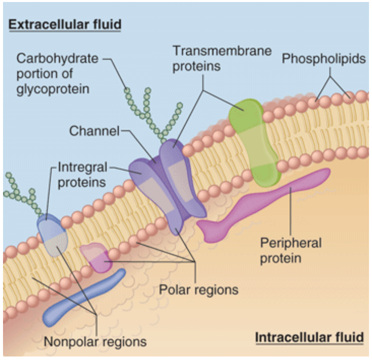
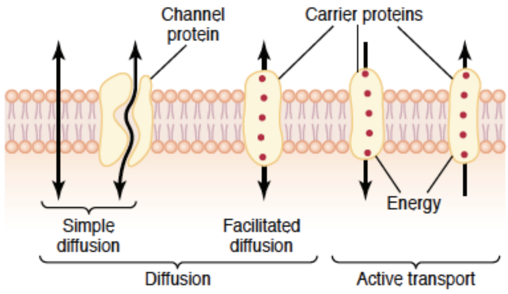
CELLULAR PHYSIOLOGY



Cellular Membrane is a thin bilayer of lipids and protiens and on average is 5-7.5 nm thick. The main structure by area is phospholipids which are composed of a head which is relatively polar due to a phophate group and a tail which is hydrophobic and non polar. The result is that the phospholipids are amphiatic, they form bilayers due their intrinsic structures in solutions. The properties of the the phospholipid layer is such that the cell membrane is relatively impermiable to ionised and hydrophilic molecules. The composition of the phospholipids varies both between cells, intracellularly and extracellularly and spatially. Ionsitol lipids are more common on the cytoplasmic side as they provide substrates for second messengers. Glycolipids are found on the cell surface. Cholesterol is also within the membrane and provides rigidity.

Many different proteins are embedded in the membrane. They exist as separate globular units and many pass through the membrane (integral proteins), whereas others (peripheral proteins) stud the inside and outside of the membrane. The amount of protein varies significantly with the function of the membrane but makes up on average 50% of the mass of the membrane; that is, there is about one protein molecule per 50 of the much smaller phospholipid molecules.The proteins in the membranes carry out many functions. Some are cell adhesion molecules that anchor cells to their neighbors or to basal laminas. Some proteins function as pumps, actively transporting ions across the membrane. Other proteins function as carriers, transporting substances down electrochemical gradients by facilitated diffusion. Still others are ion channels, which, when activated, permit the passage of ions into or out of the cell. Proteins in another group function as receptors that bind ligands or messenger molecules, initiating physiologic changes inside the cell. Proteins also function as enzymes, catalyzing reactions at the surfaces of the membrane.

Transport through the cell membrane, either directly through the lipid bilayer or through the proteins, occurs by one of two basic processes: diffusion or active transport. The energy that causes diffusion is the energy of the normal kinetic motion of matter usually along a concentration gradient or ionic gradient.



Diffusion through the cell membrane is divided into two subtypes called simple diffusion and facilitated diffusion. 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. The rate at which molecules follow the first of these pathways is greatly dependent on lipid solubility. Nitrogen, CO2, alcohols and oxygen have high lipid solubility and therefore diffuse rapidly across the lipid bilayer. For molecules transported by the second pathway the size of the molecule, and whether the channel permits (they may be very selective) and whether the gate is open (voltage or chemical/ligand dependent) determine transport. Simple diffusion is proportional to the concern-traion gradient. With ionic gradients this may be calculated with the Nerst Potential. Facilitated diffusion is also called carrier-mediated diffusion because a substance transported in this manner diffuses through the membrane using a specific carrier protein to help. An important difference is that with facilitated diffusion it reaches a point of zero order kinetics where increasing conc to not lead to increasing diffusion. The most important molecules transported in this manner are glucose and most amino acids.

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. Active transport is divided into two types according to the source of the energy used to cause the transport: primary active transport and secondary active transport. In primary active transport, the energy is derived directly from a high-energy phosphate compound such as ATP. The most important primary active transported molecules are Na-K via the sodium potassium pump discussed below and the Ca pump. 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. Secondary active transport occurs via co-transport or counter transport.

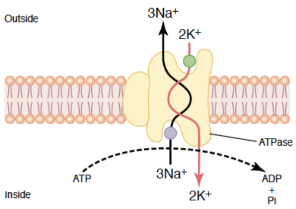
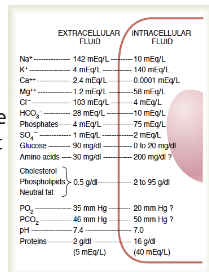


Figure 4–11

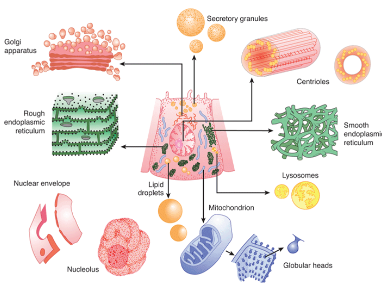
Postulated mechanism of the sodium-potassium pump. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, phosphate ion.

Sodium-Potassium Pump The sodium potassium pump is found in all parts of the body and is one of the most important and best studied examples of primary active transport in the body. Na, K ATPase catalyzes the hydrolysis of ATP to adenosine diphosphate (ADP) and uses the energy to extrude three Na+ from the cell and take two K+ into the cell for each molecule of ATP hydrolyzed. It is an electrogenic pump in that it moves three positive charges out of the cell for each two that it moves in, and it is therefore said to have a coupling ratio of 3:2. Its activity is inhibited by ouabain and related digitalis glycosides used in the treatment of heart failure. It consists of one alpha subuint and a beta subunit. The transport occurs in the larger alpha subunit, the beta subunit may be important in anchoring the pump in the cell membrane. Separation of the subunits eliminates activity. The amount of Na+ normally found in cells is not enough to saturate the pump, so if the Na+ increases, more is pumped out. Pump activity is affected by second messenger molecules, Thyroid hormones and insulin increase pump activity, aldosterone also increases the number of pumps, dopamine in the kidney inhibits the pump by phosphorylating it, causing a natriuresis. Active transport of Na+ and K+ is one of the major energy-using processes in the body. On the average, it accounts for about 24% of the energy utilized by cells, and in neurons it accounts for 70%. Thus, it accounts for a large part of the basal metabolism. A major payoff for this energy use is the establishment of the electrochemical gradient in cells.



	EXTRACELLULAR FLUID	INTRACELLULAR FLUID
Na^+	142 mEq/L	10 mEq/L
K^+	4 mEq/L	140 mEq/L
Ca^{++}	2.4 mEq/L	0.0001 mEq/L
Mg^{++}	1.2 mEq/L	58 mEq/L
Cl^-	103 mEq/L	4 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L
Phosphates	4 mEq/L	75 mEq/L
SO_4^-	1 mEq/L	2 mEq/L
Glucose	90 mg/dl	0 to 20 mg/dl
Amino acids	30 mg/dl	200 mg/dl ?
Cholesterol, Phospholipids, Neutral fat	0.5 g/dl	2 to 95 g/dl
PO_2	35 mm Hg	20 mm Hg ?
PCO_2	46 mm Hg	50 mm Hg ?
pH	7.4	7.0
Proteins	2 g/dl (5 mEq/L)	16 g/dl (40 mEq/L)

Intracellular Volume Regulation 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: Inside the cell are large numbers of proteins and other organic molecules that cannot escape from the cell. All these molecules (and ions) then cause osmosis of water to the interior of the cell. Unless this is checked, the cell will swell indefinitely until it bursts. The normal mechanism for preventing this is the Na+-K+ pump. Note again that this device pumps three Na+ ions to the outside of the cell for every two K+ ions pumped to the interior. Also, the membrane is far less permeable to sodium ions than to potassium ions, so that once the sodium ions are on the outside, they have a strong tendency to stay there. Thus, this represents a net loss of ions out of the cell, which initiates osmosis of water out of the cell as well. If a cell begins to swell for any reason, this automatically activates the Na+-K+ pump, moving still more ions to the exterior and carrying water with them. Therefore, the Na+-K+ pump performs a continual surveillance role in maintaining normal cell volume.



Cellular contents A number of structures (organelles) are common to most cells. Mitochondria are organelles that allow for oxidative phosphorylation in eukaryotic cells. They contain their own DNA, however, proteins in the mitochondria are encoded by both mitochondrial and cellular DNA. Mitochondria also are important in specialized cellular signaling. Lysosomes and peroxisomes are membrane-bound organelles that contribute to protein and lipid processing. They do this in part by creating acidic (lysosomes) or oxidative (peroxisomes) contents relative to the cell cytosol. The nucleus is an organelle that contains the cellular DNA and is the site of transcription. There are several organelles that emanate from the nucleus, including the endoplasmic reticulum (ER) and the Golgi apparatus. Attached to the outer surfaces of many parts of the ER are large numbers of minute granular particles called ribosomes. Where these are present, the reticulum is called the granular (rough) ER. The ribosomes are composed of a mixture of RNA and proteins, and they function to synthesize new protein molecules in the cell. The smooth ER does not have these ribosomes and is involved with production of lipids and other enzymes. The cytoskeleton is a network of three types of filaments that provide structural integrity to the cell as well as a means for trafficking of organelles and other structures. Actin is the fundamental building block for thin filaments and represents as much as 15% of cellular protein. Actin filaments are important in cellular contraction, migration, and signaling. Actin filaments also provide the backbone for muscle contraction. Intermediate filaments are primarily structural. Proteins that make up intermediate filaments are cell-type specific. Microtubules are made up of tubulin subunits. Microtubules provide a dynamic structure in cells that allows for movement of cellular components around the cell.