

TRANSPORTERS, CHANNELS & PUMPS

Emma Jakoi, Ph.D.

Learning objectives

- Describe how solutes cross cell membranes
- Explain how charge, size, and solubility affect solute movement across cell membranes.
- Contrast how transporters, pumps and channels work
- Describe how ion channels are gated.
- Explain transcellular transport
- Explain osmosis
- Explain osmolarity and tonicity
- Explain how effective solutes regulate fluid compartments

BODY FLUID COMPARTMENTS

Recall from the homeostasis lecture that the human body stripped of fat is ~70% water. Under normal conditions, 3/4 of the extracellular fluid (ECF) is interstitial water (IS) and 1/ 4 of ECF is blood plasma (IVS). Thus only 1/12 (i.e., 1/ 4 x 1/ 3) of the total body water is blood plasma.

Total body water = ICF + ECF where ECF = IS + IVS

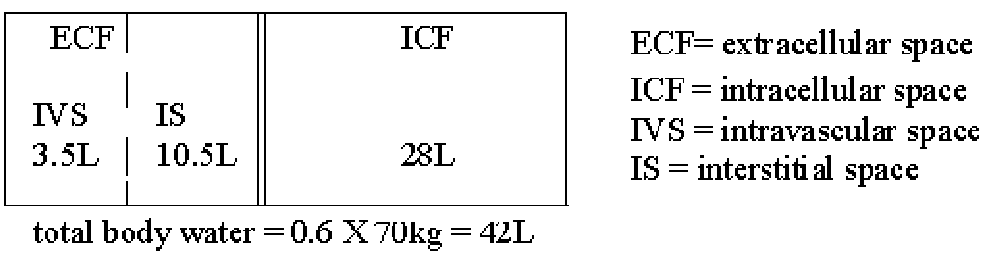

Figure 1. Fluid compartments of the body.

The fluid volumes of the body are measured by the **isotope dilution** method. In this procedure, a known quantity of a radioactive substance (marker) is administered, allowed to equilibrate within the body compartments and then its concentration is measured in a known volume of plasma. As the total amount administered is known, the volume of the diluted marker can be calculated from its final concentration in the plasma. This quantity is corrected for any of the substance excreted during equilibration and for the half-life (decay) of the radioactive isotope over time. To measure the intravascular space (plasma), radiolabeled albumin is infused; for extracellular markers, inulin is used. The whole body water volume is determined by infusing triturated water.

SOLUTE & WATER FLOW

One of the key concepts that reoccur in physiology is the importance of gradients and the movement of solutes and water across barriers to maintain normal body function. Biological membranes are bilayers of lipid which restrict the movement of water soluble molecules, such as ions and glucose, from entering cells. In contrast, lipid soluble molecules cross membranes easily.

DIFFUSION is the passive movement of materials down their concentration gradient. It takes place in an open system or across a permeable partition. There are two types of diffusion (Fig 1):

Simple diffusion - membrane permeable (lipid soluble) molecules cross membranes by simple diffusion.
Characteristics of simple diffusion include:

a. occurs from an area of higher to one of lower concentration i.e., down a concentration gradient.
b. requires no energy expenditure.
c. continues until equilibrium is reached.
d. occurs rapidly over short distances and slowly over long distances.
e. is directly related to temperature (molecules move faster at higher temperatures).
f. is inversely related to the size of the molecule (larger molecules move slower).

Facilitated diffusion- membrane impermeable (hydrophilic) molecules have restricted entry and may not enter cells at all.
Facilitated diffusion occurs with the aid of a transport protein but no input of energy is required. Transport proteins for facilitated diffusion move only one kind of molecule at a time. This process exhibits specificity, competition, and saturation. Glucose enters most cells in the body by facilitated diffusion.

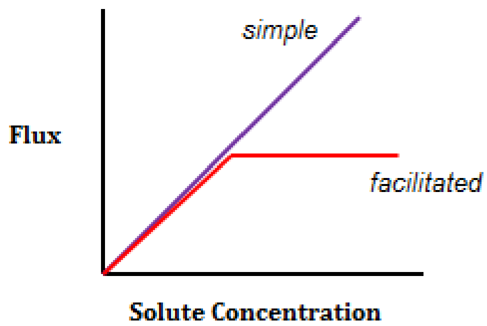

Figure 1. Comparison of solute uptake by simple diffusion and by facilitated diffusion.

Impermeable molecules can enter or leave cells using transport proteins. Transport proteins are classified as either transporters or channels.

Transporter proteins bind to specific molecules (substrates) that they carry across the membrane by changing conformation (shape) (Fig 2). They never form a direct connection between the ECF and ICF compartments. Small organic molecules such as glucose and amino acids cross membranes on transporters.

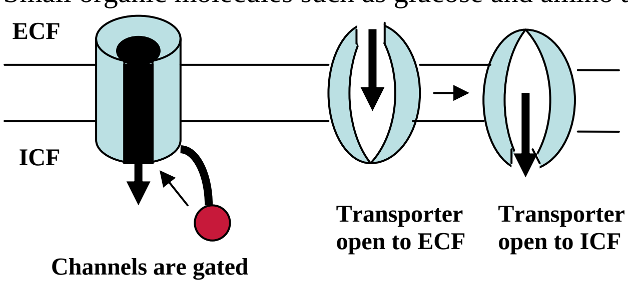

Figure 2. Channels and transporters allow membrane impermeable solutes to cross membranes.

Some transporters bind a single substrate; others bind two or more and are called **co-transporters** (Fig 3).
Co-transporters are further classified into:

Symporter moves two (or more) substances in the same direction across a membrane.
Antiporter moves two (or more) substances in opposite directions across a membrane.

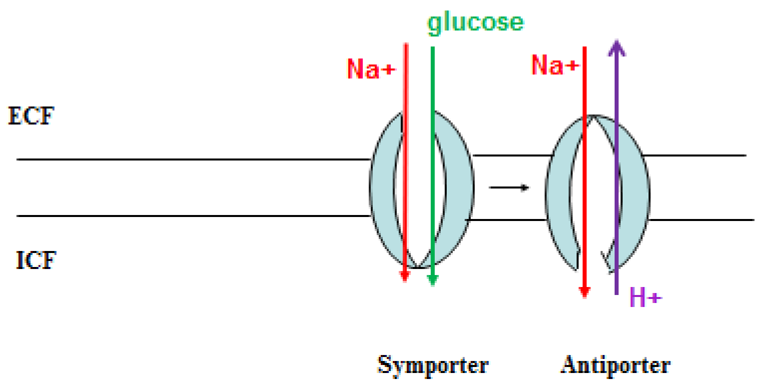

Figure 3. Co-Transporters include symporters and antiporters.

Channel proteins create a water filled passageway that connects the ECF and ICF compartments (Fig 2). Water and ions move through these channels. The open and closed state of the channels is determined by a part of the channel that acts as a "gate". The gating of the channel is controlled by ligands (**chemically gated**), electrical state of the cell (**voltage gated**) and by tension (**mechanically gated**).

Solutes can also move across membranes by active transport.

ACTIVE TRANSPORT moves a molecule against its concentration gradient and requires the input of energy (ATP). Active transporters are called "pumps". They exhibit specificity, competition, and saturation.

Active transport is involved in two types of solute movement:
Primary active transport uses ATP as energy. The transporters are enzymes with ATPase activity. The solute is "pumped" against its concentration gradient.

Secondary active transport couples two processes, primary active transport and facilitated transport. Active transport is used to generate an intracellular ion gradient, usually Na+. This ion gradient is then exploited to allow entry of a solute by either a co-transporter or a single channel. In secondary active transport solutes are moved across whole cells. The ATPase pump is located on the basal side of the cells (nearest to the blood) and the solute enters (or exits) the luminal side of the cell.

OSMOSIS IS THE DIFFUSION OF WATER

Osmosis is the movement of water across membranes. Osmosis only refers to the movement of water and is facilitated diffusion. The water channel is called **aquaporin.** Water is never actively transported. Water flows from compartments with "dilute" solutions (where concentration of water is high) to "concentrated" solutions (where concentration of water is low) until the concentrations of water and solute are equal in both compartments. **Note that the concentration of water is highest in pure water.**

Osmotic pressure prevents the movement of water across a membrane. There is no osmotic pressure across a semi-permeable membrane when the water concentration on each side of the membrane is equal.

****** Non-penetrating solutes** (e.g., Na+) determine the movement of water and consequently the size of the fluid compartment.

****** Penetrating solutes** (e.g., steroid hormones, urea) diffuse freely across cell membranes so no net water movement will occur.

Osmolarity is the number of particles per liter of solution. To predict the osmotic movement of water we must know the concentration of the solutions. In chemistry, concentrations are usually expressed as molarity (M) or number of moles per liter of solution (mol/L). A mole is 6 x 10^{23} molecules. Molarity describes the number of molecules per liter of solution. **Osmolarity (Osmol/L) deals with the number of particles in a liter of solution, not the number of molecules.** Because some molecules dissociate into particles when they dissolve in a solution, the number of particles may not equal the number of molecules.

**** Molarity (Mol/L) x (number of particles) = Osmolarity (Osmol/L).**

For example in Gatorade, the molecule NaCl dissociates into two ions (Na+ and Cl-) but the glucose in Gatorade is only one molecule. NaCl and glucose are both non-penetrating molecules but NaCl contributes 2 osmotically active particles while glucose only one.

For glucose: 1 M glucose x (1 molecule) = 1 OsM glucose
For NaCl: 1M NaCl x (2 ions) = 2 OsM NaCl

Osmolality is an Osmol of solute per kg of water. Osmolarity and osmolality are often used interchangeably because physiological solutions are very dilute and very little of their weight comes from solute.

ISOSMOTIC SOLUTIONS: both compartments (A and B, see below) have the same number of solute particles (includes membrane penetrating and non-penetrating solutes).

HYPEROSMOTIC SOLUTIONS: when solution (A) has a higher number of solute particles than solution (B), solution (A) is hyperosmotic to (B).

HYPOSMOTIC SOLUTIONS: when (A) has a lower number of solute particles than solution (B), solution (A) is hyposmotic to (B). For example:

A = 100 mOsM	A = 200 mOsM	A = 100 mOsM
B = 100 mOsM	B = 100 mOsM	B = 200 mOsM
(A and B isosmotic)	(A is hyperosmotic to B)	(A is hyposmotic to B)

Why are non-penetrating solutes important? Non-penetrating solutes are the bases for maintaining cell size at rest and for protection against cell shrinkage or swelling. To maintain homeostasis, the concentration of non-penetrating (osmotically active) particles in the ECF must be maintained within a narrow range (~300mOsM).

****** Osmolarity of the human body is ~300 mOsM.**

TONICITY: is used to compare two fluid compartments (e.g., ICF and ECF). It refers to the concentration of non-penetrating solutes only and is always comparative**.** Tonicity can be estimated but not measured directly.

To determine the relative tonicity of a solution you must know the number of **non-penetrating** solutes in the solution and in the cell. If the cell has a higher number of non-penetrating solutes then the cell is “hypertonic” with respect to the solution, water will enter the cell, and the cell swells. In this example the solution is “hypotonic” relative to the cell.

For example, if a cell has intracellular tonicity of 100 mOsM. In which of the following solutions will it swell? Shrink?

Solution A = 100 mOsM
Solution B = 50 mOsM
Solution C = 200 mOsM

Answer: The cell will not change volume in solution A (isotonic to the cell). The cell will swell in solution B. The cell will shrink in solution C.

To illustrate the role of a solute in maintaining compartment size, consider what happens when water or solute is ingested (Figure 4).

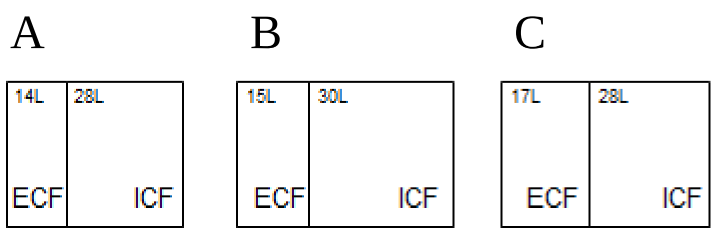

Figure 4. Effect of either water or solute addition on fluid compartment size. A.Bbasal state. B. After drinking 3L of water, the ICF increases by 2L and the ECF by 1L. C. After drinking 3L of isotonic NaCl, a solution with the same tonicity as the cells, all of the NaCl remains in the ECF compartment. Why?

What would happen if solid NaCl is ingested but no water? All of the NaCl remains within the ECF. This increases the osmolar concentration in the ECF compartment. To equalize the osmolarity inside and outside the cells, water is drawn out of the cells. The ECF will increase in volume and the cells will shrink. How does the NaCl distribute between the IS and IV spaces?

In later lectures we will see that the kidney’s primary functions are to (1) maintain fluid volumes of the body by regulating salt balance and (2) the osmolarity of the body by regulating water balance. Healthy people use two primary control systems to regulate water or sodium overload:

1. Osmolarity or ion concentration controls the elimination of water in the urine.
2. Changes in blood volume (or blood pressure) control sodium excretion-not osmolarity!

KEY CONCEPTS

1. Movement of solutes across membranes involves simple diffusion, facilitated diffusion, primary active transport and secondary active transport. Water always moves by simple diffusion called osmosis.
2. Movement of solute across a membrane is dependent on its size, charge, and lipid solubility.
3. Cellular volume is critically dependent on the steady state movement of solutes and water across membranes in exchange with the ECF. Cells swell in hypotonic conditions and shrink in hypertonic conditions.

THOUGHT PROBLEMS

1. Bob ate an anchovy pizza (very salty) during the super bowl but had nothing to drink. Did this meal alter the size of his ECF compartment? Why or why not?

2. Mark tried to pass his kidney stone by drinking 6 liters of water over 1 hour. His wife became concerned when he became confused and disoriented. At the ER, they were told that Mark had lowered (diluted) the sodium concentration of his IS compartment to 123 mOsM. Did the osmolarity of the IVS change? When the IS becomes hypotonic, does this affect the volume of brain cells (neurons)?

3. John ran a marathon. How did his perfuse sweating (loss of hyposmotic water) affect the osmolarity of the ECF (increase, decrease, remain unchanged)? Did the ECF volume increase, decrease, or remain unchanged? Was there a change in water distribution between ECF and ICF compartments?

ANSWERS

1. Yes, the ECF compartment increased. Due to an increase in osmolarity, water moved into the ECF from the ICF.
2. Yes, the sodium concentration in the IVS decreased to 123 mOsM.
   If the IS becomes hypotonic to a cell, then water enters the cell causing the cell to swell.
   Lowering the extracellular sodium concentration decreases the electrochemical gradient (i.e., makes more negative).
3. Osmolarity of ECF increases because the sweat lost is hyposmotic fluid.
   ECF volume decreases because total body water decreases.
   Yes, the ECF volume decreases which raises the osmolarity of the ECF. Water moves from the ICF to the ECF to “restore” osmotic equilibrium.