9th Edition

First Physiology Review Book by Subject Specialist

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REVIEW OF PHYSIOLOGY

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Updated Based on
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Soumen Manna

JAYPEE

Contents

Section 8: Endocrine and Reproductive System

Section 9: Special Topic

★★★★ Most important

★★★ Very important

★★ Important

CHAPTER

2

Cell Physiology and Membrane Potential

All the living things are composed of cells. A single cell is the smallest unit of life. Cell is defined as the basic structural and functional unit of the living body. Cells were discovered by Robert Hooke in 1665.

Each cell is formed by the following parts:

- Cell membrane
- Cytoplasm
- Nucleus.

CELL MEMBRANE

Cell membrane: About 7.5 to 10 nanometers thick.

- **Lipid (~ 40%)**
  - *Phospholipids (25%)*: Phospholipid phosphatidylcholine and sphingomyelin are found predominantly in the outer leaflet of the membrane, whereas phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol are found in the inner leaflet.
  - *Cholesterol (13%)*: Cholesterol found in both leaflets.
  - *Other lipids (4%)*: TG = 0%
  - Lipid-soluble substances (e.g. O_2, CO_2, steroid hormones) cross cell membranes because they can dissolve in the hydrophobic lipid bilayer.
  - Water-soluble substances (e.g. Na^+, Cl^-, glucose, H_2O) cross through water-filled channels, or pores, or may be transported by carriers.
- **Proteins (~ 55%)**
  - **Integral proteins**: Most membrane proteins fall into the integral class.
    - Are anchored to, and imbedded in the cell membrane through **hydrophobic interactions and** some by **Van der Waals Forces.**
    - May span the cell membrane.
    - Include ion channels, transport proteins, receptors, and guanosine-5′-triphosphate (GTP)-binding proteins (G proteins).
  - **Peripheral proteins (Fig. 2.1)**
    - Are loosely attached to the ***cell membrane by covalent bond*** and with ***integral protein by electrostatic interactions and hydrogen bond.***
- **Carbohydrates (3%)**
  - Glycoprotein and glycolipids

IMPORTANT

- The major lipids of the plasma membrane are phospholipids or phosphoglycerides.
- The cholesterol serves to stabilize the membrane at normal body temperature (37°C).
- Cholesterol is important for the maintenance of the correct permeability and fluidity of membrane.

IMPORTANT

Mass Ratio of protein to lipid is almost 1:1 in most biological membrane.

- The ratio is maximum in inner mitochondrial membrane (3.2) > Sarcoplasmic reticulum (2.0) > Outer mitochondrial membrane (1.1).
- The ratio is minimum in myelin (0.23) < Mouse liver cells (0.85).
- In human erythrocyte the ratio is 1.1.

IMPORTANT

Membranes are asymmetric structures because:

- Proteins have unique orientations in membranes.
- External location of the carbohydrates attached to membrane proteins.

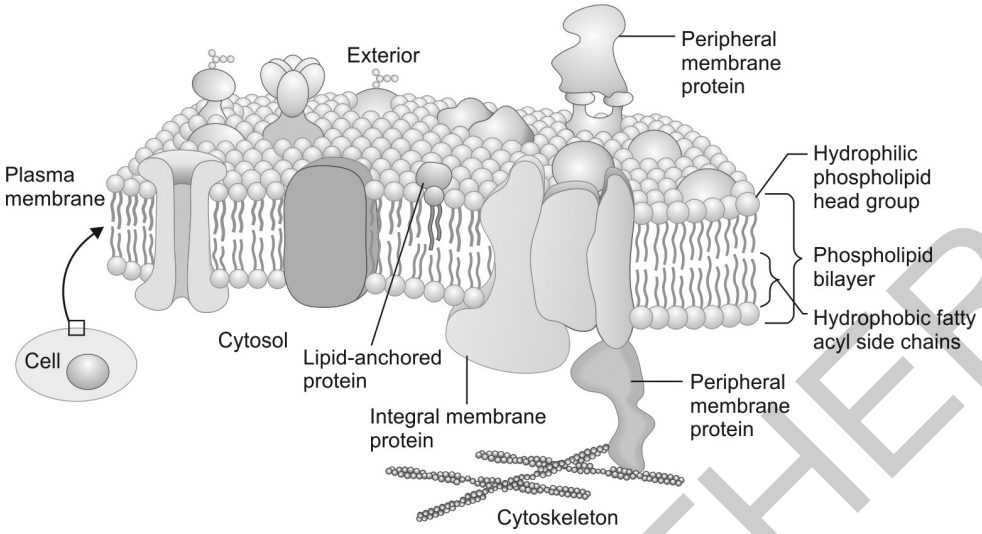

Fig. 2.1: Simplified view of cell membrane.

Membrane fluidity and the fluid mosaic model of membrane:

- The fluid mosaic model of membrane structure is proposed in 1972 by Singer and Nicolson.
- According to this model: Integral membrane proteins are like 'icebergs' floating in a sea of (predominantly) fluid formed by phospholipid molecules.
  The fluidity of the membrane is determined by the temperature and by its lipid composition.
- As *temperature* increases, the membrane becomes more fluid. Due to increase in temperature, the hydrophobic side chains undergo a transition from the ordered state (more gel-like or crystalline phase) to a disordered one taking on a more fluid arrangement.
- The temperature at which membrane structure undergoes the transition from ordered to disordered (i.e. melts) is called the 'transition temperature' (Tm).
- The presence of *unsaturated fatty acyl chains* in phospholipids and glycolipids also increases membrane fluidity. Longer and more saturated fatty acid decreases membrane fluidity and thus causes higher values of Tm.
- Cholesterol acts as a buffer to modify the fluidity of membranes.
  - At temperatures below the Tm: Increases fluidity.
  - At temperatures above the Tm: Decreases fluidity.

- **Cell membrane repairs after micro-injury (micro-needle insertion) by:** RAPID RESEALING or, self-sealing of membrane. This self-sealing process is purely based on HYDROPHOBIC INTERACTION.
- **Large break (macro-injury)** repair is done by calcium dependent process.
- Lateral diffusion of protein is a normal phenomenon which is the basis of FLUID MOSAIC MODEL by **Singer and Nicolson** in 1972. The essence of their model is that membranes are two-dimensional solutions of oriented lipids and globular proteins. Membrane proteins are free to diffuse laterally in the lipid matrix unless restricted by special interactions. But the above normal process is not for micro-injury repair.

CYTOPLASM

Cytoplasm of the cell is the jelly-like material formed by 80% of water. It contains a clear liquid portion called cytosol contains mainly dissolved proteins, electrolytes, and glucose. In the cytoplasm various cell organelles (Table 2.1) are dispersed.

Table 2.1: Cytoplasmic organelles, their special features and functions.

Organelles	*Features*	*Functions*
Nucleus	• Control center of the all activity of cell, sends messages to the cell to grow and mature, to replicate, or to die. • Contains large quantities of DNA, which comprise the genes	• Synthesis of RNA • Sending genetic instruction to cytoplasm for protein synthesis • Formation of subunits of ribosomes • Control of cell division • Storage of hereditary information in genes (DNA)

Contd…

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Organelles	*Features*	*Functions*
Ribosomes	• Cell organelle without limiting membrane • The ribosomes are composed of a mixture of RNA (65%) and proteins (35%).	Synthesis of proteins
Rough endoplasmic reticulum (RER)	Complex series of tubular structure with *attached ribosomes* on surface of the membrane	• Synthesis of proteins • Degradation of damaged organelles
Smooth endoplasmic reticulum (SER)	Similar to RER except ribosome are absent on membrane (Agranular ER)	• Synthesis of lipids and steroids • Storage and metabolism of calcium • Catabolism and detoxification of toxic substances
Lysosomes	• Lysosomes are vesicular organelles that form by breaking off from the Golgi apparatus and then dispersing throughout the cytoplasm • The interior is more acidic (pH 5.0) than rest of the cytoplasm (pH 7.2) by the action of a proton pump, or H^+, ATPase • Lysosomes can contain over 40 types of acid hydrolase enzymes.	• Lysosome provide intracellular digestive system that allow degradation of wornout organelles, removal of excess of secretory products and bacteria • Secretion of perforin, granzymes, melanin and serotonin • When a lysosomal enzyme is congenitally absent, the lysosomes become engorged with the material the enzyme normally degrades. This eventually leads to one of the **lysosomal storage diseases**. For example, α-galactosidase A deficiency causes Fabry disease, and β-galactocerebrosidase deficiency causes Gaucher disease
Peroxisomes	Peroxisomes are similar physically to lysosomes, but they are different in two important ways: 1. They are believed to be formed by self-replication (or perhaps by budding off from the SER) rather than from the Golgi apparatus 2. They contain oxidases (H_2O_2) or break it down (catalases) rather than hydrolases	• Breakdown of excess fatty acids • Detoxification of hydrogen peroxide and other metabolic products • Oxygen utilization • Acceleration of gluconeogenesis • Degradation of purine to uric acid • Role in the formation of myelin and bile acids
Mitochondria	• Sausage-shaped organelles with an outer membrane, an inter-membrane space, an inner membrane, which is folded to form shelves (cristae) • Present in all areas of cytoplasm (total number varies from <100 up to several 1000, depending on the amount of energy required by the cell). The cardiomyocytes use large amounts of energy and have far more mitochondria than do adipocytes	• Known as the "power-houses" of the cell (Production of energy & Synthesis of ATP by oxidative phosphorylation) • Initiation and regulation of apoptosis
Centrosome	Near the nucleus in the cytoplasm of eukaryotic animal cells is a centrosome. The centrosome is made up of **two centrioles** and surrounding amorphous pericentriolar material.	Movement of chromosomes during cell division. The centrosomes are microtubule-organizing centers (MTOCs) that contain γ-tubulin. When a cell divides, the centrosomes duplicate themselves, and the pairs move apart to the poles of the mitotic spindle, where they monitor the steps in cell division
Cytoskeleton	Cytoskeleton is the cellular organelle present throughout the cytoplasm. Cytoskeleton consists of three major protein components: 1. Microtubule 2. Intermediate filaments 3. Microfilaments.	It determines the shape of the cell and gives support to the cell

IMPORTANT

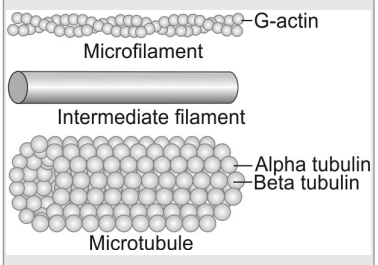


Fig. 2.2: Cytoskeletal elements of the cell.

IMPORTANT

Cell motility is due to cytoskeletal protein microtubules and microfilament. Microtubules is made up of tubulin and microfilament consists of actin.

IMPORTANT

- Actin filaments in muscle cells are critical components of the contractile apparatus. In other cells they are involved in locomotion.
- **Cyclical polymerization and depolymerization play the pivotal role in the cell locomotion.**
- Microtubule may play a role in fine-tuning of locomotion.
- Intermediate filament not directly involve in locomotion.

IMPORTANT

- *Colchicine and vinblastine* prevent microtubule assembly.
- *Paclitaxel (Taxol)* binds to microtubules and makes them so stable that organelles cannot move. Mitotic spindles cannot form, and the cells die.

CYTOSKELETON

Maintains the structure of the cell and permits it to change the shape and move.

Types of cytoskeleton:

- Dynamic
  - Microtubules (diameter 25 nM)
  - Microfilament (diameter 7 nM))
- Static
  - Intermediate filament (diameter 10 nM).

Microtubules

- Long, hollow structures with 5-nm walls; 15 nm cavity diameter.
- Made up of two globular protein subunits: α- *and* β-*tubulin* (stacked rings with each ring usually containing 13 subunits). A third subunit, γ-*tubulin, is associated with the production of microtubules by the centrosomes (Fig. 2.2).*
- The tubules interact with *GTP to facilitate* their formation.
- Microtubules are polar with assembly predominating at the '+' end and disassembly predominating at the '–' end.
- **Functions:**
  - Intracellular transport
  - Cilia and flagella
  - Centriole-mitotic spindle.

Microfilaments

- Long, solid fibers *made up of actin (Fig. 2.2).*
- *It is the most abundant protein in mammalian cells (*as much as 15% of the total protein in the cell).
- Actin filaments polymerize (ATP dependent) and depolymerize in vivo.
- Filamentous (F) actin refers to intact microfilaments and globular (G) actin refers to the unpolymerized protein actin subunits.
- **Functions:**
  - Cell junction
  - Muscle contraction
  - Slow axoplasmic transport.

Intermediate Filaments

- Made up of various subunits.
- Some of these filaments connect the nuclear membrane to the cell membrane.
- In their absence, cells rupture more easily, and when they are abnormal in humans, blistering of the skin is common.
- The proteins that make up intermediate filaments are cell-type specific, and are thus frequently used as cellular markers, for example, Vimentin: Mesenchyme, cytokeratin: Epithelial cells, glial fibrillary acidic protein: Glial cells (astrocyte).
- **Functions:**
  - Cell adhesion
  - Cell shape

INTERCELLULAR JUNCTIONS

- Junctions that fasten the cells to one another and to surrounding tissues (Fig. 2.3).
  - Zonula occludens (Tight Junction)
  - Zonula adherens (Adherens Junction)
  - Desmosome
  - Hemidesmosome
  - Focal adhesion.
- Junctions that permit transfer of ions and other molecules from one cell to another.
  - The gap junction.

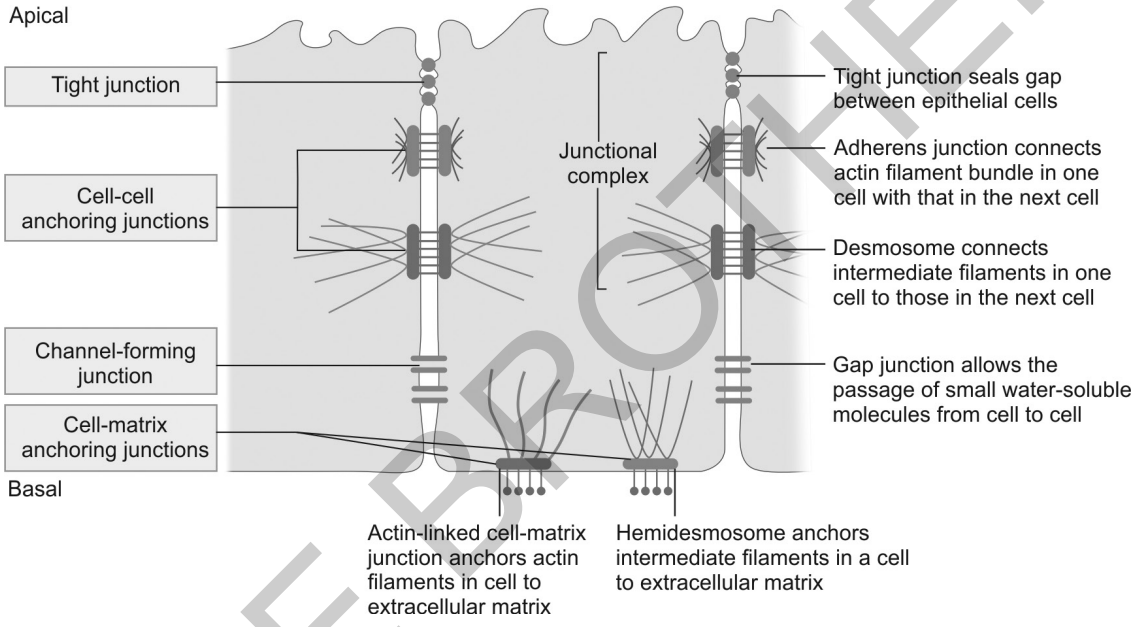


Fig. 2.3: Intercellular junctions in the mucosa of the small intestine.

Tight Junction

- Characteristically surround the apical margins of the cells in epithelia
- There are three main families of transmembrane proteins that contribute to tight junctions: Occludin, junctional adhesion molecules (JAMs), and claudins
- Tight junctions permit the passage of some ions and solute in between adjacent cells (paracellular pathway).

Adherens Junction

- Continuous structure on the basal side of the tight junction, and it is a major site of attachment for *intracellular microfilaments*
- It contains cadherins.

Desmosomes

- Apposed thickenings of the membranes of two adjacent cells
- Attached to the thickened area in each cell are *intermediate filaments*
- Contains desmoglein protein.

IMPORTANT

- Ca^{2+}-dependent interactions of the extracellular domains of transmembrane proteins cadherin forms adherent junction.
- Adhering junctions serve a signaling role during organ development and remodeling.

IMPORTANT

- Neighboring cells can be electrically and metabolically coupled by the means of gap junctions.
- The permeability of gap junctions regulated by changes in cytosolic concentrations of Ca^{2+} cAMP, H^+ and membrane potential.

Hemidesmosomes

- Look like half-desmosomes that attach cells to the *underlying basal lamina* and are connected intracellularly to *intermediate filaments*. However, they contain integrins.

Focal Adhesion

- Attach cells to their basal laminas
- They are labile structures associated with actin filaments inside the cell, and they play an important role in the cell movement.

Gap Junction

- At gap junction, intercellular space narrows from 25 nm to 3 nm, and units are called **connexons**
- Each connexon is made up of six protein subunits called **connexins**
- Permits substances to pass between the cells without entering the ECF
- The diameter is 0.8 and 1.4 nm which permits the passage of ions, sugars, amino acids, and other solutes with molecular weights up to about 1000.

Connexin mutations responsible for almost 20 different human diseases. For examples:

- Clouston syndrome (a connexin 30 (Cx30) defect)
- Erythrokeratoderma variabilis (Cx30.3 and Cx31)
- Inherited deafness (Cx26, Cx30, and Cx31)
- Predisposition to myoclonic epilepsy (Cx36)
- Predisposition to arteriosclerosis (Cx37)
- Cataract (Cx46 and Cx50)
- Idiopathic atrial Fibrillation (Cx40)
- X-linked, Charcot-Marie-Tooth disease (Cx32)
- Exocytosis/Endocytosis.

IMPORTANT

Neutral molecule transport:

To some extent they can pass hydrophobic layer by simple diffusion like very small neutral molecules (CO_2, O_2 and urea). Large neutral molecule (sugar) cannot pass by simple diffusion.

IMPORTANT

Porins

- Beta barrel proteins that act as a pore through which molecules can passively diffuse.
- Medium-sized or charged molecules (sugars, ions, and amino acids) move through a porin.
- They are present in the outer membrane of Gram-negative bacteria and some Gram-positive bacteria of the group mycolata, mitochondria, and chloroplast.

TRANSPORT ACROSS CELL MEMBRANE

Given enough time, virtually any molecule will diffuse across a protein-free lipid bilayer down its concentration gradient. The rate at which it does so, however, varies enormously depending partly on the size of the molecule, but mostly on its relative solubility in oil.

- Small nonpolar molecules such as O_2 and CO_2, readily dissolve in lipid bilayers and therefore diffuse rapidly across them.
- Small uncharged polar molecules such as water or urea, also diffuse across a bilayer, albeit much more slowly.
- By contrast, lipid bilayers are highly impermeable to charged molecules (ions), no matter how small: The charge and high degree of hydration of such molecules prevents them from entering the hydrocarbon phase of the bilayer.

There are two main classes of membrane transport proteins: Carriers and Channels

Carrier Proteins (Transporter)

The transported solute must first bind to a specific site on a transporter, a site exposed to the solute on one surface of the membrane (Fig. 2.4). A portion of the transporter then undergoes a change in shape, exposing this same binding site to the solution *on the opposite side* of the membrane. Using this mechanism, molecules can move in either direction, getting on the transporter on one side and

off at the other. Two types of carrier protein mediated transport exist: *facilitated diffusion and active transport*.

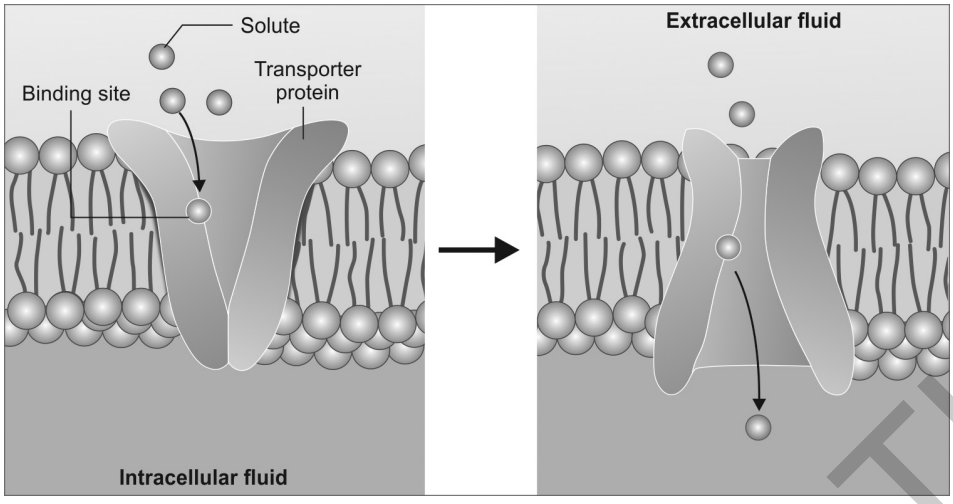


Fig. 2.4: Model of carrier protein (transporter) mediated transport. A change in the conformation of the transporter exposes the transporter binding site first to one surface of the membrane then to the other, thereby transferring the bound solute from one side of the membrane to the other.

IMPORTANT

Ionophore

- Ionophore means 'ion carriers' as these compounds catalyze ion transport across hydrophobic membranes
- Some ionophores are synthesized by microorganisms to import ions into their cells.

Example: Ionomycin is an ionophore produced by the bacterium, Streptomyces conglobatus for Ca^{++} transport. Valinomycin is an Ionophore for K^+ ion carrier.

The characteristics of carrier-mediated transport are:

- **Stereospecificity:** For example, D-glucose (the natural isomer) is transported by facilitated diffusion, but the L-isomer is not.
- **Saturation:** The transport rate increases as the concentration of the solute increases, until the carriers are saturated. The transport maximum (Tm) is analogous to the maximum velocity (Vmax) in enzyme kinetics.
- **Competition:** Structurally related solutes compete for transport sites on carrier molecules. For example, galactose is a competitive inhibitor of glucose transport in the small intestine.

Channel Proteins

Ion channels are integral membrane proteins can span the lipid bilayer and allow ions to *diffuse across* the membrane. Through ion channels ions such as Na^+, K^+, Cl^-, and Ca^{2+} diffuse across plasma membranes at much faster rates although they have very low solubility in membrane lipids.

- Ion channels can show selectivity for the type of ion or ions that can diffuse through them. This selectivity is based on the channel diameter, the charged and polar surfaces of the polypeptide subunits that form the channel walls and electrically attract or repel the ions, and the number of water molecules associated with the ions (so- called waters of hydration). For example, some channels (K^+ channels) allow only potassium ions to pass.
- Ion channels can exist in an open or closed state (Fig. 2.5). The process of opening and closing ion channels is known as *channel gating*, like the opening and closing of a gate in a fence.
- Three factors can alter the channel protein conformations (gating):
  i. The binding of specific molecules (ligand) to channel proteins may directly or indirectly produce either an allosteric or covalent change in the shape of the channel protein. Such channels are therefore termed *ligand-gated ion channels*.
  ii. Changes in the membrane potential can cause movement of certain charged regions on a channel protein, altering its shape—these are *voltage-gated ion channels*.
  iii. Physically deformation (stretching) of the membrane may affect the conformation of some channel proteins—these are *mechanically gated ion channels*.

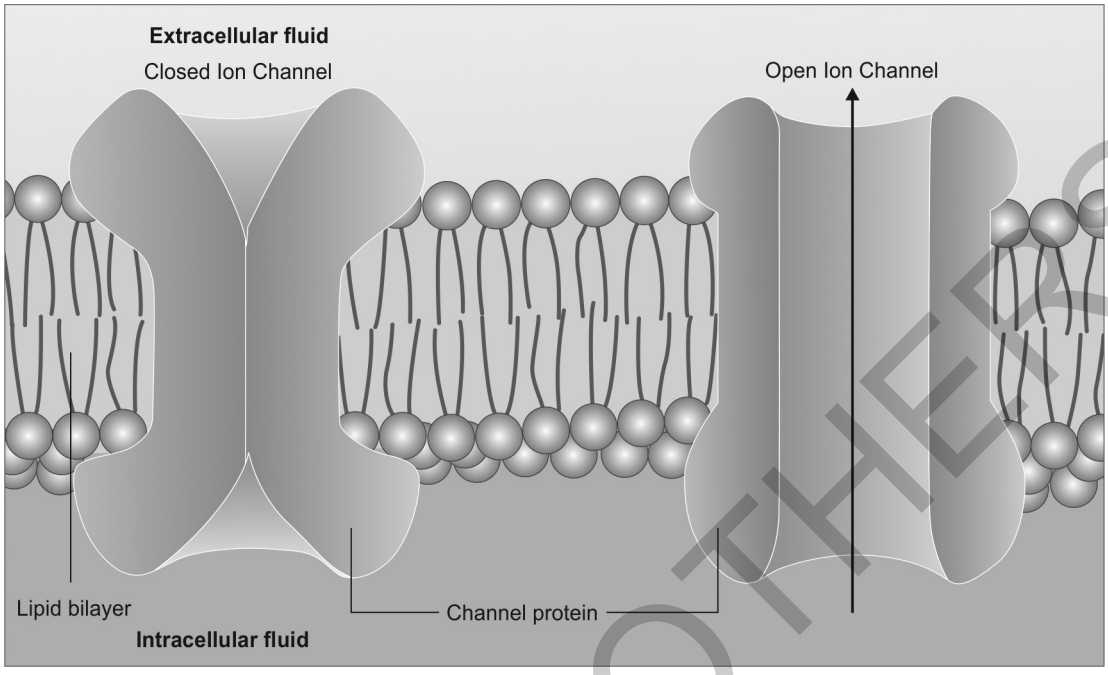
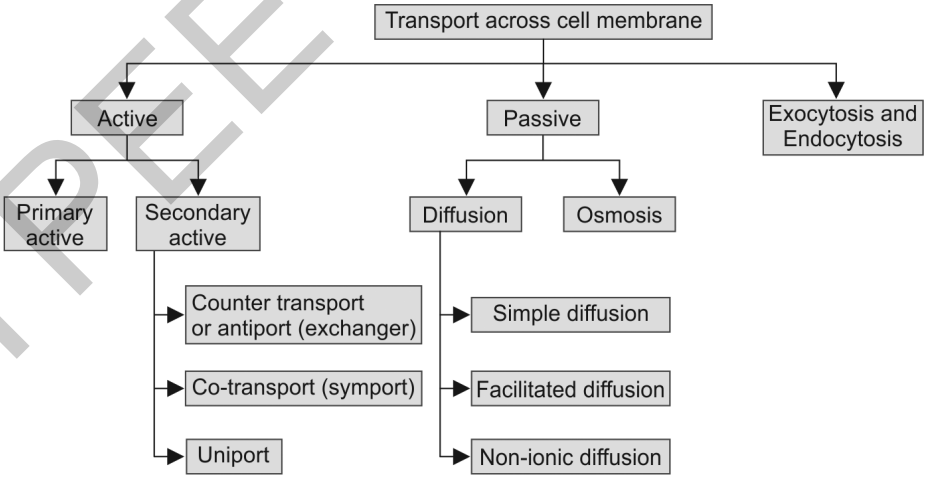


Fig. 2.5: Open and closed state of ion channels protein. Diffusion of ions occurs through open state.

- K^+ ion channels are ***tetramers*** with four identical subunits. Similarly ***Aquaporins*** are also tetramers.
- Ligand gated cations or, anion channels have ***FIVE identical subunits***.
- Several types of Cl^- channels are ***dimer***.

Transport across the cell membrane is classified as follow:



Active Transport

Energy is used.

- **Primary active transport:** Energy is derived directly by the transporter itself.
  - ***Examples:*** All transporters ending with 'ATPase' are primary active like Na^+K^+ ATPase pump.
- **Secondary active transport:** Energy is derived indirectly.
  - ***Examples:*** Sodium-linked glucose transport (SGLT) in kidney and Gastrointestinal tract (GIT).

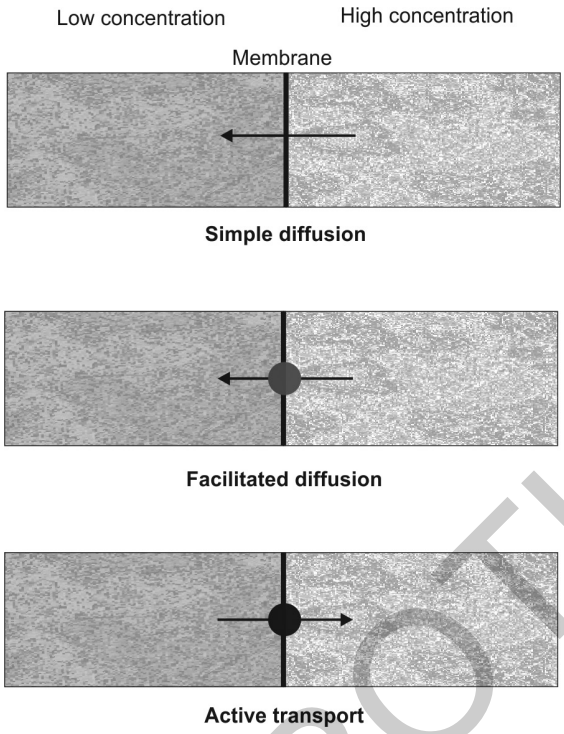


Fig. 2.6: Direction of net solute flux crossing a membrane by simple diffusion (high to low concentration), facilitated diffusion (high to low concentration), and active transport (low to high concentration). Note: Simple diffusion does not require carrier protein (transporter), although channel protein may enhances simple diffusion (not shown here). Both facilitated diffusion (no energy require) and active transport (energy dependent) require carrier protein.

Passive Transport

No energy required.

a. **Simple diffusion (Fig. 2.6)**

- No carrier molecule involved
- No Tm (No transport maximum, i.e. not saturable)
- Follows Fick's law of diffusion

Fick's Law of diffusion (net rate of diffusion):

$$J = -\frac{DA}{X}\Delta C$$

Where, J = Net rate of diffusion
D = Diffusion coefficient
A = Area
ΔC = Concentration difference
X = Thickness of the membrane

The negative sign indicates the direction of diffusion: For diffusion from higher to lower concentration, the sign is negative.

Example: O_2/CO_2 exchange in alveoli.

b. **Facilitated diffusion (Fig. 2.6)**

- No energy is required
- A carrier molecule is involved to which the substance binds, therefore, it is also called passive carrier-mediated transport
- Has a Tm (it is saturable) (Fig. 2.7)

- It can be competitively and noncompetitively inhibited
- It follows the enzyme-substrate kinetics of Michaelis-Menten
- ***Example***: Glucose transport by glucose transporters (GLUT).

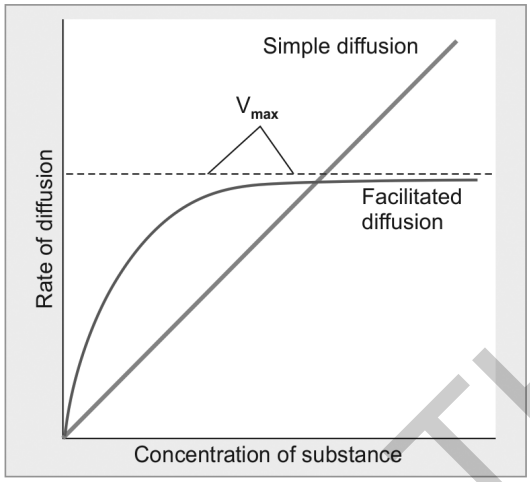


Fig. 2.7: Effect of concentration of a substance on rate of diffusion through membrane.

c. **Non-ionic diffusion**

- In case of weak acids or bases, where the acid/base can cross the membrane in the non-ionized form but cannot cross the membrane in the ionized form

***Example*:** Ammonia transport in GIT/Kidney.

- The main driving force for the passive diffusion of an uncharged solute is the difference of concentration between the inside and the outside of the cell.
- In the case of an electrically charged solute (such as an ion) diffusion is also driven by the membrane potential, which is the electrical gradient across the membrane.

Summary of different types of transport is as follows (Table 2.2):

Table 2.2: Characteristics of different types of transport.

Type	*Electrochemical gradient*	*Carrier mediated*	*Metabolic energy*	*Inhibition of Na-K ATPase*
Simple diffusion	Downhill	No	No	No
Facilitated diffusion	Downhill	Yes	No	No
Primary active transport	Uphill	Yes	Yes	Inhibits
Secondary active transport	Uphill (One or more solutes are transported uphill; Na^+ is transported downhill)	Yes	Yes	Inhibits

Na^+-K^+ ATPase pump

- Most common pumps present in all parts of body.
- It is a heterodimer made up of an α subunit and a β subunit.
- α and β subunits are heterogeneous, with α1, α2, and α3 subunits and β1, β2, and β3 subunits.
- Beta subunit contains 3 glycosylation sites on extracellular side (ECF), all of which are attached to carbohydrate residues.
- Intracellular side of α subunit binds ATP and 3 Na^+ ions. ECF side of α subunits has binding sites for ouabain and 2 K^+.
- It is a electrogenic pump with a coupling ratio of 3:2.
- It regulates cell volume, pressure and also maintains RMP of cell (5–10%).
- The pump is stimulated by thyroid hormones, insulin, aldosterone and G-actin, whereas it is inhibited by ouabain.

OSMOSIS

- Osmosis is the flow of water across a semipermeable membrane from a solution with low solute concentration to a solution with high solute concentration.
- **Calculating osmotic pressure (van't Hoff's law):** This law states that osmotic pressure depends on the concentration of osmotically active particles. The concentration of particles is converted to pressure according to the following equation:

  $$\pi = g.\ C.\ RT$$

  Where: π = osmotic pressure (mm Hg or atm), g = number of particles in solution (osm/mol), C = concentration (mol/L), R = gas constant, T = absolute temperature (K)

  To exert osmotic pressure across a membrane, a molecule must not cross the membrane.
- RBC is impermeable to sucrose, so sucrose exerts an osmotic pressure whereas, urea is readily able to cross the RBC membrane, and it cannot exert an osmotic pressure.
- Consequently, sucrose is termed an ***effective osmole***, whereas urea is an ***ineffective osmole***.

To take into account the effect of a molecule's membrane permeability on osmotic pressure, it is necessary to rewrite van't Hoff's law equation as:

$$\pi = \sigma(nCRT)$$

Where σ is the ***reflection coefficient*** or osmotic coefficient which is a measure of the relative ability of the molecule to cross the cell membrane.

- $\sigma = 0$ means the molecule can freely cross the cell membrane (such as urea) and no effective osmotic pressure is exerted (i.e. urea is an ineffective osmole for RBC).
- $\sigma = 1$ means the solute cannot cross the cell membrane (i.e. sucrose). Such a substance is said to be an effective osmole.
- Many molecules are neither completely able nor completely unable to cross cell membranes (i.e. $0 < \sigma < 1$), and they generate an osmotic pressure that is only a fraction of what is expected from the molecule's concentration in solution.

The volume of RBC placed in a NaCl solution (osmolarity of 280 mOsm/kg H_2O) is 100 fl. What will be the steady state volume when they are placed in a NaCl solution with an osmolarity of 350 mOsm/kg H_2O?

Answer: After steady state, the concentration of solute in the RBC will remain same as there will be only exchange of water (osmosis).

Formula; C1V1 = C2V2 [Where, Initial Concentration: C1, volume: V1, and Final concentration: C2, volume V2]

So, (280 × 100) = 350 × V2

Therefore, V2 = 80 fl

Oncotic Pressure

Oncotic pressure or colloid osmotic pressure is the osmotic pressure generated by the large molecules (especially proteins) in solution.

- The magnitude of the osmotic pressure generated by a solution of protein does not conform to van't Hoff's law, because van't Hoff's law is more precise with small, globular proteins than with larger protein molecules.
- The oncotic pressure exerted by proteins in human plasma has a normal value of approximately 26 to 28 mm Hg. Although this pressure appears to be small when considered in terms of osmotic pressure (28 mm Hg ≈ 1.4 mOsm/kg H_2O), it is an important force involved in fluid movement across capillaries.

EXOCYTOSIS

- The process by which the contents of secretory vesicles are delivered to the extracellular fluid is called exocytosis. Depending upon the type of cell, exocytosis may occur over the entire surface or be localized to a small discrete area.

For example, nerve cells release their neurotransmitters only at synapses that comprise only a tiny fraction of their surface area.

- Vesicular membrane fuses with cell membrane and the area of fusion then breaks down, leaving the contents of the vesicle outside and the cell membrane intact. This is the Ca^{+2} dependent process of **exocytosis.**
- Exocytosis occurs via two pathways. In the **nonconstitutive pathway,** proteins from the Golgi apparatus initially enter secretory granules, where processing occurs before exocytosis. The other pathway, the **constitutive pathway,** involves the prompt transport of proteins to the cell membrane in vesicles with little or no processing or storage (Fig. 2.8).

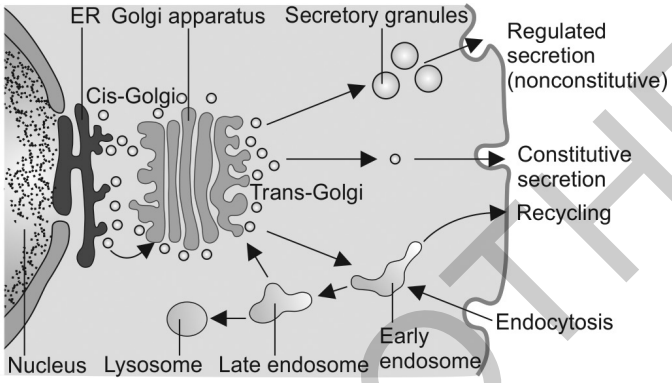
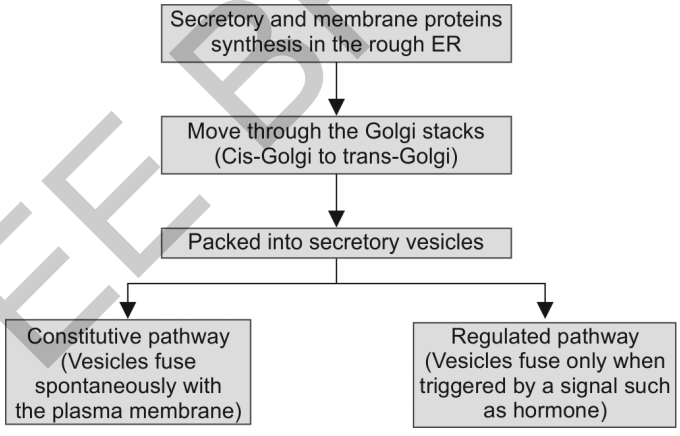


Fig. 2.8: Cellular structures involved in protein processing.

The process of exocytosis occurs in the following sequences:



The nonconstitutive pathway is sometimes called the **regulated pathway,** but this term is misleading because the output of proteins by the constitutive pathway is also regulated.

ENDOCYTOSIS

Endocytosis is the reverse of exocytosis. There are three types of endocytosis:

1. **Phagocytosis ('cell eating'):** It is the process by which bacteria, dead tissue, or other bits of microscopic material are engulfed by cells such as the polymorphonuclear leukocytes of the blood. The material makes contact with the cell membrane, which then invaginates.
2. **Pinocytosis ('cell drinking'):** It is a similar process with the vesicles much smaller in size and the substances ingested are in solution.
3. **Clathrin-mediated endocytosis:** They also known as receptor-mediated endocytosis, occurs at membrane indentations where the protein **clathrin** accumulates.

- Clathrin molecules have the shape of triskelions, with three 'legs' radiating from a central hub. As endocytosis progresses, the clathrin molecules form a geometric array that surrounds the endocytotic vesicle. Once the complete vesicle is formed, the clathrin falls off and the three-legged proteins recycle to form another vesicle.
- Clathrin-mediated endocytosis is responsible for the internalization of many receptors and the ligands bound to them including, for example, nerve growth factor and low-density lipoproteins. It also plays a major role in synaptic function.

RESTING MEMBRANE POTENTIAL (RMP)

Equations used for Membrane Potential

- Donnan effect/Gibbs-Donnan equilibrium
- Nernst equation
- Goldman-Hodgkin-Katz (G-H-K) equation or, Goldman constant field equation or chord conductance equation.

Donnan Effect or Gibbs-Donnan Equilibrium

Presence of a charged impermeant (non-diffusible) ion (for example, a protein) on one side of a semipermeable cell membrane repels similarly charged permeant (diffusible) ions to the other side and holds opposite charged permeant ions to the same side. This result in an asymmetric distribution of permeant charged ions on both side of the membrane (Fig. 2.9). This is known as Gibbs–Donnan effect or, Donnan's effect or, Gibbs–Donnan equilibrium.

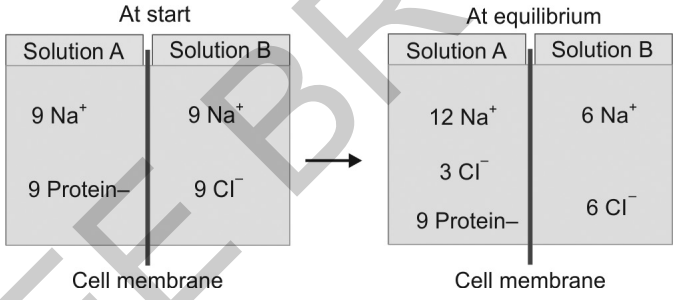


Fig. 2.9: Gibbs–Donnan effect or, Equilibrium: Cell membrane is a semipermeable membrane separating two ionized solutions (solution A and solution B) of sodium chloride. At the start, diffusible Na^+ ions are equal in both the solutions. But the presence of negatively charged protein (non-diffusible) ions on solution A, holds more positively charged Na^+ in the same compartment (solution A) and repels negatively charged Cl^- ions (diffusible) in the other compartment (solution B). Finally, when the equilibrium is reached, each solution is electroneutral (i.e. total + charged cations will be equal to total – charged anions), but there is asymmetric distribution of Na^+ and Cl^- on both side of the membrane.

The above effect described in Figure 2.9, can be expressed mathematically by Gibbs–Donnan equation *at equilibrium state*:

- The product of the concentration of the diffusible ions on one side will be equal to the product of the concentration of the diffusible ions on the other side. Means,

$$[Na^+]_{Side\ A} \times [Cl^-]_{Side\ A} = [Na^+]_{Side\ B} \times [Cl^-]_{Side\ B}$$

- Each solution is electrically neutral

$$[Cations]_{side\ A} = [Anions]_{side\ A}$$

$$\text{similarly, } [Cations]_{side\ B} = [Anions]_{side\ B}$$

- More osmotically active particle on the side containing the impermeant ion (Osmolarity of side A = 24 and that of side B is 12).

IMPORTANT

Relative permeability of different molecules: Hydrophobic molecules (CO_2, O_2, N_2, steroid hormones) >>> small uncharged polar molecules (H_2O, urea, glycerol) >>> large uncharged polar molecules (glucose, sucrose) >>> Ions (Na^+, K^+, Cl^-).

CONCEPT OF EQUILIBRIUM POTENTIAL AND RESTING MEMBRANE POTENTIAL

In most of the mammalian cell, at rest the extracellular surface of the membrane contains an excess of positive charge and the cytoplasmic surface contains an excess of negative charge (Fig. 2.10). The charge separation gives rise to a difference of electrical potential or, voltage across the membrane (V_m). The V_m of the cell at resting condition is known as Resting Membrane Potential (RMP).

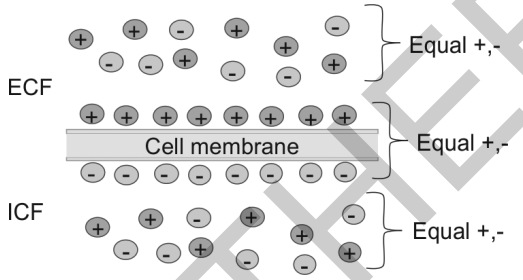


Fig. 2.10: Membrane potential. **Note:** Excess charge is distributed only on the surface of membrane whereas the center of the cell cytoplasm is electroneutral.

IMPORTANT

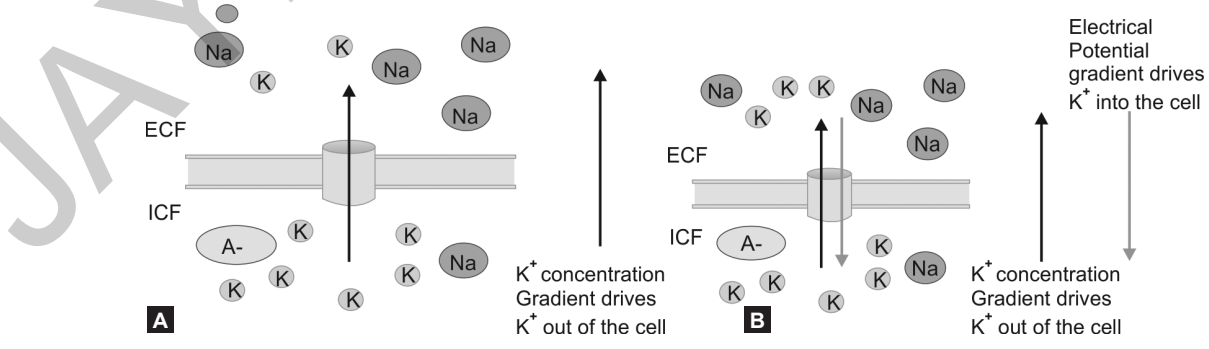
- Permeability of different ions through synthetic biological membrane: Cl^- >> K^+ >> Na^+.
- Permeability of different ions through cell membrane: K^+ >> Cl^- >> Na^+.

To understand how RMP is generated, we shall consider the RMP of glial cell first (Fig. 2.9), because in resting stage, glial cells are permeable to potassium ion only.

- Because K^+ ions are present at a high concentration inside the cell, they tend to diffuse across the membrane from the inside to the outside of the cell down their **chemical concentration gradient**. As a result, the outside of the membrane accumulates a net positive charge (caused by the slight excess of K^+). This excess K^+ gives rise to an electrical potential difference (**electrical driving force**).
- At equilibrium, the electrical driving force on K^+ exactly balances the chemical driving force. That is, the outward movement of K^+ (driven by its concentration gradient) is equal to the inward movement of K^+ (driven by the electrical potential difference across the membrane). This potential is called the K^+ **equilibrium potential**, E_K (Figs. 2.11A and B).

IMPORTANT

- In general all excitable cell membrane at rest is maximally permeable to K^+ and thus RMP is **close to** equilibrium potential of K^+ ion.
- RMP of neuron (–70 mV) is exactly **equal to** equilibrium potential of Cl^- ion (–70 mV).



Figs. 2.11A and B: Concept of membrane potential generation in glial cell. A. In a cell permeable only to K^+, the resting potential is generated by the efflux of K^+ down its concentration gradient. B. When equilibrium is reached, the electrical and chemical driving forces are equal and opposite, and as many K^+ ions move in as move out. [Na: Na ions, K: K ion, A^-: Impermeable anion (protein)]

Nernst equation: The equilibrium potential for any ion X (Ex) can be calculated from an equation derived in 1888 from basic thermodynamic principles by the German physical chemist Walter Nernst:

$$E_X = \frac{RT}{ZF} \ln \frac{[X]_o}{[X]_i}, \text{ Nernst equation}$$

where R is the gas constant, T the temperature (in degrees Kelvin), Z the valence of the ion, F the Faraday constant, and $[X]_o$ and $[X]_i$ the concentrations of the ion outside and inside the cell. The constant for converting from natural logarithms (ln) to base 10 logarithms is 2.3.

So, the value of

$2.3 \frac{RT}{F}$ = 60 mV at 37°C [Z = charge on the ion (+1 for Na^+; +2 for Ca^{2+}; –1 for Cl^-)]

Now, the Nernst equation can also be written as follows:

$E_x = -60 \log_{10} \frac{[X]_i}{[X]_o}$ [Note change in sign]

Example: If the intracellular [Na^+] is 150 mM and the extracellular [Na^+] is 150 mM, what is the equilibrium potential for Na^+?

With the help of above equation: $E_x = -60 \log_{10} \frac{15}{150}$

$= -60 \log_{10} 0.1$

$= +60 \log_{10} 10$

$= +60$ mV

Note: You need not remember which concentration goes in the numerator. Because it is a log function, perform the calculation either way to get the absolute value of 60 mV. Then use an 'intuitive approach' to determine the correct sign. (Intuitive approach: The [Na^+] is higher in extracellular fluid than in intracellular fluid, so Na^+ ions will diffuse from extracellular to intracellular, making the inside of the cell positive [i.e. +60 mV at equilibrium]).

By using the Nernst equation, the equilibrium potential of different ions in a typical mammalian cell can be calculated and given here (Table 2.3):

Table 2.3: Equilibrium potential of different ions in a typical mammalian cell.

Ion	*Equilibrium potential (mV)*
Na^+	+ 63 to +65
K^+	– 90 to – 96
Cl^-	–64 to – 70
Ca^{++}	+132 to +137
H^+	–12
HCO_3^-	–13
Mg^{2+}	+9

- So, in the above discussion of glial cell, we can understand that the equilibrium potential of K^+ (– 90 mV) will be equal to the RMP of the glial cell because glial cell is permeable to only K^+ ion in resting stage.
- Means if the cell membrane is permeable to only one type of ion (suppose ion X), the RMP of that cell shall be equal to the equilibrium potential of X ion. And this RMP can be calculated by the Nernst equation.
- But, unlike glial cells, nerve cells and most of the mammalian cell, at rest are permeable to Na^+ and Cl^- ions in addition to K^+ ions. So, the diffusion of K^+, Cl^- and Na^+ all ions shall determine the V_m of the cell and **RMP shall settles at a new level, where there is no net ion flow into or out of the cell.**
- Thus, for a cell having ion channels selective for Na^+, K^+, and Cl^-, at RMP:

$$I_{Na+} + I_{K+} + I_{Cl-} = 0$$

- *In general, the cell membrane at rest is predominantly permeable to K^+ and thus the RMP of most mammalian cell is dominated by K^+ ion. This leads to the observation that RMP of almost all cell is close to equilibrium potential of K^+.*
- The most permeable ion in resting condition of cell is $K^+ >> Cl^- >> Na^+$ with permeability of K^+: Cl^- : Na^+ = 1.0: 0.45: 0.04.

MCQ: X, Y, Z are the three ions permeable through cell membrane. X = – 50 and Y = – 30. If at RMP, when there is no net electrogenic transfer, what is the value of Z? *[AIIMS Nov 2017]*

Answer: At RMP, as explained above; the current of X + Y + Z = 0. Since X = – 50 and Y = – 30, then Z must be + 80.

Role of Na-K ATPase Pump in RMP

The action of the Na^+-K^+-ATPase pump sets up the concentration gradients for Na^+ and K^+. The concentration gradient for K^+ facilitates its movement out of the cell via K^+ channels, but its electrical gradient is in the opposite (inward) direction. Consequently, an equilibrium is reached in which the tendency of K^+ to move out of the cell is balanced by its tendency to move into the cell, and at that equilibrium there is a slight excess of cations on the outside and anions on the inside. This condition is maintained by Na-K-ATPase, which uses the energy of ATP to pump K^+ back into the cell and keeps the intracellular concentration of Na^+ low.

RECORDING OF RMP

- When two electrodes are connected through a suitable amplifier and placed on the surface of a single axon, no potential difference is observed. However, if one electrode is inserted into the interior of the cell, a constant **potential difference** is observed with the inside negative relative to the outside of the cell at rest (Fig. 2.12). A membrane potential results from separation of positive and negative charges across the cell membrane. In neurons, the **resting membrane potential** is usually about –70 mV which is close to the equilibrium potential for K^+.

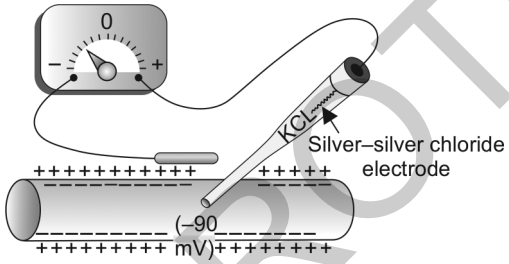


Fig. 2.12: Recording of membrane potential. The electrode used here generally has a tip diameter < 0.5 micrometer.

RMP and threshold voltage of different tissues are given in the Table 2.4.

Table 2.4: Resting membrane potential and threshold voltage of various tissues and cell.

Tissue	*RMP (mV)*	*Threshold (mV)*
Nodal tissue	Range: – 65 to – 40 SA node: – 50 AV node: – 60	– 40 to – 30
Myocardium	– 90	– 65
Purkinje fiber	– 80	
Smooth muscle	– 55 to – 40	– 40
Skeletal muscle	– 90	– 55
Neuron	– 70	– 55
Hair cell	– 60 to – 70 with respect to the perilymph – 150 with respect to the endolymph	– 50

CALCULATION OF RMP

- **Goldman–Hodgkin–Katz Equation:** Gives the magnitude of the ***membrane potential (RMP).*** It depends on:
  - The distribution of Na^+, Cl^-, K^+ between ECF and ICF
  - Permeability of the membrane to each of these ions.

If permeabilities are known, a RMP can be calculated using the theoretical Goldman-Hodgkin-Katz (GHK) or **constant field equation:**

$$V = 60 \text{ mV } \log_{10} \frac{P_{Na}Na_o^+ + P_KK_o^+ + P_{Cl}C1_i^-}{P_{Na}Na_i^+ + P_KK_i^+ + P_{Cl}C1_o^-}$$

where, $P_{Na} \rightarrow$ Permeability of Na and $Na_o^+ \rightarrow$ Concentration of Na outside (Similarly others).

CHANGE IN RMP: GRADED POTENTIAL

All cells have a RMP due to the presence of ion pumps, ion concentration gradients, and leak channels in the cell membrane. In addition, some cells have another group of ion channel that can be gated (opened or closed) under certain conditions. Such channels give a cell the ability to produce electrical signals. This property is known as excitability, and such membranes are called ***excitable membranes***. Cells of this type include all neurons and muscle cells.

The electrical signals occur in two forms: **graded potentials** and **action potentials**. Graded potentials are important in signaling over short distances, whereas action potentials are long-distance signals that are particularly important in neuronal and muscle cell membranes.

The terms depolarize, repolarize, and hyperpolarize are used to describe the direction of changes in the membrane potential relative to the RMP in an excitable cell (Fig. 2.13).

The RMP is said to be "polarized state" simply meaning that the outside and inside of a cell have a different net charge. If the membrane potential becomes more positive than it is at the resting potential, the membrane is said to be **depolarized**. **Overshoot** refers to a reversal of the membrane potential polarity—that is, when the inside of a cell becomes positive relative to the outside (more positive than 0 mV). When a membrane potential that has been depolarized returns to the resting value, it is **repolarized**. If the membrane potential becomes more negative than it is at the resting potential, the membrane is said to be **hyperpolarized**.

If a cell with a RMP of –70 mV changes to –40 mV or, +40 mV, the cell is said to be depolarized (note that one has to ignore the negative sign while commenting on the change of polarity). And if the RMP (–70 mV) changes to –90 mV, the cell is said to be hyperdepolarized.

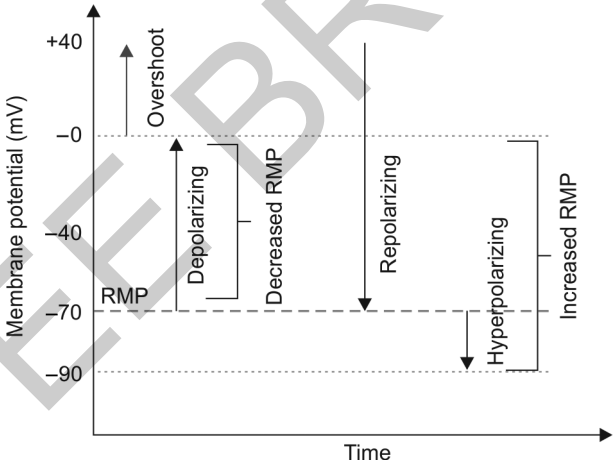


Fig. 2.13: Change in RMP: Depolarization, hyperpolarization and repolarization. Note: during depolarization, RMP closes to 0 mV (**decreased distance** between RMP & 0 mV), which is also known as **Decrease** RMP. During hyperpolarization, RMP moves away from 0 mV (**Increased distance** between RMP & 0 mV), which is also known as **increased RMP**.

Graded Potentials

A hyperpolarization or depolarization event confined to a relatively small region of the plasma membrane simply produce a **graded potential**. They are called graded potentials simply because the magnitude of the potential change can vary (is "graded"), that is proportional to the **size of the stimulus**. Thus, due to a small stimulus (such as binding of a few molecules of neurotransmitter), if just one or two channels open in cell membrane, the graded potential may be small, while if more channels open (due to a larger stimulus), it may be larger. Graded potentials don't travel long distances along the neuron's membrane, but rather, travel just a short distance and diminish as they spread, eventually disappearing. Graded potentials are given various names related to the location of the potential or the function they perform—for instance, receptor potential, synaptic potential (EPSP, IPSP), and pacemaker potential (Table 2.5).

Table 2.5: Different terms describing the membrane potential.	
Membrane potential	The voltage difference between the inside and outside of a cell
Equilibrium potential	The voltage difference across a membrane that produces a flux of a given ion species that is equal but opposite to the flux due to the concentration gradient of that same ion
Graded potential	A potential change of variable amplitude and duration that is conducted decrementally over a small distance; has no threshold or refractory period
Receptor potential	A graded potential produced at the peripheral endings of afferent neurons (or in separate receptor cells) in response to a stimulus
Synaptic potential	A graded potential change produced in the postsynaptic neuron in response to the release of a neurotransmitter by a presynaptic terminal; may be depolarizing (an excitatory postsynaptic potential or EPSP) or hyperpolarizing (an inhibitory postsynaptic potential or IPSP)
Pacemaker potential	A spontaneously occurring graded potential change that occurs in certain specialized cells (like SA node)
Threshold potential	The membrane potential at which an action potential is initiated
Action potential	A brief all-or-none depolarization of the membrane, which reverses polarity in neurons; has a threshold and refractory period and is conducted without decrement (Chapter 3)

Question: If in the ECF K^+ concentration increases from 3.5 to 5 mM, what happens to the resting membrane potential of an adipose cell?

Ans. It becomes less negative means cell depolarizes. Depolarization of the cell is known as decreases in RMP. But remember this depolarization cannot fire action potential.

Explanation: Excess ECF K^+ decreases the diffusion of K^+ from cell. This cause extra K^+ (positive charge) inside cell (depolarization). But remember this is NOT DUE TO: Increase in ECF K^+ would cause K^+ to rush into the cell down its concentration gradient (because ICF K^+ concentration is very high even after increase in ECF K^+).

Remember that membrane potential is not an absolute number, but the difference between the inside of the cell and the outside ground. Thus, a decrease in the membrane potential difference (RMP) means that the voltage has moved closer to ground or become more positive.

Effect of change in ECF Na^+/K^+ on RMP

- **Hyponatremia**: Little effect on RMP (because Na+ is least permeable in resting condition).
- **Hypernatremia**: Little effect on RMP.
- Hyperkalemia: Decreases RMP (explained above). For example, from – 70 mV, it may become – 65 mV. Hypokalemia will have opposite effect.
- **Hypokalemia**: RMP increases.

REVIEW OF PHYSIOLOGY

Physiology is more than just a foundational subject; it is the living essence of clinical medicine. It is not merely a collection of facts to be memorized; it is the very language in which the human body describes its function, both in health and in disease. In the high-stakes arena of postgraduate medical entrance examinations (PGMEE), you will find that even the most clinical questions are, at their core, rooted in physiological principles.

To master this subject, I recommend a prospective approach to your studies:

- *Build the Foundation:* Always start with the 'text or notes'. Internalize the mechanism before attempting to test yourself
- *Strategic Focus:* Identify high-yield topics frequently tested in PGMEE. Mark these sections clearly; they are your roadmaps to success
- *Active Recall:* Bridge the gap between theory and application by solving MCQs only after the concept is solidified
- *The Revision Loop:* Physiology is a vast landscape. Regular interval revision is the only way to ensure these concepts remain accessible under exam pressure

Additionally, the Book included:

- The book is updated based on Ganong's Review of Physiology (27/e), Guyton and Hall Textbook of Medical Physiology (15/e) and Berne & Levy Physiology (7/e)
- Each chapter has been divided into multiple sub-topics and explained meticulously in a simple language
- MCQs of NEET PG pattern, AIIMS, PGI, JIPMER pattern have been separated into different groups
- Answers of each MCQ in every chapter have been given after thoroughly cross-checked from standard textbooks and/or research papers
- Based on recent trends, 'FUTURE TREND' questions are included at the end of each chapter.

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Online support: Facebook group: Physiology Dr Soumen Manna

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ISBN 978-93-7202-225-4