Chapter 7: Transport Across Cellular Membranes

Plasma membranes must allow certain substances to enter and leave a cell, and prevent some harmful materials from entering and some essential materials from leaving. In other words, plasma membranes are selectively permeable—they allow some substances to pass through, but not others. Some cells require larger amounts of specific substances and must have a way of obtaining these materials from extracellular fluids. This may happen passively, as certain materials move back and forth, or the cell may have special mechanisms to facilitate transport. Some materials are so important to a cell that it spends some of its energy, hydrolyzing adenosine triphosphate (ATP), to obtain these materials. Interestingly, most cells spend a lot of their energy (approximately one third) on maintaining an imbalance of sodium and potassium ions between the cell's interior and exterior. The most direct forms of membrane transport are passive. **Passive transport** is a naturally occurring phenomenon and does not require the cell to exert any of its energy to accomplish the movement of substances from an area of higher concentration to an area of lower concentration.

# Selective Permeability

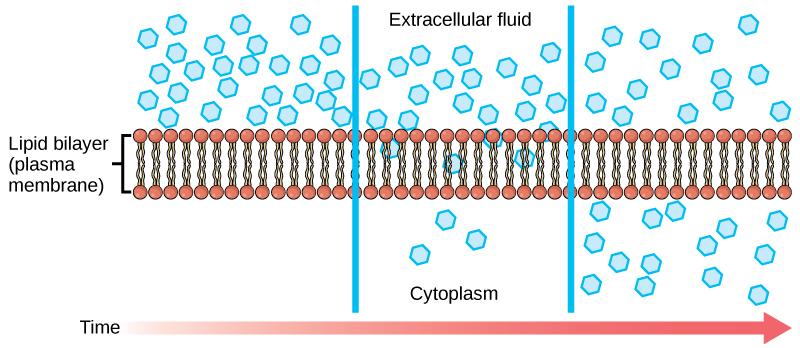
Recall that plasma membranes are amphiphilic, containing hydrophilic and hydrophobic regions (see Chapter 6). This characteristic helps move some materials through the membrane and hinders the movement of others. Non-polar and lipid-soluble material with a low molecular weight can easily slip through the membrane's hydrophobic lipid core. Substances such as the fat-soluble vitamins A, D, E, and K readily pass through the plasma membranes in the digestive tract and other tissues. Fat-soluble drugs and hormones also gain easy entry into cells and readily transport themselves into the body’s tissues and organs. Oxygen and carbon dioxide molecules have no charge and pass through membranes by simple diffusion.

Polar substances present problems for the membrane. While some polar molecules connect easily with the cell's outside, they cannot readily pass through the plasma membrane's hydrophobic lipid core. Additionally, while small ions could easily slip through the spaces in the membrane's mosaic, their charge prevents them from doing so. Ions such as sodium, potassium, calcium, and chloride must have special means of moving through plasma membranes. Simple sugars and amino acids also need the help of various transmembrane proteins to facilitate transport across plasma membranes.

# Passive Transport: Diffusion, Osmosis, and Facilitated Diffusion

## Diffusion

**Diffusion** is a passive process of transport where a single substance moves from a high concentration to a low concentration until the concentration is equal across space. You are familiar with the diffusion of substances through the air. For example, think about someone opening a bottle of perfume in a room filled with people. The perfume smell is at its highest concentration in the bottle. Its lowest concentration is at the room's edges. The perfume vapor will diffuse or spread away from the bottle, and gradually, increasingly more people will smell the perfume as it spreads. Materials move within the cell’s cytosol by diffusion, and certain materials move through the plasma membrane by diffusion (Figure 7-1). Diffusion expends no energy. The left part of Figure 7-1 shows a substance on one side of a membrane only in the extracellular fluid. The middle part shows that, after some time, some of the substance has diffused across the plasma membrane, from the extracellular fluid, and into the cytoplasm. The right part shows that, after more time, an equal amount of the substance is on each side of the membrane.



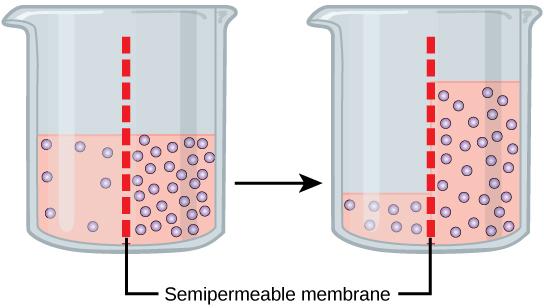
**Figure 7-1: Diffusion.** Diffusion through a permeable membrane moves a substance from a high concentration area (extracellular fluid, in this case) down its concentration gradient (into the cytoplasm).

Each separate substance in a medium, such as the extracellular fluid, has a unique concentration gradient, independent of other materials' concentration gradients. Each substance will diffuse, passively, according to that gradient. Within a system, there will be different diffusion rates of various substances in the medium.

## Osmosis

**Osmosis** is the movement of water through a semipermeable membrane according to the water's concentration gradient across the membrane, which is inversely proportional to the solutes' concentration. While the term diffusion refers to the transport of material (other than water) across membranes and within cells, the term osmosis refers specifically to the transport only of water across a membrane. Not surprisingly, the aquaporins that facilitate water movement play a large role in osmosis, most prominently in red blood cells and the membranes of kidney tubules.

Osmosis is a special case of diffusion. Water, like other substances, moves from an area of high concentration to one of low concentration. Imagine a beaker with a semipermeable membrane separating the two sides or halves. On both sides of the membrane, the water level is the same, but there are different concentrations of solutes on each side of the membrane, and the different solutes cannot cross the membrane. In figure 7-2, there is a container whose contents are separated by a semipermeable membrane. Initially, there is a high concentration of solute on the right side of the membrane and a low concentration of the left. Over time, water diffuses across the membrane toward the side of the container that initially had a higher concentration of solute (lower concentration of water not bound to solute). As a result of osmosis, the water level is higher on this side of the membrane, and the solute concentration is the same on both sides.



**Figure 7-2: The movement of water through a semi-permeable membrane.** In osmosis, water always moves from an area of higher water concentration to one of lower concentration. In the diagram, the solute cannot pass through the selectively permeable membrane, but the water can. Note at the beginning, the volume of water is the same, but the concentration of solute-unbound water is greater on the left because there is less solute. There are fewer solute-unbound water molecules on the right because there is so much more solute. Therefore, there is a higher concentration of “free” water molecules on the left than on the right of the membrane in the first beaker.

The beaker has a solute mixture on either side of the membrane. A principle of diffusion is that the molecules move around and will spread evenly throughout the medium if they can. However, only the material capable of getting through the membrane will diffuse through it. In this example, the solute cannot diffuse through the membrane, but the water can. Water has a concentration gradient in this system. Thus, water will diffuse down its concentration gradient, crossing the membrane to the side where it is less concentrated. This diffusion of water through the membrane—osmosis—will continue until the water's concentration gradient goes to zero or until the water's hydrostatic pressure balances the osmotic pressure. Osmosis constantly proceeds in living systems.

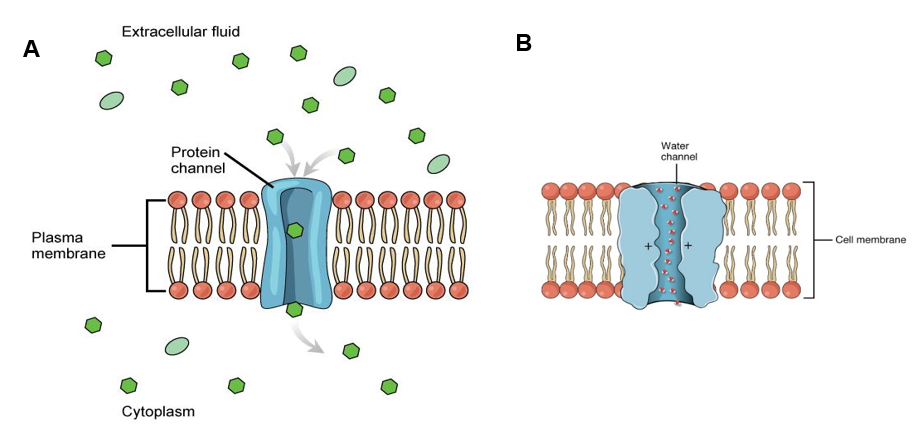
## Facilitated Transport

In **facilitated transport** or facilitated diffusion, materials that cannot use simple diffusion, are transported passively across the plasma membrane with the help of membrane proteins. A concentration gradient exists that would allow these materials to diffuse into the cell without expending cellular energy. However, these materials are polar molecules or ions that the cell membrane's hydrophobic parts repel. Facilitated transport proteins shield these materials from the membrane's repulsive force, allowing them to diffuse into the cell.

The transported material first attaches to protein or glycoprotein receptors on the plasma membrane's exterior surface. The substances then pass through specific integral proteins to move into the cell. Some of these integral proteins form a pore or channel through the phospholipid bilayer; others are carrier proteins that contain a binding site for a specific substance to aid its diffusion through the membrane.

**Channels**

The integral proteins involved in facilitated transport are types of transport proteins, and they function as either channels or carriers/transporters for the material. **Channels** are specific for the transported substance and have hydrophilic domains exposed to the intracellular and extracellular fluids with hydrophilic channels (or pathways) through their core that provides a hydrated opening through the membrane layers (Figure 7-3A). As such, channels are often described as “pores” in the membrane. Passage through the channel allows polar compounds to avoid the plasma membrane's nonpolar central layer that would otherwise slow or prevent their entry into the cell.

****

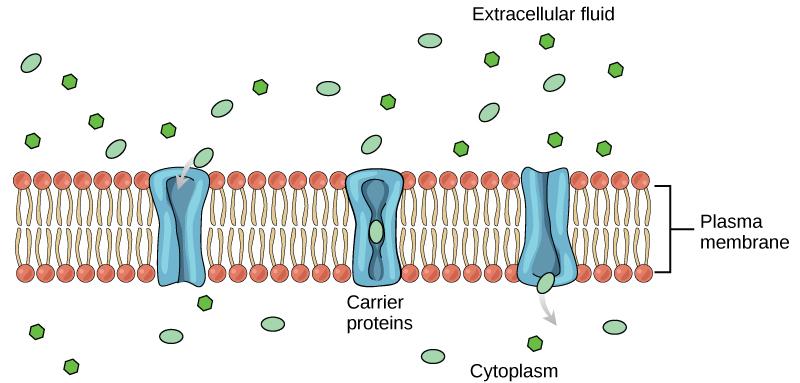
**Figure 7-3: Channel proteins.** (A) Facilitated transport moves substances down their concentration gradients. The substance may cross the plasma membrane with the aid of channel proteins. (B) View of aquaporin channel protein from the top. Aquaporins move water from the extracellular space to the cytoplasm in some cells of the body.

Channel proteins consist of two forms; one form is open at all times allowing substances to move with the gradient; the second form is “gated,” which controls the channel's opening and closing. No matter the form, channel proteins will facilitate the passive diffusion of substances with the concentration gradient. Aquaporins are channel proteins that are opened at all times to allow water to pass through the membrane at a very high rate (Figure 7-3B). Alternatively, an example of a gated channel is when a particular ion attaches to the channel protein, and controls the opening, or other mechanisms or substances may be involved. In some tissues, sodium and chloride ions pass freely through open channels, whereas, in other tissues, a gate must open to allow passage. An example of this occurs in the kidney, where there are both channel forms in different parts of the renal tubules. Cells involved in transmitting electrical impulses, such as nerve and muscle cells, have gated channels for sodium, potassium, and calcium in their membranes. Opening and closing these channels changes the relative concentrations on opposing sides of the membrane of these ions, resulting in facilitating electrical transmission along membranes (in the case of nerve cells) or in muscle contraction (in the case of muscle cells).

**Carrier/Transporter Proteins**

Another type of protein embedded in the plasma membrane is a carrier/transporter protein. This aptly named protein binds a substance and triggers a change of its shape, moving the bound molecule from one side of the membrane to another, and can result in movement that can be with (passive) or against (active) the concentration gradient (Figure 7-4). Carrier proteins are typically specific for a single substance; this selectivity adds to the plasma membrane's overall selectivity.

Figure 7-4 shows a carrier/transporter protein embedded in the membrane with an opening that initially faces the extracellular surface. After a substance binds the carrier, it changes shape so that the opening faces the cytoplasm, and the substance is released.



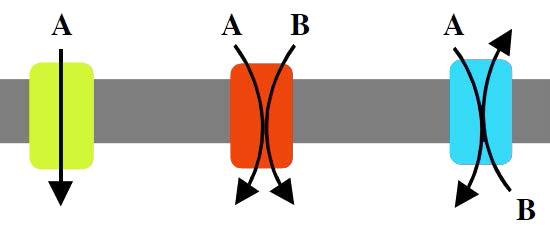
**Figure 7-4: Carrier/Transporter proteins.** Facilitated diffusion through a carrier/transporter protein. Some substances move down their concentration gradient across the plasma membrane with the aid of carrier proteins. Carrier proteins change shape as they move molecules across the membrane.

An example of this process occurs in the kidney. In one part, the kidney filters glucose, water, salts, ions, and amino acids that the body requires. This filtrate, which includes glucose, then reabsorbs in another part of the kidney. Because there are only a finite number of carrier proteins for glucose, if more glucose is present than the proteins can handle, the excess is not transported, and the body excretes this through urine. In a diabetic individual, the term is “spilling glucose into the urine.” A different group of carrier proteins, glucose transport proteins, or GLUTs, are involved in transporting glucose and other hexose sugars through plasma membranes within the body.

The rate of transport by channel and carrier proteins differs because of the way they physically interact with their substrates. Channel proteins facilitate diffusion at a rate of tens of millions of molecules per second; whereas, carrier proteins work at a rate of a thousand to a million molecules per second.

**Direction of transport: Uniports, Antiports, and Symports**

A protein involved in moving only one type of molecule across a membrane is called a **uniport**. Proteins that move two different types of molecules in the same direction across the membrane are called **symporters**. If two different types of molecules move in opposite directions across the bilayer, the protein is called an **antiport** (Figure 7-5).



**Figure 7-5: Direction of transport.** A uniport (yellow), a symport (red), and an antiport (blue).

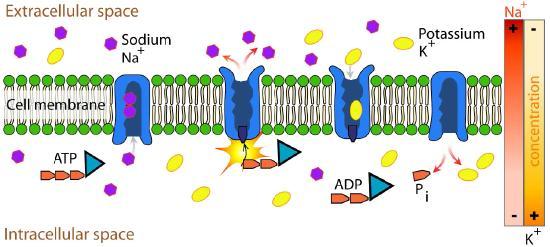
# Active transport

In some instances, cells must move materials against a concentration gradient, and when this occurs, another source of energy is required. This process is known as active transport.Active transport can be used with all three types of proteins shown in Figure 7-5 if the molecules are moved against their concentration gradient with the use of energy to drive this transport.

A good definition of active transport is that at least one molecule is moved against a concentration gradient. A common, but not exclusive energy source is ATP; other energy sources can also be employed. For example, the sodium-glucose transporter uses a sodium gradient as an energy source for actively transporting glucose into a cell. Additionally, the prokaryotic protein bacteriorhodopsin utilizes light energy to actively pump protons across cell membranes. Thus, it is essential to know that not all active transport uses ATP energy.

## Sodium Potassium Pump (Na+/K+ ATPase)

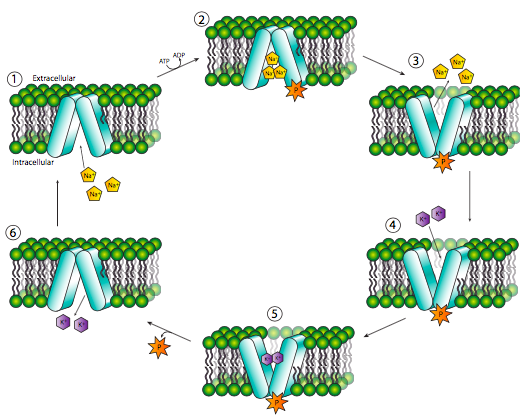
An essential, integral membrane transport protein, the Na+/K+ ATPase antiport (Na+/K+ pump) (Figures 7-6 and 7-7), moves three sodium ions out of the cell and two potassium ions into the cell with each cycle of action. In each case, the movement of both ions is against their concentration gradients. Additionally, the movement of three positive charges out of the cell and only two positive charges in; cause a membrane potential, which is vital in establishing homeostasis within cells.



**Figure 7-6: An overview of active transport by the Na+K+ ATPase.** The protein transports three sodium out of the cell and two potassium into the cell each cycle. This cycle requires the use of one ATP molecule for energy as it is driving the ions against the concentration gradient (from low concentration to high) in both directions.

The Na+/K+ pump uses the energy of ATP to create and maintain ion gradients that are important both in maintaining cellular osmotic pressure and (in nerve cells) for creating the sodium and potassium gradients necessary for signal transmission. Failure of the system to function results in swelling of the cell due to the movement of water into the cell through osmotic pressure. The transporter expends about one-third of the ATP energy of animal cells. The cycle of the action occurs as follows and as shown in Figure 7-7:

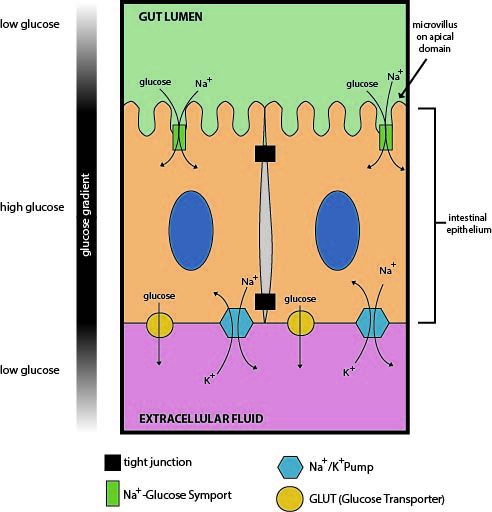
1. Pump binds three Na+ ions from the cytoplasm of the cell, followed by one ATP molecule.
2. ATP hydrolysis results in phosphorylation of aspartate residue of the pump. ADP is released.
3. Phosphorylated pump undergoes a conformational change to expose Na+ ions to the exterior of the cell. Na+ ions are released.
4. Pump binds two extracellular K+ ions.
5. Pump dephosphorylates, causing it to change conformation and release K+ ions to the cytoplasm as the pump returns to the original shape.
6. Pump binds three Na+ ions from the cytoplasm to restart the cycle.



**Figure 7-7: Active Transport by Na+/K+ ATPase.** This enzyme pushes three Na+ ions out of the cell and two K+ ions into the cell, going against the gradient in both directions and using energy from ATP hydrolysis.

## Sodium/Glucose Transporter

Hydrolysis of ATP, while a common source of energy for many biological processes, is not the only source of energy for transport. Coupling the active transport of one solute against its gradient with the energy from passive transport of another solute down its gradient is also possible. Illustrated in Figure 7-8, is the **sodium/glucose transporter**, an example of a symport with both solutes crossing the membrane in the same physical direction. However, one solute is traveling down its gradient (sodium ions), and one solute traveling up or against its concentration gradient (glucose). The movement of Na+ is the driving force behind this transport mechanism. The Na+ gradient across the membrane is an extremely important source of energy for most animal cells. However, this is not universal for all cells, or even all eukaryotic cells. In most plant cells and unicellular organisms, the H+ (proton) gradient plays the role that Na+ does in animals.



**Figure 7-8: Transporters in the gut.** In this symport, the energy release from passive transport of Na+ into the cell actively transports glucose into the cell on the apical side (green protein). On the basal side of the cell, **t**ransport proteins work together. The Na+/K+ ATPase (blue) restores the normal concentration of sodium ions that entered passively through the sodium glucose transporter and glucose transporters (yellow) move the glucose from the cell to the bloodstream in the extracellular space.

Absorbing nutrients from the digestive system is necessary for animal life. The sodium/glucose transport protein is a symporter that moves glucose into intestinal cells. This transporter is located in cellular membranes of the intestinal mucosa and the proximal tubule of the nephron of the kidney. It functions in the latter to promote reabsorption of glucose.For intestinal mucosa, the pump transports glucose out of the gut and into the cells lining the lumen of the small intestine. Later, the glucose is exported out the other side of the gut cells to the interstitial space for use in the body.A **glucose transporter** performs the export of glucose from intestinal cells. This is a uniport protein that passively transports glucose due to the spontaneous opening and closing of the transport protein. This results in movement of glucose from a high concentration within the intestinal cells to the bloodstream for transport to the cells of the body. The sodium concentration is then restored to homeostasis levels using a sodium-potassium pump (Figure 7-8).

## Calcium pumps

Unlike Na+ or K+, the Ca2+ gradient is not very important for the electrochemical membrane potential or the use of its energy. However, calcium ions are necessary for muscular contraction and play important roles as signaling molecules within cells. The Ca2+ concentration is kept very low in the cytoplasm as a result of the action of pumps. Pumps are in the plasma membrane, which pumps calcium outwards from the cytoplasm and in organelles, and the endoplasmic reticulum (sarcoplasmic reticulum of muscle cells), which pump calcium out of the cytoplasm and into these organelles.

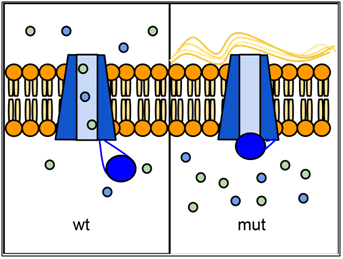
The opening of calcium channels, then, increases calcium concentration quickly in the cytoplasm resulting in a quick response, whether the intention is signaling or contraction of a muscle. After the response, the calcium is pumped back out of the cytoplasm by the respective calcium pumps. Ca2+ pumps are uniport proteins that use the energy supplied by ATP hydrolysis to drive the transport of two Ca2+ molecules from the cytoplasm to the extracellular side of the plasma membrane.

# Examples of Membrane transport in organisms

## CFTR transporter and Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive genetic disorder arising from mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This transporter system, which moves chloride and thiocyanate ions across epithelial tissue membranes, exerts its effect mostly in the lungs. Still, the pancreas, liver, kidneys, and intestine are all also affected by it.

CFTR has roles in the production of sweat, mucus, and digestive fluids. Manifestations of the disease include breathing difficulty and overproduction of mucus in the lungs. When CFTR is functional, these fluids usually are thin, but when the gene is non-functional, they become much thicker and are points of infection (Figure 7-9).



**Figure 7-9: CFTR.** Wild-type and mutant forms of CFTR in the cell membrane: In wild-type, the CFTR ion channel is gated; when activated by ATP, the channel opens and allows ions to move across the membrane. In some CFTR mutants, the channel does not open. This prevents the movement of ions and water and allows mucus to build up on the lung epithelium.

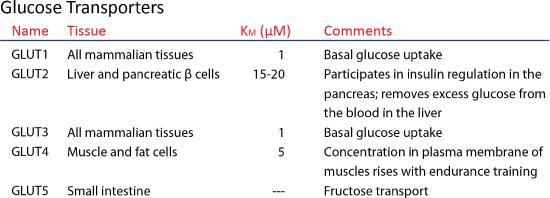
## Glucose Transport proteins (GLUTs)

GLUTs (GLUcose Transport proteins) are uniport, type III integral membrane proteins that participate in the transport of glucose across membranes into cells (Table 7-1). GLUTs are found in all phyla and are abundant in humans, with 12 GLUT genes. GLUT1, in erythrocytes, is well-studied. Through GLUT 1, glucose enters and passes through it via facilitated diffusion at a rate that is 50,000 higher than in its absence. The body contains many types of GLUTs found in different cells of the body. GLUT 1 levels in erythrocytes go up as glucose levels decrease and decrease when glucose levels go down via facilitated diffusion.

Regulated by insulin, GLUT 4 is found primarily in adipose and striated muscle tissue. Insulin alters intracellular trafficking pathways in response to increases in blood sugar to favor movement of various GLUT proteins (including GLUT 4) from intracellular vesicles to the cell membrane, thus stimulating the uptake of the glucose. Found in the hippocampus is GLUT 4, where the disruption of traffic may result in depressive behavior and cognitive dysfunction.

The key to keeping the glucose in the cell is the phosphorylation of it by the glycolysis enzyme, hexokinase, in the cytoplasm. Phosphorylated glucose molecules cannot enter the active site of the various GLUTs and therefore don’t have an easy means of exiting the cell.Essentially, phosphorylation traps glucose inside the cell.

**Table 7-1: Glucose transporters.** Glucose transporters (GLUTs) found in cells.

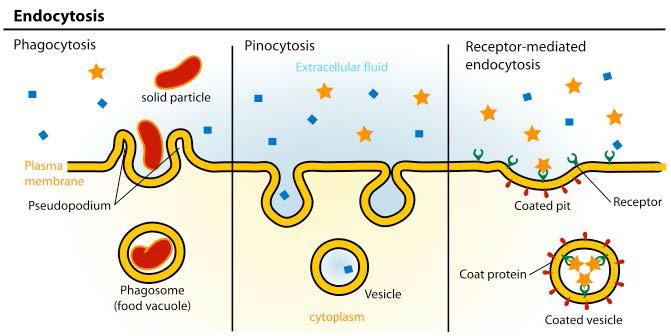


## Endocytosis

There are many functions and factors relating to cell membranes that don’t fit into broad categories. Those items will be the focus of this section.

Besides transporter proteins and ion channels, another common way for materials to get into cells is by the process of **endocytosis**. Endocytosis is an alternate form of active transport for getting materials into cells. Some of these processes, such as **phagocytosis**, can import much larger particles than would be possible via a transporter protein.

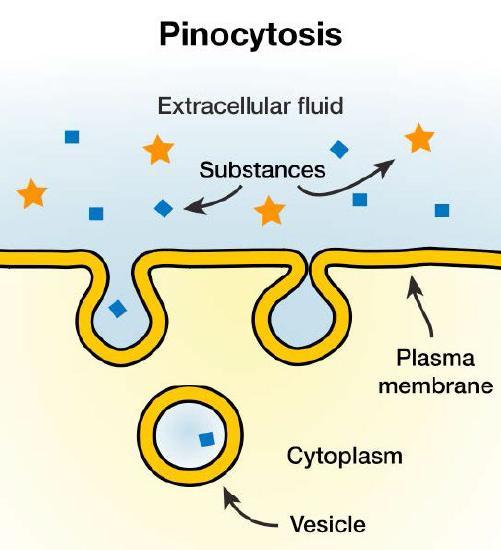
As a result, the process usually involves the import of many different molecules each time it occurs. The list of compounds entering cells in this way includes LDLs and their lipid contents, but it also has things like iron (packaged in transferrin), vitamins, hormones, proteins, and even some viruses sneak in by this means. There are three types of endocytosis we will consider (Figure 7-10).



**Figure 7-10: Three types of endocytosis.** These include (left) phagocytosis- a non-specific uptake of molecules, (middle) pinocytosis- a non-specific uptake of fluid, and (right) receptor-mediated endocytosis- the specifc uptake of molecules after binding to a cell surface receptor.

**Pinocytosis**

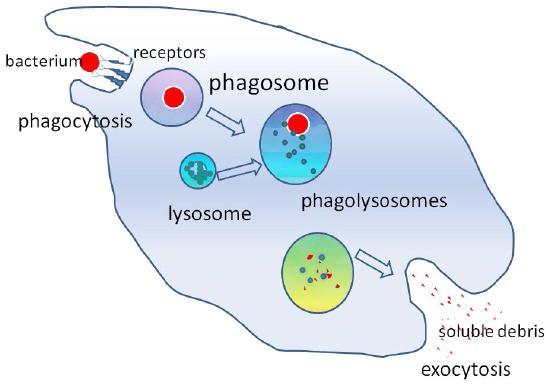
A phenomenon known as “cell drinking,” **pinocytosis**, literally involves a cell “taking a gulp” of the extracellular fluid. It does this, as shown in Figure 7-11, by a simple invagination of the plasma membrane. A pocket results, which pinches off internally to create a vesicle containing extracellular fluid and dissolved molecules. Within the cytosol, this internalized vesicle will fuse with endosomes and lysosomes. The process is non-specific for materials internalized.



**Figure 7-11: Pinocytosis.** Pinocytosis, the uptake of fluid from the extracellular side of the membrane into a vesicle on the intracellular side.

**Phagocytosis**

Phagocytosis is a process whereby relatively large particles (0.75 µm in diameter) are internalized. Cells of the immune system, such as neutrophils, macrophages, and others, use phagocytosis to internalize cell debris, apoptotic cells, and microorganisms.



**Figure 7-12: Generalized scheme for phagocytosis of a bacterium.** The bacterium is taken up by phagocytosis into a phagosome that merges with the lysosome to create a phagolysosome.

The process operates through specific receptors on the surface of the cell, and the phagocytosing cell engulfs its target by growing around it. The internalized structure is known as a phagosome, which quickly merges with a lysosome to create a phagolysosome (Figure 7-12). The phagolysosome subjects the engulfed particle to toxic conditions to kill it, if it is a cell, and/or to digest it into smaller pieces. In some cases, soluble debris may be released by the phagocytosing cell.

## Receptor-Mediated Endocytosis

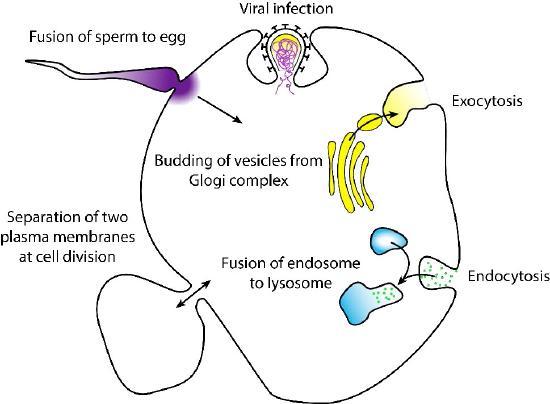
In some instances, endocytosis is a specific mechanism to take up molecules that the cell needs to function. The molecule/ligand can bind to a specific receptor on the surface of the cell and this triggers the formation of a vesicle that is formed to import the molecule, via vesicle, into the cell. This process is called receptor mediated endocytosis. Cells in a human can take up LDL (low-density lipoprotein), through receptor mediated endocytosis, where the LDL binds specific LDL receptors on the surface of the cell. The LDL is internalized into a vesicle that is specifically called the endosome, during this time the LDL receptors are recycled to the surface of the cell. The endosome will then fuse with the lysosome where the LDL can then be broken down into monomers needed for cell function (See Chapter 10).

## Exocytosis

The process of exocytosis is used by cells to export molecules out of cells that would not otherwise pass easily through the plasma membrane. In the process, secretory vesicles fuse with the plasma membrane and release their contents extracellularly. Materials, such as proteins and lipids embedded in the membranes of the vesicles, become a part of the plasma membrane when fusion between it and the vesicles occurs.

Fusion is a membrane process where two distinct lipid bilayers merge their hydrophobic cores, producing one interconnected structure. Membrane fusion involving vesicles is the mechanism by which the processes of endocytosis and exocytosis occur.

Common processes involving membrane fusion include fertilization of an egg by a sperm, separation of membranes in cell division, transport of waste products, and neurotransmitter release (Figure 7-13). Artificial membranes such as liposomes can also fuse with cellular membranes. Fusion is also important for transporting lipids from the point of synthesis inside the cell to the membrane for use. The entry of pathogens can also be governed by fusion, as many bilayer-coated viruses use fusion proteins in entering host cells.



**Figure 7-13: Membrane Fusion.** Cell membrane fusion examples including endocytosis where the endosome fuses with the lysosome, when vesicles from the Golgi fuse with the plasma membrane, and a sperm fuses with an egg.