Cell membrane transport

Cell membrane is selectively permeable membrane also regarded as semi permeable membrane, because is allow some molecules pass through it while prevent other molecule from passing.

Permeable molecules to the cell membrane include: small hydrophobic molecule like O_2, CO_2, N_2 and benzene. And small uncharged polar molecules like water, glycerol and ethanol.

Non permeable molecules to the cell membrane include: large uncharged polar molecules like sugar, amino acids. And Ions like H^+, Na^+, K^+, Cl^-, Ca^{++}, Mg^{++}, HCO_3^-.

Molecules cross the plasma membrane in 2 ways:

1. **Passive ways**: no energy used. Include: simple diffusion and facilitated diffusion.
2. **Active ways**: use energy. Include: active transport and vesicular transport.

❖ **Passive ways**

1. **Simple diffusion** is the movement of molecules from higher concentration gradient to lower concentration gradient until they are distributed equally without using energy for examples
   - Respiratory gases diffuse through the lipid bilayer, this is the mechanism by which oxygen enters cells and carbon dioxide exits cells.
   - Glycerol and ethanol diffuse simply through the plasma membrane.
   - Also lipid soluble molecules pass though the cell membrane without any energy or transport protein or carrier include steroid hormones like{ estrogen, testosterone…..ect}, vitamin D and lipid soluble drug

     All above molecules are non charged and non polar

     ❖ Water molecules, for instance, cannot cross the membrane rapidly (although to their small size and lack of a full charge, they can cross at a slow rate). The phenomena of water movement though semi permeable membrane called **osmosis**.

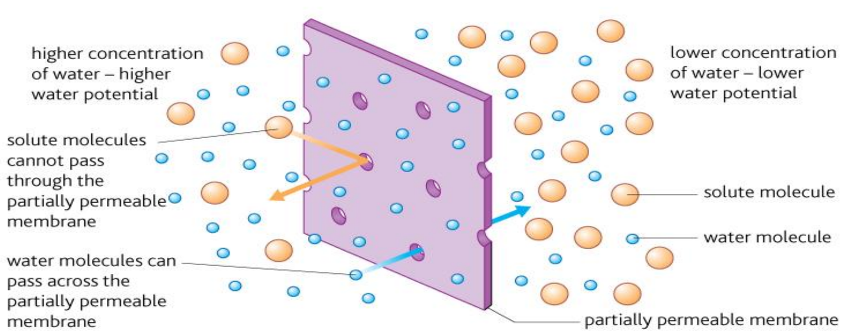


Figure: cell membrane permeability, simple diffusion (osmosis)

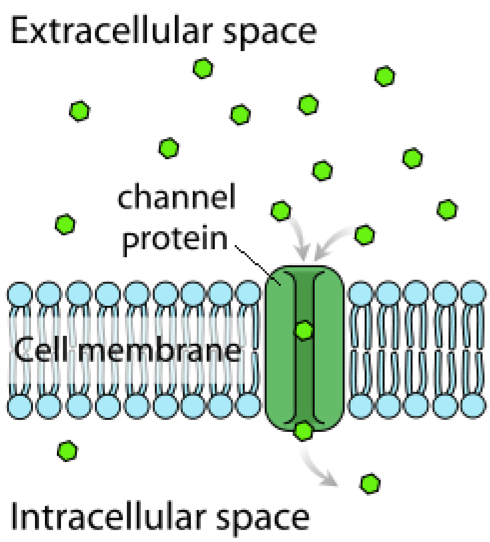
Osmosis is the movement of water molecules through semi-permeable membrane from a solution with a low solute concentration to a solution with a higher solute concentration until there is an equal solute concentration on both sides of the membrane. So that the movement of water though cell membrane depend on solute concentration inside and outside the cell.

2. **Facilitated diffusion:** this type of passive transport system also doesn't use energy, molecules diffuse across the plasma membrane with assistance from membrane proteins (transmembrane protiens), such as channels and carriers. Because these molecules are charged or polar, they can't cross the phospholipid part of the membrane without help. Facilitated transport proteins shield these molecules from the hydrophobic core of the membrane, providing a route by which they can cross. Two major classes of facilitated transport proteins are channels and carrier proteins.

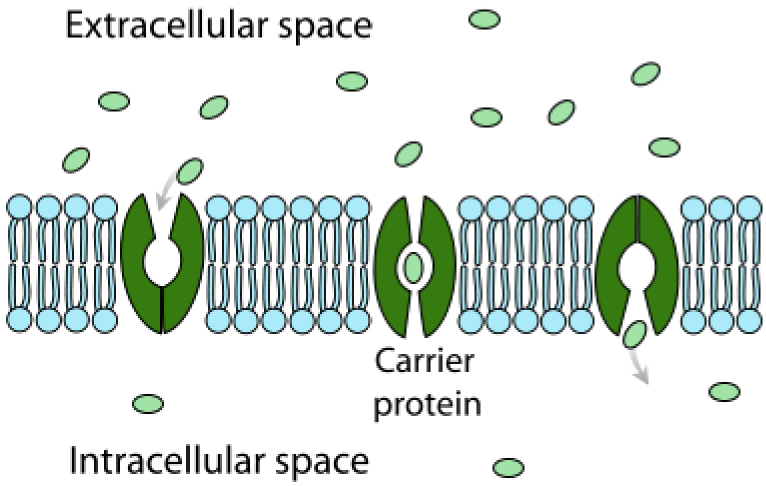
a) Channel proteins: used for movement of polar or charged molecules like water and Ions. There are particular channel proteins for each particular molecule for example the water diffuse through the plasma membrane by using specific protein channels called ***aquaporins***. Aquaporins allow water to cross the membrane very quickly, and they play important roles in red blood cells, and certain parts of the kidney (where they minimize the amount of water lost as urine).

There are two types of protein channels:

i. Leak channels are continuously opened
ii. Gated channels are stimulus to open



b) Carrier proteins: Another class of transmembrane proteins involved in facilitated transport consists of the carrier proteins assist in the movement of large molecules like sugar, carbohydrate and amino acids from high concentration gradient to low concentration gradient. Each protein carrier which actually changes shape during process, sometimes called a **transporter,** binds only to a particular molecule, such as glucose transporter or amino acids transporter. *Type 2 diabetes mellitus results when cells lack a sufficient number of glucose transporters.*



❖ **Active ways:** Active transport mechanisms can be divided into two categories.

i. **Active transport:** directly uses a source of chemical energy (e.g., ATP) to move molecules across a membrane against their gradient.

- ✓ Molecules and ions can be transported across cell membrane against their concentration gradient if the appropriate transport proteins and a source of energy (ATP) are available.
- ✓ **ATP** Adenosine Triphosphate -Nucleotide with three phosphate groups.
  The breakdown of ATP into ADP and one inorganic phosphate molecules by ATPase makes energy available for energy-requiring processes in cells.
- ✓ Proteins transporter involved in active transport mechanism often are called **pumps; pump** is used energy to move substances against their concentration gradients.
- ✓ Just as water **pump** uses energy to move water against the force of gravity.
- ✓ **Sodium-Potassium Pump** or called Na/K ATPase – is transport protein (pump) in the plasma membrane that moves sodium ions (Na^+) out of and potassium ions (K^+) into cells; important in nerve and muscle cells. The sodium potassium pump cause an electrical concentration gradient (difference of charge) across the membrane and this is known as a membrane potential. Nerve cells use this membrane potential to send electrical signals along nerves.

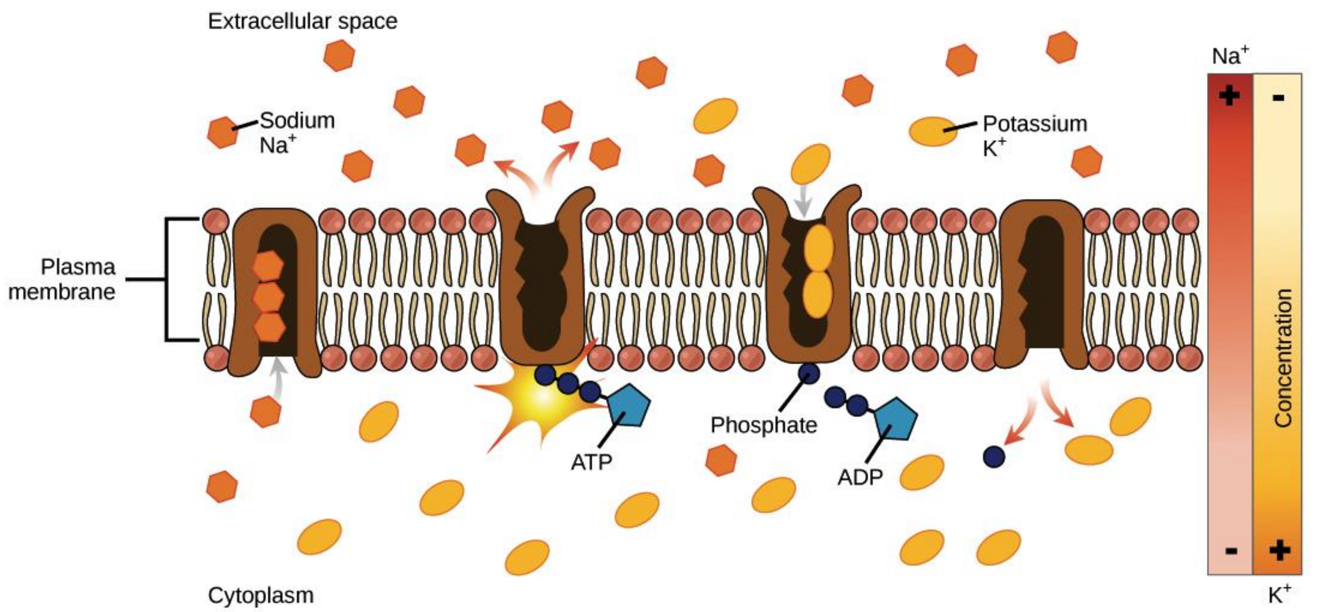


Figure shows the sodium-potassium pump cycle

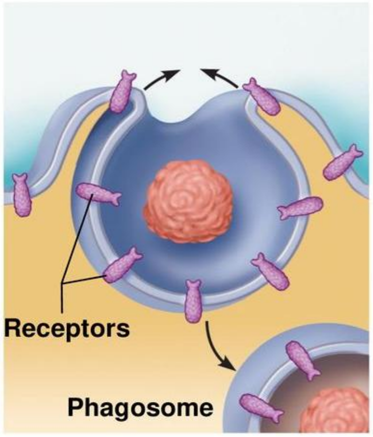
One of important clinical application on active transport is a cystic fibrosis (CF).

CF is a genetic disorder occurs when there is a defects in a gene on chromosome 7 .This gene, called CFTR (cystic fibrosis Transmembrane conductance regulator), codes for the CFTR protein is a channel protein that controls the flow of H2O and Cl- ions in and out of cells inside the lungs. When the CFTR protein is working correctly, ions freely flow in and out of the cells. However, when the CFTR protein is malfunctioning, these ions cannot flow out of the cell due to a blocked channel. This causes cystic fibrosis, characterized by the buildup of thick mucus in the lungs.

ii. Vesicular transport: is the transport of large substance across the plasma membrane by vesicle , which is a membrane bounded sac filled with materials

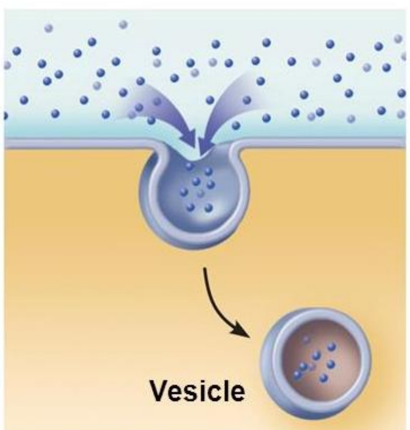
Endocytosis: is uptake process of molecules and transport it across cell membrane into the cell interior by vesicle formation, a portion of the plasma membrane invaginates to envelop the substance, and then the membrane pinches off to form an intracellular vesicle. **There are three methods of endocytosis**:

A. **Phagocytosis**: means "**cell eating**", occurs when large **solid** materials taken inside the cell, such as food particles, dead cell, cell debris or another cell such as bacteria . *Best example on phagocytic cell* *is white blood cells (WBC) can engulf bacteria and worn- out red blood cells by phagocytosis.* Digestion occurs when the resulting vacuole (phagocytic vacuole) fuses with a lysosome.



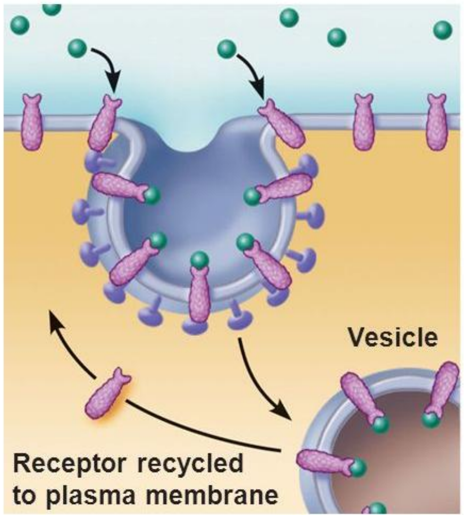
(a) Phagocytosis
The cell engulfs a large particle by forming projecting pseudopods ("false feet") around it and enclosing it within a membrane sac called a phagosome. The phagosome is combined with a lysosome. Undigested contents remain in the vesicle (now called a residual body) or are ejected by exocytosis. Vesicle may or may not be protein coated but has receptors capable of binding to microorganisms or solid particles.

B. **Pinocytosis**: means "**cell drinking**" occurs when vesicles form around fluid droplets. *Pinocytosis takes place in almost all cells, including the secretory cells and epithelial cells of the blood vessels also cells that line the kidney tubules or intestinal wall*



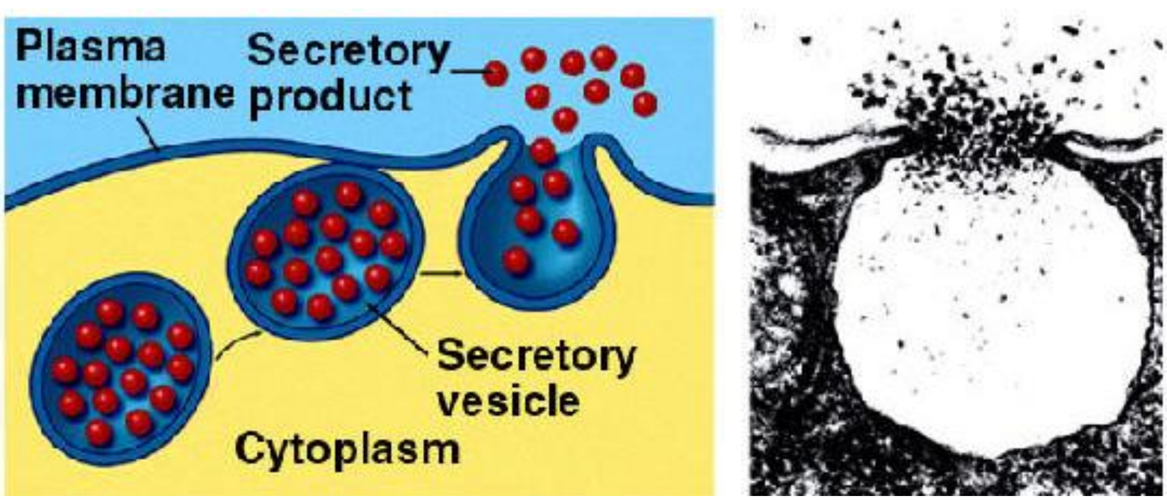
(b) Pinocytosis
The cell "gulps" a drop of extracellular fluid containing solutes into tiny vesicles. No receptors are used, so the process is nonspecific. Most vesicles are protein-coated.

C. **Receptor- mediated endocytosis**: A special form of endocytosis uses a **receptor**, a special form of membrane protein on the surface of the cell to concentrate specific molecules of interest for endocytosis. *one type of dwarfism are caused by nonfunctioning growth hormone receptors, In this condition the gland produce the hormone, but the target cells cannot respond because they lack normal receptors. Also an inherited form of cardiovascular disease (familial hypercholesterolemia) occurs when cells fail to take up a combined lipoprotein and cholesterol molecule from the blood .*



(c) Receptor-mediated endocytosis
Extracellular substances bind to specific receptor proteins in regions of coated pits, enabling the cell to ingest and concentrate specific substances (ligands) in protein-coated vesicles. Ligands may simply be released inside the cell, or combined with a lysosome to digest contents. Receptors are recycled to the plasma membrane in vesicles.

Exocytosis: is release process of material from the cell. During exocytosis vesicles often formed by Golgi apparatus and carrying a specific molecule fused with plasma membrane and secretion occurs. **e.g**. release of insulin molecules from beta **c**ells or releasing of neurotransmitter molecules into the synaptic cleft by the process of exocytosis.

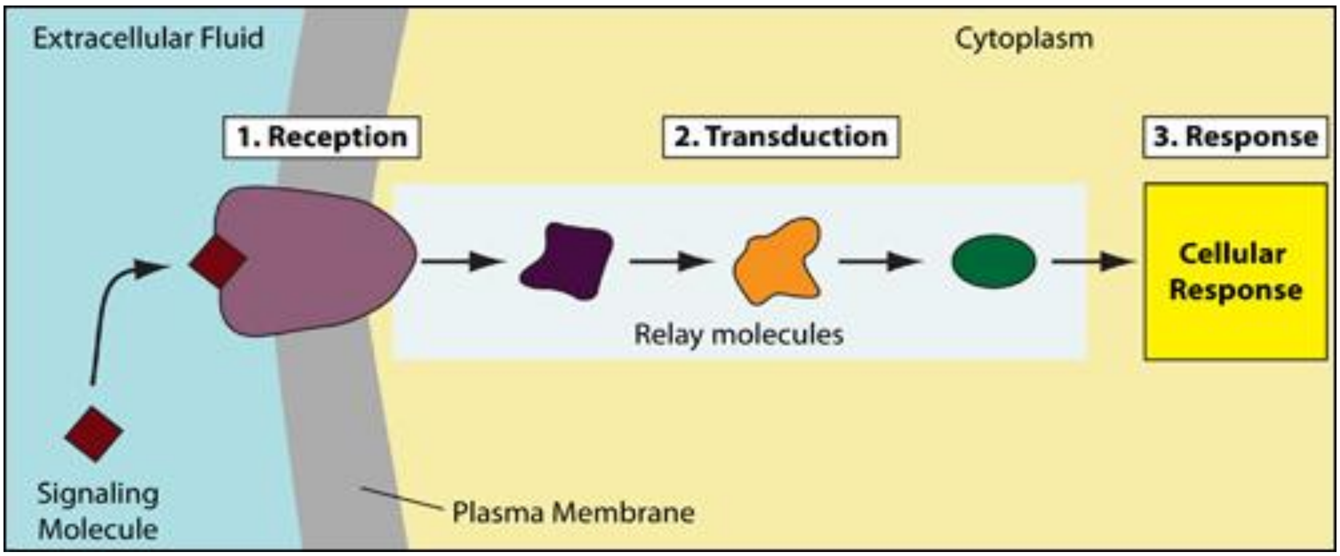


Cells in a multicellular organism communicate with one another to regulate tissue and organ development, to control their growth and division, and to coordinate their functions.

- **Cell signaling** (also known as **Signal transduction**) is the transmission of molecular signals (These chemical signals, which are proteins or other molecules) from a cell's exterior to its interior. Signals received by cells must be transmitted effectively into the cell to ensure an appropriate response. This step is initiated by cell receptors.

❖ **Phases of Signal Transduction:** There are three stages in the process of cell signaling:

1. **Reception**: It's the cell's detection of a signaling molecule (**ligand**) coming from outside of the cell. The signal is detected when the molecule binds to the receptor located at the cell's surface or inside the cell.
2. **Transduction**: The receptor protein is changed when the signaling molecule binds to it which initiates the process of transduction. In transduction the signal is converted to a form that can bring specific cellular response.
3. **Response**: It's the stage of cell signaling where the signal finally triggers a specific cellular response.



❖ **Signaling Molecules (ligands):** Signaling molecules are necessary for the coordination of cellular responses by serving as ligands and binding to cell receptors.

Types of the Signaling Molecules

The types of molecules that serve as **ligands** are incredibly varied and range from small proteins to small ions like calcium.

1. Small Hydrophobic Ligands

Small hydrophobic ligands can directly diffuse through the plasma membrane and interact with internal receptors.

Important members of this class of ligands are the steroid hormones, such as female sex hormone, estradiol; the male sex hormone, testosterone; and cholesterol. Other hydrophobic hormones include thyroid hormones and vitamin D.

In order to be soluble in blood, hydrophobic ligands must bind to carrier proteins while they are being transported through the bloodstream.

2. Water-Soluble Ligands

Water-soluble ligands are polar and, therefore, cannot pass through the plasma membrane unaided; sometimes, they are too large to pass through the membrane at all. Instead, most water-soluble ligands bind to the extracellular domain of cell-surface receptors.

These water soluble ligands are quite diverse and include small molecules, peptides, and proteins.

3. Other Ligands

Nitric oxide (NO) is **a gas** that also acts as a ligand. It is able to diffuse directly across the plasma membrane; one of its roles is to interact with receptors in smooth muscle and induce relaxation of the tissue.

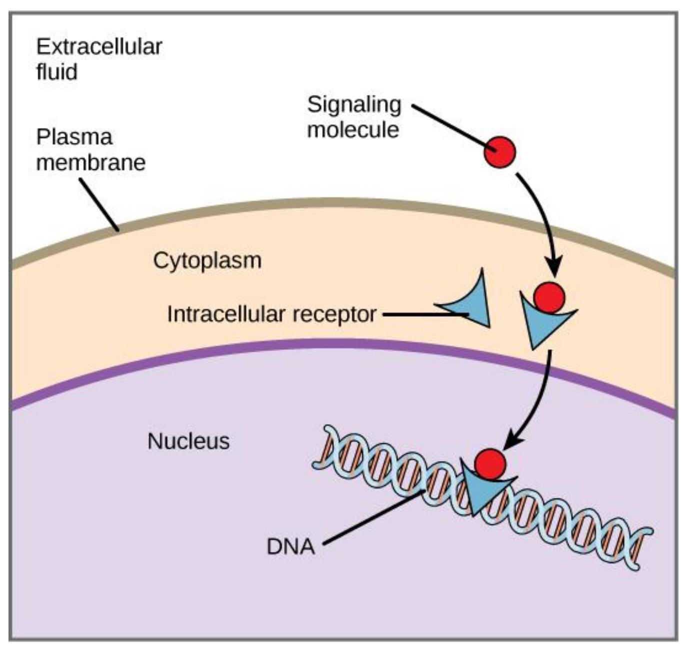
NO has a very short half-life; therefore, it only functions over short distances***. Nitroglycerin, a treatment for heart disease, acts by triggering the release of NO, which causes blood vessels to dilate (expand), thus restoring blood flow to the heart.***

❖ Types of Cell Receptors

Receptors are protein molecules in the target cell or on its surface that bind ligands. There are two types of receptors: internal receptors and cell-surface receptors.

1. Internal receptors

Internal receptors, also known as ***intracellular receptors*** **(cytoplasmic or nuclear)** are found inside the cell (the cytoplasm or the nucleus) and respond to hydrophobic ligand molecules that are able to travel across the plasma membrane.



Once inside the cell, many of these molecules bind to proteins that act as regulators of mRNA synthesis to mediate gene expression.

Internal receptors can directly influence gene expression without having to pass the signal on to other receptors or messengers.

2. Cell-Surface Receptors

Cell-surface receptors, also known as transmembrane receptors, are cell surface, membrane-anchored (peripheral), or integral proteins that bind to external ligand molecules.

This type of receptor spans the plasma membrane and performs signal transduction, converting an extracellular signal into an intracellular signal.

Ligands that interact with cell-surface receptors do not have to enter the cell that they affect.

Cell-surface receptors are also called **cell-specific proteins** or **markers** because they are specific to individual cell types.

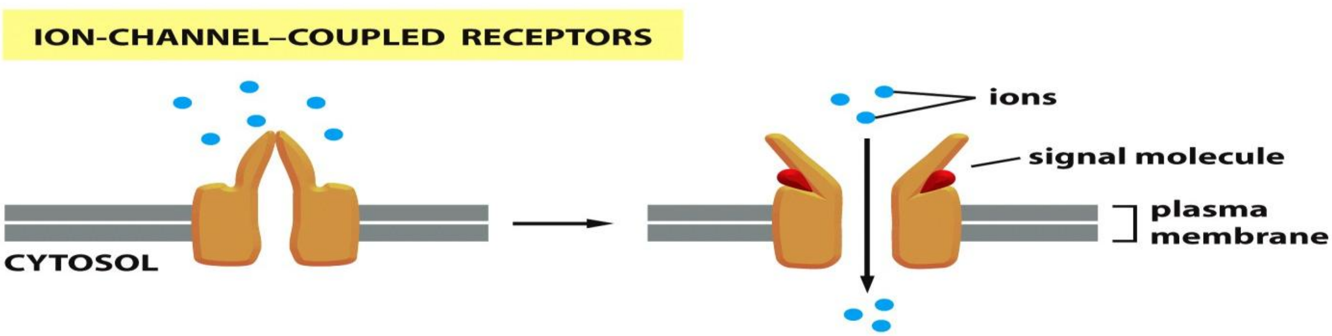
Types of Cell Surface Receptors

There are three general categories of cell-surface receptors:

1. Ion Channel-Linked Receptors

Ion channel-linked receptors bind a ligand and open a channel through the membrane that allows specific ions to pass through.

When a ligand binds to the extracellular region of the channel, there is a conformational change in the protein's structure that allows ions such as chloride ions and hydrogen ions to pass through.

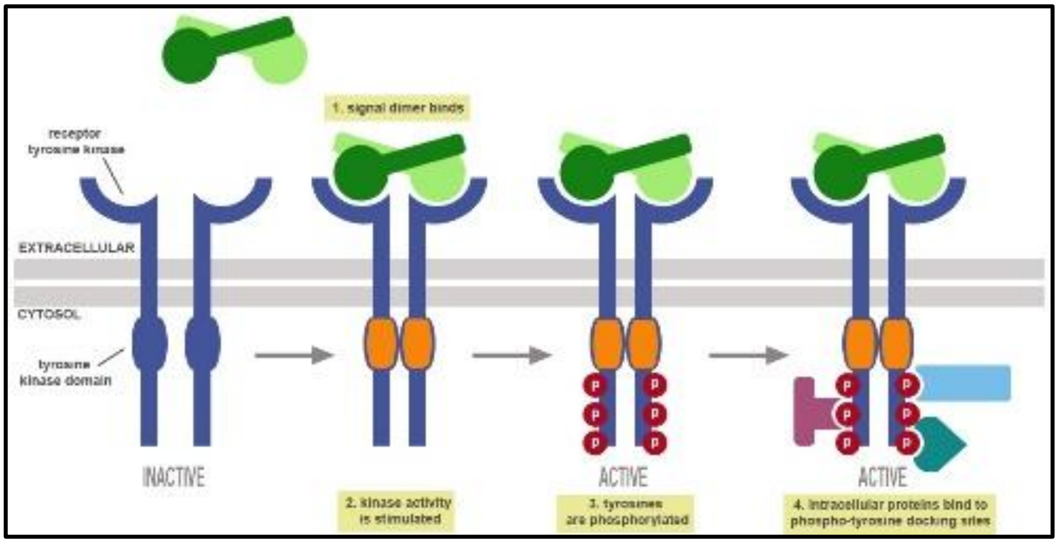


2. Enzyme-Linked Receptors

Enzyme-linked receptors are cell-surface receptors with intracellular domains that are associated with an enzyme.

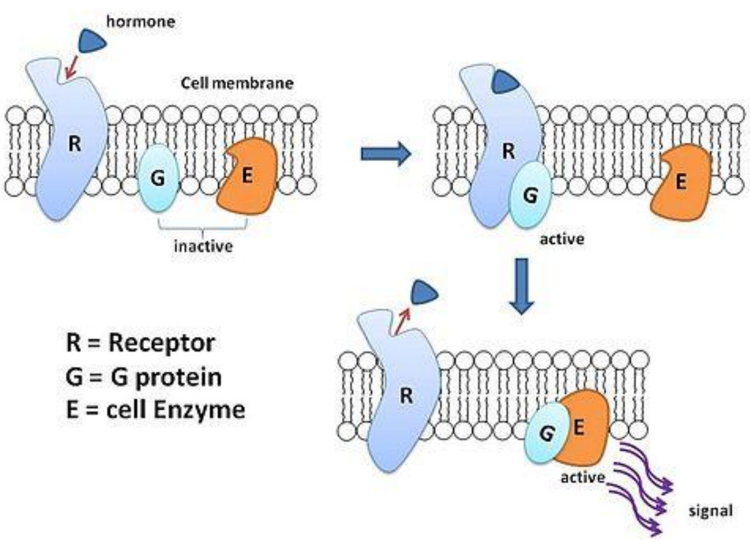
When a ligand binds to the extracellular domain, a signal is transferred through the membrane and activates the enzyme, which sets off a chain of events within the cell that eventually leads to a response.

An example of this type of enzyme-linked receptor is **the tyrosine kinase receptor**.



3. G-Protein Linked Receptors

G-protein-linked receptors bind a ligand and activate a membrane protein called a G-protein. The activated G-protein then interacts with either an ion channel or an enzyme in the membrane.



❖ Types of Signaling

The major types of signaling mechanisms that occur in multicellular organisms are**: Paracrine, Endocrine, Autocrine, and Direct Signaling (Juxtacrine).** The main difference between the different categories of signaling is the distance that the signal travels through the organism to reach the target cell.

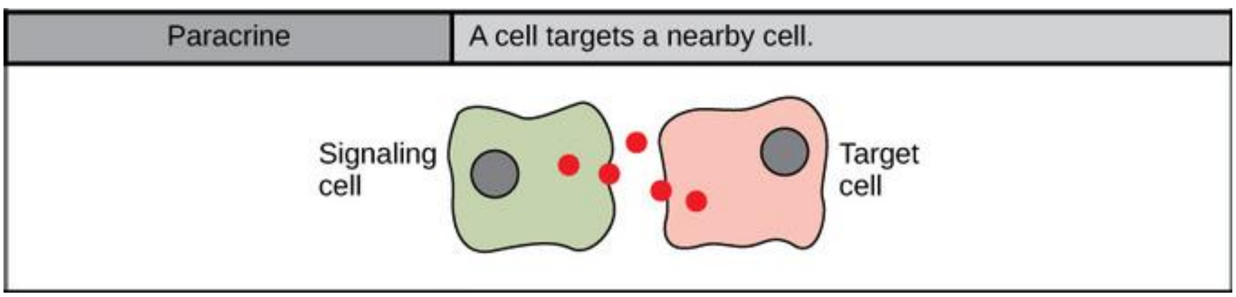
1. Paracrine Signaling

Signals that act locally between cells those are close together. Paracrine signals move by diffusion through the extracellular matrix. These types of signals usually elicit quick responses that last only a short period of time.

In order to keep the response localized, paracrine ligand molecules are normally quickly degraded by enzymes or removed by neighboring cells. Removing the signals will reestablish the concentration gradient for the signal, allowing them to quickly diffuse through the intracellular space if released again.

One example of paracrine signaling is the transfer of signals across synapses between nerve cells.

- Synaptic signaling is unique example of paracrine signaling; in which nerve cells transmit signals. This process is named for the **synapse**, the junction between two nerve cells where signal transmission occurs.

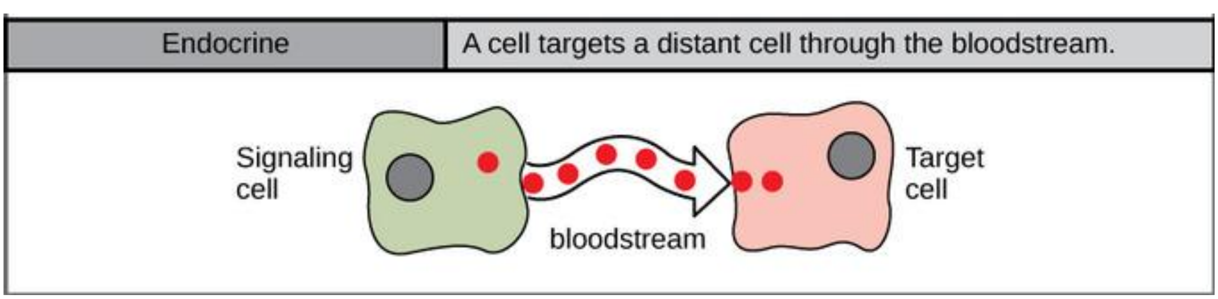


2. Endocrine Signaling

Signals from distant cells are called endocrine signals; they originate from endocrine cells, such as cells of the thyroid gland, the hypothalamus, the pituitary gland as well as the gonads (testes and ovaries) and the pancreas. These types of signals usually produce a slower response, but have a longer-lasting effect.

The ligands released in endocrine signaling are called **hormones**, which are signaling molecules that are produced in one part of the body, but affect other body regions some distance away.

Hormones travel the large distances between endocrine cells and their target cells via the bloodstream, which is a relatively slow way to move throughout the body.



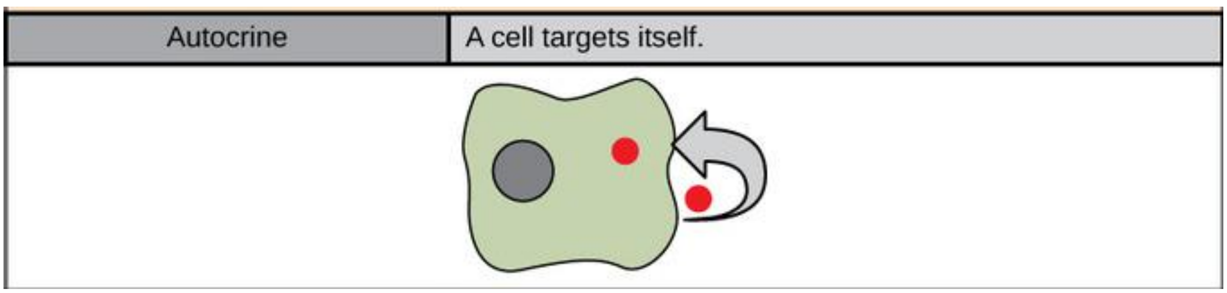
3. Autocrine Signaling

Autocrine signals are produced by signaling cells that can also bind to the ligand that is released. This means the signaling cell and the target cell can be the same or a similar cell.

This type of signaling often occurs during the early development of an organism to ensure that cells develop into the correct tissues and take on the proper function.

Autocrine signaling also regulates pain sensation and inflammatory responses.

Further, if a cell is infected with a virus, the cell can signal itself to undergo programmed cell death, killing the virus in the process.



4. Direct Signaling Across Gap Junctions

Gap junctions are connections between the plasma membranes of neighboring cells. These water-filled channels allow small signaling molecules, called **intracellular mediators**, to diffuse between the two cells. Small molecules, such as calcium ions, are able to move between cells, but large molecules, like proteins and DNA, cannot fit through the channels.

The transfer of signaling molecules communicates the current state of the cell that is directly next to the target cell; this allows a group of cells to coordinate their response to a signal that only one of them may have received.