

- The postsynaptic cell may be a neuron, muscle, or gland cell.
- Depending on the number of synapses a neuron has with other cells, its shape can vary from simple to quite complex.

Highly branched axons can transmit information to many target cells.

- Neurons with highly branched dendrites (such as interneurons) can receive input up to 100,000 synapses.

Glia are supporting cells that nourish neurons, insulate the axons of neurons, and regulate the extracellular fluid surrounding neurons.

- Glia outnumber neurons in the mammalian brain 10 to 50-fold.

Concept 48.2 Ion pumps and ion channels establish the resting potential of a neuron

- Because ions are unequally distributed between the interior of cells and the fluid that surrounds them, the inside of a cell is negatively charged relative to the outside.
  - Because the attraction of opposite charges across the plasma membrane is a source of potential energy, this charge difference, or voltage, is called the membrane potential.

- The membrane potential of a neuron that is not transmitting signals is called the resting potential and is typically between −60 and −80 mV.

- In neurons, inputs from other neurons or specific stimuli cause changes in the membrane potential that act as signals, transmitting and processing information.

The resting potential depends on ionic gradients that exist across the plasma membrane.
• Concentration gradients of potassium ions (K\(^+\)) and sodium ions (Na\(^+\)) across the plasma membrane of a neuron play critical roles in the formation of the resting potential.

• In mammalian neurons, the concentration of K\(^+\) is highest inside the cell, while the concentration of Na\(^+\) is highest outside.

• These gradients are maintained by sodium-potassium pumps in the plasma membrane.
  o The pumps use the energy of ATP hydrolysis to actively transport Na\(^+\) out of the cell and K\(^+\) into the cell.

• A sodium-potassium pump transports three Na\(^+\) ions out of the cell for every two K\(^+\) ions that it transports in.
  o This pumping generates a net export of positive charge, but the resulting voltage difference is only a few millivolts.

• Why then is there a voltage difference of 60-80 millivolts in a resting neuron?
  o Ion channels, pores formed by clusters of specialized proteins that span the membrane, allow ions to diffuse back and forth across the membrane.
  o As ions diffuse through channels, they carry with them units of electrical charge.
  o Any resulting net movement of positive or negative charge generates a membrane potential or voltage across the membrane.

• Concentration gradients of K\(^+\) and Na\(^+\) across the plasma membrane represent potential energy.
  o The ion channels that establish the membrane potential have selective permeability, allowing only certain ions to pass.
  o A potassium channel allows K\(^+\) to diffuse freely across the membrane but not other ions, such as Na\(^+\).

• Diffusion of K\(^+\) through open potassium channels is critical for formation of the resting potential.
  o The K\(^+\) concentration is 140 mM inside the cell, but only 5 mM outside. The chemical concentration gradient thus favors a net outflow of K\(^+\).

• A resting neuron has many open potassium channels, but very few open sodium channels.
  o Because Na\(^-\) and other ions can't readily cross the membrane, K\(^+\) outflow leads to a net negative charge inside the cell.
  o This buildup of negative charge within the neuron is the major source of the membrane potential.

• What stops the buildup of negative charge?
  o The excess negative charges inside the cell exert an attractive force that opposes the flow of additional positively charged potassium ions out of the cell.
  o The separation of charge (voltage) thus results in an electrical gradient that counterbalances the chemical concentration gradient of K\(^+\).

• The net flow of K\(^+\) out of a neuron proceeds until the chemical and electrical forces are in balance.

• Consider two chambers separated by an artificial membrane containing many open ion channels, all of which allow only K\(^+\) to diffuse across.
  o We place a solution of 140 mM potassium chloride (KCl) in the inner chamber and 5 mM KCl in the outer chamber.
The K⁺ ions will diffuse down their concentration gradient into the outer chamber.

Because the chloride ions (Cl⁻) cannot cross the membrane, there will be an excess of negative charge in the inner chamber.

At equilibrium, the electrical gradient will exactly balance the chemical gradient, with no further net diffusion of ions across the membrane.

- The magnitude of the membrane voltage at equilibrium for a particular ion is called that ion’s equilibrium potential ($E_{\text{ion}}$).
- For a membrane permeable to a single type of ion, $E_{\text{ion}}$ can be calculated using a formula called the Nernst equation.
- At human body temperature (37°C) and for an ion with a net charge of 1+, such as K⁺ or Na⁺, the Nernst equation is: $E_{\text{ion}} = 62 \text{ mV} (\log [\text{ion}]_{\text{outside}}/[\text{ion}]_{\text{inside}})$
- In our model, the membrane is permeable only to K⁺, and the Nernst equation can be used to calculate $E_K$, the equilibrium potential for K⁺, as -90mV.
  - The minus sign indicates that K⁺ is at equilibrium when the inside of the membrane is 90 mV more negative than the outside.
- Now assume that the membrane is permeable only to Na⁺; then $E_{Na}$, the equilibrium potential for Na⁺, is +62 mV.
  - This value indicates that, with this Na⁺ concentration gradient, Na⁺ is at equilibrium when the inside of the membrane is 62 mV more positive than the outside.
- Although the equilibrium potential for K⁺ is -90 mV, the resting potential of a mammalian neuron is somewhat less negative because of the small but steady movement of Na⁺ across the few open sodium channels in a resting neuron.
  - If the only open channels were selective for Na⁺, then a tenfold higher concentration of sodium in the outer chamber would result in an equilibrium potential ($E_{Na}$) of +62 mV.
  - Instead, the resting potential of an actual neuron is -60 to -80 mV.
  - The resting potential is much closer to $E_K$ than to $E_{Na}$ in a neuron because there are many open potassium channels but only a small number of open sodium channels.
- Neither K⁺ nor Na⁺ is at equilibrium, and there is a net flow of each ion (a current) across the membrane at rest.
  - The resting potential remains steady; the K⁺ and Na⁺ currents are equal and opposite.
  - Ion concentrations on either side of the membrane also remain steady because the charge separation needed to generate the resting potential is extremely small (about $10^{-12}$ mol/cm² of membrane).
  - This represents the movement of far fewer ions than would be required to alter the chemical concentration gradient.
- Under conditions that allow Na⁺ to cross the membrane more readily, the membrane potential will move toward $E_{Na}$ and away from $E_K$.
- This is precisely what happens during the transmission of a nerve impulse along an axon.

**Concept 48.3 Action potentials are the signals conducted by axons**

- The membrane potential of a neuron changes in response to a variety of stimuli.

*Gated ion channels are responsible for generating the signals of the nervous system.*
• Changes in membrane potential occur because neurons have **gated ion channels**, which open or close in response to stimuli.

• The opening or closing of gated ion channels alters the membrane’s permeability to particular ions, which in turn alters the membrane potential.

• Consider what happens when the gated K⁺ channels that are closed in a resting neuron open.
  o Opening K⁺ channels increases the membrane’s permeability to K⁺, increasing the net diffusion of K⁺ out of the neuron.

• The membrane potential approaches \( E_K \) (90 mV at 37°C), the separation of charge, or polarity, increases.
  o This increase in the magnitude of the membrane potential, called **hyperpolarization**, makes the inside of the membrane more negative.
  o Hyperpolarization results from any stimulus that increases either the outflow of positive ions or the inflow of negative ions.

• Although opening K⁺ channels causes hyperpolarization, opening some other types of ion channels, such as gated sodium channels, makes the inside of the membrane less negative.
  o This reduction in the magnitude of the membrane potential is called a **depolarization**.
  o Gated Na⁺ channels open and Na⁺ diffuses into the cell along its concentration gradient, causing a depolarization as the membrane potential shifts toward \( E_{Na} \) (+62 mV at 37°C).

• These changes in membrane potential are called **graded potentials** because the magnitude of the change—either hyperpolarization or depolarization—varies with the strength of the stimulus.
  o A larger stimulus causes a larger change in membrane permeability and, thus, a larger change in membrane potential.

• Graded potentials induce a small electrical current that leaks out of the neuron as it flows along the membrane. They thus decay with distance from their source.
  o Graded potentials are not the actual nerve signals that travel along axons, but they have a major effect on the generation of nerve signals.

*Changes in membrane voltage accompany an action potential.*

• If a depolarization shifts the membrane potential sufficiently, the result is a massive change in membrane voltage called an **action potential**.
  o Unlike graded potentials, actions potentials have a constant magnitude and can regenerate in adjacent regions of the membrane.
  o Action potentials can therefore spread along axons, making them well suited for transmitting a signal over long distances.

• Action potentials arise because some ion channels in neurons are **voltage-gated ion channels**, opening or closing when the membrane potential passes a particular level.

• If a depolarization opens voltage-gated sodium channels, the resulting flow of Na⁺ into the neuron results in further depolarization.

• Because the sodium channels are voltage gated, an increased depolarization in turn causes more sodium channels to open, leading to an even greater flow of current.
  o The result is a process of positive feedback that triggers a very rapid opening of all the voltage-gated sodium channels and a change in membrane potential.

• Action potentials occur whenever a depolarization increases the membrane voltage to a particular value, called the **threshold**.
For mammalian neurons, the threshold is a membrane potential of about -55 mV.

- Action potential occurs fully or not at all; it is an all-or-none response to stimuli.
  - Once an action potential is initiated, its magnitude is independent of the strength of the triggering stimulus.
  - This all-or-none property reflects the fact that depolarization opens voltage-gated sodium channels and the opening of sodium channels causes further depolarization.
  - The positive-feedback loop of depolarization and channel opening triggers an action potential whenever the membrane potential reaches the threshold.

*Let's take a closer look at the generation of action potentials.*

- The characteristic shape of the graph of an action potential reflects the large change in membrane potential resulting from the flow of ions through voltage-gated Na\(^+\) and K\(^+\) channels.
- Na\(^+\) channels open first, initiating the action potential.
- As the action potential proceeds, the Na\(^+\) channels undergo inactivation as movement of a portion of the channel blocks ion flow through the opening.
- Na\(^+\) channels remain inactivated until after the membrane returns to the resting potential and the channels close.
- K\(^+\) channels open more slowly than Na\(^+\) channels, but remain open and functional throughout the action potential.

- Voltage-gated channels shape the action potential in a series of stages:
  1. The membrane of the axon is at the resting potential and most voltage-gated Na\(^+\) channels are closed.
     - Some K\(^+\) channels are open, but most voltage-gated K\(^+\) channels are closed.
  2. When a stimulus depolarizes the membrane, some gated Na\(^+\) channels open, allowing more Na\(^+\) to diffuse into the cell.
     - The Na\(^+\) inflow causes further depolarization, which opens still more gated Na\(^+\) channels, allowing even more Na\(^+\) to diffuse into the cell.
  3. When the threshold is crossed, this positive-feedback cycle rapidly brings the membrane potential close to \(E_{Na}\). This stage is called the *rising phase*.
  4. Two events prevent the membrane potential from actually reaching \(E_{Na}\).
     - Voltage-gated Na\(^+\) channels inactivate soon after opening, halting Na\(^+\) inflow, while most voltage-gated K\(^+\) channels open, causing a rapid outflow of K\(^+\).
     - Both events quickly bring the membrane potential back toward \(E_{K}\). This stage is called the *falling phase*.
  5. In the final phase of an action potential, called the *undershoot*, the membrane’s permeability to K\(^+\) is higher than at rest, so the membrane potential is closer to \(E_{K}\) than it is at the resting potential.
     - The K\(^+\) channels eventually close, and the membrane potential returns to the resting potential.

- The Na\(^+\) channels remain inactivated during the falling phase and the early part of the undershoot.
  - A second depolarizing stimulus during this period is unable to trigger an action potential.
• The “downtime” when a second action potential cannot be initiated, is called the **refractory period** and sets a limit on the maximum frequency at which action potentials can be generated.
  - The refractory period is caused by inactivation of Na\(^+\) channels, not by a change in the ion gradients across the plasma membrane.
  - The flow of charged ions during an action potential involves far too few molecules to change the concentration of ions on either side of the plasma membrane.

• Action potentials of neurons are very brief—only 1–2 milliseconds (msec).
  - As a result, a neuron can produce action potentials at high frequencies, up to hundreds of times per second.

• The frequency with which a neuron generates action potentials varies in response to input, and differences in action potential frequency convey information about signal strength.
  - In hearing, an increased volume of a sound increases the action potential frequency in neurons connecting the ear to the brain.
  - Differences in the time interval between action potentials are in fact the only variable in transmission of information by an axon.

• Gated ion channels and action potentials have a central role in all nervous system function.
  - As a consequence, mutations in genes that encode ion channel proteins can cause nerve, muscle, brain, or heart diseases.

• The type of disease depends largely on where in the body the ion channel protein is expressed.
  - Mutations that affect voltage-gated Na\(^+\) channels expressed in skeletal muscle cells can cause myotonia, a periodic spasming of those muscles.
  - Mutations in a gene for a Na\(^+\) ion channel protein in the brain can cause epilepsy, in which excessive synchronized firing of groups of nerve cells causes seizures.

*Nerve impulses propagate themselves along an axon.*

• At the site where an action potential is initiated (usually the axon hillock), Na\(^+\) inflow during the rising phase creates an electrical current that depolarizes the neighboring region of the axon membrane.

• The depolarization in the neighboring region is large enough to reach the threshold, causing the action potential to be re-initiated there.

• This process is repeated as the action potential travels the length of the axon.
  - Because an action potential is an all-or-none event, the magnitude and duration of the action potential remain constant at each position along the axon.

• Immediately behind the traveling zone of depolarization due to Na\(^+\) inflow is a zone of repolarization due to K\(^+\) outflow.
  - In the repolarized zone, the Na\(^+\) channels remain inactivated.

• Consequently, the inward current that depolarizes the axon membrane ahead of the action potential cannot produce another action potential behind it.

• Thus, an action potential that starts at one end of an axon moves in only one direction—toward the synaptic terminals.

*Axon diameter and myelination affect conduction speed.*
• One factor that affects the speed at which action potentials are conducted along an axon is the diameter of the axon: The larger the axon’s diameter, the faster the conduction.

• This is because resistance to the flow of electrical current is inversely proportional to the cross-sectional area of a conductor (such as a wire or an axon).
  o In invertebrates, the conduction speed varies from several centimeters per second in very narrow axons to about 30 m/sec in the giant axons of some arthropods and molluscs, which function in rapid behavioral responses.

• How do narrow vertebrate axons conduct action potentials at high speed?

• The adaptation that enables fast conduction in the absence of large diameter is a myelin sheath, a layer of electrical insulation that surrounds vertebrate axons.
  o Insulation causes the depolarizing current associated with an action potential to spread farther along the axon interior, bringing more distant regions to the threshold sooner.

• Myelin sheaths are produced by two types of glia: oligodendrocytes in the CNS and Schwann cells in the PNS.
  o During development, specialized glia wrap axons in many layers of membrane.
  o These layers are mostly lipid, which is a poor conductor of electrical currents.

• In a myelinated axon, voltage-gated sodium channels are restricted to gaps in the myelin sheath called nodes of Ranvier.
  o Because extracellular fluid is in contact with the axon membrane only at the nodes, action potentials are not generated in the regions between the nodes.

• The inward current produced during the rising phase of the action potential at a node travels to the next node, where it depolarizes the membrane and regenerates the action potential.
  o This mechanism is called saltatory conduction because the action potential appears to jump along the axon from node to node.

• The great advantage of myelination is its space efficiency.
  o A myelinated axon 20 µm in diameter has a conduction speed faster than that of a squid giant axon that has a diameter 40 times greater.
  o Over 2,000 myelinated axons can be packed into the space occupied by one giant axon.

Concept 48.4 Neurons communicate with other cells at synapses

• In most cases, action potentials are not transmitted from neurons to other cells.
  o However, information is transmitted at the synapse.

• Electrical synapses contain gap junctions that do allow electrical current to flow directly from cell to cell.
  o In both vertebrates and invertebrates, electrical synapses synchronize the activity of neurons responsible for rapid, invariant behaviors.
  o For example, electrical synapses associated with the giant axons of squids and lobsters facilitate the swift execution of escape responses.
  o There are also many electrical synapses in the vertebrate brain.

• The vast majority of synapses are chemical synapses, which involve the release of a chemical neurotransmitter by the presynaptic neuron.
o The presynaptic neuron synthesizes the neurotransmitter and packages it in membrane-bound synaptic vesicles, which are stored in the neuron’s synaptic terminals.

- When an action potential reaches a synaptic terminal, it depolarizes the terminal membrane, opening voltage-gated calcium channels in the membrane.
  o Calcium ions (Ca\(^{2+}\)) diffuse into the terminal, and the rise in Ca\(^{2+}\) concentration in the terminal causes some of the synaptic vesicles to fuse with the terminal membrane, releasing the neurotransmitter.

- The neurotransmitter diffuses across the narrow synaptic cleft that separates the presynaptic neuron from the postsynaptic cell.
  o Diffusion time is very short because the gap is less than 50 nm across.

- The neurotransmitter binds to and activates a specific receptor in the postsynaptic membrane.

- Information transfer at the synapse can be modified more readily at chemical synapses than at electrical synapses.
  o A variety of factors can affect the amount of neurotransmitter that is released or the responsiveness of the postsynaptic cell.
  o Such modifications underlie an animal’s ability to alter its behavior and form the basis for learning or memory.

**Neural integration occurs at the cellular level.**

- At many chemical synapses, **ligand-gated ion channels** (also called **ionotropic receptors**) capable of binding to neurotransmitters are clustered in the membrane of the postsynaptic cell, directly opposite the synaptic terminal.

- Binding of the neurotransmitter (the receptor’s ligand) to the receptor opens the channel and allows specific ions to diffuse across the postsynaptic membrane.
  o The result is a **postsynaptic potential**, a change in the membrane potential of the postsynaptic cell.

- At some synapses, the ligand-gated ion channel is permeable to both Na\(^+\) and K\(^+\).
  o When the channel opens, the membrane potential depolarizes towards a value between \(E_K\) and \(E_{Na}\).
  o Because this depolarization brings the membrane potential toward threshold, it is called an **excitatory postsynaptic potential (EPSP)**.

- At other synapses, the ligand-gated ion channel is selectively permeable to only K\(^+\) or Cl\(^-\).
  o When the channel opens, the postsynaptic membrane hyperpolarizes to produce an **inhibitory postsynaptic potential (IPSP)** that moves the membrane potential farther from threshold.

- Various mechanisms rapidly clear neurotransmitters from the synaptic cleft and limit the duration of postsynaptic potentials.
  o Some neurotransmitters simply diffuse out of the synaptic cleft.
  o Other neurotransmitters are removed from the synaptic cleft by an enzyme that catalyzes hydrolysis of the neurotransmitter.
  o Neurotransmitters may be taken up by the presynaptic neuron through active transport and repackaged into synaptic vesicles.
  o Glia actively take up neurotransmitters at some synapses and metabolize them as fuel.

- The cell body and dendrites of a single postsynaptic neuron may receive inputs from chemical synapses with hundreds or thousands of synaptic terminals.
The magnitude of a postsynaptic potential varies with a number of factors, including the amount of neurotransmitter released by the presynaptic neuron.

As a graded potential, a postsynaptic potential becomes smaller with distance from the synapse.
  - By the time a single EPSP reaches the axon hillock, it is usually too small to trigger an action potential in a postsynaptic neuron.

Two EPSPs produced in rapid succession at the same synapse can be added in an effect called temporal summation.
  - Two EPSPs produced nearly simultaneously by different synapses on the same postsynaptic neuron can be added in an effect called spatial summation.

Through spatial and temporal summation, several EPSPs can depolarize the membrane at the axon hillock to the threshold, causing the postsynaptic neuron to produce an action potential.

Summation also applies to IPSPs: Two or more IPSPs occurring nearly simultaneously or in rapid succession have a larger hyperpolarizing effect than a single IPSP.

Through summation, an IPSP can also counter the effect of an EPSP.

This interplay between multiple excitatory and inhibitory inputs allows for integration in the nervous system.
  - The axon hillock is the neuron’s integrating center, where the membrane potential at any instant represents the summed effect of all EPSPs and IPSPs.
  - Whenever the membrane potential at the axon hillock reaches the threshold, an action potential is generated and travels along the axon to its synaptic terminals.
  - After the refractory period, the neuron may produce another action potential, provided the membrane potential at the axon hillock once again reaches threshold.

At some synapses, a neurotransmitter binds to a receptor that is not part of an ion channel.
  - At these synapses, the neurotransmitter binds to a metabotropic receptor.

Binding of a neurotransmitter to a metabotropic receptor activates a signal transduction pathway in the postsynaptic cell involving a second messenger.
  - This form of transmission has a slower onset, but its effects have a longer duration of minutes or even hours.
  - Second messengers modulate the responsiveness of postsynaptic neurons to inputs in diverse ways, such as by altering the number of open potassium channels.

cAMP is one of the best-studied secondary messengers in indirect synaptic transmission.

When the neurotransmitter norepinephrine binds to its metabotropic receptor, the neurotransmitter-receptor complex activates a G protein, which in turn activates adenylyl cyclase, the enzyme that converts ATP to cAMP.

Cyclic AMP activates protein kinase A, which phosphorylates specific ion channel proteins in the postsynaptic membrane, causing them to open or close.

Because of the amplifying effect of the signal transduction pathway, binding of a neurotransmitter to a metabotropic receptor can open or close many channels.

The same neurotransmitter can produce different effects on different types of cells.

There are more than 100 known neurotransmitters, belonging to five groups: acetylcholine, biogenic amines, amino acids, neuropeptides, and gases.
  - The response triggered depends on which receptor is expressed by the postsynaptic cell.
A single neurotransmitter may have more than a dozen receptors, including ionotropic and metabotropic types.

- The same neurotransmitter can excite postsynaptic cells expressing one receptor and inhibit postsynaptic cells expressing a different receptor.

Acetylcholine is vital for nervous system functions that include muscle stimulation, memory formation, and learning.

In vertebrates, there are two major classes of acetylcholine receptor: ligand-gated ion channels and metabotropic receptor.

- Ligand-gated ion channel function at the neuromuscular junction, where motor neurons synapse with skeletal muscle cells.
  - When acetylcholine released by motor neurons binds this receptor, the ion channel opens, producing an EPSP.
  - This excitatory activity is terminated by acetylcholinesterase, an enzyme in the synaptic cleft that hydrolyzes the neurotransmitter.

- The acetylcholine receptor active at the neuromuscular junction is also found in the PNS, where this ionotropic receptor can bind nicotine.
  - Nicotine’s effects as a physiological and psychological stimulant result from its binding to this receptor.

- Metabotropic acetylcholine receptors are found in the vertebrate CNS and heart.
  - In heart muscle, acetylcholine released by neurons activates an inhibitory signal transduction pathway.
  - The G proteins in the pathway inhibit adenylyl cyclase and open potassium channels in the muscle cell membrane. Both effects reduce the rate at which the heart pumps.

- Several natural and synthetic toxins disrupt neurotransmission by acetylcholine.
  - The nerve gas sarin inhibits acetylcholinesterase, causing a buildup of acetylcholine to levels that trigger paralysis.

- Certain bacteria produce a toxin that inhibits presynaptic release of acetylcholine to cause botulism.
  - Untreated botulism is fatal because muscles required for breathing fail to contract when acetylcholine release is blocked.
  - Injections of the toxin, Botox, smooth wrinkles by blocking transmission at synapses that control particular facial muscles.

Amino acid neurotransmitters are active in the vertebrate CNS and PNS.

- Glutamate is the most common CNS neurotransmitter.
  - Glutamate that binds to any of several types of ligand-gated ion channels has an excitatory effect on postsynaptic cells and plays a key role in the formation of long-term memory.

- The amino acid gamma-aminobutyric acid (GABA) is the neurotransmitter at most inhibitory synapses in the brain.
  - Binding of GABA to receptors in postsynaptic cells increases membrane permeability to Cl⁻, resulting in an IPSP.
  - Valium reduces anxiety through binding to a site on a GABA receptor.

- A third amino acid, glycine, acts at inhibitory synapses in parts of the CNS outside the brain.
  - Glycine binds to an ionotropic receptor inhibited by strychnine, used as a rat poison.
Biogenic amines are synthesized from amino acids.
- Norepinephrine, made from tyrosine, is an excitatory neurotransmitter in the autonomic nervous system.
- Outside the nervous system, norepinephrine functions as a hormone, as does the related biogenic amine epinephrine.
- The biogenic amines dopamine, made from tyrosine, and serotonin, made from tryptophan, are released at many sites in the brain and affect sleep, mood, attention, and learning.
  - Psychoactive drugs such as LSD and mescaline produce hallucinatory effects by binding to brain receptors for these neurotransmitters.
- Biogenic amines play a role in several nervous system disorders and treatments.
  - Parkinson’s disease is associated with a lack of dopamine in the brain.
  - Depression can be treated with drugs that increase the brain concentrations of biogenic amines: Prozac enhances the effect of serotonin by inhibiting its reuptake after release.

Neuropeptides, short amino acid chains, serve as neurotransmitters that operate via metabotropic receptors.
- The neuropeptide substance P is an excitatory neurotransmitter that mediates pain perception.
- Neuropeptide endorphins function as natural analgesics, decreasing pain perception.
  - Endorphins are produced in the brain during times of physical or emotional stress.
  - These neurotransmitters relieve pain, decrease urine output, depress respiration, and produce euphoria.
  - Because opiates bind to the same receptor proteins as endorphins, opiates mimic endorphins and produce many of the same physiological effects.
- Some neurons in vertebrates release dissolved gases like nitric oxide (NO) that act as local regulators.
  - During sexual arousal, certain neurons in human males release NO into the erectile tissue of the penis.
  - In response, smooth muscle cells in the blood vessel walls of the erectile tissue relax, which causes the blood vessels to dilate and fill the spongy erectile tissue with blood, producing an erection.
  - The erectile dysfunction drug Viagra increases the ability to achieve and maintain an erection by inhibiting an enzyme that terminates the action of NO.
- Unlike other neurotransmitters, NO is not stored in cytoplasmic vesicles but is instead synthesized on demand.
- NO diffuses into neighboring target cells, produces a change, and is broken down within a few seconds.
  - In its target cells, NO works like many hormones, stimulating an enzyme to synthesize a second messenger that directly affects cellular metabolism.
- Vertebrates produce small amounts of CO as a neurotransmitter.
- Carbon monoxide is generated by the enzyme heme oxygenase, one form of which is found in certain populations of neurons in the brain and PNS.
  - In the brain, CO regulates the release of hypothalamic hormones.
  - In the PNS, it acts as an inhibitory neurotransmitter that hyperpolarizes intestinal smooth muscle cells.