Transport of Substances Through Cell Membranes

Transport through the cell membrane, either directly through the lipid bilayer or through the proteins, occurs via one of two basic processes diffusion or active transport.

Although many variations of these basic mechanisms exist, diffusion means random molecular movement of substances molecule by molecule, either through intermolecular spaces in the membrane or in combination with a carrier protein. The energy that causes diffusion is the energy of the normal kinetic motion of matter. In contrast, active transport means movement of ions or other substances across the membrane in combination with a carrier protein in such a way that the carrier protein causes the substance to move against an energy gradient, such as from a low-concentration state to a high-concentration state. This movement requires an additional source of energy besides kinetic energy.

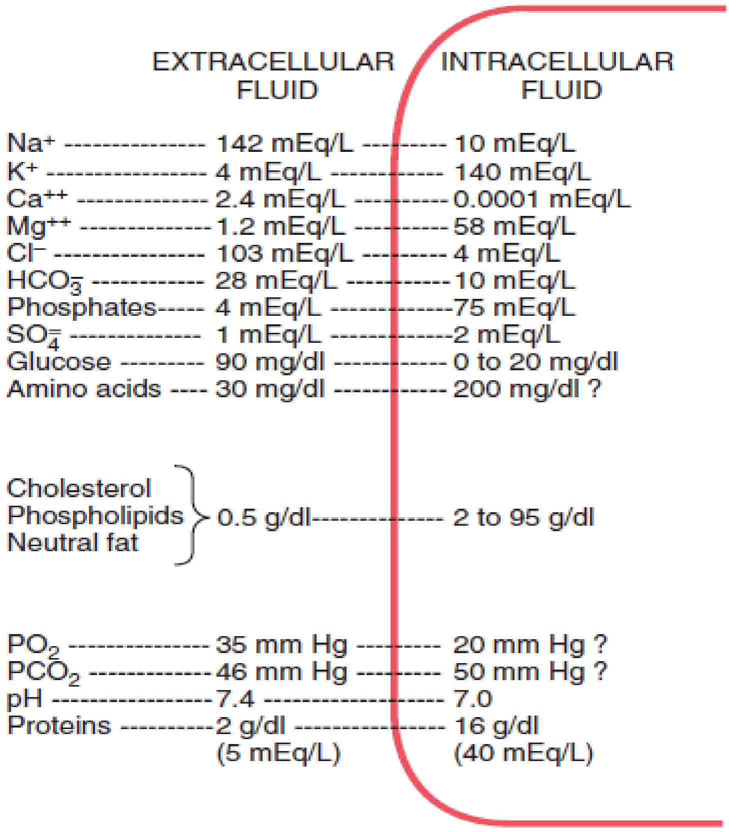

Figure 4-1. Chemical compositions of extracellular and intracellular fluids. The question mark indicates that precise values for intracellular fluid are unknown. The red line indicates the cell membrane.

CELL COMPARTMENT

1.ECF

The main component of the extracellular fluid is the interstitial fluid which surrounds the cells in the body. The other major component of the ECF is the intravascular fluid of the circulatory system called blood plasma. The remaining small percentage of ECF includes the transcellular fluid. These constituents are often called fluid compartments. The transcellular fluid includes the aqueous humour in the eye, the synovial fluid in the joints, the cerebrospinal fluid in the brain and spinal cord, the serous fluid in the serous membranes lining body cavities and in the saliva and other gut fluids (gastric juice, pancreatic juice and other intestinal secretions), as well as the perilymph and endolymph in the inner ear. The volume of extracellular fluid in a young adult male of 70 kg, is 20% of body weight – about fourteen litres.

The interstitial fluid and the plasma make up about 97% of the ECF, and a small percentage of this is lymph. Interstitial fluid is fluid that surround cells providing them with nutrients and removing their waste products. Eleven litres of the ECF is interstitial fluid and the remaining three litres is plasma. Plasma and interstitial fluid are very similar because water, ions, and small solutes are continuously exchanged between them across the walls of capillaries, through pores and capillary clefts.

Interstitial fluid consists of a water solvent containing sugars, salts, fatty acids, amino acids, coenzymes, hormones, neurotransmitters, white blood cells and cell waste-products. This solution accounts for 26% of the water in the human body. The composition of interstitial fluid depends upon the exchanges between the cells in the biological tissue and the blood. This means that tissue fluid has a different composition in different tissues and in different areas of the body.

The plasma that filters through the capillaries into the interstitial fluid does not contain red blood cells or platelets as they are too large to pass through but can contain some white blood cells to help the immune system.

Once the extracellular fluid collects into small vessels it is considered to be lymph, and the vessels that carry it back to the blood are called the lymphatic vessels. The lymphatic system returns protein and excess interstitial fluid to the circulation.

2.ICF

The intracellular fluid, also known as cytosol, is all fluid contained inside the cells. It is the matrix in which cellular organelles are suspended. The cytosol and organelles together compose the cytoplasm. The cell membranes are the outer barrier. In humans, the intracellular compartment contains on average about 8 litres of fluid, and under ordinary circumstances remains in osmotic equilibrium. It contains moderate quantities of magnesium and sulphate ions.

DIFFUSION THROUGH THE CELL MEMBRANE

Diffusion through the cell membrane is divided into two subtypes, called *simple diffusion* and *facilitated diffusion.* Simple diffusion means that kinetic movement of molecules or ions occurs through a membrane opening or through intermolecular spaces without any interaction with carrier proteins in the membrane. The rate of diffusion is determined by the amount of substance available, the velocity of kinetic motion, and the number and sizes of openings in the membrane through which the molecules or ions can move.

Facilitated diffusion requires interaction of a carrier protein. The carrier protein aids passage of the molecules or ions through the membrane by binding chemically with them and shuttling them through the membrane in this form.

Simple diffusion can occur through the cell membrane by two pathways: (1) through the interstices of the lipid bilayer if the diffusing substance is lipid soluble and (2) through watery channels that penetrate all the way through some of the large transport proteins

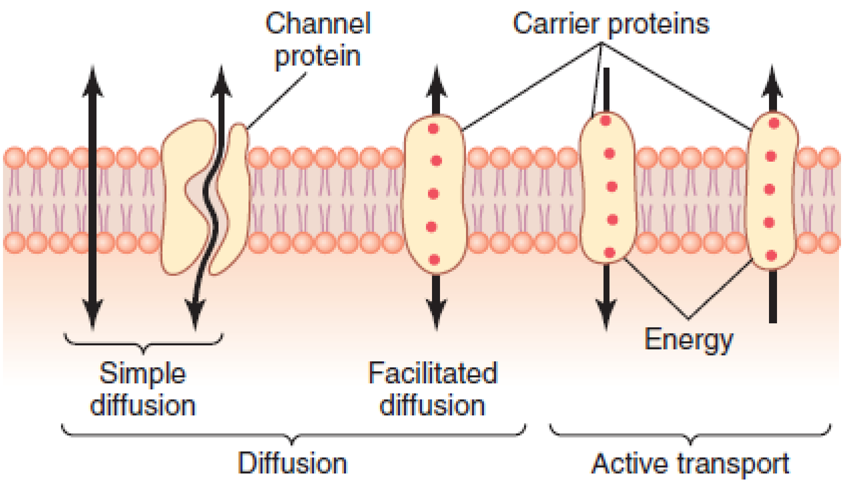

Figure 4-2. Transport pathways through the cell membrane and the basic mechanisms of transport.

An important factor that determines how rapidly a substance diffuses through the lipid bilayer is the *lipid solubility* of the substance. For instance, the lipid solubilities of oxygen, nitrogen, carbon dioxide, and alcohols are high, and all these substances can dissolve directly in the lipid bilayer and diffuse through the cell membrane in the same manner that diffusion of water solutes occurs in a watery solution. The rate of diffusion of each of these substances through the membrane is directly proportional to its lipid solubility. Especially large amounts of oxygen can be transported in this way; therefore, oxygen can be delivered to the interior of the cell almost as though the cell membrane did not exist.

Even though water is highly insoluble in the membrane lipids, it readily passes through channels in protein molecules that penetrate all the way through the membrane. Many of the body's cell membranes contain protein "pores" called *aquaporins* that selectively permit rapid passage of water through the membrane. The aquaporins are highly specialized, and there are at least 13 different types in various cells of mammals.

The protein channels are distinguished by two important characteristics: (1) They are often *selectively permeable* to certain substances, and (2) many of the channels can be opened or closed by *gates* that are regulated by electrical signals *(voltage-gated channels)* or chemicals that bind to the channel proteins *(ligand-gated channels).*

Many of the protein channels are highly selective for transport of one or more specific ions or molecules. This selectivity results from the characteristics of the channel, such as its diameter, its shape, and the nature of the electrical charges and chemical bonds along its inside surfaces

Potassium channels permit passage of potassium ions across the cell membrane about 1000 times more readily than they permit passage of sodium ions.

One of the most important of the protein channels, the *sodium channel,* is only 0.3 to 0.5 nanometer in diameter, but more important, the inner surfaces of this channel are lined with amino acids that are *strongly negatively charged,* These strong negative charges can pull small *dehydrated* sodium ions into these channels, actually pulling the sodium ions away from their hydrating water molecules. Once in the channel, the sodium ions diffuse in either direction according to the usual laws of diffusion. Thus, the sodium channel is highly selective for passage of sodium ions.

Gating of Protein Channels. Gating of protein channels provides a means of controlling ion permeability of the channels. The opening and closing of gates are controlled in two principal ways

1.Voltage gating. In the case of voltage gating, the molecular conformation of the gate or of its chemical bonds responds to the electrical potential across the cell membrane. For instance, a strong negative charge on the inside of the cell membrane could presumably cause the outside sodium gates to remain tightly closed; conversely, when the inside of the membrane loses its negative charge, these gates would open suddenly and allow sodium to pass inward through the sodium pores. This process is the basic mechanism for eliciting action potentials in nerves that are responsible for nerve signals

2. *Chemical (ligand) gating.* Some protein channel gates are opened by the binding of a chemical substance (a ligand) with the protein, which causes a conformational or chemical bonding change in the protein molecule that opens or closes the gate. One of the most important instances of chemical

gating is the effect of acetylcholine on the so-called *acetyl-choline channel.* Acetylcholine opens the gate of this channel, providing a negatively charged pore about 0.65 nanometer in diameter that allows uncharged molecules or positive ions smaller than this diameter to pass through. This gate is exceedingly important for the transmission of nerve signals from one nerve cell to another.

FACILITATED DIFFUSION REQUIRES MEMBRANE CARRIER PROTEINS

Facilitated diffusion is also called *carrier-mediated diffusion* because a substance transported in this manner diffuses through the membrane with the help of a specific carrier protein. That is, the carrier *facilitates* diffusion of the substance to the other side.

Facilitated diffusion differs from simple diffusion in the following important way: Although the rate of simple diffusion through an open channel increases proportionately with the concentration of the diffusing substance, in facilitated diffusion the rate of diffusion

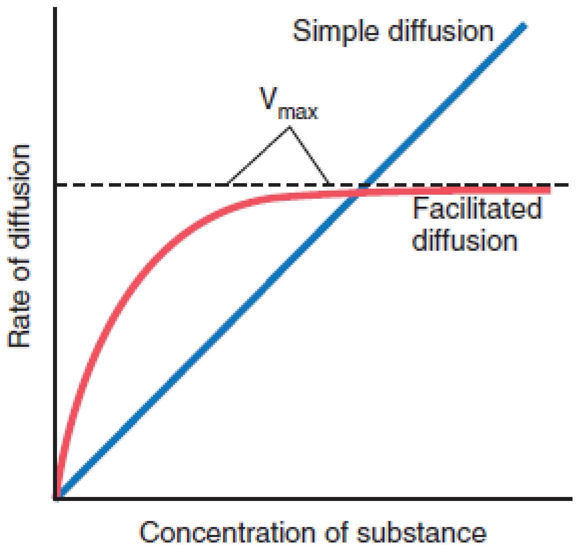

Figure 4-7. The effect of concentration of a substance on the rate of diffusion through a membrane by simple diffusion and facilitated diffusion. This graph shows that facilitated diffusion approaches a maximum rate called the V_{max}.

approaches a maximum, called Vmax, as the concentration of the diffusing substance increases. so that as the concentration of the diffusing substance increases, the rate of simple diffusion continues to increase proportionately, but in the case of facilitated diffusion, the rate of diffusion cannot rise greater than the Vmax level.

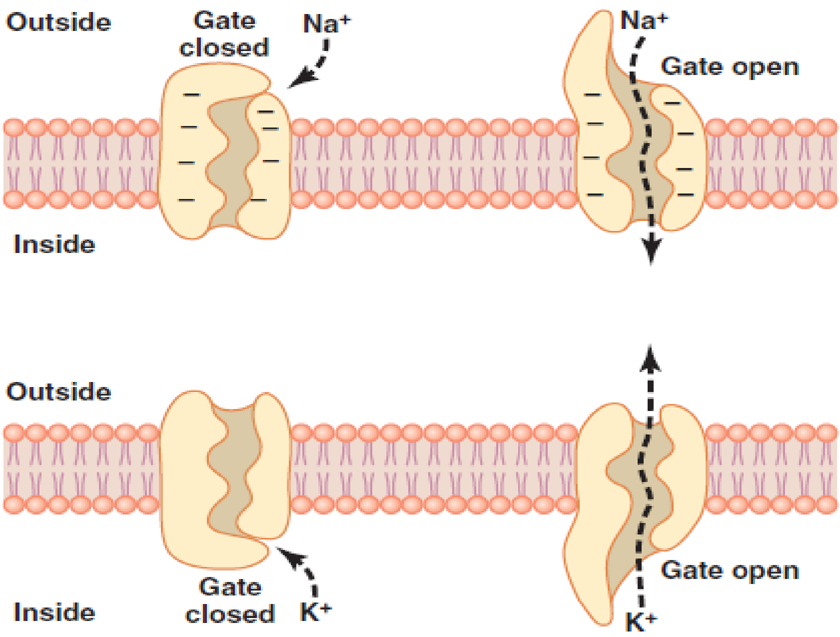

Figure 4-5. Transport of sodium and potassium ions through protein channels. Also shown are conformational changes in the protein molecules to open or close "gates" guarding the channels.

ACTIVE TRANSPORT" OF SUBSTANCES THROUGH MEMBRANES

At times, a large concentration of a substance is required in the intracellular fluid even though the extracellular fluid contains only a small concentration. This situation is true, for instance, for potassium ions. Conversely, it is important to keep the concentrations of other ions very low inside the cell even though their concentrations in the extracellular fluid are great. This situation is especially true for sodium ions. Neither of these two effects could occur by simple diffusion because simple diffusion eventually equilibrates concentrations on the two sides of the membrane. Instead, some energy source must cause excess movement of potassium ions to the inside of cells and excess movement of sodium ions to the outside of cells. When a cell membrane moves molecules or ions "uphill" against a concentration gradient (or "uphill" against an electrical or pressure gradient), the process is called *active* *transport.*

Different substances that are actively transported through at least some cell membranes include sodium, potassium, calcium, iron, hydrogen, chloride, iodide, and urate ions, several different sugars, and most of the amino acids. Active transport is divided into two types according to the source of the energy used to facilitate the transport: *primary active transport* and *secondary active transport.* In primary active transport, the energy is derived directly from breakdown of adenosine triphosphate (ATP) or some other high-energy phosphate compound. In secondary active transport, the energy is derived secondarily from energy that has been stored in the form of ionic concentration differences of secondary molecular or ionic substances between the two sides of a cell membrane, created originally by primary active transport.

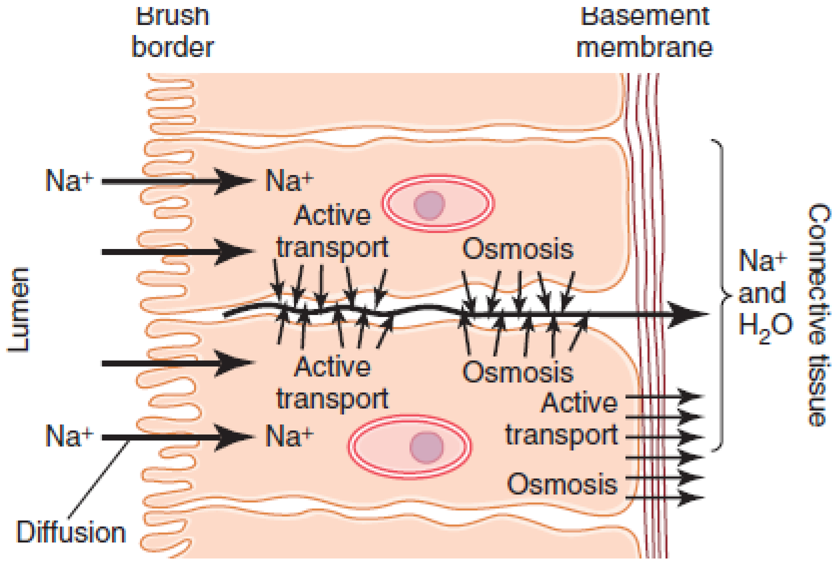

Figure 4-15. The basic mechanism of active transport across a layer of cells.

Sodium-Potassium Pump Transports Sodium Ions Out of Cells and Potassium Ions Into Cells

Among the substances that are transported by primary active transport are sodium, potassium, calcium, hydrogen, chloride, and a few other ions.

The active transport mechanism that has been studied in greatest detail is the *sodium-potassium (Na+-K+)* pump, a transport process that pumps sodium ions outward through the cell membrane of all cells and at the same time pumps potassium ions from the outside to the inside. This pump is responsible for maintaining the sodium and potassium concentration differences across the cell membrane, as well as for establishing a negative electrical voltage inside the cells.

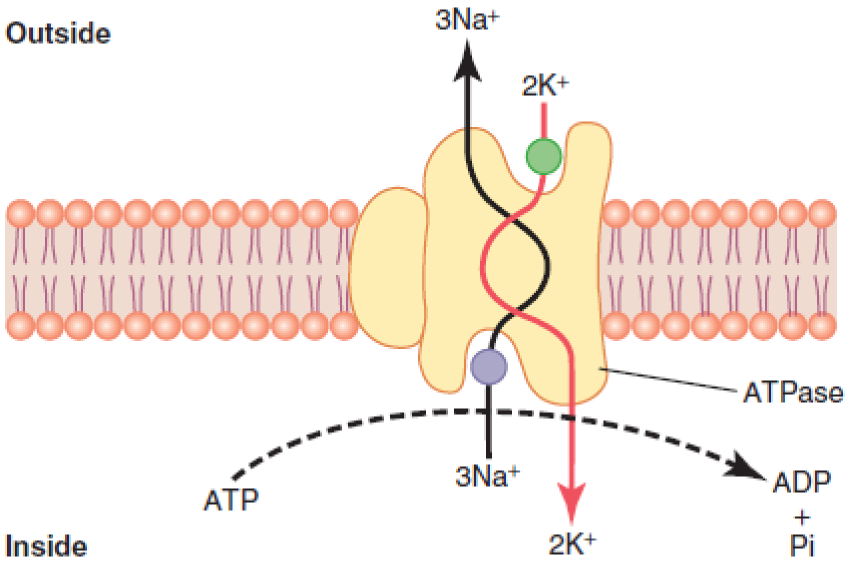

Figure 4-12. The postulated mechanism of the sodium-potassium pump. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, phosphate ion.

The Na+-K+ Pump Is Important for Controlling Cell Volume. One of the most important functions of the Na+-K+ pump is to control the volume of each cell. Without function of this pump, most cells of the body would swell until they burst. The mechanism for controlling the volume is as follows, Inside the cell are large numbers of proteins and other organic molecules that cannot escape from the cell. Most of these proteins and other organic molecules are negatively charged and therefore attract large numbers of potassium, sodium, and other positive ions as well. All these molecules and ions then cause osmosis of water to the interior of the cell. Unless this process is checked, the cell will swell indefinitely until it bursts.

Primary Active Transport of Calcium Ions

Another important primary active transport mechanism is the *calcium pump.* Calcium ions are normally maintained at an extremely low concentration in the intracellular cytosol of virtually all cells in the body, at a concentration about 10,000 times less than that in the extracellular fluid.

Primary Active Transport of Hydrogen Ions

Primary active transport of hydrogen ions is important at two places in the body: (1) in the gastric glands of the stomach, and (2) in the late distal tubules and cortical collecting ducts of the kidneys.

In the gastric glands, the deeplying *parietal cells* have the most potent primary active mechanism for transporting hydrogen ions of any part of the body. This mechanism is the basis for secreting hydrochloric acid in stomach digestive secretions. At the secretory ends of the gastric gland parietal cells, the hydrogen ion concentration is increased as much as a million-fold and then is released into the stomach along with chloride ions to form hydrochloric acid.

In the renal tubules, special *intercalated cells* found in the late distal tubules and cortical collecting ducts also transport hydrogen ions by primary active transport. In this case, large amounts of hydrogen ions are secreted from the blood into the urine for the purpose of eliminating excess hydrogen ions from the body fluids. The hydrogen ions can be secreted into the urine against a concentration gradient of about 900-fold.