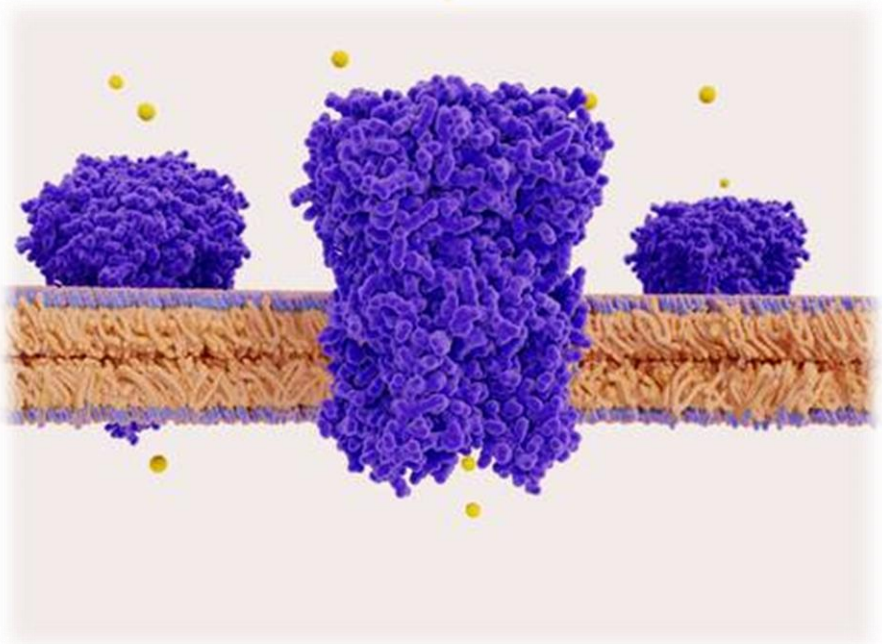


Transport of Substances Across Cell Membrane

Cell Biology

Assoc. Prof. Güvem GÜMÜŞ AKAY

guvemakay@gmail.com

Ankara University School of Medicine

Department of Physiology

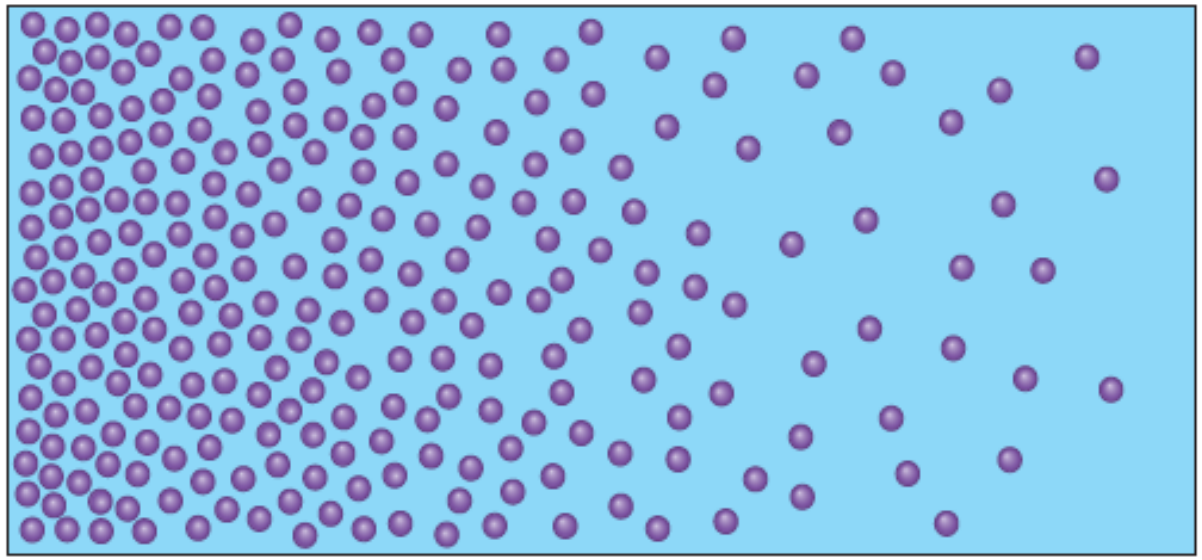
Key Points

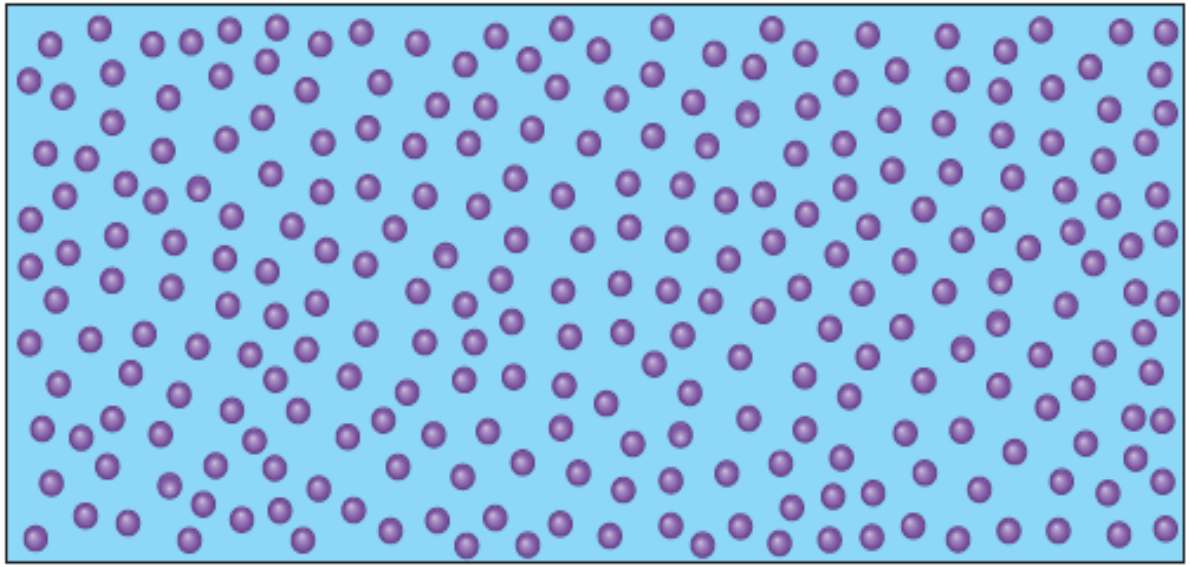
- Importance of transport of substances across the cell membrane
- What is diffusion?
- Basic principles of mebrane transport
  - Transport of small molecules
  - Epithelial transport
  - Transport of large molecules

The importance of transport of substances across the membrane

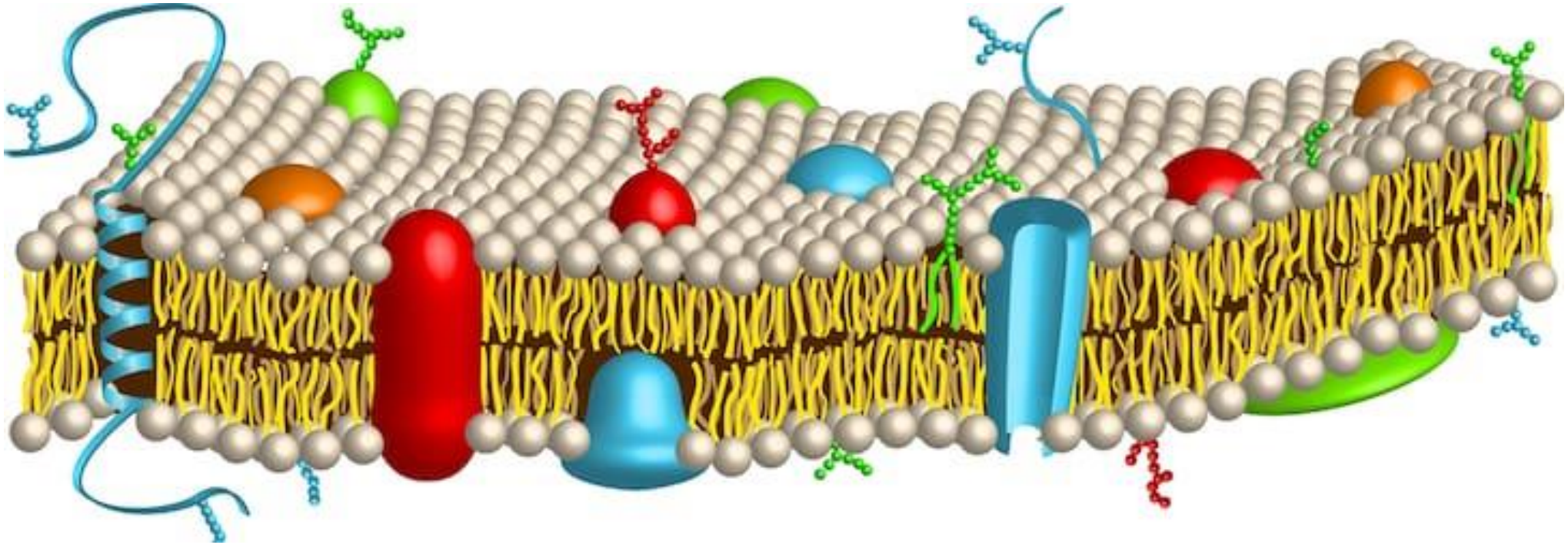
- Many of the protein-coding genes in different organisms encode transport proteins.
- 15-30% of membrane proteins are transport proteins.
- Some specialized mammalian cells use 2/3 of their total metabolic energy for transportation processes.

Diffusion





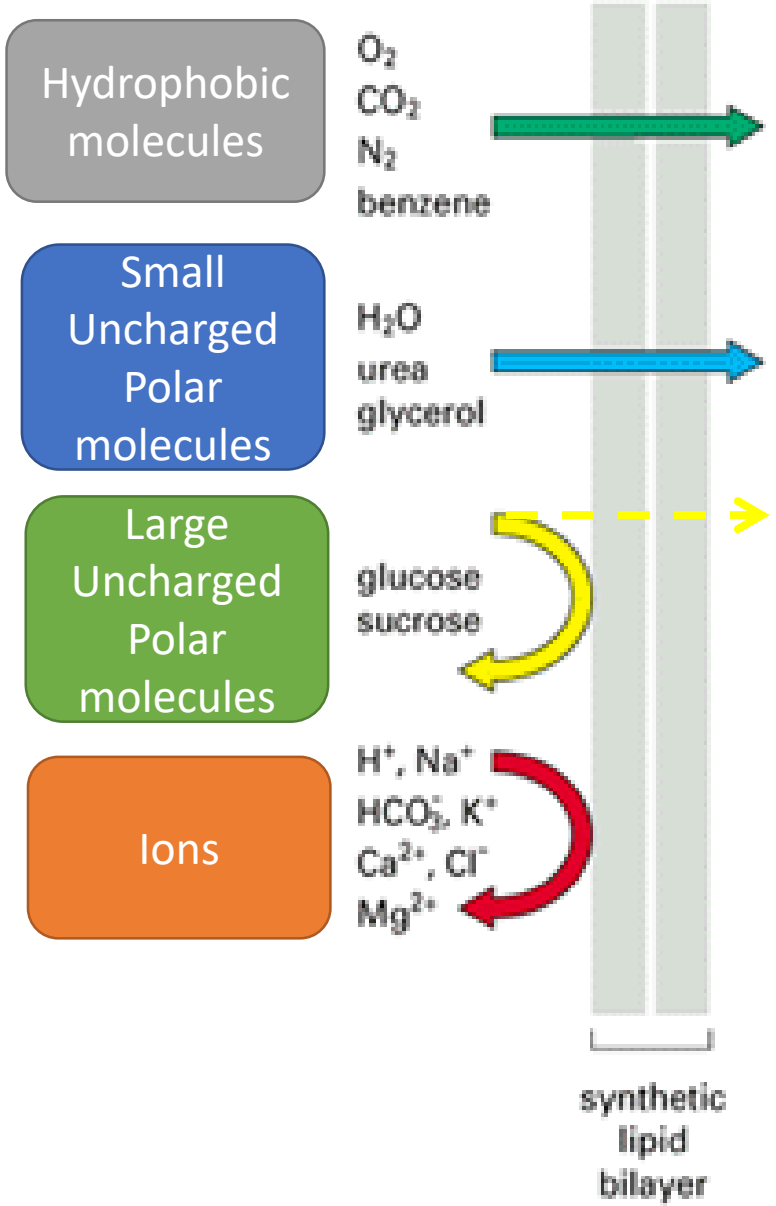
Basic structure of the cell membrane

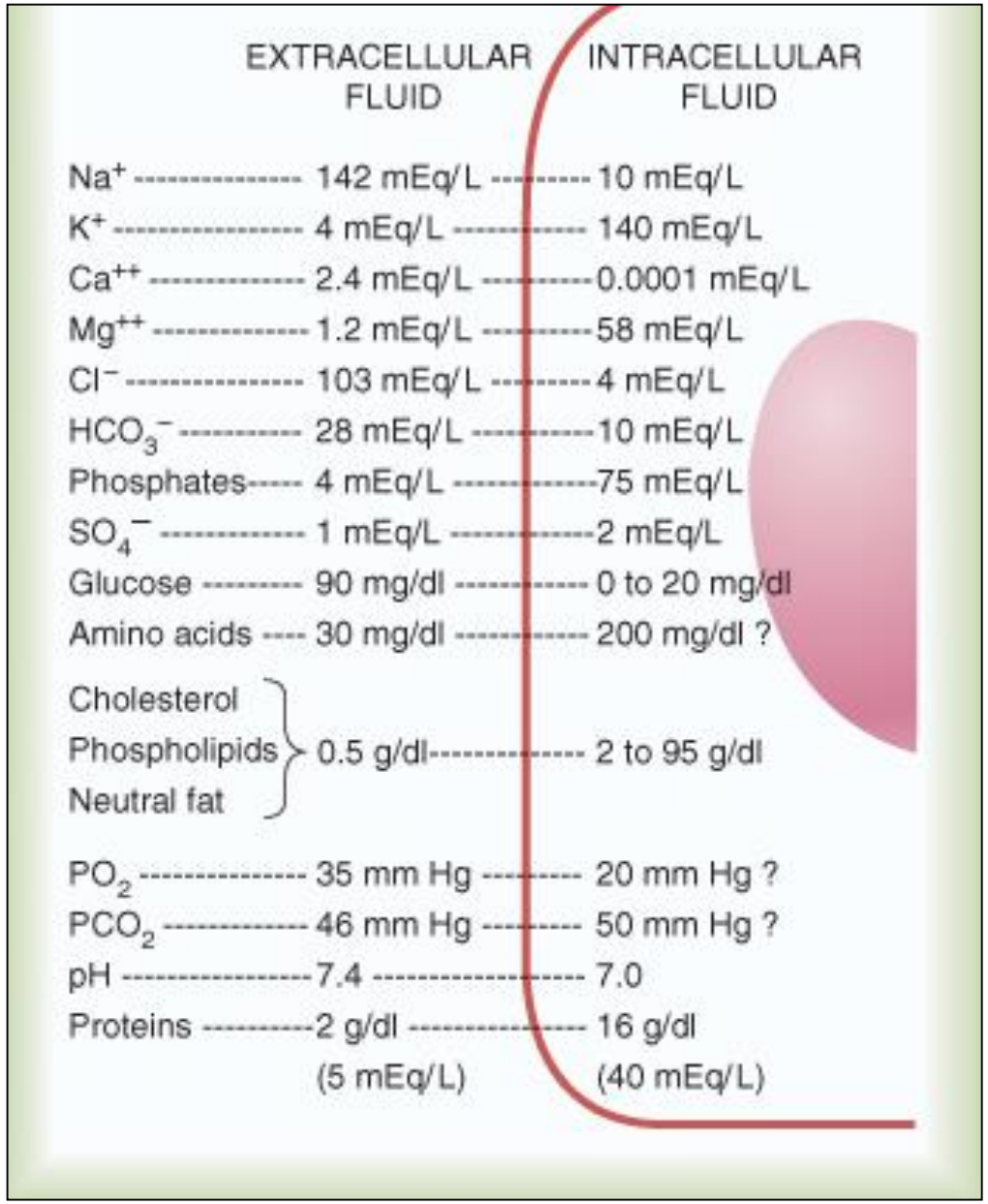


Transport of substances accross cell membranes

Because of their hydrophobic internal parts, lipid bilayer:

- is **permeable** to
  - Small, uncharged, polar molecules
  - Hydrophobic molecules
  - Gases
- is **impermeable** to
  - Charged molecules (e.g. Na^+, Cl^-, K^+, Ca^{2+})
  - Large water soluble molecules (e.g. Proteins, nucleic acids, sugars, nucleotides etc.)
- **Selective permeability**





Guyton and Hall Textbook of Medical Physiology, 13th Ed

Principles of Transport Across Plasma Membrane

Transport of Small Molecules

Transport of small molecules and ions

A) Passive transport

- Simple diffusion
- Facilitated diffusion
  - **Pores** (un-gated channels)
  - **Channel proteins** (gated pores)
  - **Carrier proteins** (permeases)
  - Osmosis

B) Active transport

- ATP dependent (Primary active transport)
- Dependent on ion gradients (Secondary active transport)

A) Passive Transport: **No energy required**

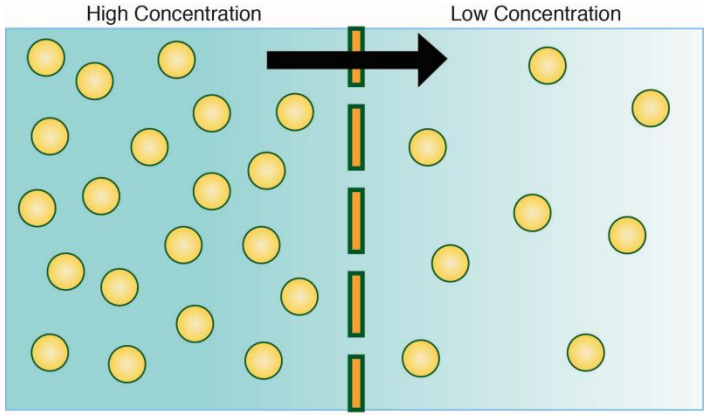
1) Simple diffusion
2) Facilitated diffusion

Direction and driving force of transport

Uncharged molecules
The concentration difference of the molecule on both sides of the membrane:
In the direction of the concentration gradient

Molecules with a net charge
Concentration gradient+
Electrical potential difference=
In the direction of the electrochemical gradient

1) Simple diffusion



Hydrophobic molecules

Small Uncharged Polar molecules

O_2, CO_2, H_2O, alcohol, steroid hormones etc.

Cooper. The Cell: A molecular approach, 2nd edition

2) Facilitated diffusion

Integral Membrane Proteins

i. Pores (ungated channels)

ii. Channel proteins (gated pores)

iii. Carrier proteins (transporters, carriers, permeases)

✓They are found in all biological membranes and in very different forms.

✓Each protein carries a specific group of molecules (eg. **sugars, amino acids, ions**).

Large Uncharged Polar molecules

Charged molecules Ions

2) Facilitated diffusion

✓No external source of energy is provided.

✓Molecules travel across the membrane in the direction determined by their concentration gradients / the electric potential across the membrane.

✓High → Low

Large Uncharged Polar molecules

Charged molecules Ions

Pores (ungated channels)

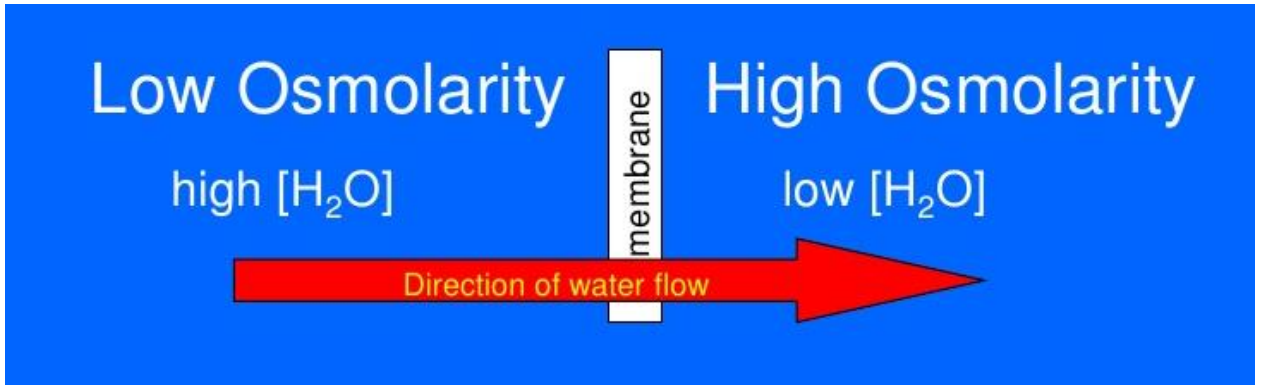
- Both sides are always open
- Aquaporins

Osmosis

- Net diffusion of water across a membrane
- Aquaporins: Water channels
- Different numbers in different membranes and the numbers can be altered in response to various signals

Osmolarity

- The total solute concentration of a solution
- 1 osmol (osm) = 1 mol of solute particles
  - 1 M glucose= 1 osm
  - 1 M NaCl=2 osm



Channel Proteins (Gated pores)

- ✓ They form an aqueous, hydrophilic pore through the lipid bilayer.
- ✓ When opened, they generally allow transport of ions that have appropriate charge and size.
- ✓ There is a very weak interaction between the transported molecule and the channel protein.

Ion channels

- Extremely rapid transport
- High selectivity
- Most ion channels are not permanently open

They always mediate transport in the direction of the electrochemical gradient (passive)

- Na^+, K^+, Ca^{2+}, Cl^- channels

Ion channels

They show **ion selectivity**

- ✓Only ions of the proper size and charge can pass through a particular ion channel.
- ✓In order to pass through the narrowest part of the channel (selectivity filter), ions have to leave the water molecules they are in contact with.

Prolonged stimulation causes desensitization

Stimuli that cause ion channels to open

1. Ion channels that are always open (Leak channels)
2. Ligand-gated ion channels
3. Voltage-gated ion channels
4. Mechanically-gated ion channels

Leak channels: Always open

- Na^+, K^+, Cl^- leak channels
- K^+ leaks 100 times more than Na^+ , and K^+ leak channels are more abundant
- It makes the plasma membrane more permeable to potassium compared to other ions.
- This is crucial to maintain membrane potential

Ligand-gated ion channels

- The binding of the ligand causes conformational change in the protein and the pore region of the channel opens.
- Ex: Acetylcholine, Glutamate, IP3 etc.

Voltage-gated ion channels

- The change in membrane potential leads to conformational change in the protein, causing the channel to open.
- For example: Na_v, K_v channels etc.
- Important role in initiating and spreading action potentials.

Mechanically-gated ion channels

- Physical distortion leads to conformational change in the protein, causing the channel to open.
- Physical → Chemical
- Touch, hearing, regulation of blood pressure

iii- Facilitated diffusion via **Carrier Proteins**

- ✓ The transported molecule binds to the carrier protein.
- ✓ Conformational change occurs in the carrier protein.
- ✓ Transport occurs in the direction of concentration gradient: High → Low
- ✓ Transport is slower than channel proteins.

The magnitude of the net flux (J) can be measured using the following equation

Fick's first law of diffusion

$$J = P.A\ (C_o - C_i)$$

- ✓ **J** = *Flux (flow) (mmol/sec)*
- ✓ **C_o** = Concentration$_{outside}$ (mmol/L)
- ✓ **Ci** = Concentration$_{inside}$ (mmol/L)
- ✓ **A**= The surface area of the membrane (cm^2)
- ✓ **P**= The membrane permeability coefficient (cm/sec)

B) Active Transport: **REQUIRES ENERGY**

- ✓Transport against electrochemical gradient
- ✓Require specialized proteins
- ✓From low conc. to high conc.
    1. ATP hydrolysis (Primary active transport)
    2. Ion gradient (Secondary active transport)

Alberts et al. Molecular Biology of the Cell, 5th edition

1. Active transport via ATP-driven pumps: **Primary active transport**

- ✓Carrier-ATPase
- ✓ATP → ADP + Pi

Na^+-K^+ ATPase (Na^+-K^+ pump)

- ATP-driven pump
- Member of a P-type pump family.
- Extremely important in maintaining intracellular and extracellular concentration differences of sodium and potassium.
- A typical animal cell uses 1/3 of its energy for this pump to work.
- The Na + gradient it creates
  - Transport of many nutrients across the membrane
  - Regulation of cytosolic pH
  - Regulation of osmolarity

2. Ion greadient_driven pumps: Secondary active ransport

- Same direction: **Symport** (Cotransporter)
- Different direction: **Antiport** (Exchanger)

Epithelial cells are highly polarized

Transport of molecules across epithelium

- **Paracellular transport:** H_2O and small molecules
- **Transcellular transport:** Passing directly through the cell
- **Transcytosis:** Passing through the cell by vesicles

Transport of glucose in the small intestine epithelium

- ✓ **Na^+-K^+ ATPase** localized to the basolateral membrane
- ✓ Symporter SGLT1 restricted to the apical membrane: **Na^+/glucose symporter**
- ✓ **Uniporter GLUT5** restricted to basolateral membrane

Transport of Large Molecules

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Epithelial transport

II. Transport of large molecules

A) Endocytosis

- Phagocytosis
- Pinocytosis
- Receptor dependent endocytosis

B) Exocytosis

Endocytosis

- Macromolecules can only be taken into cells by membrane-covered carrier vesicles that result from membrane invagination.
- Makromolecules:
  - Ligands and their receptors
  - Membrane components of other cells
  - Bacteria
  - Viruses
- Functions
  - Nutrition
  - Defense
  - Maintaining homeostasis

Types of endocytosis

1. Phagocytosis
2. Pinocytosis
3. Receptor-mediated endocytosis

1. Phagocytosis

2. Pinocytosis

- Non-specific uptake of small droplets of extracellular fluid with endocytic vesicles.
- If large endocytic structures are formed: **Macropinocytosis**
- An important physiological mechanism in bulk food intake.
- Observed in many eukaryotic cells.

3. Receptor-mediated endocytosis: Clathrin-mediated endocytosis

- Initiated by receptors located on the plasma membrane.
- Taking essential nutrients such as cholesterol and iron into the cell
- Removal of signal molecules such as hormones and neurotransmitters from the extracellular environment to terminate their effects
- Recycling of receptors in the plasma membrane
- Ensuring plasma membrane balance

Exocytosis

- Process of expelling substances from cells through the fusion of vesicles with the cell membrane.
- Extremely important in the secretory pathway.
- Triggerd by Ca2+
- SNARE proteins
  - V-SNARE (Synaptobrevin)
  - T-SNARES (SNAP25 and Syntaxin)

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References

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