Chapter 48

Neurons, Synapses, and Signaling

Lecture Outline

Overview

- **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 current, consisting of the movement of charged ions.
- The connections made by a neuron specify what information is transmitted.
- Interpreting signals in the nervous system involves sorting a complex set of neuronal paths and connections.
- In more 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.

- In general, 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 CO₂ 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 make local connections.
- Neurons leave the processing centers in bundles called **nerves**, which may trigger muscle or gland activity.
  - For example, **motor neurons** transmit signals to muscle cells, causing them to contract.
• In many animals, such as the planarian, the neurons that carry out integration are organized in a **central nervous system (CNS)**, which includes a brain and a nerve cord.

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

**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.
  o **Dendrites** are highly branched extensions that receive signals from other neurons.
  o The **axon** is a longer extension that transmits signals to neurons or effector cells.
  o 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**.
  o 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**.
  o The postsynaptic cell may be a neuron, muscle, or gland cell.
  o Depending on the number of synapses a neuron has with other cells, its shape can vary from simple to quite complex.

• **Glia** are supporting cells that are essential for the structural integrity of the nervous system and for the normal functioning of neurons.
  o Different types of glia may nourish neurons, insulate the axons of neurons, or regulate the extracellular fluid surrounding neurons.
  o Glia outnumber neurons in the mammalian brain 10- to 50-fold.

**Concept 48.2 Ion pumps and ion channels maintain the resting potential of a neuron.**

• All cells have a voltage (difference in electrical charge) across their plasma membrane; this voltage is called the **membrane potential**.

• In neurons, inputs from other neurons or specific stimuli cause changes in this membrane potential, which act as signals to transmit and process information.

• 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 all neurons, the resting potential depends on the ionic gradients that exist across the plasma membrane.
  o In mammalian neurons, the extracellular fluid has a Na\(^+\) concentration of 150 millimolar (mM) and a K\(^+\) concentration of 5 mM.
  o In the cytosol, the Na\(^+\) concentration is 15 mM and the K\(^+\) concentration is 150 mM.

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

Gradients of K\(^+\) and Na\(^+\) across the plasma membrane represent potential energy.

Converting this chemical potential to electrical potential involves ion channels, pores formed by clusters of specialized proteins that span the membrane.

Ion channels allow ions to diffuse back and forth across the membrane.
- As ions diffuse through channels, they carry with them units of electrical charge.
- Any resulting net movement of positive or negative charge generates a voltage or potential across the membrane.

The ion channels that establish the membrane potential have selective permeability, meaning that they allow only certain ions to pass.
- For example, a potassium channel allows K\(^+\) to diffuse freely across the membrane but not other ions, such as Na\(^+\).

A resting neuron has many open potassium channels but very few open sodium channels.
- The diffusion of K\(^+\) through open potassium channels is critical for the formation of the resting potential.
- In the resting mammalian neuron, ion channels allow K\(^+\) to pass in either direction across the membrane.

Because the concentration of K\(^+\) is much higher inside the cell, there is a net outflow of potassium ions.

Because the potassium channels allow only K\(^+\) to pass, Cl\(^-\) and other anions inside the cell cannot accompany the K\(^+\) across the membrane.

As a result, the outflow of K\(^+\) leads to an excess of negative charge inside the cell.

This buildup of negative charge within the neuron is the source of the membrane potential.

The electrical potential itself prevents the buildup of negative charge from increasing indefinitely.

The excess negative charges inside the cell exert an attractive force that opposes the flow of additional positively charged K\(^+\) ions out of the cell.

The separation of charge (voltage) results in an electrical gradient.

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.
- 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 (\(E_{ion}\)).

For a membrane permeable to a single type of ion, \(E_{ion}\) 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:

\[ E_{\text{ion}} = \frac{62 \text{ mV} \log \frac{[\text{ion}]_{\text{outside}}}{[\text{ion}]_{\text{inside}}}}{ } \]

• 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.
  o 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.
  o 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.
  o 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.
  o Instead, the resting potential of an actual neuron is -60 to -80 mV.
  o 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.
  o The resting potential remains steady; the K⁺ and Na⁺ currents are equal and opposite.
  o 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 \( 10^{-12} \text{ mol/cm}^2 \) of membrane).
  o 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 plasma membrane of a resting neuron contains many open K⁺ channels but only a few open Na⁺ channels.
• When neurons are active, the number of open channels for these ions changes.
• The change occurs because neurons have **gated ion channels**, which open or close in response to stimuli.

**Gated ion channels are responsible for generating the signals of the nervous system.**

• If a cell has gated ion channels, the membrane's permeability to certain ions and its membrane potential may change in response to stimuli that open or close the ion channels.
  o The resulting changes in membrane potential can be measured directly by intracellular recordings of the state of a single neuron in real time.
• Consider what happens when the gated K⁺ channels that are closed in a resting neuron open.
• Opening more K\(^+\) channels increases the membrane’s permeability to K\(^+\), increasing the net diffusion of K\(^+\) out of the neuron.
• The inside of the membrane becomes more negative.
• As the membrane potential approaches \(E_K\) (90 mV at 37°C), the separation of charge, or polarity, increases.
• This increase in the magnitude of the membrane potential is a **hyperpolarization**.
  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.
• This reduction in the magnitude of the membrane potential is called a **depolarization**.
  o Gated Na\(^+\) channels open, Na\(^+\) diffuses into the cell, and the inside of the membrane becomes less negative.
• 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.
  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.
• Many of the gated ion channels in neurons are **voltage gated**, opening or closing in response to a change in the membrane potential.
• 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.
• The result is a very rapid opening of all the voltage-gated sodium channels.

**Changes in membrane voltage accompany an action potential.**
• **Action potentials** are changes in membrane voltage that serve as nerve impulses to carry information along an axon.
• Action potentials occur whenever a depolarization increases the membrane voltage to a particular value, called the **threshold**.
  o For mammalian neurons, the threshold is a membrane potential of about -50 mV.
• Action potential occurs fully or not at all; it is an all-or-none response to stimuli.
  o Once an action potential is initiated, its magnitude is independent of the strength of the triggering stimulus.
  o This all-or-none property reflects the fact that depolarization opens voltage-gated sodium channels and the opening of sodium channels causes further depolarization.
  o This positive-feedback loop of depolarization and channel opening triggers an action potential of maximal amplitude whenever the membrane potential reaches the threshold.
• Action potentials of neurons are very brief—only 1–2 milliseconds (msec).
• Therefore, a neuron can produce action potentials at high frequencies of up to hundreds of times per second.
• 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.

- 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. At the resting potential, 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 \(E_{Na}\).
     a. Voltage-gated Na\(^+\) channels inactivate soon after opening, thus halting Na\(^+\) inflow.
     b. 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 will be unable to trigger an action potential.
- The “downtime” following an action potential, 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.

_Nerve impulses propagate themselves along an axon._

- An action potential regenerates itself as it travels from the cell body to the synaptic terminals.
- 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 over and over again as the action potential travels the length of the axon.
  o At each position along the axon, the process is identical, such that the shape and magnitude of the action potential remain constant.
• 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.
• Action potentials are therefore prevented from traveling back toward the cell body.
• 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 mollusks, 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.
• Myelin sheaths are produced by two types of glia: oligodendrocytes in the CNS and Schwann cells in the PNS.
• During development, these specialized glia wrap axons in many layers of membrane.
• The membranes forming these layers are mostly lipid, which is a poor conductor of electrical currents.
• The myelin sheath provides electrical insulation for the axon, analogous to the plastic insulation that covers many electrical wires.
• The insulation provided by the myelin sheath has the same effect as increasing the axon’s diameter: It causes the depolarizing current associated with an action potential to spread farther along the interior of the axon, bringing more distant regions of the membrane to the threshold sooner.
• 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 More than 2,000 of those myelinated axons can be packed into the space occupied by just one giant axon.
• In a myelinated axon, voltage-gated sodium channels are restricted to gaps in the myelin sheath called nodes of Ranvier.
  o The extracellular fluid is in contact with the axon membrane only at the nodes.
As a result, 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 all the way to the next node, where it depolarizes the membrane and regenerates the action potential.
- This mechanism is called **saltatory conduction** because the action potential appears to jump along the axon from node to node.

**Concept 48.4 Neurons communicate with other cells at synapses.**

- When an action potential reaches the terminal of the axon, it generally stops.
- However, information is transmitted from a neuron to another cell at the synapse.
- Some synapses, called **electrical synapses**, contain gap junctions that allow electrical current to flow directly from cell to cell.
  - Action potentials travel directly from the presynaptic to the postsynaptic cell.
  - In both vertebrates and invertebrates, electrical synapses synchronize the activity of neurons responsible for rapid, invariant behaviors.
  - For example, electrical synapses associated with the giant axons of squids and lobsters facilitate the swift execution of escape responses. 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.
  - The cell body and dendrites of a single postsynaptic neuron may receive inputs from chemical synapses with hundreds or thousands of synaptic terminals.
  - 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.
  - Calcium ions (Ca$^{2+}$) then 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 gap, called the **synaptic cleft**, that separates the presynaptic neuron from the postsynaptic cell.
- Information transfer at the synapse can be modified more readily at chemical synapses than at electrical synapses.
  - A variety of factors can affect the amount of neurotransmitter that is released or the responsiveness of the postsynaptic cell.
  - 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** capable of binding to the neurotransmitter are clustered in the membrane of the postsynaptic cell, directly opposite the synaptic terminal.
• Binding of the neurotransmitter opens the channel and allows specific ions to diffuse across the postsynaptic membrane.
• The result is generally a postsynaptic potential, a change in the membrane potential of the postsynaptic cell.
• At some synapses, the neurotransmitter binds to a type of channel through which both Na\(^+\) and K\(^+\) can diffuse.
  o When the channel opens, the postsynaptic membrane depolarizes as the membrane potential approaches a value roughly midway between \(E_K\) and \(E_{Na}\).
  o Because these depolarizations bring the membrane potential toward threshold, they are called excitatory postsynaptic potentials (EPSPs).
• At other synapses, a different neurotransmitter binds to channels that are 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.
  o The binding of neurotransmitter to postsynaptic receptors opens gated channels that allow K\(^+\) to diffuse out of the cell and/or Cl\(^-\) to diffuse into the cell.
• Various mechanisms rapidly clear neurotransmitters from the synaptic cleft, ending their effect on postsynaptic cells.
  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.
• Unlike action potentials, which are all-or-none events, postsynaptic potentials are graded.
• Their magnitude varies with a number of factors, including the amount of neurotransmitter released by the presynaptic neuron.
• Postsynaptic potentials do not regenerate but rather diminish with distance from the synapse.
  o Most synapses on a neuron are located on its dendrites or cell body, whereas action potentials are generally initiated at the axon hillock.
  o Therefore, a single EPSP is usually too small to trigger an action potential in a postsynaptic neuron.
• Graded potentials (EPSPs and IPSPs) are summed to either depolarize or hyperpolarize a postsynaptic neuron.
  o Two EPSPs produced in rapid succession at the same synapse can be added in an effect called temporal summation.
  o Two EPSPs produced nearly simultaneously by different synapses on the same postsynaptic neuron can be added in an effect called spatial summation.
• 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 is the essence of 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.
- This binding activates a signal transduction pathway involving a second messenger in the postsynaptic cell.
  - This form of transmission has a slower onset, but its effects have a longer duration, over 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 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 channel proteins in the postsynaptic membrane, causing them to open or close.
- Because of the amplifying effect of the signal transduction pathway, the binding of a neurotransmitter to a single 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.
- Nearly all these neurotransmitters fall into a small number of groups based on chemical structure.
- The major classes of neurotransmitters are acetylcholine, biogenic amines, amino acids, neuropeptides, and gases.
- A single neurotransmitter may have more than a dozen receptors.
- The receptors for a specific neurotransmitter can vary significantly in their effects on postsynaptic cells.
  - For this reason, many drugs used to treat nervous system diseases or affect brain function are targeted to specific receptors rather than to particular neurotransmitters.

- **Acetylcholine** is one of the most common neurotransmitters in both invertebrates and vertebrates.
- Except in the heart, vertebrate neurons that form a synapse with muscle cells release acetylcholine as an excitatory transmitter.
- Acetylcholine binds to receptors on ligand-gated channels in the muscle cell, producing an EPSP.
- Nicotine binds to the same receptors, which are also found elsewhere in the PNS and in the CNS.
  - Nicotine’s stimulant effects result from this affinity.
- Acetylcholine activity is terminated by hydrolysis by _acetylcholinesterase_, an enzyme in the synaptic cleft.
- Certain bacteria produce a toxin that specifically inhibits the presynaptic release of acetylcholine.
- This toxin is the cause of a rare but severe form of food poisoning called botulism.
- Untreated botulism is fatal because the muscles required for breathing fail to contract.
- Recently, the botulinum toxin has become a controversial tool in cosmetic surgery.
- Injections of the toxin, known as Botox, reduce wrinkles by blocking transmission at synapses that control facial muscles.

- Acetylcholine has inhibitory rather than excitatory effects in regulating heart muscle.
  - In the heart, acetylcholine released by neurons activates a signal transduction pathway.
  - The G proteins in the pathway inhibit adenylyl cyclase and open K+ channels in the muscle cell membrane.
  - Both effects reduce the rate at which cardiac muscle cells contract.

- **Biogenic amines** are neurotransmitters derived from amino acids.
  - The biogenic amine **serotonin** is synthesized from tryptophan.
  - Several other biogenic amines, the catecholamines, are derived from tyrosine.
  - One catecholamine, **dopamine**, acts only as a neurotransmitter.
  - Two others—**epinephrine** and **norepinephrine**—act both as neurotransmitters and as hormones.

- Norepinephrine and acetylcholine are the two major neurotransmitters in the PNS of vertebrates.
- Acting through a G protein-coupled receptor, norepinephrine generates EPSPs in the autonomic nervous system, a branch of the PNS.
- In the CNS, biogenic amines are involved in modulating synaptic transmission.
  - Dopamine and serotonin, released in the brain, affect sleep, mood, attention, and learning.
  - LSD and mescaline produce hallucinations by binding to brain receptors for serotonin and dopamine.

- Biogenic amines have a central role in many nervous system disorders and treatments.
  - Parkinson’s disease is associated with a lack of dopamine in the brain.
  - Depression may be treated with drugs that increase the brain concentrations of biogenic amines.
  - Prozac inhibits the uptake of serotonin after its release, thus increasing its effect.

- Two amino acids serve as the major neurotransmitters in the vertebrate CNS: **gamma aminobutyric acid (GABA)** and **glutamate**.
  - GABA is the neurotransmitter at most inhibitory synapses in the brain, where it produces IPSPs by increasing the permeability of the postsynaptic membrane to Cl-.
  - Glutamate, the most common neurotransmitter in the brain, is always excitatory.
  - A third amino acid, glycine, acts at inhibitory synapses in parts of the CNS that lie outside of the brain.

- Several **neuropeptides**, relatively short chains of amino acids formed by cleavage of much larger proteins, serve as neurotransmitters that operate via signal transduction pathways.
- The neuropeptide **substance P** is a key excitatory neurotransmitter that mediates our perception of pain.
- Other neuropeptides, **endorphins**, act as natural analgesics to decrease pain perception.
• Candace Pert and Solomon Snyder discovered endorphins in the 1970s as an outcome of their research on the biochemistry of behavior.
  o Pert and Snyder studied the activity of different drugs in the brain to demonstrate the existence of specific receptors for opiates, painkilling drugs such as morphine and heroin.
  o In setting out to find any molecules normally present in the brain that could also activate these receptors, they identified endorphins.
• Endorphins are produced in the brain during times of physical or emotional stress, such as childbirth.
• In addition to relieving pain, endorphins decrease urine output, depress respiration, and produce euphoria, as well as other emotional effects.
  o Because opiates bind to the same receptors as endorphins, opiates mimic endorphins and produce many of the same physiological effects.
• Some vertebrate neurons release dissolved gases, especially nitric oxide (NO) and carbon monoxide (CO), that act as local regulators.
  o During male sexual arousal, certain neurons release NO into the erectile tissue of the penis.
  o In response, smooth muscle cells in the blood vessel walls of the erectile tissue relax, allowing the blood vessels to dilate and fill the spongy erectile tissue with blood, producing an erection.
  o Viagra inhibits an enzyme that slows the muscle-releasing effects of NO.
• Unlike most neurotransmitters, NO is not stored in cytoplasmic vesicles but is instead synthesized on demand.
  o NO diffuses into neighboring target cells, produces a change, and is broken down—all within a few seconds.
  o In many of its targets, including smooth muscle cells, NO stimulates an enzyme to synthesize a second messenger that directly affects cellular metabolism.
• CO is synthesized in small amounts in the human body.
  o CO is generated by the enzyme heme oxygenase, found in some neurons in the brain and PNS.
  o In the brain, CO regulates the release of hypothalamic hormones.
  o In the PNS, CO acts as an inhibitory neurotransmitter that hyperpolarizes intestinal smooth muscle cells.