CELLULAR & MOLECULAR BASIS OF MEDICAL PHYSIOLOGY

The cells that make up the bodies of all but the simplest multicellular animals, both aquatic and terrestrial, exist in an "internal sea"of extracellular fluid (ECF) enclosed within the integument of the animal. From this fluid, the cells take up O2 and nutrients; into it, they discharge metabolic waste products. The ECF is more dilute than present-day seawater, but its composition closely resembles that of the primordial oceans in which, presumably, all life originated. In animals with a closed vascular system, the ECF is divided into two components: the interstitial fluid and the circulating blood plasma. The plasma and the cellular elements of the blood, principally red blood cells, fill the vascular system, and together they constitute the total blood volume.

The interstitial fluid is that part of the ECF that is outside the vascular system, bathing the cells. The special fluids considered together as transcellular fluids. About a third of the total body water is extracellular; the remaining two thirds is intracellular (intracellul fluid). In the average young adult male, 18% of the body weight is protein and related substances, 7% is mineral, and 15% is fat. The remaining 60% is water.

CONCENTRATION OF SOLUTES

In considering the effects of various physiologically important substances and the interactions between them, the number of molecules, electric charges, or particles of a substance per unit volume of a particular body fluid are often more meaningful than simply the weight of the substance per unit volume. For this reason, physiological concentrations are frequently expressed in moles, equivalents, or osmoles.

Moles

A mole is the gram-molecular weight of a substance, ie, themolecular weight of the substance in grams. Each mole (mol) consists of 6×10^{23} molecules. The millimole (mmol) is 1/1000 of a mole, and the micromole (μmol) is 1/1,000,000 of a mole. Thus, 1 mol of NaCl = 23 g + 35.5 g = 58.5 g, and 1 mmol = 58.5 mg. The mole is the standard unit for expressing the amount of substances in the SI unit system. The normality (N) of a solution is the number of gram equivalents in 1 liter. A 1 N solution of hydrochloric acid contains both H+ (1 g) and Cl– (35.5 g) equivalents, = (1 g + 35.5 g)/L = 36.5 g/L.

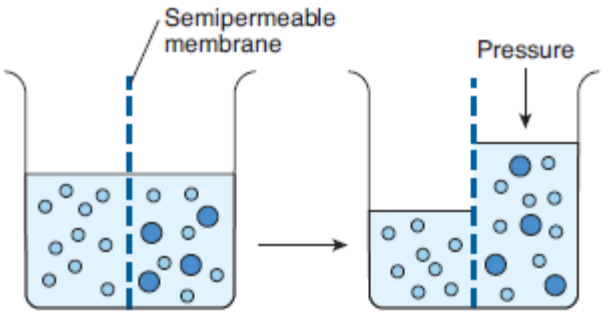
Equivalents

The concept of electrical equivalence is important in physiology because many of the solutes in the body are in the form of charged particles. One equivalent (eq) is 1 mol of an ionized substance divided by its valence. One mole of NaCl dissociates into 1 eq of Na+ and 1 eq of Cl–. One equivalent of Na+ = 23 g, but 1 eq of Ca2+ = 40 g/2 = 20 g. The milliequivalent (meq) is 1/1000 of 1 eq.

WATER, ELECTROLYTES, & ACID/BASE

The water molecule (H2O) is an ideal solvent for physiological reactions. The resultant hydrogen bond network in water allows for several key properties in physiology: (1) water has a high surface tension, (2) water has a high heat of vaporization and heat capacity, and (3) water has a high dielectric constant. In layman's terms, H2O is an excellent biological fluid that serves as a solute; it provides optimal heat transfer and conduction of current.

DIFFUSION



OSMOSIS

the osmotic pressure is proportional to the number of particles in solution per unit volume of solution. For this reason, the concentration of osmotically active particles is usually expressed in **osmoles.** One osmole (Osm) equals the gram-molecular weight of a substance divided by the number of freely moving particles that each molecule liberates in solution. For biological solutions, the milliosmole (mOsm; 1/1000 of 1 Osm) is more commonly used. For example, NaCl would dissociate into Na+ and Cl– ions, so that each mole in solution would supply 2 Osm. One mole of Na2SO4 would dissociate into Na+, Na +, and $SO4^{2-}$supplying 3 Osm. The **osmolarity** is the number of osmoles per liter of solution (eg, plasma), whereas the **osmolality** is the number of osmoles per kilogram of solvent. Therefore, osmolarity is affected by the volume of the various solutes in the solution and the temperature, while the osmolality is not.

OSMOLAL CONCENTRATION OF PLASMA: TONICITY

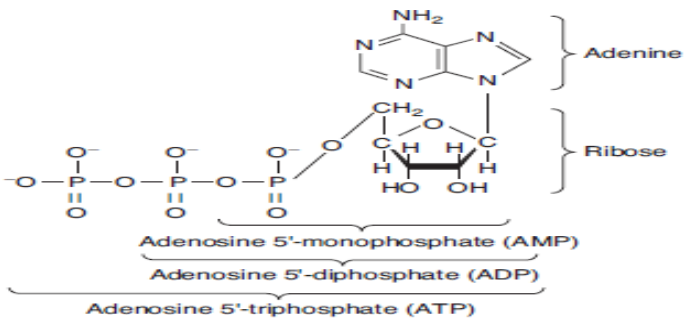
All fluid compartments of the body are in (or nearly in) osmotic equilibrium. The term tonicity is used to describe the osmolality of a solution relative to plasma. Solutions that have the same osmolality as plasma are said to be isotonic; those with greater osmolality are hypertonic; and those with lesser osmolality are hypotonic.

TABLE 1–1 Concentration of some ions inside and outside mammalian spinal motor neurons.

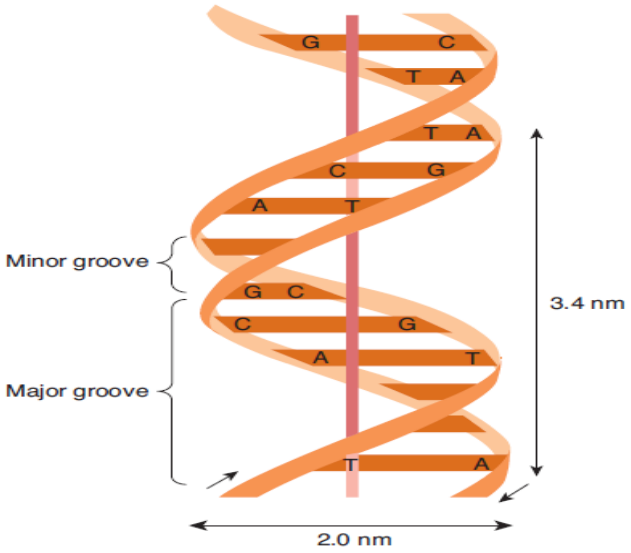
	Concentration (mmol/L of H_2O)		
Ion	Inside Cell	Outside Cell	Equilibrium Potential (mV)
Na^+	15.0	150.0	+60
K^+	150.0	5.5	–90
Cl^-	9.0	125.0	–70

Resting membrane potential = –70 mV

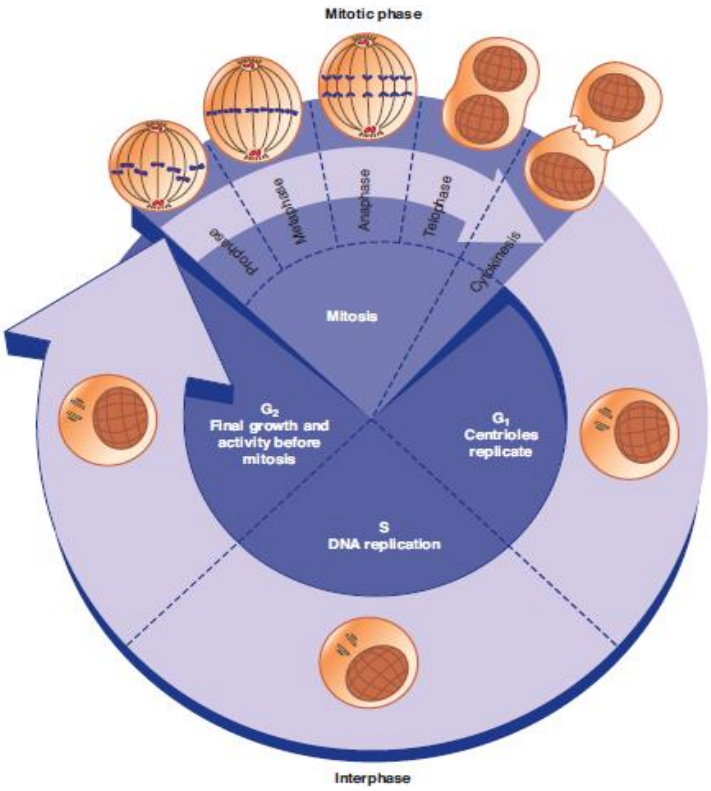
ENERGY PRODUCTION



MOLECULAR BUILDING BLOCKS



REPLICATION: MITOSIS & MEIOSIS



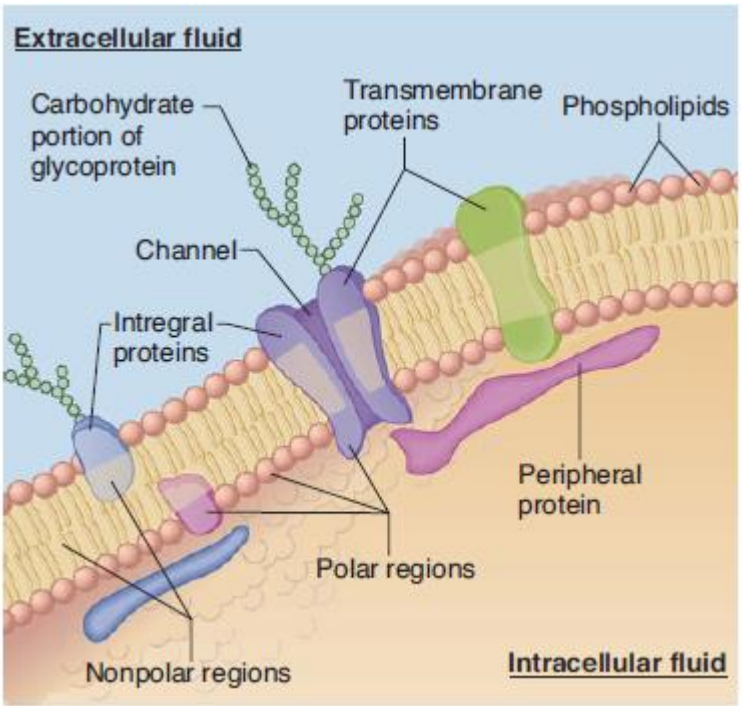
Sequence of events during the cell cycle

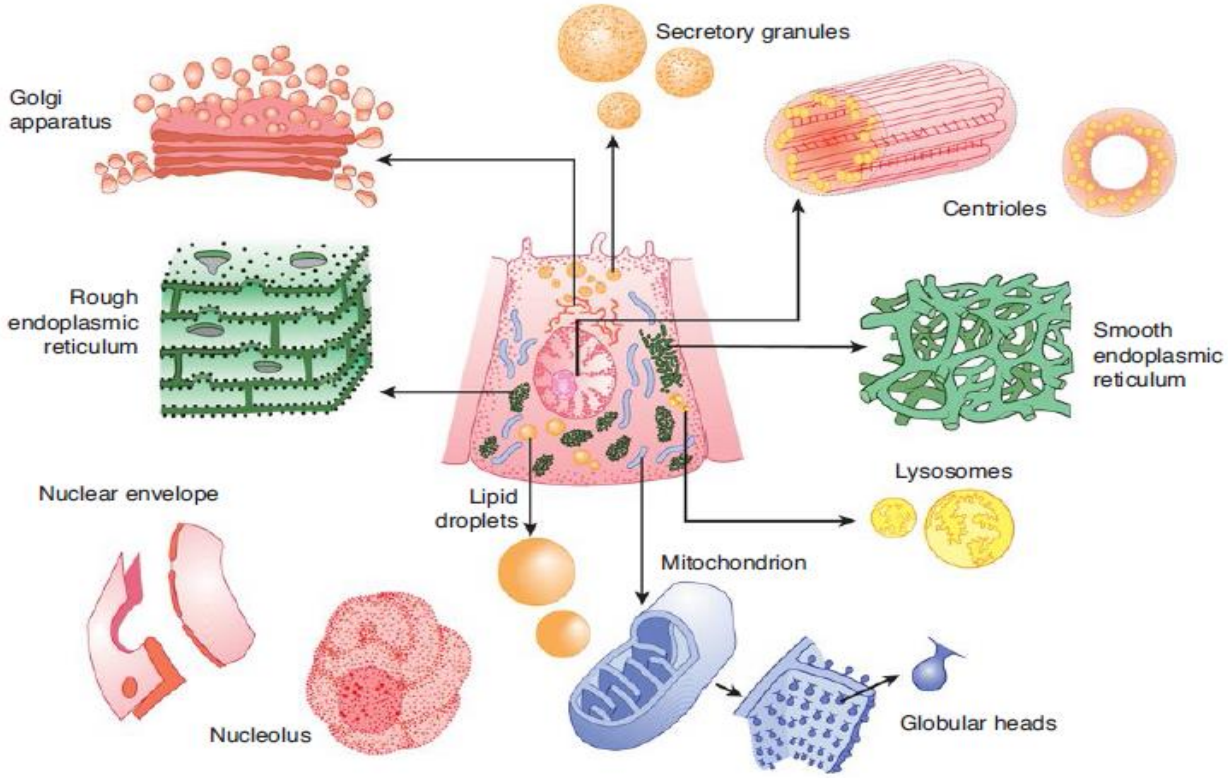
FUNCTIONAL MORPHOLOGY OF THE CELL

A key tool for examining cellular constituents is the microscope. A light microscope can resolve structures as close as 0.2µm, while an electron microscope can resolve structures as close as 0.002µm. Although cell dimensions are quite variable, this resolution can give us a good look at the inner workings of the cell. The advent of common access to fluorescent, confocal, and other microscopy along with specialized probes for both static and dynamic cellular structures further expanded the examination of cell structure and function.

CELL MEMBRANES

It is made up of lipids and proteins and is semipermeable, allowing some substances to pass through it and excluding others.

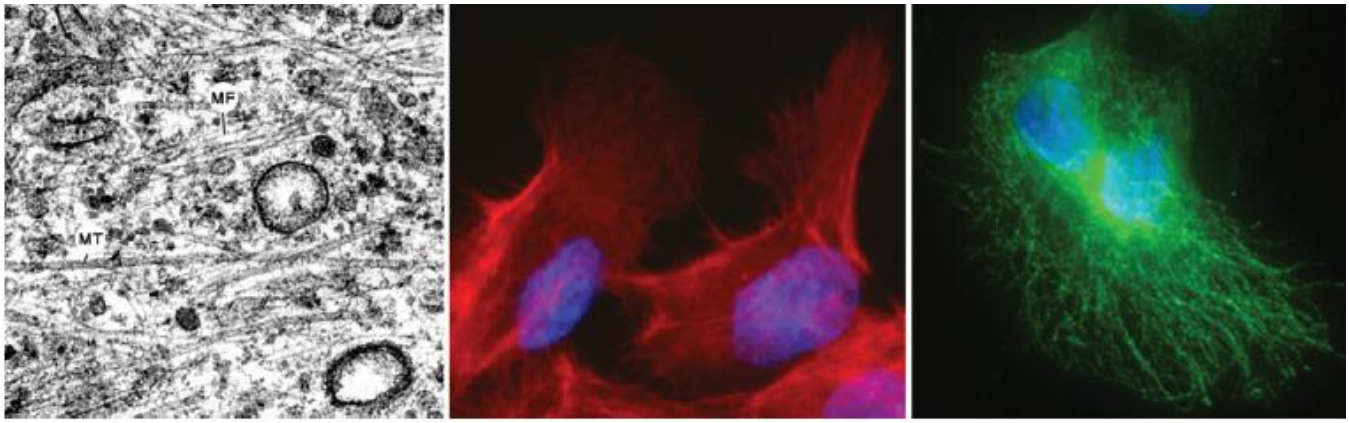




CYTOSKELETON

All cells have a **cytoskeleton,** a system of fibers that not only maintains the structure of the cell but also permits it to change shape and move. The cytoskeleton is made up primarily of **microtubules, intermediate filaments,** and **microfilaments** , along with proteins that anchor them and tie them together.

In addition, proteins and organelles move along microtubules and microfilaments from one part of the cell to another, propelled by molecular motors.



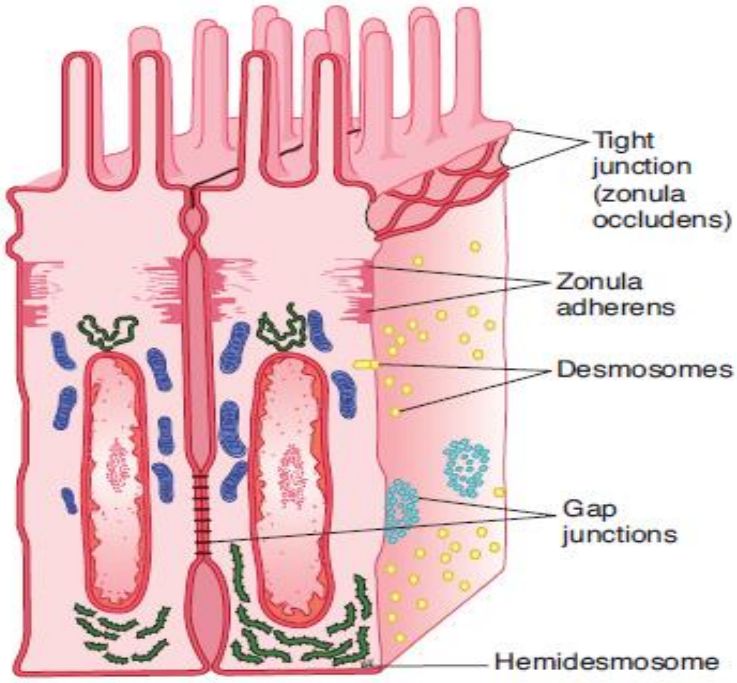
Microfilaments and microtubules. Electron micrograph **(Left)** of the cytoplasm of a fibroblast, displaying actin microfilaments (MF) and microtubules (MT).

PEROXISOMES

Peroxisomes are 0.5μm in diameter, are surrounded by a membrane, and contain enzymes that can either produce H2O2 **(oxidases)** or break it down **(catalases).**

CENTROSOMES

CELL ADHESION MOLECULES



Intercellular junctions in the mucosa of the small intestine.

NUCLEUS & RELATED STRUCTURES

ENDOPLASMIC RETICULUM

In **rough,** or **granular, endoplasmic reticulum,** ribosomes are attached to the cytoplasmic side of the membrane, whereas in **smooth,** or **agranular, endoplasmic reticulum,** ribosomes are absent. Free ribosomes are also found in the cytoplasm. The granular endoplasmic reticulum is concerned with protein

synthesis and the initial folding of polypeptide chains with the formation of disulfide bonds. The agranular endoplasmic reticulum is the site of steroid synthesis in steroid-secreting cells and the site of detoxification processes in other cells.

RIBOSOMES

GOLGI APPARATUS & VESICULAR TRAFFIC

One or more Golgi apparati are present in all eukaryotic cells It is a collection of membrane-enclosed sacs (cisterns) that are stacked like dinner plates, usually near the nucleus. Much of the organization of the Golgi is directed at proper glycosylation of proteins and lipids. There are more than 200 enzymes that function to add, remove, or modify sugars from proteins and lipids in the Golgi apparatus.

APOPTOSIS

Cells can die and be absorbed under genetic control. This process is called programmed cell death, or apoptosis, it should be distinguished from necrosis (“cell murder”), in which healthy cells are destroyed by external processes such as inflammation. Apoptosis is also an important factor in processes such as removal of the webs between the fingers in fetal life and regression of duct systems in the course of sexual development in the fetus. In adults, it participates in the cyclic breakdown of the endometrium that leads to menstruation.

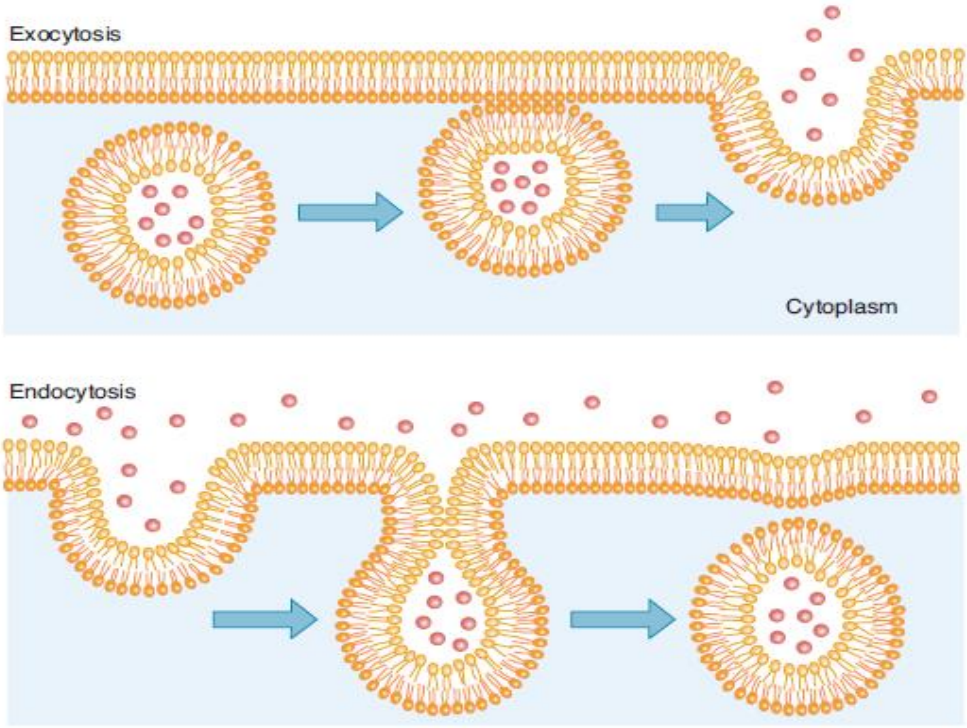
TRANSPORT ACROSS CELL MEMBRANES

EXOCYTOSIS

Vesicles containing material for export are targeted to the cell membrane where they bond and the area of fusion then breaks down, leaving the contents of the vesicle outside and the cell membrane intact, this is the Ca2+-dependent process of **exocytosis**. Secretion from the cell occurs via two pathways: In the **nonconstitutive pathway,** proteins from the Golgi apparatus initially enter secretory granules, where processing of prohormones to the mature hormones occurs before exocytosis. The other pathway, the **constitutive pathway,** involves the prompt transport of proteins to the cell membrane in vesicles, with little or no processing or storage.

ENDOCYTOSIS

Is the reverse of exocytosis where there are various types of endocytosis named for the size of particles being ingested as well as the regulatory requirements for the particular process. These include **phagocytosis, pinocytosis, clathrinmediated endocytosis, caveolae-dependent uptake,** and **nonclathrin/noncaveolae endocytosis.**



Phagocytosis ("cell eating"), **Pinocytosis** ("cell drinking"), **Clathrin-mediated endocytosis** occurs at membrane indentations where the protein **clathrin** accumulates. Clathrin molecules have the shape of triskelions, with three "legs" radiating from a central hub. Some areas of the cell membrane are especially rich in cholesterol and sphingolipids and have been called **rafts.** These rafts are probably the precursors of flask-shaped membrane depressions called **caveolae** (little caves) when their walls become infiltrated with a protein called **caveolin** that resembles clathrin.

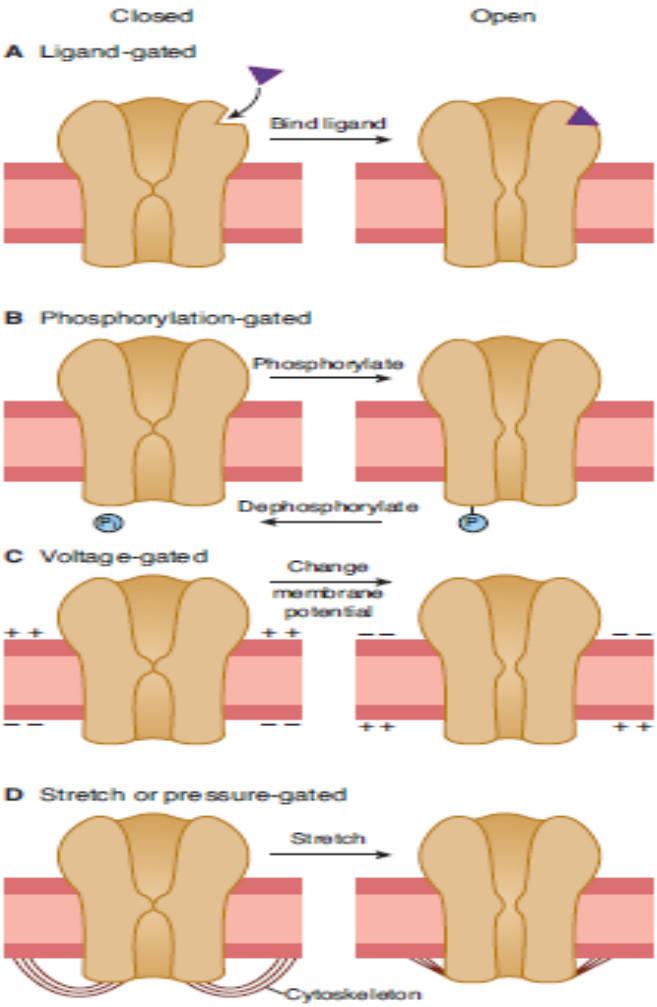
MEMBRANE PERMEABILITY & MEMBRANE TRANSPORT PROTEINS

Small, nonpolar molecules (including O2 and N2) and small uncharged polar molecules such as CO2 diffuse across the lipid membranes of cells. However, the membranes have very limited permeability to other substances. Instead, they cross the membranes by endocytosis and exocytosis and by passage through highly specific transport proteins, transmembrane proteins that form channels for ions or transport substances such as glucose, urea, and amino acids. The limited permeability applies even to water, with simple diffusion being supplemented throughout the body with various water channels (aquaporins).

Some transport proteins are simple aqueous **ion channels,** though many of these have special features that make them selective for a given substance such as Ca2+ or, in the case of aquaporins, for water. These membrane-spanning proteins (or collections of proteins) have tightly regulated pores that can be **gated** opened or closed in response to local changes **often external (eg, a neurotransmitter or a hormone).** However**,** it can also be internal; intracellular Ca2+, cAMP, lipids, or one of the G proteins produced in cells can bind directly to channels and activate them. Some channels are also opened by mechanical stretch, and these mechanosensitive channels play an important role in cell movement. Other transport proteins are carriers that bind ions and other molecules and then change their configuration, moving the bound molecule from one side of the cell membrane to the other.

Molecules move from areas of high concentration to areas of low concentration (down their chemical gradient), and cations move to negatively charged areas whereas anions move to positively charged areas (down their electrical gradient).

When carrier proteins move substances in the direction of their chemical or electrical gradients, no energy input is required and the process is called facilitated diffusion.



Regulation of gating in ion channels

Na, K ATPase

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.

SECONDARY ACTIVE TRANSPORT

In many situations, the active transport of Na+ is coupled to the transport of other substances **(secondary active transport).** For example, the luminal membranes of mucosal cells in the small intestine contain a symport that transports glucose into the cell only if Na+ binds to the protein and is transported into the cell at the same time. From the cells, the glucose enters the blood. The electrochemical gradient for Na+ is maintained by the active transport of Na+ out of the mucosal cell into ECF. In the heart, Na,K ATPase indirectly affects Ca2+ transport. An antiport in the membranes of cardiac muscle cells normally exchanges intracellular Ca2+ for extracellular Na+. 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.