Transport Through The Cell Membrane I

Code: CBF-103

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Learning Objectives:

At the end of the lecture the students should be able to:

- Describe different mode of transport through cell membrane.
- Basic principles of osmosis and osmotic pressure.
- Define isotonic, hypotonic, hypertonic.

Membrane Transport

Molecules capable of move across the plasma membrane by:
1-Diffusion
2-Osmosis
3-Carrier-mediated transport
4-Vesicular transport

Diffusion

All molecules are in continuous random motion as a result of their thermal energy.

Characters:

1-Diffusion occurs downhill (down the concentration gradient

2- Not need energy.

Passive (Simple) Diffusion

I- Simple diffusion through lipid bilayer:

1- Diffusion of lipid-soluble substances

1. The substances become dissolved in the lipid and transported to the other side.
2. The rate of diffusion is directly proportional to their lipid solubility.

For example:

Oxygen,
Nitrogen,
Carbon dioxide,
Alcohols

2-Transport of water

The causes of water diffusion through the lipid bilayer is that water
- are small molecules
- uncharged
- had great kinetic energy that they can penetrate it like a bullets

3-Transport of lipid-insoluble substances

1. If they are small enough can pass in the same way as H2O molecules.
2. The penetration falls off if they become larger. e.g: urea and glucose.
3. Ions-even small ones, such as Na+ and K+ penetrate the lipid bilayer about one million times less rapidly than H2O. As the electrical charge of these ions form hydrated ions with water and the electrical charge of the ions also interacts with the charges of the lipid bilayer causing its repel.

II- Simple diffusion through protein channels

I-Classification of channels according to their selective permeability:

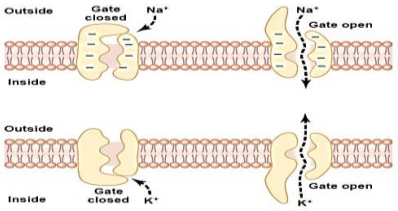
- characteristics of the channel itself such as: its diameter, its shape, and the nature of the electrical charges lining its inside surface.
- according to the type of the charges lining them to:

1. Positively charged channels for negatively charged particles as chloride.
2. Negatively charged channels for positively charged particles.
3. Un-charged channels for the passage of water, know as aquaporines.

II- Classification according to the presence or absence of the gate:

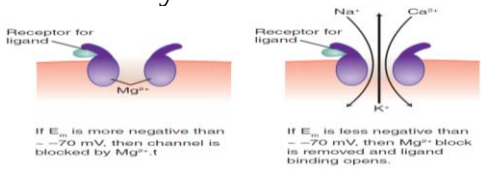
1-Leak channels. Some of channels have no gate and are continuously open.

2-Gated-channels. The gates are gate like extension



1. Voltage-gated channels: The gate open or close by alteration membrane potential.
2. Ligand-gated (Chemical-gated) channels: The gate open and close by binding to chemical substances (ligand).
3. Mechanically-gated channels: The gate open and close by mechanical stimulation.

*N.B.:There is one **exception** to the 3 classes: the **NMDA (N-methyl-D-aspartic acid) receptor** is both voltage- and ligand-gated.*



Factors that affect net rate of diffusion

I. Permeability of the membrane affected by:

1.Thickness of the membrane. The greater is the thickness of the membrane, the less the rate of diffusion.

2. Lipid solubility. The greater the solubility of the substance, the greater the molecules quantity of substances that dissolves in the membrane

3. Number of the protein channels. The rate of diffusion is directly related to the number of channels per unit area.

4.Temperature. The greater the temperature the greater is the thermal motion of molecules

5.**The molecular diameter.** The smaller is the diameter, the greater the permeability of the channels.

II-The diffusion coefficient (D):

It equals the multiply of membrane permeability (P) (which measures the movements of substances through a unite membrane area) by the total area of the membrane (A).

D = P X A

III-Effect of a concentration difference

The substances diffuse from the site of high concentration to the site of low concentration.

Net diffusion α (C_o - Ci)

In which, C_o: is the concentration on the outside Ci is the concentration on the inside

IV-Effect of an electrical potential

- If the concentration of negative ions is high on the outside of the membrane, and a positive charge has been applied to the inside of the membrane and a negative charge to the outside, creating an electrical gradient across the membrane.

The positive charge attracts the negative ions.

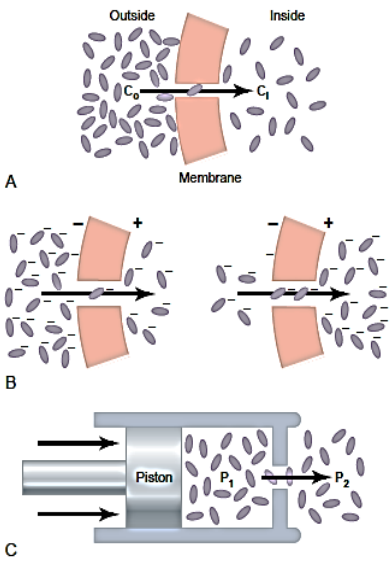
After much time, large quantities of negative ions will have moved to the inside creating a concentration gradient

The electromotive force (EMF) can be determined from formula called the ***Nernst equation*** at normal body temperature of 37°C.

$$EMF\ (millivolts) = \pm 61 \log \frac{Ci}{Co}$$

V- Effect of a pressure difference:

When the pressure is higher on one side of a membrane than the other (figure "C"), the molecules moves from the high pressure side toward the low pressure side.



Effect of concentration difference *(A)*, electrical potential difference affecting negative ions *(B)*, and pressure difference *(C)* to cause diffusion of molecules and ions through a cell membrane.

Factors that affect net rate of diffusion

Diffusion is described **by Fick's law**

$$J = P \times A \times C$$

Where ***J*** is the net flux (movement) of the compound; ***P*** is the permeability (diffusion) coefficient, specific for the compound and for the barrier; ***A*** is the membrane surface area involved; and ***C*** is the concentration gradient;

Factor	Effect on Rate of Net Diffusion
↑ Concentration gradient of substance (ΔC)	↑
↑ Surface area of membrane (A)	↑
↑ Lipid solubility (β)	↑
↑ Molecular weight of substance (MW)	↓
↑ Distance (thickness) (ΔX)	↓

Modified Fick's equation:

$$\text{Net rate of diffusion } (Q) = \frac{\Delta C \cdot A \cdot \beta}{\sqrt{MW} \cdot \Delta X}$$

$$\left[\text{diffusion constant } (D) \propto \frac{\beta}{\sqrt{MW}}\right]$$

$$\left[\text{permeability } (P) = \frac{D}{\Delta X}\right]$$

$$\text{Restated } Q \propto \Delta C \cdot A \cdot P$$

Osmosis

- **Osmosis** is the ***net movement of water*** through a membrane down its concentration.

In other words, water moves toward an area of higher ***solute*** concentration.

- Need ***semipermeable membrane to*** maintains a concentration difference
- The **osmotic pressure (π)** of a solution is the amount of pressure required to stop osmosis. An increase in the number of particles in the solution results in an increase in the osmotic pressure.
- If a solute does not easily cross a membrane, then it is an **"effective" osmole** for that compartment, i.e., it creates an osmotic force for water. For example, plasma proteins & Na^+.

Osmolar Gap

It is the difference between the **measured** osmolality and the **estimated** osmolality using the equation below. We can estimate the extracellular osmolality using the following formula:

ECF estimated osmolality= 2(Na^+) mEq/L + glucose mg %/18 + urea mg %/2.8

- Na+ is the most abundant osmole of the extracellular space. Na+ is doubled because it is a positive charge,
- The 18 and 2.8 are converting glucose and BUN into their respective osmolarities (their units are mg/dL).

Determining the osmolar gap (normal ≤15) is helpful for narrowing the differential diagnosis.

- **Osmolality** is concentration of particles per kg of solvent (water) (mOsm (milliosmoles)/kg)
  More practically, is to measure **osmolarity**, which is concentration of particles per liter of solution mOsm (milliosmoles)/L

  where: **Osmolarity** = g x c

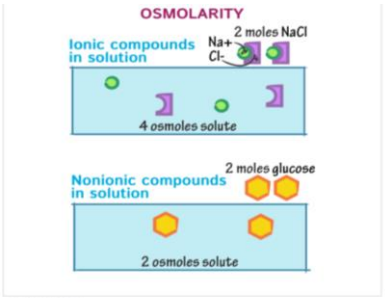
  g = number of particles in solution (Osm/mol),

  c = concentration (mmol/L)

e.g. A solution of 1 mol/L NaCl is separated from a solution of 2 mol/L glucose by a semipermeable membrane:

- NaCl is completely dissociated i.e., separated into two particles thus for NaCl, g = 2.0.
  NaCl Osmolarity = g x C
  = 2 × 1 mol/L = 2 Osm/L
- Glucose does not dissociate in solution;
  thus for glucose , g = 1.0.
  Glucose Osmolarity = g x C
  = 1 × 2 mol/L= 2 Osm/L

Each solution has an osmolarity of 2 Osm/L. They are isosmotic



OSMOLARITY
- Osmolarity (osmotic concentration)
- Measure of solute concentration (osmoles of solute per liter)

Ionic compounds
- Often dissociate in solution (NaCl becomes Na+ and Cl-)
- 2 moles of NaCl therefore become 4 osmoles of solute (2 Na+ and 2 Cl-)

Nonionic compounds
- Don't dissociate in solution
- 2 moles of glucose therefore become 2 osmoles of solute

Types of Solutions on the basis of osmotic pressure

1-Isotonic solution

Two solutions that have the same osmolarity. **The red blood cells** are suspended in the ***plasma*** (isotonic solution). The sizes remain unchanged.

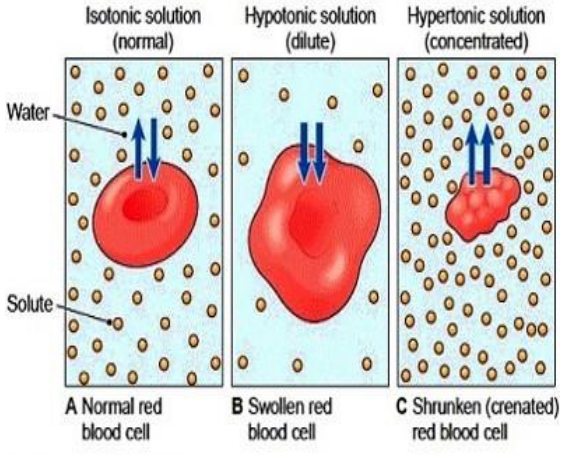
2-Hypotonic solution

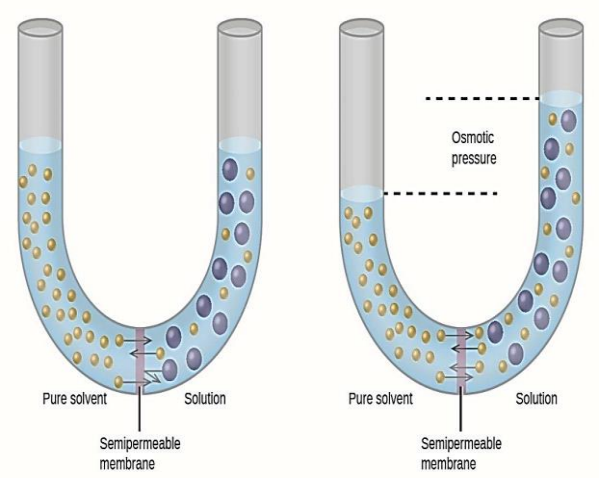
. The cell swells and may burst or rupture.

3-Hypertonic solution

The cells shrink.

Intravenous injections are often prepared with 0.9% sodium chloride or 5% glucose

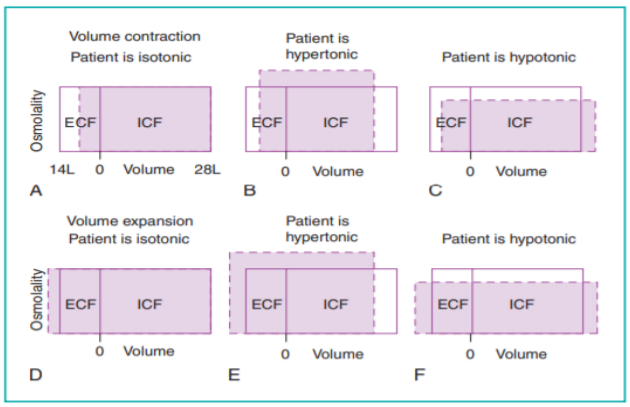




Summary of volume change and body osmolarity following changes in body hydration

	ECF Volume	Body Osmolarity	ICF Volume	D-Y Diagram
Loss of isotonic fluid Hemorrhage Diarrhea Vomiting	↓	No change	No change	
Loss of hypotonic fluid Dehydration Diabetes insipidus Alcoholism	↓	↑	↓	
Gain of isotonic fluid Isotonic saline	↑	No change	No change	
Gain of hypotonic fluid Hypotonic saline Water intoxication	↑	↓	↑	
Gain of hypertonic fluid Hypertonic saline Hypertonic mannitol	↑	↑	↓	

ECF: extracellular fluid; ICF: intracellular fluid



The six Darrow-Yannet (D-Y) diagrams show the relative changes in volume (x-axis) and osmolarity (y-axis) of the extracellular fluid (ECF) and intracellular fluid (ICF). Zero for the x-axis is on the line separating the ICF and the ECF. An increase in ECF volume expands the figure along the x-axis to the left, and an increase in ICF volume expands the figure to the right. A, There is a loss of an isotonic fluid, and only the extracellular volume is changed. B, There is a loss of a hypotonic fluid, and the original decrease in extracellular fluid volume is attenuated by movement of water from the intracellular volume to the extracellular volume. C, There is a loss of a hypertonic fluid, and the original decrease in extracellular fluid volume is augmented by a shift of fluid from the extracellular space into the cells. D, There is a gain of an isotonic fluid, and only the extracellular volume is changed. E, There is an addition of a hypertonic fluid, and any extracellular volume increase is a result both of the additional fluid and the movement of fluid from the cell volume to the extracellular fluid volume. F, There is a gain of a hypotonic fluid, and the expansion of the extracellular fluid volume space is attenuated by the movement of some of the new fluid into the intracellular fluid volume

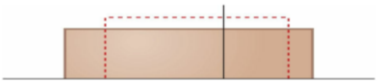
6 Darrow-Yannet diagrams illustrating changes in volume and/or osmolality.

- The y axis is solute concentration or osmolality. The x axis is the volume of intracellular (2/3) and extracellular (1/3) fluid.
- If the solid line represents the control state, the dashed lines show the changes in volume and/or osmolality.
- Extracellular volume always **enlarges** when there is a net gain of fluid by the body and always **decreases** when there is a net loss of body fluid. Concentration of solutes is equivalent to body osmolality.
- If ECF osmolality increases, cells lose water and shrink. If ECF osmolality decreases, cells gain water and swell.

Loss of fluid:

A- Patient shows **loss of extracellular volume with no change in intracellular volume or osmolality**. Since extracellular osmolality is the same, this represents an isotonic fluid loss (equal loss of fluid and osmoles). Possible causes are hemorrhage, isotonic urine, or the immediate consequences of diarrhea or vomiting.

B- Patient shows **loss of extracellular and intracellular volume with rise in osmolality**. This represents a net loss of water (greater loss of water than osmoles). Possible causes are inadequate water intake or sweating. Pathologically, this could be hypotonic water loss from the urine resulting from diabetes insipidus.

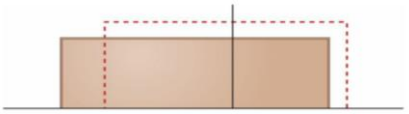


C- Patient shows **decrease in extracellular volume and osmolality with an increase in intracellular volume**. The rise in intracellular volume is the result of the decreased osmolality. This represents a net loss of hypertonic fluid (more osmoles lost than fluid). The cause is adrenal insufficiency e.g Lack of aldosterone causes excess Na+loss.

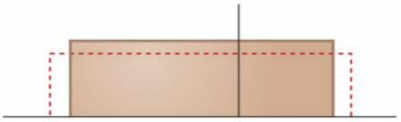
Gain of Fluid:

D- Patient shows **increase in extracellular volume with no change in osmolality or intracellular volume.** Since extracellular osmolality didn't change, then intracellular volume is unaffected. This represents a net gain of isotonic fluid (equal increase fluid and osmoles). Possible causes are isotonic fluid infusion (saline).

E- Patient shows **gain of extracellular volume, increase in osmolality, and a decrease in intracellular volume.** The rise in osmolality shifted water out of the cell. Possible causes are ingestion of salt, hypertonic infusion of solutes that distribute extracellularly (saline, mannitol). or hypertonic infusion of colloids. e.g. dextran.



F- Patient shows **increase in extracellular and intracellular volumes with a decrease in osmolality.** The fall in osmolality shifted water into the cell. Possible causes are drinking significant quantities of water (polydipsia), drinking significant quantities of a hypotonic fluid, or a hypotonic fluid infusion (saline, dextrose in water). Pathologically this could be abnormal water retention such as that which occurs with syndrome of inappropriate ADH.



Carrier-Mediated Transport

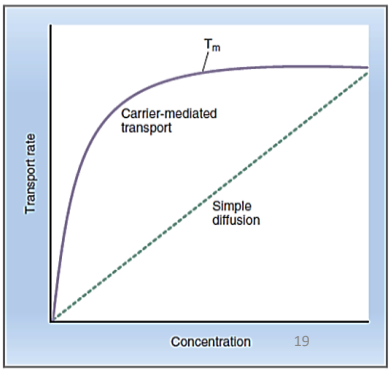
Characters of the carrier:

1-Specificity: Each carrier protein is specialized to transport a specific substance.

2-Competition: Several closely related compounds may compete for a ride across the membrane on the same carrier.

3-Saturation:

- There is a limit to the amount of a substance that can be transported via a carrier in a given time. This limit is known as the *transport maximum (Tm).*
- Until Tm is reached, the rate of transport is directly related to its concentration.
- When Tm is reached, the increase in the substance's concentration is not accompanied by corresponding increase in the rate of transport.



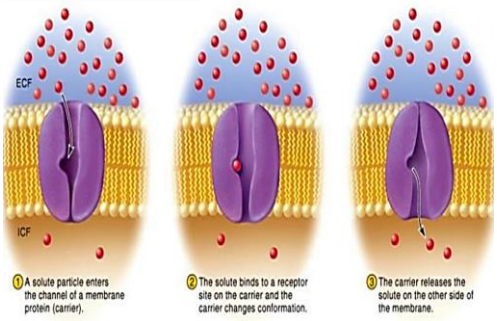
Carrier-mediated transport

1. Facilitated diffusion
2. Active transport

I- Facilitated Diffusion

Characters

1. Need carrier protein.
2. Down the concentration gradient ***(downhill)***
3. No energy is needed.
4. Example: transport of glucose and amino acids.



The mechanism

Binding of extracellular solute to the carrier, causes conformation change of the carrier. Bound solute dissociates from the carrier because of the low intracellular concentration of solute. The carrier revert to its original conformation to begin the cycle again.

References:

- Lippincott' integrated systems book
- Human body in health and diseases
- Elsevier's integrated physiology
- USMLE lectures note by kaplan