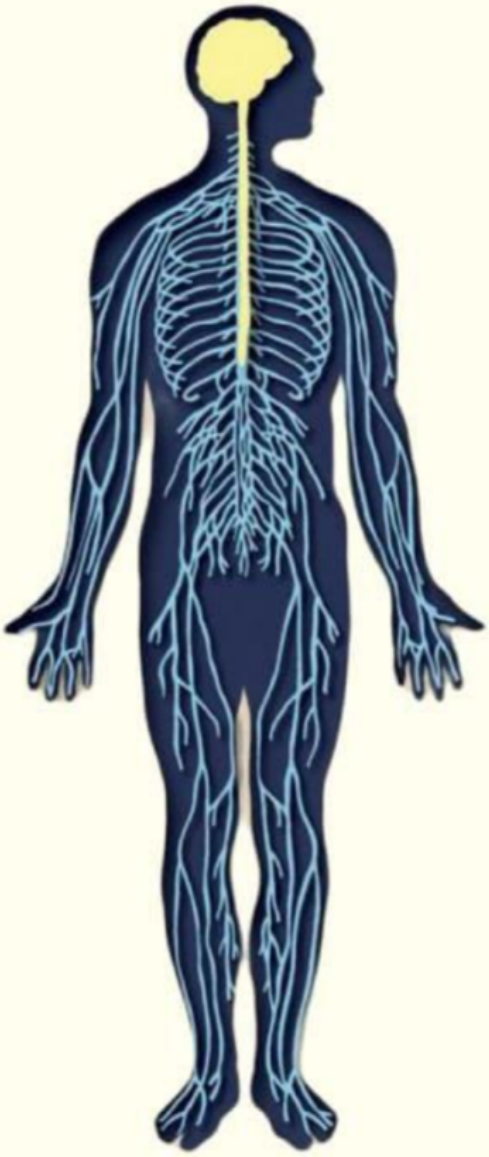
Wisdom
Dentistry 2023

SHEET NUMBER : 2B,3



2023

PHYSIOLOGY

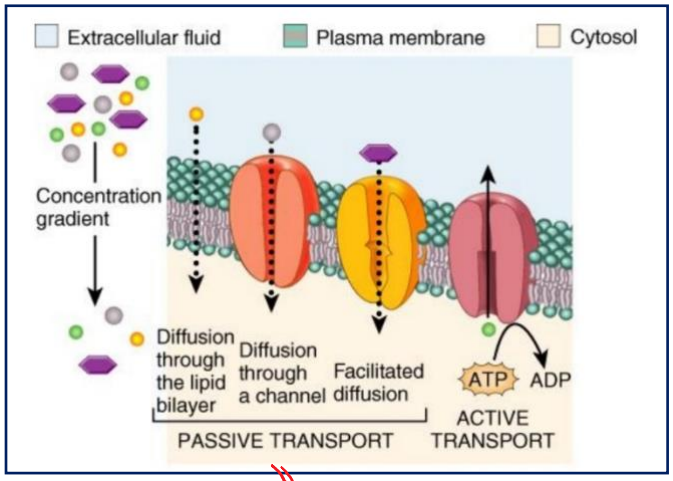
Written by: Sama Shannak
Ahmad Adel

Edited by: Leen Saleh

Doctor: MOHAMMED KHATATBEH

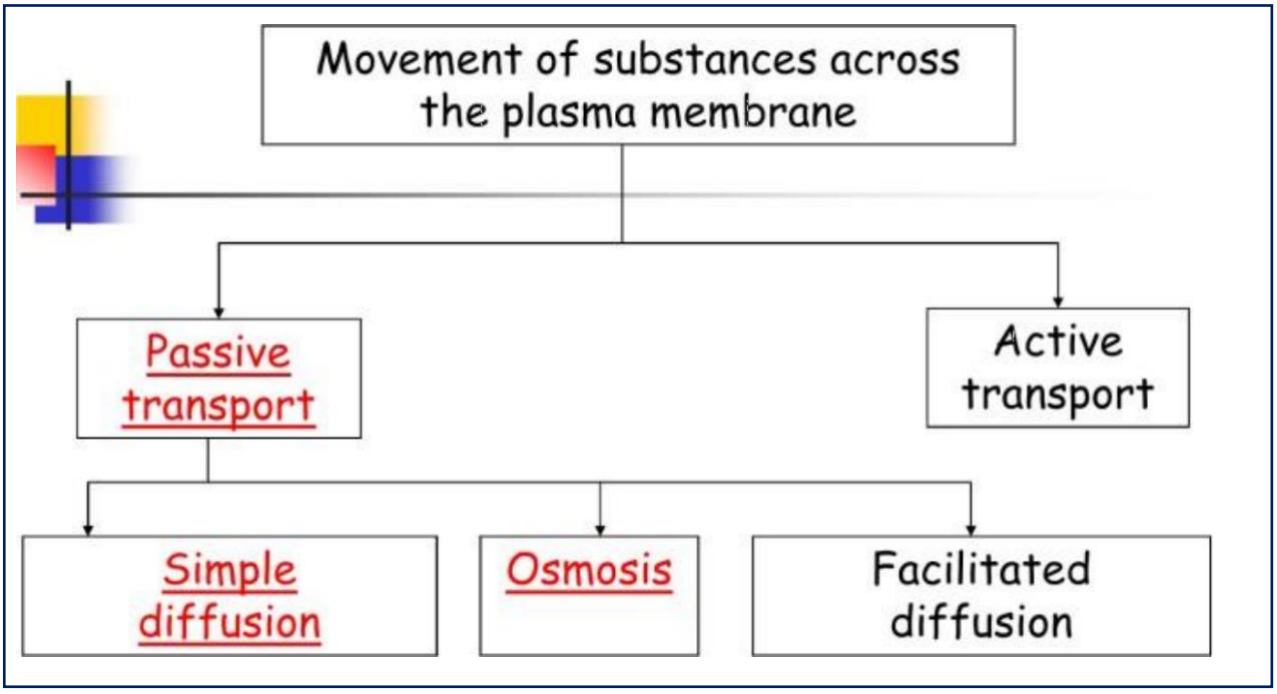
《Transport across Plasma Membranes》

In this lecture we will talk about transport modalities across the plasma membranes.
To understand the general idea of the transportation, you can follow the link below:



https://www.youtube.com/watch?v=A9ihz5gYxU4

We talked previously about the plasma membranes , and that we have proteins impeded in them . These proteins help with transportation across the membrane ,for example using carriers or channels.
But besides that, we can have some particles passing through the Lipid bilayer structure(its simply transported that way) . Also ,we have some carriers that consumes energy to transport particles from low to high concentration (we call it active transport modalities) .



■ **Diffusion** :

Generally, dissolved particles found in solution are in Constant movement. This random motion is due to thermal energy In particles that found themselves at a temperature above the Absolute zero (in living systems about 310 degrees K). The random Motion in liquids and gases will result in a random collision of Particles with each other and with the wall. These haphazard Collisions will cause a transfer of kinetic energy from one particle To another and change in the direction of motion. This continuous Movement in liquids and gases is known as diffusion.

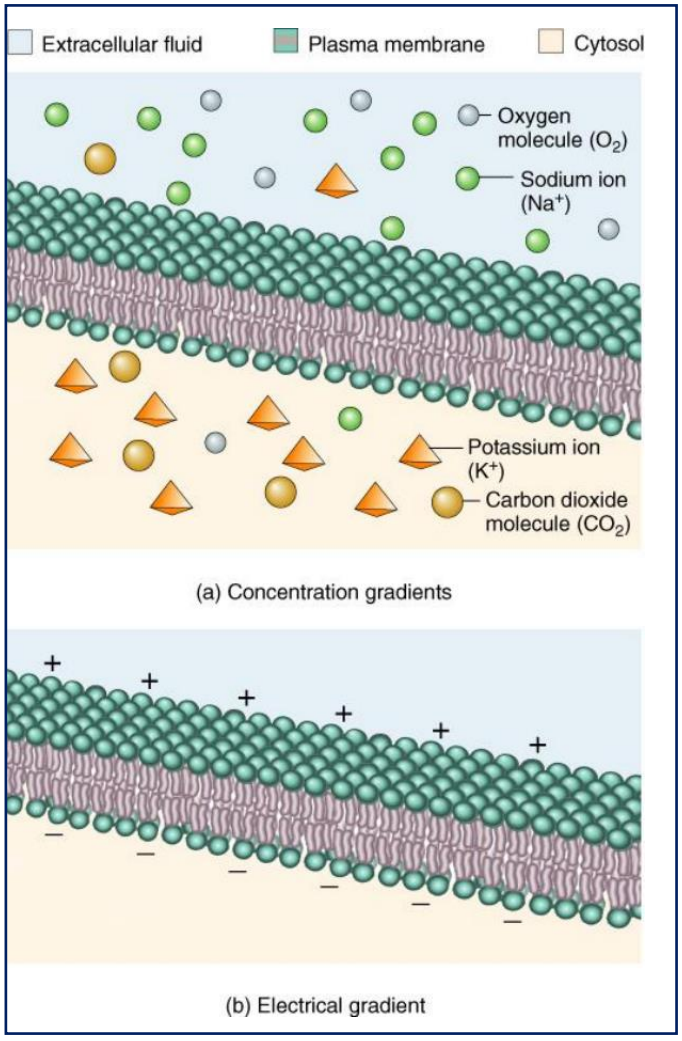
Particles can move across membrane by diffusion. This type of transport does not need consumption of energetic compounds ATP(Passive)

□ Diffusion through lipid Bilayer

● We have some particles (lipid soluble substances):

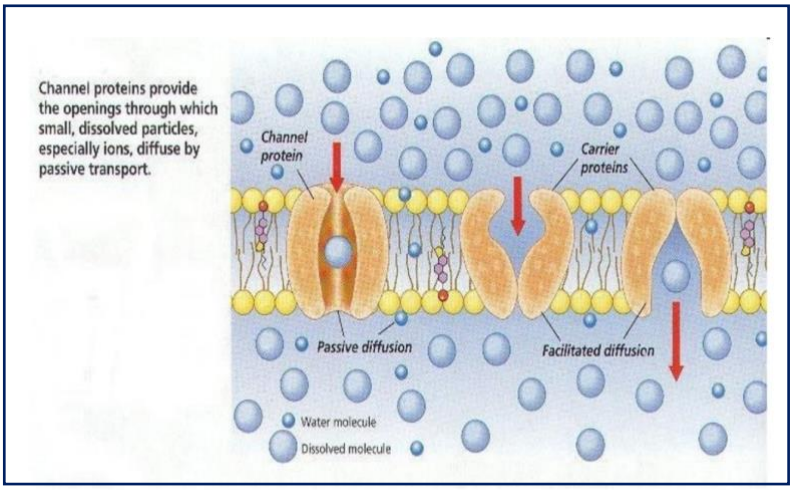
- *CO2*
- *O2*
- *NO*
- *Steroid Hormones*
- *Monoglycerides*

These can move through the Lipid bilayer structure (Their diffusion depends on the solubility of particles in the lipid bilayer.)



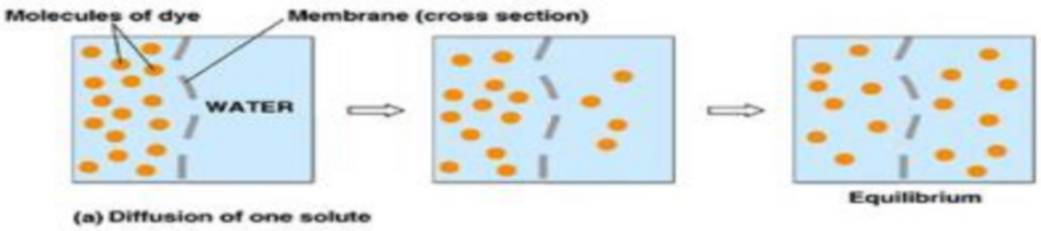
□ Diffusion through channels

Other particles (<u>charged particles for example or bigger particles</u>) , we need protein structures that can help them to move across the membrane.

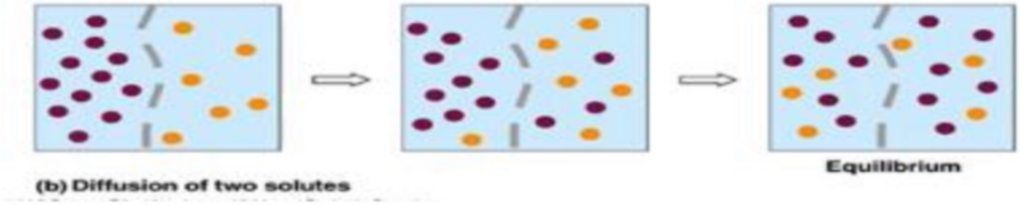


•The Concept of Simple Diffusion

In this example, we have a membrane that separate two compartments, one contains number of dies and the other is empty. The dies start to move (**downhill**) from the higher concentration to the lower concentration until it reaches a state of **Equilibrium** where the **net diffusion is zero**. Equilibrium <u>doesn't mean</u> that there are no diffusion between the two compartments, it means that **the rate of diffusion to the right is <u>the same</u> rate of diffusion to the left**.(net diffusion=zero)



This example is the same as above, but notice that there are **two different dies** (**red** and yellow), the movement of each particle depends on it **its own concentration** gradient throw the membrane,not the number of all particles in each compartment.(the yellow dies move according to the number of only yellow dies in each section, not the number of red and yellow dies).



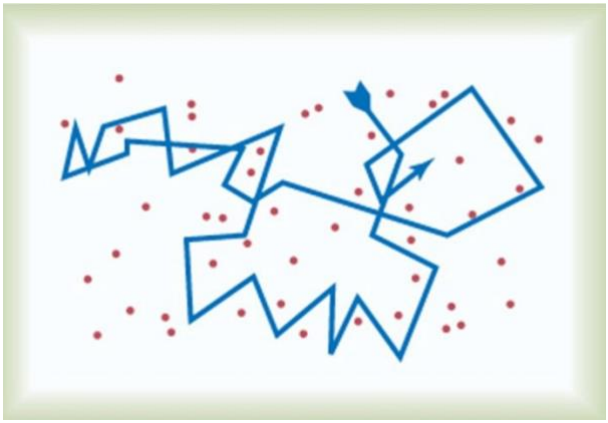
So ,For simple diffusion we need :

- the membrane to be semi-permeable for the substance/both substances.
- to have low concentration in one compartment and high concentration in the other one .
- we don't need to consume Macro-energetic molecules (ATP)

instead

❖ The energy is held in the particle, its called ***KINETIC ENERGY***

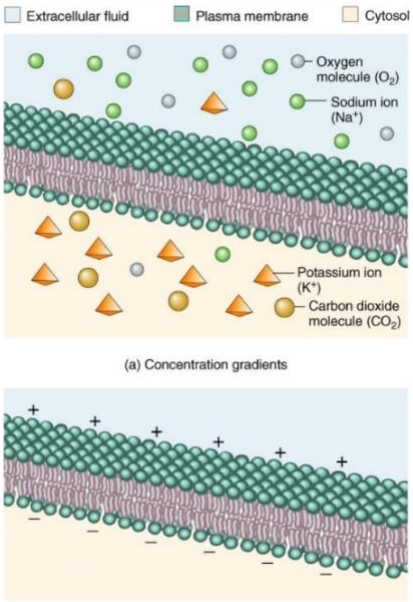
(If you have high concentration in a compartment, you have high kinetic energy in that compartment, and so on).



Simple diffusion

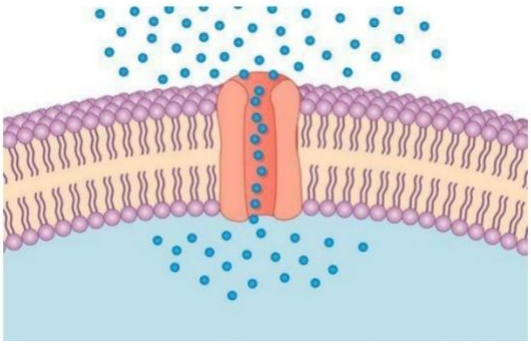
Diffusion through lipid bilayer

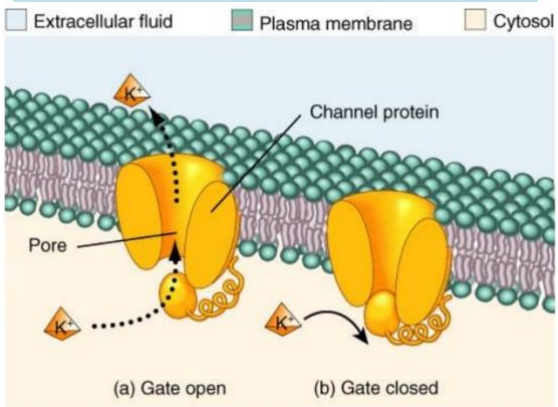
- CO_2
- O_2
- NO
- Steroid Hormones
- Monoglycerides



(a) Concentration gradients

Diffusion through Channels





* changing the permeablity *

■As we said , diffusion depends on the permeability of the membrane and the concentration gradient.

Fick's Law

- $J = P.\Delta C$
- $P = D.A/\Delta X$
- $J = D.A.\Delta C/\Delta X$

J = Flux (Rate of diffusion)
P = Permeability
D = Diffusion Coefficient
A = Surface area
C = Concentration
X = Membrane thickness

This law combines these parameters to **calculate the rate of diffusion**

■ Diffusion net rate:

the number of particles that moves from one side to another .
(more precisely : [from high to low - from low to high])

▪ One of the **factors** that influence the Rate of net diffusion is **concentration gradient** (ΔC= CA-CB), which represents the Chemical Potential for movement of particles across membranes.

▪ In addition to concentration gradient, net rate of diffusion (Q) Depends also on:

❖ **Permeability** of the membrane to a given substance (P): the Higher the permeability for a substance the greater the diffusion rate is Through membrane.

❖ **Surface area** of transport (A): diffusion increases by increasing (A). The increase in surface area in biological membranes will result in More protein channels that can be used for diffusion from one

Compartment to another.

❖ **Molecular weight** (MW): lighter molecules move more quickly Than heavier.

❖ **Membrane thickness** (X) (distance of movement): the greater the Distance the slower the rate of diffusion.

■ All these **factors** form the Ficks' law of diffusion:

- J = P.ΔC…….(J = Flux, P=Permeability, ΔC = Concentration gradient)
- P = D.A/ΔX ……. (, A: surface Area, ΔX = membrane Thickness)
- J = D.A.ΔC/ΔX…… (D=Diffusion Coefficient)

In addition to all these factors, diffusion can also be *influenced* by:

➢ Effect of membrane electrical potential: mainly influences Electrically charged particles.

The presence of a negative potential inside the cell prevents movement of negative (-) charged particles from the extracellular Compartment to the intracellular compartment and the positive charged particles from the intracellular to the extracellular compartment.

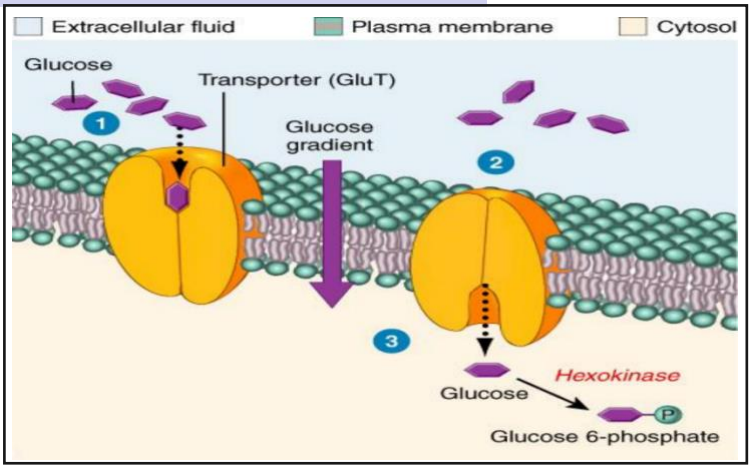
⊖ : outside → inside ⊕ : inside → outside

So, movement of charged particles is governed by an electrochemical Potential. This will be discussed in more details later.

➢ Effect of pressure:

The presence of pressure difference between two compartments will cause more kinetic energy in particles in the compartment with Higher pressure. This will cause movement of more particles from the High pressure side to the low pressure side.

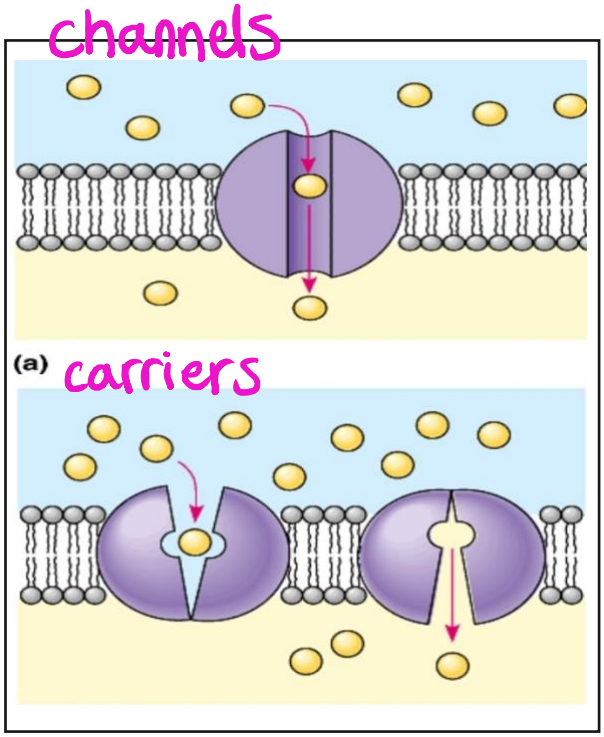
Facilitated Diffusion



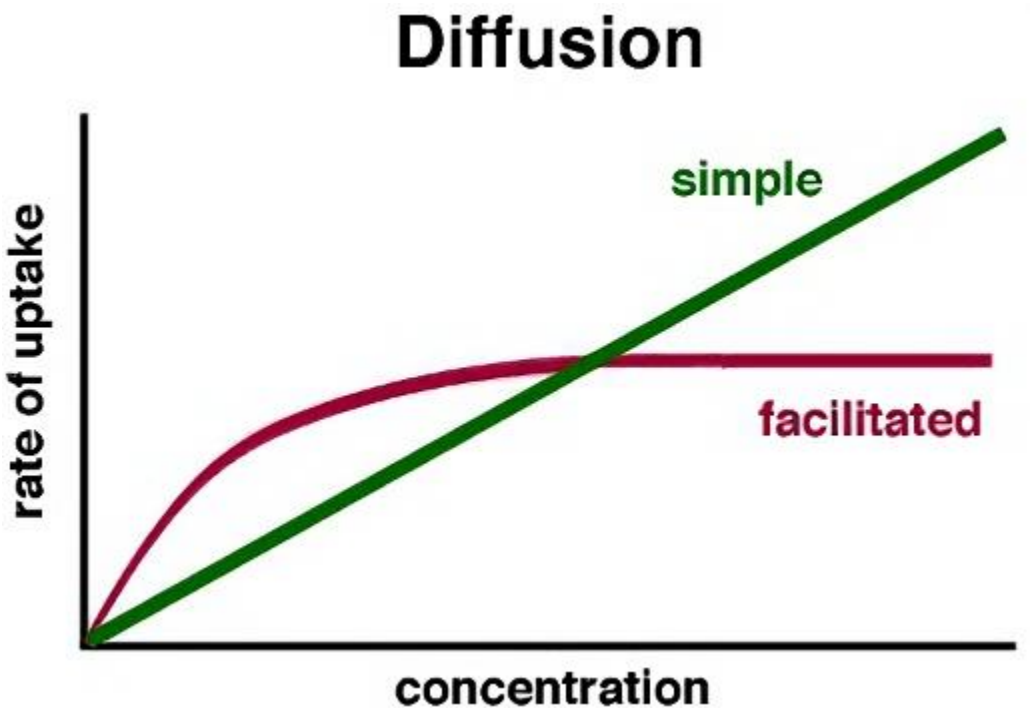
● Sometimes, we need to transport bigger molecules .For these particles, we don't have channels , instead we have carriers that can help these particles to transport across the plasma membrane.
These carriers are specific,
(for example, we have specific carriers for glucose different from the carriers of galactos, and so on).
These carriers have binding sites for these particles, it an get some changes in the protein structure so it can move the particles **from high concentration to low concentration**.

▪ Examples on big molecules:

- Aminoacids
- Glucose
- Galactose
- Fructose



Kinetics of Diffusions



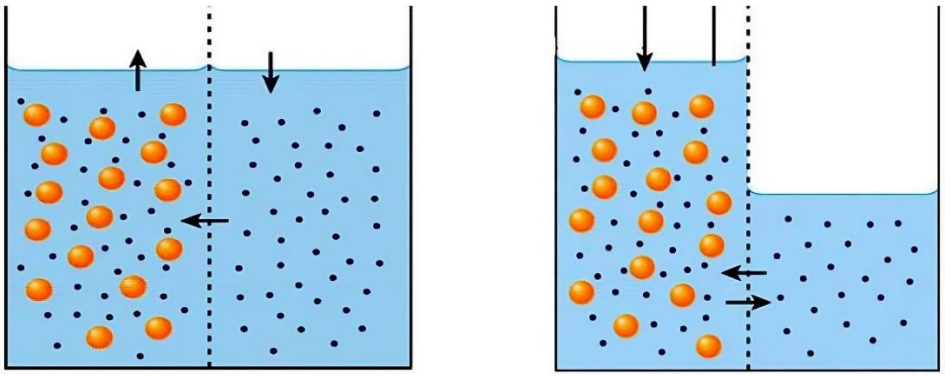
As you can see, the simple diffusion curve is linear and always **increasing**, but the facilitated one is increasing at the beginning, and after one point it will stop increasing, this is the **limitation point** and at this point it have the maximum velocity of transport (Vmax), why this happens? Because we have a **limited number of carriers**, when all these carriers are busy in transporting (they are all under using) even if we increased the concentration of specific particle on one side, these carriers won't be able to transport these particles to the other side, **so the curve will stop increasing**.

Now we should go back to the channels, channels follow simple diffusion curve, so at this point they are considered as simple diffusion, but as we mentioned before, channels are protein structures, and for that they should be considered as facilitated diffusion, from our doctor perspective they are just "**diffusion**", neither simple nor facilitated.

At this point you should ask: The number of carriers is limited, and the channels number too, so why there is limitation point in the curve of facilitated diffusion (carriers) and not in channels (as we mentioned above, they follow simple diffusion curve)?
The answer is: as long as the channel is opened, any number of particles can pass through it, but carriers must do this particle by particle.

Osmosis

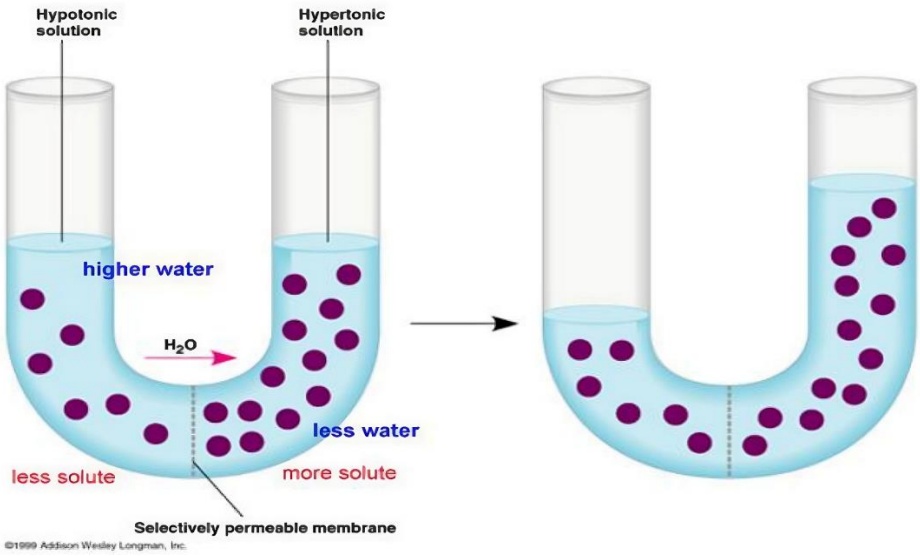
If we assume that there is a membrane that it's not permeable for particles, and permeable for water, what will happen? The water will move from the compartment that has a **high** concentration of **water** to the **low** one, in other words: from **low** concentration of **particles** to **high** concentration of **particles**, this is **Osmosis**.



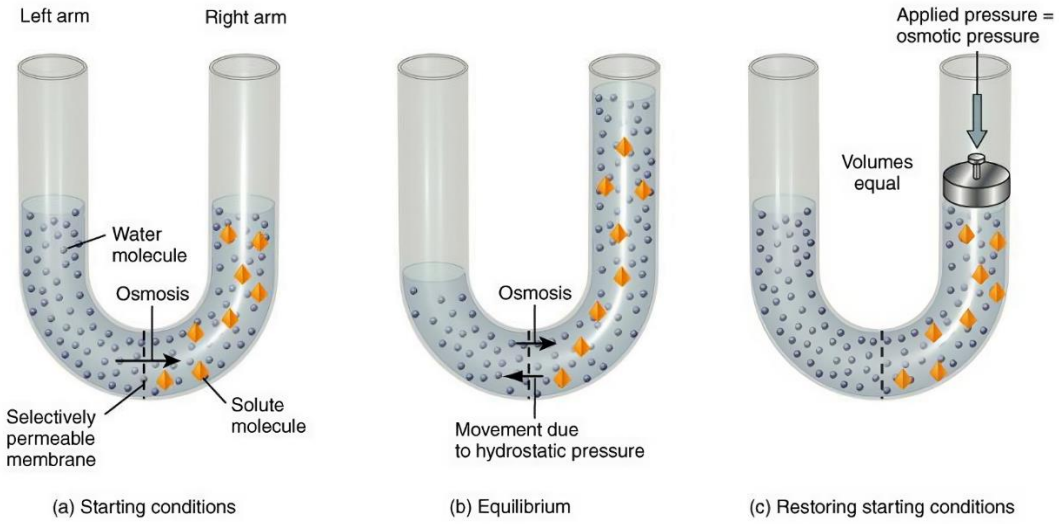
We can reach equilibrium in osmosis.

We reach equilibrium in osmosis when hydrostatic pressure is created.

Hydrostatic pressure opposing more movement of the water is called **the osmotic pressure of that solution**, here is another example:

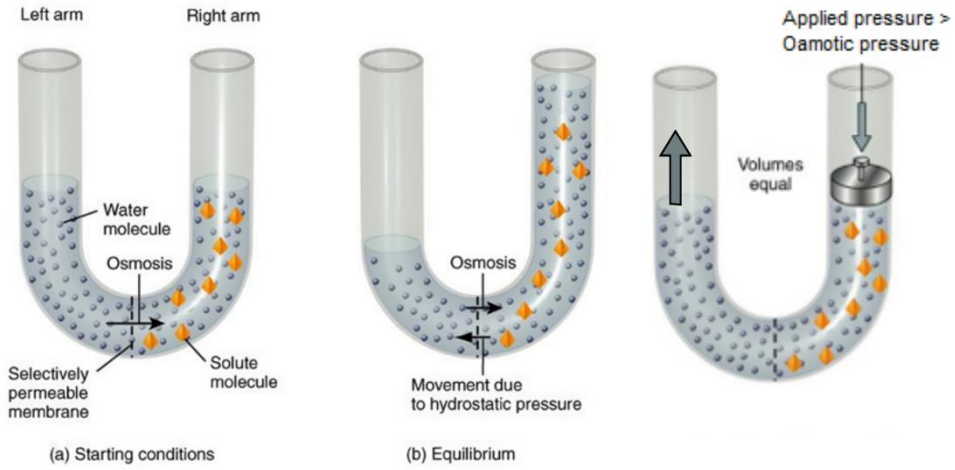


What if we applied external pressure that is opposite to osmotic pressure and equal to it? Look at the next page.



Simply, if we applied an external pressure that is opposite and equal to the osmotic pressure, we will go back to the starting condition.

Did you think about applying an external pressure that is more than the osmotic pressure and opposite to it? The water will move from the lower to the higher concentration of it, this is called **filtration**.



Van't Hoff's Law

$$\pi = RTC$$

π = osmotic pressure

R = Gas constant

T = Absolute temperature

C = Concentration

-Osmatic pressure depends mainly on the molar concentration or molarity of a solution.

-**Important note:** the equations are for understanding the correlation between the elements (positive/negative), solving with numbers isn't required.

Osmole, Osmolality and Osmolarity

We know that if we get a specific grams of particle that is equal to its molecular weight, then we have 1 gram molecular weight of it, as an example: glucose molecular weight is 180 grams, so if we have 180 g of glucose, then we have 1 gram molecular weight.

Osmole: A unit used to express the concentration of a solution in terms of numbers of particles in place of grams.

Based on that, if we have 180 grams of glucose, then we have 1 osmole of glucose.

In glucose situation, the glucose doesn't dissociate into ions in water, so we said **1 osmole**, but what if we are dealing with something that dissociate into ions in water?

Let's take sodium chloride as an example, if we have 58.8 grams of it (equal to its molecular weight) then we have 1 gram molecular weight of sodium and 1 gram molecular weight of chlore, if we are talking in terms of osmosis, that's **2 osmoles**.

If we take a solution that has 1 osmole of solute dissolved in each kilogram of water is said to have **Osmolality** of 1 osmole per kilogram.

If we take a solution that has 1 osmole of solute dissolved in each liter of water is said to have **Osmolarity** of 1 osmole per liter.

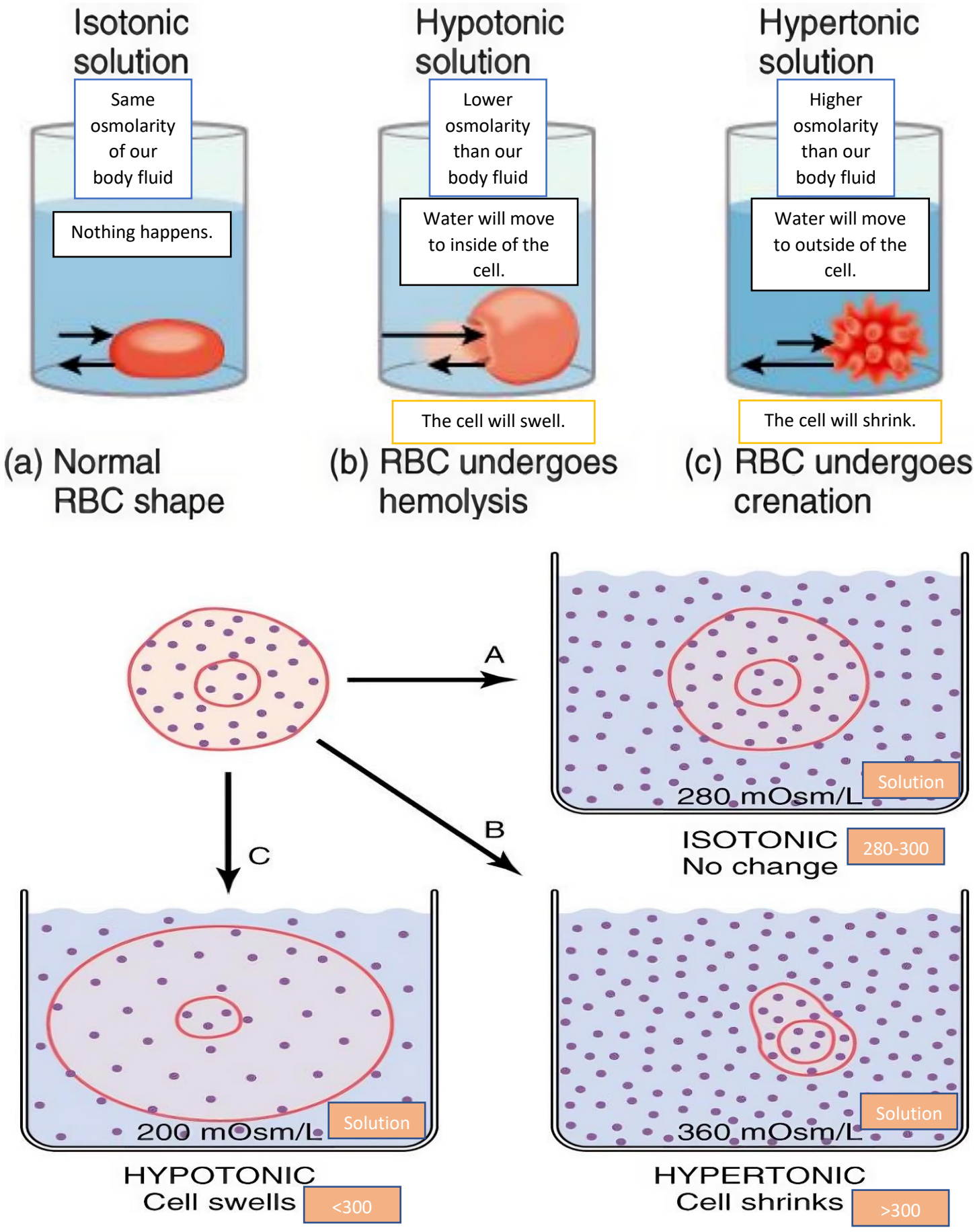
To sum up:

1 gram molecular weight -> 1 osmole

Osmolality -> osmole per kilogram

Osmolarity -> osmole per liter

Our cells contain a fluid, that is in composition has differences with extracellular fluid, but they must be similar in osmolarity, why? Let's find out on the next page.

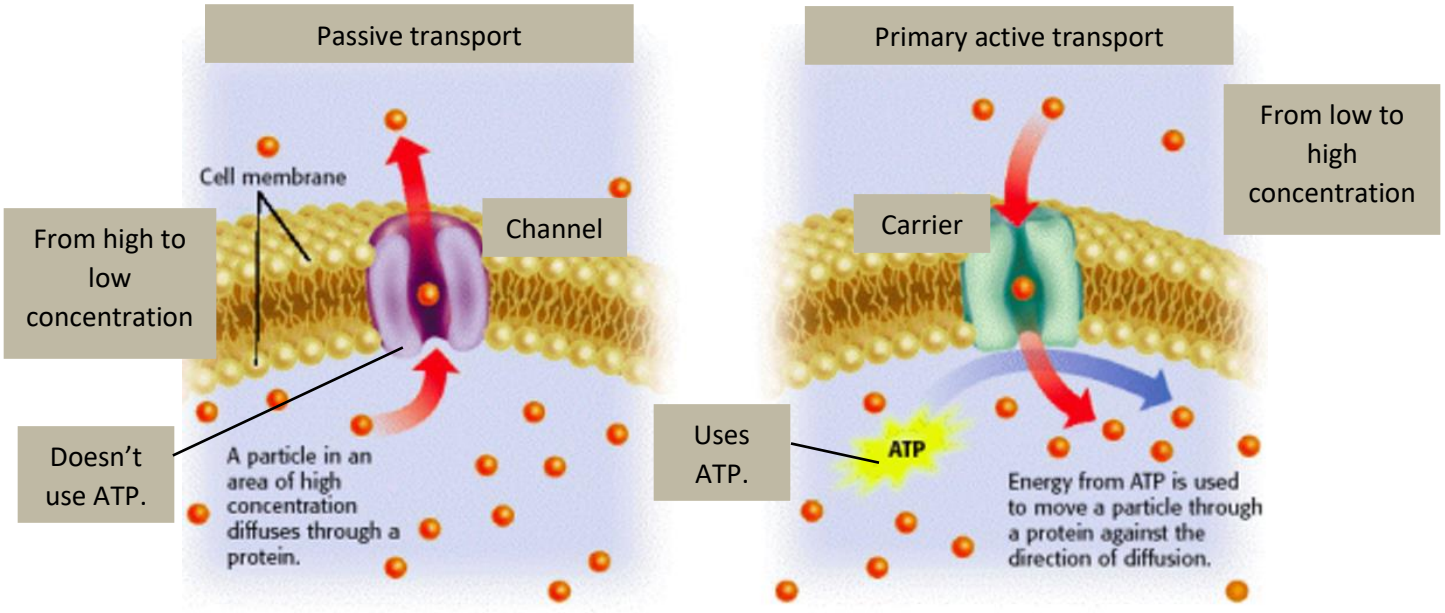

Isotonic solution
Same osmolarity of our body fluid
Nothing happens.
(a) Normal RBC shape
Hypotonic solution
Lower osmolarity than our body fluid
Water will move to inside of the cell.
The cell will swell.
(b) RBC undergoes hemolysis
Hypertonic solution
Higher osmolarity than our body fluid
Water will move to outside of the cell.
The cell will shrink.
(c) RBC undergoes crenation
A
B
C
280 mOsm/L
Solution
ISOTONIC
No change
280-300
200 mOsm/L
Solution
HYPOTONIC
Cell swells
<300
360 mOsm/L
Solution
HYPERTONIC
Cell shrinks
>300

Active Transport

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

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.

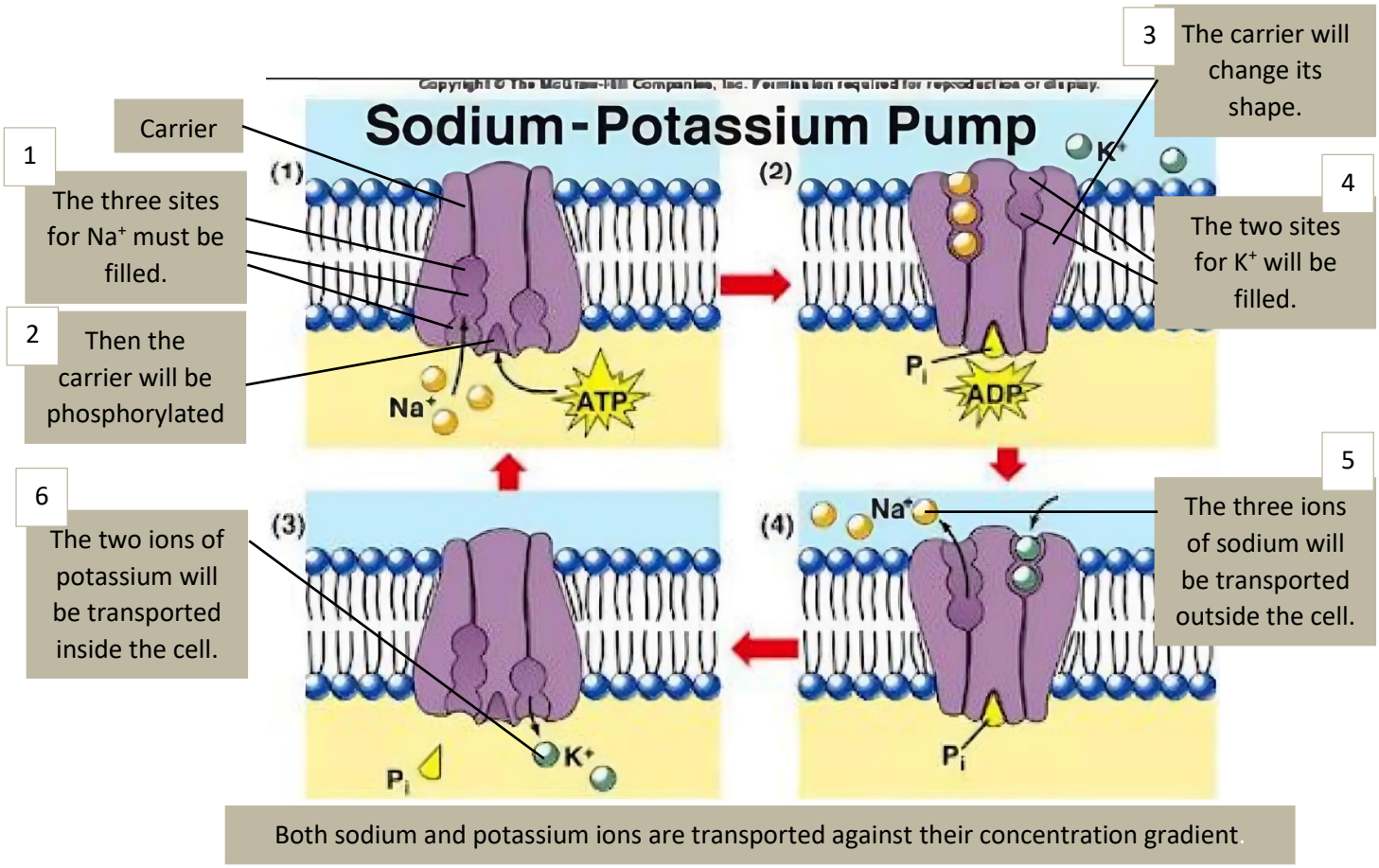


Pumps are carriers, whenever you hear "**Pump**" you should know it's **primary active transport**.

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

A- Na⁺/K⁺ pump:

Transporting sodium and potassium, there is a high concentration of sodium outside the cell, and high concentration of potassium inside, 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.



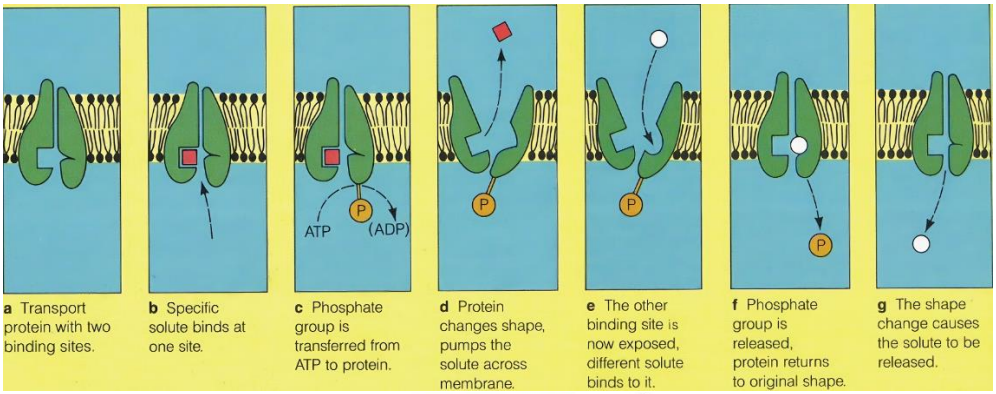
Both sodium and potassium ions are transported against their concentration gradient.

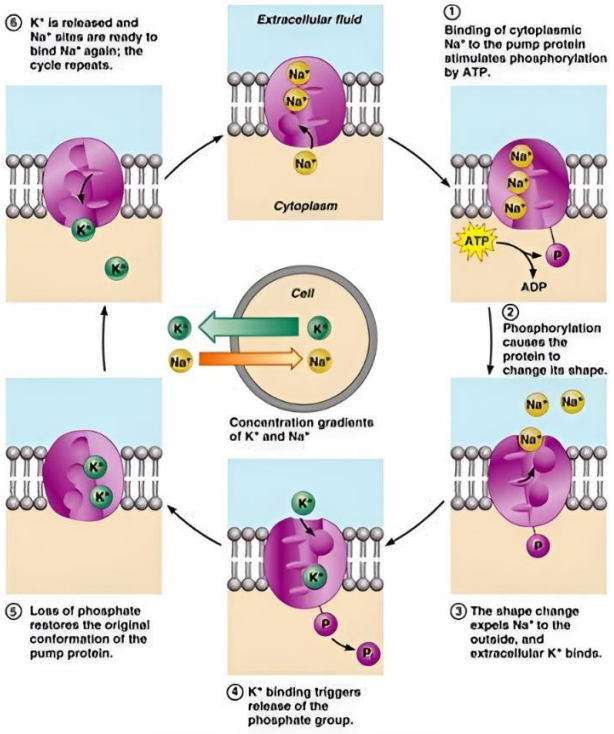
You noticed that this pump keeps high concentration of sodium outside the cell (by transporting 3 sodium ions outside the cell), you will know that this high concentration of sodium outside the cell leads the secondary active transport when we talk about it.

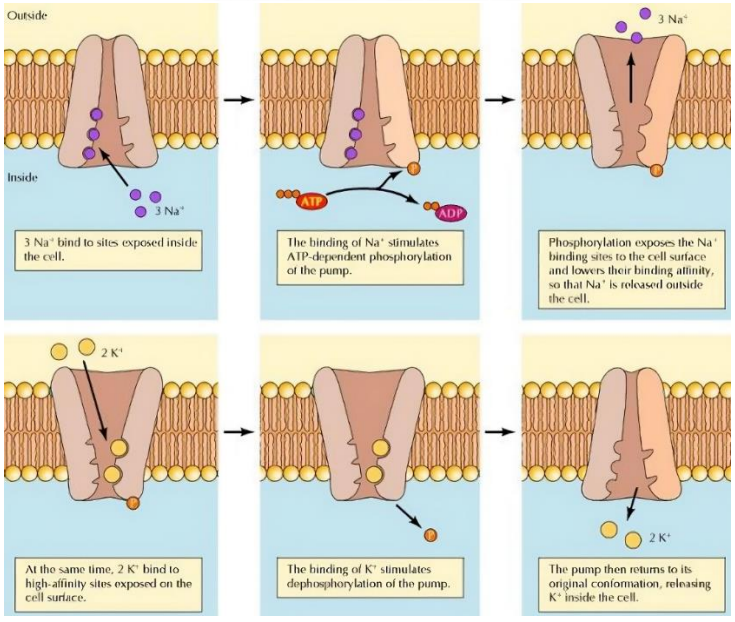
Now imagine if this pump isn't working, what will happen? The sodium ions will have a high condense to diffuse inside the cell (from high to low concentration), and the osmolarity inside the cell will increase, leading the cell to be swelled (burst).

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

These are extra pictures of this pump, our doctor didn't say more information about these pictures than the above picture.







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**.

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.

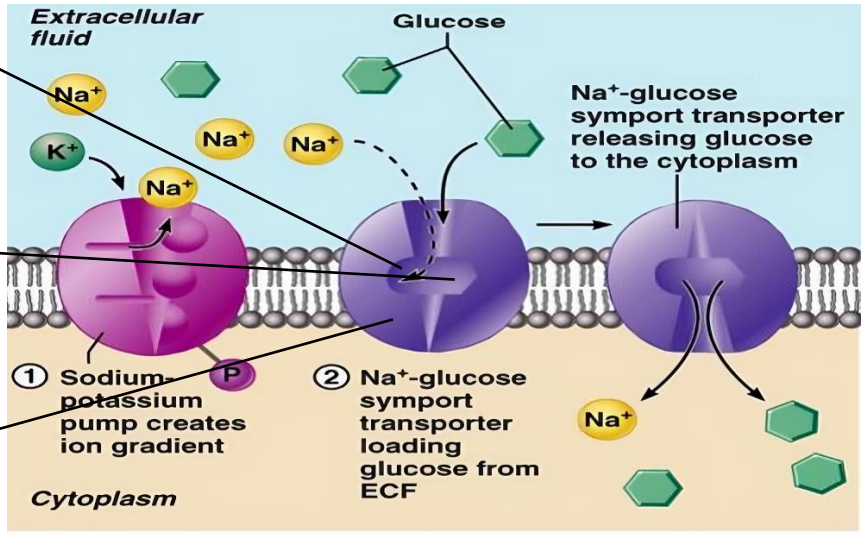
2-Secondary active transport:

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

A binding site for Na^+.

A binding site for another particle.

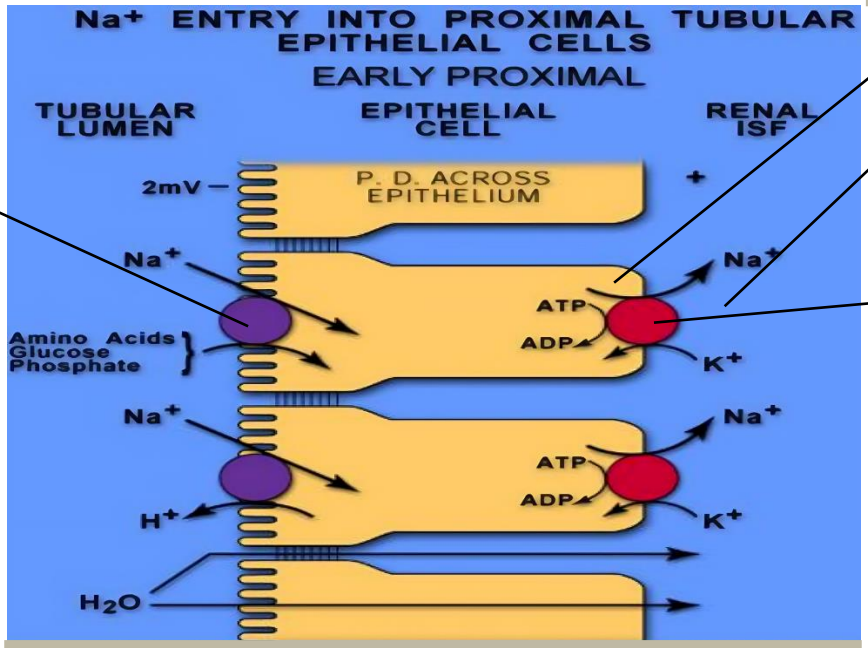
This carrier is called **sodium dependent carrier**.



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.

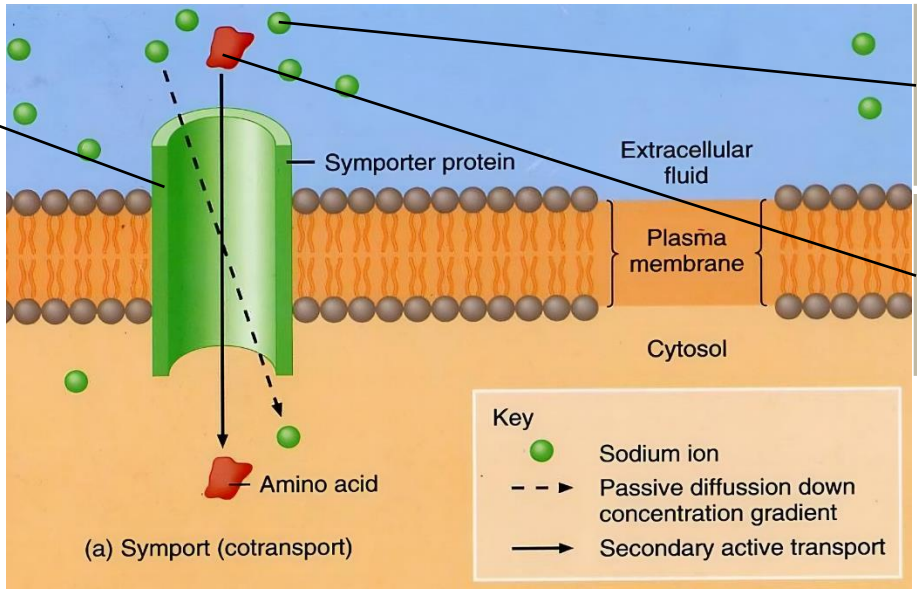
A- Co-transport:

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.

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.

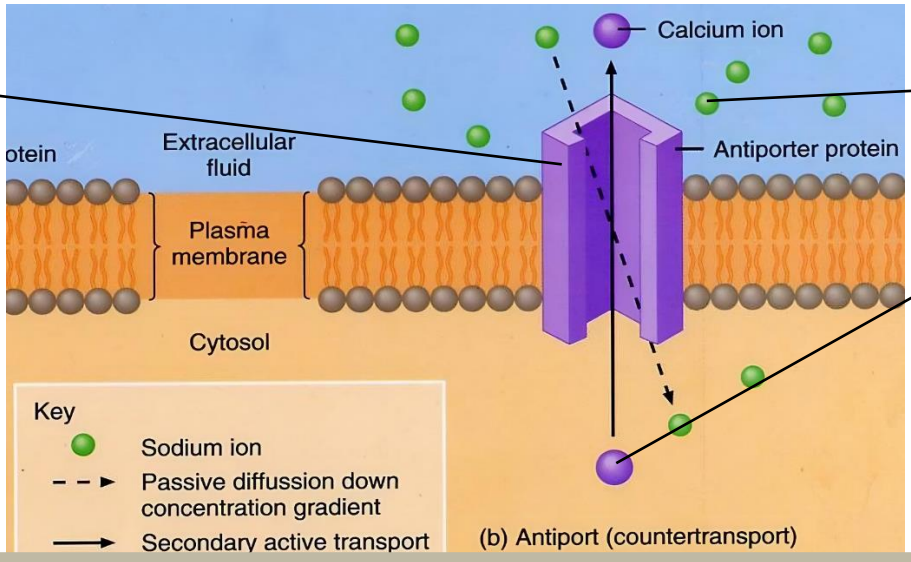
B- Counter transport:

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.

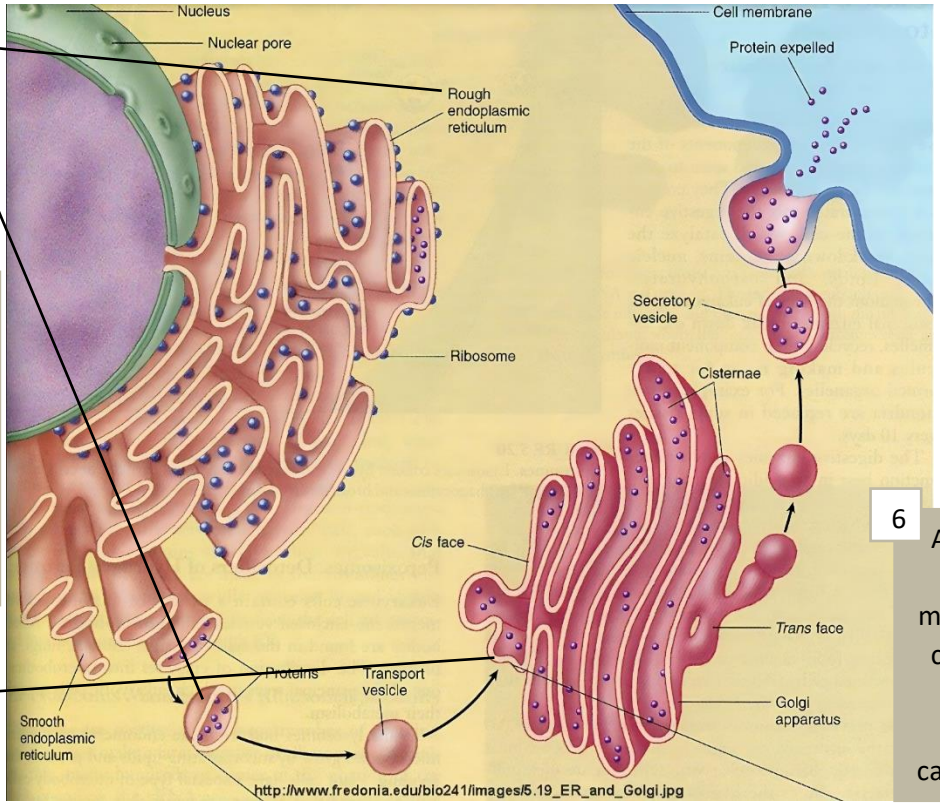
3-Vesicular transport:

1 Synthesizes proteins.

2 Proteins are transported in vesicles.

3 These vesicles are transported on the cytoskeleton (Microtubules) by phosphorylation and dephosphorylation (Uses ATP)

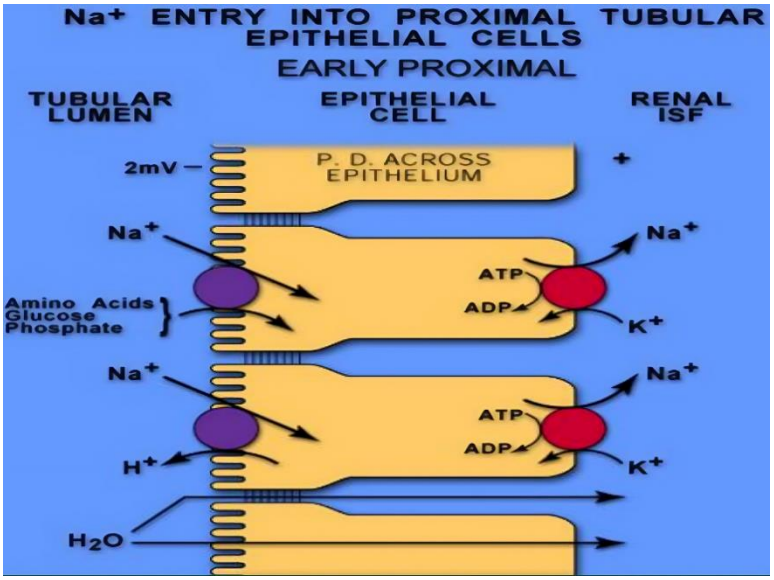
4 Then they reach Golgi Apparatus.



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

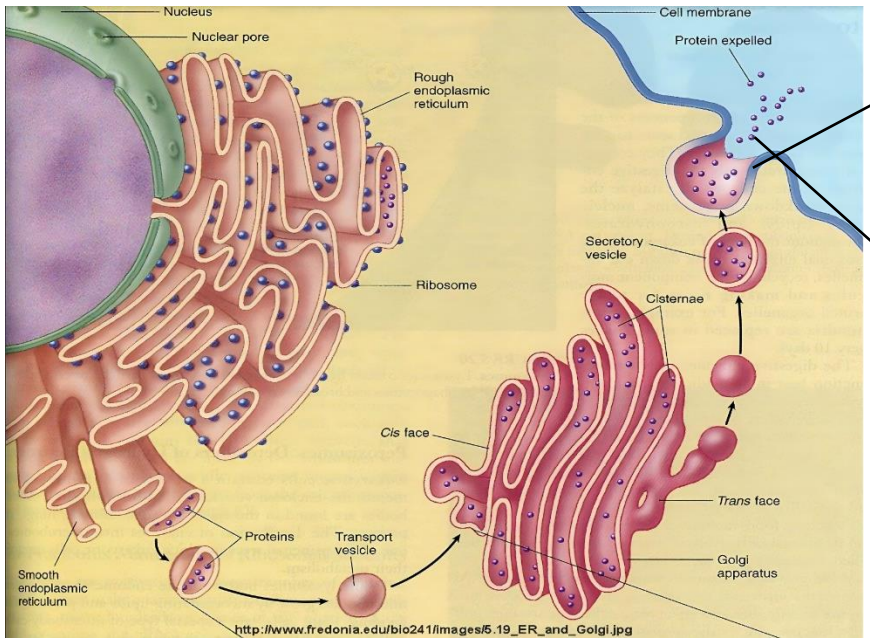
6 After the vesicle is fused with the membrane, proteins could be secreted, or used in the membrane, as carriers for example.

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:

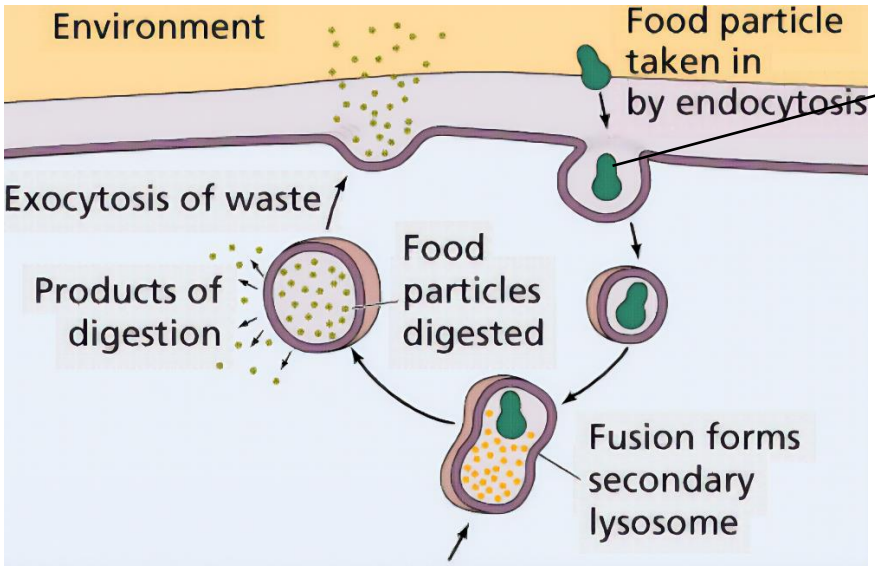


The fusing of vesicle with the membrane.

Secretion the content of the vesicle outside the cell.

This is called Exocytosis.

B- Endocytosis:



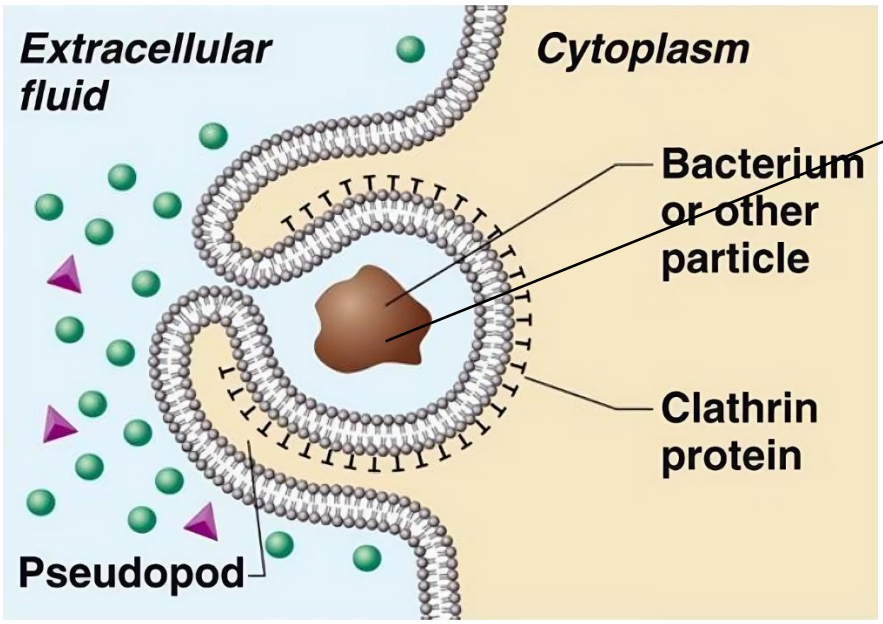
A reversal of Exocytosis, engulfing particles into the cell.

This is called Endocytosis.

C- Phagocytosis:

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.



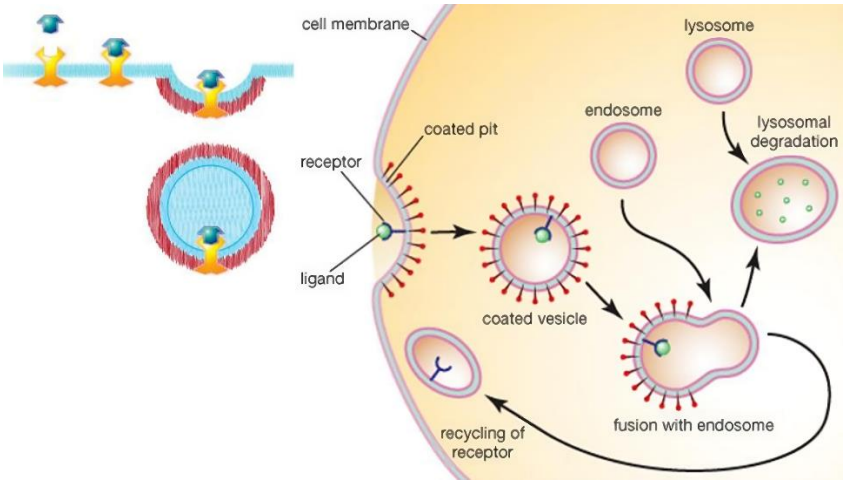
It's also Endocytosis, but engulfing Pathogens, Bacteria and Viruses.

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.

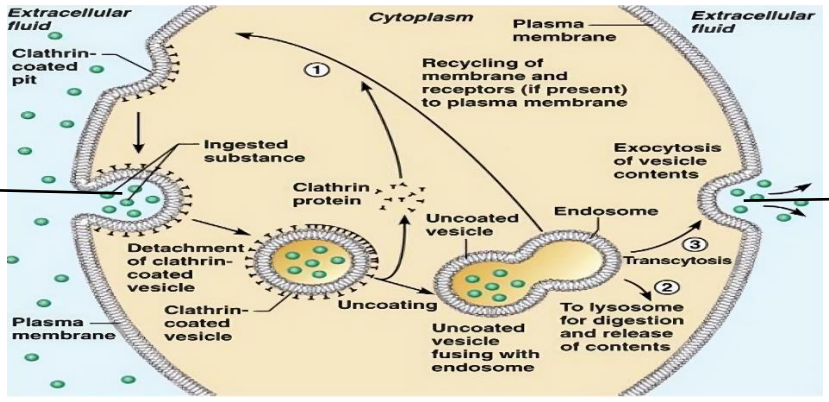


Lysosome will degrade the vesicle and destroy the Ligand.

The receptor will be recycled.

E- Transcytosis:

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



And secreted by Exocytosis from other side of the cell.

F- Pinocytosis:
Engulfing water inside the cell (drinking), that happens in some types of Bacteria, not in our bodies.

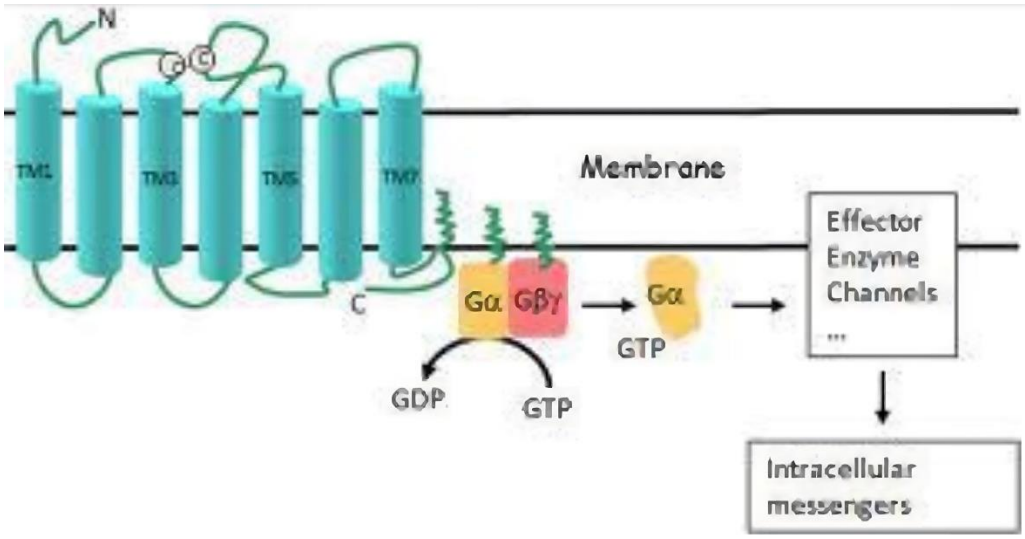
الدكتور تكلم عنه وغير موجود بالسلايدات

Control of Transport and Activity of Enzymes

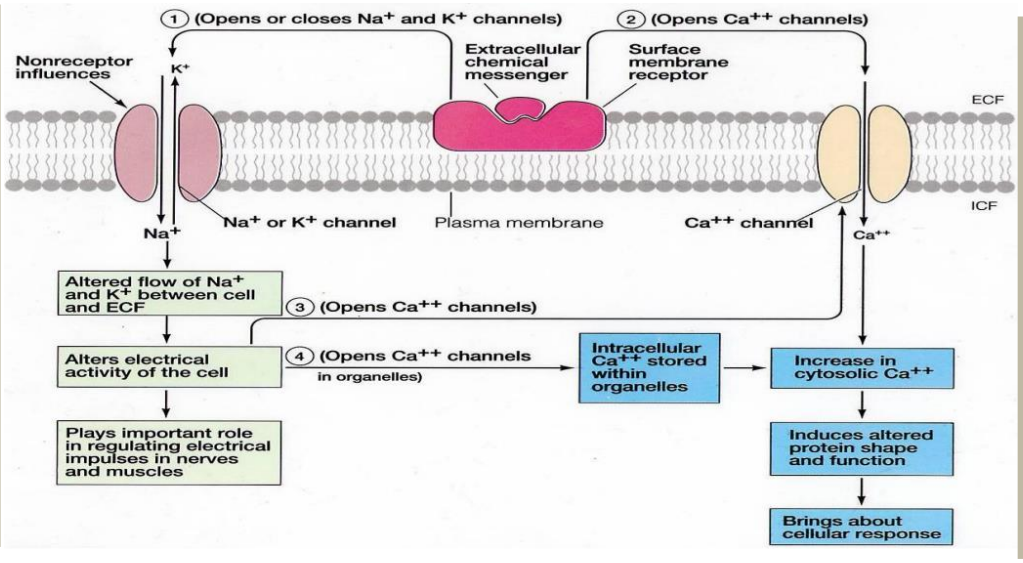
Over plasma membrane we have receptors, those receptors are specific, some of them are linked to channels through G-proteins (A group of protein structures, G because they use GTP).

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.

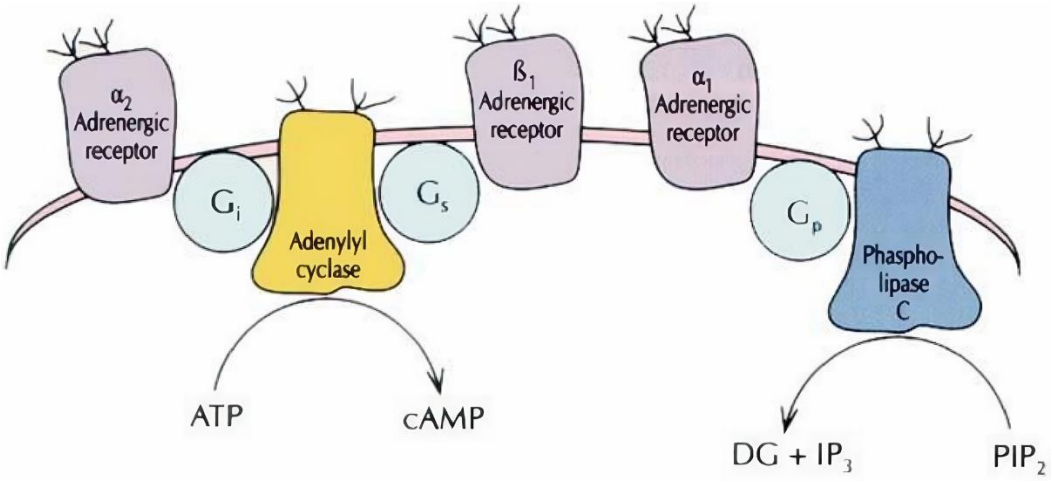
Also, the activity of channels can be controlled by specific enzymes, as you can see in the picture, we can have some type of receptors linked to:

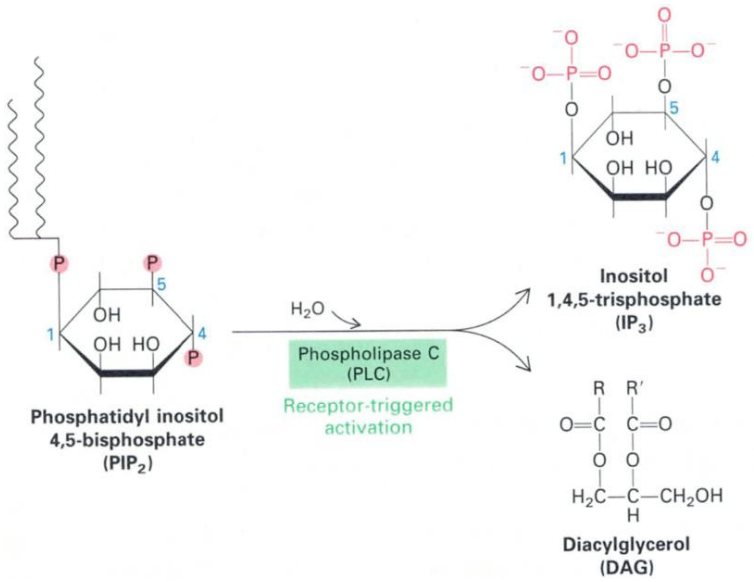
A- An enzyme called **Adenylyl cyclase**:

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

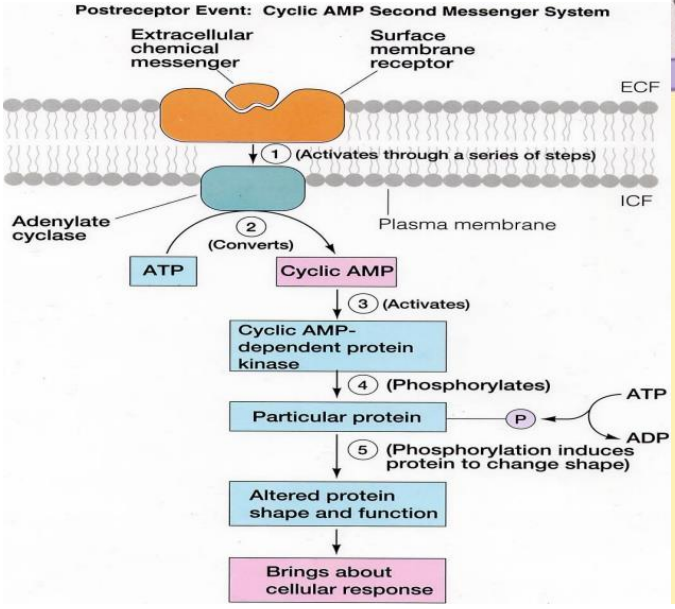
B- An enzyme called **Phospholipase C**:

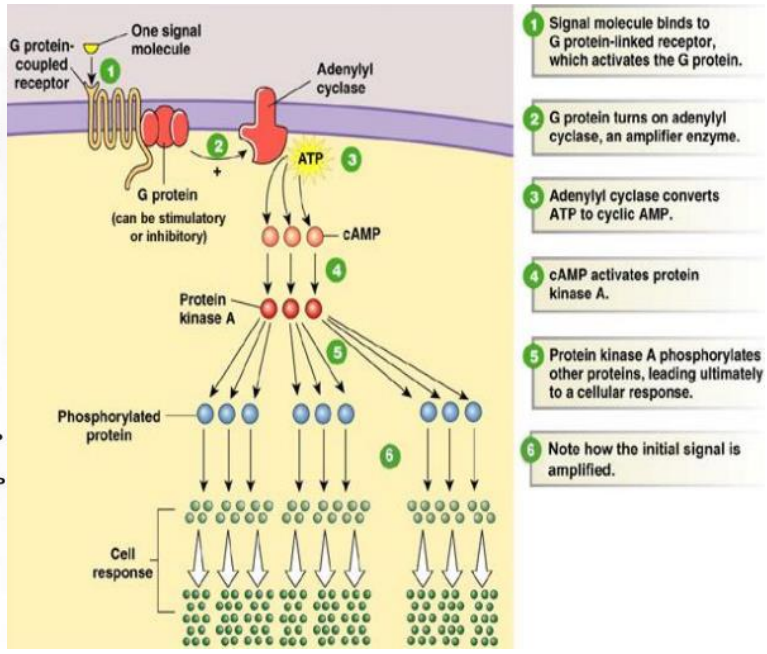
Splits PIP_2 (Phosphatidylinositol 4,5-bisphosphate) into IP3 (inositol 1,4,5-trisphosphate) and DG (Diacylglycerol), IP3 can change the activity of Ca^{+2} channels on the membrane of endoplasmic reticulum causing the release of Ca^{+2} ions from the endoplasmic reticulum into cytosol to change the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

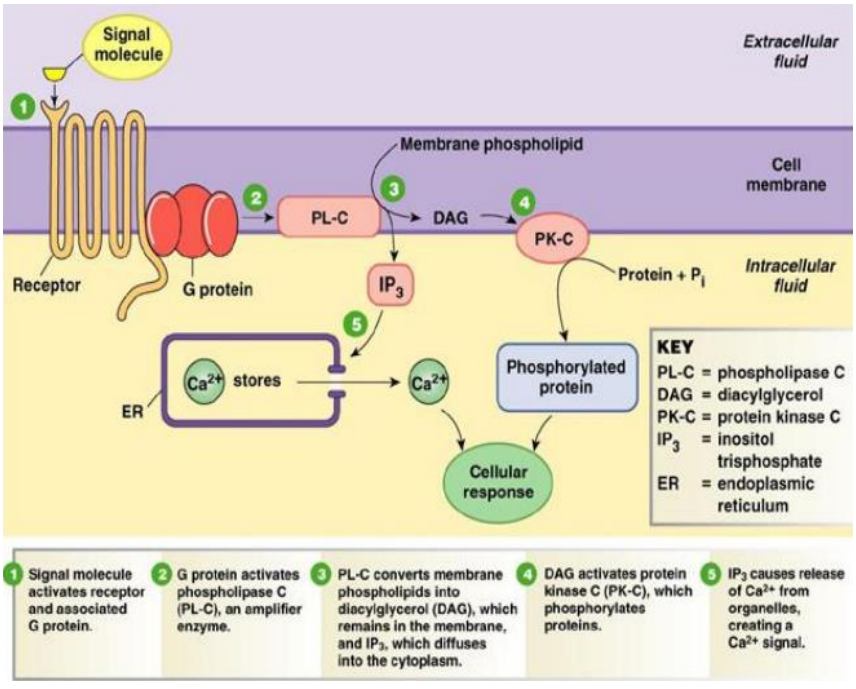




Extra pictures, our doctor didn't say more information about them than the above picture.

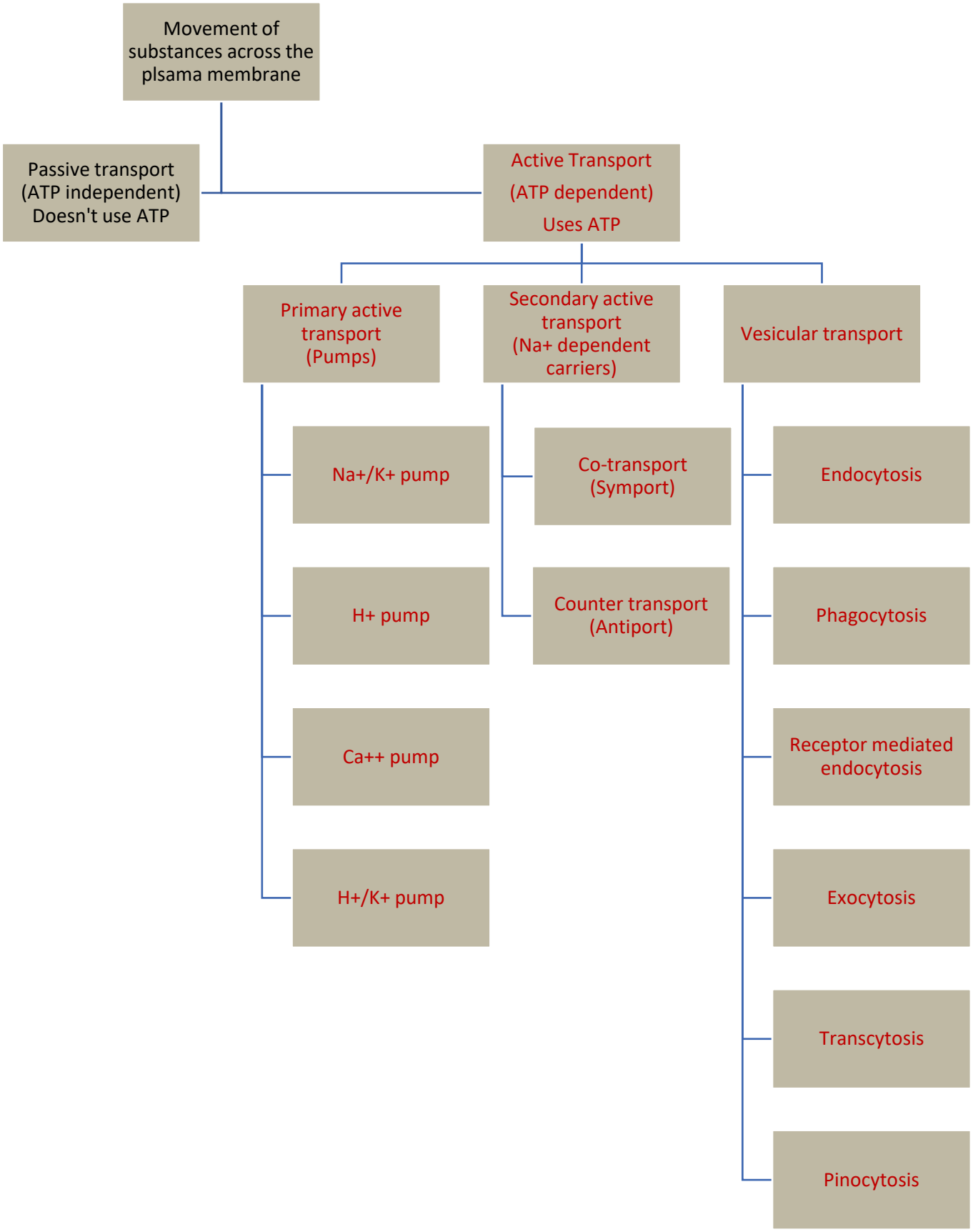






Transport Across Plasma Membranes

Summary



IMPORTANT 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.

The End of Sheet

v2

تم اضافة صفحات ٢٨، ٢٩، ٣٤، ٣٤

يارب توفيقًا منك يُلازم الخُطى

وعونًا منك إذا صعُب المسير

Please check on the professor's handout,
Very Important ..

University of Jordan
Faculty of Medicine
Department of Physiology and Biochemistry

Introduction to Physiology
Med I and Den I students 2023/2024
Outline for Cell Physiology and Transport through biological membranes.

Ref: Textbook of Medical Physiology. Jordan Edition, By Guyton and Hall.
Pp: 11-14, 47-59.

Membranes and Transport:

Modalities of transport:

DIFFUSION:

Generally, dissolved particles found in solution are in constant movement. This random motion is due to thermal energy in particles that found themselves at a temperature above the absolute zero (in living systems about 310 degrees K). The random motion in liquids and gases will result in a random collision of particles with each other and with the wall. These haphazard collisions will cause a transfer of kinetic energy from one particle to another and change in the direction of motion. This continuous movement in liquids and gases is known as ***diffusion***.

Diffusion through biological membranes:

Particles can move across biological membrane by diffusion. This type of transport does **not** need consumption of energetic compounds (ATP). It is passive. Because of the lipid constituents of the membrane, only lipid soluble substances can diffuse through the lipid structures. Their diffusion depends on the solubility of particles in the lipid bilayer. Example: O2, CO2, NO and lipid particles can diffuse through the lipid structures.

While water soluble particles cannot pass the bilayer. But, they can be transported across membrane through protein channels. This type of transport is can also be characterized as ***simple diffusion (in some literature is considered as FACILITATD DIFFUSION*** by considering have a protein structure (channel) helped these particles to move across membrane. Also, there are some particles can NOT diffuse through membrane only with the help of a protein structures known as **carriers**. This type of diffusion of particles is known as **facilitated diffusion**.

Factors that influence simple diffusion:

- *Concentration*: More concentration of a substance means more kinetic energy in particles in a given compartment.

Movement of particles across membranes depends on the ***concentration of substances***. Less particles from compartment B where are found in a lower concentration will move to compartment A where are found in a higher concentration.

The Net rate of diffusion (Q) of particles is (diffusion rate from A to B (-) diffusion rate from B to A). One of the factors that influence the rate of net diffusion is *concentration gradient* ($\Delta C = C_A - C_B$), which represents the **Chemical Potential** for movement of particles across membranes.

In addition to concentration gradient, net rate of diffusion (Q) depends also on:

- ***Permeability*** of the membrane to a given substance (P): the higher the permeability for a substance the greater the diffusion rate is through membrane.

- ***Surface area*** of transport (A): diffusion increases by increasing (A). The increase in surface area in biological membranes will result in more protein channels that can be used for diffusion from one compartment to another.

- ***Molecular weight*** (MW): lighter molecules move more quickly than heavier.

-***Membrane thickness*** (X) (distance of movement): the greater the distance the slower the rate of diffusion.

All these factors form the Ficks' law of diffusion:

$J = P.\Delta C$.....(J = Flux, P=Permeability,
ΔC = Concentration gradient)

$P = D.A/\Delta X$ ..... (, A: surface Area, ΔX = membrane Thickness)

$J = D.A.\Delta C/\Delta X$..... (D=Diffusion Coefficient)

In addition to all these factors, diffusion can also be influenced by:

- ***Effect of membrane electrical potential***: mainly influences electrically charged particles.

The presence of a negative potential inside the cell prevents movement of negative (-) charged particles from the extracellular compartment to the intracellular compartment and the positive charged particles from the intracellular to the extracellular compartment.

So, movement of charged particles is governed by an **electro-chemical potential**. This will be discussed in more details later.

- ***Effect of pressure***:

The presence of pressure difference between two compartments

will cause more kinetic energy in particles in the compartment with higher pressure. This will cause movement of more particles from the high pressure side to the low pressure side.

* Factors that influence facilitated diffusion:

This carrier mediated transport also depends on *concentration gradient* of transported substance, with the difference that the rate of transport approaches a maximum called V_{max} . The increase in the rate of net diffusion in simple diffusion is proportional with the ΔC, while in facilitated diffusion when V_{max} is approached no more increase in diffusion will be by increasing ΔC. The limitation is due to the presence of limited number of *carrier molecules* at the membrane.

OSMOSIS:

Not only the particles of solute are transported across membranes, but also water can move across membranes. Under normal circumstances the **net** movement of water across plasma membrane is zero. This keeps the cell volume constant. Under the condition that membrane is NOT permeable to solute particles and there is a concentration difference of particles between the two sides of a membrane. Water can move from the compartment of higher concentration of water (low solute concentration) to the compartment of lower water concentration (high solute concentration). This movement of water is known as **osmosis**.

If a pressure is applied to the side where the concentration of solute is high, this will reduce, stop movement of water molecules to that side. The amount of pressure needed to stop osmosis is known as **osmotic pressure** of that solution.

The osmotic pressure of a solution depends on the concentration of particles in that solution (osmolar concentration). So, one mole of NaCl solution will dissociate in solution to Na+ and Cl- and will have twice osmotic pressure (2 osmolar concentration) as one mole of glucose (one osmolar concentration).

Osmolality = number of osmoles per kg water

Osmolarity = number of osmoles per liter of solution

Tonicity of solution: is osmolarity with regard to the osmolarity of plasma (300 mosmoles). (hypertonic solution has osmolarity higher than plasma. Hypotonic solution has osmolarity lower than plasma. In Isotonic solution, the osmolarity is equal to that of plasma)

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

K+ 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

reducing 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 co-transport 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.