9

Cytology

Doctor 2019 | Medicine | JU

◉ Sheet ○ Slides

Done By

Obada Abusheikha

Contributed in the Scientific Correction

...

Contributed in the Grammatical Correction

...

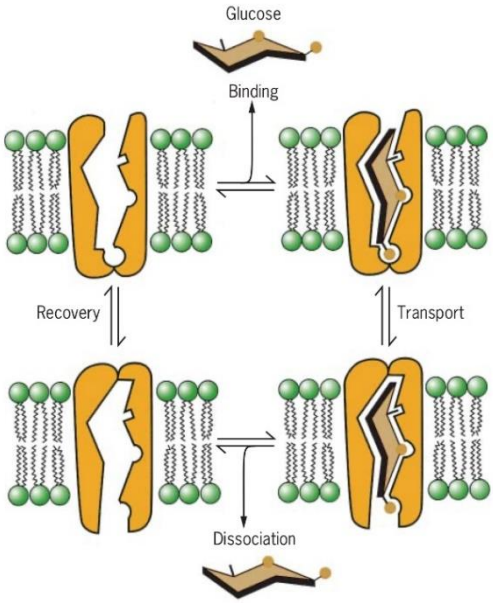
Doctor

Dr.Amer Imraish

8.12 Facilitated Diffusion

When substances diffuse across the plasma membrane, they do not always diffuse through the lipid bilayer or through a channel.

In many cases, a **facilitative transporter** that spans the plasma membrane is required to transport the substance. This is the case with polar solutes, such as sugars and amino acids. This process is called **facilitated diffusion**, and it takes the following steps:

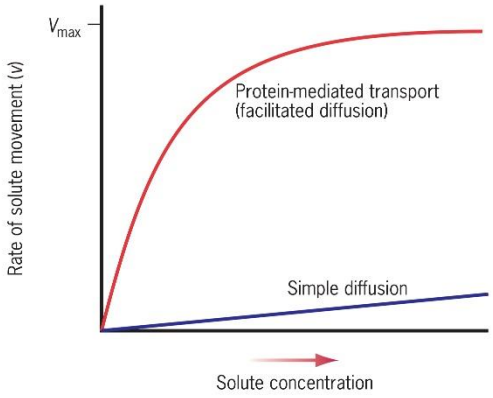


1. The substance selectively binds to this facilitative transporter.
2. This causes the protein to change its conformation.
3. The substance is exposed to the other side of the membrane.
4. The substance diffuses down its concentration gradient.

Facilitative transporters can transport substances equally well in both directions, and the direction of the net movement of the substance depends on the direction of the concentration gradient of the substance, as in simple diffusion.

Despite it being passive, facilitated diffusion is similar to enzyme-catalyzed reaction in many ways:

1. Facilitative transporters are **specific** for the molecule they transport, just like enzymes.
2. Transporters, like enzymes, exhibit saturation-type kinetics. The rate of facilitated diffusion depends on both the concentration gradient and the number of transporter proteins present. Each transporter can only move hundreds to thousands of molecules each second. As the concentration of the solute becomes very large, the transport rate levels off to its maximum value as the transporters are **saturated.**

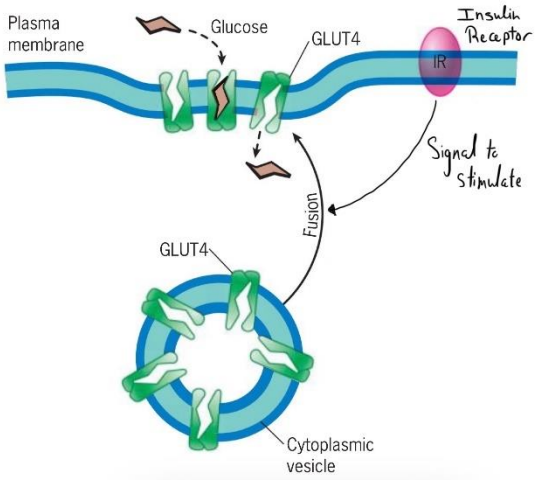


3. The activity of these channels can be **regulated**, like enzymes and ion channels.

Glucose is transported from the bloodstream into our cells by a family of related glucose transporters named GLUT1-GLUT5.

Insulin is a hormone produced by the pancreas, and it plays a key role in maintaining proper blood sugar levels.

An increase in blood sugar levels triggers the secretion of insulin, which stimulates the uptake of glucose into cells.



When insulin levels in the blood are low, insulin responsive cells contain few glucose transporters on their plasma membrane, as these transporters are stored in the walls of cytoplasmic vesicles that form by budding from the plasma membrane(endocytosis).

When insulin levels rise, this acts on target cells, stimulating the fusion of cytoplasmic vesicles to the plasma membrane(exocytosis), which moves transporters to the cell surface, where they can transport glucose into the cell.

The cell maintains a gradient favoring the entry of glucose into the cell by phosphorylating glucose after it enters the cytoplasm, thus keeping the concentration of glucose lower inside the cell.

8.13 Active Transport

Our cells are able to produce and maintain the necessary concentration gradients of substances across the plasma membrane using Active transport, which relies on integral membrane proteins(called pumps) that selectively bind to a substance and move it across the membrane as the protein's conformation changes. Unlike transporter proteins in facilitated diffusion, pumps transport substances in one direction only.

As this movement happens against the electrochemical gradient of a substance(it is endergonic), it must be coupled to an exergonic process such as the hydrolysis of ATP, the absorbance of light, the transfer of electrons or the flow of other substances down their gradients.

Primary Active Transport: Coupling Transport to ATP Hydrolysis

Pumps that directly use energy from ATP are called **P-type** pumps. ATP is hydrolyzed and the phosphate group is transferred to the protein. This phosphorylation of the protein changes its conformation and affinity to different ions.

An example of this type of pump is the **Sodium-Potassium pump**, which is found in all animal cells (only in animal cells as well).

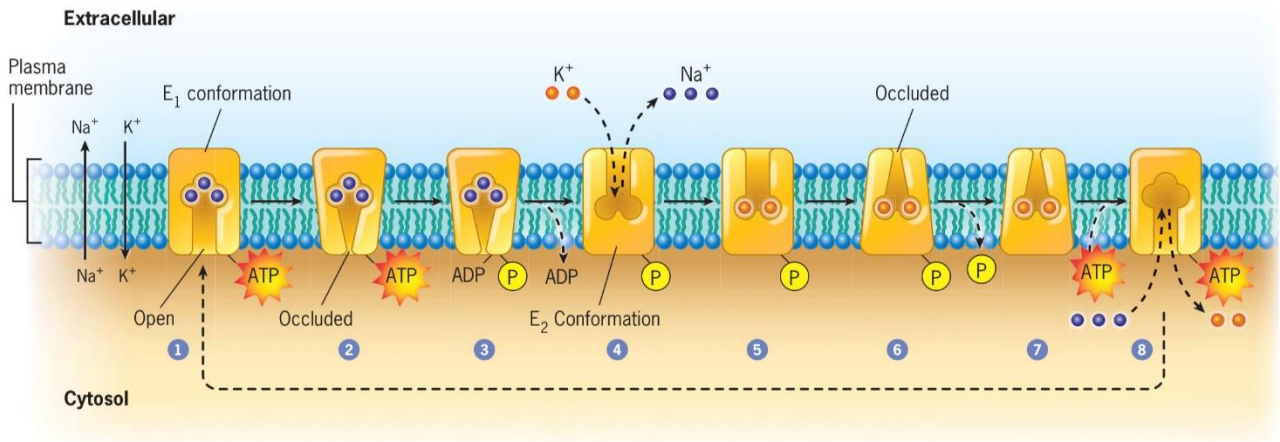
As the pump catalyzes the hydrolysis of ATP, it is often called Na^+/K^+-ATPase. However, hydrolysis of ATP does not occur unless K^+ is present on the outside (to be moved in) and Na^+ on the inside (to be moved out) of the cell. The toxic compound **ouabain** acts by inhibiting this pump.

The Na+/K+ pump is said to be **electrogenic**, which means that it contributes directly to the charge (and so the presence of a membrane potential) across the membrane.

The pump can exist in one of two different conformations:

1. **E_1 conformation**: the ion binding sites are accessible to the **inside** of the cell, and the protein has a higher affinity to Na^+ than to K^+
2. **E_2 conformation**: the ion binding sites are accessible to the **outside** of the cell, and the protein has a higher affinity to K^+ than to Na^+

Mechanism of action:



1. The pump is in the E_1 conformation. ATP then 3 Na^+ ions bind to it.
2. A gate within the protein closes and the protein is in an *occluded* E1 state.
3. The bound ATP is hydrolyzed into ADP and phosphate, then the ADP is released.

4. The release of the ADP causes the protein to change to the E_2 conformation and release the Na^+ ions outside of the cell.
5. Once the 3 Na^+ ions have been released, the protein picks up 2 K^+ ions.
6. Another gate in the protein is closed, shifting the pump into an occluded state and preventing the backflow of K^+ ions.
7. The protein is Dephosphorylated (release of phosphate group is released)
8. ATP binds to the pump, causing it to return to the E_1 conformation and releasing the K^+ ions into the cell.

The ratio of Na^+ to K^+ ions pumped is **3:2**.

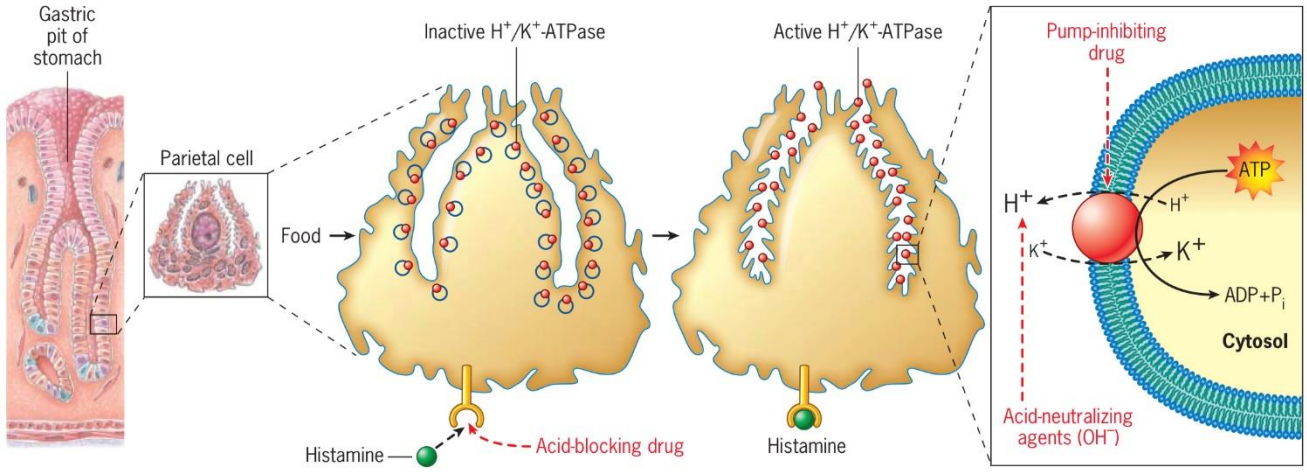
The sodium-potassium pump consumes approximately one-third of the energy produced by most cells and two-thirds of the energy produced in by nerve cells.

Other Primary Ion Transport Systems

*The best studied P-type pump is the Ca^{2+}-ATPase, which is present in the membranes of the ER and pumps Ca^{2+} ions from the cytosol into the ER.

*Plant cells have a H^+-transporting P-type plasma membrane pump, which plays a key role in secondary transport of solutes, control of cytosolic pH, and possibly control of cell growth.

*The epithelial lining of the stomach (called parietal tissue) contains H^+/K^+-ATPase (a P-type pump) which secretes a solution of concentrated acid into the stomach chamber.



In the resting state, the H^+/K^+-ATPase molecules are present in the walls of cytoplasmic vesicles and are inactive. Food entering the stomach triggers the release of histamine (an organic nitrogenous compound) which binds to a receptor on the surface of the acid-secreting parietal cells. Binding of histamine to its receptor stimulates a response that causes the H^+/K^+ -ATPase-containing vesicles to fuse to the plasma membrane.

Once at the surface, the pump activates, pumping H^+ into the stomach cavity against its concentration gradient.

The drug **Prilosic** prevents heartburn by **inhibiting the stomach's H^+/K^+-ATPase.**

Other **acid-blocking** heartburn medications like Zantac, Pepcid, and Tagamet block a receptor on the surface of the parietal cells, thereby stopping the cells from becoming activated by the hormone instead of inhibiting the pumps directly.

Acid-neutralizing medications provide basic anions (OH^-) that combine with the secreted protons.

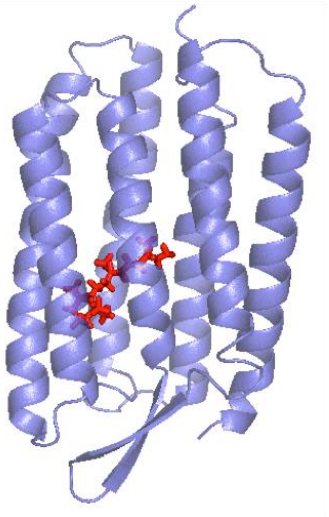
V-type pumps are another type of pump. They use energy from ATP without forming a phosphorylated intermediate like P-type pumps. They pump H^+ ions across the walls of cytoplasmic organelles and *vacuoles*(hence the name).

They are present on the membranes of lysosomes, secretory granules and plant cell vacuoles to maintain a low pH inside, and in kidney tubules to maintain the bloods pH by pumping H^+ ions into urine.

ATP-binding cassette (ABC) transporters are another type of pump. Members of this superfamily share a homologous ATP-binding domain.

Using Light Energy to Actively Transport Ions

H. halobium is a prokaryotic species that contains **bacteriorhodopsin**, which is a light-driven proton pump.



To the right is a picture of bacteriorhodopsin, and in red is the prosthetic group **retinal**, which is also present rhodopsin, the light absorbing protein of the rod cells in the retinas of our eyes.

When light energy is absorbed by the retinal group in bacteriorhodopsin, a series of conformational changes occur in the protein, causing a protein (H^+ ion) to move from the retinal group, through a channel in the protein, to the outside of the cell. This proton is then replaced by a proton from the cytoplasm.

So effectively, bacteriorhodopsin pumps protons from the cytoplasm to the exterior of the cell. The H^+ gradient generated can then be used to drive the synthesis of ATP from ADP and P_i.

Secondary Active Transport (or Cotransport): Coupling Transport to Existing Ion Gradients

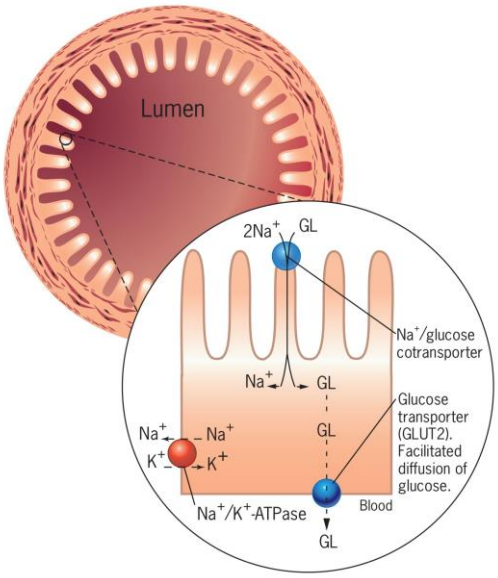
As energy is needed in creating ionic gradients (in active transport), these gradients store potential energy that could be used by cells to do work, which includes the movement of other solutes.

There are 2 types of secondary active transport:

1. **Symport**, where the two transported substances move in the same direction.

An example of this is how glucose is actively transported against its concentration gradient from the lumen of the intestine into the epithelial cells that line it.

In the epithelial cells, the Na^+ concentration is kept very low by Na^+/K^+-ATPase (primary active transport), located in the *basal and lateral* plasma membrane. The tendency of Na^+ ions to diffuse back inside is used by the cell to drive the **cotransport** of glucose into the cell against their concentration gradient, this is secondary active transport. Once inside, the glucose molecules diffuse to and cross the *basal* membrane of the cell by facilitated diffusion.



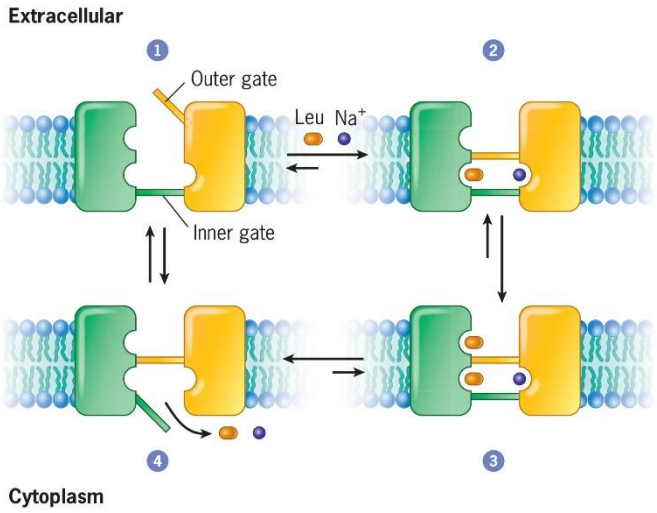
There are no GLUT transporters on the apical membrane of the cells (so glucose does not diffuse out into the lumen).

- Remember, each side of the membrane of epithelial cells (apical/lateral/basal) serves a different function and so has a different structure.

The transporter protein, called **Na^+/glucose-transporter**, moves 2 Na^+ ions and one glucose molecule with each cycle. The 2:1 Na+/glucose ratio provides a much greater driving force for moving glucose into the cell that a 1:1 ratio. This cotransporter is capable of transporting glucose into a cell against a concentration gradient greater than 20,000-fold.

Another example on symport is how plant cells use an H^+ gradient to uptake certain nutrients, including sucrose, amino acids and nitrate into the cell, where the H^+ is at a higher concentration outside of the cell.

The figure shows the mechanism of action of one the major families of secondary transporters (LeuT), where an established Na^+ gradient is used to actively transport the amino acid Leucine into bacterial cells.



In **step 1**, the outer gate is open, which allows both Na^+ and leucine to reach their binding sites from the extracellular space.

In **step 2**, the outer gate closes, occluding(trapping) the substrates within the protein.

In **step 3**, a second leucine molecule binds to another site just outside the outer gate.

In **step 4**, the inner gate opens, and the substrates are released into the cytoplasm.

The protein returns to its original state when the inner gate is closed and the outer gate is opened.

2. **Antiport**, where the two transported substances move in opposite directions.

Cotransporters that mediate antiport are usually called **exchangers**.

An example of antiport is how cells couple the inward movement of Na^+ to the outward movement of H^+ in order to maintain a proper cytoplasmic pH.

Like the Na^+/K^+-ATPase, antiporters exhibit a transport cycle in which their binding sites gain alternating access to the cytoplasm and the extracellular space.