Physiology | Lecture 4

Active transport

Reviewed by: Jana Sawafta
Lamar Khorma

Active Transport

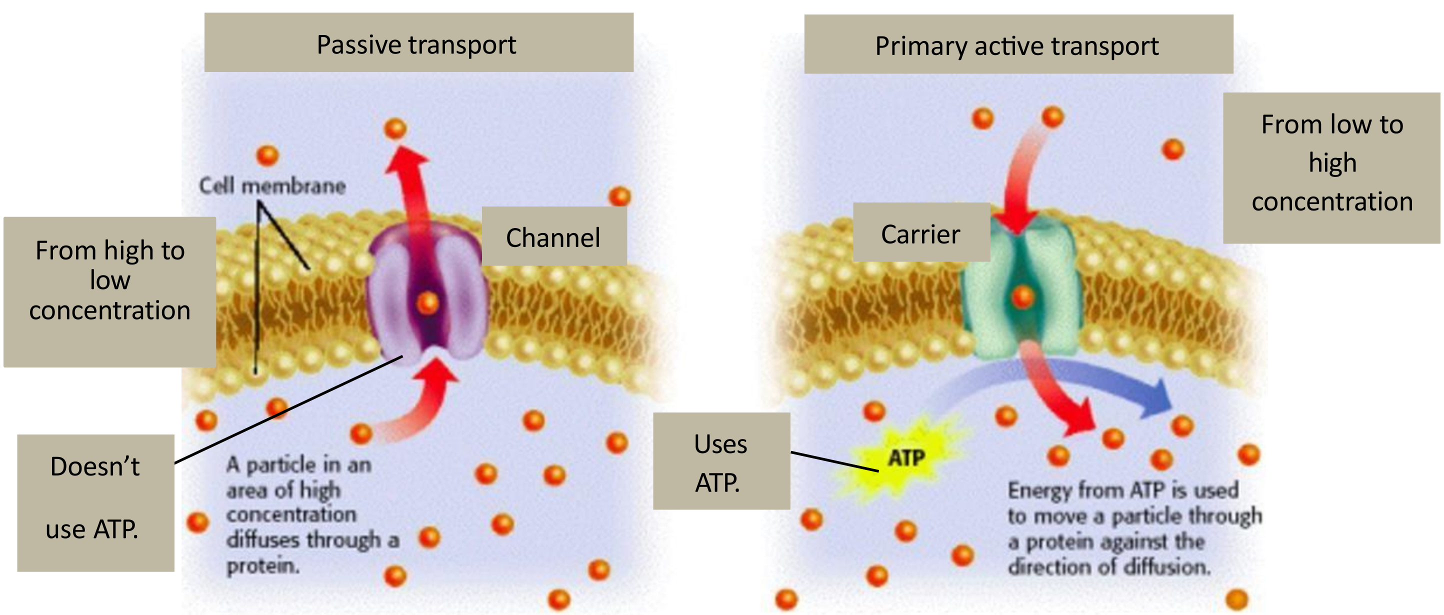
Active transport **consumes** macro energetic molecules, we divide it into three main subcategories: **Primary**, **secondary** active transport and **vesicular** transport.

All active transport systems are equipped with ***carrier proteins*** that move transported substances across membranes.

1-Primary active transport:

In this type, we have carriers (not channels) that must be phosphorylated (getting phosphate group from ATP) to transport particles from the low concentration to high concentration.

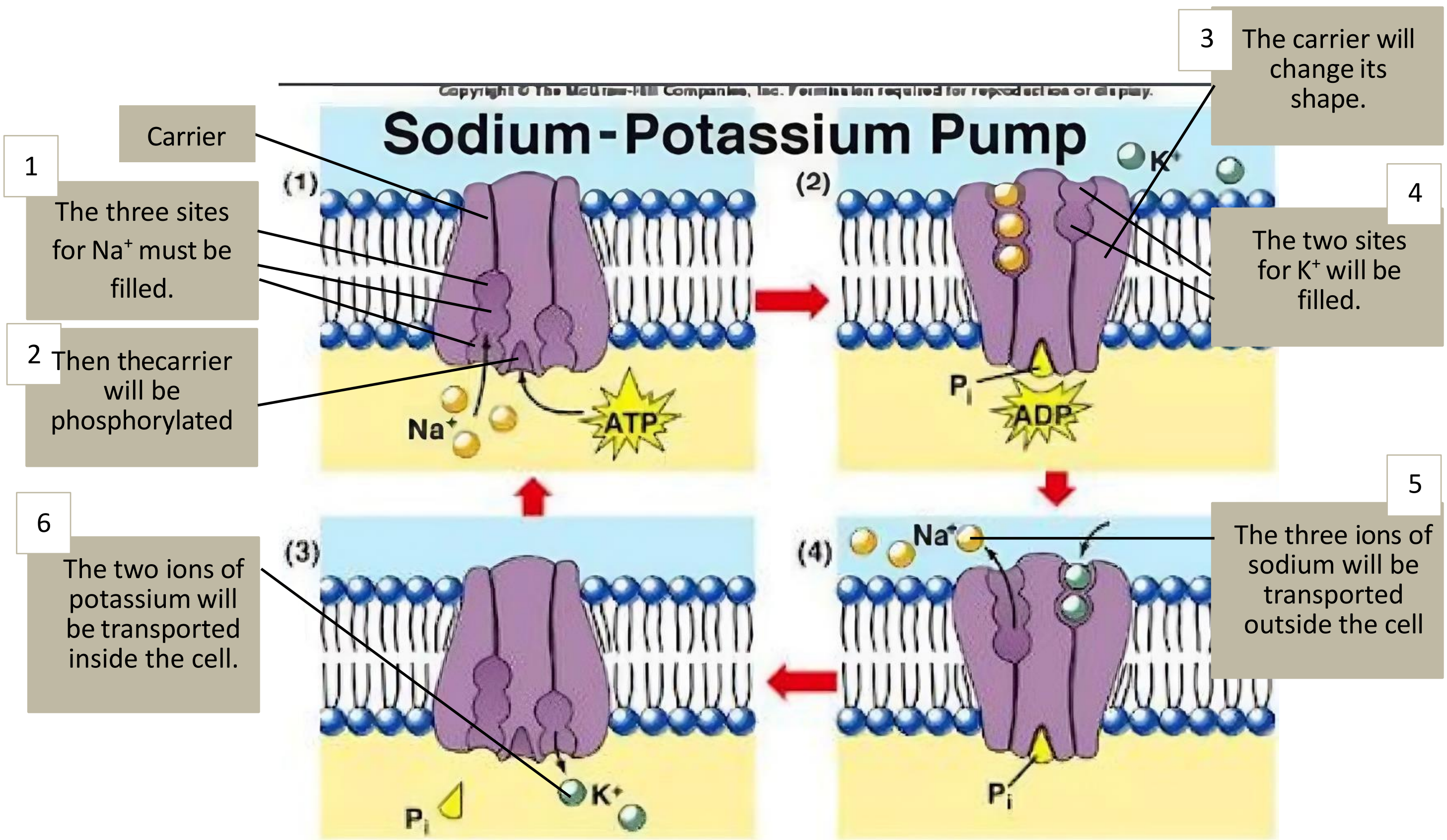
Pumps are carriers, whenever you hear "**Pump**" you should know it's **primary active transport**.



We will talk about 4 pumps in this sheet, with some information about each one of them:

A- <u>Na^+/K^+ pump</u>:

Transporting sodium and potassium, there is a high concentration of sodium <u>outside</u> the cell, and high concentration of potassium <u>inside</u>, as we know, Active transport is a transporting from low concentration to high concentration, so it transports sodium outside the cell and potassium inside the cell.



Both sodium and potassium ions are transported against their concentration gradient.

When the carrier <u>phosphorylated</u> by ATP there are conformational **changes happen to the shape** of the protein ,then when the carries <u>de-phosphorylated</u> the protein **return to its previous shape**

This pump helps in the ***<u>regulation of cell volume</u>*** by controlling concentration of solutes inside the cell (it results in a net loss of one ion) which controls water osmosis to the cell .

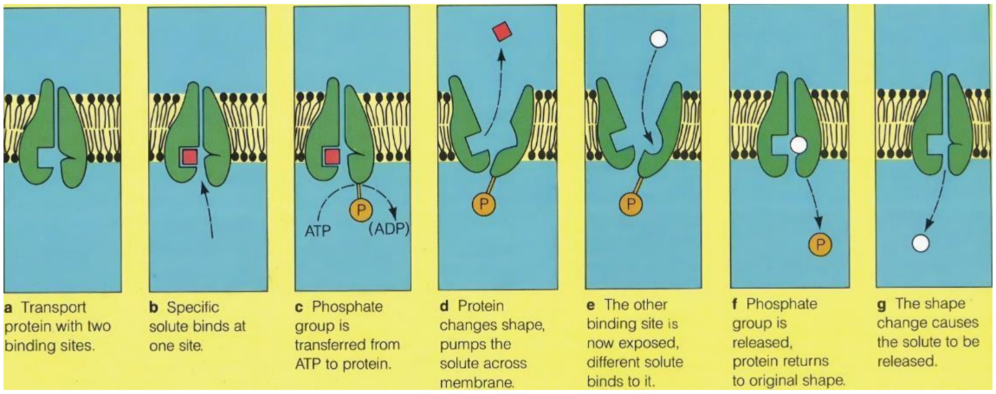
By expelling 3 positive ions for 2 transported into the cell , this pump creates positivity outside the cell . This *electrogenic* nature of the pump creates a potential difference of about (-4 mv) if it works alone.

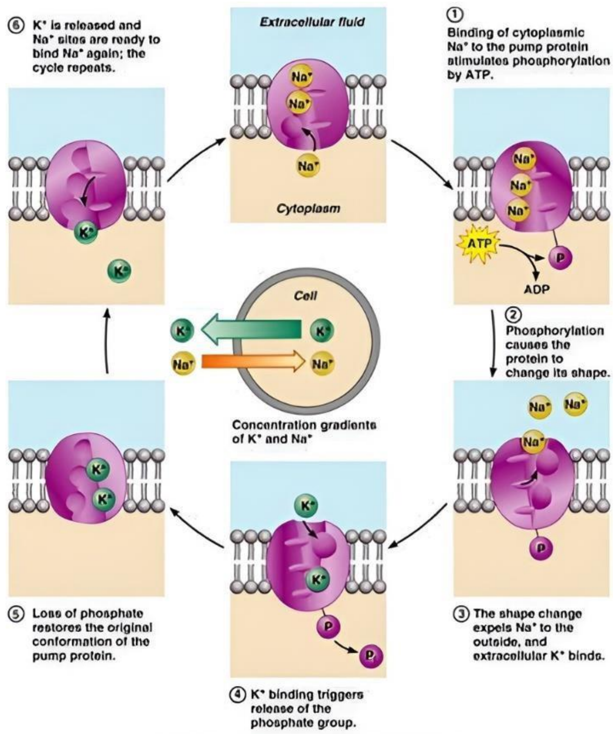
You noticed that this pump keeps high concentration of sodium outside the cell (by transporting 3 sodium ions outside the cell), you will know that this high concentration of sodium outside the cell leads the secondary active transport when we talk about it.

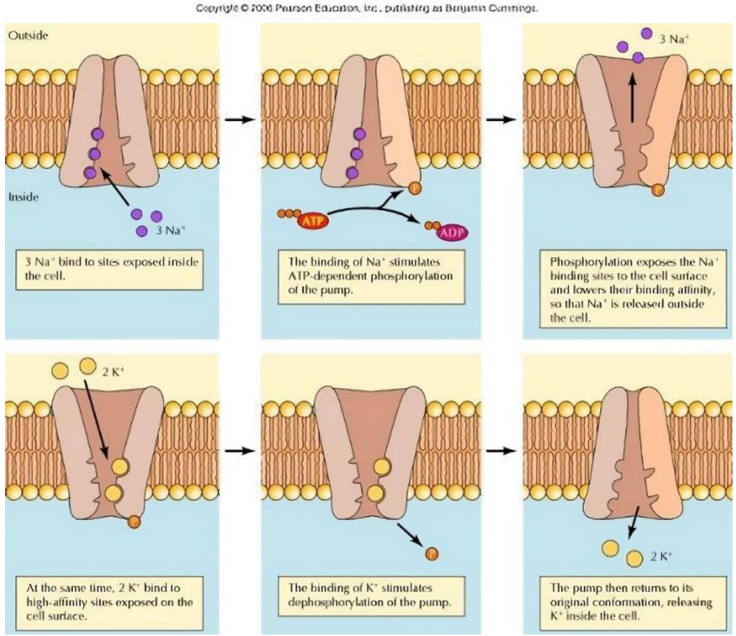
Now imagine if this pump isn't working, what will happen? The sodium ions will have a high condense to diffuse inside the cell (from high to low concentration), and the osmolarity inside the cell will increase, leading the cell to be swelled (burst).

In conclusion, **this pump is important for the cell and its activity**.

These are extra pictures of this pump, doctor said we will not be asked about the steps, we just have to know the outcome of the process.







B- **H^+ pump**:

In stomach, we are releasing hydrochloric acid, to synthesize this acid, the H^+ ions must be transported from the low concentration of it (outside the stomach) to the high concentration of it (inside the stomach) using H^+ pumps, and along with the chloride ions, hydrochloric acid is synthesized.
This mechanism could be done using H^+/K^+ pumps too.

C- **H^+/K^+ pump**.

(We will compare it with another protein in the following pages)

D- **Ca^{+2} pump**:

Inside the endoplasmic reticulum, we have a high concentration of calcium, we are getting this concentration by Ca^{+2} pumps, we have a plenty of these pumps in the membrane of endoplasmic reticulum transporting calcium from the cytosol into endoplasmic reticulum.

Also, it keeps a low concentration of Ca^{+2} ions inside the cells, for example: In the cardiac muscle, Ca^{+2} pump is used to transport Ca^{+2} ions out of it, if the Ca^{+2} ions kept inside the muscle it will remain contracted, that will stop the heart from working.

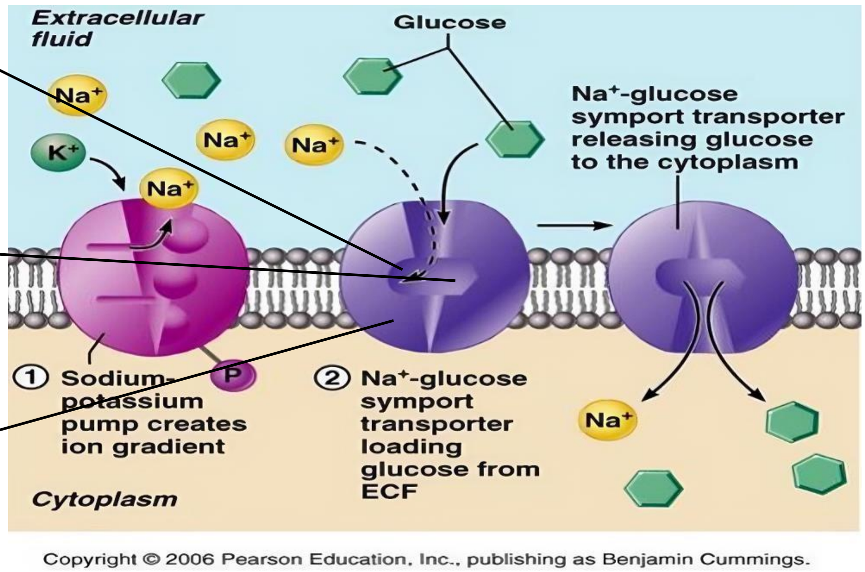
2-Secondary active transport:

Carriers that can transport Na^+ along with another particle, **Na^+** in this type is transported from the **high** concentration to the **low** concentration (***diffuse*** inside cells), the **other particle** is transported from the **low** concentration to the **high** concentration.

A binding site for Na^+.

A binding site for another particle.

This carrier is called **sodium dependent carrier**.

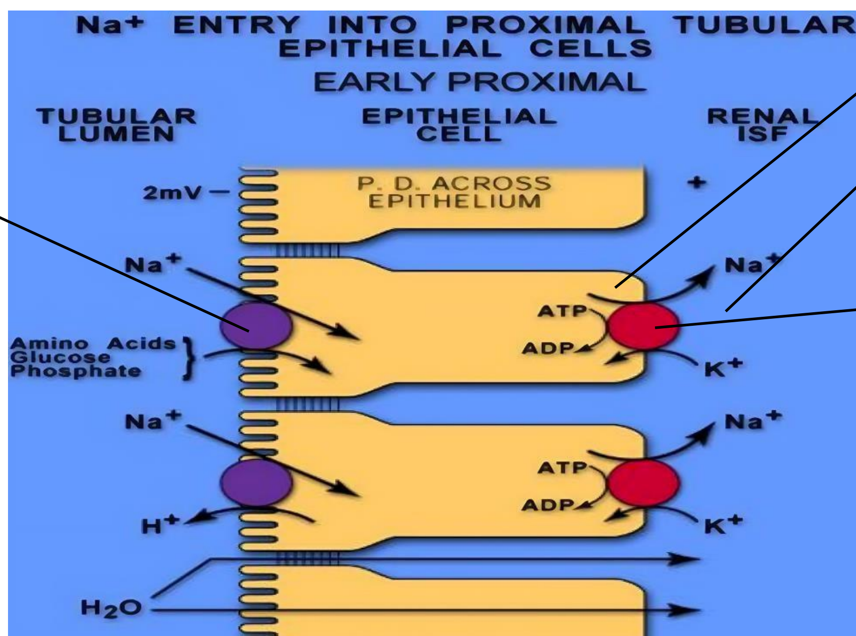


In this type of active transport, there is not directly use of ATP.

But, it happens because of the primary active transport which uses ATP.

Secondary uses the driving force that is created by primary active transport to transport other molecules.

Secondary active transport carrier (**called sodium dependent carrier**) that uses Na^+ transporting (from high to low concentration of Na^+) to transport other particles from low to high concentration of it.



Inside the cell.

outside the cell.

Primary active transport carrier (Na^+/K^+ pump) keeping high concentration of Na^+ ions outside the cell.

This example occurs especially through the epithelial cells of the intestinal tract to promote (increase) absorption of these (Glucose and Amino Acids) substances into the blood.

When you hear "Na^+ dependent carrier" then this transport is **Secondary active transport**.

Based on the movement direction of particles, we can divide Secondary active transport into Co-transport and Counter transport.

A- Co-transport:

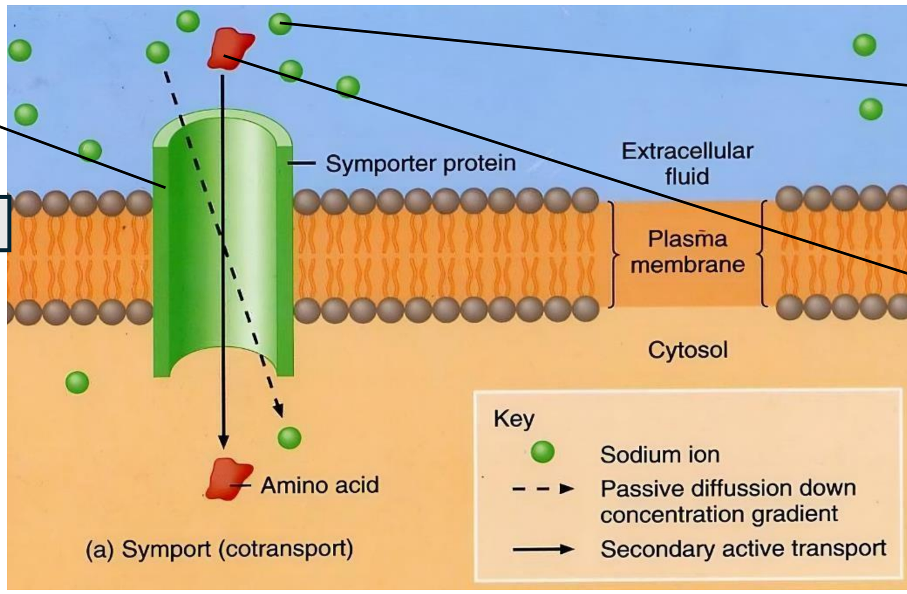
In this type, both particles are transported in the same direction.

It could be called Symport too.

This is a carrier not a channel, don't let its shape fool you.

sodium dependent carrier

It transports particles in the same direction, so it's Co-transport (symport).



It's transporting Na+ ions from high to low concentration.

It's transporting Amino Acids from low to high concentration.

B- Counter transport:

It is also called

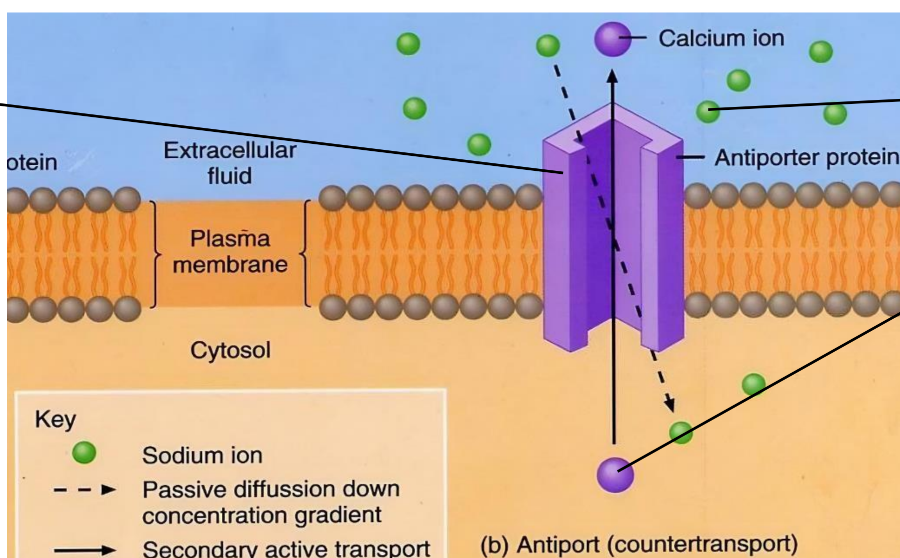
Sodium- calcium exchange

In this type, particles are transported in opposite directions.

It could be called Antiport too.

Again, this is a carrier not a channel, don't let its shape fool you.

It transports particles in opposite directions, so it's Counter transport (antiport).



It's transporting Na+ ions from high to low concentration.

It's transporting Ca^{+2} ions from low to high concentration.

In conclusion, the work of secondary active transport depends on Na+ ions concentration, so as we mentioned before, Na^+/K^+ pump (primary active transport) is important for the cell.

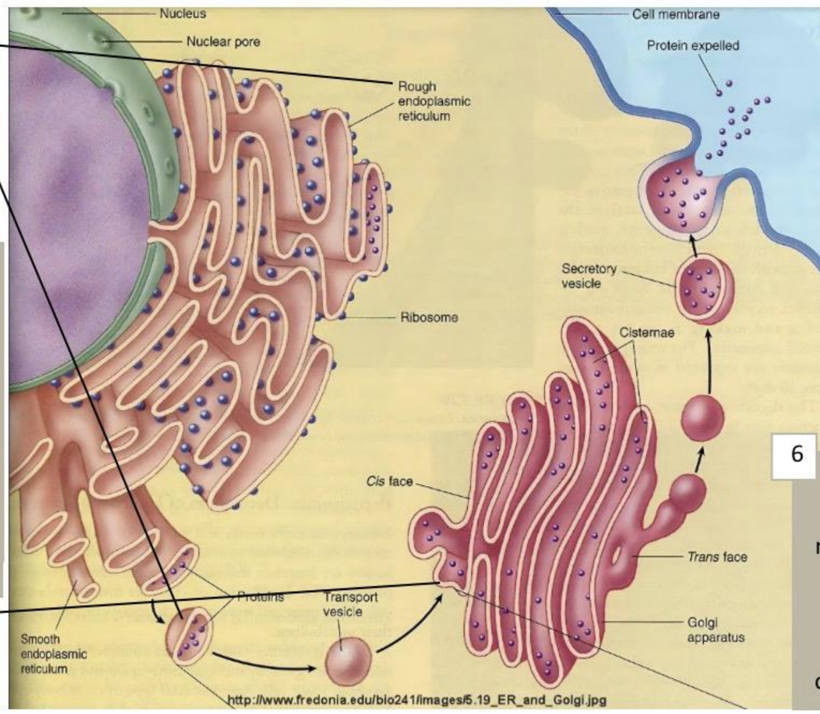
Sodium independent carrier is a transporter that **does not use Na^+ gradient,** It usually works by ***facilitated diffusion*** It does not use ATP directly.

** ***H+/K+ pump*** in different than ***proton dependent carrier***, as **H+/K+ pump-**is an active transporter that uses ATP directly and moves both protons and potassium **against their gradients** (primary active transport), while **proton dependent carrier** (H+ dependent carrier) is a symporter/antiporter protein that moves H+ down gradient leading another molecule to move up gradient (secondary active transport).

3-Vesicular transport:

Vascular transport is an **active transport** as it needs energy comes from phosphorylation.

Large particles can <u>NOT</u> pass membranes. But these particles are packaged and enclosed into vesicles by certain organelles.



1 Synthesizes proteins.

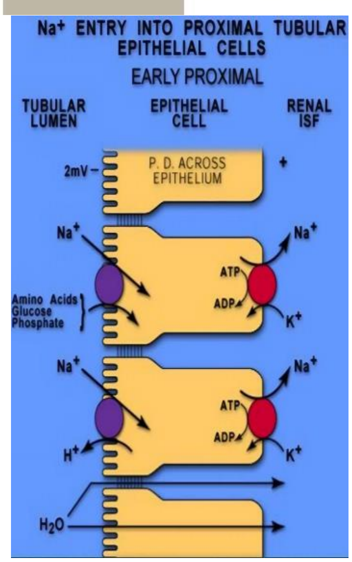
2 Proteins are transported in vesicles.

3 These vesicles are attached to motor proteins which are transported on the cytoskeleton (Microtubules) by phosphorylation and dephosphorylation (Uses ATP)

4 Then they reach Golgi Apparatus.

5 Golgi Apparatus packages these proteins and send them to their exact destinations, how Golgi knows their destinations? Each protein has an **<u>address sequence</u>**, which specify its destination.

6 After the vesicle is fused with the membrane, proteins could be secreted, or used in the membrane, as carriers for example.

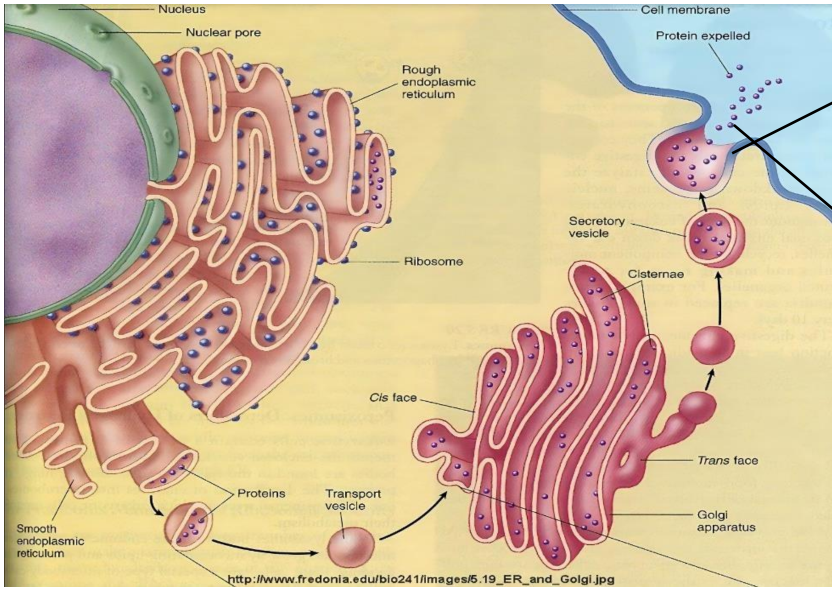


The cell is highly regulated, one of these regulations is the specificity of Golgi Apparatus in sending vesicles to their exact destination, for example, Golgi sends Na^+/K^+ pump exactly to Renal ISF part not to Tubular lumen part.

Terms Related to Vesicular Transport

A- Exocytosis:

We can transport molecules from the endoplasmic reticulum to golgi then to the plasma membrane towards outside the cell.



The fusing of vesicle with the

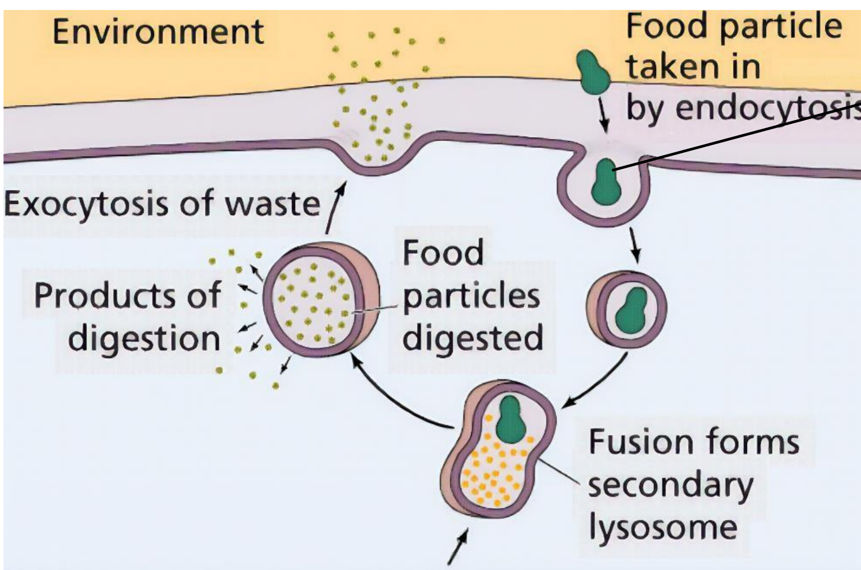
Secretion the content of the vesicle outside the cell.

↓

This is called Exocytosis.

B- Endocytosis:

Also we can have these vesicles fuse at the plasma membrane towards inside the cell.



A reversal of Exocytosis, engulfing particles into the cell.

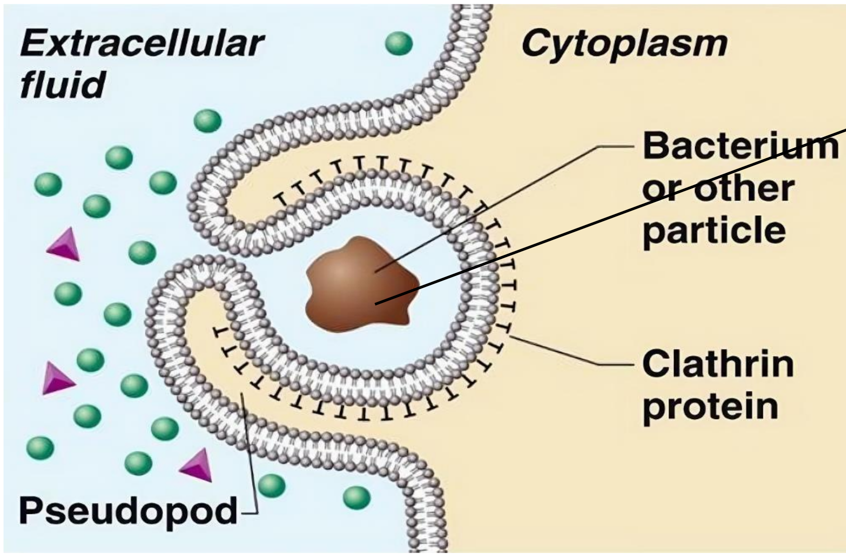
↓

This is called Endocytosis.

C- Phagocytosis: it's the same as endocytosis but the difference is the particles which have been ingested.

There are many cells having phagocytic function in our body.

These cells must recognize pathogens, for example antibodies on pathogens are recognized by phagocytic cells.



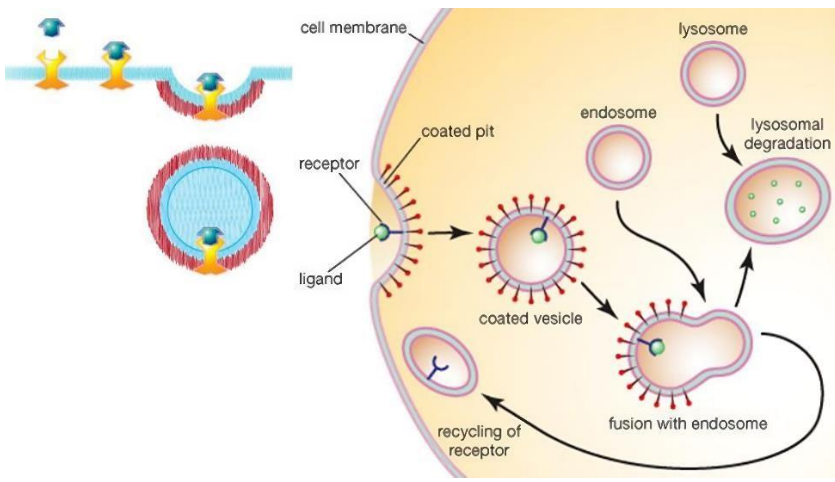
It's also Endocytosis, but engulfing Pathogens, Bacteria and Viruses.

Called Phagocytosis.

D- Receptor Mediated Endocytosis:

There are some particles that can be recognized by their specific receptor.

Once these Ligands bind to their receptor, the endocytosis will be activated.

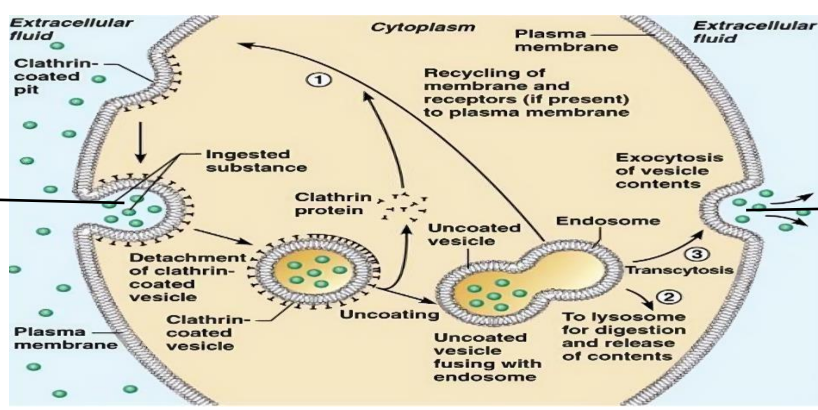


Lysosome will degrade the vesicle and destroy the Ligand.

The receptor will be recycled.

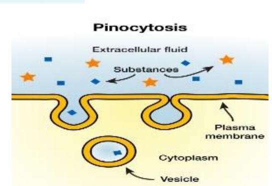
E- Transcytosis: transport across the whole cell.

Simply, particles will be engulfed by Endocytosis from one side of the cell.



And secreted by Exocytosis from other side of the cell.

Pinocytosis is a type of endocytosis in which a cell engulfs extracellular fluid, including dissolved substances, by forming small vesicles. It is often referred to as "cell drinking."

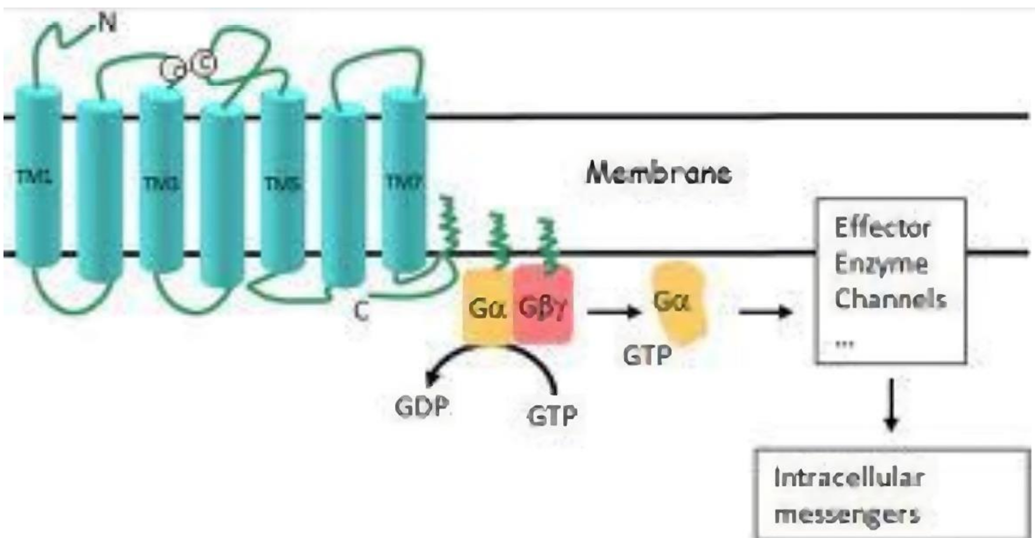


الدكتور تكلم عنه
وغير موجود
بالسلايدات

Control of Transport and Activity of Enzymes

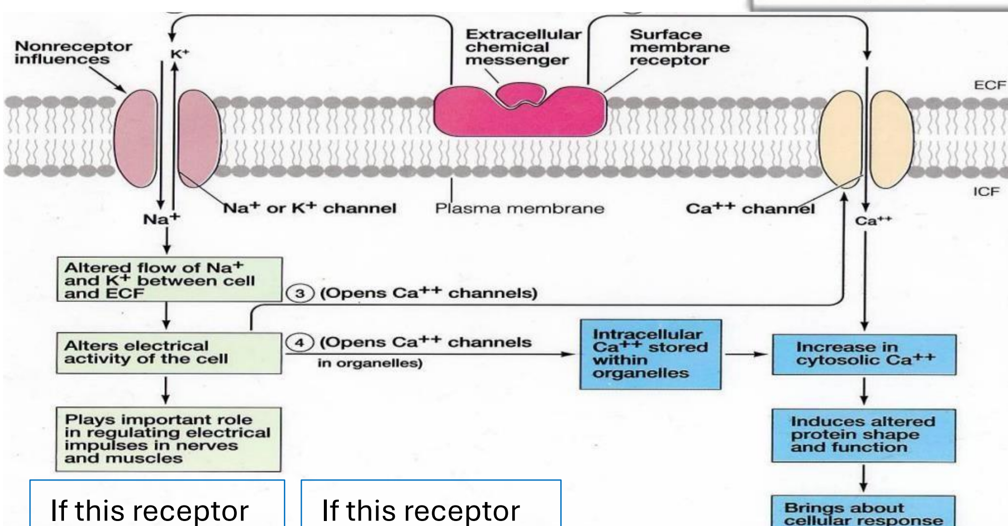
Over plasma membrane we have receptors, those receptors are specific, some of them are linked to channels through G-proteins (A group of protein structures, G because they use GTP). This is some sort of signal transduction mechanism that control the activity of the cell.

Once we have a ligand bound to the specific receptor, one of the G-protein subunits will dissociate (alpha subunit in this example), this subunit will cause the opening of sodium channel.



This picture isn't true, because the receptor is linked to two types of channels, Na^+ and Ca^{++}.

Each receptor could be linked to one type of channels.



Anyway, by these receptors we can control the activity of channels, by activating or deactivating them.

If this receptor link to a sodium channel, we will get more sodium ions moving from outside to inside.

If this receptor link to a potassium channel, we will get more potassium ions moving from inside to outside .

If this receptor link to a calcium channel, we will get more calcium ions moving from outside to inside .

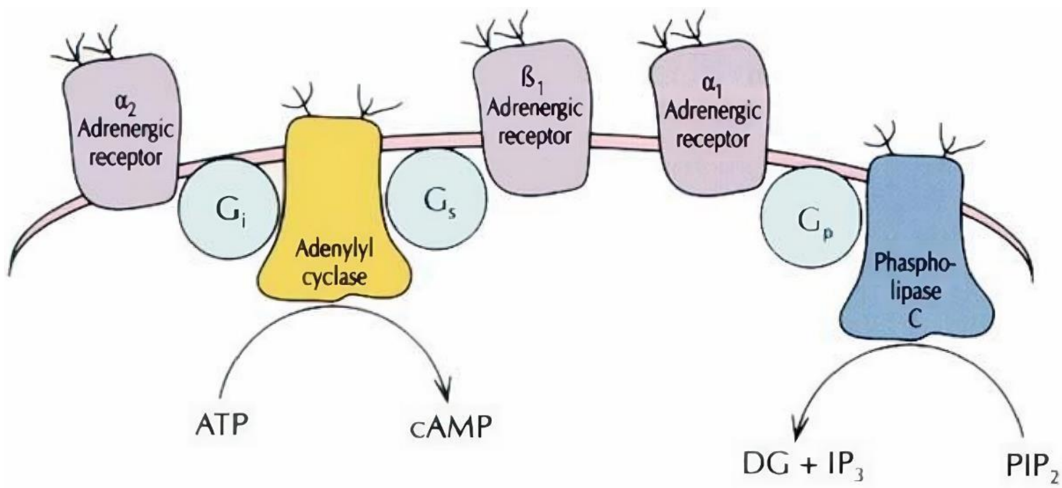
Also, the activity of channels can be controlled by specific enzymes, as you can see in the picture, we can have some type of receptors linked to:

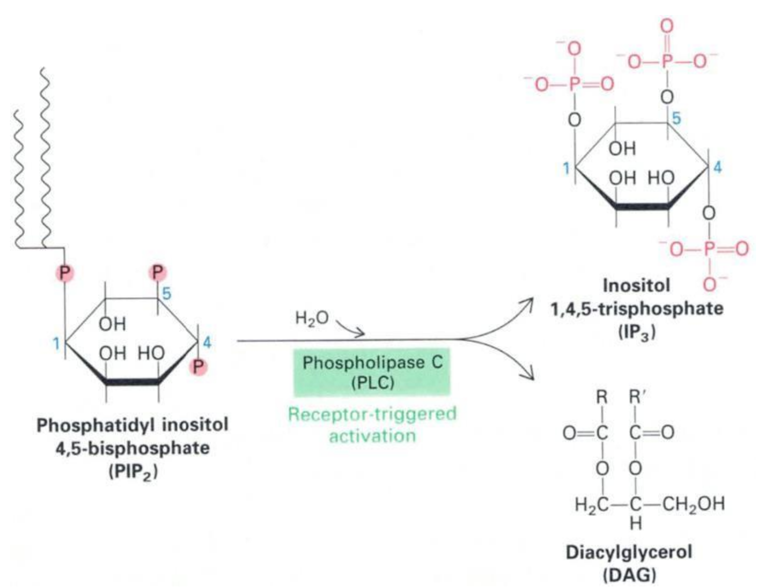
A- An enzyme called **Adenylyl cyclase**:

increases the concentration of cAMP, some channels according to the concentration of cAMP become more active.

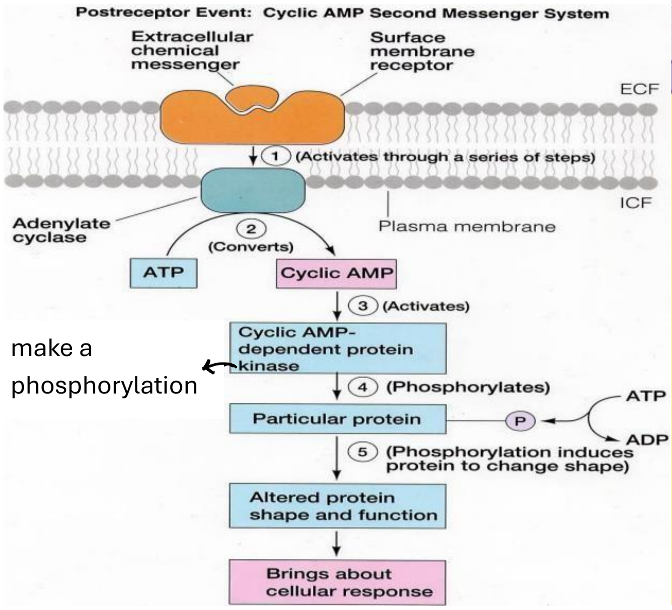
B- An enzyme called **Phospholipase C**:

Splits PIP_2 (Phosphatidylinositol 4,5-bisphosphate) into IP3 (inositol 1,4,5-trisphosphate) and DG (Diacylglycerol), IP3 can change the activity of Ca^{+2} channels on the membrane of endoplasmic reticulum causing the release of Ca^{+2} ions from the endoplasmic reticulum into cytosol to change the activity of that cell.

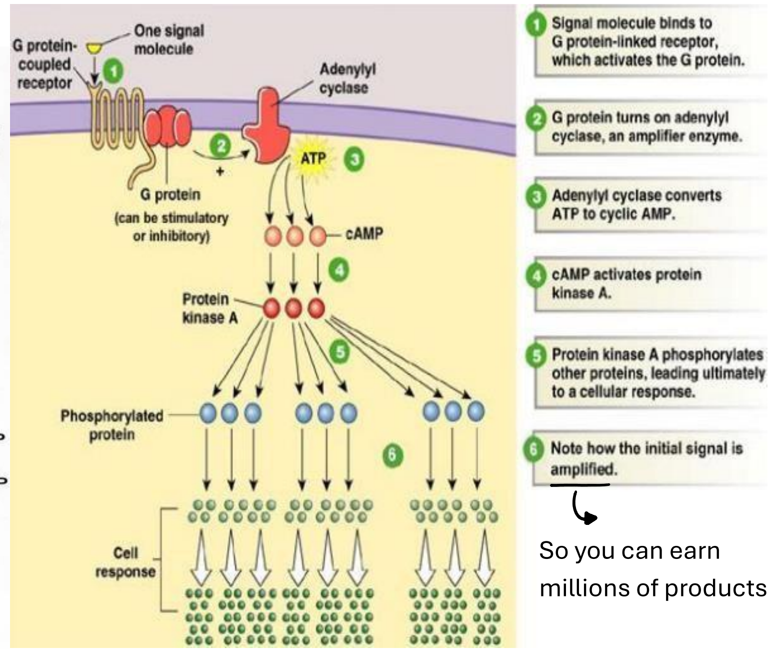




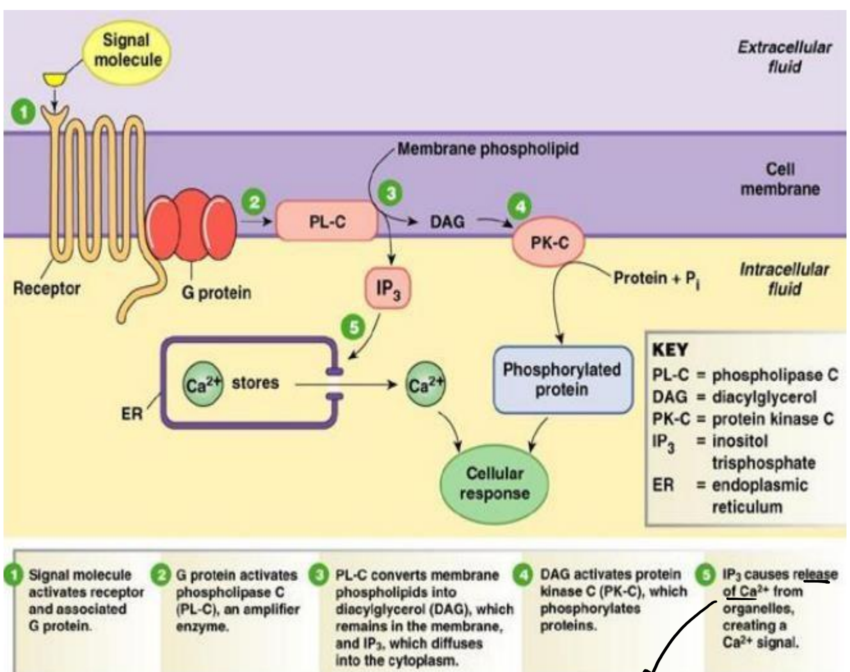
Extra pictures, our doctor didn't say more information about them than the above picture.



make a phosphorylation



So you can earn millions of products



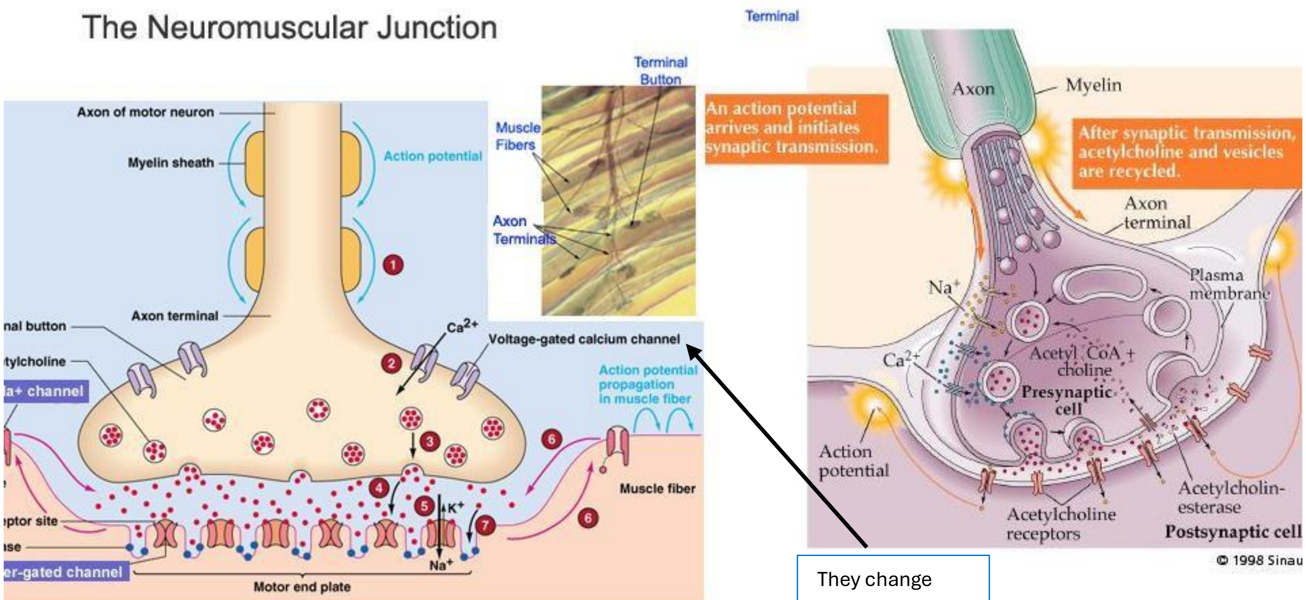
At the end of the endoplasmic reticulum there are some cells have receptors linked to a calcium channel, so by increasing IP_3 concentration , it causes release of calcium ions.

The calcium which stores in these type of cells, at the ER is about 10^{-3} mol and in the cytosol is very low 10^{-7} mol(greater 10000 times than in the cytosol).

Some called the calcium ions that released or IP_3 as a second message (that we have changed the activity inside cell by that messenger which is increased upon having the first messenger bound to its specific receptor.

Control of Exocytosis

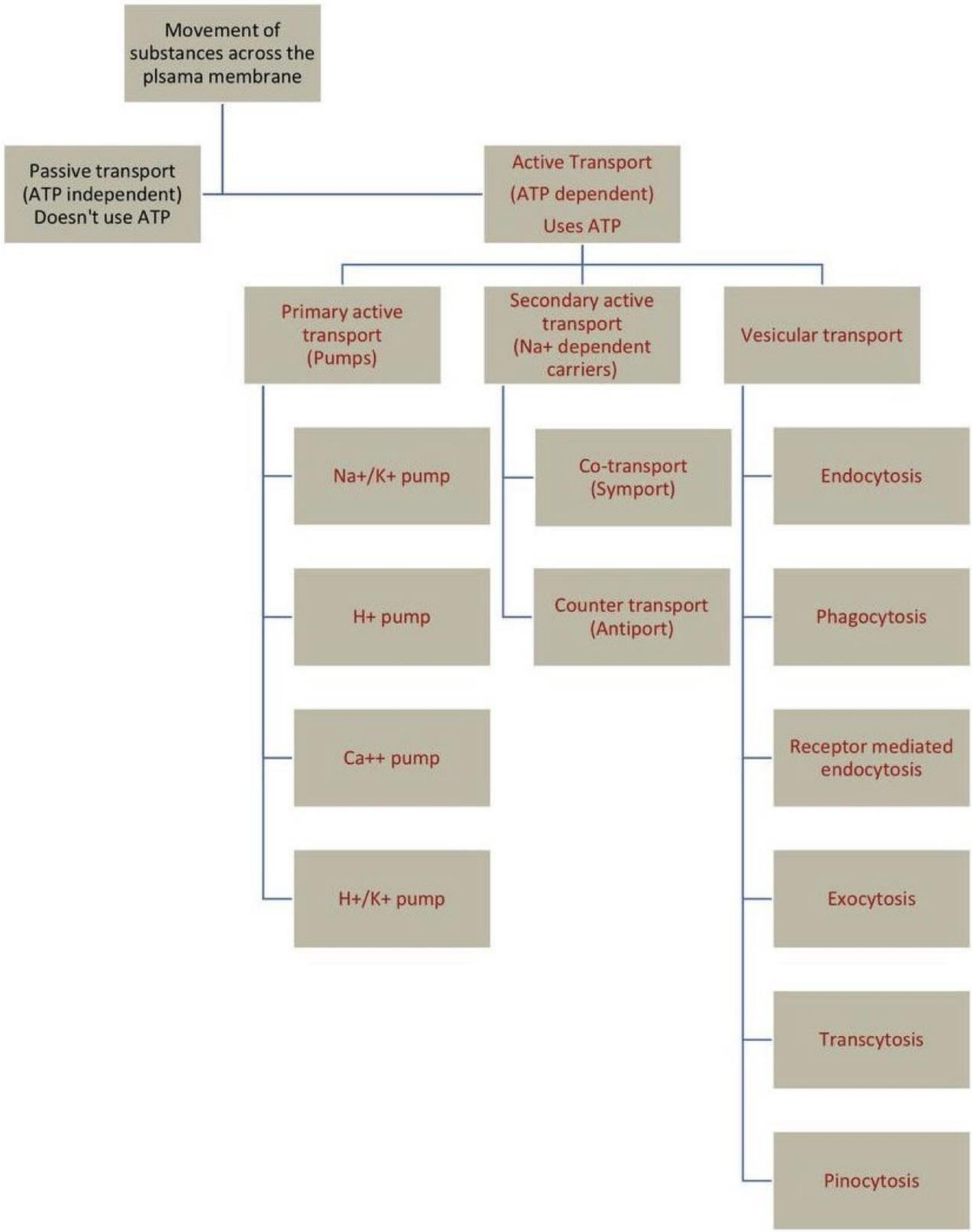
Exocytosis at the neuromuscular junction (NMJ) is the calcium-dependent release of acetylcholine (ACh) from motor neuron terminals, triggered by action potentials.



They change their activation (that open or close)according to the voltage changing

Transport Across Plasma Membranes

Summary



PROCESS	ENERGY SOURCE	DESCRIPTION	EXAMPLES
DIFFUSION			
Simple diffusion	Kinetic energy	Net movement of particles (ions, molecules, etc.) from an area of their higher concentration to an area of their lower concentration, that is, along their concentration gradient	Movement of fats, oxygen, carbon dioxide through the lipid portion of the membrane
Facilitated diffusion	Kinetic energy	Same as simple diffusion, but the diffusing substance is attached to a lipid-soluble membrane carrier protein or moves through a membrane channel	Movement of glucose and some ions into cells
Osmosis	Kinetic energy	Simple diffusion of water through a selectively permeable membrane	Movement of water into and out of cells directly through the lipid phase of the membrane or via membrane pores (aquaporins)
FILTRATION			
	Hydrostatic pressure	Movement of water and solutes through a semipermeable membrane (either through the plasma membrane or between cells) from a region of higher hydrostatic pressure to a region of lower hydrostatic pressure, that is, along a pressure gradient	Movement of water, nutrients, and gases through a capillary wall; formation of kidney filtrate

Transport Process	Description	Substances Transported
Osmosis	Movement of water molecules across a selectively permeable membrane from an area of higher water concentration to an area of lower water concentration.	Solvent: water in living systems.
Diffusion	Random mixing of molecules or ions due to their kinetic energy. A substance diffuses down a concentration gradient until it reaches equilibrium.	
Diffusion through the lipid bilayer	Passive diffusion of a substance through the lipid bilayer of the plasma membrane.	Nonpolar, hydrophobic solutes: oxygen, carbon dioxide, and nitrogen; fatty acids, steroids, and fat-soluble vitamins; glycerol, small alcohols; ammonia. Polar molecules: water and urea.
Diffusion through membrane channels	Passive diffusion of a substance down its electrochemical gradient through channels that span a lipid bilayer; some channels are gated.	Small inorganic solutes, mainly ions: K^+, Cl^-, Na^+, and Ca^{2+}. Water.
Facilitated Diffusion	Passive movement of a substance down its concentration gradient via transmembrane proteins that act as transporters; maximum diffusion rate is limited by number of available transporters.	Polar or charged solutes: glucose, fructose, galactose, and some vitamins.
Active Transport	Transport in which cell expends energy to move a substance across the membrane against its concentration gradient through transmembrane proteins that act as transporters; maximum transport rate is limited by number of available transporters.	Polar or charged solutes.
Primary active transport	Transport of a substance across the membrane against its concentration gradient by pumps; transmembrane proteins that use energy supplied by hydrolysis of ATP.	Na^+, K^+, Ca^{2+}, H^+, I^-, Cl^-, and other ions.
Secondary active transport	Coupled transport of two substances across the membrane using energy supplied by a Na^+ or H^+ concentration gradient maintained by primary active transport pumps. Antiporters move Na^+ (or H^+) and another substance in opposite directions across the membrane; symporters move Na^+ (or H^+) and another substance in the same direction across the membrane.	Antiport: Ca^{2+}, H^+ out of cells. Symport: glucose, amino acids into cells.
Transport in Vesicles	Movement of substances into or out of a cell in vesicles that bud from the plasma membrane; requires energy supplied by ATP.	
Endocytosis	Movement of substances into a cell in vesicles.	
Receptor-mediated endocytosis	Ligand-receptor complexes trigger infolding of a clathrin-coated pit that forms a vesicle containing ligands.	Ligands: transferrin, low-density lipoproteins (LDLs), some vitamins, certain hormones, and antibodies.
Phagocytosis	"Cell eating"; movement of a solid particle into a cell after pseudopods engulf it to form a phagosome.	Bacteria, viruses, and aged or dead cells.
Pinocytosis	"Cell drinking"; movement of extracellular fluid into a cell by infolding of plasma membrane to form a pinocytic vesicle.	Solutes in extracellular fluid.
Exocytosis	Movement of substances out of a cell in secretory vesicles that fuse with the plasma membrane and release their contents into the extracellular fluid.	Neurotransmitters, hormones, and digestive enzymes.

❖ D.MK's handout :

ACTIVE TRANSPORT:

As and example: Cells keep more K+ inside. The simple diffusion will cause K+ to move out of the cell. To maintain a constant and high 7K+ concentration inside the cell, K+ must be transported inside by other type of transport that can move K+ against a concentration gradient. Movement of particles against their concentration, electrical or pressure gradient is known as active transport. In this type of transport energetic compounds (ATP) are needed. The need for ATP could be by direct breakdown of energetic compounds by the ATP-ase activity of the carrier in Primary Active Transport, or by an indirect use of ATP as in Secondary Active Transport. All active transport systems are equipped with carrier proteins that move transported substances across membranes.

- PRIMARY ACTIVE TRANSPORT:

Examples of Primary active transport:

Na+ - K+ pump: This pump is able to expel 3 molecules of Na+ outside the cell and transport 2 K+ inside by a use of 1 ATP molecule. The carrier protein of this pump has 3 receptive sites for Na+ and 2 receptive sites for K+. Binding of 3 Na+ to the carrier protein in the inside and 2 K+ at the outside will cause activation of ATP-ase that split ATP into ADP and P. The liberated energy will cause conformational change in the carrier protein which results in extruding the 3 Na+ to the outside and transport of 2 K+ to the inside. The importance of this pump is to maintain concentration difference of Na+ and K+ across plasma and helps in the regulation of cell volume by controlling concentration of solutes inside the cell. The presence of high concentration of negatively charged proteins inside tends to attract positive ions. These particles tend to cause osmosis of water to the interior of the cell. If this is not controlled, the cells will swell until they burst. The presence of the pump that expels 3 particles outside for 2 transported inside represents a net loss of ions out of the cell, which controls water osmosis to the cell. In addition to that cell membrane is less permeable to Na+ than K+, which gives Na+ more tendency to remain outside the cell and reduce water osmosis.By expelling 3 positive ions for 2 transported inside, this pump will create positivity outside the cell and leaving deficit of positive ions inside of about. This electrogenic nature of the pump will create a potential difference of about (- 4mv) (if works alone) between the inside and the outside. Ca++ pump: cells maintain very low Ca++ concentration in their cytosol (10,000 times less of the concentration in ECF). The low Ca++ concentration is maintained by activity of two types of Ca++ pumps. One is found at plasma membrane and expels Ca++ to the ECF. The other is found on membranes of internal vesicular organelles such as sarcoplasmic reticular of muscle cells and mitochondria of most cells. By 8reducing Ca++ ions in the sarcoplasm (cytoplasm of muscle cells) by Ca++ pumps this will induce relaxation of muscle cells.H+ pump: Some cells are specialized in expelling H+, such as parietal cells of gastric mucosa, intercalated cells of the distal tubules and cortical collecting ducts in the kidney. The presence of H+ pumps at the lumenal side of plasma membrane in the gastric mucosa is responsible for decreasing the pH of gastric juice. While H+ of the lower parts of the nephron are responsible for controlling H+ concentration in the body.

- SECONDARY ACTIVE TRANSPORT:

The high Na+ concentration gradient between the cytosol and the extracellular fluid is maintained by the activity of Na+ - K+ ATP-ase pump. Cells are profiting from the tendency of Na+ to diffuse inside the cells and transport other molecules against their concentration gradient along with Na+ in case of secondary active co-transport or expelling other particles against their concentration gradient in exchange as in case of secondary active counter-transport. In this kind of transport cells are using ATP, but this use is to create a concentration gradient for Na+ (by the activity of Na+ - K+

pump). Then cells can use this concentration gradient to transport certain particles against their concentration gradient across membranes. The use of ATP is NOT direct as in pumps (it's indirect use).

Examples of co-transport:

Glucose and aminoacids are transported in the enterocytes (intestinal epithelial cells) during absorption by this mean of secondary active transport. The presence of low Na+ inside the enterocytes by the activity of Na+ - K+ pump at the basolateral membrane will create a driving force for movement of Na+ from intestinal lumen. Carriers at the lumenal membrane will not transport Na+ but only with a particle of glucose or aminoacid. Depends on the type of carrier, many protein carriers have been identified. For aa transport **at least 5 types** of carriers have been identified. As a result of this transport aminoacids and glucose are transported along with Na+ from the intestinal lumen and these carriers are specific. Other ions can also be transported by cotransport system, such as Fe++, Cl-, iodine and urate.

Examples of counter-transport:

Transport of Ca++ by secondary active transport:

In addition to its active transport by Ca++ pumps, Ca++ can also bind to specialized carrier that can move Na+ inside the cell in exchange with Ca++. This kind of transport is found in most cells including heart muscle. Transport of H+ by secondary active transport: This kind occurs in proximal tubules where Na+ moves from the lumen to the tubular cells in exchange for H+ which is counter-transported into the lumen. Other Modalities of Transport:

VESICULAR TRANSPORT:

Large particles can NOT pass membranes. But these particles are packaged and enclosed into vesicles by certain organelles, then these vesicles can fuse with the plasma membrane in case of transport from the intracellular to the extracellular compartment or engulfed into vesicles at plasma membrane, then transported inside. In the second case plasma membrane surround the substance that would be ingested by the cell then pinch off with the engulfed materials and form a vesicle. This mechanism is known as endocytosis. Vesicular transport can appear between plasma membrane and the membranes of organelles (such as lysosomes, Endoplasmic reticulum, etc) or between the membranes of organelles. When vesicles are transported through the whole cytoplasm (from one pole to the other pole of plasma membrane) the process is known as (transcytosis). If only fluids are transported by vesicular transport from the extracellular compartment, the process is called pinocytosis. When large and multimolecular particles are transported by endocytosis, the process is called phagocytosis.

The opposite of endocytosis is exocytosis. Large synthesized molecules such as enzymes, hormones, neurotransmitters are packaged into vesicles and transported toward plasma membrane. When these vesicles fuse with plasma membrane, their content is released into extracellular fluid.By vesicular transport not only secretory particles are transported toward plasma membrane, but also specific components of the membrane such as channels, receptors, and carriers are added to membrane by fusion of vesicles with plasma membrane. The release of vesicular content appears to be stimulated event in secretory cells. When the cell is triggered by stimulus, Ca++ increases inside the cytosol, which results in fusion of vesicles and secretion. An example of exocytosis is the release of neurotransmitter at neuromuscular junction. This release of transmitter from the nerve endings appears via Ca++ induced exocytosis.

Intercellular communication and signal transduction mechanisms:

The coordination of cellular activities is critical for maintaining homeostasis and survival of living system as well as control of growth and development of the body as a whole. In addition to cellular communication between cells by gap junctions, control systems that are found in the body, such as endocrine system, nervous system, and paracrine cells release particles (ligands) that can bind to specific receptor at the target cell and change its activity.

Cellular events after ligand binding to receptor:

1. Activation of channels:

When ligand binds to its receptor this activates membrane bound intermediary protein known as G protein (a protein composed of many subunits). The activation of G protein will induce opening of specific channel such as chemical gated Na+ channels. The opening of Na+ or K+ will change the potential difference across membrane, which in turn may cause activation (opening) of other type of channels known as voltage sensitive channels such as opening of voltage gated Na+ channels or voltage gated Ca++ channels.

2. Activation of second messenger system:

Binding of specific ligand to its receptor may result in activation of second messenger that relays order through a series of biochemical events to induce changes in cell activity such as metabolic, secretory, or contractile responses according to cellular function.

c-AMP as second messenger:

Binding of ligand will induce activation of G protein freeing the α subunit of G protein which activates a membrane bound enzyme known as adenylyl cyclase. This enzyme converts ATP to c-AMP. The formed second messenger will activate c-AMP dependent protein kinase which phosphorylates particular protein which in turn bring responses inside cell. The process is amplified inside the cell. Activation of one receptor may result in millions of end products of activated protein kinase enzyme.

Ca++ as second messenger:

Some G proteins activate other type of enzyme. In this pathway phospholipase C is activated. This enzyme breaks down **phosphatidyl inositol biphosphate** (PIP2) (a phospholipid molecule that is anchored to the inner side of plasma membrane). The products of PIP2 breakdown are **diacylglycerol** (DAG) and **inositol triphosphate** (IP3). The IP3 induces release of Ca++ from endoplasmic reticulum into the cytosol of the cell. Ca++ binds to and activates a protein called calmodulin. The activation of calmodulin triggers Ca++ dependent cellular responses by altering activity of other functional proteins inside target cells.

رسالة من الفريق العلمي:

عن ابنِ عبَّاسٍ رَضِيَ اللهُ عنهما، قال: كنتُ خَلفَ رَسولِ اللهِ صلّى اللهُ عليه وسلّم يومًا، فقال: ((يا غُلامُ، إنِّي أعلِّمُك كَلِماتٍ: احفَظِ اللهَ يحفَظْك، احفَظِ اللهَ تَجِدْه تُجاهَك، إذا سألْتَ فاسألِ اللهَ، وإذا استعَنْتَ فاستَعِنْ باللهِ، واعلَمْ أنَّ الأُمَّة لو اجتمَعَت على أن ينفعوك بشَيءٍ لم ينفعوك إلَّا بشَيءٍ قد كتبه اللهُ لك، واعلَمْ أنَّ الأُمَّة لو اجتمَعَت على أن يضُرُّوك بشَيءٍ لم يضرُّوك إلَّا بشَيءٍ قد كتبه اللهُ عليك، رُفِعَت الأقلامُ وجَفَّت الصُّحُفُ))

حين تخطو خطوةً كبيرة، **اتَّكِل بكُلّك على الله**، لا تَخَف، ولا تتردّد، استِعن تُعان، واعمل بكُلّ ثقلك صادقًا.

For any feedback, scan or click the code.

Versions	Slide #	Before	After
V0 → V1			
V1 → V2			