Cells to Systems Lecture 9

MOVEMENT OF MOLECULES ACROSS CELL MEMBRANES

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Intended learning outcomes:

- Describe the composition of the cell membrane and explain how the distribution of phospholipids and proteins influences the membrane permeability to ions, hydrophilic and hydrophobic compounds, and cell-cell communication
- Describe how cells regulate the movement of substances across their membranes and the role of diffusion, facilitated diffusion, and primary and secondary active transport mechanisms
- Explain how energy from the Na+ and K+ electrochemical gradients across the plasma membrane are maintained

Cell membranes

Biological membranes are composed mainly of lipids and proteins. They are selective permeable barriers and carry out a number of important cellular functions. All animal cells are surrounded by a plasma membrane and they also contain a number of internal membranes that surround organelles.

Properties of cell membranes

- Separate the intracellular and extracellular fluid, allowing these to differ in composition
- Provide a selective barrier that is permeable to water and some molecules, but impermeable to others
- Cell membranes control the flow of information between cells and their environment:
    - Contain specific molecular pumps, channels and transport mechanisms for small and large molecules
    - Permit selective exchanges to take place (e.g. ions & metabolites), thus maintaining the unique intracellular composition
    - Proteins, nucleic acids, nucleotides & sugars that the cell synthesises or accumulates at great metabolic cost are controlled
    - Contain specific receptors for external stimuli, and some membranes generate signals which can be chemical or electrical
- Internal organelle membranes allow functional compartments to exist within a cell
    - Nucleus, mitochondria, lysosomes, endoplasmic reticulum and golgi apparatus are all contained within membranes
    - Enzymes or ions within organelles can be kept separate from the cell cytoplasm

Common features of cell membranes (fluid-mosaic model)

Consist of a phospholipid bilayer containing different types and amounts of lipids, with cholesterol and protein molecules embedded. The combinations of these components give each cell membrane its distinctive identity and specialized functions.

- Membrane lipids are relatively small molecules that are amphipathic in that they have:
    - A hydrophilic (water loving) polar ‘head group’ eg glycerol,

phosphate and alcohol
    - A hydrophobic (water hating) non-polar region made up of two fatty acid chains.
        - hydrophobic interior provides the barrier function, making the membrane essentially impermeable to polar molecules such as amino acids, sugars, proteins and nucleic acids
- The fluidity of the membrane bilayer, which has acts like a two-dimensional liquid, allows movement of individual molecules
    - Phospholipids (and proteins) can diffuse sideways freely within their own monolayer so that neighbouring phospholipid molecules can change places with each other
    - Movement of lipids and proteins within the membrane is functionally important as it can permit molecules to associate for expression of their activity as well as aiding or inhibiting diffusion of particular substances
- Membrane proteins are scattered throughout the bilayer and perform many functions. Protein functions include:
    - Transport of molecules (focus of this lecture)
    - Enzymatic activity
    - Signal transduction
    - Cell to cell recognition
    - Intercellular joining
    - Attachment to extracellular matrix

- Proteins are crucial both for membrane stability and function
    - Integral proteins
        - Have transmembrane helices that span the entire lipid bilayer once or several times
    - Peripheral proteins
        - Only bound to one side of the lipid bilayer
        - Can be attached to an integral membrane protein

Transport of molecules across cell membranes

The permeability of biological membranes is highly selective**.** The flow of molecules and ions between a cell and its environment is precisely regulated by specific transport systems. Such systems:

- Regulate cell volume and maintain intracellular pH and ionic composition within a narrow range to provide a favourable environment for enzyme activity.
- They extract and concentrate metabolic fuels and building blocks from their environment and extrude toxic substances.
- Generate ionic gradients essential for excitability of nerves and muscles.

Three basic processes of movement across cell membranes

- Simple diffusion down an electrochemical gradient
    - Due to the kinetic motion of the molecule
- Facilitated diffusion
    - Requires interaction with a carrier protein
- Active transport
    - Carrier mediated and energy dependent

Simple Diffusion

Diffusion is the random molecular movement of substances, molecule by molecule, either through intermolecular spaces in the membrane or using a carrier protein. The

driving force for diffusion is the **concentration or electrical gradient**

- Net rate of diffusion is proportional to the concentration difference (or partial pressure difference for a gas).

Movement of ions is affected by their electrical charge**.** Anions move to positively charged areas and cations to negatively charged areas, leading to a difference in charge between two adjacent areas. This produces an electrical gradient. Movement of ions is regulated by the **electrochemical gradient** (both a concentration gradient and an electrical gradient contribute).

Larger charged molecules can across a cell membrane through pores or channels lined by proteins provided that:

- There is an electrochemical gradient favouring diffusion and
- Integral membrane proteins are present to help get the molecule across the membrane
- Protein channels involved in simple diffusion are of two classes:
  - Membrane pores or ungated channels, e.g. aquaporin
  - Gated channels, e.g. ion, ligand or mechanically gated channels

Gates can be controlled in several ways:

- Voltage gating, where conformational state depends upon the difference between ionic charges on two sides of the membrane. Transmembrane ion channels selective for K^+, Na^+, Cl^-, and Ca_2^+ are present in virtually every living cell and have a gate that can be open or closed.
- Chemical or ligand gating, where binding of the ligand alters the conformational state and opens (or closes) the gate e.g. for the neurotransmitter (acetylcholine)
- Mechanical gating, where a stimulus such as stretch alters the conformation state

Facilitated Diffusion

Facilitated diffusion involves a conformational change of the channel protein following binding of the transport molecule to a receptor. The receptor can become saturated and the **rate** of diffusion is dependent on the binding and release of the transported molecule, rather than the concentration or electrical gradient. Facilitated diffusion does not require energy.

- The molecule moves down its concentration gradient
- Transport proteins show substrate specificity, but competition can occur between structurally similar substrates
- Receptor can become saturated if the solute concentration is high

Active Transport

Passage of some molecules does not rely upon diffusion. They are transported against an electrochemical gradient (uphill). They are dependent on carrier proteins and require energy, either directly (primary active transport) or indirectly (secondary active transport).

- **Primary active transport** (ATP dependent)
  - e.g. Na^+K^+ATPase, pumps are integral membrane glycoproteins found in all animal cells and pump $3Na^+$ out for each 2 K^+ into a cell.
  - This pump uses about 1/3 of an animal's entire energy output.
    i. ATPase cleaves 1 molecule of ATP (ATP ➔ADP), which changes the conformation of the protein and flips the ion binding

site to the opposite side of the membrane. Dephosphorylation restores the pump to its original state.
    - The pump is also an electrogenic pump as it generates a voltage across the membrane (membrane potential) by releasing an excess of positive ions outside and leaves the inside negative
    - Membrane potentials are necessary for nerve cell excitability and represent a stored form of energy for secondary active transport

- **Secondary active transport (co-transport)**
    - Relies on a concentration gradient set up by primary active transport and couples the transport of two compounds across a membrane.
    - It effectively uses transmembrane solute gradients as a source of energy.
    - Occurs when uphill transport of one molecule e.g. glucose from the gut, is coupled with the simple downhill transport of an ion e.g. Na^+.
    - The electrochemical gradient into the cell for Na^+ (created by the Na^+/K^+ pump in the basolateral membrane) provides the driving force needed for active uptake of glucose into the cell.
    - Classified as
        i. Symporters (two solutes move in the same direction) e.g. Na^+ and amino acids
        ii. Antiporters (two solutes move in the opposite direction or counter- transport) e.g. the exchange of Na^+ (in) and H^+ (out)

Large molecule transport

Some molecules are too large to be transported by channels and instead bind to specific protein receptor molecules in the cell membrane to form intracytoplasmic vesicles. The vesicles are then incorporated into the plasma membrane by invagination (endocytosis) or pinched off from the plasma membrane (exocytosis)

- **Endocytosis:** The extracellular face of the cell membrane fuses to form vesicles around the macromolecule and the vesicle is pulled into the cell. There are three types of endocytosis:
    - Pinocytosis is the continuous unspecific uptake of extracellular fluid and molecules dissolved in it
    - Receptor mediated endocytosis via clathrin–coated pits or caveolin- coated pits. Pits contain integral protein receptors for molecules being endocytosed e.g. low-density lipoproteins.
    - Phagocytosis involves the endocytosis of particulate matter such as microorganisms or cell debris by phagocytes.

- **Exocytosis:** selective export of macromolecules out of the cell, e.g. hormones for secretion kept in secretory vesicles can fuse with the cell membrane and be released.

FURTHER READING

Hall JE: *Guyton and Hall Textbook of Medical Physiology*, Elsevier, 2021.Ebook. Chapters 1&2.
Klein BG: *Cunningham's textbook of veterinary physiology*. Elsevier, 2020. Available in BioMed and Werribee libraries.