Mammalian Physiology

Cellular Membranes
Membrane Transport
Objectives

- Describe the structure of the cell membrane
- Describe the special membrane structures connecting cells
- Describe the methods of transport across the cell membrane
- Describe the methods of transport through the cell membrane
  - Diffusion
  - Osmosis
  - Facilitated Transport
  - Active Transport
Cell Membrane

Not just a wall - it is active, ‘fluid’

Function:
- Boundary between inside and outside
- Control substances coming and going
- Receptor site
- Site of cell-cell recognition

Composition:
- Lipids (30-80%)
- Carbohydrates
- Proteins
- Steroids
- (cholesterols)
Compartmentalization

Membrane separates cell from extracellular environment – serves as a permeability barrier
Membrane Structure

Phospholipid Bilayer – hydrophilic head, hydrophobic tail
Lipid Bilayer Composition

- Phosphatidylcholine – most common phospholipid in cell membrane
- Other phospholipids: sphingomyelins, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol,
- Cholesterol, glycolipids, glycoproteins
Common Membrane Lipids

A Phosphatidylinositol
B Phosphatidylserine
C Phosphatidylcholine

D Sphingomyelin
E Galactocerebroside
F Cholesterol

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Lipid Bilayer

Selectively permeable barrier
Small nonpolar molecules: $O_2$, $CO_2$ diffuse rapidly
Uncharged polar molecules: $H_2O$, glycerol and ETOH diffuse rapidly
Lipid bilayer is highly impermeable to charged molecules and ions
(charge and strong attraction to water inhibit them from entering the bilayer)
Fluid Mosaic Model

Integral proteins are embedded in the membrane.
Peripheral proteins are associated with external surface of integral proteins.
Membrane Constituents

Cholesterol – aids in stiffening membrane – 20% of membrane lipids
Phosphatidyl inositol – 2\textsuperscript{nd} messenger: inositol triphosphate & diacylglycerol
Glycolipids – receptors, antigens – only on outer surface of membrane
Membrane Proteins

A. Integral protein that transmits signal from outside to inside cell

B. Integrin is adhesion protein that attaches cell to the extracellular matrix
Membrane Transporters vs Ion Channels

Transporter binds substrate and after undergoing a conformational change releases it on the opposite side of the membrane. Ion channel is either open or closed, allowing substrate to move in either direction.
Membrane Pores

Specific transport proteins or channels in membrane

Passive, non-coupled transport

Voltage-gated ion channels
-excitable cells (muscle, nerve)
Ion Channels

Membrane channels are specific transport proteins spanning membrane.
Fluid Mosaic Model

Constituent molecules are free to move in plane of membrane
Fluid Mosaic

Diffusion of membrane proteins within the plane of the cell membrane – indicates fluidity of cell membrane; not a rigid fixed structure
Functions of Membrane Proteins

- Transport
  - Ion channels
  - Ion pumps
- Enzymatic activity
  - Adenylate cyclase
  - Phosphatidyl inositol
- Receptors for signal transduction
  - Hormones
Functions of Membrane Proteins

- **Intercellular adhesion**
  - Gap junctions – connexons
  - Tight junctions – integral proteins
  - Desmosomes – cadherins

- **Cell-cell recognition**
  - Glycoproteins
  - Antigens

- **Attachment to cytoskeleton and extracellular matrix**
  - Integrins
Special Membrane Structures
Lipid Rafts

- Tightly packed phospholipid region of membrane
- More stable and orderly and less fluid than the rest of the membrane
- Make up 20% of the outer membrane surface
- Composed of sphingolipids and cholesterol
- Can include or exclude various proteins
- Are concentrating platforms for cell-signaling molecules
Roles of Membrane Receptors

- Contact signaling – important in normal development and immunity
- Electrical signaling – voltage-regulated “ion gates” in nerve and muscle tissue
- Chemical signaling – neurotransmitters bind to chemically gated channel-linked receptors in nerve and muscle tissue
- G protein-linked receptors – ligands bind to a receptor which activates a G protein, causing the release of a second messenger, such as cyclic AMP
Movement Across a Membrane

**Bulk Transport of material across the membrane**

**Endocytosis**
- Phagocytosis
- Pinocytosis
- Receptor mediated endocytosis (coated pits)

**Exocytosis**
Endocytosis

Phagocytosis – particulate matter is engulfed by pseudopod (cytoplasmic extension) and internalized

Phagosome fuses with lysosome and contents are digested
Endocytosis

Pinocytosis – fluid containing solublized molecules is taken up

Routine cellular activity – allows cell to nonselectively sample extracellular fluid
Endocytosis

Receptor-mediated endocytosis – coated pit (clathrin)
Protein specific receptors are located in clathrin coated pit
Endocytosis is an active process that requires metabolic energy

(c) Receptor-mediated endocytosis

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Exocytosis

Release of secreted proteins or neurotransmitters by exocytosis requires fusion of vesicles with cell membrane

Release of neuromuscular at presynaptic junction
Hormone secretion
Release of digestive enzymes from pancreatic acinar cells
Exocytosis

Release of acetylcholine at neuromuscular junction

Depolarization of nerve increases Ca$^{2+}$ permeability at nerve ending. Ca$^{2+}$ causes mobilization of vesicles containing acetylcholine to membrane where Ach is released into the synaptic cleft.
Exocytosis

Release of digestive enzymes from pancreatic acinar cells

Synthesis of digestive enzymes is initiated on ribosomes on ER

Enzymes are incorporated into vesicles, which then become zymogen granules

When cell is stimulated, vesicles fuse with plasma membrane and granules are discharged
Membrane Transport

Ion channels, and membrane transporters in a typical cell
Passive Membrane Transport

- Simple diffusion
- Channel-mediated facilitated diffusion
- Carrier-mediated facilitated diffusion

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Passive Membrane Transport: Diffusion

- Simple diffusion – nonpolar and lipid-soluble substances
  - Diffuse directly through the lipid bilayer
  - Diffuse through channel proteins
- Facilitated diffusion
  - Transport of glucose, amino acids, and ions
  - Transported substances bind carrier proteins or pass through protein channels
Diffusion

Simple diffusion - movement along a concentration gradient

Net flux stops when equilibrium is reached

$O_2$ transit from alveolus to pulmonary capillary
Fick’s Law of Diffusion

Diffusion coefficient within the wall (cm²/sec).

Concentration of solute in capillary.

Concentration of solute in interstitial space.

Blood

Capillary wall

Surface area (cm²)

Solute flux per unit area and unit time (moles/[cm²•sec]).

Thickness of the capillary wall (cm).
Fick’s Law of Diffusion

Net rate of diffusion

\[
\text{Net rate of diffusion} = \frac{(C_1 - C_2) \times \text{surface area} \times \text{permeability}}{\text{distance} \times \sqrt{\text{molecular weight}}}
\]

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on net diffusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Concentration gradient</td>
<td>↑</td>
</tr>
<tr>
<td>↑ Membrane permeability</td>
<td>↑</td>
</tr>
<tr>
<td>↑ Membrane surface area</td>
<td>↑</td>
</tr>
<tr>
<td>↑ Molecular weight</td>
<td>↓</td>
</tr>
<tr>
<td>↑ Membrane thickness</td>
<td>↓</td>
</tr>
</tbody>
</table>
Membrane Solubility

Permeability of non-electrolytes as a function of lipid solubility

Non-electrolyte permeability increases in proportion to lipid concentration
## Permeability Effects

<table>
<thead>
<tr>
<th>Substance</th>
<th>Diameter (nm)</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Urea</td>
<td>0.36</td>
<td>0.0006</td>
</tr>
<tr>
<td>Hydrated Cl⁻</td>
<td>0.386</td>
<td>0.0000001</td>
</tr>
<tr>
<td>Hydrated K⁺</td>
<td>0.396</td>
<td>0.0000000006</td>
</tr>
<tr>
<td>Hydrated Na⁺</td>
<td>0.512</td>
<td>0.0000000002</td>
</tr>
<tr>
<td>Glycerol</td>
<td>0.62</td>
<td>0.0006</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.86</td>
<td>0.000009</td>
</tr>
</tbody>
</table>
# Molecule Size Effects

<table>
<thead>
<tr>
<th>Substance</th>
<th>Molecular Wt.</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>18</td>
<td>1.00</td>
</tr>
<tr>
<td>NaCl</td>
<td>58.5</td>
<td>0.96</td>
</tr>
<tr>
<td>Urea</td>
<td>60</td>
<td>0.8</td>
</tr>
<tr>
<td>Glucose</td>
<td>180</td>
<td>0.6</td>
</tr>
<tr>
<td>Sucrose</td>
<td>342</td>
<td>0.4</td>
</tr>
<tr>
<td>Inulin</td>
<td>5,000</td>
<td>0.2</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17,600</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>68,000</td>
<td>0.01</td>
</tr>
<tr>
<td>Albumin</td>
<td>69,000</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Membrane Thickness

<table>
<thead>
<tr>
<th>Diffusion distance (μm)</th>
<th>Time required for diffusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 msec</td>
</tr>
<tr>
<td>10</td>
<td>50 msec</td>
</tr>
<tr>
<td>100</td>
<td>5 sec</td>
</tr>
<tr>
<td>1000 (1 mm)</td>
<td>8.3 min</td>
</tr>
<tr>
<td>10,000 (1 cm)</td>
<td>14 hr</td>
</tr>
</tbody>
</table>

*The time required for the “average” molecule (with diffusion coefficient taken to be $1 \times 10^{-5}$ cm$^2$/sec) to diffuse the required distance was computed from the Einstein relation: $t = (\Delta X)^2/2D$, where $t$ is time and $\Delta X$ is the average diffusion distance.
Passive Membrane Transport: Osmosis & Filtration

• Occurs when the concentration of a solvent is different on opposite sides of a membrane
• Diffusion of water across a semi-permeable membrane
• Osmolarity – total concentration of solute particles in a solution
• Tonicity – how a solution affects cell volume
  – Hypertonic solution = cell shrinkage
  – Hypotonic solution = cell swelling
• Filtration
  – The passage of water and solutes through a membrane by hydrostatic pressure
  – Pressure gradient pushes solute-containing fluid from a higher-pressure area to a lower-pressure area
Osmosis

Osmosis - movement of water through a semi-permeable membrane along its concentration gradient

Osmotic Pressure (van’t Hoff’s law)

\[ \pi = RT(\Phi ic) \]

- \( \pi \) = osmotic pressure
- \( R \) = ideal gas constant
- \( T \) = absolute temperature
- \( \Phi \) = osmotic coefficient
- \( i \) = number of ions
- \( c \) = molar concentration

\( \Phi ic \) = osmolarity of solution
Tonicity

Cells will shrink if extracellular fluid is hypertonic and will swell if extracellular fluid is hypotonic as a consequence of water moving down its concentration gradient.
Facilitated Transport

Facilitated diffusion or carrier mediated transport - movement down a concentration gradient using integral membrane transport proteins

Carriers
-Are resident in membrane or sequestered in intracellular vesicles

-Show specificity for certain polar molecules including sugars and amino acids

Glucose transport into muscle or adipose tissue
Fusion of Membrane Vesicles

Two types of glucose transporters in muscle and adipose tissue
Glut 1 – membrane resident
Glut 4 – in intracellular vesicles

Stimulation by insulin or contractile activity causes translocation of vesicles to membrane when they are incorporated into cell membrane to promote glucose uptake.
Facilitated Transport

Facilitated Diffusion or Carrier Mediated transport

1. The carrier is open to the outside.
2. X enters from outside and binds at a binding site.
3. The outer gate closes and X becomes occluded, still attached to its binding site.
4. The inner gate opens with X still bound.
5. X exits and enters the inside of the cell.
6. The cycle can also flow in reverse order.

Carriers are conduits that are gated by two “doors” that are never open at the same time.
Facilitated Transport

- Facilitated Diffusion or Carrier Mediated Transport
- More rapid than simple diffusion
- Characteristics
  - Saturation kinetics
  - Chemical Specificity
  - Inhibition
  - Counter transport

![Graph showing the relationship between rate of transport and [transported substance]](image)
Saturation Kinetics

Finite number of transporters means substrate concentration can exceed transport capacity

$V_{\text{max}}$ is the maximum rate of transport for the transporter
$K_m$ is the substrate concentration which gives $\frac{1}{2}$ the maximal rate of transport

$V_{\text{max}}$ reflects transporter number

$K_m$ reflects transporter affinity for substrate
Chemical Specificity

Spatial orientation of molecule
Only molecules with the requisite chemical structure are transported

(+)-Lactic acid

(-)-Lactic acid

L-Glycerose (L-glyceraldehyde)

d-Glycerose (d-glyceraldehyde)

L-Glucose

d-Glucose
Inhibition

Transport is inhibited when a structurally unrelated compound binds to the transport protein, decreasing affinity of transport protein for the normally transported substance.

Competitive Inhibition - transport of a substance is reduced when another substance which can use the same transporter is added.
Counter Transport

Carriers function as airlocks, not ferry boats
Concentration gradient limits counter transport
Types of Active Transport

Primary active transport – hydrolysis of ATP phosphorylates the transport protein causing conformational change
Secondary active transport – co-transport – simultaneous movement of two molecules through the same transport protein
Primary Active Transport

Movement of a substance against its concentration gradient
Requires energy – ATP and carrier proteins

Na\(^+\)/K\(^+\) ATPase pump

Ca\(^{2+}\) uptake in muscle sarcoplasmic reticulum
Active Transport

Calcium reuptake into the sarcoplasmic reticulum of skeletal muscle is an active transport process
Secondary Active Transport

Transport protein binds both molecules (Na\(^+\) and glucose or amino acid) Energy released by transporting Na\(^+\) down its electrochemical gradient is used to transport glucose or amino acid against its concentration gradient Mechanism for glucose and amino acid uptake in small intestine

Symport system – two substances are moved across a membrane in the same direction (Na\(^+\) and glucose or amino acid)

Antiport system – two substances are moved across a membrane in opposite directions (Na\(^+\) and H\(^+\))
Secondary Active Transport

Representative co-transporters
Energy from downhill movement of one solute is used to move another solute uphill
Epithelial Transport

Transport on one side of the cell is different from transport on the other side. 
\( \text{Na}^+ \) - glucose co-transport on luminal side and facilitated transport (GLUT 2 transporter) on basolateral side.

Transport occurs in small intestine and renal tubules.
# Passive Membrane Transport – Review

<table>
<thead>
<tr>
<th>Process</th>
<th>Energy Source</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple diffusion</td>
<td>Kinetic energy</td>
<td>Movement of $O_2$ through membrane</td>
</tr>
<tr>
<td>Facilitated diffusion</td>
<td>Kinetic energy</td>
<td>Movement of glucose into cells</td>
</tr>
<tr>
<td>Osmosis</td>
<td>Kinetic energy</td>
<td>Movement of $H_2O$ in &amp; out of cells</td>
</tr>
<tr>
<td>Filtration</td>
<td>Hydrostatic pressure</td>
<td>Formation of kidney filtrate</td>
</tr>
</tbody>
</table>
# Active Membrane Transport – Review

<table>
<thead>
<tr>
<th>Process</th>
<th>Energy Source</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active transport of solutes</td>
<td>ATP</td>
<td>Movement of ions across membranes</td>
</tr>
<tr>
<td>Exocytosis</td>
<td>ATP</td>
<td>Neurotransmitter secretion</td>
</tr>
<tr>
<td>Endocytosis</td>
<td>ATP</td>
<td>White blood cell phagocytosis</td>
</tr>
<tr>
<td>Fluid-phase endocytosis</td>
<td>ATP</td>
<td>Absorption by intestinal cells</td>
</tr>
<tr>
<td>Receptor-mediated endocytosis</td>
<td>ATP</td>
<td>Hormone and cholesterol uptake</td>
</tr>
</tbody>
</table>