Unit 3: The Cell **Name______________________**

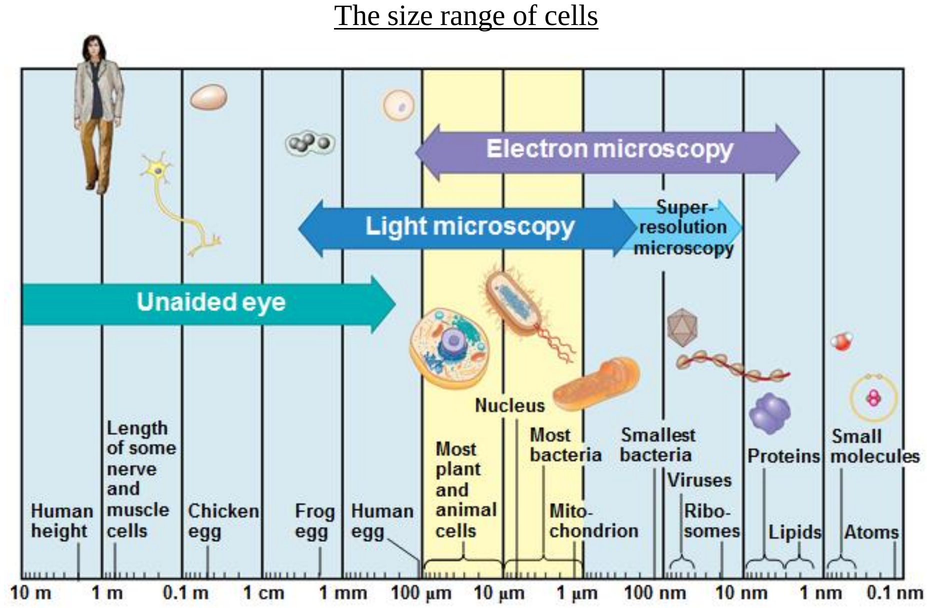
Chapter 6: A Tour of the Cell

Overview

6.1 Biologists use microscopes and the tools of biochemistry to study cells

- The discovery and early study of cells progressed with the invention of microscopes in 1590 and their improvement in the 17th century.
- In a **light microscope (LM)**, visible light passes through the specimen and then through glass lenses.
  - The lenses refract light so that the image is magnified into the eye or a camera.
- Microscopes vary in magnification, resolution, and contrast.
  - **Magnification** is the ratio of an object's image to its real size. A light microscope can magnify effectively to about 1,000 times the real size of a specimen.
  - **Resolution** is a measure of image clarity. It is the minimum distance two points can be separated and still be distinguished as two separate points. The minimum resolution of an LM is about 200 nanometers (nm), the size of a small bacterium.
  - **Contrast** accentuates differences in parts of the sample. It can be improved by staining or labeling of cell components so they stand out.
- Although an LM can resolve individual cells, it cannot resolve much of the internal anatomy, especially the **organelles**, membrane-enclosed structures within eukaryotic cells.

The size range of cells

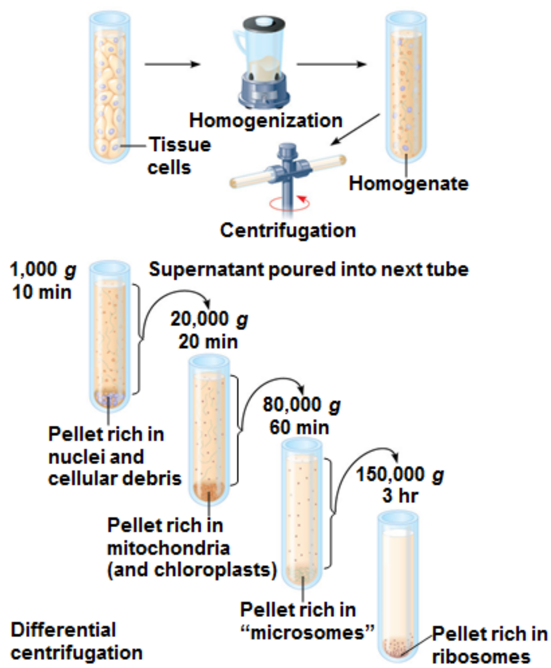


- To resolve smaller structures, scientists use an **electron microscope (EM)**, which focuses a beam of electrons through the specimen or onto its surface.
  - Theoretically, the resolution of a modern EM could reach 0.002 nm, but the practical limit is closer to about 2 nm.
- **Scanning electron microscopes (SEMs)** are useful for studying the surface structure or topography of a specimen.
  - SEMs have great depth of field, resulting in an image that seems three-dimensional.
- **Transmission electron microscopes (TEMs)** are used to study the internal structure of cells.
  - A TEM aims an electron beam through a very thin section of the specimen.
- Although EMs reveal organelles that are impossible to resolve with LMs, the methods used to prepare cells for viewing under an EM kills them.
  - LMs do not have as high a resolution as EMs, but they can be used to study live cells.
- Recently, confocal and deconvolution microscopy have sharpened images of three-dimensional tissues and cells.
- ○ New techniques and labeling molecules have also allowed researchers to "break" the resolution barrier and distinguish subcellular structures as small as 10-20 nm.
- Microscopes are important tools in **cytology**, the study of cell structures.

Cell biologists can isolate organelles to study their functions.

- Cell structure and function can by studied by **cell fractionation**, a technique that takes cells apart and separates major organelles and other subcellular structures from one another.
  - A centrifuge spins test tubes holding mixtures of disrupted cells at various speeds.
  - The resulting forces cause a fraction of the cell components to settle to the bottom of the tube, forming a pellet.
  - At lower speeds, the pellet consists of larger components; higher speeds yield a pellet with smaller components.
- Cell fractionation can be used to isolate specific cell components so that the functions of these organelles can be studied.
  - For example, one cellular fraction was enriched in enzymes that function in cellular respiration. Electron microscopy revealed that this fraction is rich in mitochondria.

<u>Cell Fractionation Process</u>

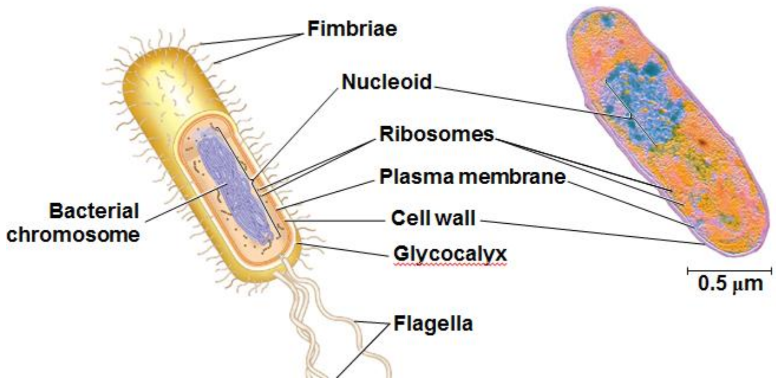


6.2 Eukaryotic cells have internal membranes that compartmentalize their functions

Prokaryotic and eukaryotic cells differ in size and complexity.

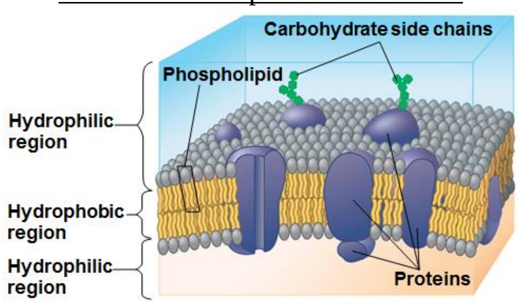
- Organisms of the domains Bacteria and Archaea consist of prokaryotic cells. Protists, fungi, animals, and plants consist of eukaryotic cells.
- All cells are surrounded by a selective barrier, the **plasma membrane.**
- The semifluid substance within the membrane is the **cytosol**, in which subcellular components are suspended.
- All cells contain **chromosomes** that carry genes in the form of DNA.
- All cells have **ribosomes**, tiny complexes that make proteins based on instructions contained in genes.
- A major difference between prokaryotic and eukaryotic cells is the location of the DNA.
  - In a **eukaryotic cell**, most of the DNA is in an organelle bounded by a double membrane, the **nucleus**.
  - In a **prokaryotic cell**, the DNA is concentrated in the **nucleoid**, without a membrane separating it from the rest of the cell.

A prokaryotic cell



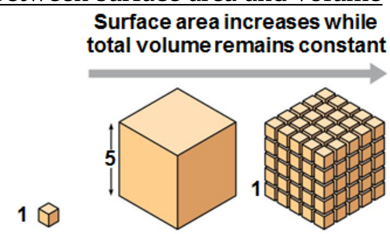
- The interior of a prokaryotic cell and the region between the nucleus and the plasma membrane of a eukaryotic cell is the **cytoplasm**.
- Within the cytoplasm of a eukaryotic cell are a variety of membrane-bound organelles with specialized form and function. These membrane-bound organelles are absent in prokaryotes.
- Eukaryotic cells are generally much larger than prokaryotic cells.
- The logistics of carrying out cellular metabolism set limits on cell size.
  - At the lower limit, the smallest bacteria, mycoplasmas, are 0.1–1.0 µm in diameter.
  - Most bacteria are 1–5 µm in diameter.
  - Eukaryotic cells are typically 10–100 µm in diameter.
- Metabolic requirements also set an upper limit to the size of a single cell.
- The **plasma membrane** functions as a selective barrier that allows the passage of oxygen, nutrients, and wastes for the whole volume of the cell.

Structure of the plasma membrane



- As a cell increases in size, its volume increases faster than its surface area.
    - Area is proportional to a linear dimension squared, whereas volume is proportional to the linear dimension cubed.
    - As a result, smaller objects have a higher ratio of surface area to volume.
    - Rates of chemical exchange across the plasma membrane may be inadequate to maintain a cell with a very large cytoplasm.
- The need for a surface sufficiently large to accommodate the volume explains the microscopic size of most cells.
- Larger organisms do not generally have *larger* cells than smaller organisms, simply *more* cells

Geometric relationship between surface area and volume



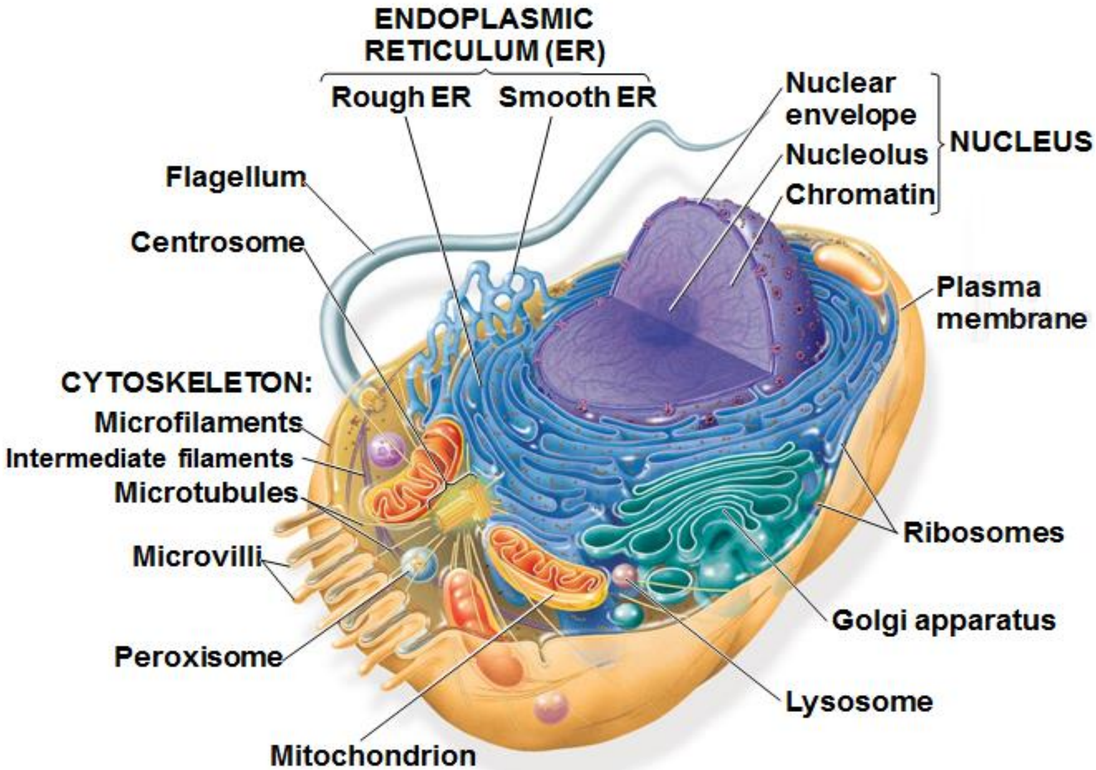
Total surface area [sum of the surface areas (height × width) of all box sides × number of boxes]	6	150	750
Total volume [height × width × length × number of boxes]	1	125	125
Surface-to-volume (S-to-V) ratio [surface area ÷ volume]	6	1.2	6

- Cells that exchange a lot of material with their surroundings, such as intestinal cells, may have long, thin projections from the cell surface called **microvilli**, which increase the surface area without significantly increasing the cell volume.

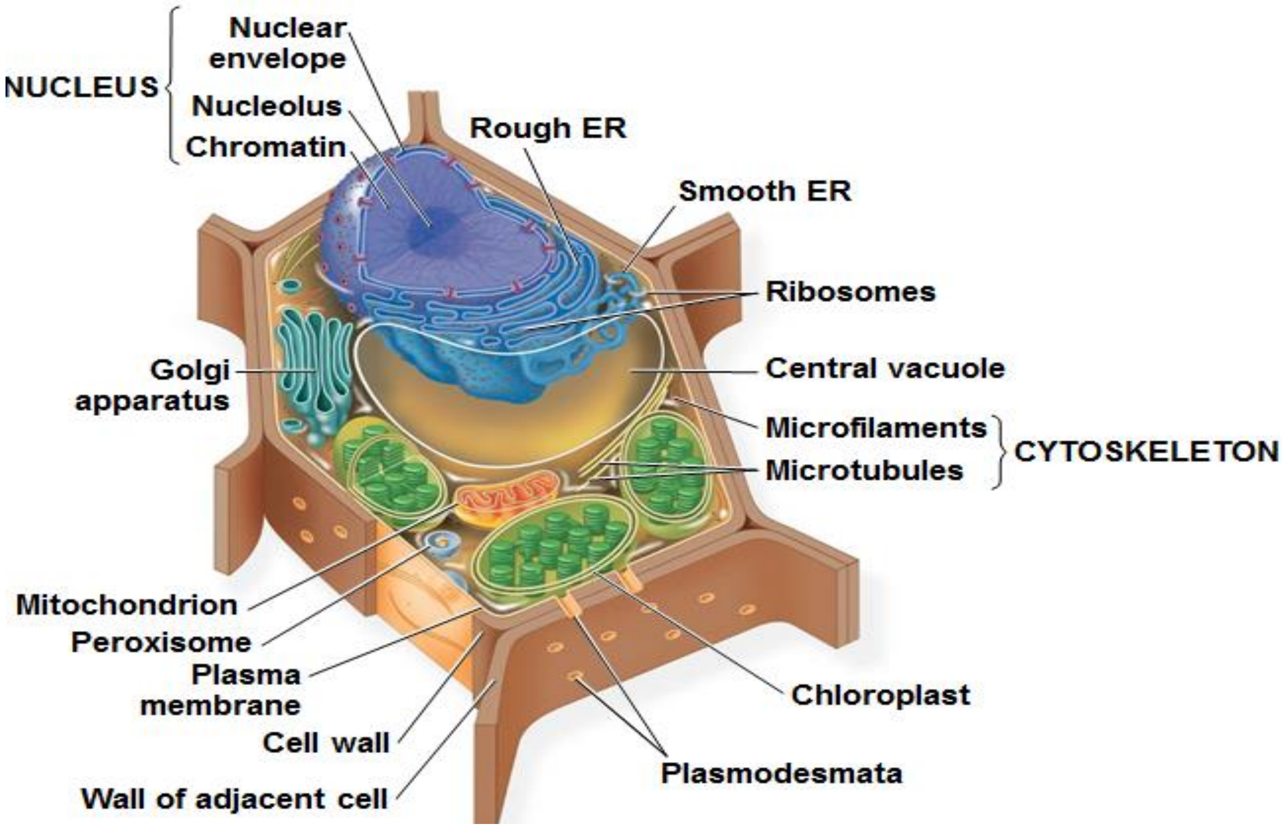
Internal membranes compartmentalize the functions of a eukaryotic cell.

- A eukaryotic cell has extensive and elaborate internal membranes, which partition the cell into compartments.
    - These membranes also participate directly in metabolism because many enzymes are built into membranes.
- The compartments created by membranes provide different local environments that facilitate specific metabolic functions, allowing several incompatible processes to go on simultaneously in a cell.
- The general structure of a biological membrane is a double layer of phospholipids.
- Other lipids and diverse proteins are embedded in the lipid bilayer or attached to its surface.
- Each type of membrane has a unique combination of lipids and proteins for its specific functions.
    - For example, enzymes embedded in the membranes of mitochondria function in cellular respiration.

Animal Cell



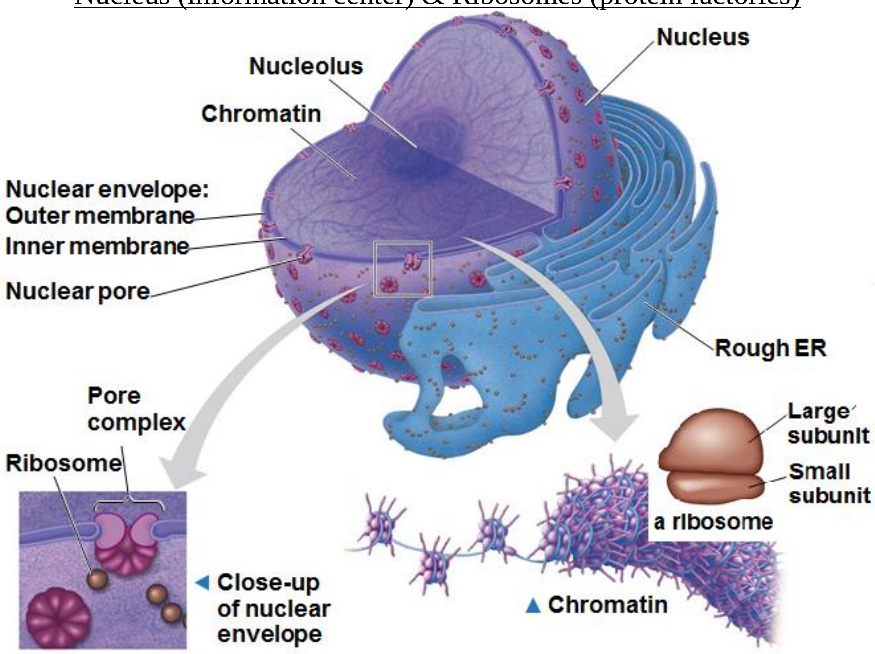
Plant Cell



Concept 6.3 The eukaryotic cell's genetic instructions are housed in the nucleus and carried out by the ribosomes

- The **nucleus** contains most of the genes in a eukaryotic cell.
  - Additional genes are located in mitochondria and chloroplasts.
- The nucleus is separated from the cytoplasm by a *double* membrane called the **nuclear envelope**.
  - The envelope is perforated by pores that are about 100 nm in diameter.
  - At the lip of each pore, the inner and outer membranes of the nuclear envelope are fused to form a continuous membrane.
  - A protein structure called a *pore complex* lines each pore, regulating the passage of certain large macromolecules and particles.
- The nuclear side of the envelope is lined by the **nuclear lamina**, a network of protein filaments that maintains the shape of the nucleus.
- Within the nucleus, the DNA and associated proteins are organized into discrete units called **chromosomes**, structures that carry the genetic information.
  - Each chromosome contains one long DNA molecule associated with many proteins. This complex of DNA and protein is called **chromatin**.
- As the cell prepares to divide, the chromatin fibers coil up and condense, becoming thick enough to be recognized as the familiar chromosomes.
- Each eukaryotic species has a characteristic number of chromosomes.
  - A typical human cell has 46 chromosomes.
  - A human sex cell (egg or sperm) has only 23 chromosomes.
- In the nucleus is a region of densely stained fibers and granules adjoining chromatin, the **nucleolus**.
- In the nucleolus, *ribosomal RNA* (rRNA) is synthesized and assembled with proteins from the cytoplasm to form large and small ribosomal subunits.
  - The subunits pass through the nuclear pores to the cytoplasm, where they combine to form ribosomes.
- The nucleus directs protein synthesis by synthesizing messenger RNA (mRNA).
- The mRNA is transported to the cytoplasm through the nuclear pores.
- Once in the cytoplasm, ribosomes translate mRNA's genetic message into the primary structure of a specific polypeptide.

Nucleus (information center) & Ribosomes (protein factories)



Ribosomes are protein factories.

- **Ribosomes**, containing rRNA and protein, are the cellular components that carry out protein synthesis.
    - Cell types that synthesize large quantities of proteins (such as pancreas cells) have large numbers of ribosomes and prominent nucleoli.
- **Free ribosomes** are suspended in the cytosol and synthesize proteins that function within the cytosol.
- **Bound ribosomes** are attached to the outside of the endoplasmic reticulum or nuclear envelope.
    - Bound ribosomes synthesize proteins that are inserted into membranes, packaged into organelles such as ribosomes, or exported (secreted) from the cell.
    - Cells that specialize in protein secretion—for instance, the cells of the pancreas that secrete digestive enzymes—frequently have a high proportion of bound ribosomes.

6.4 The endomembrane system regulates protein traffic and performs metabolic functions in the cell

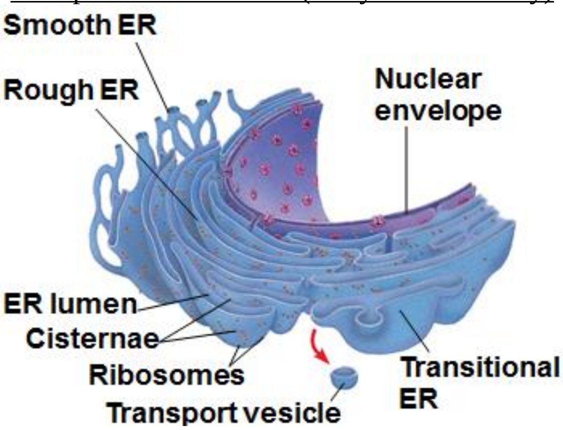
- Many of the internal membranes in a eukaryotic cell are part of the **endomembrane system**, which includes the nuclear envelope, endoplasmic reticulum, Golgi apparatus, lysosomes, vesicles, vacuoles, and plasma membrane.
- The tasks of the endomembrane system include synthesis of proteins and their transport into membranes and organelles or out of the cell, metabolism and movement of lipids, and detoxification of poisons.
- These membranes are either directly continuous or connected via the transfer of **vesicles**, sacs of membrane.
- In spite of the connections, these membranes are diverse in function and structure.

The endoplasmic reticulum manufactures membranes and performs many other biosynthetic functions.

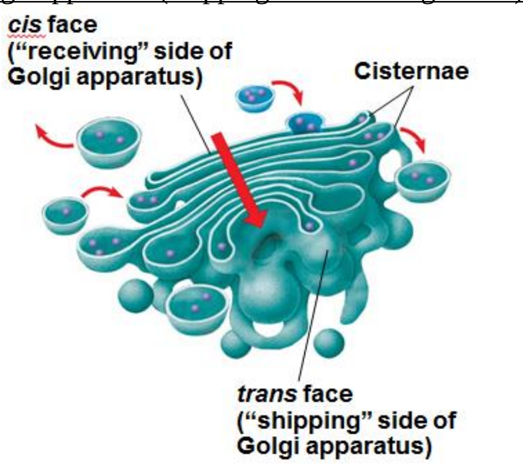
- The **endoplasmic reticulum (ER)** accounts for more than half the membranes in a eukaryotic cell.
- The ER includes a network of membranous tubules and sacs called cisternae that separate the internal compartment of the ER, the ER lumen or cisternal space, from the cytosol.
- The ER membrane is continuous with the nuclear envelope, and the cisternal space of the ER is continuous with the space between the two membranes of the nuclear envelope.
- There are two connected regions of ER that differ in structure and function.
    - **Smooth ER** looks smooth because it lacks ribosomes.
    - **Rough ER** looks rough because ribosomes are attached to the outside, including the outside of the nuclear envelope.
- **Smooth ER** is rich in enzymes and plays a role in a variety of metabolic processes, including synthesis of lipids, metabolism of carbohydrates, detoxification of drugs and poisons, and storage of calcium ions.
- Enzymes of smooth ER synthesize lipids, including oils, phospholipids, and steroids.
    - These include the sex hormones of vertebrates and adrenal steroids.
- In the smooth ER of the liver, enzymes help detoxify poisons and drugs such as alcohol
- Smooth ER stores calcium ions.
    - Muscle cells have a specialized smooth ER that pumps calcium ions from the cytosol into the ER lumen.
    - When a nerve impulse stimulates a muscle cell, calcium ions rush from the ER into the cytosol, triggering contraction of the muscle cell.
- **Rough ER** is especially abundant in cells that secrete proteins.
    - As a polypeptide chain grows from a bound ribosome, it is threaded into the ER lumen through a pore formed by a protein complex in the ER membrane.
    - As the new polypeptide enters the ER lumen, it folds into its native shape.

- Most secretory polypeptides are **glycoproteins**, proteins to which a carbohydrate is covalently bonded.
    - The carbohydrate is attached to the protein in the ER by enzymes in the ER membrane.
- Secretory proteins are packaged in **transport vesicles** that bud from a specialized region called transitional ER.
- Transport vesicles carry proteins from one part of the cell to another.
- Rough ER is also a membrane factory for the cell.
    - Membrane-bound proteins are synthesized directly into the ER membrane and anchored by their own hydrophobic portions.
- Enzymes in rough ER also synthesize phospholipids from precursors in the cytosol.
- As the ER membrane expands, membrane can be transferred as transport vesicles to other components of the endomembrane system.

Endoplasmic Reticulum (biosynthetic factory)



Golgi Apparatus (shipping and receiving center)



The Golgi apparatus is the shipping and receiving center for cell products.

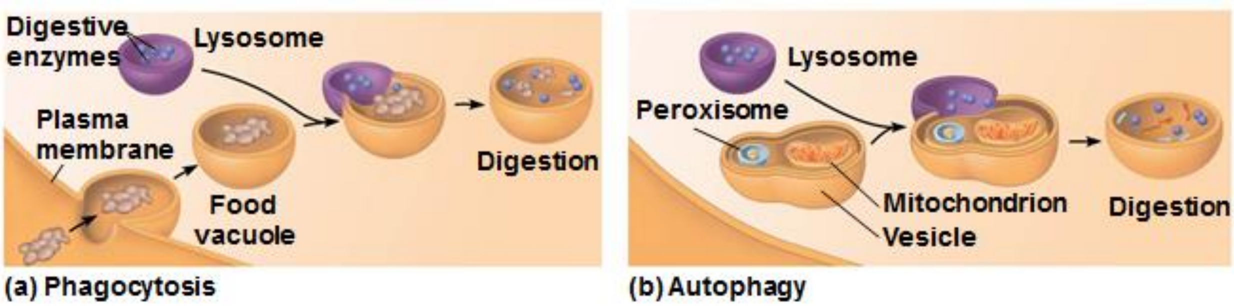
- Many transport vesicles from the ER travel to the **Golgi apparatus** for modification of their contents.
- The Golgi apparatus is a center of manufacturing, warehousing, sorting, and shipping.
- The Golgi apparatus is especially extensive in cells specialized for secretion.
- The Golgi apparatus consists of flattened membranous sacs—cisternae—that look like a stack of pita bread.
- One side of the Golgi apparatus, the *cis* face, is located near the ER. The *cis* face receives material by fusing with transport vesicles from the ER.
    - The other side, the *trans* face, buds off vesicles that travel to other sites.
- Various Golgi enzymes modify the carbohydrate portions of glycoproteins.
    - Carbohydrates are first added to proteins in rough ER, often during the process of polypeptide synthesis.
    - The carbohydrate on the resulting glycoprotein is modified as it passes through the rest of the ER and the Golgi.
    - The Golgi removes some sugar monomers and substitutes others, producing a large variety of carbohydrates.
- Golgi products that will be secreted depart from the *trans* face of the Golgi inside transport vesicles that eventually fuse with the plasma membrane.
- The Golgi manufactures and refines its products in stages, with different cisternae between the *cis* and *trans* regions containing unique teams of enzymes.
- According to the *cisternal maturation model*, the cisternae of the Golgi progress from the *cis* to the *trans* face, carrying and modifying their protein cargo as they move.

- Finally, the Golgi sorts and packages materials into transport vesicles.
  - Molecular identification tags such as phosphate groups are added to products to aid in sorting.
  - These tags act like ZIP codes on mailing labels to identify the product's final destination.
- Transport vesicles budded from the Golgi may have external molecules on their membranes that recognize "docking sites" on the surface of specific organelles or on the plasma membrane, thus targeting them appropriately.

Lysosomes are digestive compartments.

- A **lysosome** is a membrane-bound sac of hydrolytic enzymes that an animal cell uses to digest macromolecules.
- Lysosomal enzymes work best at acidic pH.
  - The rupture of one or a few lysosomes has little impact on a cell because the lysosomal enzymes are not very active at the neutral pH of the cytosol.
  - Massive rupture of many lysosomes can destroy a cell by autodigestion.
- Lysosomal enzymes and membranes are synthesized by rough ER and then transferred to the Golgi apparatus for further modification.
- Proteins on the inner surface of the lysosomal membrane are spared by digestion by their three-dimensional conformations, which protect vulnerable bonds from hydrolysis.
- Lysosomes carry out intracellular digestion in a variety of circumstances.
  - Amoebas eat by engulfing smaller organisms by **phagocytosis**.
  - The *food vacuole* formed by phagocytosis fuses with a lysosome, whose enzymes digest the food.
- Lysosomes can play a role in recycling the cell's organelles and macromolecules. This recycling, or **autophagy**, renews the cell.
  - During autophagy, a damaged organelle or region of cytosol becomes surrounded by a double membrane of unknown origin.
  - A lysosome fuses with the outer membrane of the vesicle, digesting the macromolecules and returning the organic monomers to the cytosol for reuse.
- The cells of people who have inherited lysosomal storage diseases lack a functioning hydrolytic enzyme normally present in lysosomes.
  - The lysosomes become engorged with indigestible substrates, which begin to interfere with other cellular activities.
  - In people who have Tay-Sachs disease, a lipid-digesting enzyme is missing or inactive, and the brain becomes impaired by an accumulation of lipids in the cells.

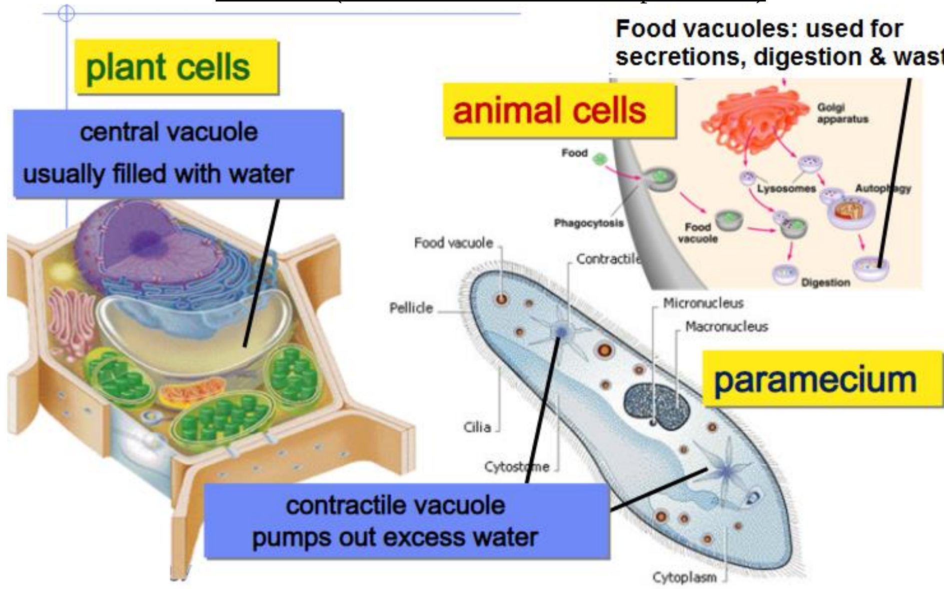
<u>Lysosome (digestive compartments)</u>



Vacuoles have diverse functions in cell maintenance.

- Vacuoles are large vesicles derived from the ER and Golgi apparatus.
- These membrane-bound sacs have a variety of functions.
- **Food vacuoles** are formed by phagocytosis and fuse with lysosomes.
- **Contractile vacuoles**, found in freshwater protists, pump excess water out of the cell to maintain the appropriate concentration of ions and molecules inside the cell.
- In plants and fungi, vacuoles carry out enzymatic hydrolysis, like animal lysosomes do.

Vacuoles (diverse maintenance compartments)



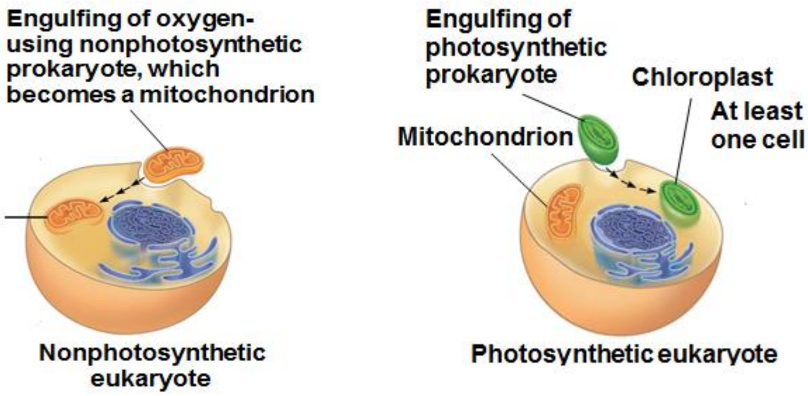
- A large **central vacuole** is found in many mature plant cells.
  - The vacuolar membrane is selective in its transport of solutes into the central vacuole.
  - As a result, the solution inside the vacuole, called cell sap, differs in composition from the cytosol.
- The functions of the central vacuole include stockpiling proteins or inorganic ions, disposing of metabolic by-products, holding pigments, and storing defensive compounds that protect the plant against herbivores.
  - The vacuole has a major role in the growth of plant cells, which enlarge as their vacuoles absorb water, enabling the cell to become larger with little investment in new cytoplasm.
- Because of the large vacuole, the cytosol occupies only a thin layer between the plasma membrane and the central vacuole. The presence of a large vacuole increases the ratio of surface area to volume for the cell.

Concept 6.5 Mitochondria and chloroplasts change energy from one form to another

- Mitochondria and chloroplasts are the organelles that convert energy to forms that cells can use for work.
- **Mitochondria** are the sites of cellular respiration, using oxygen to generate ATP by extracting energy from sugars, fats, and other fuels.
- **Chloroplasts**, found in plants and algae, are the sites of photosynthesis.
  - Chloroplasts convert solar energy to chemical energy by absorbing sunshine and using it to synthesize new organic compounds such as sugars from CO_2 and H_2O.

Mitochondria and chloroplasts have a similar evolutionary origin.

- The **endosymbiont theory** states that an early ancestor of eukaryotic cells engulfed an oxygen-using nonphotosynthetic prokaryotic cell.
  - The engulfed cell became an *endosymbiont* within its *host cell.*
  - Over the course of evolution, the host cell and its endosymbiont merged into a single organism, a eukaryotic cell with a mitochondrion.
  - One of these cells engulfed a photosynthetic prokaryote and evolved into a eukaryotic cell containing chloroplasts.



- There is considerable evidence to support the endosymbiont theory for the origin of mitochondria and chloroplasts.
  - In contrast to organelles of the endomembrane system, each mitochondrion or chloroplast has two membranes separating the innermost space from the cytosol.
  - Mitochondria and chloroplasts contain ribosomes and circular DNA molecules that are attached to their inner membranes.
  - The DNA directs the synthesis of some of the organelle's proteins, which are made on the ribosomes inside the organelles.
  - Mitochondria and chloroplasts grow and reproduce as semiautonomous organelles.

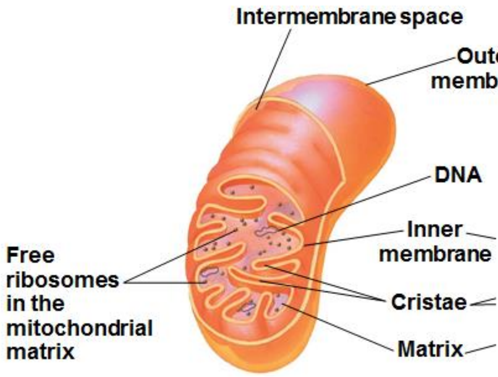
Mitochondria convert chemical energy within eukaryotic cells.

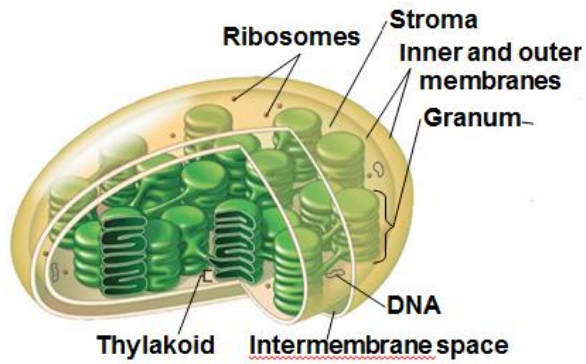
- Almost all eukaryotic cells have mitochondria.
  - Cells may have one very large mitochondrion or hundreds to thousands of individual mitochondria.
  - The number of mitochondria is correlated with aerobic metabolic activity.
  - Mitochondria have a smooth outer membrane and a convoluted inner membrane with infoldings called **cristae**.
- The inner membrane divides the mitochondrion into two internal compartments.
  - The first compartment is the intermembrane space, a narrow region between the inner and outer membranes.
  - The inner membrane encloses the **mitochondrial matrix**, a fluid-filled space with mitochondrial DNA, ribosomes, and enzymes.
- Some of the metabolic steps of cellular respiration are catalyzed by enzymes in the matrix.
- Other proteins that function in respiration, including the enzyme that makes ATP, are built into the inner membrane.
  - The highly folded cristae present a large surface area for these enzymes.
- Mitochondria are about 1–10 µm long, in general.
  - Mitochondria are dynamic: moving, changing shape, fusing, and dividing.

Chloroplasts capture light energy and convert it to chemical energy.

- Chloroplasts contain the green pigment chlorophyll as well as enzymes and other molecules that function in the photosynthetic production of sugar.
  - They are 3–6 µm in diameter and are found in leaves and other green organs of plants and algae.
- The contents of the chloroplast are separated from the cytosol by an envelope consisting of two membranes separated by a narrow intermembrane space.

Mitochondria **Chloropast**





- Inside the innermost membrane is a fluid-filled space, the **stroma**, in which float membranous sacs, the **thylakoids**.
  - The stroma contains chloroplast DNA, ribosomes, and enzymes.
  - The thylakoids are flattened sacs that play a critical role in converting light to chemical energy. In some regions, thylakoids are stacked like poker chips into **grana**.
- The membranes of the chloroplast divide the chloroplast into three compartments: the intermembrane space, the stroma, and the thylakoid space.
- Like mitochondria, chloroplasts are dynamic structures.
  - Their shape is plastic. They are mobile and move around the cell along tracks of the cytoskeleton.
- The chloroplast belongs to a family of plant structures called plastids.
  - *Amyloplasts* are colorless plastids that store starch in roots and tubers.
  - *Chromoplasts* store pigments for fruits and flowers.

The peroxisome is an oxidative organelle.

- Peroxisomes, bound by a single membrane, contain enzymes that transfer hydrogen from various substrates to oxygen, producing hydrogen peroxide (H_2O_2) as a byproduct.
- Some peroxisomes use oxygen to break fatty acids down to smaller molecules that are transported to mitochondria as fuel for cellular respiration.
  - Peroxisomes in the liver detoxify alcohol and other harmful compounds by transferring hydrogen from these molecules to oxygen.

Anatomy of the Peroxisome

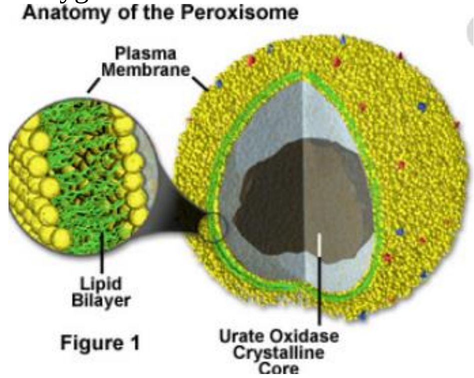


Figure 1

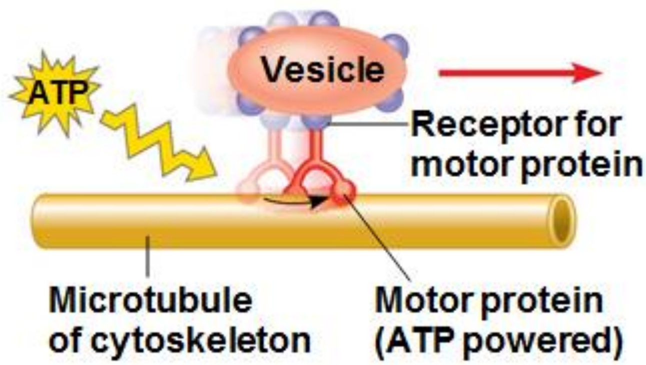
- The H_2O_2 formed by peroxisomes is itself toxic, but peroxisomes also contain an enzyme that converts H_2O_2 to water.
- The enzymes that produce hydrogen peroxide and those that dispose of it are sequestered in the same space, away from other cellular components that could otherwise be damaged.
- Specialized peroxisomes, *glyoxysomes*, convert the fatty acids in seeds to sugars, which the seedling can use as a source of energy and carbon until it is capable of photosynthesis.

- Peroxisomes grow by incorporating proteins made in the cytosol and ER and lipids synthesized in the ER and within the peroxisome itself.
- Peroxisomes split in two when they reach a certain size, suggesting a possible endosymbiotic origin. This hypothesis is still under debate.

Concept 6.6 The cytoskeleton is a network of fibers that organizes structures and activities in the cell

The cytoskeleton provides support, motility, and regulation.

- The **cytoskeleton** is a network of fibers extending through the cytoplasm that provides mechanical support and maintains the cell's shape.
  - This function is especially important in animal cells, which lack walls.
- The cytoskeleton provides anchorage for many organelles and cytosolic enzymes.
- The cytoskeleton is dynamic and can be dismantled in one part and reassembled in another to change the shape of the cell.
- The cytoskeleton also plays a major role in *cell motility*, including changes in cell location and limited movements of parts of the cell.
- The cytoskeleton interacts with **motor proteins** to produce motility.
  - Cytoskeleton elements and motor proteins work together with plasma membrane molecules to move the whole cell along fibers outside the cell.
  - Motor proteins bring about movements of cilia and flagella by gripping cytoskeletal components such as microtubules and moving them past each other.
  - A similar mechanism causes muscle cells to contract.
- Inside the cell, vesicles use motor protein "feet" to "walk" to destinations along a track provided by the cytoskeleton.

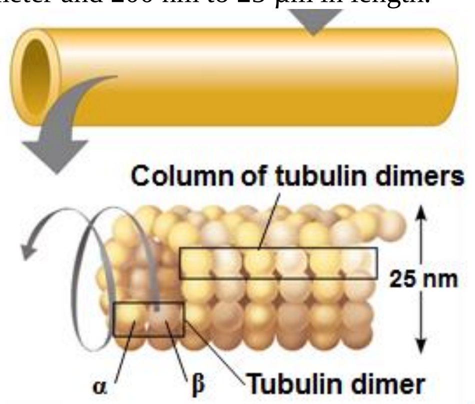


  - This is how vesicles containing neurotransmitter molecules migrate to the tips of axons.
- The vesicles that bud off from the ER travel to the Golgi apparatus along tracks built of cytoskeletal elements.
- The cytoskeleton manipulates the plasma membrane to form food vacuoles during phagocytosis.
- Cytoplasmic streaming in plant cells is caused by the cytoskeleton.
- The cytoskeleton also plays a role in the regulation of biochemical activities in the cell in response to mechanical stimulation.
  - Cytoskeletal elements transmit forces exerted by extracellular molecules on cell surface proteins into the cell—and even into the nucleus.
  - In an experiment, investigators used a micromanipulation device to pull on certain plasma membrane proteins attached to the cytoskeleton, leading to almost instantaneous rearrangements of nucleoli and other structures in the nucleus.
  - In this way, cytoskeletal transmission of naturally occurring mechanical signals may help regulate and coordinate the cell's response.

Three main types of fibers make up the cytoskeleton: microtubules, microfilaments, and intermediate filaments.

- *Microtubules* are the thickest of the three types of fibers; *microfilaments* (or actin filaments) are the thinnest; and *intermediate filaments* are fibers with diameters in a middle range.
- **Microtubules** are hollow rods about 25 nm in diameter and 200 nm to 25 µm in length.

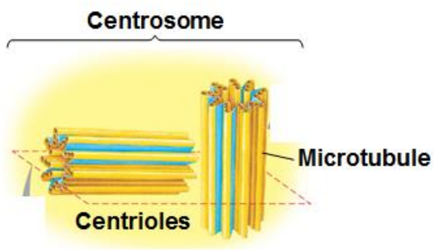
Microtubules (Tubulin Polymers)
Hollow tubes
25 nm with 15-nm lumen
Tubulin, a dimer consisting of α-tubulin and β-tubulin
Maintenance of cell shape (compression-resisting "girder"); cell motility (as in cilia or flagella); chromosome movements in cell division; organelle movements



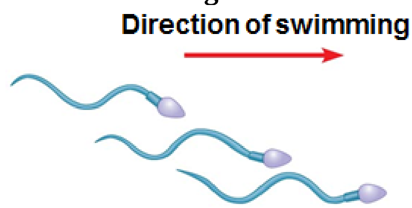
- Microtubule fibers are constructed of the globular protein tubulin.
  - Each tubulin molecule is a *dimer* consisting of two subunits.
  - A tubulin dimer consists of two slightly different polypeptides: α-tubulin and β-tubulin.
- A microtubule changes in length by adding or removing tubulin dimers.
  - The two ends of a microtubule are slightly different.
  - The "plus" end can accumulate or release tubulin dimers at a much higher rate than the other end.
- Microtubules shape and support the cell and serve as tracks to guide motor proteins carrying organelles to their destination.
  - Microtubules guide secretory vesicles from the Golgi apparatus to the plasma membrane.
  - Microtubules are also responsible for the separation of chromosomes during cell division.
- In many animal cells, microtubules grow out from a **centrosome** near the nucleus.
  - These microtubules resist compression to the cell.
- Within the centrosome is a pair of **centrioles**, each with nine triplets of microtubules arranged in a ring.
- Before an animal cell divides, the centrioles replicate.
- Although centrosomes with centrioles may help organize microtubule assembly in animal cells, they are not essential for this function.
  - Fungi and most plant cells lack centrosomes with centrioles but have well-organized microtubules.
- A specialized arrangement of microtubules is responsible for the beating of **cilia** and **flagella**.
  - Many unicellular eukaryotic organisms are propelled through water by cilia and flagella.
  - The sperm of animals, algae, and some plants have flagella.
- When cilia or flagella extend from cells within a tissue layer, they can beat to move fluid over the surface of the tissue.
  - For example, cilia lining the trachea sweep mucus carrying trapped debris out of the lungs.
  - In the reproductive tract, cilia lining the oviducts help move an egg toward the uterus.
- Cilia usually occur in large numbers on the cell surface.
  - Cilia are about 0.25 µm in diameter and 2–20 µm long.
- Flagella are the same diameter as cilia, but are 10–200 µm long.
  - There are usually just one or a few flagella per cell.
- Cilia and flagella differ in their beating patterns.

- A flagellum has an undulatory movement that generates force in the same direction as the flagellum's axis, like the tail of a fish.
- Cilia move more like oars, with alternating power and recovery strokes that generate force perpendicular to the cilium's axis.

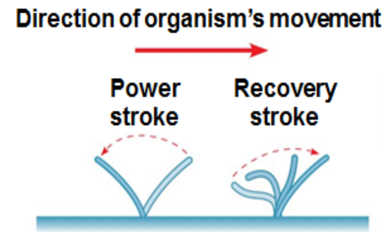
Centrioles



Flagella

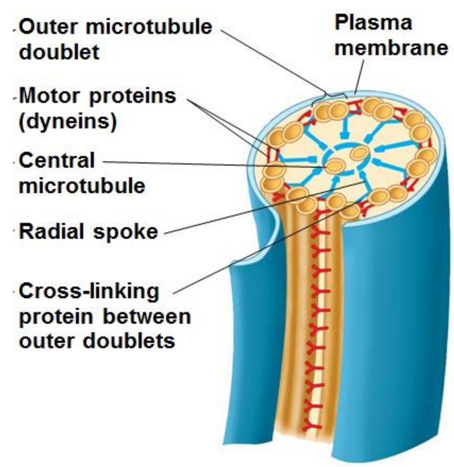


Cilia



- A single nonmotile cilium may also act as a kind of "antenna" for a cell.
  - Membrane proteins on this *primary cilium* transmit molecular signals from the environment outside the cell to the cell's nucleus, resulting in changes in the cell's activities.
  - Such pathways involving cilia-based signaling appear to be crucial to brain function and to embryonic development.

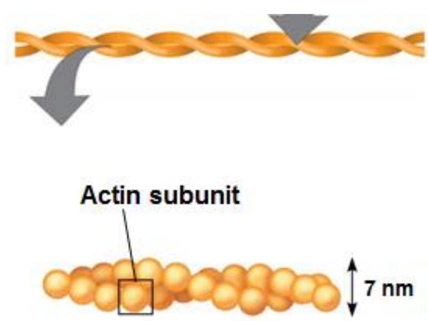
- In spite of their differences, both cilia and flagella share a common structure.
  - Each motile cilium and flagellum has a group of microtubules sheathed by an extension of the plasma membrane.
  - Nine doublets of microtubules are arranged in a ring around a pair at the center. This "9 + 2" pattern is found in nearly all eukaryotic flagella and motile cilia.
  - Nonmotile primary cilia have a "9 + 0" pattern, lacking the central pair of microtubules.

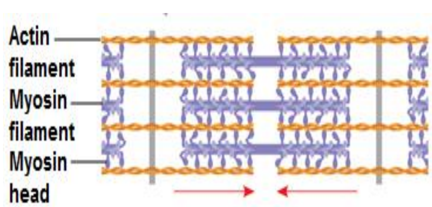


- The cilium or flagellum is anchored in the cell by a **basal body**, whose structure is identical to that of a centriole.
  - In many animals (including humans), the basal body of the fertilizing sperm's flagellum enters the egg and becomes a centriole.
- Flexible cross-linking proteins connect outer doublets to each other and to the two central microtubules.
- Each outer doublet also has pairs of large protruding motor proteins called **dyneins** spaced along its length and reaching toward the neighboring doublet.
  - Dyneins are responsible for the bending movements of the organelle, as they perform a complex cycle of movements caused by changes in the shape of the protein.
  - These changes in shape are powered by ATP.
- The mechanics of dynein-based bending involve a process that resembles walking.
  - A typical dynein protein has two "feet" that "walk" along the microtubule of the adjacent doublet; one foot maintains contact while the other releases and reattaches one step farther along the microtubule.

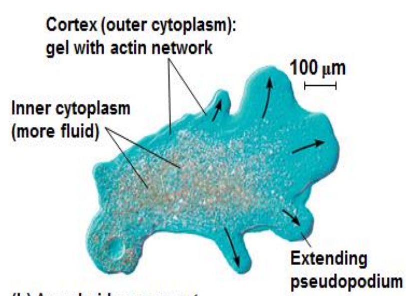
- ○ Without restraint on the movement of the microtubule doublets, one doublet continues to "walk" along and slide past the surface of the other, elongating the cilium or flagellum rather than bending it.
  - ○ For lateral movement of a cilium or flagellum, the dynein "walking" must have something to pull against, as when the muscles in your leg pull against your bones to move your knee.
- In cilia and flagella, the microtubule doublets seem to be held in place by the cross-linking proteins just inside the outer doublets and by the radial spokes and other structural elements.
  - ○ Thus, neighboring doublets cannot slide past each other very far. Instead, the forces exerted by dynein "walking" cause the doublets to curve, bending the cilium or flagellum.
- **Microfilaments** or actin filaments are solid rods about 7 nm in diameter, present in all eukaryotic cells.
- Each microfilament is built as a twisted double chain of actin subunits.
- Microfilaments can form structural networks because of their ability to branch.
- The structural role of microfilaments in the cytoskeleton is to bear tension, resisting pulling forces within the cell.
- *Cortical microfilaments* form a three-dimensional network just inside the plasma membrane to help support the cell's shape, giving the cell **cortex** the semisolid consistency of a gel.
  - ○ This consistency contrasts with the more fluid (*sol*) state of the interior cytoplasm.
- In animal cells specialized for transporting materials across the plasma membrane, such as intestinal cells, bundles of microfilaments make up the core of microvilli.

Microfilaments (Actin Filaments)
Two intertwined strands of actin
7 nm
Actin
Maintenance of cell shape (tension-bearing elements); changes in cell shape; muscle contraction; cytoplasmic streaming in plant cells; cell motility (as in amoeboid movement); division of animal cells

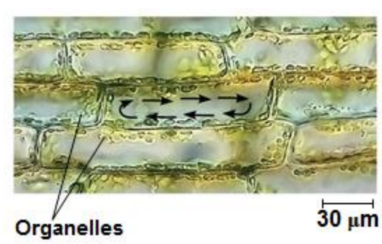




(a) Myosin motors in muscle cell contraction



(b) Amoeboid movement

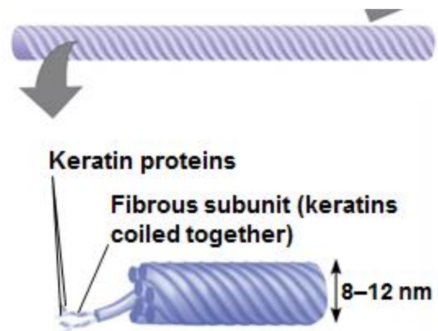


(c) Cytoplasmic streaming in plant cells

- Microfilaments are important in cell motility, especially as part of the contractile apparatus of muscle cells.
  - ○ In muscle cells, thousands of actin filaments are arranged parallel to one another.
  - ○ Thicker filaments composed of **myosin** interdigitate with the thinner actin fibers.
  - ○ Like dynein with microtubules, myosin acts as a motor protein, walking along the actin filaments to shorten the cell.
- In other cells, actin-myosin aggregates are less organized but still cause localized contraction.

- A contracting belt of microfilaments forms a cleavage furrow that divides the cytoplasm of animal cells during cell division.
- Localized contraction brought about by actin and myosin also drives amoeboid movement.
  - **Pseudopodia**, cellular extensions, extend and contract through the reversible assembly and contraction of actin subunits into microfilaments.
  - Microfilaments assemble into networks that convert sol to gel.
- According to a widely accepted model, filaments near the cell's trailing edge interact with myosin, causing contraction.
  - The contraction forces the interior fluid into the pseudopodium, where the actin network has been weakened.
  - The pseudopodium extends until the actin reassembles into a network.
- Many cells in the animal body, including some white blood cells, also move by crawling.
- In plant cells, actin-myosin interactions and sol-gel transformations drive **cytoplasmic streaming,** which creates a circular flow of cytoplasm in the cell, speeding the distribution of materials within the cell.
- **Intermediate filaments** range in diameter from 8 to 12 nm, larger than microfilaments but smaller than microtubules.

Intermediate Filaments
Fibrous proteins coiled into cables
8–12 nm
One of several different proteins (such as keratins)
Maintenance of cell shape (tension-bearing elements); anchorage of nucleus and certain other organelles; formation of nuclear lamina



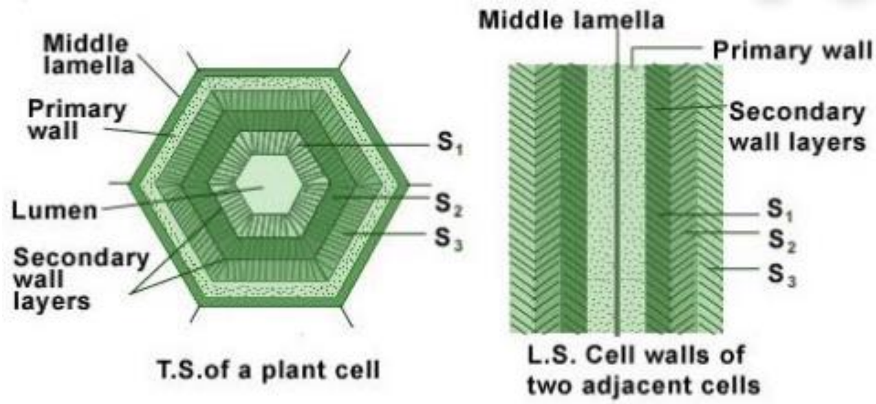
- Intermediate filaments are a diverse class of cytoskeletal units, built from a family of proteins that includes the keratins.
- Like microfilaments, intermediate filaments are specialized for bearing tension.
- Intermediate filaments are more permanent fixtures of the cytoskeleton than are the other two classes.
  - Even after cells die, intermediate filament networks often persist.
  - The networks reinforce cell shape and fix organelle location.
- The nucleus sits within a cage made of intermediate filaments, fixed in location by branches of the filaments that extend into the cytoplasm.
  - Other intermediate filaments make up the nuclear lamina that lines the interior of the nuclear envelope.
- When the shape of the entire cell is correlated with function, intermediate filaments support that shape.
  - The axons of nerve cells are strengthened by one class of intermediate filament.
- Various kinds of intermediate filaments function as the framework of the entire cytoskeleton.

Concept 6.7 Extracellular components and connections between cells help coordinate cellular activities

Plant cells are encased by cell walls.

- In plants, the **cell wall** protects the cell, maintains its shape, prevents excessive uptake of water, and supports the plant against the force of gravity.
- The thickness of plant cell walls ranges from 0.1 µm to several micrometers.

- The chemical composition of the cell wall differs with species and among cell types within a plant.
- The basic design of cell walls consists of microfibrils of cellulose synthesized by an enzyme called cellulose synthase.
- The cellulose microfibrils are secreted to the extracellular space, where they are embedded in a matrix of proteins and other polysaccharides.
    - This is the basic design of steel-reinforced concrete or fiberglass.

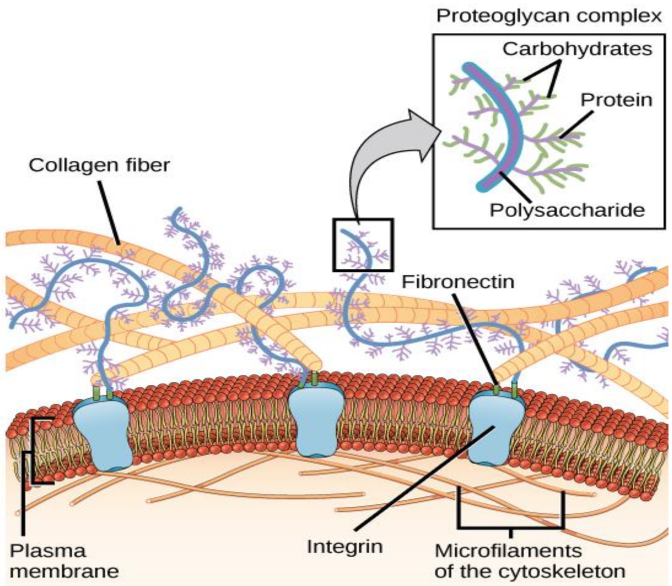


- A young plant cell secretes a relatively thin and flexible wall called the **primary cell wall**.
    - In actively growing cells, the cellulose fibrils are oriented at right angles to the direction of cell expansion.
    - David Ehrhardt and colleagues found that cortical microtubules guide cellulose synthase as it synthesizes and deposits the fibrils.
    - By orienting the deposition of cellulose, microtubules affect the growth pattern of the cells.
- Between the primary walls of adjacent cells is a **middle lamella**, a thin layer with sticky polysaccharides called pectins that glues cells together.
- When a plant cell stops growing, it strengthens its wall by secreting hardening substances into the primary wall or by adding a **secondary cell wall** between the plasma membrane and the primary wall.
    - The secondary wall may be deposited in several layers.
    - It has a strong and durable matrix that provides support and protection.
    - Wood consists mainly of secondary walls.
- Plant cell walls are perforated by channels between adjacent cells called plasmodesmata.

The extracellular matrix of animal cells provides support, adhesion, movement, and regulation.

- Though lacking cell walls, animal cells do have an elaborate **extracellular matrix (ECM)**.
- The primary constituents of the ECM are glycoproteins, especially **collagen** fibers, embedded in a network of glycoprotein **proteoglycans**.
    - Collagen accounts for about half the total protein in the human body.
    - A proteoglycan molecule consists of a small core protein with many carbohydrate chains covalently attached, so that it may be up to 95% carbohydrate.
    - Large proteoglycan complexes can form when hundreds of proteoglycans become noncovalently attached to a single long polysaccharide molecule.
- In many cells, **fibronectins** in the ECM connect to **integrins,** cell-surface receptor proteins that span the membrane and bind on their cytoplasmic side to proteins attached to microfilaments of the cytoskeleton.
- The interconnections from the ECM to the cytoskeleton via the fibronectin-integrin link permit the integration of changes inside and outside the cell.
- The ECM can regulate cell behavior.
    - Embryonic cells migrate along specific pathways by matching the orientation of their microfilaments to the "grain" of fibers in the ECM.

  - The ECM can influence the activity of genes in the nucleus via a combination of chemical and mechanical signaling pathways.
- Mechanical signaling involves fibronectin, integrins, and microfilaments of the cytoskeleton.
  - Changes in the cytoskeleton may in turn trigger chemical signaling pathways inside the cell, leading to changes in the set of proteins being made by the cell and thus changes in the cell's function.
  - This may coordinate the behavior of all the cells within a tissue.

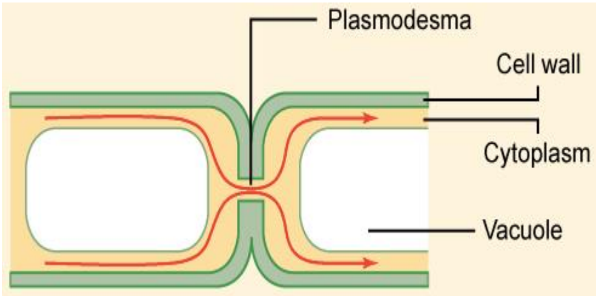


Intercellular junctions help integrate cells into higher levels of structure and function.

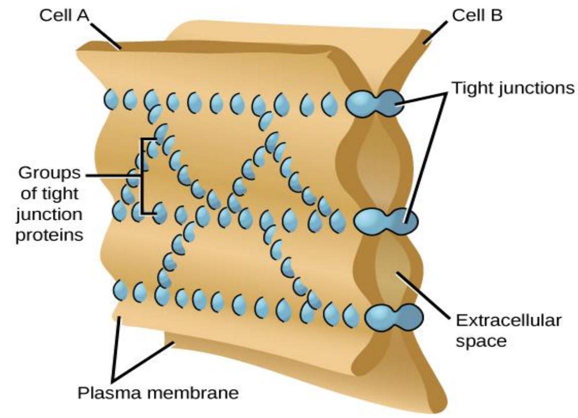
- Neighboring cells in tissues, organs, and organ systems often adhere, interact, and communicate through direct physical contact.
- Plant cells are perforated with **plasmodesmata**, channels allowing cytosol to pass between cells.
  - Water and small solutes can pass freely from cell to cell.
  - In certain circumstances, proteins and RNA can be exchanged.
- Macromolecules being transported to neighboring cells reach the plasmodesmata by moving along fibers of the cytoskeleton.
- Animals have three main types of intercellular links: *tight junctions*, *desmosomes*, and *gap junctions*.
  - All three types of intercellular junctions are especially common in epithelial tissue, which lines the external and internal surfaces of the body.
- In **tight junctions,** membranes of adjacent cells are fused, forming continuous belts around cells that prevent leakage of extracellular fluid.
- **Desmosomes** (or anchoring junctions) fasten cells together into strong sheets, much like rivets.
  - Intermediate filaments of keratin reinforce desmosomes.
- **Gap junctions** (or communicating junctions) provide cytoplasmic channels between adjacent cells.
  - Special membrane proteins surround these pores.
  - Ions, sugars, amino acids, and other small molecules can pass.

In embryos, gap junctions facilitate chemical communication during development

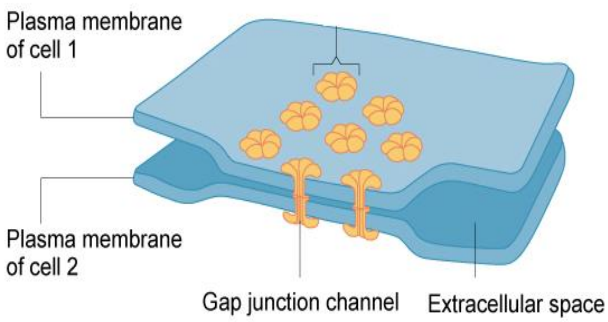
Plasmodesmata



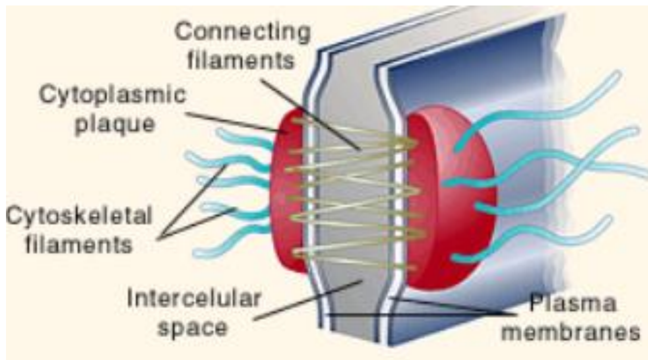
Tight Junction



Gap Junction



Desmosomes



Chapter 11: Cell Communication

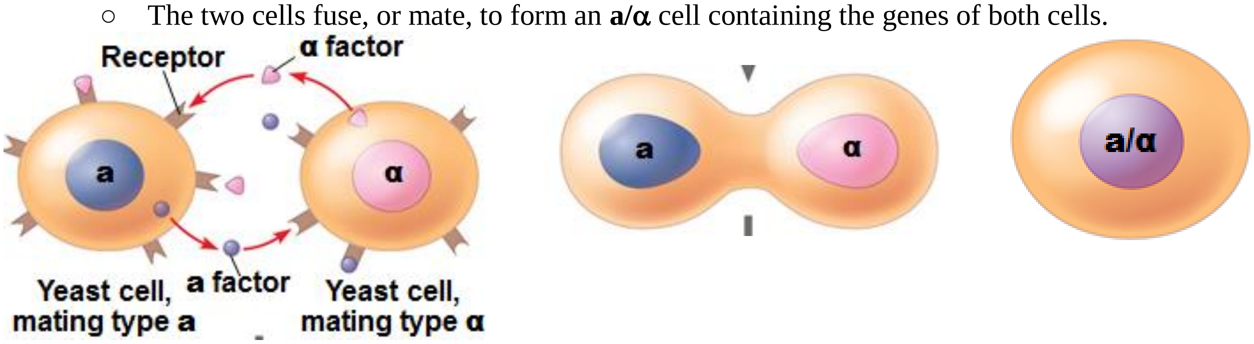
Overview

Concept 11.1 External signals are converted to responses within the cell

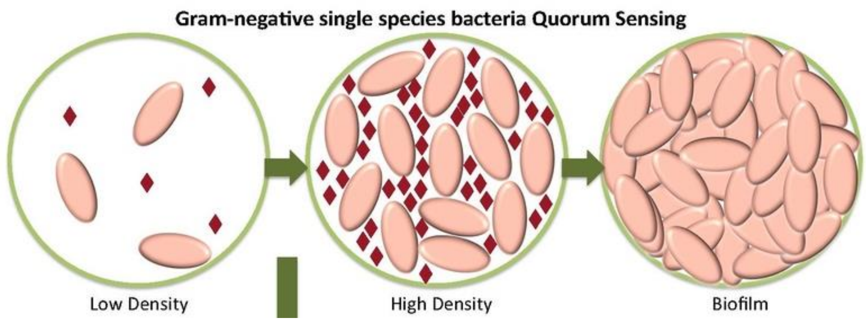
- What messages are passed from cell to cell? How do cells respond to these messages?

Cell signaling evolved early in the history of life.

- One topic of cell "conversation" is sex.
- The cells of *Saccharomyces cerevisiae*, the yeast of bread, wine, and beer, identify potential mates by chemical signaling.
- There are two sexes, **a** and **α,** each of which secretes a specific signaling molecule, **a** factor and **α** factor, respectively.
  - These factors each bind to receptor proteins on the other mating type.
- After the mating factors have bound to the receptors, the two cells grow toward each other and undergo other cellular changes.
  - The two cells fuse, or mate, to form an **a/α** cell containing the genes of both cells.



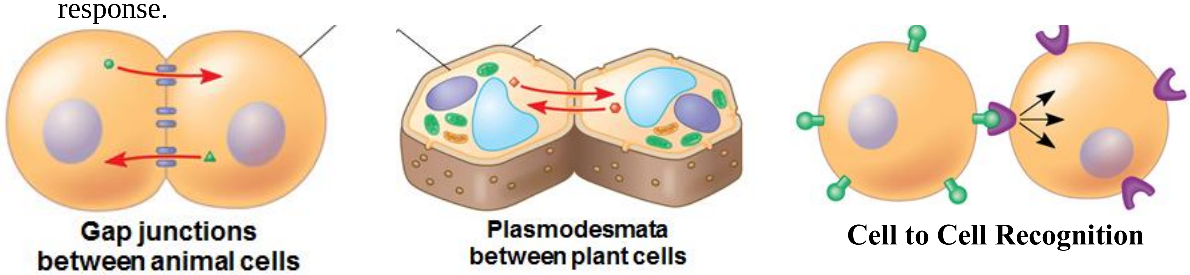
- The process by which a signal on a cell's surface is changed or *transduced* into a specific cellular response is a series of steps called a **signal transduction pathway**.
  - The molecular details of these pathways are strikingly similar in yeast and mammalian cells, even though their last common ancestor lived over a billion years ago.
  - Signaling systems of bacteria and plants also share similarities.
- Similarities in signal transduction pathways suggest that ancestral signaling molecules evolved long ago in ancient prokaryotes and single-celled eukaryotes and have since been adopted for new uses by their multicellular descendants.
- Cell signaling remains important in the microbial world.
- Cells of many bacterial species secrete small molecules that can be detected by other bacterial cells.
- The concentration of signaling molecules enables bacteria to sense the local density of bacterial cells, a phenomenon called *quorum sensing*.
- Signaling among members of a bacterial population can lead to coordination of their activities.
- In response to a signal, bacterial cells come together to form *biofilms*, aggregations of bacteria containing regions of specialized function.



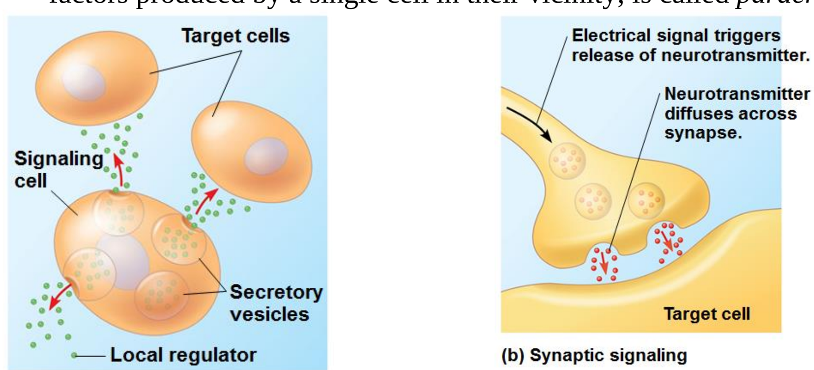
- ○ The cells in the film generally derive nutrition from the surface.
- ○ The slimy coatings on a fallen log, on leaves lying in a forest path, or on your unbrushed teeth are produced by biofilms.

Communicating cells may be close together or far apart.

- Multicellular organisms release signaling molecules that target other cells.
- Cells may communicate by direct contact.
    - ○ Both animals and plants have cell junctions that connect to the cytoplasm of adjacent cells.
    - ○ Signaling substances dissolved in the cytosol can pass freely between adjacent cells.
    - ○ Animal cells can communicate by direct contact between membrane-bound cell-surface molecules.
    - ○ Such cell-cell recognition is important to processes like embryonic development and the immune response.



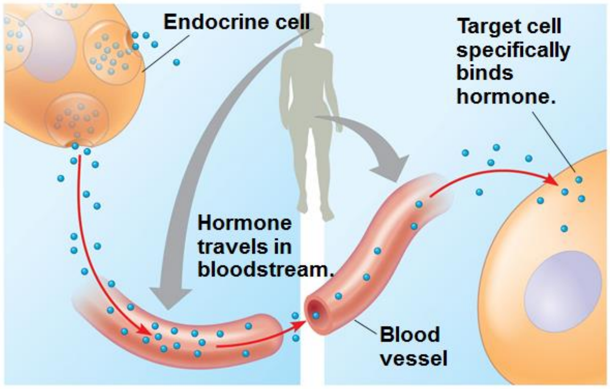
- In other cases, the signaling cell secretes messenger molecules.
- Some transmitting cells release **local regulators** that influence cells in the local vicinity.
- One class of local regulators in animals, *growth factors,* includes compounds that stimulate nearby target cells to grow and multiply.
    - ○ This type of local signaling, when numerous cells simultaneously receive and respond to growth factors produced by a single cell in their vicinity, is called *paracrine signaling*.



(a) Paracrine signaling

- *Synaptic signaling* occurs in animal nervous systems.
    - ○ An electrical signal along a nerve cell triggers the secretion of neurotransmitter molecules carrying a chemical signal.

- The molecules diffuse across a narrow synapse between the nerve cell and its target cell, triggering a response in the target cell.
- Beyond communication through plasmodesmata (plant cell junctions), local signaling in plants is not as well understood.
  - Because of their cell walls, plants use different mechanisms from those operating locally in animals.
- Plants and animals use **hormones** for long-distance signaling.
  - In hormonal or *endocrine signaling* in animals, specialized cells release hormones into the circulatory system, through which they travel to target cells in other parts of the body.
  - Plant hormones, called *plant growth regulators*, may travel in vessels but more often travel from cell to cell or diffuse through air.



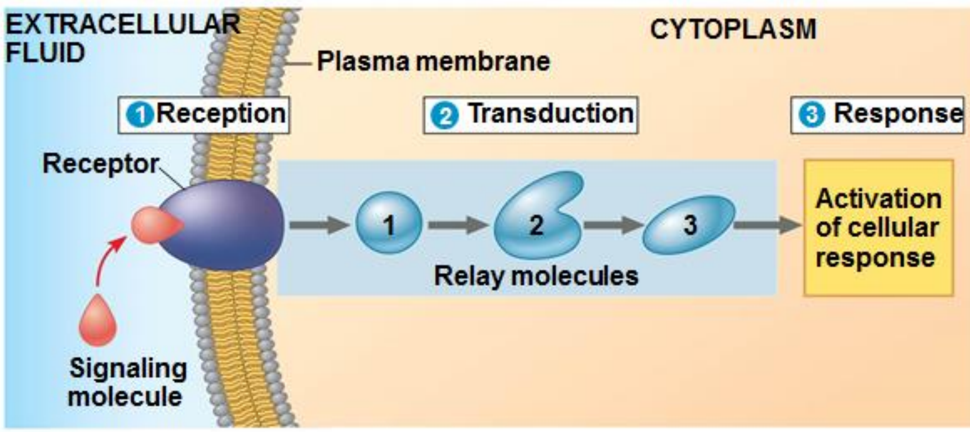
(c) Endocrine (hormonal) signaling

- Hormones and local regulators range widely in molecular size and type.
  - The plant hormone ethylene (C_2H_4), a gas that promotes fruit ripening and regulates growth, is a hydrocarbon with only six atoms, capable of passing through cell walls.
  - The mammalian hormone insulin, which regulates blood sugar levels in mammals, is a protein with thousands of atoms.
- The transmission of a signal through the nervous system is also an example of long-distance signaling.
  - An electrical signal travels the length of a nerve cell and is then converted to a chemical signal when a signaling molecule is released and crosses the synapse to another nerve cell. It is then converted back to an electrical signal.
  - In this way, a nerve signal can travel along a series of nerve cells, sometimes over great distances.

The three stages of cell signaling are reception, transduction, and response.

- What happens when a cell encounters a secreted signaling molecule?
- The signal must be recognized and bound by a specific receptor molecule.
  - The information conveyed by this binding (the signal) must be changed into another form, or transduced, inside the cell, before the cell can respond.
- E. W. Sutherland and his colleagues pioneered our understanding of cell signaling by investigating how the animal hormone epinephrine stimulates the breakdown of the storage polysaccharide glycogen in liver and skeletal muscle cells.
  - The breakdown of glycogen releases glucose derivatives that can be used for fuel in glycolysis or released as glucose in the blood for fuel elsewhere.
  - Thus, one effect of epinephrine is mobilization of fuel reserves.
- Sutherland's research team discovered that epinephrine stimulates glycogen breakdown by activating a cytosolic enzyme, glycogen phosphorylase.
  - Epinephrine does not activate the phosphorylase directly *in vitro*, however, but acts only via *intact* cells.

- This suggests that there is an intermediate step or steps occurring inside the cell.
- It also suggests that the plasma membrane is involved in transmitting the epinephrine signal.
- Cell signaling involves three stages: reception, transduction, and response.
    1. In **reception**, a chemical signal binds to a cellular protein, typically at the target cell's surface or inside the cell.
    2. In **transduction**, binding of the signaling molecule changes the receptor protein in some way, initiating the process of transduction.
        - Transduction may occur in a single step but more often triggers a series of changes in a series of different molecules along a *signal transduction pathway.*
        - The molecules in the pathway are called relay molecules.
    3. In **response**, the transduced signal triggers a specific cellular activity.
- The cell-signaling process helps ensure that crucial activities occur in the right cells, at the right time, and in proper coordination with the other cells of the organism.



Concept 11.2 Reception: A signal molecule binds to a receptor protein, causing it to change shape

- The cell targeted by a particular chemical signal has a receptor protein on or in the target cell that recognizes the signal molecule.
    - Recognition occurs when the signal binds to a specific site on the receptor that is complementary in shape to the signal.
- The signal molecule behaves as a **ligand**, a small molecule that binds with specificity to a larger molecule.
- Ligand binding generally causes the receptor protein to undergo a change in shape.
- Ligand binding may activate the receptor so that it can interact with other molecules.
    - For other receptors, ligand binding causes aggregation of receptor molecules, leading to further molecular events inside the cell.
- Most signal receptors are plasma membrane proteins, whose ligands are large, water-soluble molecules that are too large to cross the plasma membrane.
    - Other signal receptors are located inside the cell.

Most signal receptors are plasma membrane proteins.

- Water-soluble signaling molecules bind to specific sites on receptor proteins that span the cell's plasma membrane.
    - The transmembrane receptor transmits information from the extracellular environment to the inside of the cell by changing shape or aggregating with other receptors.
- There are three major types of membrane receptors: G-protein-linked receptors, receptor tyrosine kinases, and ion channel receptors.

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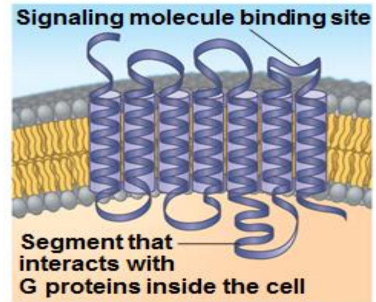
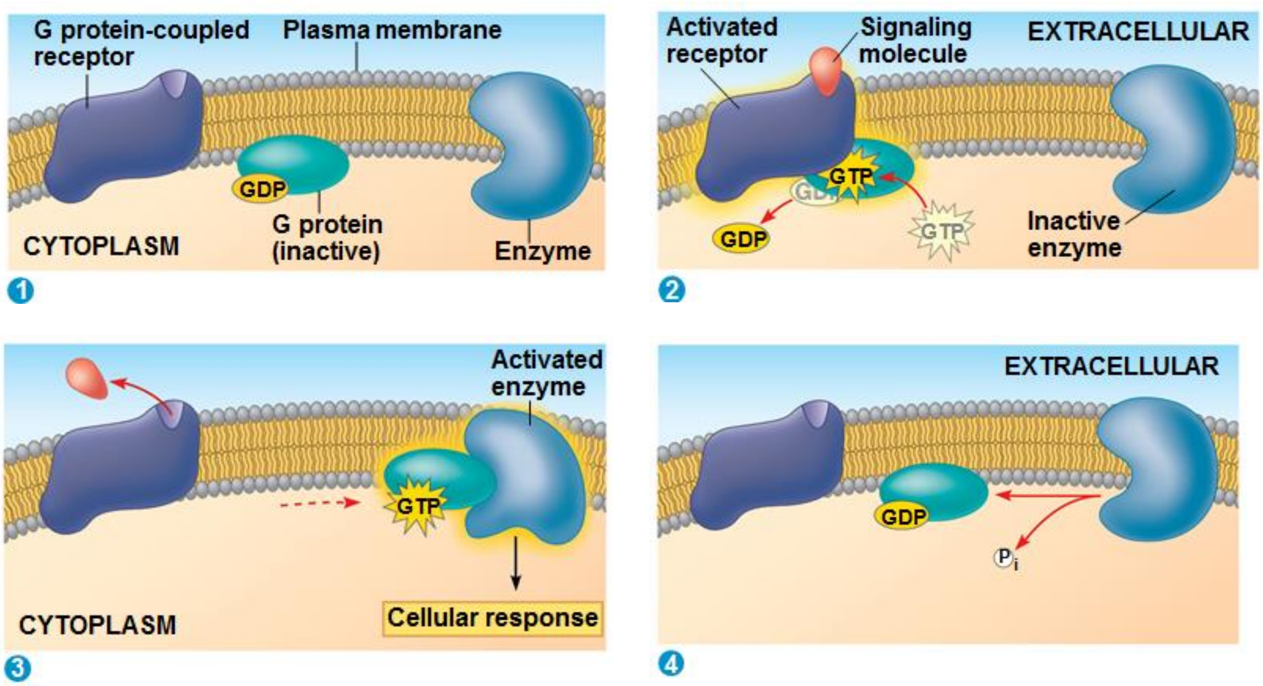
- A **G-protein-linked receptor** consists of a receptor protein associated with a G protein on the cytoplasmic side.
  - Seven α helices span the membrane.
  - G-protein-linked receptors bind many different signal molecules, including yeast mating factors, epinephrine and many other hormones, and neurotransmitters.

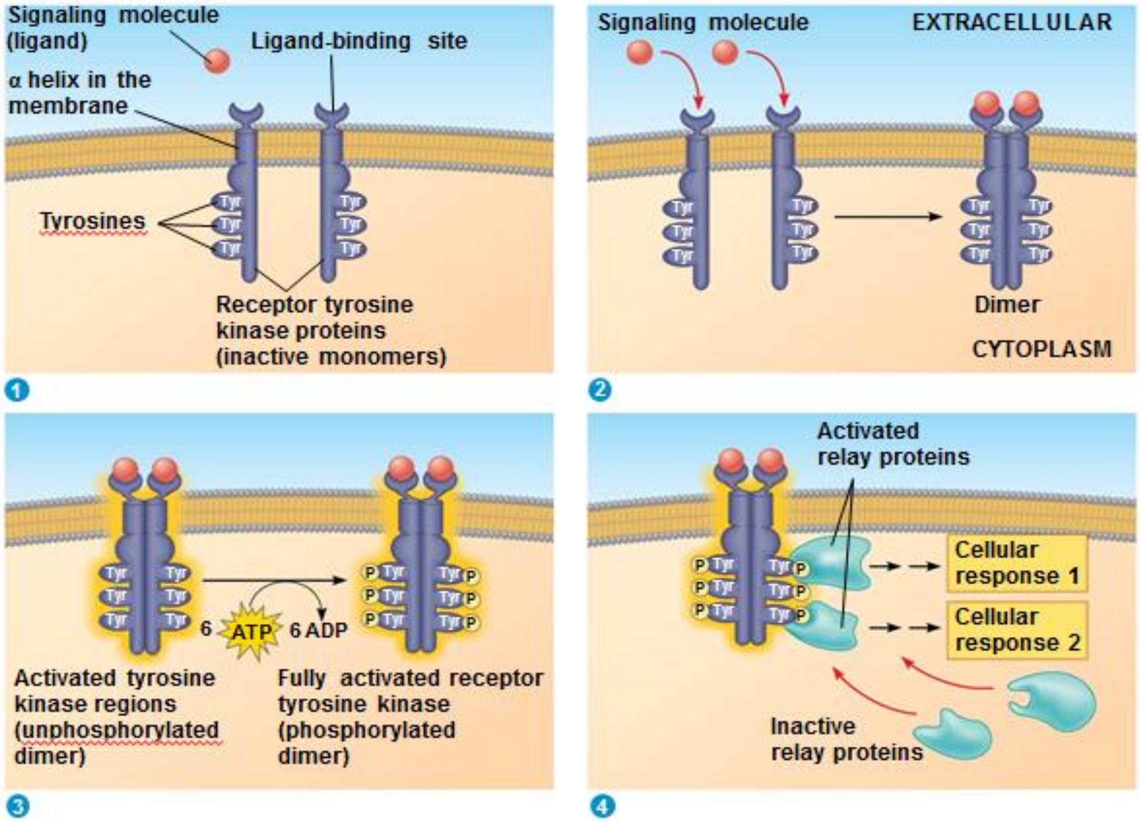


G protein-coupled receptor

- The **G protein** acts as an on-off switch.
  - If GDP is bound to the G protein, the G protein is inactive.
  - When the appropriate signal molecule binds to the extracellular side of the receptor, the G protein binds GTP (instead of GDP) and becomes active.
  - The activated G protein dissociates from the receptor and diffuses along the membrane, where it binds to an enzyme, altering its activity.
  - The activated enzyme triggers the next step in a pathway leading to a cellular response.
- The G protein can also act as a GTPase enzyme to hydrolyze GTP to GDP.
  - This change turns the G protein off.
  - Now inactive, the G protein leaves the enzyme, which returns to its original state.
- The whole system can be shut down quickly when the extracellular signal molecule is no longer present.
- G-protein receptor systems are extremely widespread and diverse in their functions.
  - They play important roles during embryonic development.
  - Vision and smell in humans depend on these proteins.
- Similarities among G proteins and G-protein-linked receptors of modern organisms suggest that this signaling system evolved very early.
- Several human diseases involve G-protein systems.
  - For example, bacterial infections that cause cholera and botulism interfere with G-protein function.

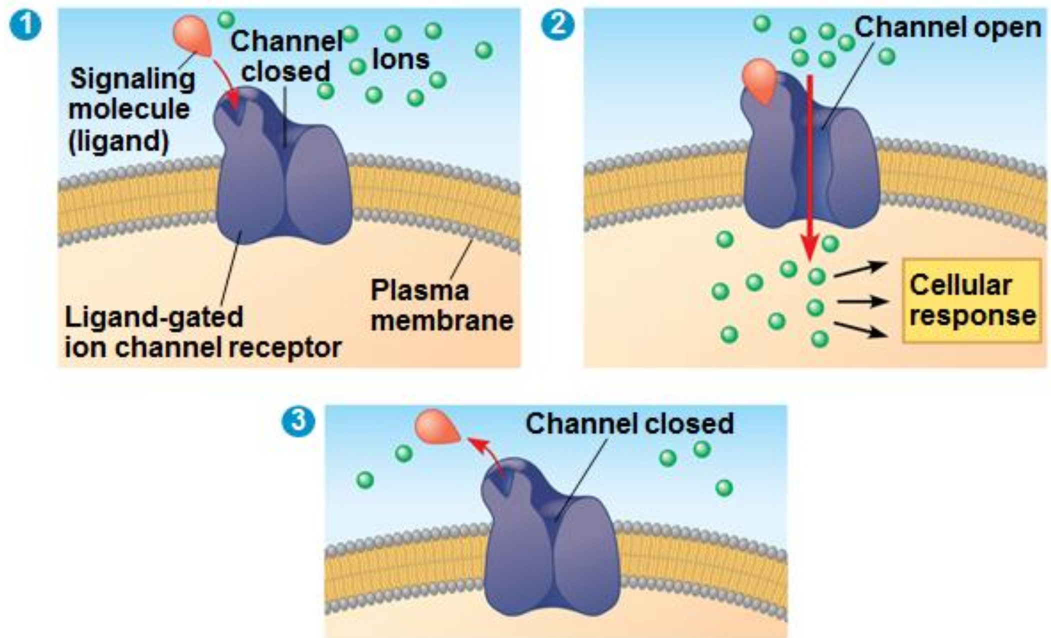


- The **tyrosine-kinase receptor** system is especially effective when the cell needs to trigger several signal transduction pathways and cellular responses at once.
  - This system helps the cell regulate and coordinate many aspects of cell growth and reproduction.
  -



- The tyrosine-kinase receptor belongs to a major class of plasma membrane receptors that have enzymatic activity.
  - A **kinase** is an enzyme that catalyzes the transfer of phosphate groups.
  - The cytoplasmic side of these receptors functions as a tyrosine kinase, transferring a phosphate group from ATP to tyrosine on a substrate protein.
- An individual tyrosine-kinase receptor consists of three parts: an extracellular signal-molecule-binding site, a single α helix spanning the membrane, and an intracellular tail with several tyrosines.
- The signal molecule binds to an individual receptor.
- Ligands bind to two receptors, causing the two receptors to aggregate and form a dimer.
- This dimerization activates the tyrosine-kinase section of the receptors, each of which then adds phosphate from ATP to the tyrosine tail of the other polypeptide.
- The fully activated receptor proteins activate a variety of specific relay proteins that bind to specific phosphorylated tyrosine molecules.
  - One tyrosine-kinase receptor dimer may activate ten or more different intracellular proteins simultaneously.
  - These activated relay proteins trigger many different transduction pathways and responses.
- A **ligand-gated ion channel** is a type of membrane receptor that can act as a gate when the receptor changes shape.
- When a signal molecule binds as a ligand to the receptor protein, the gate opens to allow the flow of specific ions, such as Na^+ or Ca^{2+}, through a channel in the receptor.
  - Binding by a ligand to the extracellular side changes the protein's shape and opens the channel.
  - When the ligand dissociates from the receptor protein, the channel closes.

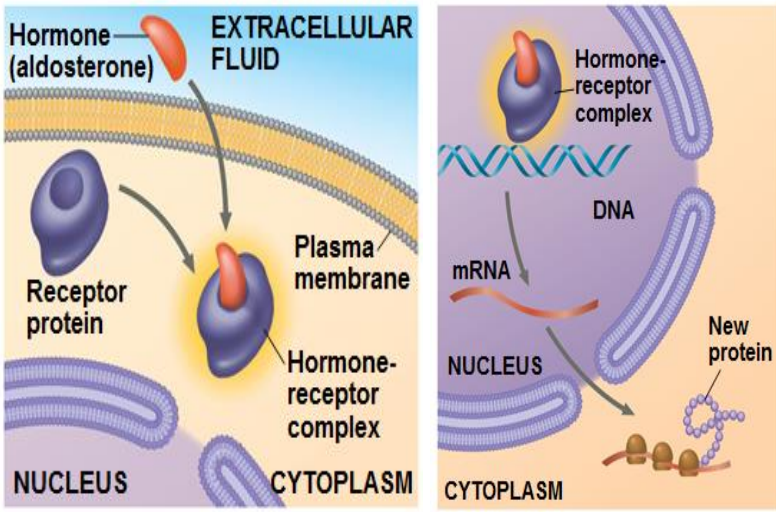
The change in ion concentration within the cell may directly affect the activity of the cell.



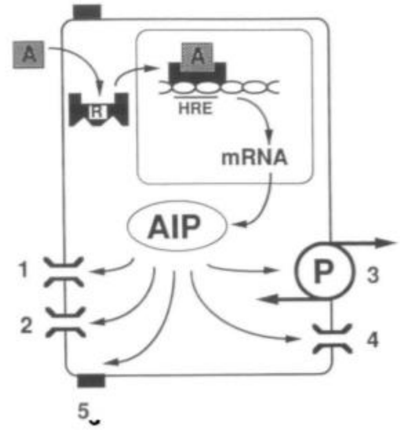
- Ligand-gated ion channels are very important in the nervous system.
  - For example, neurotransmitter molecules released at a synapse between two neurons bind as ligands to ion channels on the receiving cell, causing the channels to open.
  - Ions flow in and trigger an electrical signal that propagates down the length of the receiving cell.
- Some gated ion channels respond to electrical signals instead of ligands.
- Malformations of cell-surface receptor molecules are associated with many human diseases, including cancer, heart disease, and asthma.
  - Although cell-surface receptors make up 30% of human proteins, they make up only 1% of all proteins whose structures have been determined by X-ray crystallography.
  - Their structures are very hard to determine experimentally.
- The largest family of human cell-surface receptors consists of the nearly 1,000 G protein-coupled receptors (GPCRs).
  - The structure of several G protein-coupled receptors has been elucidated over the past few years.
- Abnormal functioning of receptor tyrosine kinases (RTKs) is associated with many types of cancers.
  - Excessive levels of a receptor tyrosine kinase called HER2 on breast cancer cells correlates with a poorer prognosis for patients.
  - Using molecular biological techniques, researchers have developed a protein called Herceptin that binds to HER2 on cells and inhibits their growth, reducing tumor development.
  - In some clinical studies, treatment with Herceptin improved patient survival rates by more than one-third.
- One goal of ongoing research into cell-surface receptors and other cell signaling proteins is development of successful treatments.

Some receptor proteins are intracellular.

- Intracellular signal receptors are found in the cytoplasm or nucleus of target cells.
- To reach these receptors, a chemical messenger passes through the target cell’s plasma membrane.
  - Such chemical messengers are either hydrophobic enough or small enough to cross the phospholipid interior of the plasma membrane.
- Hydrophobic messengers include the steroid and thyroid hormones of animals.



Steroid Hormone: Cytoplasm → Nucleus→ Protein



1) apical Na channel

2) apical K channel

3) basolateral Na-K pump

4) basolateral K channel

5) tight junctions

- Another chemical signaling molecule with an intracellular receptor is nitric oxide (NO), a gas whose small size allows it to pass between membrane phospholipids.
- Testosterone is secreted by the testis and travels through the blood to enter cells throughout the body.
  - Only cells that contain receptor molecules for testosterone respond.
  - In these cells, the hormone binds and activates the receptor protein.
  - The activated proteins enter the nucleus and turn on specific genes that control male sex characteristics.
- How does the activated hormone-receptor complex turn on genes? These activated proteins act as *transcription factors.*
  - Transcription factors control which genes are turned on—that is, which genes are transcribed into messenger RNA.
- Some intracellular receptors (such as thyroid hormone receptors) are found in the nucleus and bind to the signal molecules there.
- Many intracellular receptor proteins are structurally similar, suggesting an evolutionary kinship.

Concept 11.3 Transduction: Cascades of molecular interactions relay signals from receptors to target molecules in the cell

- The transduction stage of signaling is usually a multistep pathway that greatly amplifies the signal.
  - If some molecules in a pathway transmit a signal to multiple molecules at the next step in the series, the result can be a large number of activated molecules at the end of the pathway.
- Multistep pathways also provide more opportunities for coordination and regulation than do simpler systems.

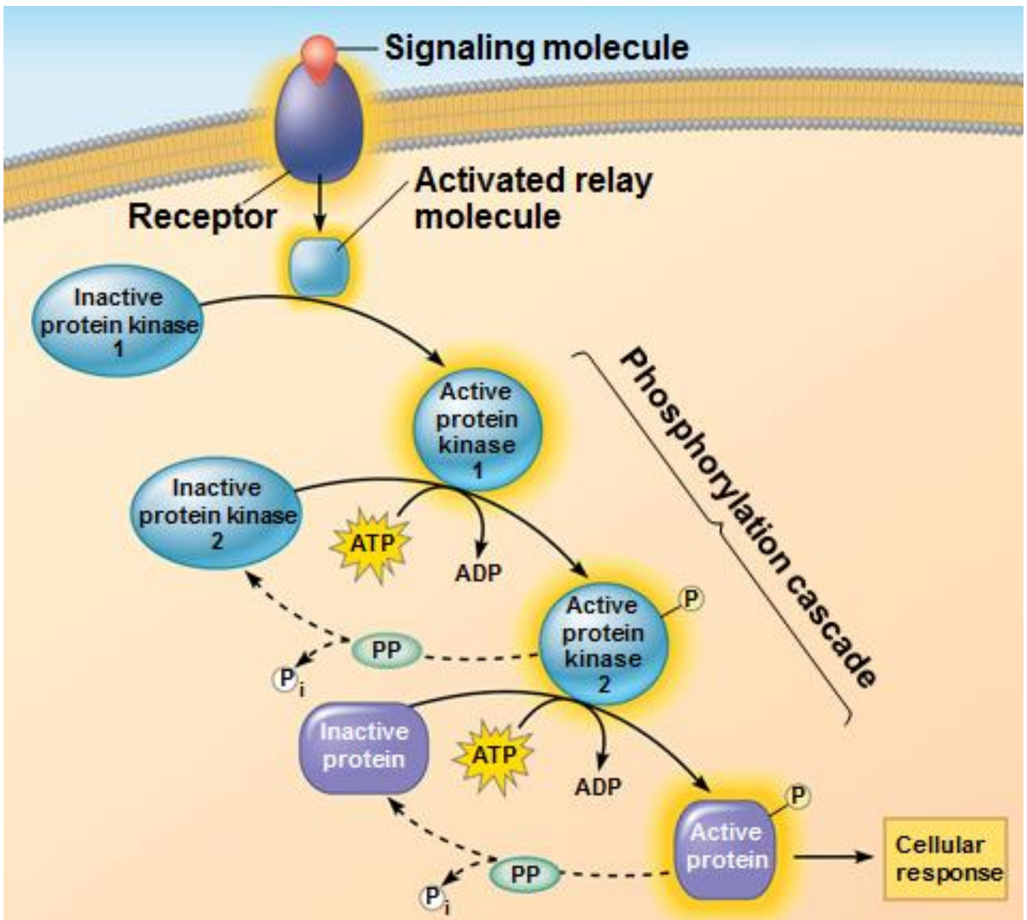
Pathways relay signals from receptors to cellular responses.

- The binding of a specific signaling molecule to a receptor in the plasma membrane triggers the first step in the chain of molecular interactions—the signal transduction pathway—that leads to a particular response within the cell.
- Signal transduction pathways act like falling dominoes. The signal-activated receptor activates another protein, which activates another, and so on, until the protein that produces the final cellular response is activated.

- The relay molecules that relay a signal from receptor to response are often proteins.
  - The interaction of proteins is a major theme of cell signaling.
  - Protein interaction is a unifying theme of all cellular regulation.
- The original signal molecule is not passed along the pathway and may not even enter the cell.
- When the signal is relayed along a pathway, information is passed on.
  - At each step, the signal is transduced into a different form, often by a conformational change in a protein.
  - The conformational change is often brought about by phosphorylation.

Protein phosphorylation, a common mode of regulation in cells, is a major mechanism of signal transduction.

- The phosphorylation of proteins by a specific enzyme (a **protein kinase**) is a widespread cellular mechanism for regulating protein activity.
- Most protein kinases act on other substrate proteins, unlike tyrosine kinases, which act on themselves.
- Most phosphorylation occurs at serine or threonine amino acids of the substrate protein.
- Many of the relay molecules in a signal transduction pathway are protein kinases that act on other protein kinases to create a "**phosphorylation cascade**."

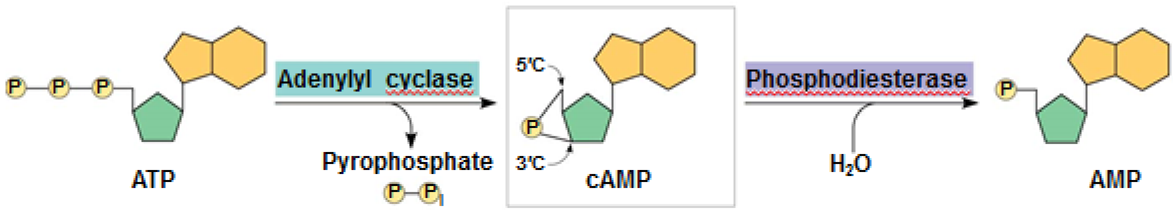


- Each protein phosphorylation leads to a conformational change because of the interaction between the newly added phosphate group and charged or polar amino acids on the protein.
- Phosphorylation of a protein typically converts it from an inactive form to an active form.
  - Only rarely does phosphorylation *decreases* the activity of the protein.

- A single cell may have hundreds of different protein kinases, each specific for a different substrate protein.
    - Fully 2% of our genes are thought to code for protein kinases.
    - Together, they regulate a large proportion of the thousands of the proteins in a cell.
- Abnormal activity of protein kinases can cause abnormal cell growth and may contribute to the development of cancer.
- The responsibility for turning off a signal transduction pathway belongs to **protein phosphatases**.
- These enzymes rapidly remove phosphate groups from proteins, a process called *dephosphorylation*.
    - By dephosphorylating and thus inactivating protein kinases, phosphatases provide the mechanism for turning off the signal transduction pathway when the initial signal is no longer present.
    - Phosphatases also make the protein kinases available for reuse, enabling the cell to respond again to a signal.
- The phosphorylation/dephosphorylation system acts as a molecular switch in the cell, turning activities on and off as required.
    - At any given moment, the activity of a protein regulated by phosphorylation depends on the balance between active kinase molecules and active phosphatase molecules.
    - When the extracellular signal molecule is absent, active phosphatase molecules predominate, and the signaling pathway and cellular response are shut down.

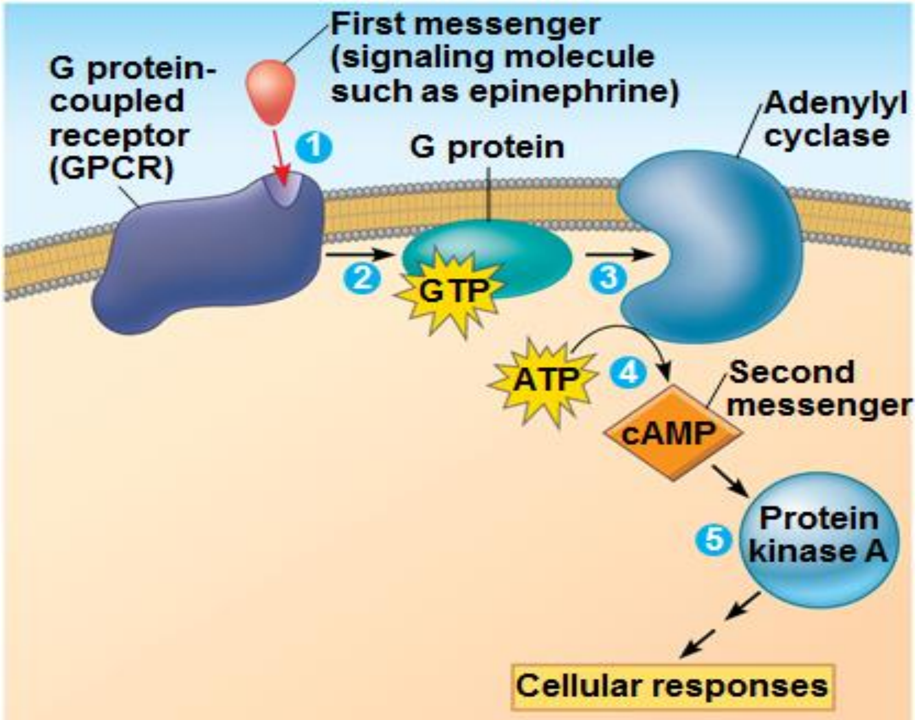
Certain signal molecules and ions are key components of signaling pathways (second messengers).

- Many signaling pathways involve small, water-soluble, nonprotein molecules or ions called **second messengers**.
    - The extracellular signaling molecule that binds to the membrane receptor is a pathway's "first messenger."
- Second messengers diffuse rapidly throughout the cell.
- Second messengers participate in pathways initiated by both G-protein-linked receptors and tyrosine-kinase receptors.
    - Two of the most widely used second messengers are cyclic AMP and Ca^{2+}.
    - A large variety of relay proteins are sensitive to the cytosolic concentration of one or the other of these second messengers.
- Once Sutherland knew that epinephrine causes glycogen breakdown without entering the cell, he looked for a second messenger that transmits the signal from the plasma membrane to the metabolic machinery in the cytoplasm.
- Binding by epinephrine leads to increases in the cytosolic concentration of **cyclic AMP**, or **cAMP**.
    - This increase occurs because the activated receptor activates **adenylyl cyclase**, which converts ATP to cAMP in response to epinephrine.
    - When epinephrine outside the cell binds to a specific receptor protein, the normal cellular concentration of cAMP can be boosted 20-fold within seconds.
    - cAMP is short-lived because phosphodiesterase converts it to AMP.
    - Another surge of epinephrine is needed to reboost the cytosolic concentration of cAMP.



- Many hormones and other signal molecules trigger the formation of cAMP.

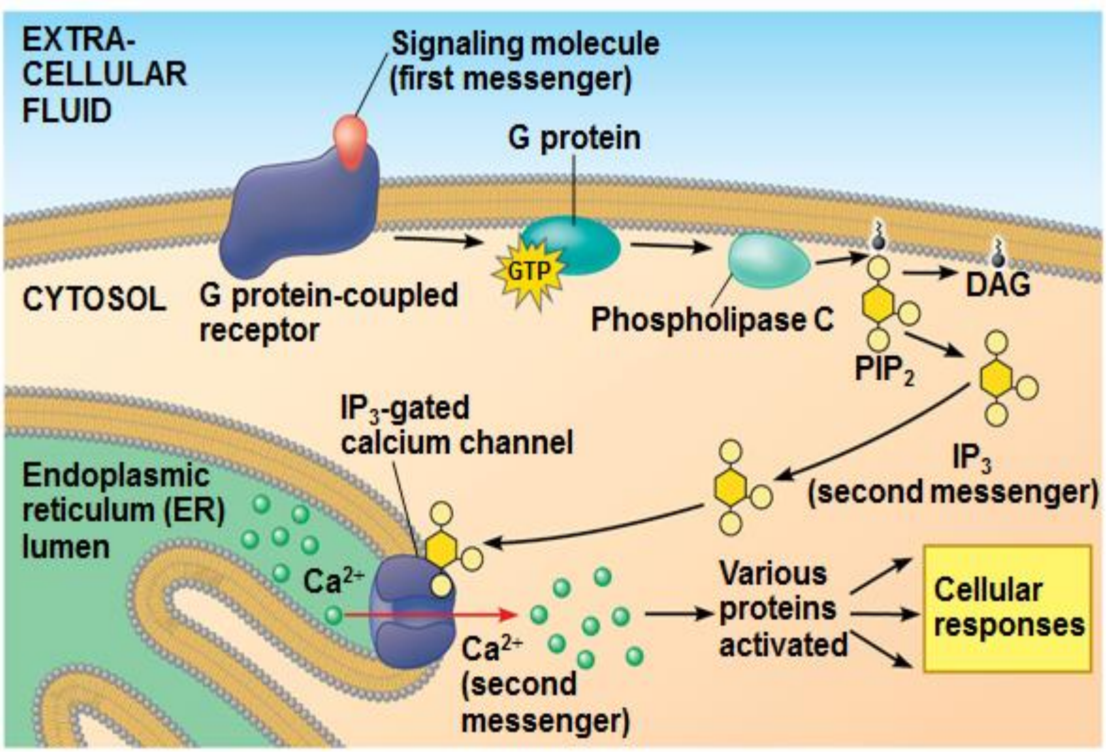
- G-protein-linked receptors, G proteins, and protein kinases are other components of cAMP pathways.



- cAMP diffuses through the cell and activates a serine/threonine kinase called *protein kinase A.*
  - The activated kinase phosphorylates various other proteins, depending on cell type.
- Cell metabolism is also regulated by G-protein systems that *inhibit* adenylyl cyclase.
  - These systems use a different signal molecule to activate a different receptor that activates an *inhibitory* G protein.
- Certain microbes cause disease by disrupting G-protein signaling pathways.
  - For example, the cholera bacterium, *Vibrio cholerae*, may be present in water contaminated with human feces.
  - This bacterium colonizes the small intestine and produces a toxin that modifies a G protein that regulates salt and water secretion.
  - The modified G protein is unable to hydrolyze GTP to GDP and remains stuck in its active form, continuously stimulating adenylyl cyclase to make cAMP.
  - The resulting high concentration of cAMP causes the intestinal cells to secrete large amounts of water and salts into the intestines, leading to profuse diarrhea and possible death from loss of water and salts.
- Treatments for certain human conditions involve signaling pathways.
- One pathway uses *cyclic GMP*, or *cGMP*, as a signaling molecule. Its effects include the relaxation of smooth muscle cells in artery walls.
  - A compound was developed to treat chest pains. This compound inhibits the hydrolysis of cGMP to GMP, prolonging the signal and increasing blood flow to the heart muscle.
  - Under the trade name Viagra, this compound is now widely used as a treatment for erectile dysfunction.
  - Viagra causes dilation of blood vessels, allowing increased blood flow to the penis.
- Many signaling molecules in animals, including neurotransmitters, growth factors, and some hormones, induce responses in their target cells via signal transduction pathways that increase the cytosolic concentration of Ca^{2+}.

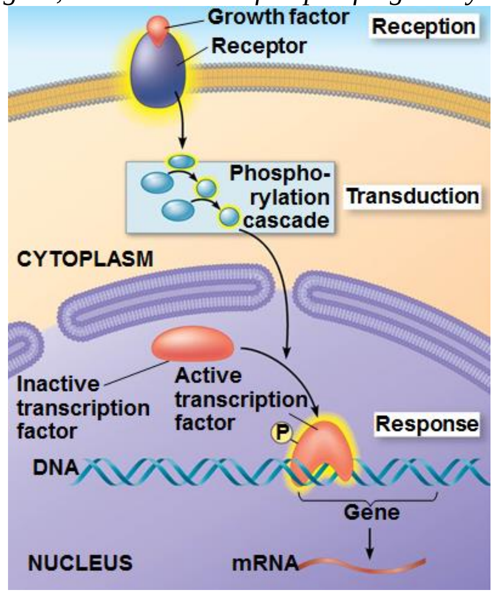
- Calcium is even more widely used than cAMP as a second messenger.
  - In animal cells, increases in Ca^{2+} concentrations may cause contraction of muscle cells, secretion of certain substances, and cell division.
  - In plant cells, increases in Ca^{2+} trigger responses such as the pathway for greening in response to light.
- Cells use Ca^{2+} as a second messenger in both G-protein pathways and tyrosine-kinase pathways.
- The Ca^{2+} concentration in the cytosol is typically much lower than the concentration outside the cell, often by a factor of 10,000 or more.
  - Various proteins actively transport Ca^{2+} outside the cell or into the endoplasmic reticulum (ER) or other organelles.
  - As a result, the concentration of Ca^{2+} in the ER is usually much higher than the concentration in the cytosol.
- Because the concentration of cytosolic Ca^{2+} is so low, small changes in the absolute numbers of ions cause a relatively large percentage change in the Ca^{2+} concentration.

- Signal transduction pathways trigger the release of Ca^{2+} from the cell's ER.
- The pathways leading to calcium release involve still other second messengers, **diacylglycerol (DAG)** and **inositol trisphosphate (IP_3)**.
  - DAG and IP_3 are created when a phospholipase cleaves a specific membrane phospholipid.
  - The phospholipase may be activated by a G protein or by a tyrosine-kinase receptor.
  - IP_3 activates a gated calcium channel, releasing Ca^{2+} from the ER.
  - Calcium ions activate the next protein in a signal transduction pathway.
- Because IP_3 acts before calcium in these pathways, calcium could be considered a *third* messenger.
  - However, scientists use the term *second messenger* for all small, nonprotein components of signal transduction pathways.



Concept 11.4 Response: Cell signaling leads to regulation of transcription or cytoplasmic activities

- Ultimately, a signal transduction pathway leads to the regulation of one or more cellular activities.
- The response may occur in the nucleus or the cytoplasm.
- Many signaling pathways ultimately regulate protein synthesis, usually by turning specific genes on or off in the nucleus.
  - Like an activated steroid receptor, the final activated molecule in a signaling pathway may function as a transcription factor. Often a transcription factor regulates several different genes. *Nuclear response to a signal; the activation of a specific gene by a growth factor*



- Signaling pathways may regulate the *activity* of proteins rather than their *synthesis*, directly affecting proteins that function outside of the nucleus.
  - A signal may cause the opening or closing of an ion channel or a change in cell metabolism.
  - For example, epinephrine helps regulate cellular energy metabolism by activating enzymes that catalyze the breakdown of glycogen.
- Signaling events may also affect cellular attributes such as overall cell behavior.
- One example of this regulation can be found in the activities leading to the mating of yeast cells.
  - In yeast, the mating process depends on the growth of localized projections in one cell toward a cell of the opposite mating type.
  - Binding of the mating factor causes directional growth via activation of signaling-pathway kinases that affect the orientation of the growth of cytoskeletal microfilaments.
  - Cell projections emerge from areas that receive the highest concentration of the mating factor and thus have the highest likelihood of reaching the cell of the opposite mating type, the source of the signaling molecule.
- Signal receptors and relay molecules participate in a variety of nuclear and cytoplasmic response pathways, some leading to cell division.
  - The molecular messengers that produce these responses include growth factors and certain plant and animal hormones.
- ○ Malfunctioning of growth factor pathways can contribute to the development of cancer.

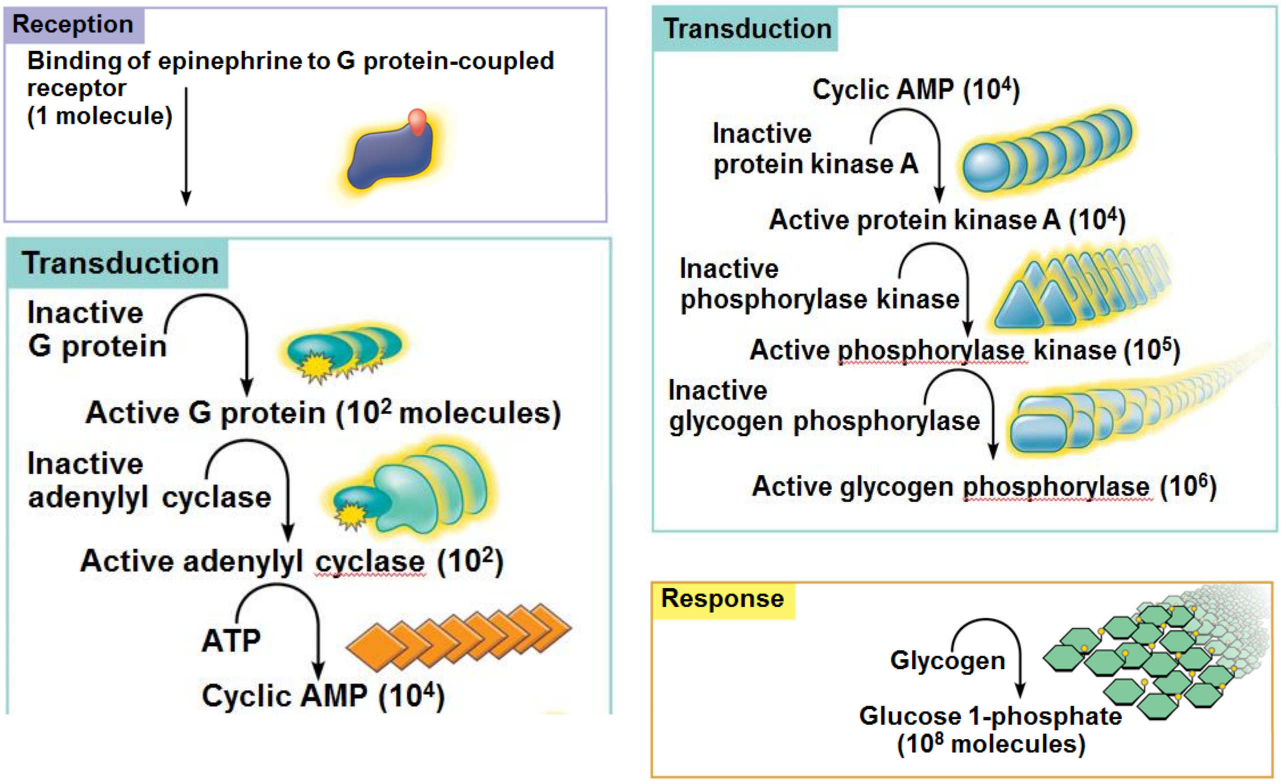
Signaling pathways with multiple steps provide signal amplification, allow fine-tuning of the cell's response, and contribute to the specificity of the response.

- Whether the response occurs in the nucleus or cytoplasm, it is fine-tuned at multiple points.
- Consider four aspects of this fine-tuning:

1. Signaling pathways with numerous steps between a signaling event at the cell surface and the cell's response can amplify the signal and thus the response.
2. Multi-step pathways have many different points at which a cell's response can be regulated, contributing to the specificity of each response and allowing coordination with other signaling pathways.
3. Overall efficiency of the response is enhanced by the presence of scaffolding proteins.
4. A crucial point in fine-tuning the response is the termination of the signal.

- Elaborate enzyme cascades amplify the cell's response to a signal.
    - At each catalytic step in a cascade, the number of activated products is much greater than in the preceding step.
    - In the epinephrine-triggered pathway, binding by a small number of epinephrine molecules can lead to the release of hundreds of millions of glucose molecules.

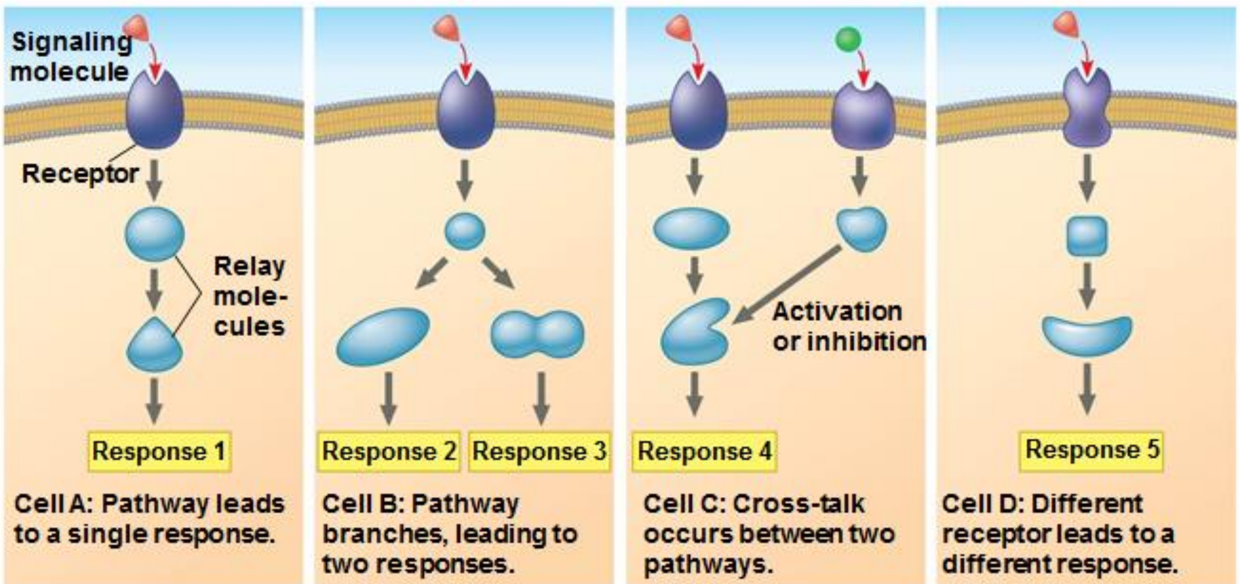
Cytoplasmic response to a signal: the stimulation of glycogen breakdown by epinephrine



- Various types of cells may receive the same signal but produce very different responses.
    - For example, epinephrine triggers liver cells to break down glycogen, but stimulates cardiac muscle cells to contract, leading to a more rapid heartbeat.
- The explanation for this specificity is that *different kinds of cells have different collections of proteins.*
    - This is because different kinds of cells turn on different sets of genes.
- The response of a particular cell to a signal depends on its particular collection of receptor proteins, relay proteins, and proteins needed to carry out the response.
    - Two cells that respond differently to the same signal differ in one or more of the proteins that handle and respond to the signal.
- Different pathways may have some molecules in common.
    - Cells may use the same receptor protein, but differences in other proteins lead to different responses.
    - Cells may use differing receptor proteins for the same signaling molecule, leading to different responses.

- A signal may trigger a single pathway in one cell but trigger a branched pathway in another.
  - Such branched pathways often involve receptor tyrosine kinases (which can activate multiple relay proteins) or second messengers (which can regulate numerous proteins).
- Two pathways triggered by separate signals may converge to modulate a single response.
- Branching of pathways and interactions between pathways are important for regulating and coordinating a cell's response to incoming information.
- Using the same proteins in more than one pathway allows the cell to economize on the number of different proteins it must make.

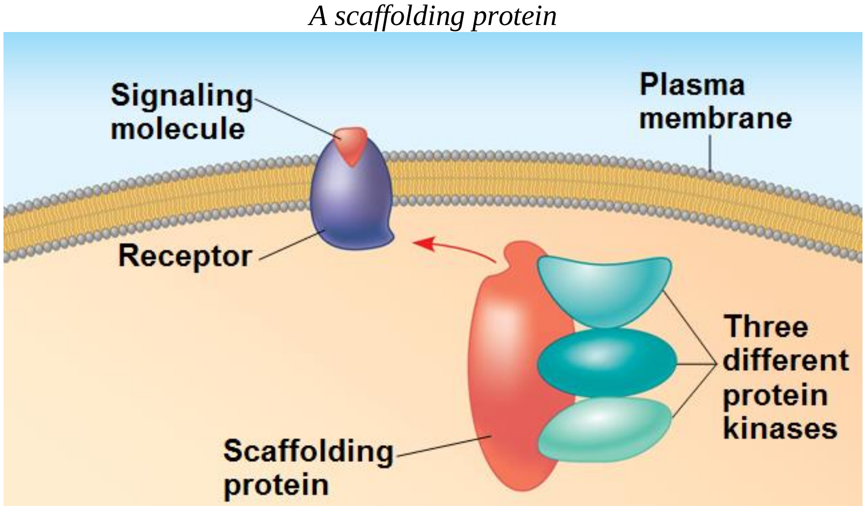
The specificity of cell signaling



Scaffolding proteins and signaling complexes contribute to signaling efficiency.

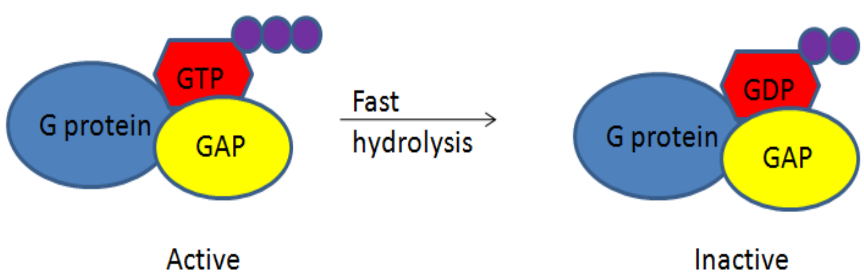
- Rather than relying on the diffusion of large relay molecules such as proteins, many signal pathways are linked together physically by **scaffolding proteins**.
- Scaffolding proteins may themselves be large relay proteins to which several other relay proteins attach.
  - For example, one scaffolding protein isolated from mouse brain cells holds three protein kinases and carries these kinases with it when it binds to an appropriately activated membrane receptor, facilitating a specific phosphorylation cascade.

A scaffolding protein

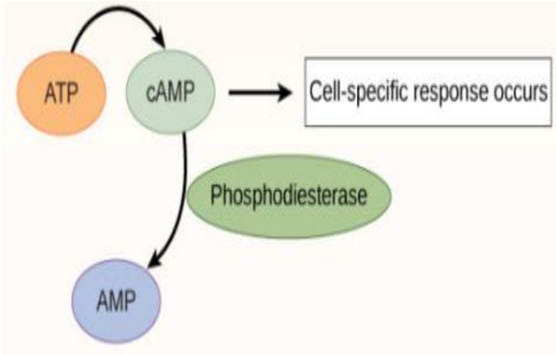


- Some scaffolding proteins in brain cells *permanently* hold together networks of signaling-pathway proteins at synapses.
    - This hardwiring enhances the speed and accuracy of signal transfer between cells.
- When signaling pathways were first discovered, they were thought to be linear, independent pathways.
    - In fact, some proteins participate in more than one pathway, either in different cell types or in the same cell at different times or under different conditions.
    - Permanent or transient protein complexes are very important in the functioning of a cell.
- The importance of relay proteins that serve as branch or intersection points in signaling pathways is underscored when these proteins are defective or missing.
    - For example, the inherited disorder Wiskott-Aldrich syndrome (WAS) is caused by the absence of a single relay protein.
    - Symptoms of WAS include abnormal bleeding, eczema, and a predisposition to infections and leukemia, due to the absence of the protein in immune system cells.
    - The WAS protein is located just beneath the cell surface, where it interacts with the microfilaments of the cytoskeleton and with several signaling pathways, including those that regulate immune cell proliferation.
    - When the WAS protein is absent, the cytoskeleton is not properly organized and signaling pathways are disrupted.
- As important as activating mechanisms are *inactivation* mechanisms.
- For a cell to receive new signals, each molecular change in its signaling pathways must last only a short time.
- If signaling pathway components become locked into one state, whether active or inactive, the proper function of the cell can be disrupted.
- Binding of signal molecules to receptors must be reversible, allowing the receptors to return to their inactive state when the signal is released.
- As the external concentration of signaling molecules declines, fewer receptors are bound and unbound receptors revert to their inactive form.
    - The cellular response only occurs when the concentration of receptors with bound signaling molecules is above a certain threshold.
    - When enough receptors become inactive so their number falls below that threshold, the cellular response ceases.
- By a variety of means, the relay molecules return to their inactive forms;; and so forth.

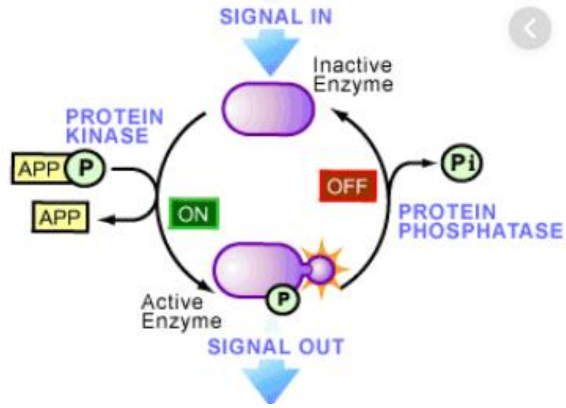
The GTPase activity intrinsic to a G protein hydrolyzes its bound GTP



The enzyme phosphodiesterase converts cAMP to AMP



Protein phosphatases inactivate phosphorylated kinases and other proteins



- As a result, the cell is soon ready to respond to a fresh signal.

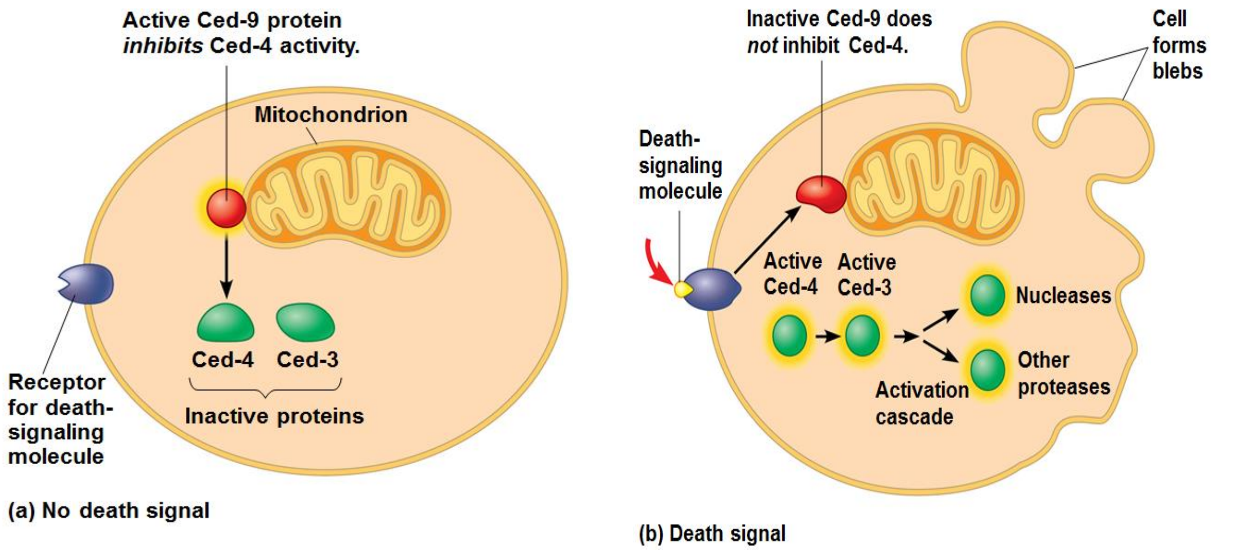
Concept 11.5 Apoptosis integrates multiple cell-signaling pathways

- Cells that are infected or damaged, or have reached the end of their functional lifespan, often enter a program of controlled cell suicide called **apoptosis**.
- During this process, cellular agents chop up the DNA and fragment the organelles and other cytoplasmic components.
- The cell shrinks and becomes lobed (called "blebbing"), and the cell's parts are packaged up in vesicles that are engulfed and digested by specialized scavenger cells.
- Apoptosis protects neighboring cells from the damage that would result if a dying cell leaked out all its contents, including its many digestive and other enzymes.

Apoptosis plays an important role in embryonic development.

- The molecular mechanisms underlying apoptosis were worked out in detail by researchers studying the embryonic development of a small soil worm, a nematode called *Caenorhabditis elegans.*
  - Because the adult worm has only about a thousand cells, the entire ancestry of each cell is known.
  - Cell suicide occurs exactly 131 times during the normal development of *C. elegans*, at precisely the same points in the cell lineage of each worm.
- In worms and other species, apoptosis is triggered by signals that activate a cascade of "suicide" proteins in the cells destined to die.
- Two key apoptosis genes, called *ced-3* and *ced-4,* encode proteins essential for apoptosis.
  - Proteins involved in apoptosis are continually present in cells but in inactive form; regulation occurs at the level of protein activity rather than trough gene activity and protein synthesis.
- In *C. elegans*, a protein in the outer mitochondrial membrane, called Ced-9 (the product of the *ced-9* gene), serves as a master regulator of apoptosis, acting as a brake in the absence of a signal promoting apoptosis.
- When the cell receives a death signal, the apoptotic pathway activates proteases and nucleases, enzymes that cut up the proteins and DNA of the cell.
- The main proteases of apoptosis are called *caspases*. In the nematode, the chief caspase is Ced-3.

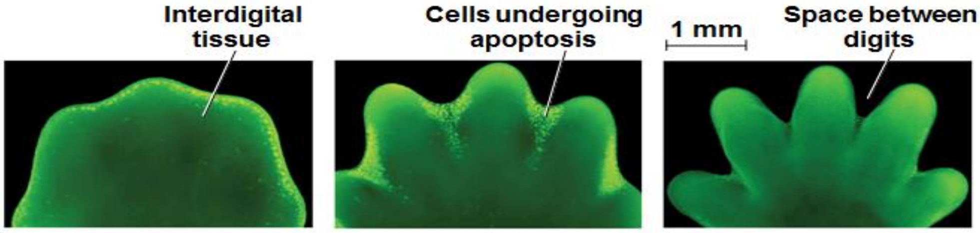
Molecular basis of apoptosis in C. elegans



Apoptosis is important in vertebrate development and maintenance.

- In humans and other mammals, several different pathways, involving about 15 different caspases, can carry out apoptosis.
  - The pathway that is used depends on the type of cell and on the particular signal that initiates apoptosis.
- One major pathway involves certain mitochondrial proteins that form molecular pores in the mitochondrial outer membrane, causing it to leak and release proteins that promote apoptosis.
  - Cytochrome *c*, which functions in mitochondrial electron transport in healthy cells, acts as a cell death factor when released from mitochondria.
  - The process of mitochondrial apoptosis in mammals uses proteins homologous to the nematode proteins Ced-3, Ced-4, and Ced-9.
  - These can be thought of as relay proteins capable of transducing the apoptotic signal.
- At key gateways into the apoptotic program, relay proteins may integrate signals from several different sources and send a cell down an apoptotic pathway.
- The signal may originate outside the cell, perhaps released by a neighboring cell.
- Two other types of alarm signals originate from inside the cell.
  - One alarm signal comes from the nucleus, generated when the DNA has suffered irreparable damage, and a second comes from the endoplasmic reticulum when excessive protein misfolding occurs.
- Mammalian cells make life-or-death "decisions" by integrating the death signals and life signals they receive from these external and internal sources.
- A built-in cell suicide mechanism is essential to development and maintenance in all animals.
- The similarities between apoptosis genes in nematodes and mammals, as well as the observation that apoptosis occurs in multicellular fungi and even in single-celled yeasts, indicate that the basic mechanism evolved early in animal evolution.

- In vertebrates, apoptosis is essential for normal development of the nervous system, for normal operation of the immune system, and for normal morphogenesis of hands and feet in humans and paws in other mammals**.**



    - A lower level of apoptosis in developing limbs accounts for the webbed feet of ducks and other water birds, in contrast to chickens and other land birds that have nonwebbed feet.
    - In humans, the failure of appropriate apoptosis can result in webbed fingers and toes.
- Apoptosis is involved in certain degenerative diseases of the nervous system such as Parkinson's disease and Alzheimer's disease.
- Cancer can also result from a failure of cell suicide.
    - Some cases of human melanoma are linked to faulty forms of the human version of the *C. elegans* Ced-4 protein.
- The signaling pathways that feed into apoptosis are quite elaborate.
    - The life-or-death question is the most fundamental one imaginable for a cell.

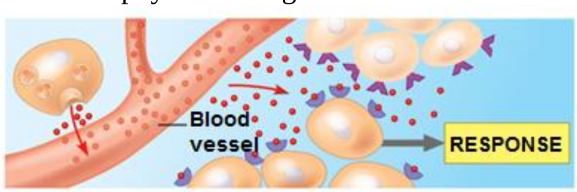
Chapter 45: Hormones and the Endocrine

Overview: The Body's Long-Distance Regulators

- An animal **hormone** is a chemical signal that is secreted into the extracellular fluid, circulates in the blood or hemolymph, and communicates regulatory messages within the body.
  - A hormone may reach all parts of the body, but only specific target cells have the receptors that enable a response.
  - A given hormone traveling in the bloodstream elicits specific responses—such as a change in metabolism—only from *its target cells* while other cells are unaffected.
- Chemical signaling by hormones is the function of the **endocrine system**, one of two basic systems for communication and regulation throughout the body.
  - Hormones secreted by endocrine cells regulate reproduction, development, energy metabolism, growth, and behavior.
- The other major communication and control system is the **nervous system**, a network of specialized cells called neurons that transmit signals along dedicated pathways.
  - These signals in turn regulate other cells, including neurons, muscle cells, and endocrine cells.
- Because signaling by neurons can regulate the release of hormones, the nervous and endocrine systems often overlap in function.

Concept 45.1 Hormones and other signaling molecules bind to target receptors, triggering specific response pathways.

- Endocrine signaling is one of several ways information is transmitted between animal cells.
  - The ways that signals are transmitted between animal cells are often classified by the type of secreting cell and the route taken by the signal in reaching its target.
- Hormones are secreted into extracellular fluids and reach target cells via the bloodstream or hemolymph.
- Endocrine signaling maintains homeostasis, mediates responses to environmental stimuli, and regulates growth and development.
  - Hormones coordinate responses to stress, dehydration, and low blood glucose levels.
  - They trigger behavioral and physical changes that underlie sexual maturity and reproduction.

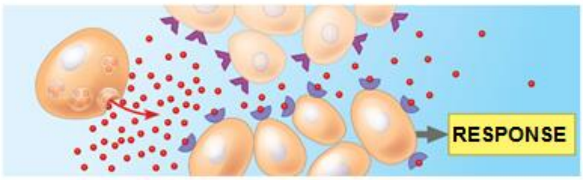


(a) Endocrine signaling

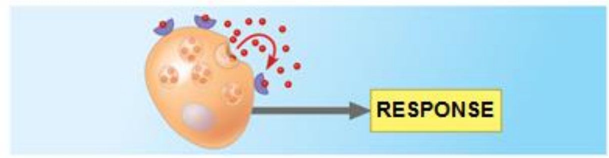
- **Local regulators** are chemical signals that act over short distances, reaching their target cells by diffusion.

- For example, immune cells communicate with each other by local regulators called cytokines.
- Local regulators function in many other processes, including blood pressure regulation, nervous system function, and reproduction.

- Local regulators are divided into paracrine and autocrine signals.
  - **Paracrine** signals act on cells near the secreting cell.
  - **Autocrine** signals are secreted regulators that act on the secreting cell itself.
  - Some signals have both paracrine and autocrine activity.

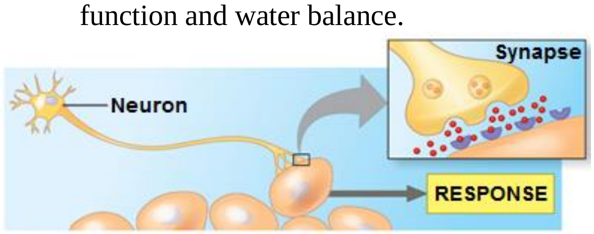


(b) Paracrine signaling



(c) Autocrine signaling

- Local regulators called **prostaglandins (PGs)** are modified fatty acids, first discovered in prostate-gland secretions.
- Released by many types of cells into interstitial fluids, PGs regulate nearby cells in various ways, depending on the tissue.
  - In semen that reaches the female reproductive tract, PGs trigger the contraction of the smooth muscles of the uterine wall, helping sperm to reach the egg.
  - PGs secreted by the placenta cause the uterine muscles to become more excitable, helping to induce uterine contractions during childbirth.
  - In the immune system, PGs promote fever and inflammation and also intensify the sensation of pain. These responses contribute to the body's defense.
  - The anti-inflammatory effects of aspirin and ibuprofen are due to the drugs' inhibition of PG synthesis.
  - PGs also help regulate the aggregation of platelets, one step in the formation of blood clots. This is why people at risk for a heart attack may take daily low doses of aspirin.
  - PGs also help maintain a protective lining in the stomach, and long-term aspirin therapy can cause debilitating stomach irritation.
- Secreted molecules are crucial for two types of signaling by neurons.
- In *synaptic signaling*, neurons form specialized junctions called synapses with target cells, such as other neurons and muscle cells.
  - At synapses, neurons secrete molecules called **neurotransmitters**, which diffuse a very short distance to bind to receptors on the target cell.
- In *neuroendocrine signaling*, specialized neurons called neurosecretory cells secrete chemical signals that diffuse from nerve cell endings into the bloodstream.
  - These signals are a class of hormones called **neurohormones**.
  - One example is ADH (antidiuretic hormone, or vasopressin), a hormone critical to kidney function and water balance.



(d) Synaptic signaling

(e) Neuroendocrine signaling

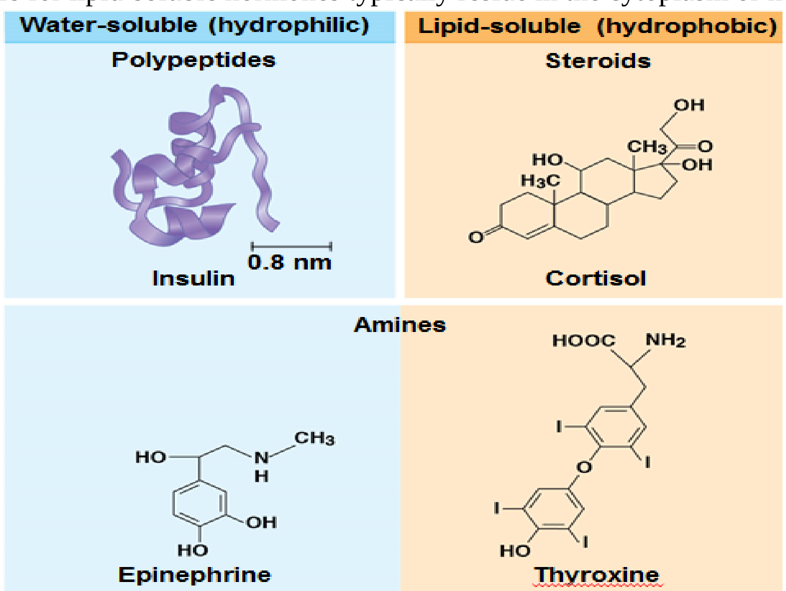
- Members of the same animal species may communicate with **pheromones**, chemical signals released into the external environment.

- Pheromones serve many functions, including defining territories, marking trails leading to food sources, warning of predators, and attracting potential mates.

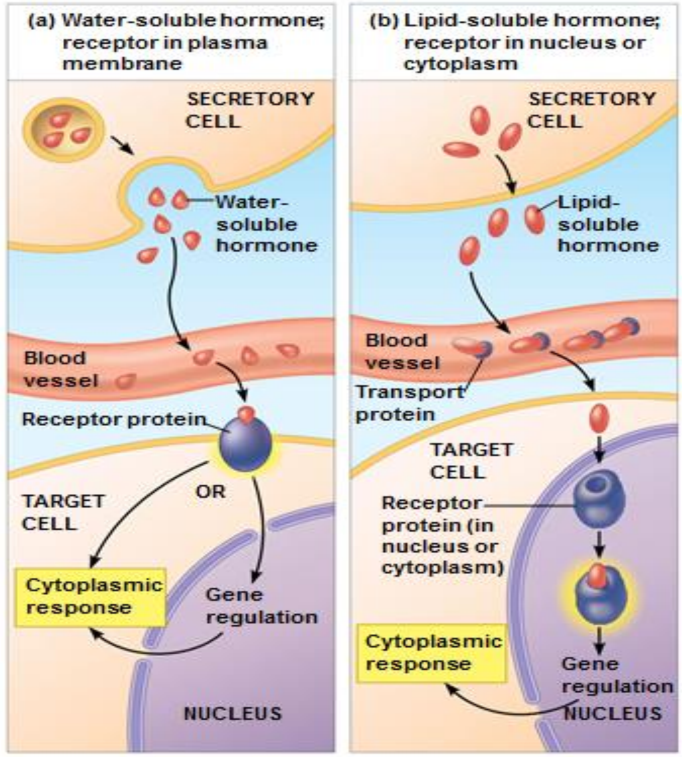
- Some endocrine cells are found in organs and tissues that are part of other organ systems.
  - For example, the stomach contains endocrine cells.
- Other endocrine cells are grouped in ductless organs called **endocrine glands**.
  - Endocrine glands secrete hormones directly into the surrounding fluid.
  - In contrast, *exocrine glands*, such as salivary glands, have ducts that secrete substances onto body surfaces or into body cavities.

There are three groups of hormones: polypeptides, amines, and steroids.

- The polypeptide hormone insulin is made up of two polypeptide chains, formed by cleavage of a longer protein chain.
- Epinephrine and thyroxine are amine hormones, which are synthesized from a single amino acid, either tyrosine or tryptophan.
- Steroid hormones, such as cortisol and ecdysteroid, are lipids that contain four fused carbon rings. All are derived from the steroid cholesterol.
- Polypeptides and most amine hormones are water-soluble.
  - Because they are insoluble in lipids, these hormones cannot pass through cell membranes.
  - Instead, they bind to cell-surface receptors that relay information to the nucleus through intracellular pathways.
- Steroid hormones, as well as other largely nonpolar hormones such as thyroxine, are lipid-soluble and can pass through cell membranes readily.
  - Receptors for lipid-soluble hormones typically reside in the cytoplasm or nucleus.



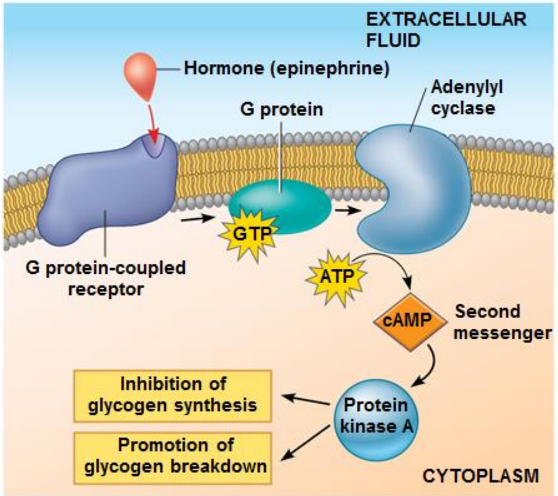
- There are several differences in the response pathways of water-soluble and lipid-soluble hormones. One difference is the location of the target cells' signal receptors.
- Water-soluble hormones are secreted by exocytosis, travel freely in the bloodstream, and bind to cell-surface receptors.
  - Binding of water-soluble hormones to receptors induces changes in cytoplasmic molecules and may alter gene transcription.
- Lipid-soluble hormones diffuse out across the membranes of endocrine cells.
  - Outside the cell, they bind to transport proteins that keep them soluble in the aqueous environment of the bloodstream.
  - Upon leaving the bloodstream, they diffuse into target cells, bind to intracellular signal receptors, and trigger changes in gene transcription.



Epinephrine is an example of a water-soluble hormone.

- A water-soluble hormone binds to a receptor protein, triggering events at the plasma membrane that result in a cellular response such as enzyme activation, uptake or secretion of a molecule, or cytoskeletal rearrangement.
    - Cell-surface receptors may cause cytoplasmic proteins to move into the nucleus and alter the transcription of specific genes.
- The series of changes in cellular proteins that converts the extracellular chemical signal to a specific intracellular response is called **signal transduction**.
    - Signal transduction pathways involve multiple steps with specific molecular interactions.
- In response to a stressful situation, the adrenal gland secretes **epinephrine**.
- When epinephrine reaches liver cells, it binds to a G-protein-linked receptor on the plasma membrane.
    - This triggers a cascade of events involving the synthesis of cyclic AMP (cAMP) as a short-lived *second messenger*.
- cAMP activates protein kinase A, leading to activation of an enzyme required for glycogen breakdown and inactivation of an enzyme necessary for glycogen synthesis.
    - The liver releases glucose into the bloodstream, providing the fuel needed to deal with the stressful situation.

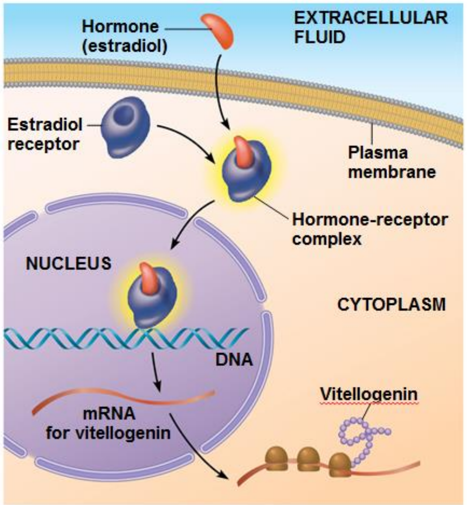
Signal transduction triggered by a cell-surface hormone receptor (Epinephrine)



Estradiol is an example of a lipid-soluble hormone.

- Intracellular receptors for lipid-soluble hormones perform the entire task of transducing a signal within a target cell.
- Binding of a steroid hormone to its cytoplasmic receptor forms a hormone-receptor complex that moves into the nucleus.
- In the nucleus, the receptor portion of the complex alters transcription of particular genes by interacting with a specific DNA-binding protein or response element in the DNA.
- Estradiol is a form of estrogen that has a specific receptor in liver cell.
- Estradiol binds to its receptor, activating the transcription of the vitellogenin gene.
  - Following translation, vitellogenin protein is transported in the blood to the ovary, where it is used to produce egg yolk

Direct regulation of gene expression by a steroid hormone receptor (Estradiol)



- Thyroxine, vitamin D, and other lipid-soluble hormones that are not steroid hormones diffuse from the bloodstream across both the plasma membrane and the nuclear membrane, binding with receptors located in the nucleus.
  - The receptor then binds to specific sites in the cell's DNA and stimulates the transcription of specific genes.
- Recent experiments indicate that lipid-soluble hormones can sometimes trigger responses at the cell surface without first entering the nucleus. How and when these responses arise are currently the subjects of active investigation.

Many hormones have multiple effects.

- Many hormones elicit many different responses in the body, depending on the target cell.
- Target cells may differ in the molecules that receive, transduce, or act upon the hormone signal.
    - For example, epinephrine simultaneously triggers glycogen breakdown in the liver, decreased blood flow to the digestive tract, and increased blood flow to major skeletal muscles.
    - All of these effects enhance the rapid reactions of the body in emergencies.
- Responding tissues vary in their expression of receptors or signal transduction pathways.
    - Target cell recognition of epinephrine involves G-protein-linked receptors.
    - β-type epinephrine receptors of liver cells activate protein kinase A, which regulates enzymes in glycogen metabolism.
    - In blood vessels supplying skeletal muscle, the same kinase activated by the same epinephrine receptor *inactivates* a muscle-specific enzyme, resulting in smooth muscle relaxation and increased blood flow.
    - Intestinal blood vessels have an α-type epinephrine receptor, which triggers a distinct signaling pathway involving a different G protein and a different enzyme.
    - The result is smooth muscle contraction and restricted blood flow to the intestines.
- Lipid-soluble hormones often exert different effects on different target cells as well.
    - The estrogen that stimulates a bird's liver to synthesize the yolk protein vitellogenin also stimulates its reproductive system to synthesize proteins that form the egg white.

Local regulators are signals that link neighboring cells or directly regulate the secreting cell.

- Local regulators can act on their target cells within seconds or milliseconds, eliciting responses more quickly than hormones can.
- Binding of local regulators to their receptors triggers events within target cells similar to those elicited by hormones.
- Several types of chemical compounds function as local regulators.
- Polypeptide local regulators include **cytokines**, which play a role in immune responses, and most **growth factors**, which stimulate cell proliferation and differentiation.
- Another important local regulator is the gas **nitric oxide (NO)**, which serves as a neurotransmitter and local regulator.
    - When the blood oxygen level falls, endothelial cells synthesize and release NO.
    - NO activates an enzyme that relaxes surrounding smooth muscle cells, dilating the walls of blood vessels and improving blood flow to tissues.
- NO plays a role in male sexual function, increasing blood flow to the penis to produce an erection.
    - Highly reactive and potentially toxic, NO usually triggers changes in the target cell within a few seconds of contact and then breaks down.
    - Viagra (sildenafil citrate) sustains an erection by prolonging activity of the NO response pathway.

The human endocrine glands and their hormones

Table 45.1 Major Vertebrate Endocrine Glands and Some of Their Hormones (Hypothalamus – Parathyroid glands)

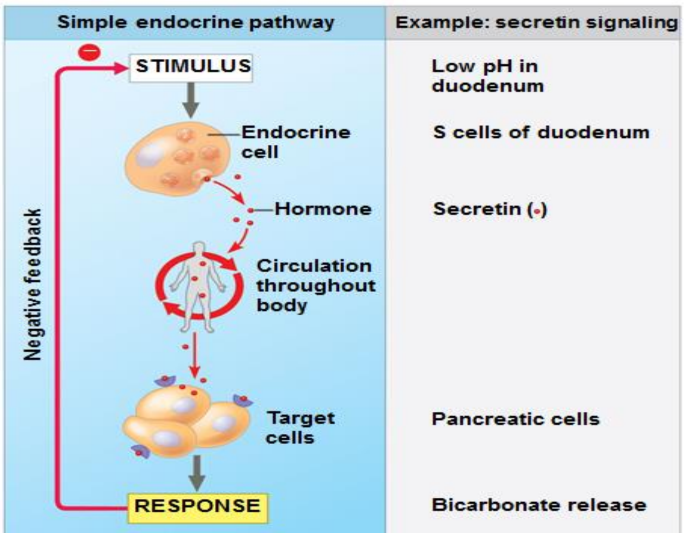
Gland		Hormone	Chemical Class	Representative Actions	Regulated By
Hypothalamus		Hormones released by the posterior pituitary and hormones that regulate the anterior pituitary (see below)			
Pituitary gland Posterior pituitary (releases hormones made by hypo-thalamus)		Oxytocin	Peptide	Stimulates contraction of uterus and mammary gland cells	Nervous system
		Antidiuretic hormone (ADH)	Peptide	Promotes retention of water by kidneys	Water/salt balance
Anterior pituitary		Growth hormone (GH)	Protein	Stimulates growth (especially bones) and metabolic functions	Hypothalamic hormones
		Prolactin (PRL)	Protein	Stimulates milk production and secretion	Hypothalamic hormones
		Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates production of ova and sperm	Hypothalamic hormones
		Luteinizing hormone (LH)	Glycoprotein	Stimulates ovaries and testes	Hypothalamic hormones
		Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid gland	Thyroxine in blood; hypothalamic hormones
		Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates adrenal cortex to secrete glucocorticoids	Glucocorticoids; hypothalamic hormones
Thyroid gland		Triiodothyronine (T_3) and thyroxine (T_4)	Amine	Stimulate and maintain metabolic processes	TSH
		Calcitonin	Peptide	Lowers blood calcium level	Calcium in blood
Parathyroid glands		Parathyroid hormone (PTH)	Peptide	Raises blood calcium level	Calcium in blood

Table 45.1 Major Vertebrate Endocrine Glands and Some of Their Hormones (Pancreas – Thymus)

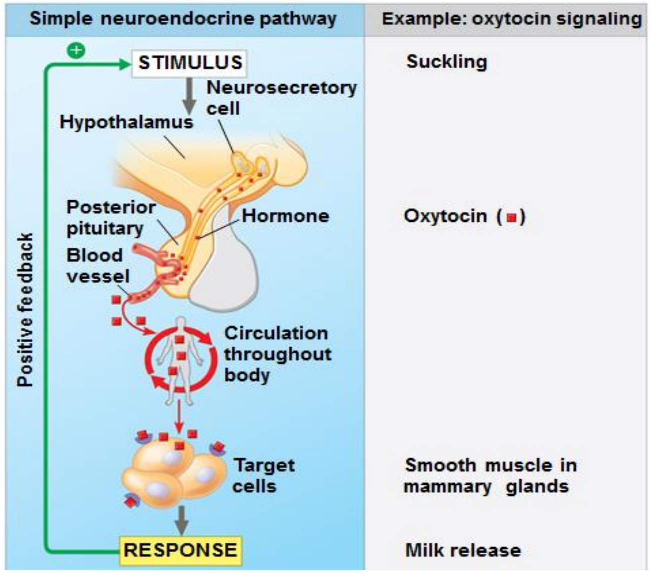
Gland		Hormone	Chemical Class	Representative Actions	Regulated By
Pancreas		Insulin	Protein	Lowers blood glucose level	Glucose in blood
		Glucagon	Protein	Raises blood glucose level	Glucose in blood
Adrenal glands Adrenal medulla		Epinephrine and norepinephrine	Amine	Raise blood glucose level; increase metabolic activities; constrict certain blood vessels	Nervous system
Adrenal cortex		Glucocorticoids	Steroid	Raise blood glucose level	ACTH
		Mineralocorticoids	Steroid	Promote reabsorption of Na^+ and excretion of K^+ in kidneys	K^+ in blood
Gonads Testes		Androgens	Steroid	Support sperm formation; promote development and maintenance of male secondary sex characteristics	FSH and LH
Ovaries		Estrogens	Steroid	Stimulate uterine lining growth; promote development and maintenance of female secondary sex characteristics	FSH and LH
		Progesterone	Steroid	Promotes uterine lining growth	FSH and LH
Pineal gland		Melatonin	Amine	Involved in biological rhythms	Light/dark cycles
Thymus		Thymosin	Peptide	Stimulates T lymphocytes	Not known

Concept 45.2 Feedback regulation and coordination with the nervous system are common in endocrine signaling.

- In a *simple endocrine pathway*, endocrine cells respond directly to an internal or environmental stimulus by secreting a particular hormone.
  - The hormone travels in the bloodstream to target cells where it interacts with its specific receptors.
- Signal transduction within target cells brings about a physiological response, which reduces the stimulus and causes the pathway to shut off.
  - Signal transduction within target cells brings about a physiological response.
- For example, the low pH of stomach contents entering the duodenum stimulates S cells, endocrine cells in the duodenum, to secrete the hormone *secretin*.
  - Secretin travels via blood vessels to target cells in the **pancreas**, causing the release of bicarbonate, which raises the pH in the duodenum.



- In a *simple neuroendocrine pathway*, the stimulus is received by a sensory neuron, which stimulates a neurosecretory cell.
  - The neurosecretory cell secretes a neurohormone, which diffuses into the bloodstream and travels to target cells.
- Such a pathway regulates milk release during nursing in mammals.
  - Suckling by an infant stimulates sensory neurons in the nipples, generating signals in the nervous system, which reach the hypothalamus.
  - Nerve impulses from the hypothalamus trigger the release of the neurohormone oxytocin from the posterior pituitary gland.
  - In response to circulating oxytocin, the mammary glands secrete milk.

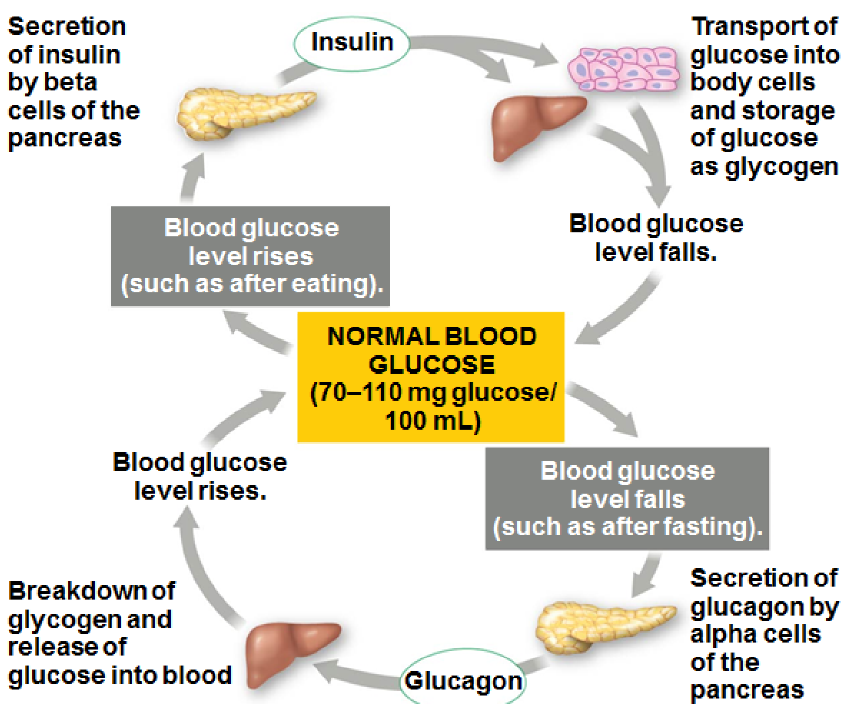


A feedback loop connecting the response to the initial stimulus is characteristic of control pathways.

- The response pathway for many hormones involves **negative feedback**, a loop in which the response reduces the initial stimulus.
  - By decreasing or abolishing hormone signaling, negative feedback regulation prevents excessive pathway activity.
  - Negative feedback loops are an essential part of many hormone pathways, especially those involved in maintaining homeostasis.
- Unlike negative feedback, which dampens a stimulus, **positive feedback** reinforces a stimulus, leading to an even greater response.
- Positive feedback is important in oxytocin pathways.
  - In response to circulating oxytocin, the mammary glands secrete milk. Milk released in response to oxytocin leads to more suckling and therefore more stimulation. Activation of the pathway is sustained until the baby stops suckling.
  - When mammals give birth, oxytocin induces target cells in the uterine muscles to contract. This pathway, too, is characterized by positive-feedback regulation, such that it drives the birth process to completion.
- While positive feedback amplifies both stimulus and response, negative feedback helps restore a preexisting state.
  - The hormone pathways involved in homeostasis typically involve negative rather than positive feedback.

Homeostatic control systems may rely on pairs of negatively regulated hormone pathways, each counterbalancing the other.

- Sets of simple hormone pathways with coordinated activities form homeostatic control systems.
  - Often pathways are paired, with each providing a counterbalance for the other.
  - Regulation of blood glucose levels provides an example of such a control system.
- Metabolic balance in humans depends on maintaining blood glucose concentrations near a set point of about 90 mg/100 mL.
  - Glucose is a major fuel for cellular respiration and a key source of carbon skeletons for the synthesis of other organic compounds.
- Insulin and glucagon are antagonistic hormones that regulate the concentration of glucose in the blood.
  - When the blood glucose concentration exceeds the set point, **insulin** is released and triggers uptake of glucose from the blood into body cells, decreasing blood glucose.

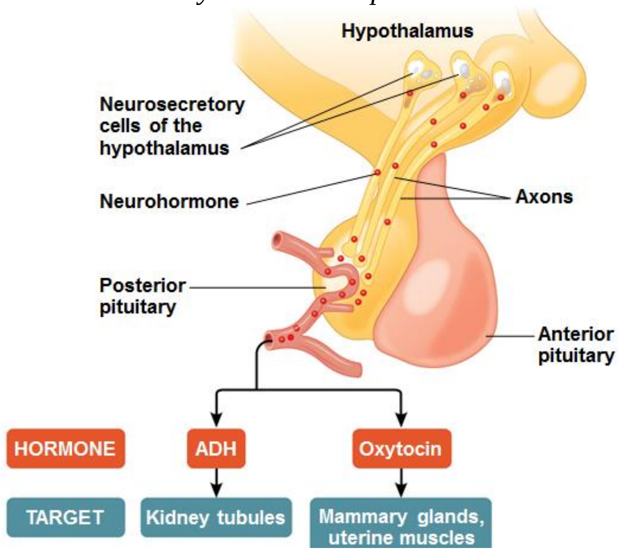
- When the blood glucose concentration falls below the set point, **glucagon** is released and promotes release of glucose into blood from liver glycogen, increasing blood glucose.
- Each hormone operates in a simple endocrine pathway regulated by negative feedback.
- Glucagon and insulin are produced in the pancreas, an organ with both endocrine and exocrine functions.
- Clusters of endocrine cells called pancreatic islets are scattered throughout the pancreas.
  - Each pancreatic islet has a population of *alpha cells*, which make glucagon, and a population of *beta cells*, which make insulin.
  - Both hormones are secreted into the extracellular fluid and enter the circulatory system.
- Hormone-secreting endocrine cells make up only 1–2% of the mass of the pancreas.
  - The pancreas is also an exocrine gland, releasing digestive enzymes and bicarbonate ions into the small intestine via the pancreatic duct.
- Insulin lowers blood glucose levels by stimulating all body cells (except brain cells) to take up glucose from the blood.
  - Brain cells can take up glucose without insulin, and have access to circulating fuel at all times.
- Insulin also decreases blood glucose levels by slowing glycogen breakdown in the liver and inhibiting the conversion of amino acids and glycerol to glucose.
- Glucagon influences blood glucose levels through its effects on target cells in the liver.
  - The liver, skeletal muscles, and adipose tissues store large amounts of fuel.
  - The liver and muscles store sugar as glycogen, whereas adipose tissue cells convert sugars to fats.
- When glucose levels decrease to below the set point, a primary effect of glucagon is to signal liver cells to increase glycogen hydrolysis, convert amino acids and glycerol to glucose, and release glucose into the circulation.
  - The net effect is to restore the blood glucose concentration to the set point, 70-110 mg/100 mL.
- The antagonistic effects of glucagon and insulin are vital to glucose homeostasis and the regulation of fuel storage and fuel consumption by body cells.
- 

- The liver's ability to perform its vital roles in glucose homeostasis results from the metabolic versatility of its cells and its access to absorbed nutrients via the hepatic portal vein.

- A number of disorders can disrupt glucose homeostasis with potentially serious consequences, especially for the heart, blood vessels, eyes, and kidneys.
- **Diabetes mellitus** is caused by a deficiency of insulin or a decreased response to insulin in target tissues.
  - In people who have diabetes, blood glucose levels rise, but cells are unable to take up enough glucose to meet their metabolic needs.
  - Without sufficient glucose to meet the needs of most body cells, fat becomes the main substrate for cellular respiration.
  - In severe cases of diabetes, acidic metabolites formed during fat breakdown accumulate in the blood, threatening life by lowering blood pH and depleting sodium and potassium ions.
- In people with diabetes mellitus, the level of glucose in the blood may exceed the capacity of the kidneys to reabsorb it.
  - Glucose remains in the filtrate and is reabsorbed.
  - As glucose is concentrated in the urine, more water is excreted with it, resulting in excessive volumes of urine and persistent thirst.
- *Type 1 diabetes* (insulin-dependent diabetes) is an autoimmune disorder in which the immune system destroys the beta cells of the pancreas.
  - Type I diabetes usually appears in childhood and destroys the person's ability to produce insulin.
- The treatment is insulin injections, usually several times a day.
  - Human insulin is available from genetically engineered bacteria.
  - Stem cell research may someday offer a cure, introducing functional beta cells into the body.
- *Type 2 diabetes* (non-insulin-dependent diabetes) is characterized by decreased responsiveness to insulin in target cells because of some change in insulin receptors.
  - This form of diabetes occurs after age 40, and the risk increases with age.
  - Although heredity can play a role in type 2 diabetes, excess body weight and lack of exercise significantly increase the risk.
  - Type 2 diabetes accounts for more than 90% of diabetes cases.
- Many people with type 2 diabetes can manage their blood glucose level with regular exercise and a healthy diet, although some require insulin injections.
- Type 2 diabetes is the seventh most common cause of death in the United States and a growing public health problem worldwide.
- The resistance to insulin signaling in type 2 diabetes may be due to a genetic defect in the insulin receptor or the insulin response pathway.
  - In many cases, events in target cells suppress activity of an otherwise functional response pathway.
  - One source of this suppression appears to be inflammatory signals generated by the innate immune system.
  - How obesity and inactivity relate to this suppression is being studied in both humans and laboratory animals.
- In vertebrates, the **hypothalamus** integrates vertebrate endocrine and nervous functions.
  - One of several endocrine glands located in the brain, the hypothalamus receives information from nerves throughout the body and brain.
  - In response, it initiates endocrine signals appropriate to environmental conditions.
- Signals from the hypothalamus travel to the **pituitary gland** located at its base.
- The **posterior pituitary** is an extension of the hypothalamus.
  - Hypothalamic axons that extend into the posterior pituitary secrete neurohormones synthesized in the hypothalamus.
- The **anterior pituitary** is an endocrine gland that synthesizes and secretes hormones.
  - Secretion of each hormone by the anterior pituitary is regulated by one or more signals from the hypothalamus.
- Neurosecretory cells of the hypothalamus synthesize two hormones: oxytocin and antidiuretic hormone (ADH).

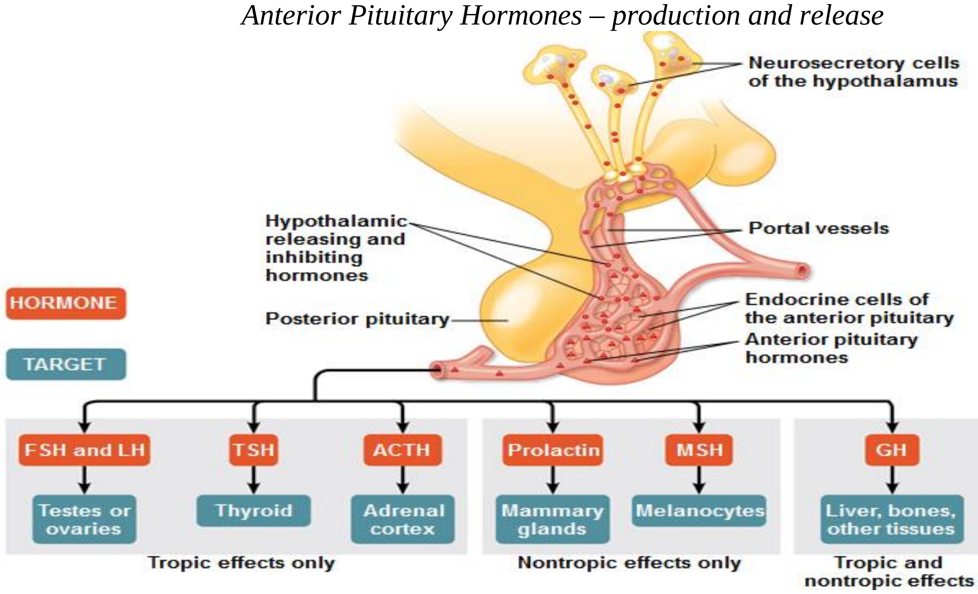
- These hormones travel along the long axons of neurosecretory cells to the posterior pituitary, where they are stored and released in response to nerve impulses transmitted by the hypothalamus.
- Oxytocin regulates milk secretion by the mammary glands and contractions of the uterus during birthing.
  - Oxytocin also influences behaviors related to maternal care, pair bonding, and sexual activity.
- **Antidiuretic hormone (ADH)**, or *vasopressin*, also regulates both physiology and behavior.
  - ADH acts on the kidneys to increase their water retention, thus decreasing urine volume and regulating blood osmolarity.
  - It also plays an important role in social behavior.

Posterior Pituitary Hormones – production and release



- Endocrine signals generated by the hypothalamus regulate hormone secretion by the anterior pituitary.
- Each hypothalamic hormone is either a *releasing hormone* or an *inhibiting hormone,* reflecting its role in promoting or inhibiting the release of one or more specific hormones by the anterior pituitary.
  - *Prolactin-releasing hormone* is a hypothalamic hormone that stimulates the anterior pituitary to secrete **prolactin (PRL)**, which stimulates milk production

Anterior Pituitary Hormones – production and release

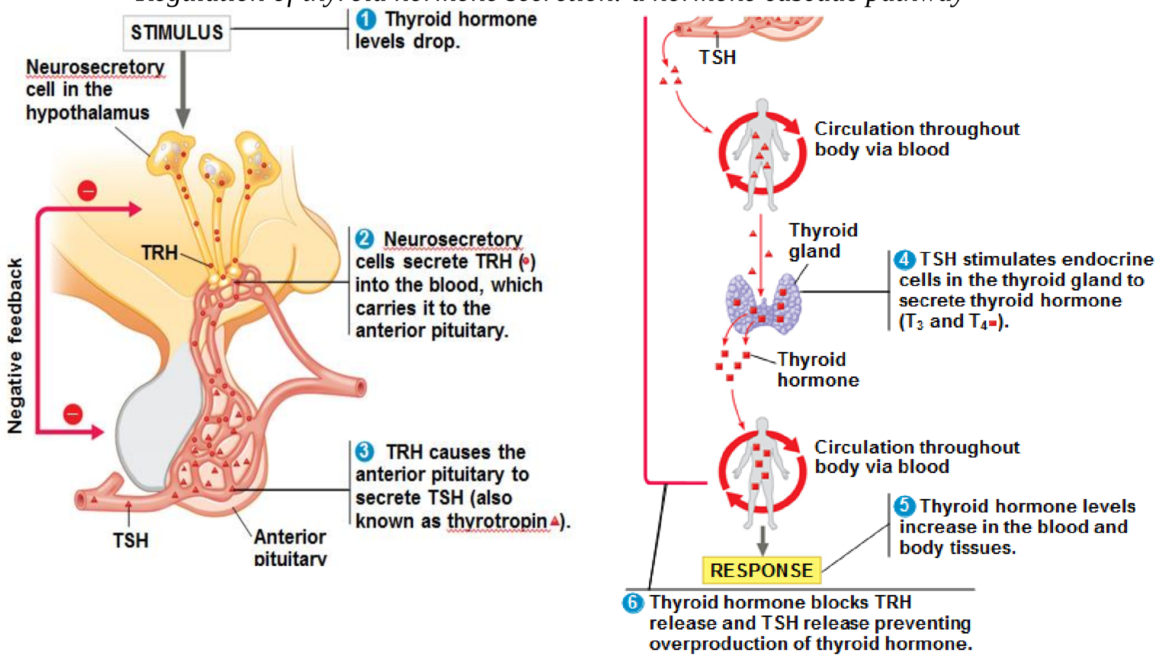


- Every anterior pituitary hormone is controlled by at least one releasing hormone.
    - Some (such as prolactin) have both a releasing hormone and an inhibiting hormone.
- Hypothalamic releasing and inhibiting hormones are secreted near capillaries at the base of the hypothalamus.
    - The capillaries drain into short portal vessels, which subdivide into a second capillary bed within the anterior pituitary.
    - Releasing and inhibiting hormones thus have direct access to the gland they control.

Hormones from the hypothalamus, anterior pituitary, and a target endocrine gland are often organized into a hormone cascade pathway.

- Signals to the brain stimulate the hypothalamus to secrete a hormone that stimulates or inhibits the release of a particular anterior pituitary hormone.
- The anterior pituitary hormone acts on a target endocrine tissue, stimulating the secretion of yet another hormone that exerts systemic metabolic or developmental effects.

Regulation of thyroid hormone secretion: a hormone cascade pathway



- As an example of a *hormone cascade pathway*, consider the activation of the thyroid gland upon exposure of an infant to cold temperatures.
    - When the infant's body temperature drops, the hypothalamus secretes *thyrotropin-releasing hormone (TRH).*
    - TRH stimulates the anterior pituitary to secrete thyrotropin, or *thyroid-stimulating hormone (TSH).*
    - TSH acts on the **thyroid gland** to stimulate the release of *thyroid hormone*.
    - Thyroid hormone increases the metabolic rate, raising body temperature.
- Like simple hormone pathways, hormone cascade pathways typically involve negative feedback.
    - In the thyroid hormone pathway, thyroid hormone itself carries out negative feedback.
    - Thyroid hormone blocks TSH release from the anterior pituitary and TRH release from the hypothalamus, preventing overproduction of thyroid hormone.
    - The hormone cascade pathway links the original stimulus to a self-limiting response in the target cells.

Too much or too little thyroid hormone can cause serious metabolic disorders.

- An insufficient amount of thyroid hormones is known as hypothyroidism, producing symptoms such as weight gain, lethargy, and intolerance to cold in adults.
- Hyperthyroidism is the excessive secretion of thyroid hormones, leading to high body temperature, profuse sweating, weight loss, irritability, and high blood pressure.
    - The most common form of hyperthyroidism is Graves' disease.
    - In this autoimmune disorder, the immune system produces antibodies that bind to the receptor for TSH, activating sustained thyroid hormone production.
    - Protruding eyes, caused by fluid accumulation behind the eyes, are a typical symptom.
- Malnutrition can also alter thyroid hormone production.
- The term *thyroid hormone* refers to a pair of very similar hormones derived from the amino acid tyrosine: **triiodothyronine (T_3)**, which contains three iodine atoms, and tetraiodothyronine or **thyroxin (T_4)**, which contains four iodine atoms.
    - In mammals, the same receptor molecule in the cell nucleus binds both hormones.
- The thyroid gland secretes mainly T_4, but target cells convert most of it to T_3 by removing one iodine atom.
- Although iodine is readily available from seafood or iodized salt, people in many parts of the world suffer from inadequate dietary iodine.
    - Without sufficient iodine, the thyroid gland cannot synthesize adequate amounts of T_3 and T_4.
    - The resulting low blood levels of these hormones cannot exert negative feedback on the hypothalamus and anterior pituitary.
    - The pituitary continues to secrete TSH, elevating TSH levels and enlarging the thyroid into a goiter, a characteristic swelling of the neck.
- All vertebrates require thyroid hormones for normal functioning of bone-forming cells and branching of nerve cells during embryonic brain development.
    - In humans, congenital hypothyroidism, an inherited condition of thyroid deficiency, results in retarded skeletal growth and poor mental development.
    - These problems can often be remedied by treatment with thyroid hormones early in life.
    - Iodine deficiency in childhood is fully preventable if iodized salt is used in food preparation.
- A given hormone may have different effects in different species.
- Thyroxine regulates metabolism in frogs, humans, and other vertebrates.
    - In frogs, thyroxine stimulates resorption of the tadpole's tail in its metamorphosis into an adult.
- Prolactin stimulates mammary gland growth and milk production and secretion in mammals.
    - PRL also regulates fat metabolism and reproduction in birds, delays metamorphosis in amphibians, and regulates salt and water balance in freshwater fishes.
    - These varied roles suggest that prolactin is an ancient hormone whose functions have diversified during the evolution of vertebrate groups.

Tropic hormones regulate the function of endocrine cells or glands.

- Several tropic hormones are secreted by the anterior pituitary: thyroid-stimulating hormone (TSH), **follicle-stimulating hormone (FSH)**, **luteinizing hormone (LH)**, and **adrenocorticotropic hormone (ACTH)**.
    - FSH and LH are also called *gonadotropins* because they stimulate the activities of the gonads. Their hypothalamic regulator is called *gonadotropin-releasing hormone* (*GnRH*).
    - ACTH stimulates the production and secretion of steroid hormones by the adrenal cortex.
- **Growth hormone (GH)**, which is secreted by the anterior pituitary, acts on a wide variety of target tissues with both tropic and nontropic effects.
    - The major tropic action of GH is to signal the liver to release *insulin-like growth factors (IGFs)*, which circulate in the blood and directly stimulate bone and cartilage growth.
    - In the absence of GH, the skeleton of an immature animal stops growing.
    - GH also exerts diverse metabolic effects that raise blood glucose levels, opposing the effects of insulin.