CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

Cell physiology

1

Introduction

The cell is the **structural and functional unit of life**. Bounded by a cell membrane, which maintains the homeostasis of the cell interior, it contains various membrane-bound compartments or **organelles** within, which subserve specialised functions. These membrane-bound organelles are characteristic of all eukaryotic cells, including those in humans.

Cell membrane

The **cell membrane** bounds all cells in the human body, forming a dynamic interface between the intracellular and extracellular environments.

It serves, or facilitates, the following **functions**:

- The maintenance of **cell shape and structure**. This is achieved by the presence of anchoring sites for cytoskeletal filaments and extracellular matrix components.
- A **transport** function. This is brought about by selective permeability to ions and macromolecules, allowing the maintenance of cytosolic ionic composition, osmotic pressure and pH (around 7.2–7.4).
- **Intercellular communication**, involving signal transduction, i.e. the detection of chemical signals (messengers) from other cells. These signals mediate nerve transmission, hormone release, muscle contraction and the stimulation of growth. This is the result of the binding of signalling molecules by transmembrane receptors.
- **Intercellular adhesion**. This is brought about by the fusion of the membrane with other cell membranes via specialised junctions.
- Directed **cell movement**.

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

Structure of cell membranes

The thickness of cell membranes ranges from 6–10 nm, typically being about 7.5 nm.

- One nanometre is equal to 10^{-9} metre.

Cell membranes are composed primarily of lipids and proteins. Lipids are the major components of membranes, including glycerophospholipids (phosphoglycerides), sphingolipids (sphingomyelin) and cholesterol. Cephalin (phosphatidylethanolamine) and lecithin (phosphatidylcholine) are the most common glycerophospholipids in membranes. Membrane lipids form **self-sealing bilayers**. They are amphipathic molecules, with hydrophobic and hydrophilic moieties. The hydrophobic groups, the long fatty acyl side chains, form the core, with the polar hydrophilic groups lining both surfaces.

Carbohydrates comprise 5%–10% of cell membranes. They consist of glycolipids and glycoproteins and form the **glycocalyx** coat on the surface of the plasma membrane. This layer is responsible for the immunological characteristics of the cell and carries surface receptors that are involved in molecular recognition.

According to the **fluid mosaic model** of Singer and Nicolson cell membranes possess fluid structures, being considered as two-dimensional solutions of oriented globular proteins and lipids. They take the form of a continuous fluid but stable lipid bilayer, studded with an array of membrane-associated or membrane-spanning proteins. The fluidity of the membrane is determined by the degree of unsaturation of the constituent fatty acids. The lipids and proteins can undergo rotational and lateral movement.Membranes are **structurally and functionally asymmetrical**. This is due to asymmetrical orientation of integral and peripheral membrane proteins, laterally and transversely. Membranes are also **electrically polarised**, with the inside being negative with respect to the exterior.

On electron microscopy, a **trilaminar structure** is evident. This consists of two dark outer bands, representing the polar heads of the membrane phospholipids and protein molecules on the inner and outer surfaces of the membrane, and an inner lighter band due to the nonpolar tails of the lipid molecules.

Membrane proteins

Classification of membrane proteins

Membrane proteins can be classified according to their structural relationship to the lipid bilayer into:

Integral proteins, which penetrate the lipid bilayer;

Peripheral or extrinsic proteins, which are located outside the lipid bilayer;

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

Membrane protein functions

Transport carriers in facilitated diffusion processes;
Ion channels;
Pumps involved in active transport;
Receptors for hormones and neurotransmitters, e.g. G-proteins, which act as molecular switches: signal transduction;
Cell to cell recognition and interaction;
Junctional proteins in intercellular junctions: cell adhesion molecules;
Second messenger enzymes.

Lipid-anchored proteins, which lie outside the lipid bilayer but are covalently linked to lipid molecules within the bilayer.

Properties of integral membrane proteins

Integral membrane proteins demonstrate asymmetrical orientation in the membrane. They are amphipathic, with both hydrophobic and hydrophilic regions. If they span the membrane, they are known as transmembrane proteins. Removal from the membrane can be achieved by denaturation of the membrane, using either a detergent, e.g. ionic detergent sodium tetradecyl sulphonate, or the non-ionic detergent Triton X-100, or an organic solvent. Examples of integral membrane proteins include hormone receptors, ion channels, gap junction proteins, Na^+/K^+-ATPase and histocompatibility antigens.

Classification of cell membrane receptors

Cell membrane receptors are classified according to the signal transduction mechanism involved into:

- Ion channel-linked (ionotropic) receptors, which are coupled directly to ligand-gated ion channels. Examples include nicotinic acetylcholine receptors, ionotropic glutamate receptors, and gamma-aminobutyric acid (GABA) A receptors.
- Catalytic receptors, which possess a cytoplasmic catalytic region that usually behaves as a tyrosine kinase.
- G-protein-linked receptors, which are further discussed in the chapter on endocrine physiology (see p. 258).

Cell membrane receptors structurally comprise the following groups, depending on the number of times they span the membrane:

- **Single trans-luminal domain receptors**, which are directly or indirectly coupled to intracellular kinase enzymes.

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

Tyrosine kinase receptors consist of a tyrosine kinase domain, a hormone-binding domain, and a carboxy-terminal segment with multiple tyrosines for auto-phosphorylation.
The activation of signalling by tyrosine kinase receptors involves:
Ligand-induced oligomerisation of the receptor;
Trans-phosphorylation of the activation loop;
Phosphorylation of additional sites and recruitment of proteins to the receptor complex;
Phosphorylation of substrates.

Tyrosine kinase receptor family, which includes epithelial growth factors, fibroblast growth factors and insulin-like growth factors;
Cytokine receptor superfamily;
Serine-threonine kinase receptor family;
Guanyl cyclase receptor family;
Phosphotyrosine phosphatase family.

- **Seven transmembrane domain receptors**, associated with GTP-activated protein (G-protein)-coupled receptors.
- **Four transmembrane domain receptors**, that form ligand- or transmitter-gated ion channels.

Intercellular junctions

Types of intercellular junctions

- **Adherent junctions**, which hold epithelial cells, as well as cardiac muscle cells, together. This is achieved by connecting cytoskeletal elements of the cells.
- **Tight (occluding) junctions**, which segregate the apical and basolateral domains of the cell membrane by sealing the lateral intercellular junctions. They prevent pericellular diffusion of water and ions, thereby performing a barrier function.
- **Gap (communicating) junctions**, which allow intercellular diffusion of ions and signalling molecules. These are composed of hexagonal arrays of identical and tightly packed connexins or gap junction channel proteins, each of which shows a central pore of an approximate diameter of 1.5 nm. They form a connexon. Gap junctions permit electrical coupling between cells.

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

Types of adherent junctions
Actin filament (microfilament) attachments
Cell-to-cell: adherens junctions: cadherins
Cell-to-extracellular matrix: focal adhesions: integrins
Intermediate filament attachment sites
Cell-to-cell: desmosomes (spot and belt): cadherins
Cell-to-extracellular matrix: hemi-desmosomes: integrins

Cell–cell signalling mechanisms may be:

Endocrine: inter-glandular or inter-structure, i.e. hormones produced by an endocrine gland act on target cells at a distant body site.

Paracrine: local intercellular, i.e. act on neighbouring target cells.

Autocrine: intracellular, i.e. act on the cell responsible for production.

Cell adhesion molecules

Surface molecules involved in cell–cell interactions **(cell adhesion molecules**) are integral membrane proteins with extracellular, transmembrane and cytoplasmic domains. They mediate cell adhesion by forming non-covalent bonds with corresponding surface molecules of neighbouring cells.

Adhesion molecules can be classified as being involved in:

- **Cell body to cell body adhesion**:
  Calcium-dependent adhesion molecules: **cadherins** (classic cadherins; desmosomal cadherins). Cadherins are involved in homophilic cell-to-cell adhesion in the presence of calcium ions. They are cell surface adhesion molecules that interact with the intracellular actin cytoskeleton via plakoglobulin and catenin molecules. Neural (N)-cadherins, placental (P)-cadherins, and epithelial (E)-cadherins are recognised.
  Calcium-independent adhesion molecules, which belong to the immunoglobulin superfamily including intercellular adhesion molecules (ICAMs) and neural cell adhesion molecules(N-CAMs).
  Cell to cell surface carbohydrate ligand-binding proteins: selectins, which are divalent cation-dependent glycoproteins.
- **Cell to extracellular matrix adhesion**: the **integrins**. Integrins are a family of transmembrane proteins that act as receptors for extracellular matrix molecules, integrating the matrix and the cytoskeleton functionally and structurally. They are non-covalently attached heterodimeric glycoproteins, composed of alpha and beta subunits.

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

The role of cell adhesion molecules

Cell–cell recognition
Cell signalling
Cell growth
Cell migration
Embryogenesis
Information transfer from the extracellular matrix to the cell
Establishment of the blood–brain barrier
Cancer metastasis

Cell membrane transport

Classification of transport mechanisms

Membrane transport mechanisms can be **classified** as:

- **Passive diffusion**: along an electrochemical gradient. Diffusion refers to the random movement of particles in solution from an area of higher concentration to one of lower. This may involve either dissolution and diffusion in membrane lipid, or passage through ion channels. **Ion channels** may be permanently open (non-gated, passive, or leakage) or be gated, i.e. can be opened or closed: e.g., voltage-gated; extracellular or intracellular ligand-gated; mechanically gated (mechanical deformation); ion-gated; or gap junction activation. Voltage-gated channels are found in neurons and muscle cells. Mechanical gating is exemplified by the mechanical deformation of cilia of the hair cells of the inner ear brought about by sound waves.
- **Facilitated transport**: aided by membrane **transporters (carrier proteins)** in the direction of the electrochemical gradient. The process is more rapid than simple diffusion. Carriers must be able to recognise the substance transported, to permit translocation, followed by release of the substance with recovery of the carrier.
- **Active transport**: an energy requiring process operating against an electrochemical gradient. The process can be mediated by:

  Primary ATPases: Na^+/K^+-ATPase; H^+-ATPase; K^+/H^+-ATPase; Ca^{2+}-ATPase: these transporters are known as pumps.

  Adenosine 5′-triphosphate (ATP)-binding cassette proteins, which bind ATP and use the free energy from ATP hydrolysis to selectively transport materials, e.g. the cystic fibrosis transmembrane conductance regulator. These

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

Steps in receptor-mediated endocytosis

Specific binding of ligand to high-affinity receptor, which is clustered in pits coated with clathrin.
Internalisation of the receptor in its coated pit, forming a coated vesicle.
Coated vesicles lose their clathrin coats after endocytosis, and fuse with other vesicles to form early endosomes.
The receptors are recycled to the surface in vesicles that fuse with the cell membrane.
The process is used in cellular uptake of cholesterol (via the low density lipoprotein (LDL) receptor) and of iron, among other substances.

proteins comprise a ligand-binding domain at one surface and an ATP-binding domain at the other.

Secondary mechanisms, being coupled to Na^+ or H^+ transport. The mechanism can be either a **co-transport (symport)** or a **counter-transport (antiport system)**: K^+/H^+-ATPase or proton pump.

- **Osmosis**: the passage of water from a region where its concentration is high, through a semi-permeable membrane, into a region where its concentration is lower.
- **Vesicular transport**, which can be classified as:

Endocytosis:

Pinocytosis: the plasma membrane forms vesicles that trap extracellular fluid;
Phagocytosis;
Receptor-mediated endocytosis.

Exocytosis: fusion of membrane-bound vesicles with the plasma membrane, allowing their contents to be released into the extracellular space.

Diffusion across a membrane

This depends on:

The concentration gradient of the solute across the membrane;
The permeability of the membrane to the solute;
The transmembrane voltage gradient;
The molecular weight of the solute;
The membrane surface area;
The distance over which diffusion occurs.

The rate of diffusion is proportional to the cross-sectional area and to the change in concentration per unit distance, i.e. the concentration gradient across the membrane (**Fick's law**). Fick's law may be stated as:

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

$Q = - \times AD$ (dc/dx)

Where Q = the rate of flow of solute at right angles to the interface between two solutions (mg/s)

dc/dx = the concentration gradient (mg/ml) across the interface

A = the area of the interface (cm)

D = the diffusion coefficient (sq cm/s)

The permeability constant $P = D/d$, where D is the diffusion coefficient and d is the width of the membrane

Facilitated transport

Facilitated transport demonstrates the following characteristics:

Specificity for the transported solute;

Movement along an electrochemical gradient;

Saturation kinetics: saturation at high substrate concentrations owing to the limited number of binding sites on the carrier;

Inhibition by structurally similar substrates;

No energy expenditure.

Active transport

Active transport demonstrates the following characteristics:

Specificity for the transported solute.

Movement against an electrochemical gradient.

Saturation kinetics: saturation at high substrate concentrations.

Metabolic energy requirement. Energy dependence leads to active transport being substrate and oxygen dependent. Inhibition by metabolic poisons such as cyanide and dinitrophenol may occur. Profound inhibition may result from lowering of ambient temperature.

Competition for uptake by similar substrates.

Kinetic characteristics shared by facilitated diffusion and active transport processes

These include:

- **Stereochemical specificity**. Thus amino acid transport systems of cell membranes are much more active with L-amino acids than the D isomers.
- **Saturation**, i.e. the transport system can become saturated with the substance being transported. Plots of the rate of transport against substrate concentration usually show a hyperbolic curve approaching a maximum at which the rate is zero order with respect to substrate concentration.

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

- **Competitive inhibition** by other transported species (structurally related compounds).
- **Non-competitive inhibition by carrier poisons**, which can block or alter specific functional groups of proteins.

Ion channels

Ion channels are integral membrane proteins that form aqueous (water-filled) macromolecular membrane-spanning pores in the plasma membrane. They are involved in the generation and propagation of nerve impulses, synaptic transmission, muscle contraction, salt balance and hormone release.

The advantages of ion channel transport

- High selectivity for specific ion species (**substrate specificity**).
- The **ability to be gated**. The gating mechanism is a regulatory system controlling the opening and closing of gates in ion channels. Gating is a process of transition through open (conducting), closed and inactive states accompanied by conformational changes in the ion channels. Forward and backward rate constants for the transitions determine the likelihood of the various channel states.
- The ability to allow very large ion fluxes in short time periods, i.e. a **very high catalytic power** to substantially increase the flow rate of ions over the free diffusion rate in water.

Ion channel flow rates

The **rate of ion flow** through an open ion channel depends on:

The concentration gradient across the plasma membrane.

The voltage gradient across the plasma membrane.

The conductance of the ion channels, which is expressed in units of charge/second per volt. A high conductance channel allows more ionic flow for a given driving voltage than a low conductance channel.

Opening may lead to either inward current generation, leading to depolarisation; outward current generation, leading to hyperpolarisation; or increased conductance, leading to stabilisation of membrane potential.

Closure may lead to either switching off of the inward current, leading to hyperpolarisation; switching off of the outward current, leading to depolarisation; or reduced conductance, leading to increased sensitivity of the cell to other components.

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-54226-5 - Clinical Physiology: An Examination Primer
Ashis Banerjee
Excerpt
More information

Classification of ion channels

Ion channels are classified according to their electrophysiological properties, drug sensitivity, and by molecular cloning.

- **Ligand (agonist)-gated ion channels** (direct-coupled; G-protein-coupled; second messenger-coupled), which include acetylcholine receptors (muscle (nicotinic); neural), glycine receptors, GABA A receptors and glutamate receptors.
- **Calcium channels** are present in cell membranes in smooth muscle, cardiac muscle and other tissues, and in cellular organelle membranes such as the sarcoplasmic reticulum and mitochondria. Calcium functions as a primary generator of the cardiac action potential and as an intracellular second messenger. Calcium channels are further subdivided into three subgroups based on their threshold for activation and on the spread of inactivation:

  L-type (long-lasting): slowly inactivating; high threshold calcium conductance; sensitive to dihydropyridines; involved in excitation–contraction coupling in smooth and cardiac muscle (where they carry current in the plateau phase of the action potential), and in excitation-secretion coupling in endocrine cells and in some neurons.

  T-type (transient): low voltage activated, rapidly inactivated.

  N-type (neuronal): transient, high threshold calcium conductance; blocked by omega-conotoxin

The T and L channels are located in smooth and cardiac muscle tissue, whereas the N channels are located only in neuronal tissue.

Calcium channel blockers interact with the L-type calcium channel and consist of four classes of drugs: the 1,4-dihydropyridine derivatives (nifedipine, nimodipine, amlodipine), the phenylalkyl-amines (verapamil), the benzothiazepines (diltiazem), and a diarylaminopropylamine ether (bepridil).

- **Potassium channels** are tetrameric and composed of four identical peptide subunits (alpha subunits) that are symmetrically arranged to form a conical pore that spans the cell membrane. Many potassium channels also contain auxiliary proteins, beta subunits, that may alter electrophysiological or biophysical properties, expression levels or expression patterns. They are divided into:

  Six transmembrane-helix voltage-gated channels, which are activated by membrane depolarisation.

  Two transmembrane-span G-protein-coupled inward rectifying channels, which favour the influx rather than efflux of potassium ions.

  Calcium-activated channels, which are sensitive to intracellular calcium concentrations:

  Large conductance: blocked by charybdotoxin and iberiotoxin;

  Small conductance: blocked by apamin.

© in this web service Cambridge University Press www.cambridge.org