Chapter 3

Transport Across Cell Membranes

The Plasma Membrane

Introduction

- The cell membrane not only limits the cell cytosol, but it has a variety of functions like membrane transport, signal transduction and neuro transmission

Chemical Composition

_To study the chemical composition of the cell membrane, the preferred source is RBC.

The membranes of the RBCs ======Four major constituents are present in the cell membrane. They are

(i) **lipids**

(ii) **proteins**.

(iii) **Oligosaccharides**

(iv) **water**

Chemical Composition of the cell membrane

1. Lipids

- Depending upon the tissue from which the cell membrane is isolated, the composition also differs. Nearly 80% of the myelin sheath is made up of lipids, while in liver, it constitutes only 28%. The main lipid components of the membranes are phospholipids, cholesterol and glycolipids.
- **Phospholipids:** Contains 2 fatty acid chains that are nonpolar&

Head is polar & contains a –PO4 group

The major phospholipids present are phophatidyl choline (lecithin), phophatidyl ethanolamine, phophatidyl serine and phophatidyl inositol

- Membrane lipids are amphipathic in nature and they have a head portion, which is hydrophilic and a tail portion which is hydrophobic.
- Cholesterol

  Increases bilayer strength, flexibility

  Reduces membrane fluidity

  Reduces permeability to water-soluble substances

2 Proteins

All the major functions of the plasma membrane are completed by the proteins present in the membrane. Proteins account for about 20 – 70% of the membrane depending on the type of the cell.

They can be classified into two types.

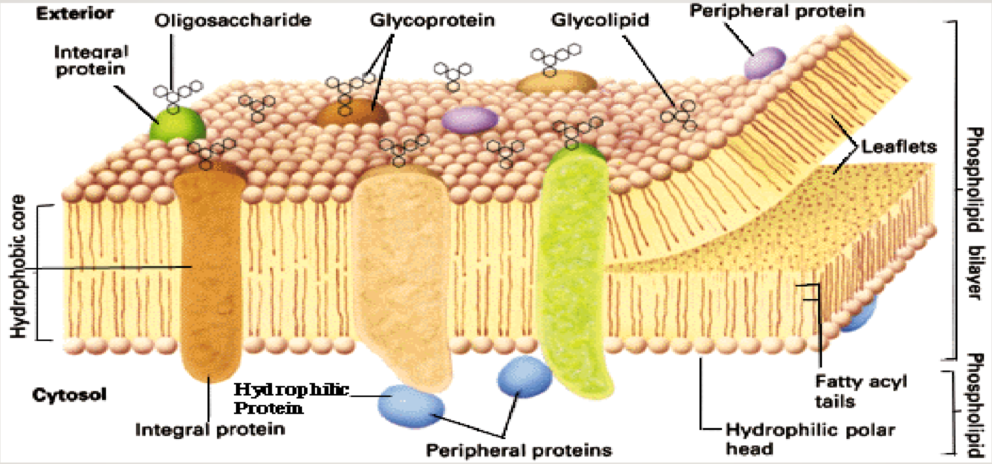
- **Integral** membrane proteins
- **peripheral** membrane proteins.

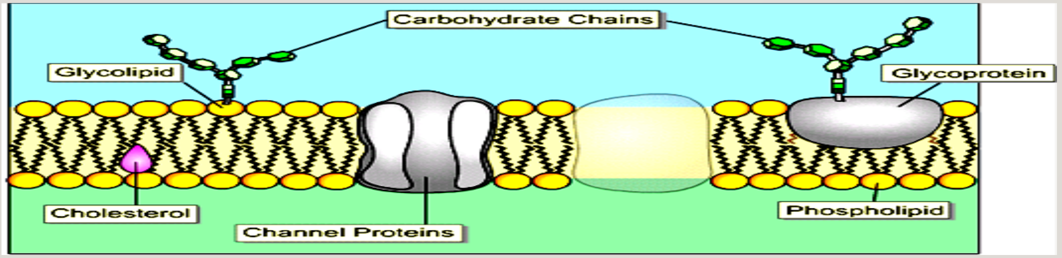
Integral Proteins Some of the membrane proteins are tightly embedded in the membrane and they cannot be isolated unless, the membrane is disintegrated. They are called as **Integral or Intrinsic membrane proteins**.

Peripheral Proteins Those proteins that are present on the surface of the membrane are called as peripheral proteins. They can be easily isolated from the membrane.

3 Carbohydrates

Oligosaccharides on glycoproteins


Exterior
Oligosaccharide
Glycoprotein
Glycolipid
Peripheral protein
Integral protein
Leaflets
Phospholipid bilayer
Hydrophobic core
Cytosol
Hydrophilic Protein
Integral protein
Peripheral proteins
Fatty acyl tails
Hydrophilic polar head
Phospholipid


Carbohydrate Chains
Glycolipid
Glycoprotein
Cholesterol
Channel Proteins
Phospholipid

FUNCTIONS OF MEMBRANE MACROMOLECULES

Membrane Proteins can serve a variety of key function

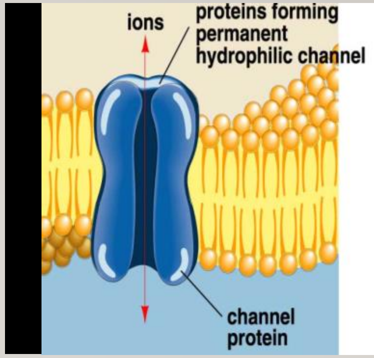
- Junction serve to connect and join 2 cells togethers
- **Transport proteins responsible for facilitated diffusion and active transport**

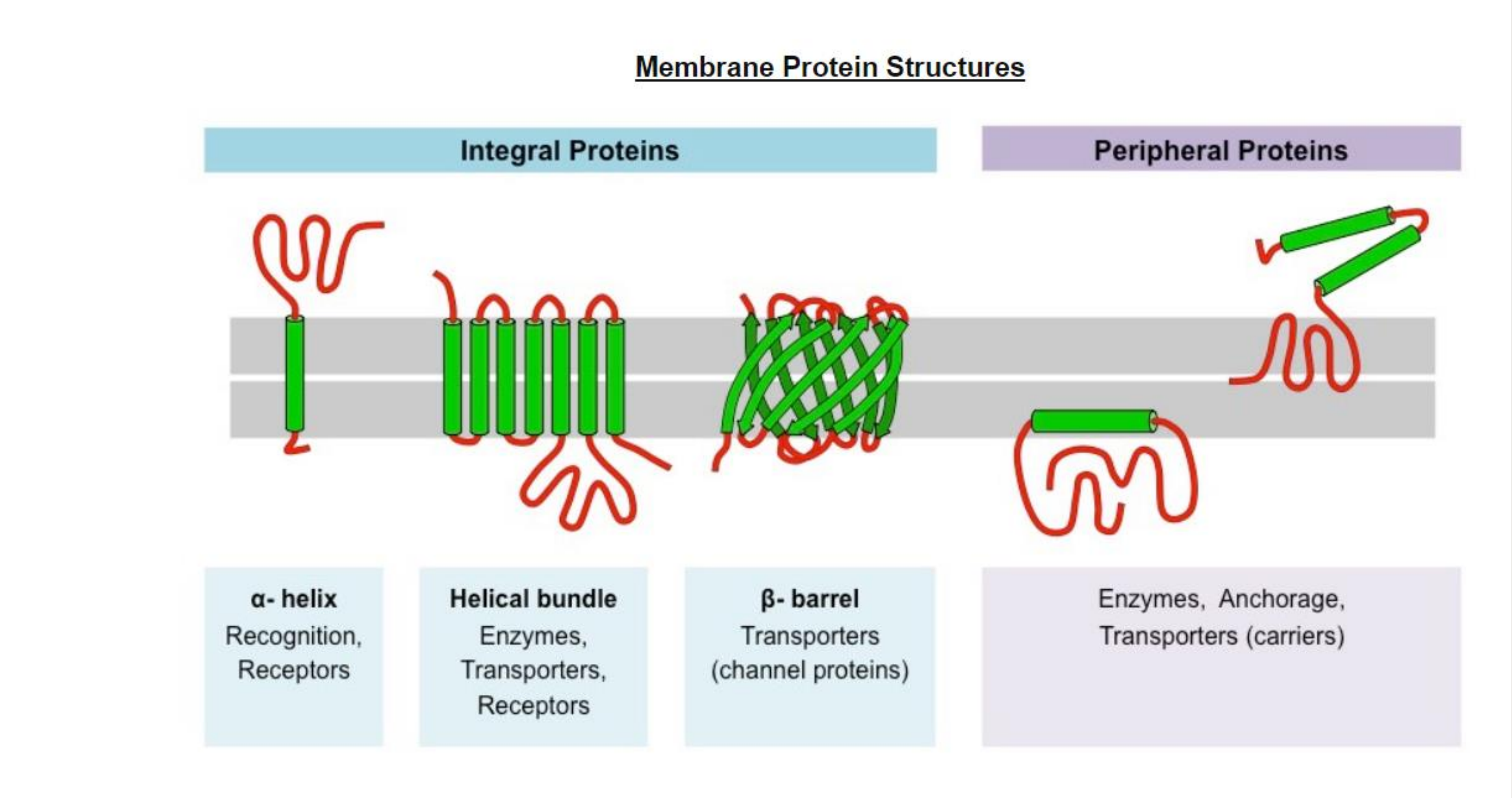
  Regulate movement of water soluble substances

  -**Carrier proteins** bind to molecules and change shape for delivery across membrane

  -**Channel proteins** have pores that allow passage of ions and small water-soluble molecules

  - **Recognition** –May function as markers for cellular identification
  - Transduction (**Receptor proteins) function as receptors for peptide hormones**(Attachment site for molecules outside the cell)



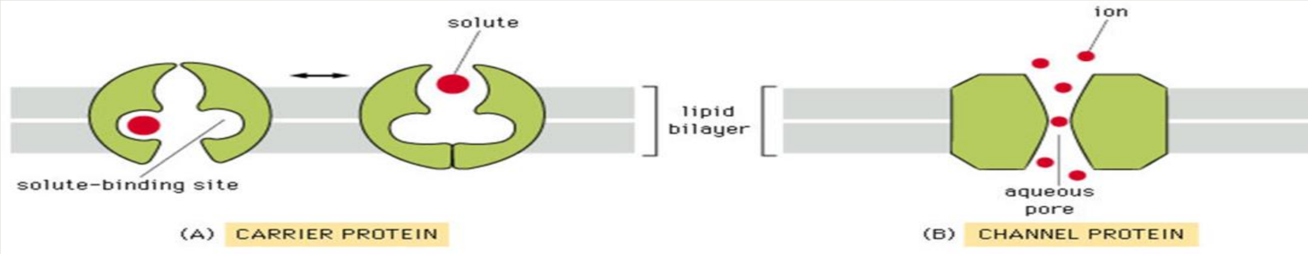

Membrane Protein Structures
Integral Proteins
Peripheral Proteins
α- helix
Recognition,
Receptors
Helical bundle
Enzymes,
Transporters,
Receptors
β- barrel
Transporters
(channel proteins)
Enzymes, Anchorage,
Transporters (carriers)

CHARACTERISTICS OF PROTEIN CHANNELS

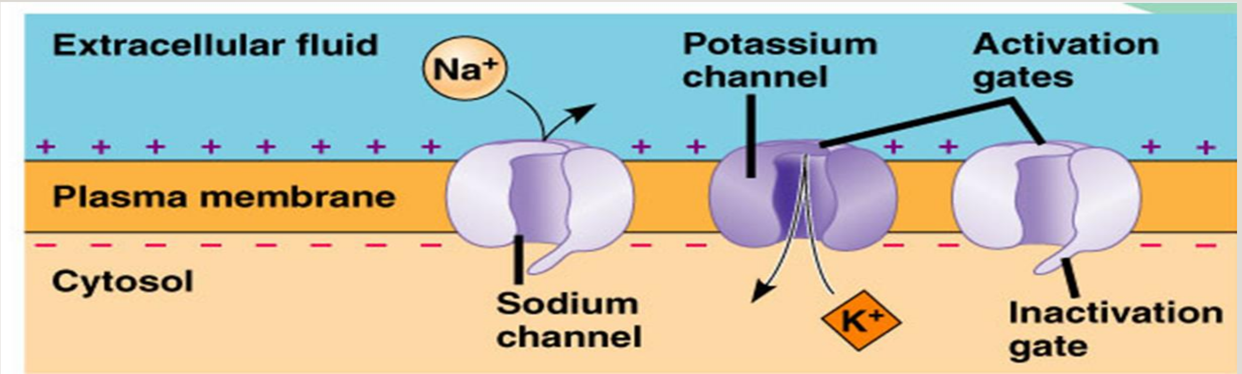
The protein channels are distinguished by two important characteristics:

1- Selective permeability

Most protein channels are highly selective for the transport of one or more specific ions or molecules. This results from the characteristics of the channel itself such as, its diameter, shape, and the nature of the electrical charges along its inside surface.



To give an example, sodium channel has only 0.3x0.5 nm size and its inner surface is negative charged to pull small Na+ ions into the channel. On the other hand, potassium channel has only 0.3x0.3 nm size . Therefore the smaller K+ ion can pass easily, whereas Na+ ions are mainly rejected.



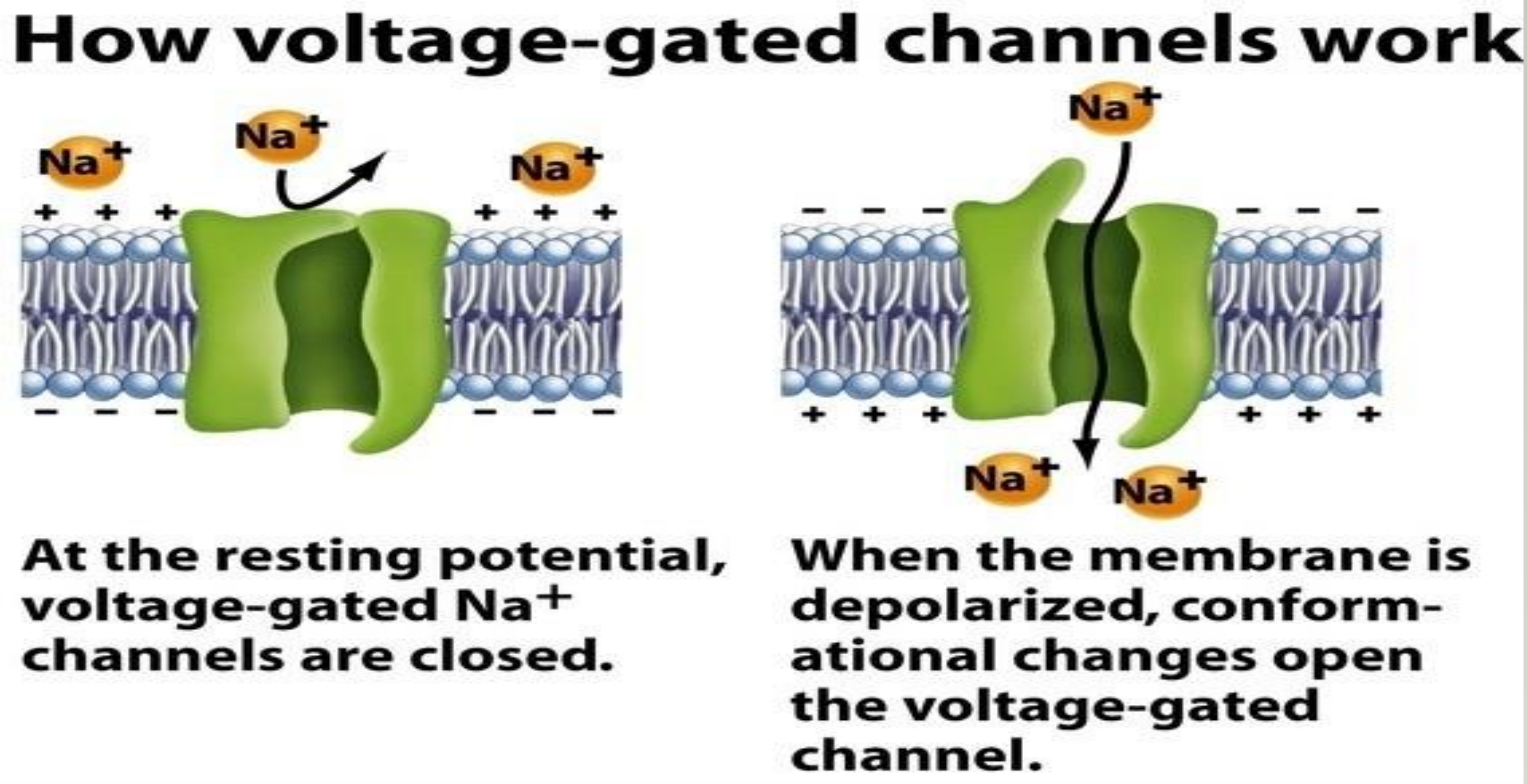
2-Gating

Gating of protein channels provides a mean for controlling the permeability of the channels.

The opening and closing of gates are controlled in two principle ways:

Voltage gating: When the inside of the cell membrane is negative, the outside Na+ gate is closed (resting potential) , and when the inside loses its negative charge, these gates open and allow Na+ to pass (action potential).

For K+, when the inside becomes positive it too open (action potential) but less than that of Na+.


How voltage-gated channels work
Na+
Na+
Na+
+ + +
+ + +
– – –
– – –
Na+
– – –
– – –
+ + +
+ + +
Na+
Na+
At the resting potential, voltage-gated Na+ channels are closed.
When the membrane is depolarized, conform-ational changes open the voltage-gated channel.

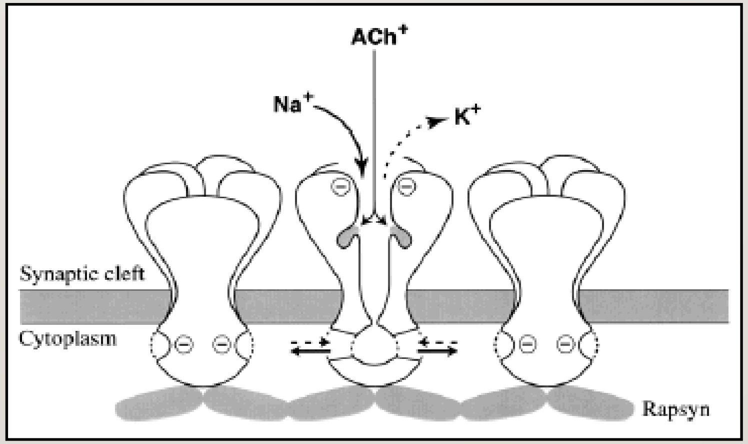
Chemical gating (**Ligand-gated ion channels)**

are a group of transmembrane ion channel proteins which open to allow ions such as Na^+ , K^+, Ca^+, and Cl^- to pass through the membrane in response to the binding of a chemical messenger (ligand) such as a neurotransmitter (ex. acetylcholine).

- Some protein channel gates are opened by the binding of another molecules with the protein, this causes a conformational change in the protein molecule that opens or close the gate.

This gates are important in the transmission of signals from one nerve cell to another and from nerve cells to muscle cells.

This pore allows Na+ ions to flow down their electrochemical gradient into the cell.



TRANSPORT PROCESSES

- The variations in concentrations are extremely important to the life of the cell. These differences are brought about by the transport mechanisms of the cell membrane.

- Cell membrane is a barrier between intracellular and extracellular fluids. Transport of ions occurs by diffusion (**passive transport** or **active transport)**

Composition of the intracellular and the

	Extracellular Fluid	Intracellular Fluid
Na^{+}	142 mEq/L	10 mEq/L
K^{+}	4 mEq/L	140 mEq/L
Ca^{++}	5 mEq/L	<1 mEq/L
Mg^{++}	3 mEq/L	58 mEq/L
Cl^{-}	103 mEq/L	4 mEq/L
HCO_3^{+}	28 mEq/L	10 mEq/L
Phosphates	4 mEq/L	75 mEq/L
SO_4^{--}	1 mEq/L	2 mEq/L
Osmolality	281 mOsm/L	281 mOsm/L

TRANSPORT ACROSS THE MEMBRANE

Molecule can be across the membrane by the following mechanism :

- Transport of small **molecules by :**

1. passive diffusion
2. Facilitated Diffusion
3. Active transport

- Transport of large **molecules by :**

1. Endocytosis
2. Exocytosis

Passive transport

- Substances move from [high]→[low]
- No energy input required

-*Diffusion*

Simple Diffusion

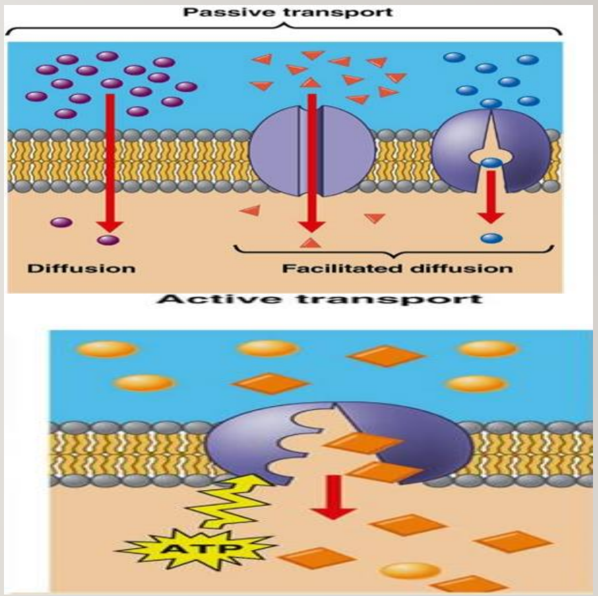
Facilitated Diffusion

-*Osmosis*

Active transport

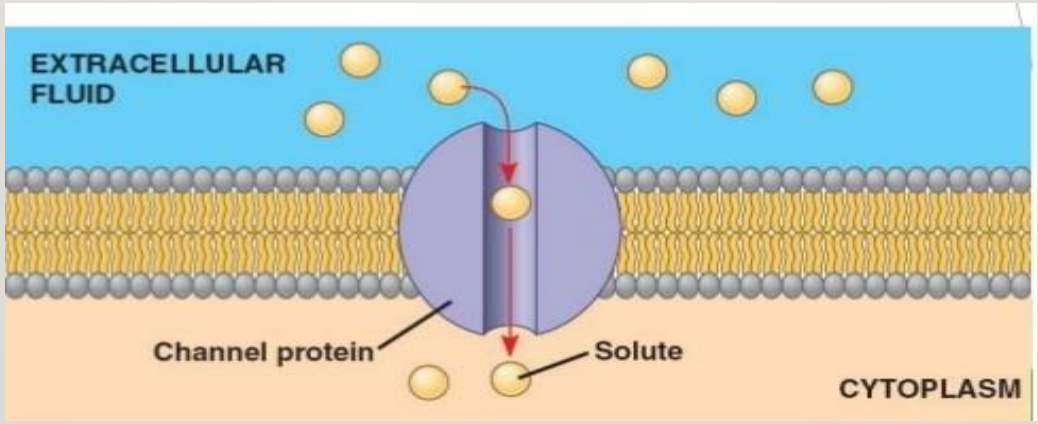
- Substances move from [low]→[high]
- Requires energy input (ATP)

- involve the use of an electrochemical gradient.

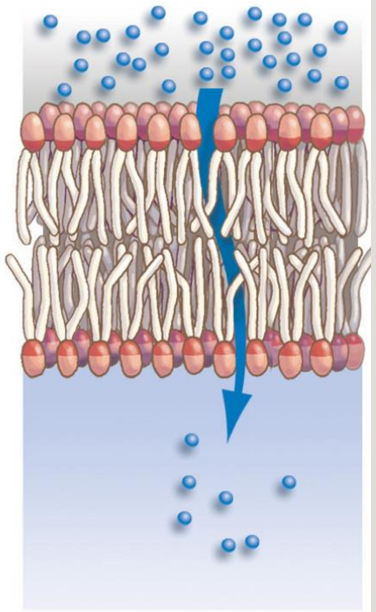


DIFFUSION

Diffusion through cell membrane is divided into two subtypes called **simple** and **facilitated** diffusion.



PASSIVE TRANSPORT
TYPE A: SIMPLE DIFFUSION



Materials move down their concentration gradient through the phospholipid bilayer.

It is the free movement of molecules or ions.

It is characterized by:

1. Passive.

2. Requires a concentration gradient.

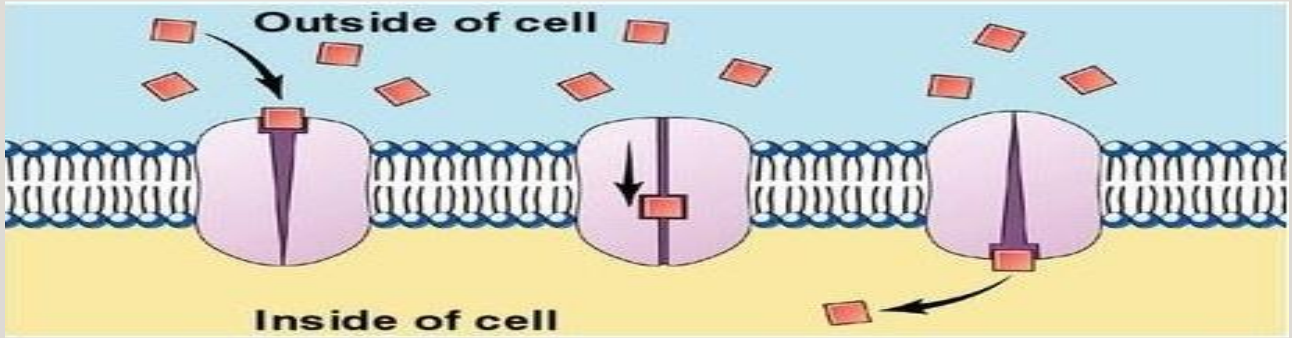
3. Occurs until a dynamic equilibrium is reached.

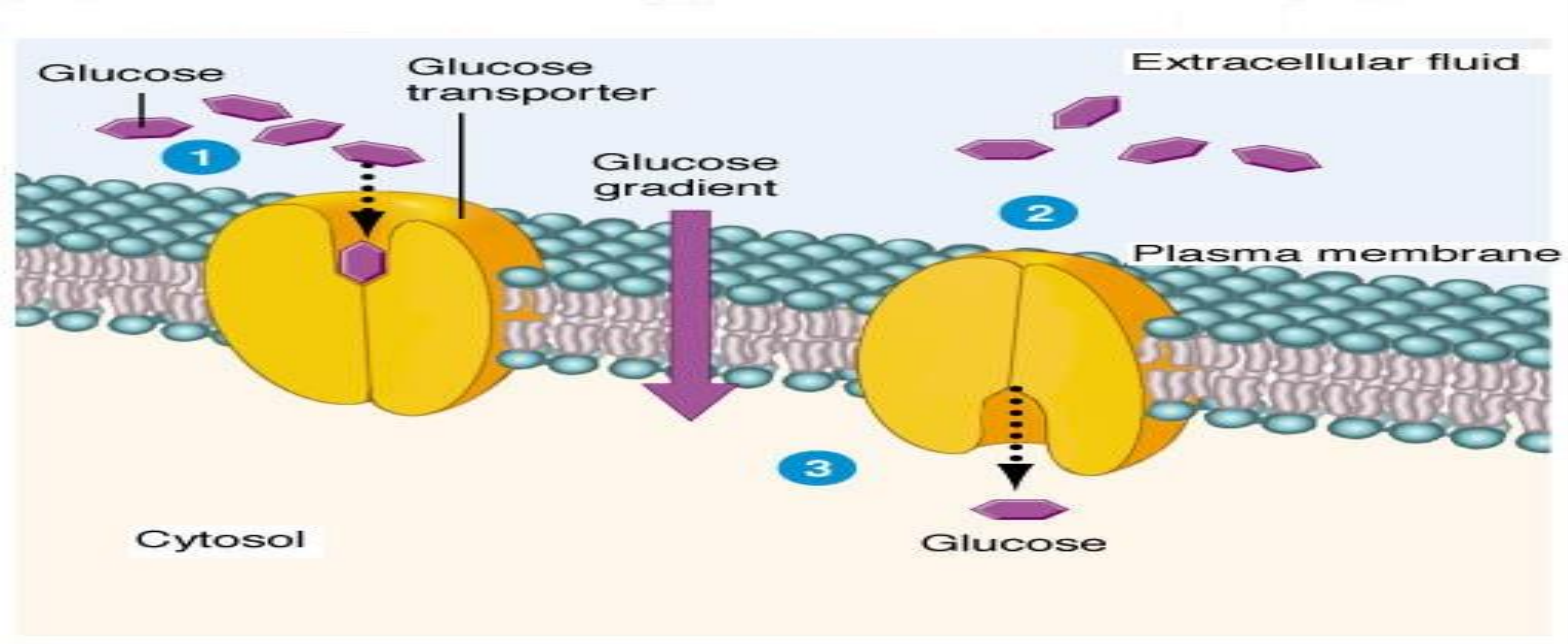
4. Rapid over short distance, slow over long distance.

5. Inversely related to molecular size, as molecular size increases the resistance.

B-FACILITATED DIFFUSION (CARRIER-MEDIATED DIFFUSION)

Substances in this case cannot pass through membrane without a specific carrier protein helping them or facilitates the diffusion. The mechanism is shown in the following figure



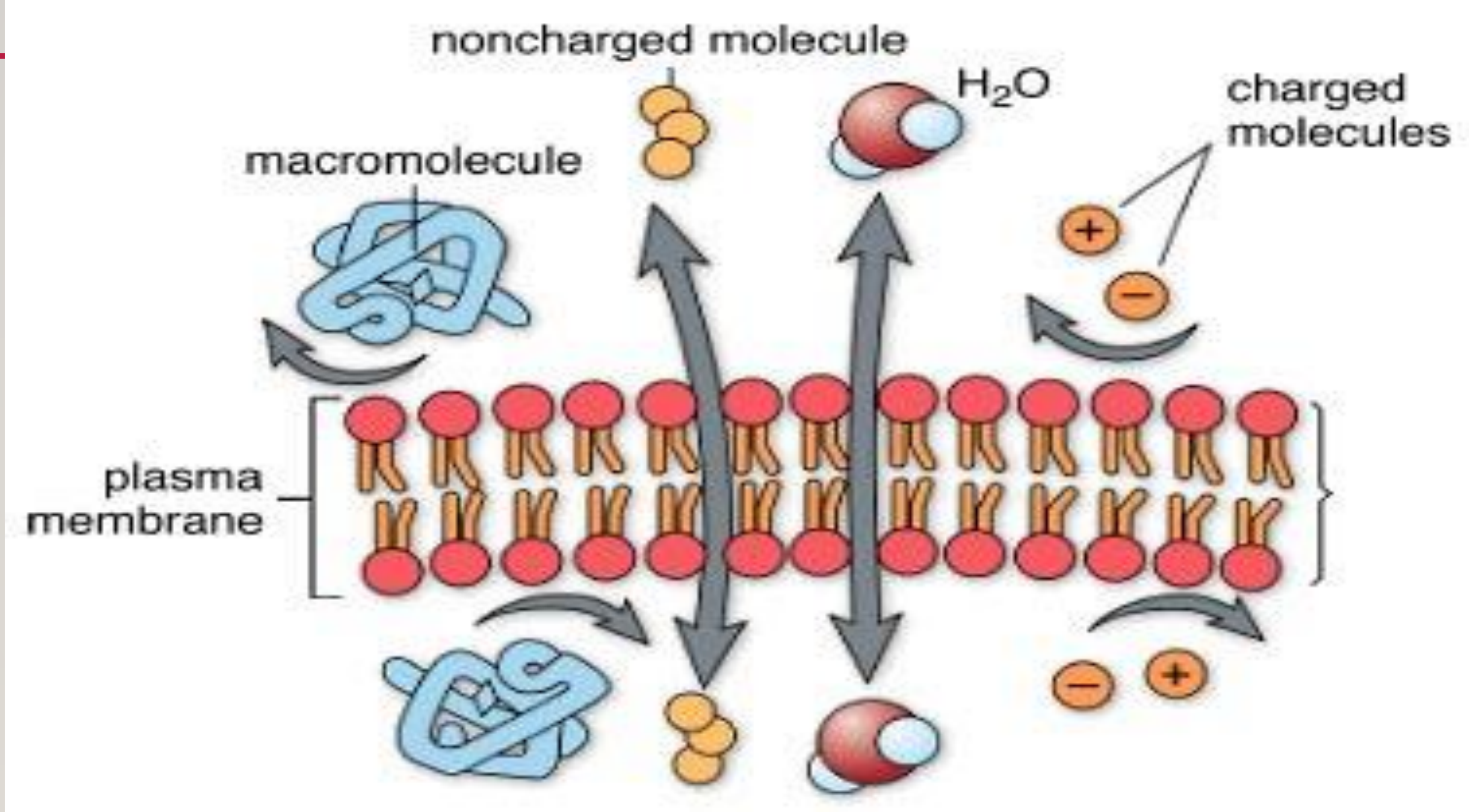


Note that this mechanism allows the transported molecule to diffuse in either direction through the membrane .

Among the most important substances that cross cell membranes by facilitated diffusion are glucose and most of the amino acids.

Insulin can increase the rate of facilitated diffusion of glucose as much as 10-20 fold (insulin controls glucose use in the body).

MEMBRANE PERMEABILITY



2-Active Transport

❖Requires energy or **ATP**

❖Moves materials from **LOW to HIGH** concentration

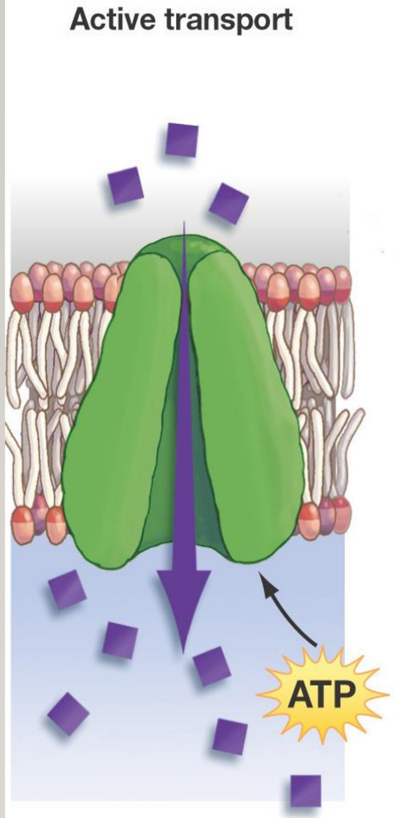
❖**AGAINST** concentration gradient

Examples: **Na+-K+ Pump** (Pumping **Na^+** (sodium ions) out and **K^+** (potassium ions) in **against** strong concentration gradients

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

https://www.youtube.com/watch?v=xweYA-IJTqs

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

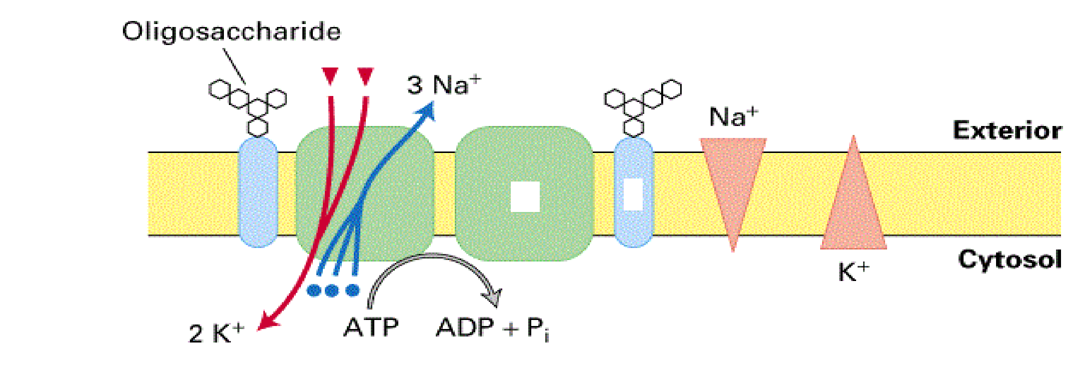


Molecules again move through a transport protein, but now energy must be expended to move them against their concentration gradient.

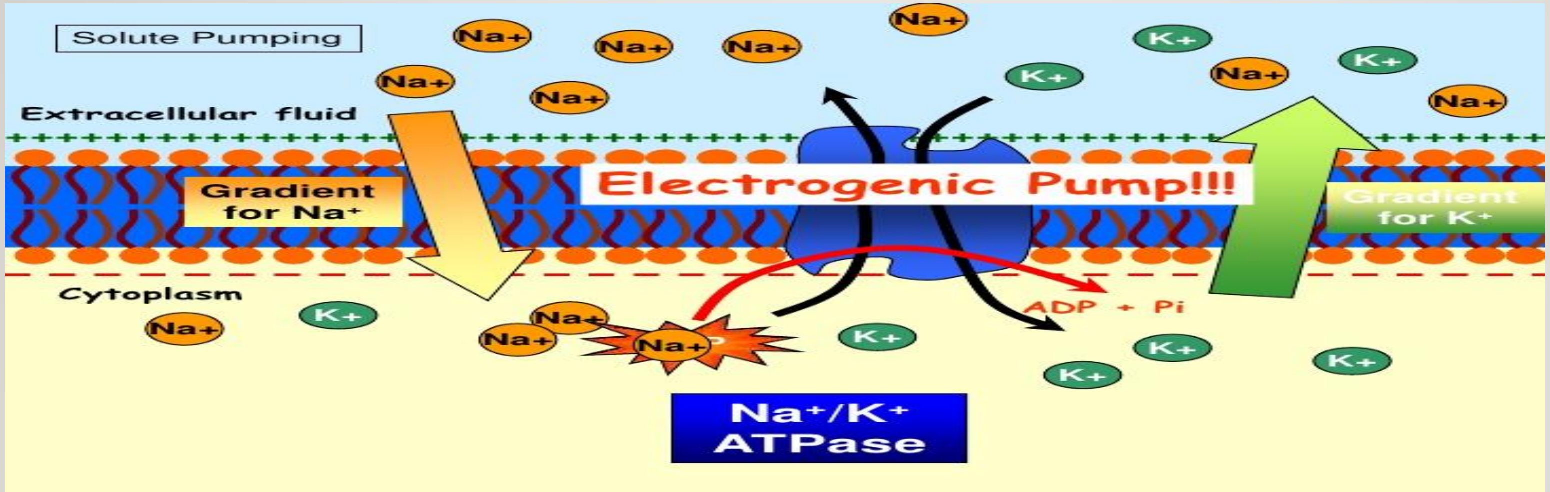
Sodium-Potassium Pump

This pump is the basis of nerve function to transmit nerve signals through the nervous system. The following figure shows the basic physical components of the Na^+-K^+ pump.

When three sodium ions bind on the inside of the carrier protein, the Na^+/K^+-ATPase becomes activated. This cleaves one molecule of ATP, splitting it to ADP and liberating high energy.
This energy is believed to cause a conformational change in the protein carrier molecule, taking three sodium ions to the outside and two potassium ions to the inside.



This creates positivity outside the cell but leaves a deficit of positive ions inside the cell, that is, it causes negativity on the inside. Therefore, the Na^+-K^+ pump is said to be **electrogenic** because it creates an electrical potential across the cell membrane.



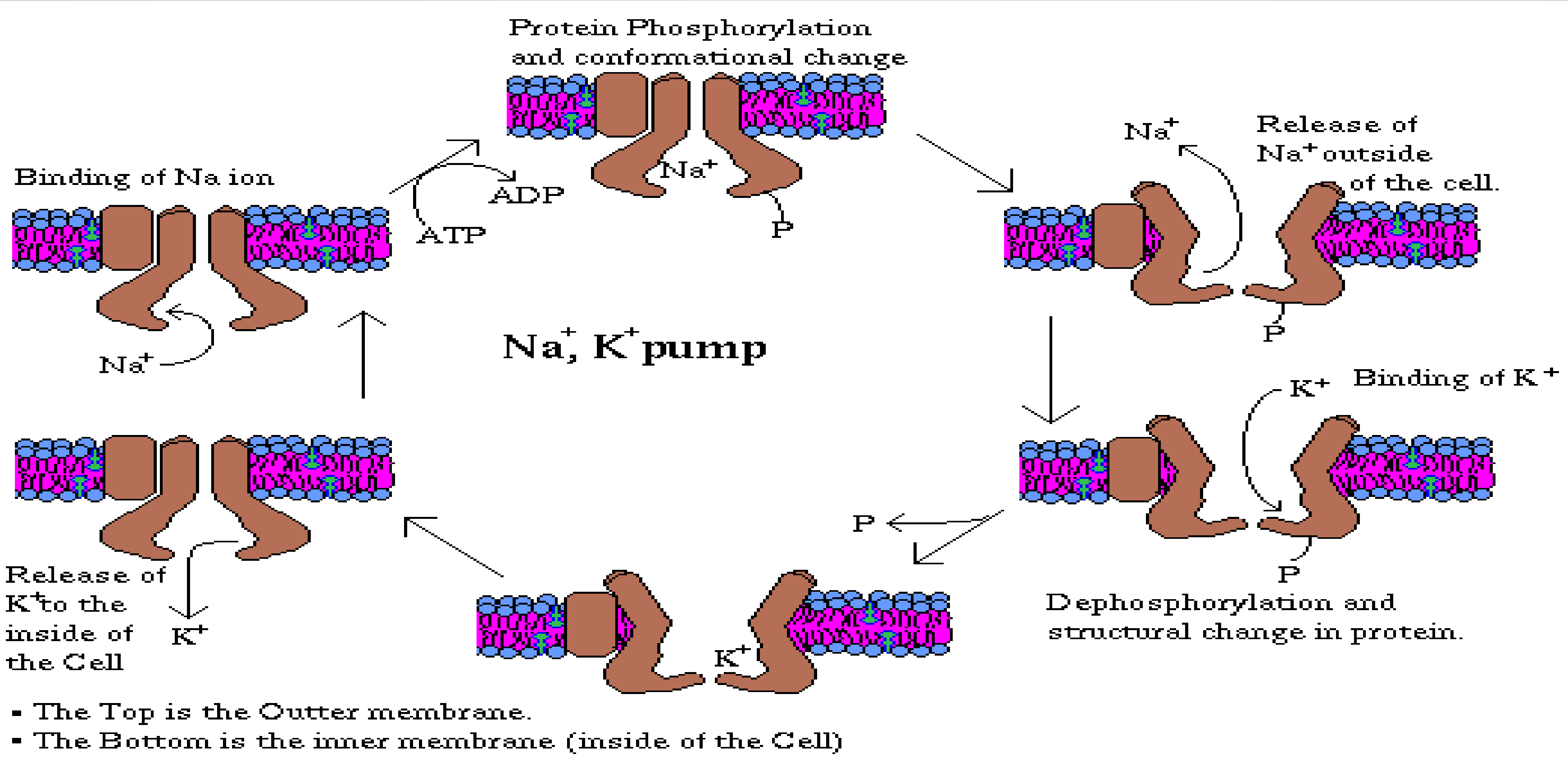
Sodium–potassium (Na^+–K^+) pump

Direct use of ATP for **<u>active transport</u>**

The sodium potassium pump uses energy to generate and maintain these concentration gradients

Uses an antiporter to move 3 Na^+ out of the cell and 2 K^+ into the cell
Against their concentration gradient
ATP energy is used to change the conformation of the carrier protein
Affinity of the carrier protein for either Na^+ or K^+ changes so the ions can be carried across the membrane
Uses up approx. 30% cell's energy

$$\left.\begin{matrix} 3Na^+(\text{inside}) \\ + \\ 2K^+(\text{outside}) \end{matrix}\right\} + ATP \longrightarrow ADP + \text{phosphate} + \left\{\begin{matrix} 3Na^+(\text{outside}) \\ + \\ 2K^+(\text{inside}) \end{matrix}\right.$$



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

Nernst equation:

- A protein complex called the sodium-potassium pump uses the free energy of hydrolysis of ATP to pump Na ions out of the cell and K ions into the cell.
- **The free energy of the net reaction must be negative.**
- This means that the positive free energy of the actively transporting ions against concentration and voltage gradient must be more than balanced by the negative free energy of atp hydrolysis

$$\Delta\mu = RT \ln \frac{A_{Na+}\ (outside)}{A_{Na+}\ (inside)} + zfv \qquad \text{Nernst equation}$$

, R= gas constant =8.3145 J/K mol

T = temperature in kelvin

A_{na+} (outside)= concentration of sodium ions outside

A_{na+} (inside)= concentration of sodium ions inside

Z = charge on ion ± 1, ± 2, ± 3,..

F= faraday constant =9.6485x 10^4 C/mol

V= $\Phi_2 - \Phi_1$ is the potential difference in volts between the two phases

outside=FINAL,,,, inside=INITIAL

CHARACTERISTICS OF ACTIVE TRANSPORT

1- It depends on a source of metabolic energy to pump a solute against a gradient of concentration.

- e.g: Red blood cells obtain the energy required to pump K^+ into the cell across the membrane and this needs a highly active glycolytic pathway to provide ATP needed to this transport.
- When we add fluoride which inhibits glycolysis, the intracellular conc of K^+ will decrease and Na^+ will rise.

2- They are specific for given solutes. Some cells have a pump specific for certain amino acids but can not transport glucose. Others can pump glucose but not amino acids.

3- The active transport system depends on the conc of substance being transported.

- e.g: when glucose is actively transported into a cell, the rate of glucose influx increases with the external conc of glucose.

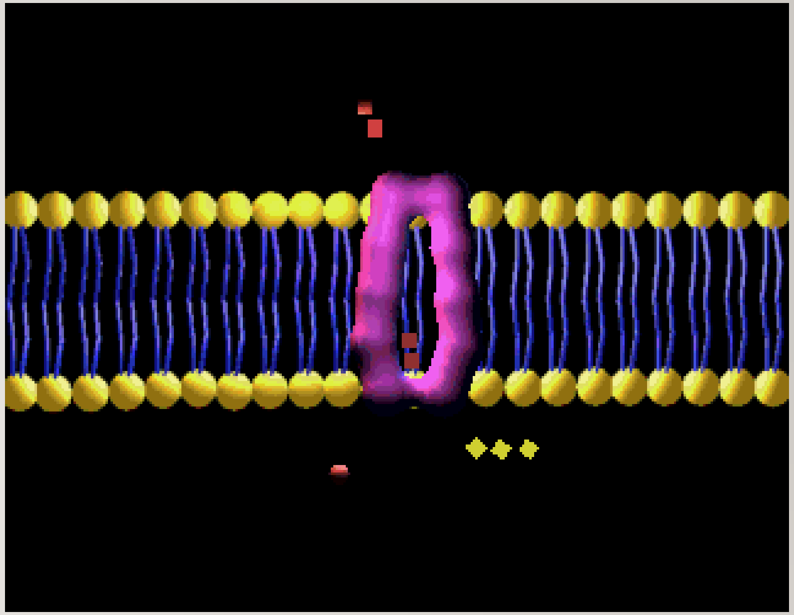
4- Active transport have a specific directionality

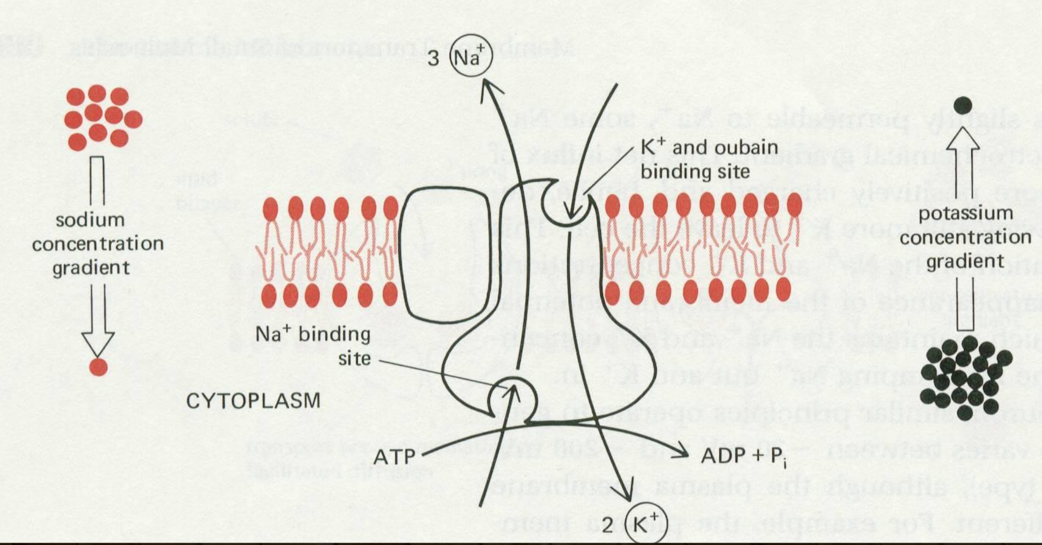
- K^+ is pumped only inward
- Na^+ is pumped outward

5- They may be selectively poisoned.

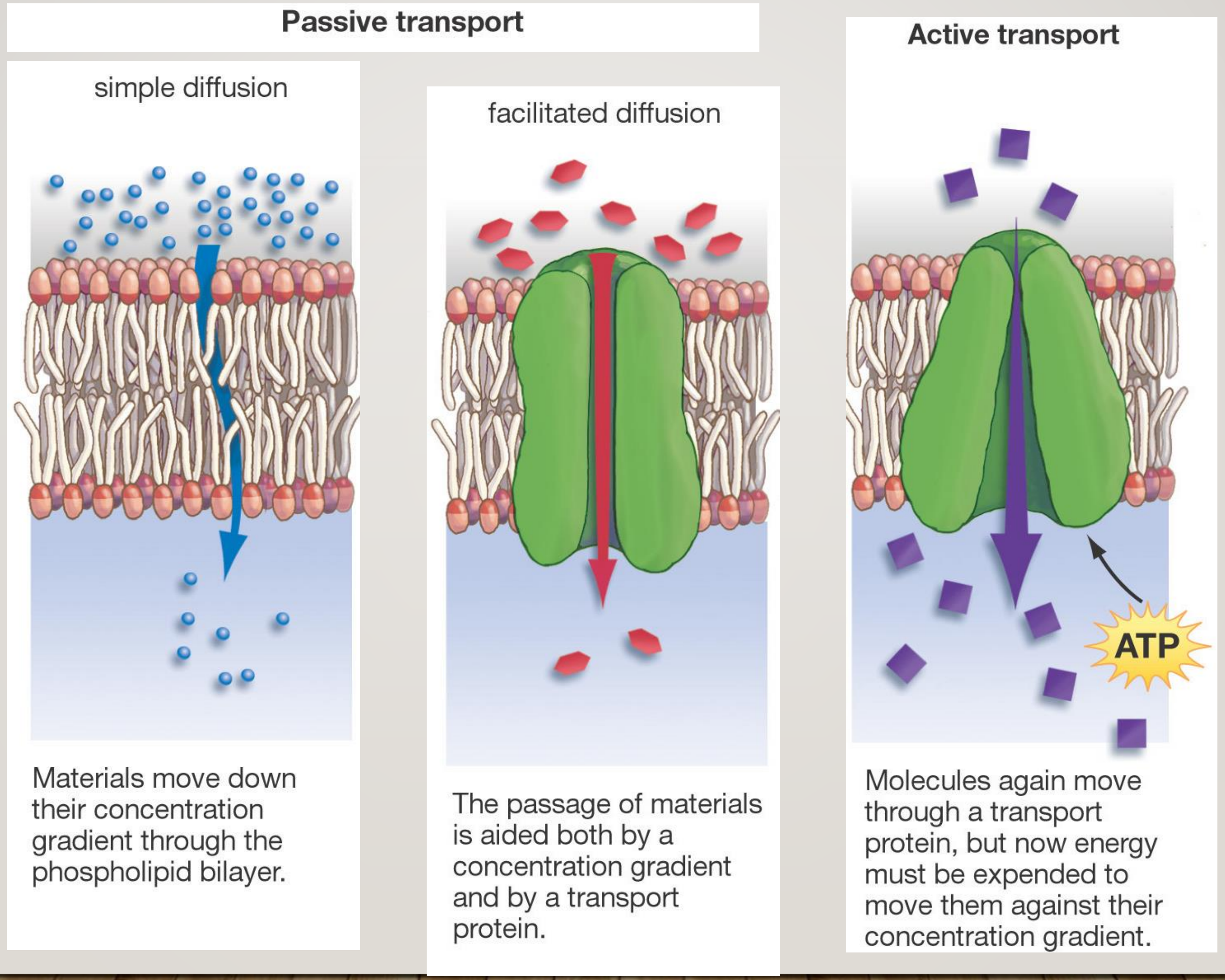
- e.g:

-active transport of glucose in the kidney is poisoned by phlorizin.





Three Forms of Transport Across the Membrane



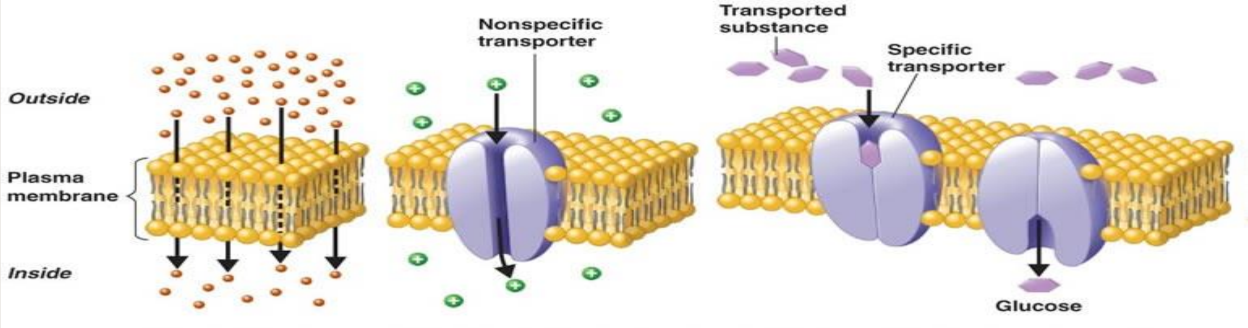
FACTORS THAT AFFECT NET RATE OF DIFFUSION

1- Membrane permeability

2- Concentration difference

3- Electrical potential

4- Pressure difference



(a) Simple diffusion through the lipid bilayer (b) Facilitated diffusion through a nonspecific transporter (c) Facilitated diffusion through a specific transporter

PERMEABILITY OF THE PLASMA MEMBRANE= PERMEABILITY OF THE PHOSPHOLIPID BILAYER.

1. Permeable means allowing something to pass through.
2. The plasma membrane is selective permeable or semi-permeable as it allows only certain substances to pass through it but not others.
3. The phospholipid bilayer is permeable to:

a) small non-polar (hydrophobic) molecules that are lipid-soluble, such as fatty acids, glycerol, steroid, vitamin A, D, E and K.

b) Small unchanged molecules, such as water, oxygen and carbon dioxide. These molecules are small enough to squeeze through between the phospholipid gaps by simple diffusion or osmosis down their respective concentration gradients.

4. The phospholipid bilayer is not permeable to:

a) large polar molecule, that are not soluble in lipid, such as glucose, amino acids, nucleic acids and polysaccharides.

b) Ions (charged), regardless of size, such as: H^+, Na^+, HCO_3^-, K^+, ca^{2+}, and Mg^2

1- **Membrane permeability for a given substance (P)**

The different factors that affect cell membrane permeability are

a- membrane thickness (d) [inversely proportional]

b- lipid solubility [directly proportional]

c- number of protein channels/unit area [directly proportional]

d- temperature [directly proportional]

e- molecular weight of the diffusing substance

[inversely proportional]

f- membrane area (A) [directly proportional]

2-Concentration difference

The rate at which the substance diffuses from side of high concentration to other with low concentration is proportional to the concentration difference

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Concentration Gradient =

change in the concentration of a substance from one area to another

3- Electrical potential

Electric potential or membrane voltage is the difference in membrane potential between the interior and the exterior of a biological cell.

If we have in the two sides of a membrane, two equal concentrations of substance and an electrical potential is applied across membrane, the application of that potential will cause the positive potential to attract negative ions, and the negative potential will repels them.

Action Potential:

When the inside of the cell membrane is negative ,

Resting potential:

Na ions are conc more{outside}
K ions are conc more (inside}
No move in ions during rest potential.

Depolarization (0.03s)

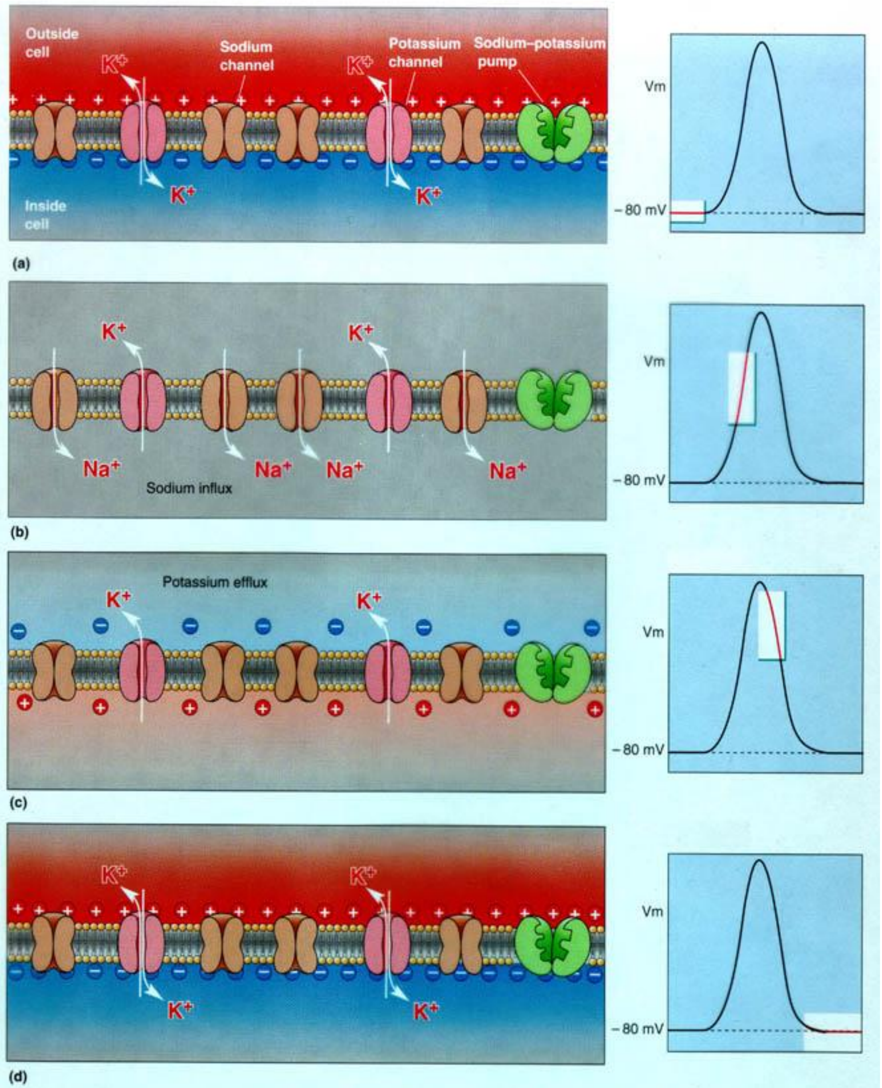
It is start when sodium ion start move inside
the nerve membrane .the resting potential fall from -70to-50mv

Threshold potential.

For sudden inflow of maximum sodium ions occur, this known
AP. 15mv is necessary to reach firing threshold, if it

Repolarization (0.07s):

Start with stopping of increased movement of sodium ion to inside the nerve .Now potassium ions start moving outside .This efflux of potassium ions result in repolarization and result in return of membrane potential to rest potential (-70 mv).The inflex of sodium and efflux of potassium are passive no ATP.



lower than 15 mv it will not initiate the impulse
There is rapid influx of the sodium ions from outside to inside the nerve as the membrane channels are wide open.
In the end of depolarization the electrical potential is reverse and become +40mv
AP is associated with rapid influx of sodium ion inside the membrane

Electrochemical Driving Force:

The total forces acting upon **ions** across a membrane is a combination of both chemical and electrical forces and is referred to as the electrochemical driving force. The net direction of this force is equal to the sum of both forces.

If the chemical and electrical forces on the ion are in opposite directions, and are equal, there is no net force on the ion and the **equilibrium potential** equals the membrane potential.

Electrical potential gradient exists across membrane because of the presence of ions plays an important role in a number of physiological situations.

Electrical potential gradients in living systems exist only across membranes because the fluid media are good conductors of electricity. If the number of electronic charges on an ion is (n) and (V) is the potential difference in volts across the membrane, the difference in the free energies (due to electrical charge distribution) inside and outside the membrane is given by **$\Delta G = nFV$** J/mole where,

F= Faraday constant (is the magnitude of electric charge per mole of electrons).

= 96.500 Joule or = 23 Kcal

ΔG = difference in free energy

So, **ΔG= 23nV Kcal/mole**

This value represents the free energy available to do useful work when the concentrations of ions are equal on each side of the membrane.

4-Pressure difference

Pressure actually means the sum of all the forces of the different molecules affecting a unit surface area at a given moment.

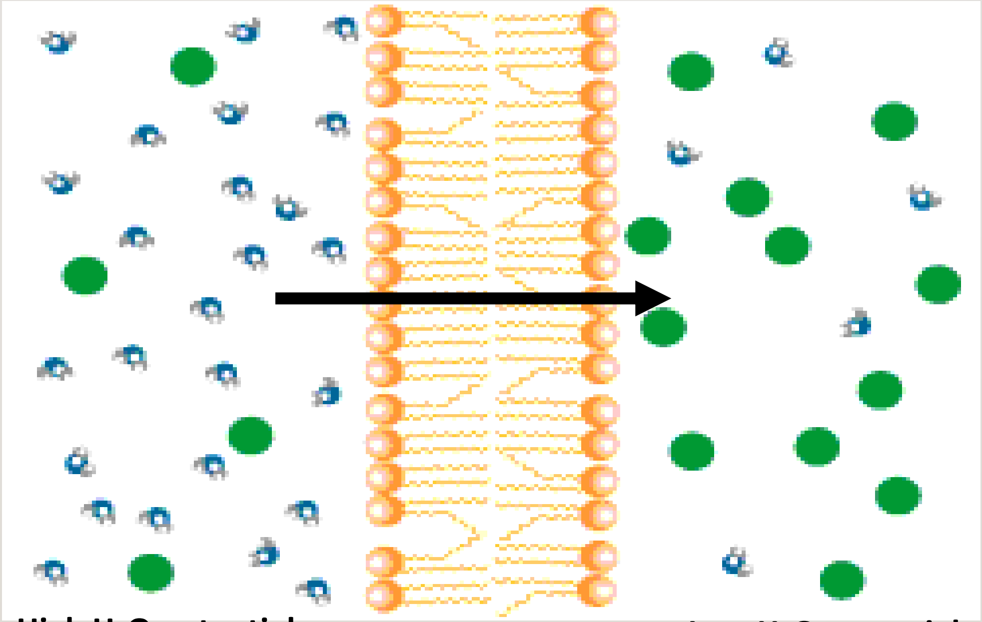
Therefore, when the pressure is higher on one side of a membrane than on the other, the result is that increased amount of energy are available to cause net movement of molecules from the high pressure side toward the low pressure side.

Higher pressure ⟶ molecules move faster

OSMOSIS

- It is the diffusion of water across a membrane
- Moves from **HIGH water potential** (low solute) to **LOW water potential** (high solute)

DIFFUSION OF H_2O ACROSS A MEMBRANE



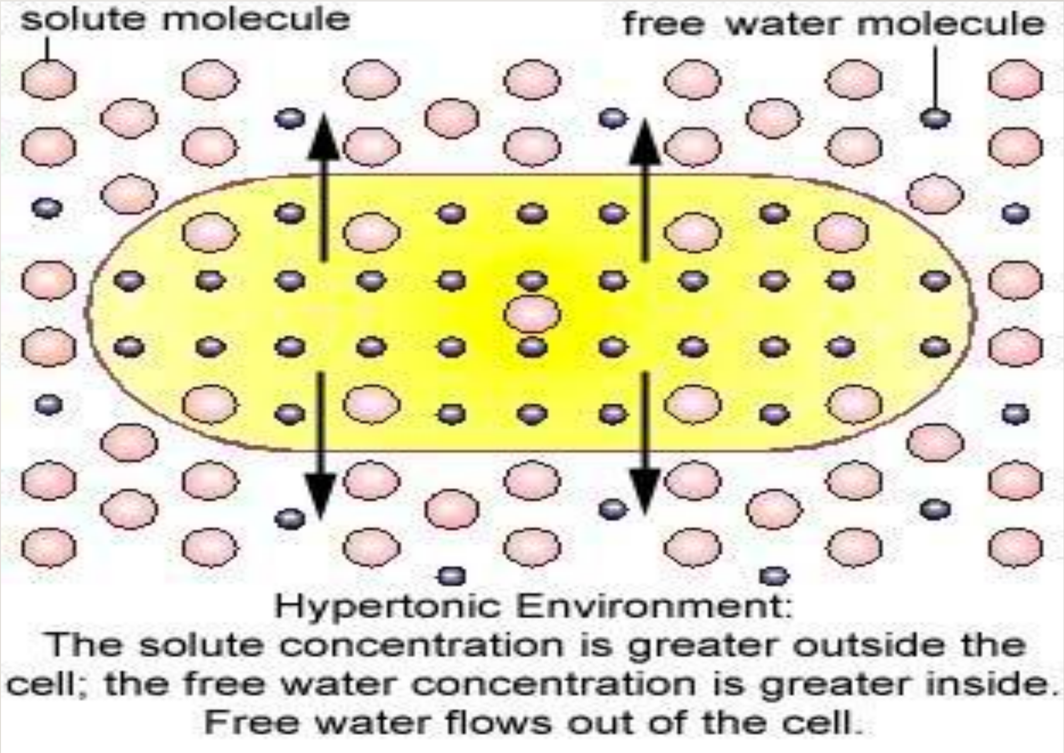
High H_2O potential
Low solute concentration

Low H_2O potential
High solute concentration

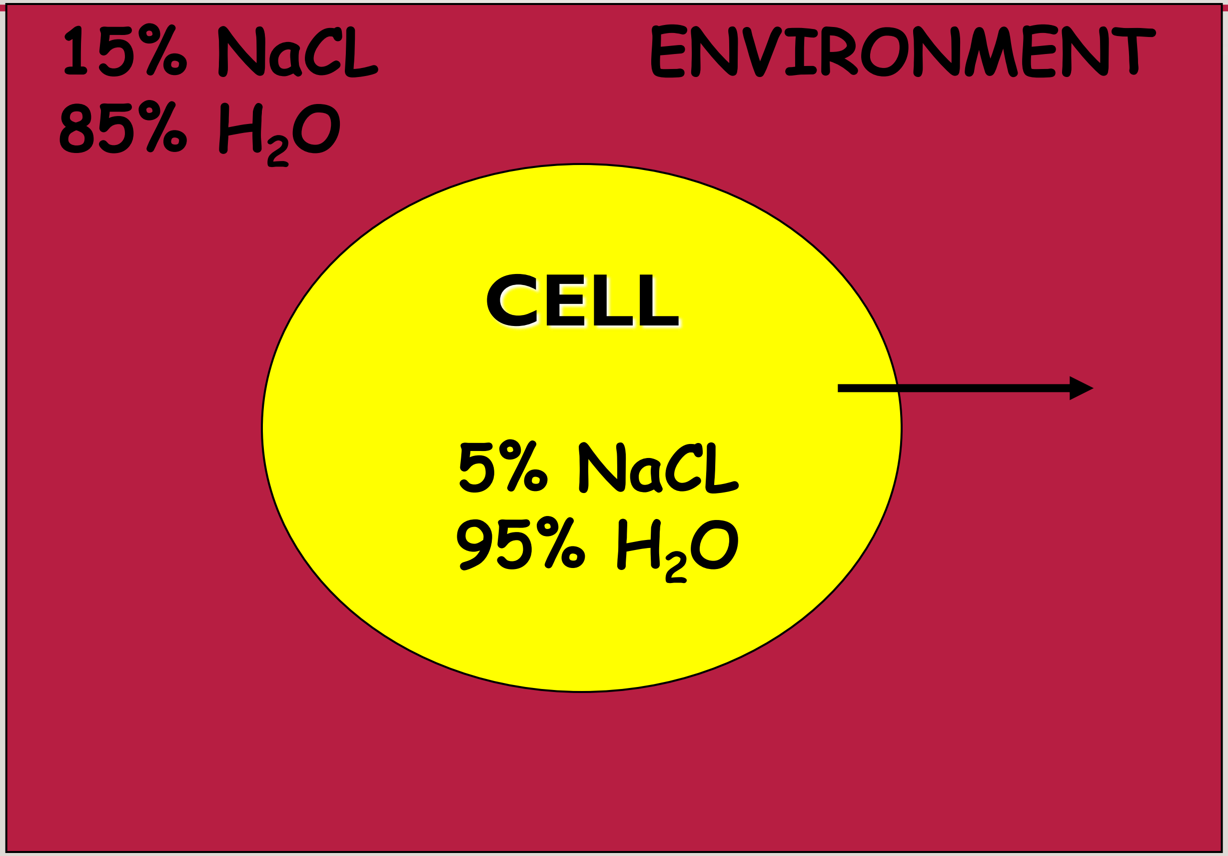
Biological application of osmosis

Hypotonic, hypertonic and isotonic solution

A **hypertonic solution** is a particular type of **solution** that has a greater concentration of solutes on the outside of a cell when compared with the inside of a cell.



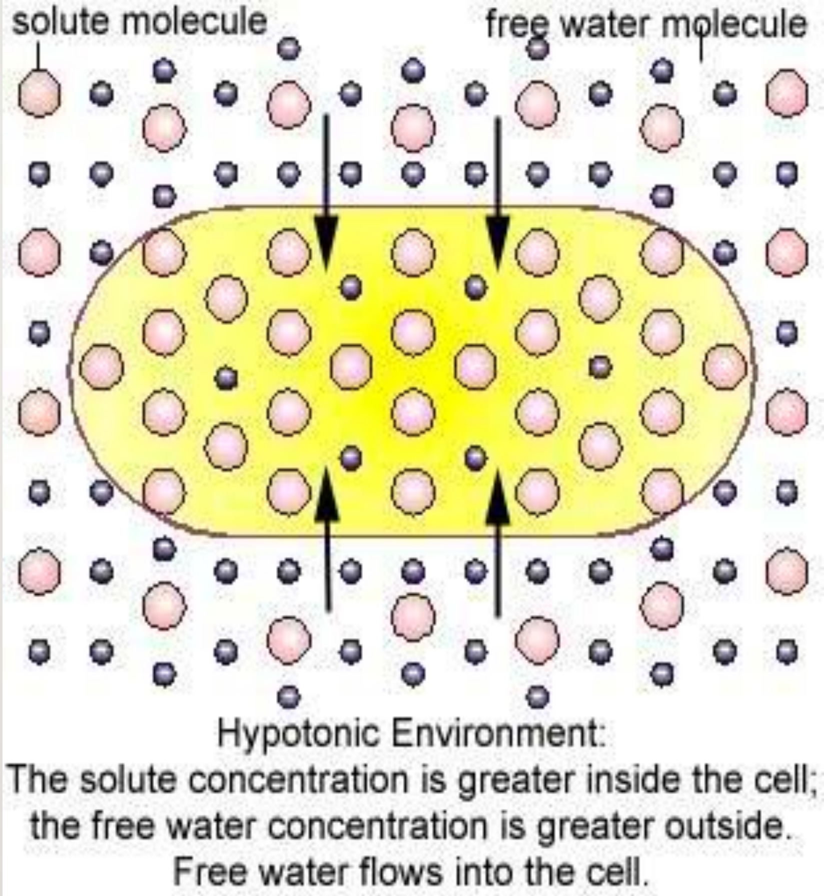
CELL IN HYPERTONIC SOLUTION



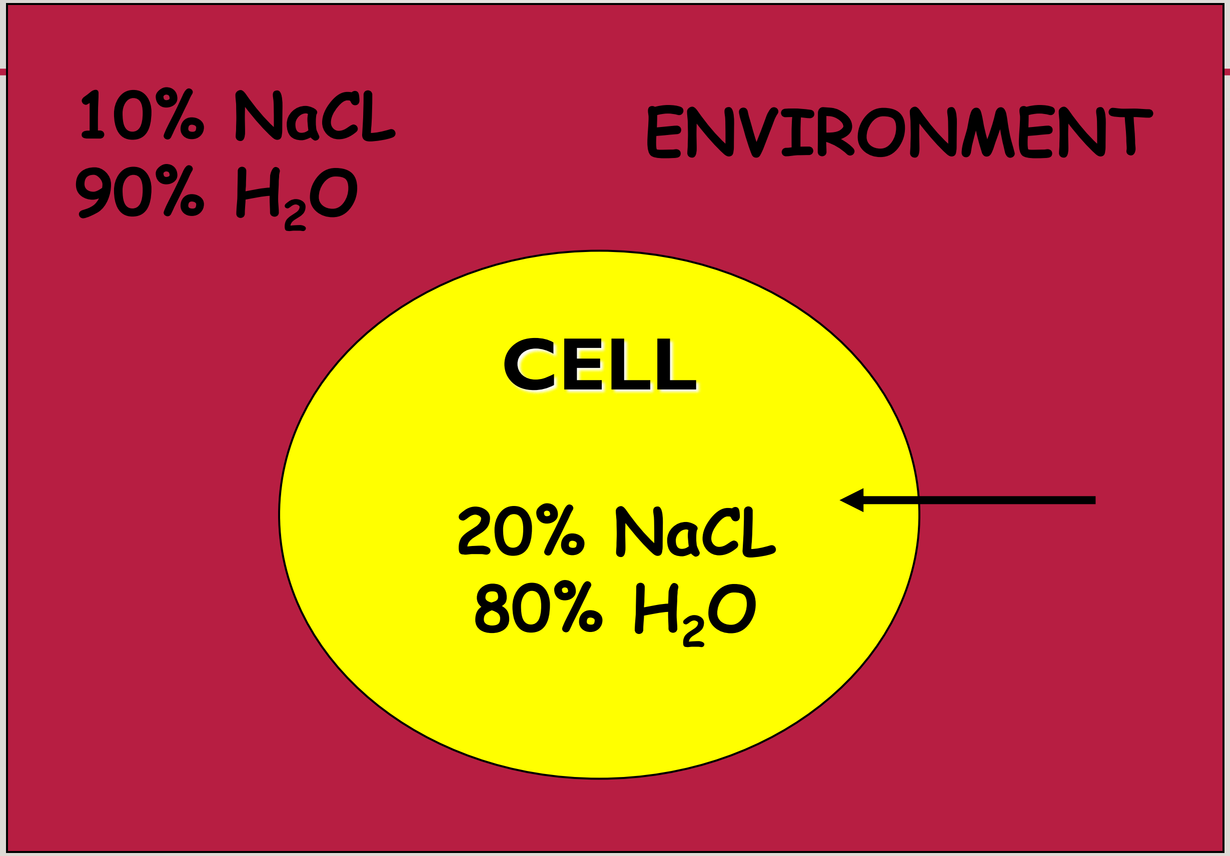
Hypotonic Solution

A hypotonic solution contain A solution with a lower salt concentration than in normal cells

When a cell is placed in a hypotonic solution, the water diffuses into the cell, causing the cell to swell and possibly explode.



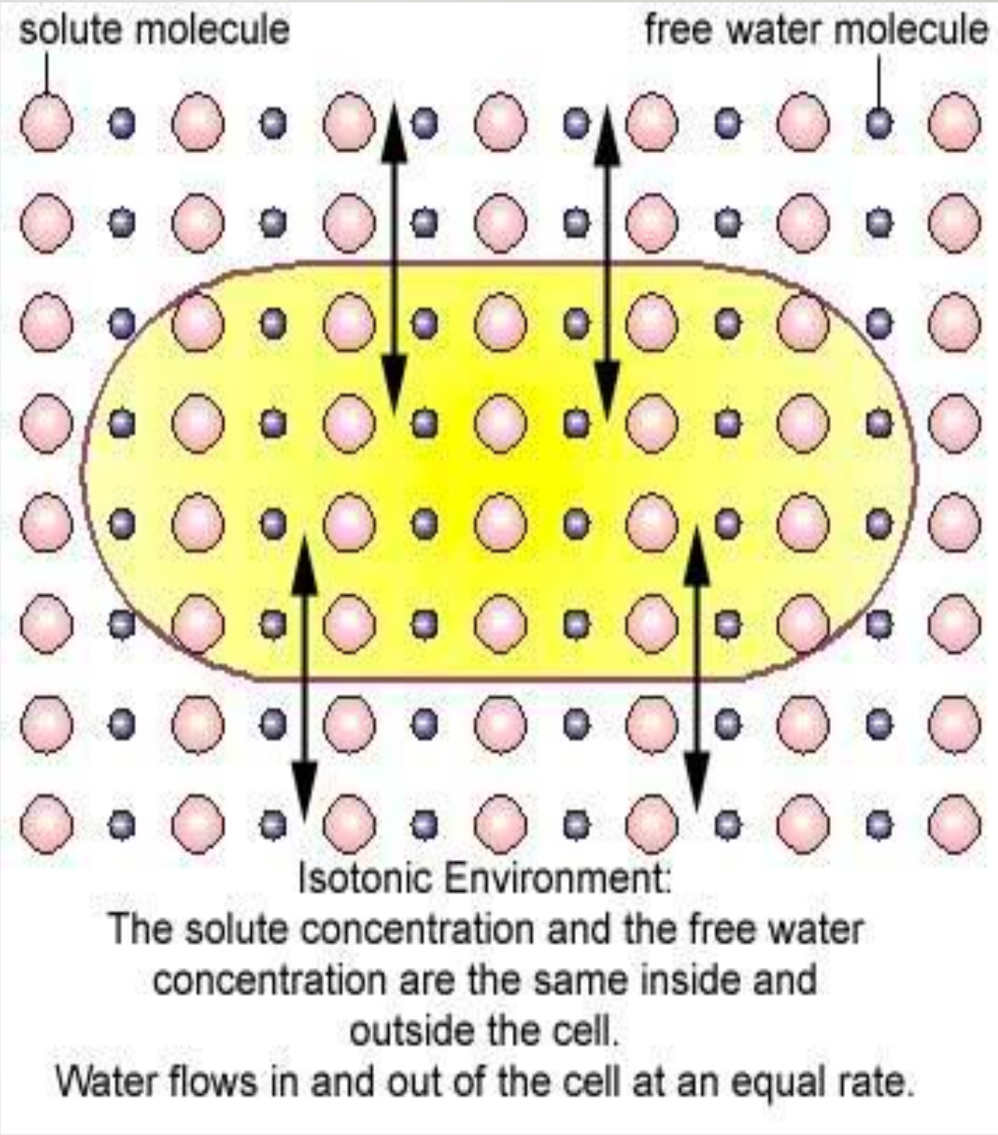
CELL IN HYPOTONIC SOLUTION



Isotonic Solution

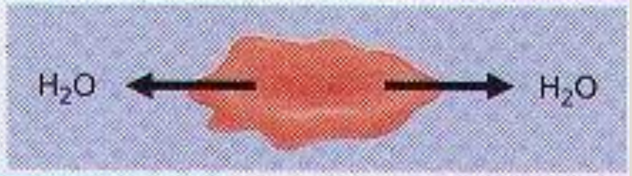
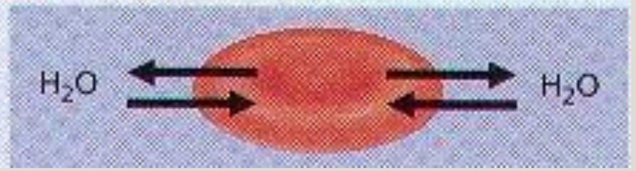
A solution that has the same salt concentration as the normal cells of the body and the blood.

When a cell is placed in an isotonic solution, the water diffuses into and out of the cell at the same rate. The fluid that surrounds the body cells is isotonic.

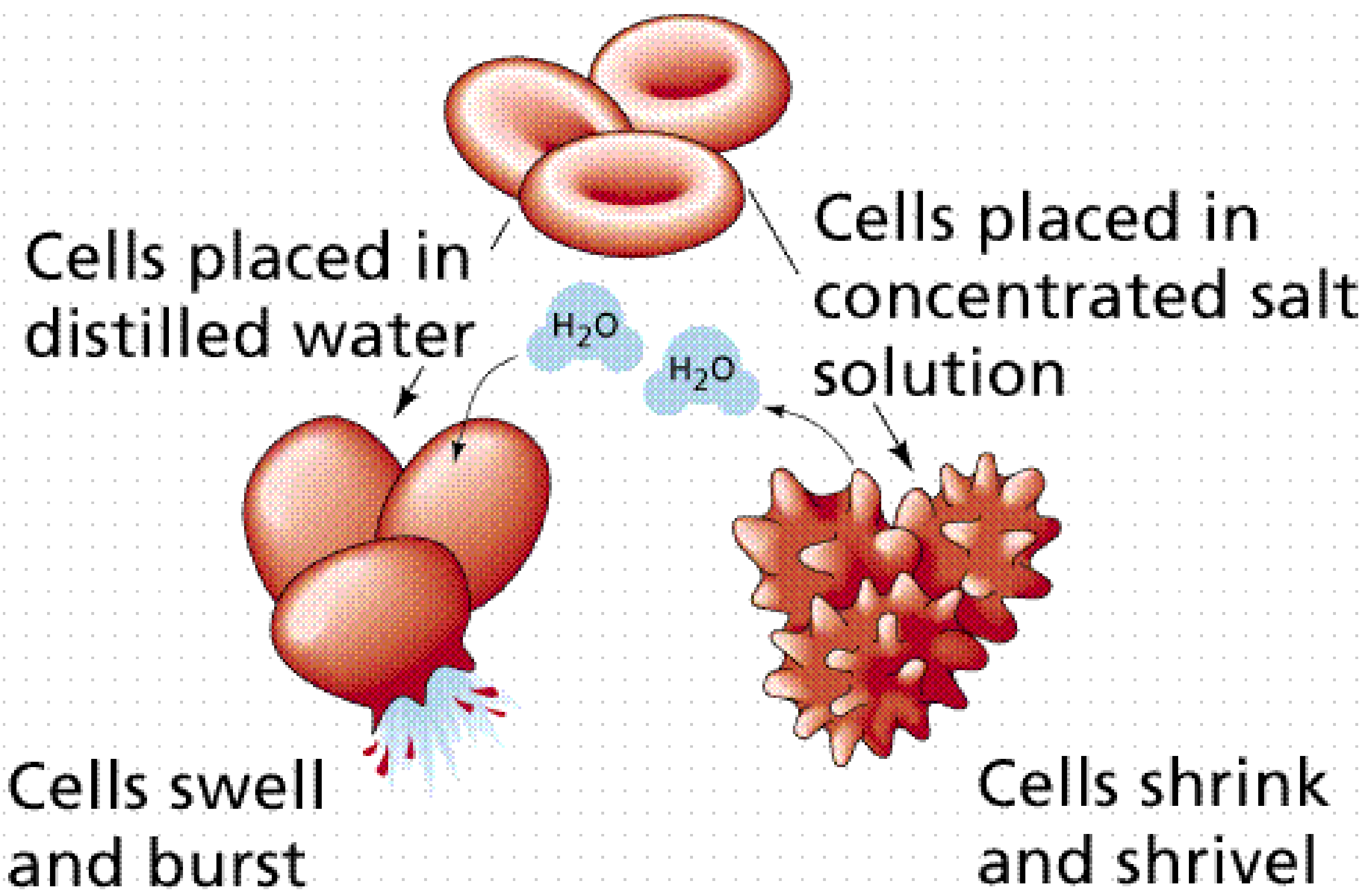


CELLS IN SOLUTIONS

TABLE 5-1 ***Direction of Osmosis***

Condition	Net movement of water	
External solution is hypotonic to cytosol	into the cell	
External solution is hypertonic to cytosol	out of the cell	
External solution is isotonic to cytosol	none	

CYTOLYSIS & PLASMOLYSIS



Cytolysis

Plasmolysis

- Transport of large **molecules by :**

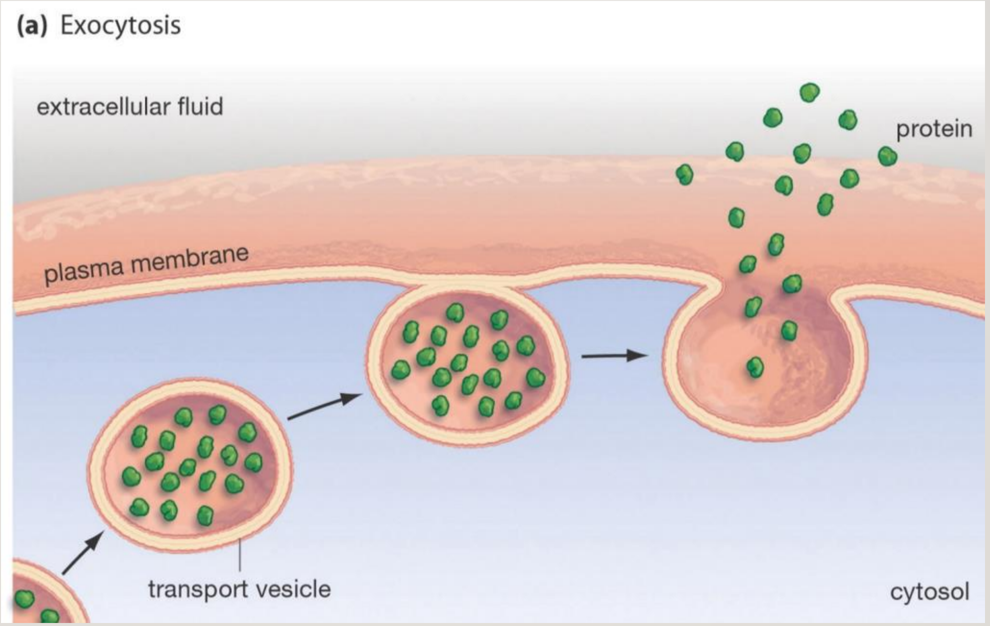
1. Endocytosis
2. Exocytosis

Endocytosis is the process of capturing a substance or particle from outside the cell by engulfing it with the cell membrane, and bringing it into the cell.

Exocytosis describes the process of vesicles fusing with the plasma membrane and releasing their contents to the outside of the cell

Moving the "Big Stuff" (EXOCYTOSIS)

Exocytosis- moving things out.

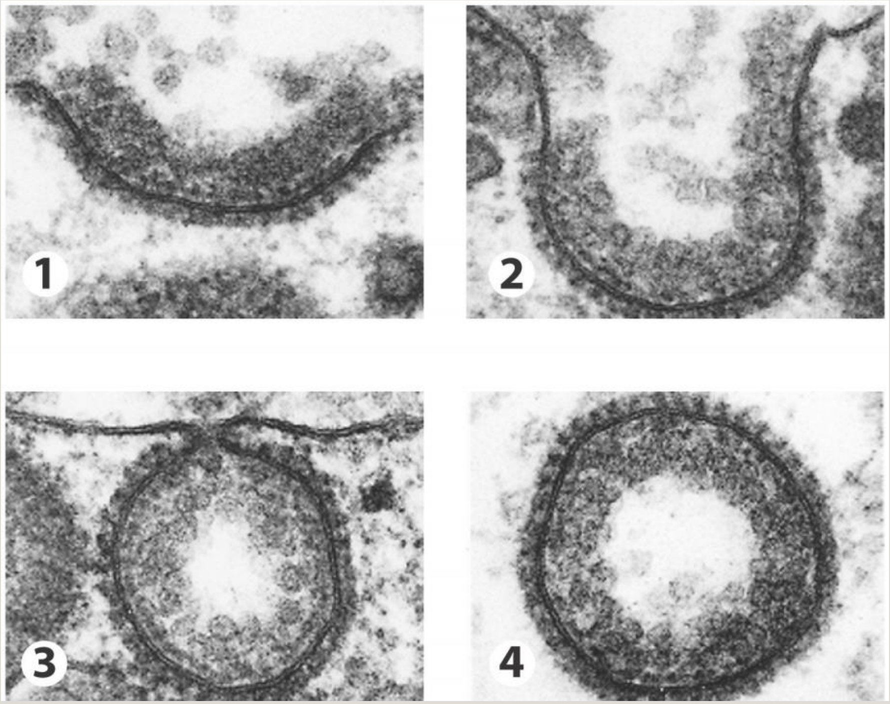


Molecules are moved out of the cell by vesicles that fuse with the plasma membrane.

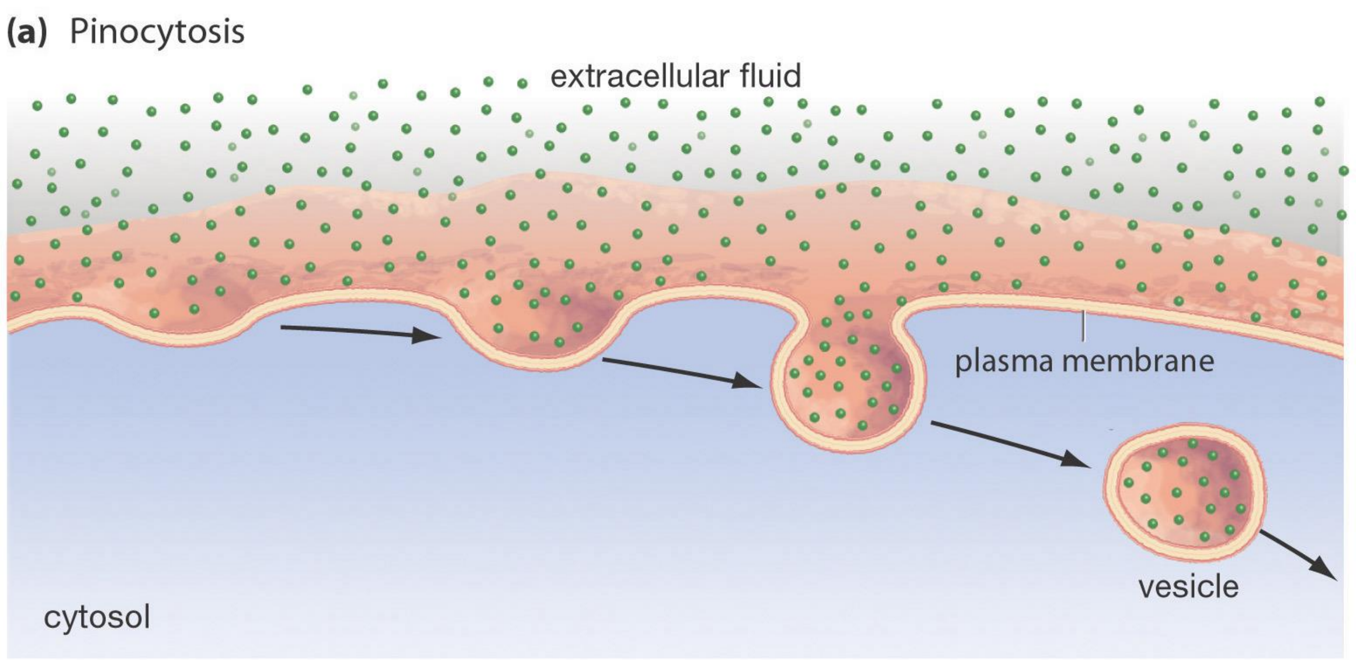
This is how many hormones are secreted and how nerve cells communicate with one another.

Moving the "Big Stuff" (ENDOCYTOSIS)

Large molecules move materials into the cell by one of
three forms of endocytosis



Endocytosis types
1- Pinocytosis

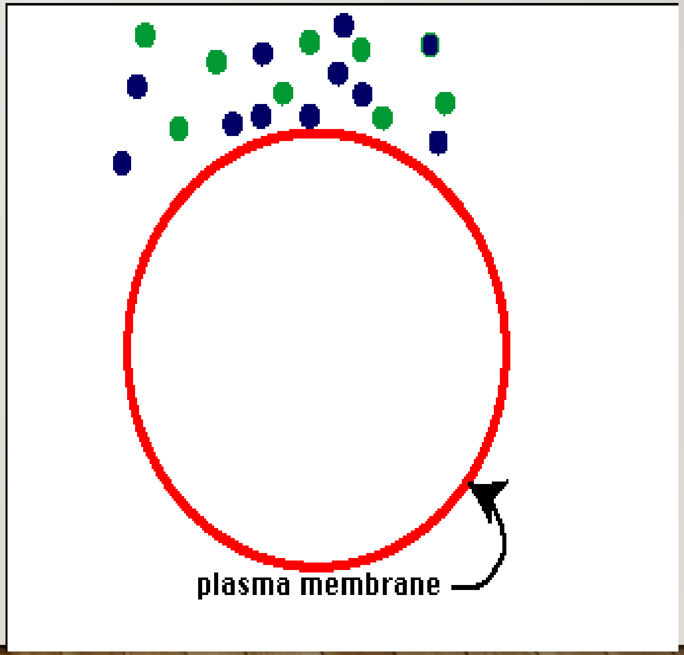


Most **common** form of endocytosis

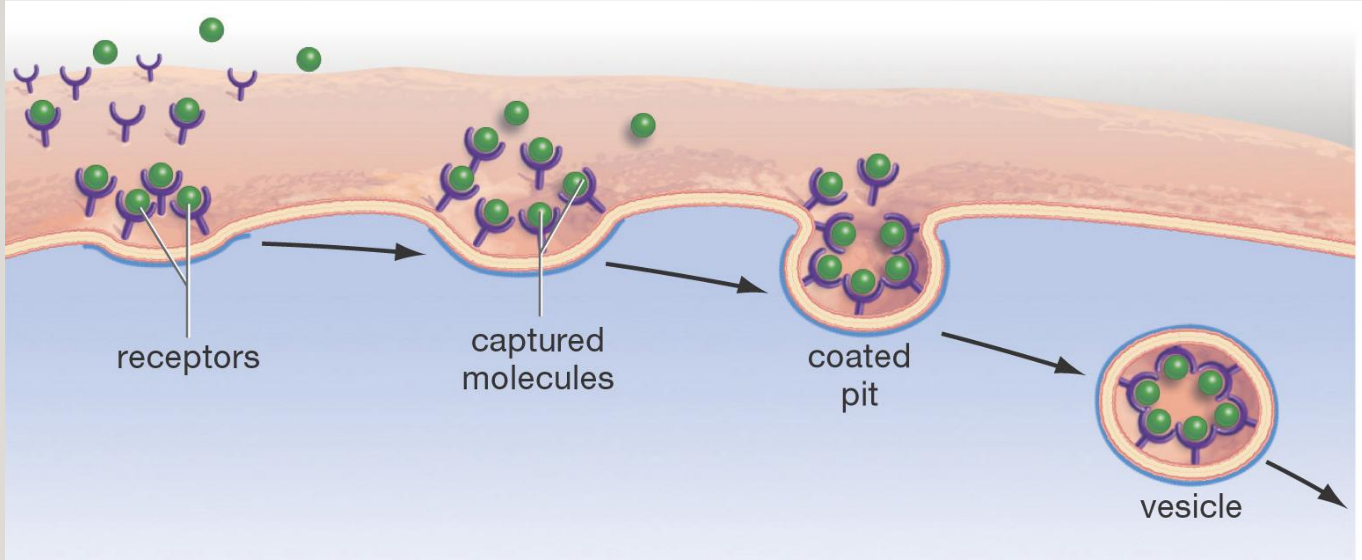
Takes in **dissolved** molecules as a vesicle

Endocytosis types
1- Pinocytosis

- Cell forms an **invagination**
- Materials **dissolve in water** to be brought into cell
- Called **"Cell Drinking"**

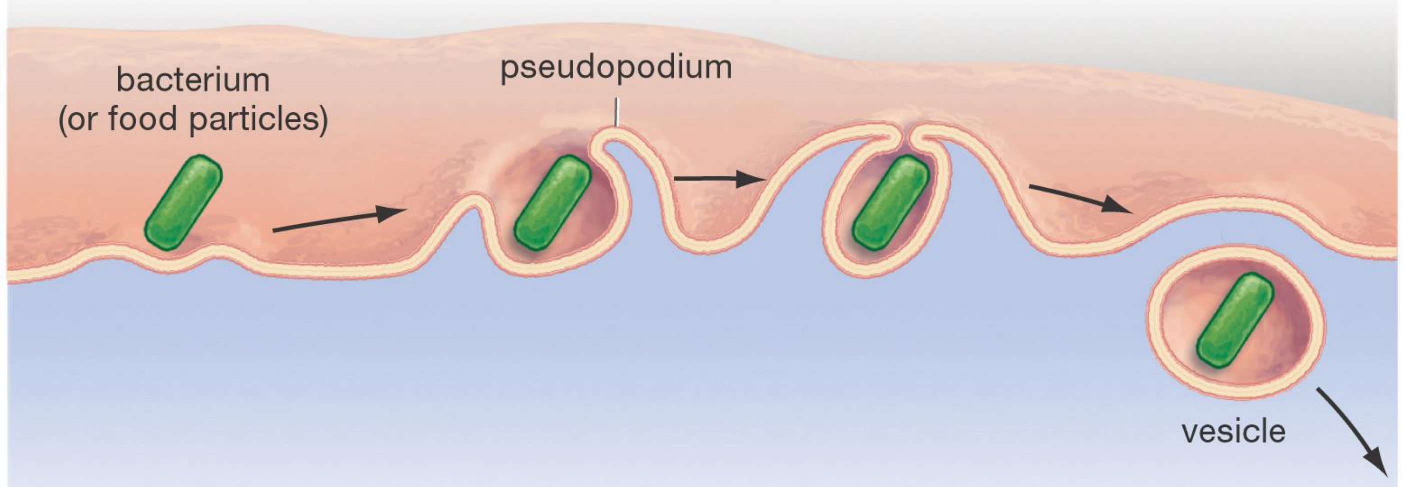


Endocytosis Types
2- Receptor-Mediated Endocytosis



Some **integral proteins** have **receptors** on their surface to recognize & take in **hormones, cholesterol**, etc.

Type of Endocytosis
3- Phagocytosis



Used to **engulf large particles** such as **food**, **bacteria**, etc. into vesicles

Called **"Cell Eating"**