## INTRODUCTION

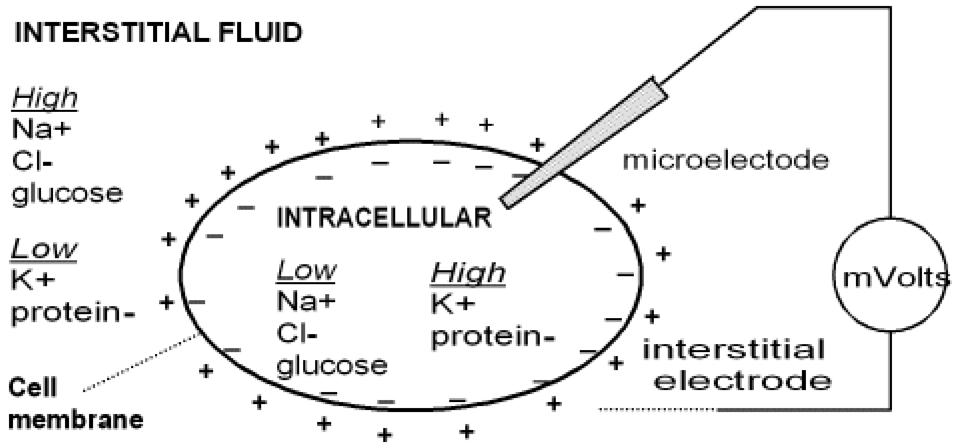
### A. Intracellular and Interstitial Distribution

1. Concentrations of dissolved substances

Example: Mammalian Nerve or Skeletal Muscle Cell

| | *Interstitial* | | *Intracellular* | |
|---|---|---|---|---|
| Na$^+$ (Sodium ion) | 145 | | 10 | mM/l (millimoles/liter) |
| Cl$^-$ (Chloride ion) | 110 | | 5.5 | mM/l |
| K$^+$ (Potassium ion) | 5 | | 155 | mM/l |
| Protein$^-$ | 1 | | 35 | g/dl (grams/100 ml) |
| Glucose | 5 | (90) | Low | mM/l (mg/dl, milligrams/100 ml) |

2. Electrical charges



Inside of the cell is generally negative relative to the outside of the cell

Intracellular electrical potential ($V_m$) typically $\approx$ -70 to -80 millivolts (mV)

3. Unexpected, because concentration and electrical gradients would be expected to dissipate spontaneously

4. Concentration and electrical differences associated with cell vitality

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Intracellular fluid: fluid within the cell (ICF); part of the cytoplasm

Interstitial fluid: fluid in the interstitial space surrounding the cell (part of "extracellular" fluid (ECF); generally similar to blood plasma except less plasma protein)

## RATE OF MEMBRANE MOVEMENT

### A. Major Factors

$$\boxed{\text{TRANSPORT RATE = AREA x PERMEABILITY x NET DRIVING FORCE}}$$

### B. Area (A)

1. Define: Area available for transport across cell wall or organ surface

### C. Permeability (P)

1. Define: ease with which a particular particle passes through the membrane

   example: $P_{Na+}$ = Sodium ion permeability

   NOTE: For the common monovalent ions $Na^+$, $K^+$, and $Cl^-$, the relative permeabilities in resting mammalian nerve and skeletal muscle cells are

   $$P_K \approx P_{Cl} >> P_{Na}$$

### D. Net Driving Force

1. Sum of passive forces (such as diffusion and electric forces) and active forces requiring energy developed by living systems (more later)

## MODES OF MEMBRANE TRANSPORT

### A. Cell Membrane Structure

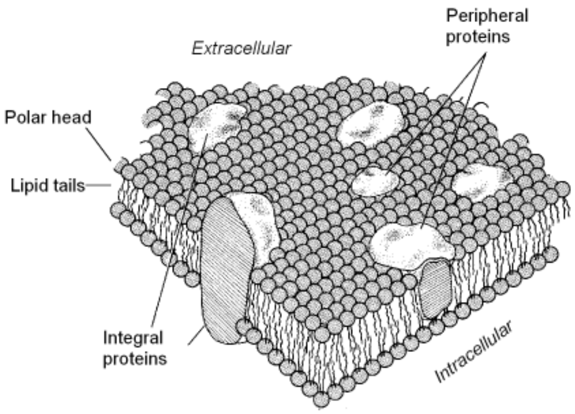
1. Phospholipid bilayer

   Note: Lipid core is impermeable to charged particles (ions) and polar substances

2. Proteins, including membrane-spanning proteins (integral proteins or transmembrane proteins) which can aid in membrane transport

3. Carbohydrates, associated with membrane proteins (glycoprotein) or membrane lipids (glycolipid)

4. Cholesterol (membrane flexibility)



MODES OF MEMBRANE TRANSPORT (continued)

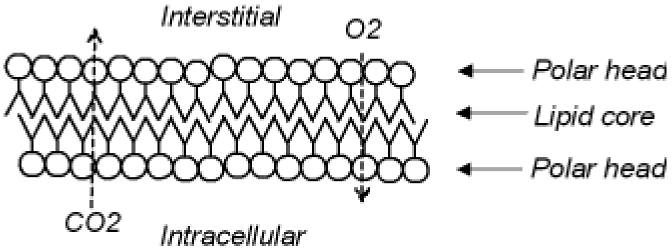
B. Dissolve in Membrane Lipid

1. Only applicable to lipid-soluble substances

2. Permeability depends on degree of lipid solubility (sometimes measured by oil-water partition coefficient)

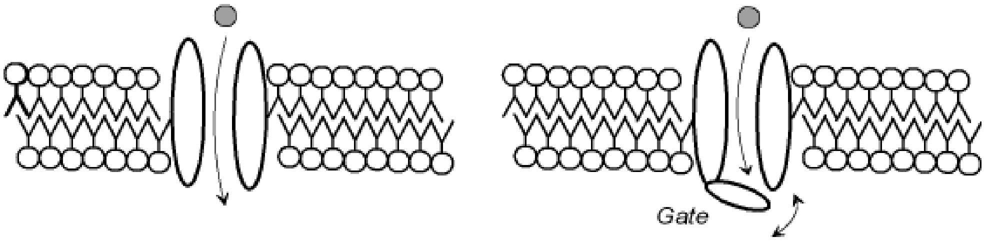
3. Substances utilizing this mechanism include

    a. small, lipid-soluble organic molecules
    b. dissolved gases ($O_2$, $CO_2$, etc.)
    c. water (!)



C. Simple, Passive Movement Through Channels

1. Channel: membrane-spanning macromolecule with an aqueous pore in its center



2. Aqueous-soluble particles can move through pores (charged particles and polar particles)

3. Some channels are selective for one or a small group of substances (e.g. Na-channel, K-channel); some channels are non-selective (e.g. “leak” channel)

4. Permeability depends upon

    a. particle size (generally only small particles can pass through channels)
    b. channel density (number of channels/area)
    c. presence and state of channel gates -- element of a channel that can open (increase permeability) or close (decrease permeability)
    d. gated channels are classified by their control
        1) voltage-gated or electrically-gated: open or close depends upon membrane potential
        2) ligand-gated: open or close depends upon a chemical substance binding to a membrane receptor
        3) physically-gated: open or close depends upon a physical influence -- mechanical, thermal, etc.

Note: Ligand: chemical that can bind to a receptor

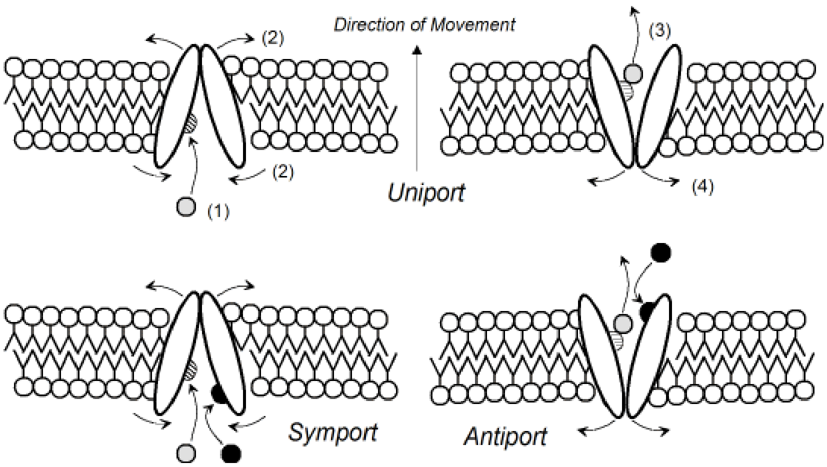
MODES OF MEMBRANE TRANSPORT (continued)

D. Facilitated Diffusion

1. Define: passive movement by binding to specific sites (receptor sites) on membrane-spanning or membrane-mobile proteins

2. Mechanism

   a. particle on one side of the membrane binds to receptor site
   b. channel reconfigures, exposing the receptor site to the solution on the other side of the membrane
   c. particle dissociates from the receptor and diffuses into the solution on the other side
   d. may move several particles simultaneously in the same direction (symport) or in opposite directions (antiport)



3. Selectivity: facilitated diffusion channels are generally selective because of specificity of receptor binding sites

4. Permeability depends upon

   a. same factors as simple, passive movement through channels
   b. affinity of receptor for transported particle
   c. number of receptors; note saturation (maximum transport rate) as concentration of transported particles increases and all receptors are occupied
   d. possible presence of other particles that can bind to the same receptors (agonist, antagonist)

Note:
Agonist: substance that binds to a receptor and has the same effect as the substance that normally binds to the receptor
Antagonist (or Blocking Agent): substance that binds to the receptor preventing the agonist from binding and/or preventing the normal response

## PASSIVE FORCES AND ACTIVE TRANSPORT

### A. Diffusion (concentration gradient force)

1. statistical "force", based on tendency of any substance to diffuse from regions where its concentration is high to regions where its concentration is low (depends on absolute temperature)

2. diffusion force in membrane transport is proportional to the concentration difference between the two sides of the membrane; e.g., for a cell

   $\Delta C = C_o - C_i$ where $C_i$ = intracellular concentration
   $C_o$ = extracellular (outside) concentration

3. Each substance diffuses according to its own concentration difference at a rate dependent on its own permeability

### B. Electrical Force

1. based on the force on charged particles in an electric field

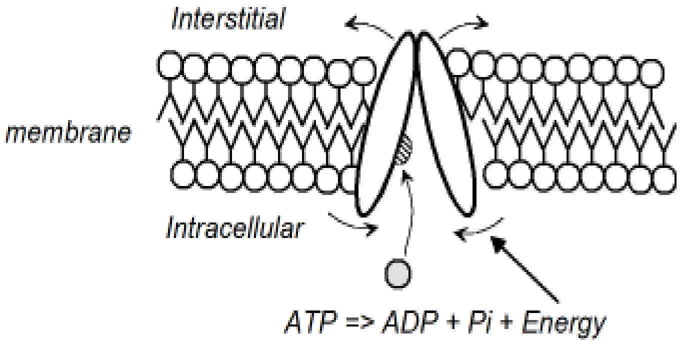
2. in membrane transport, electrical force depends on particle charge and membrane electrical potential, e.g.

   Force ~ particle charge x $V_m$ (membrane potential)

3. Positively charged particles are attracted to the negative side of the membrane, while negative particles are attracted to the positive side of the membrane (opposite charges attract, like charges repel)

Note: The combined effect of the concentration and electrical differences or gradients is called the <u>electrochemical</u> gradient

### C. Active Transport



1. Define: Movement of particles coupled to a metabolic energy supply, frequently ATP (adenosine triphosphate), which is degraded to ADP (adenosine diphosphate) and inorganic phosphate (Pi), releasing energy in the process)

2. Similar characteristics and mechanism as Facilitated Diffusion, <u>except</u>

3. May transport particles <u>against</u> their passive (concentration and electrical) gradients

## ESTABLISHMENT OF CONCENTRATION DISTRIBUTION AND MEMBRANE POTENTIAL
(for resting nerve and skeletal muscle cells)

A. Electrogenic 3:2 Na-K-ATPase Pump

1. Powered by the energy stored in intracellular ATP

2. Every cycle of the active transport pump moves 3 Na+ out of the cell and 2 K+ ions into the cell; this results
   a) intracellular K+ increase
   b) intracellular Na+ decrease
   c) net removal of 1 positive charge from the cell

3. Although this contributes to the negative intracellular potential, it is responsible for only a few mV of the resting potential

B. Donnan (or Gibbs-Donnan) Equilibrium

1. Intracellular fluid contains negative ions (e.g., proteins) to which the cell membrane is relatively impermeable, contributing to the excess of negative charges within the cell

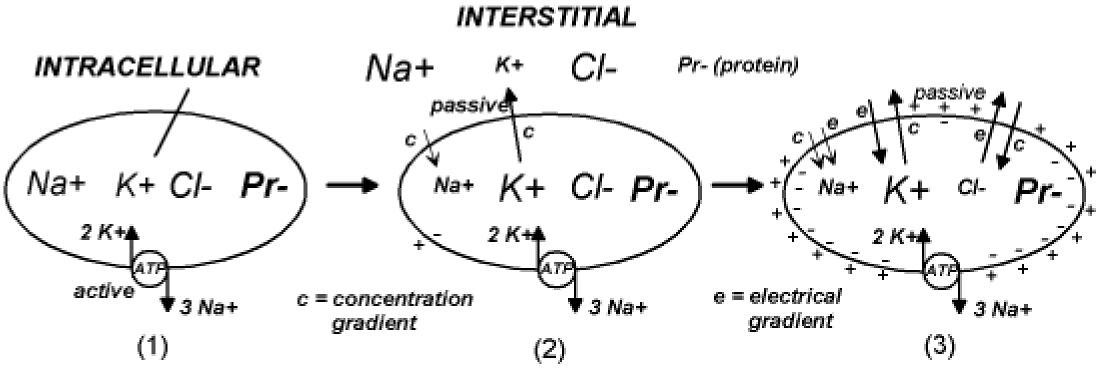
2. Also contributes to the negative resting potential, but is not the major cause

C. $P_K >> P_{Na}$ (combined with the concentration gradients)

1. Active transport by the Na-K-ATPase pump leading in concentration gradients for sodium and potassium

2. This is followed by passive back diffusion; since the membrane is much more permeable to $K^+$ than to $Na^+$, potassium back diffusion predominates, causing the intracellular potential to become negative

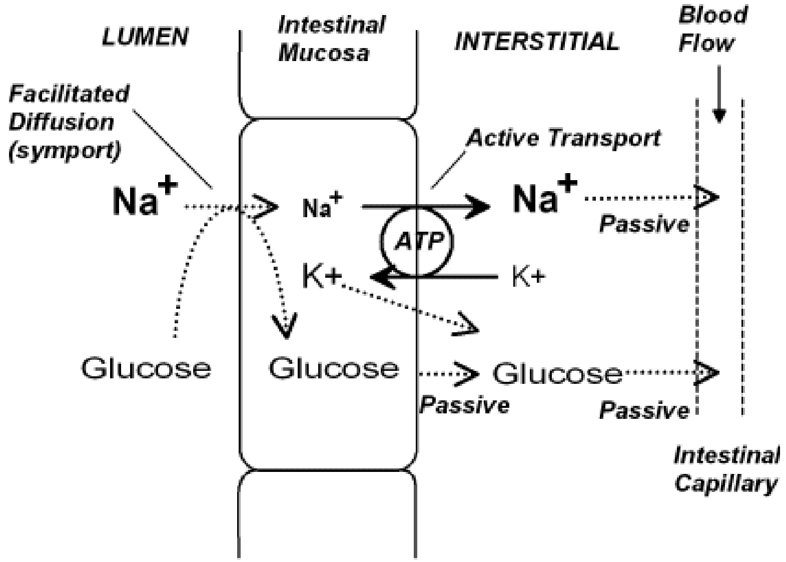
3. Eventually, the concentration and electrical gradients so developed lead to a steady state for $K^+$, $Na^+$, and $Cl^-$



ROLES OF ACTIVE TRANSPORT

A. Establish an appropriate intracellular chemical environment (e.g. Na+, K+, acidity -- pH/H+)

B. Transport particles across tissue layers, from one body compartment to another (e.g. intestinal mucosa, renal tubule, secretory glands)



Note: Involves asymmetrical membrane transport – different transport mechanisms on opposite sides of the cell

C. Converts metabolic energy to electrochemical potential energy, to be used in

1. electrical transmission of information

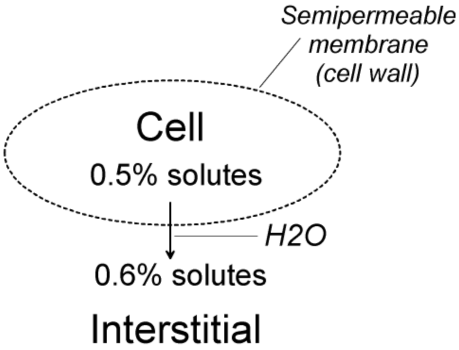
2. movement of other substances across membranes -- cotransport (e.g. intestinal glucose absorption)

D. Helps regulate cell volume by controlling osmotic movement of water

## WATER TRANSPORT

A. Membrane Water Permeability: most (but not all) cell membranes are highly permeable to H2O molecules

B. Osmosis: the major driving force for water transport across cell membranes is the relative number of water molecules vs. the number of solute (dissolved) particles; water movement under this driving force is termed osmosis (similar to diffusion of dissolved particles)



C. Osmolarity (or Osmolality): the relative concentration of water can be derived from adding the molar concentration of all the solutes; this is termed the osmolarity of the solution

1. typical osmolarity for interstitial fluid or blood plasma in humans is about 300 mosmoles/liter (mosm/l) (range 285-310 mosm/l)

2. solutions are classified by their osmolarity relative to normal

| | |
|---|---|
| isosmotic: | same osmolarity as normal interstitial fluid or blood plasma |
| hyperosmotic: | greater than normal osmolarity |
| hyposmotic: | lower than normal osmolarity |

D. Water moves from regions of low osmolarity (dilute) to regions of high osmolarity (concentrated)

Example: response of erythrocytes (red cells) placed in isosmotic saline (NaCl solution) vs. erythrocytes placed in distilled water

E. Solutes with the same intracellular and interstitial concentrations and solutes that equilibrate across the cell membrane do not contribute to net water movement

Solutes with different intracellular-interstitial concentrations determine the tendency of cells to change size (swell or shrink); the sum of the concentrations of these substances is termed the tonicity of the solution (the term “tone” in this context refers to the tendency of cells to swell or shrink)

1. solutions can also be classified by their tonicity

| | |
|---|---|
| isotonic: | same tonicity as normal interstitial fluid |
| hypertonic: | greater than normal tonicity (cells will shrink) |
| hypotonic: | lower than normal tonicity (cells will swell) |

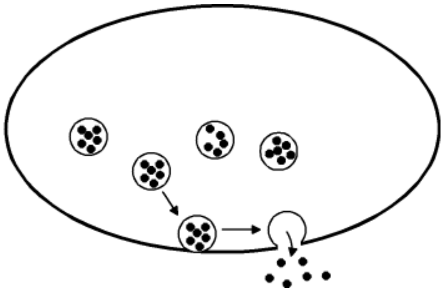
Example: place erythrocytes in isosmotic urea (note: urea easily penetrates the membranes of most cells)

## VESICULAR TRANSPORT

A. Vesicle: Subcellular membrane-bounded container used in intracellular storage and/or membrane transport

B. Exocytosis: Movement from cytoplasm to the interstitial fluid

1. Vesicle migrates to the cell membrane and attaches ("docks") to the membrane
2. Vesicle membrane fuses with the cell membrane
3. Vesicle contents are released into the interstitial fluid



C. Endocytosis: Movement from interstitial fluid to intracellular vesicle

1. Substance to be transported binds to cell membrane receptors
2. Cell membrane invaginates, forming vesicle containing the transported substance
3. Vesicle migrates intracellularly

D. Utility

1. Membrane transport of large molecules
2. Intracellular storage in vesicles (endocytosis)