Introduction to Physiology: the cell and general physiology

Physiology studies the normal mechanical, physical, and biochemical processes of animals and plants. In *human physiology,* we attempt to explain the specific characteristics and mechanisms of the human body that make it a living being. Physiology is the scientific study of an organism's vital functions, including growth and development, the absorption and processing of nutrients, the synthesis and distribution of proteins and other organic molecules, and the functioning of different tissues, organs, and other anatomic structures. The human being is actually an automaton, and the fact that we are sensing, feeling, and knowledgeable beings is part of this automatic sequence of life; these special attributes allow us to exist under widely varying conditions.

The basic living unit of the body is the cell. Each organ is an aggregate of many different cells held together by intercellular supporting structures. The entire body contains about 100 trillion cells. Although the many cells of the body often differ markedly from one another, all of them have certain basic characteristics that are alike. For instance, in all cells, oxygen reacts with carbohydrate, fat, and protein to release the energy required for cell function. Further, the general chemical mechanisms for changing nutrients into energy are basically the same in all cells, and all cells deliver end products of their chemical reactions into the surrounding fluids. Almost all cells also have the ability to reproduce additional cells of their own kind. Fortunately, when cells of a particular type are destroyed from one cause or another, the remaining cells of this type usually generate new cells until the supply is replenished.

Distribution of water in the organism

About 60 percent (total body water) of the adult human body is fluid, mainly a water solution of ions and other substances. This percentage can change, depending on age, gender, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This is due in part to the fact that aging is usually associated with an increased percentage of the body weight being fat, which decreases the percentage of water in the body. Because women normally have more body fat than men, they contain slightly less water than men in proportion to their body weight. Therefore, when discussing the “average” body fluid compartments, we should realize that variations exist, depending on age, gender, and percentage of body fat. Sedentary, overweight persons contain only 50-55 % water dependent on the body fat content.

Although most of this fluid is inside the cells and is called intracellular fluid, about one third is in the spaces outside the cells and is called extracellular fluid. This extracellular fluid is in motion throughout the body. It is transported rapidly in the circulating blood and then mixed between the blood and the tissue fluids by diffusion through the capillary walls. In the extracellular fluid are the ions and nutrients needed by the cells to maintain cell life. The extracellular fluid is also called the internal environment of the body. Extracellular fluid volume (about 20 per cent of the body weight) or ECV refers to the interstitial and the plasma volume. Interstitial fluid (ISF) is the tissue fluid between the cells in the extravascular space. The plasma is the noncellular part of the blood; it exchanges substances continuously with the interstitial fluid through the pores of the capillary membranes.There is another small compartment of fluid that is referred to as transcellular fluid. This compartment includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal fluid; it is usually considered to be a specialized type of extracellular fluid, although in some cases, its composition may differ markedly from that of the plasma or interstitial fluid. All the transcellular fluids together constitute about 1 to 2 liters.

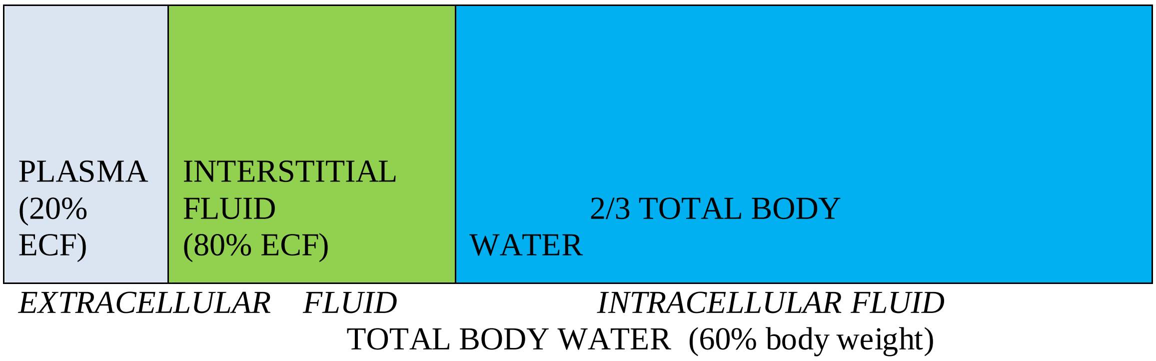


Figure 1.1 The body fluid compartments

The extracellular fluid contains large amounts of sodium, chloride, and bicarbonate ions plus nutrients for the cells, such as oxygen, glucose, fatty acids, and amino acids. It also contains carbon dioxide that is being transported from the cells to the lungs to be excreted, plus other cellular waste products that are being transported to the kidneys for excretion.

The intracellular fluid differs significantly from the extracellular fluid; specifically, it contains large amounts of potassium, magnesium, and phosphate ions instead of the sodium and chloride ions found in the extracellular fluid. Special mechanisms for transporting ions through the cell membranes maintain the ion concentration differences between the extracellular and intracellular fluids. Extracellular fluid is transported through all parts of the body in two stages. The first stage is movement of blood through the body in the blood vessels, and the second is movement of fluid between the blood capillaries and the intercellular spaces between the tissue cells.

	Extracellular concentration mM	Intracellular concentration mM
Na^+	145	15
K^+	4	150
Ca^{2+}	1	1,5
Mg^{2+}	1,5	12
Cl^-	110	10
HCO_3^-	24	10
Pi	2	40
Aminoacids	2	8
Glucose	5,6	1
ATP	0	4
Protein	0,2	4

Table 1.1 Composition of extracellular and intracellular fluids

*The intracellular concentrations differ slightly from one to another, but the concentrations shown above are typical of most cells.

Water permeable membranes separate the three compartments, so that they contain almost the same number of osmotically active particles per kg. The compartments have the same concentration expressed as mOsmol per kg of water (300 mOsmol/ l) of water or the same freeze-point depression. They are said to be isosmolal, because they have the same osmolality.

The relative constancy of the body fluids is remarkable because there is continuous exchange of fluid and solutes with the external environment as well as within the different compartments of the body. For example, there is a highly variable fluid intake that must be carefully matched by equal output from the body to prevent body fluid volumes from increasing or decreasing. Water is added to the body by two major sources:
(1) it is ingested in the form of liquids or water in the food, which together normally add about 2100 ml/day to the body fluids, and
(2) it is synthesized in the body as a result of oxidation of carbohydrates, adding about 200 ml/day.

This provides a total water intake of about 2300 ml/day. Intake of water, however, is highly variable among different people and even within the same person on different days, depending on climate, habits, and level of physical activity.

Water is lost in the urine (1500 ml), in the stools (100 ml), in sweat and evaporation from the respiratory tract (900 ml) as a typical example. The total loss of water is 2500 ml, and this corresponds perfectly to the intake plus a normal production of 300 ml of metabolic water per 24 hours.

Because the plasma and interstitial fluid are separated only by highly permeable capillary membranes, their ionic composition is similar. The most important difference between these two compartments is the higher concentration of protein in the plasma; because the capillaries have a low permeability to the plasma proteins, only small amounts of proteins are leaked into the interstitial spaces in most tissues. Because of the Donnan effect, the concentration of positively charged ions (cations) is slightly greater (about 2 per cent) in the plasma than in the interstitial fluid. The plasma proteins have a net negative charge and, therefore, tend to bind cations, such as sodium and potassium ions, thus holding extra amounts of these cations in the plasma along with the plasma proteins. Conversely, negatively charged ions (anions) tend to have a slightly higher concentration in the interstitial fluid compared with the plasma, because the negative charges of the plasma proteins repel the negatively charged anions. The Donnan effect is the extra osmotic pressure of protein solutions caused by the unequal distribution of small, permeable cations and anions. The Donnan effect causes a 5% and 10% concentration difference across the capillary barrier between the plasma and ultra filtrate concentrations of monovalent and divalent ions, respectively. In the above equations Na^+ and Cl^- are model ions for all the cations and anions. In our body other anions and cations are present, the Na^+ and Cl^- concentrations are not alike, and the capillary membrane is far from rigid. Nevertheless, the Donnan equilibrium implies an accumulation of charges on the side with the negatively charged proteins (because their size, they cannot live the cell). This potential difference across the capillary membrane is termed the Donnan potential – a potential, which is developed across cell membranes without a sodium-potassium.

Edema refers to the presence of excess fluid in the body tissues. In most instances, edema occurs mainly in the extracellular fluid compartment, but it can involve intracellular fluid as well.

Homeostasis

The term homeostasis is used by physiologists to mean maintenance of nearly constant conditions in the internal environment. Essentially all organs and tissues of the body perform functions that help maintain these constant conditions. For instance, the lungs provide oxygen to the extracellular fluid to replenish the oxygen used by the cells, the kidneys maintain constant ion concentrations, and the gastrointestinal system provides nutrients. A large segment of this text is concerned with the manner in which each organ or tissue contributes to homeostasis. All the different functional systems of the body contributes to homeostasis.

Regulation of body functions

Nervous System. The nervous system is composed of three major parts: the sensory input portion, the central nervous system (or integrative portion), and the motor output portion. Sensory receptors detect the state of the body or the state of the surroundings. For instance, receptors in the skin apprise one whenever an object touches the skin at any point. The eyes are sensory organs that give one a visual image of the surrounding area. The ears also are sensory organs. The central nervous system is composed of the brain and spinal cord. The brain can store information, generate thoughts, create ambition, and determine reactions that the body performs in response to the sensations. Appropriate signals are then transmitted through the motor output portion of the nervous system to carry out one's desires. A large segment of the nervous system is called the autonomic system. It operates at a subconscious level and controls many functions of the internal organs, including the level of pumping activity by the heart, movements of the gastrointestinal tract, and secretion by many of the body's glands.

Hormonal System of regulation. Located in the body are eight major endocrine glands that secrete chemical substances called hormones. Hormones are transported in the extracellular fluid to all parts of the body to help regulate cellular function. For instance, thyroid hormone increases the rates of most chemical reactions in all cells. Insulin controls glucose metabolism; adrenocortical hormones control sodium ion, potassium ion, and protein metabolism; and parathyroid hormone controls bone calcium and phosphate. Thus, the hormones are a system of regulation that complements the nervous system. The nervous system regulates mainly muscular and secretory activities of the body, whereas the hormonal system regulates many metabolic functions.

Transport through membranes

Membrane transport refers to solute and solvent transfer across both cell membranes, epithelial and capillary membranes. Biological membranes are composed of phospholipids stabilized by hydrophobic interactions into bilayers. The membranes contain approximately 50% lipids and 50% proteins. Phospholipids are amphipathic. One region is polar consisting of charged choline, ethanolamine and phosphate head-groups (bullets in figure). The other region is non-polar, consisting of tails of fatty acyl chains. The non-polar regions tend to avoid contact with water by self-association. Integral proteins are deeply imbedded in the membrane and the model shows 3 protein molecules spanning the membrane (i.e., trans membrane proteins). Surface proteins are not shown. The proteins carry receptors to which transmitter substance bind. Carbohydrate chains are shown forming glycolipids with antigenic or receptor function or glycoproteins with other receptor functions. Mechanical, electrical, thermal, or gravitational forces drive migration of molecules. These forces move the molecules passively in a direction determined by the vector of the force.

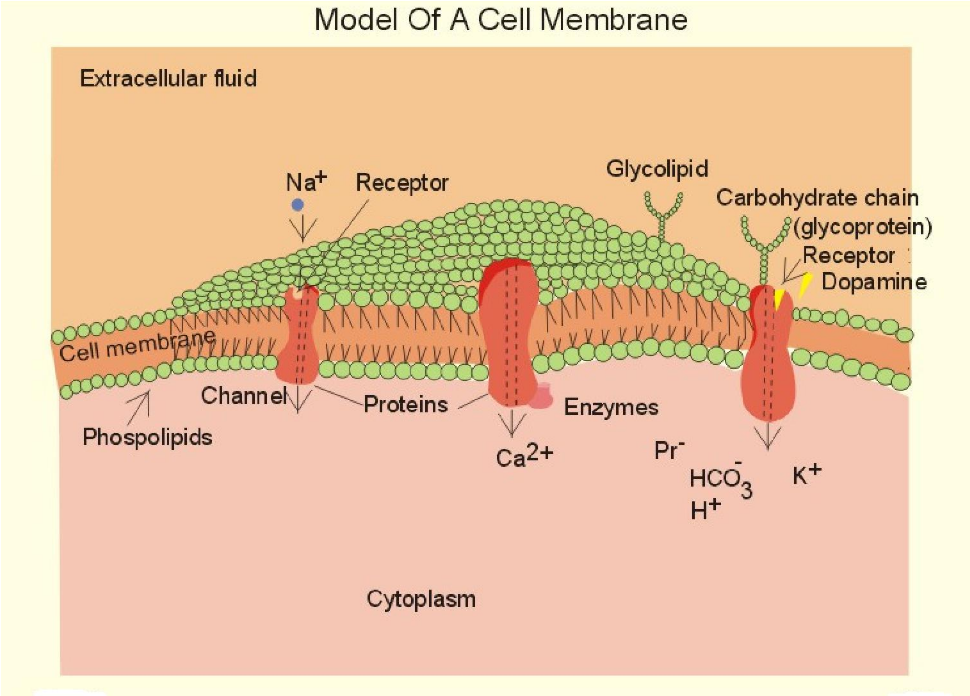


Figure 1.2 Model of a cell membrane built by phospholipids separating receptors, channels, proteins (Pr^-), glycoproteins (receptors, antigens etc) and glycolipids. (http://www.zuniv.net/physiology/book/images/)

Transport mechanisms are: Osmosis, diffusion, filtration (when fluid is under pressure), facilitated diffusion (diffusion through a membrane with help from a transport protein), and active transport (use of energy to move materials through a membrane),

Diffusion is a net transport of atoms or molecules caused by their random thermal motion in an attempt to equalize concentration differences. A molecule diffuses from higher to lower concentration that is down its concentration gradient. This relationship was first recognized as early by the anatomist and physiologist Fick, and it has since been named after him: Fick's first law of diffusion. The flux by simple passive diffusion is directly proportional to the concentration dissolved molecules.Diffusion (passive transport) - the movement of a substance from an area of high concentration to an area of lower concentration (a concentration gradient). Facilitated diffusion takes place through transport proteins not linked directly to metabolic energy processes. Facilitated diffusion shows saturation or Michaelis-Menten kinetics, because the number of transport proteins is limited. The saturation kinetics is different from the energy limitation in primary active transport. Amino acids, glucose, galactose and other monosaccharides cross many cell membranes by facilitated diffusion.

Osmosis is transport of solvent molecules (mainly water) through a semipermeable membrane. The water flows from a compartment of high water concentration (or low solute concentration) to one of low water concentration (or high solute concentration). The greater difference between the solute concentrations of the two compartments, the more is water unevenly distributed between the two compartments. Water diffuses down its chemical potential gradient into the compartment with higher solute concentration, causing the chemical potential gradient to be reduced until solute equilibrium is reached. Osmotic pressure is the hydrostatic pressure that must be applied to the side of an ideal semipermeable membrane with higher solute concentration in order to stop the water flux, so that the net water flux is zero. The size of the osmotic pressure of a solution depends of the number of dissolved particles per volume unit. The osmotic pressure p depends on the absolute temperature (T Kelvin or K) and on the number of dissolved particles per volume unit (*N*/V equal to the molar fraction).

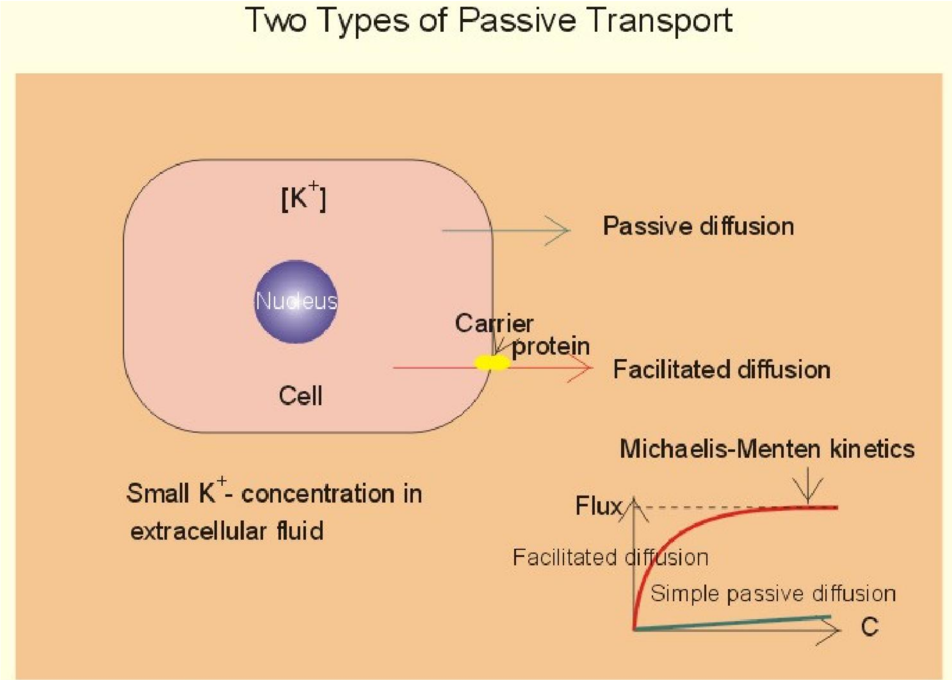
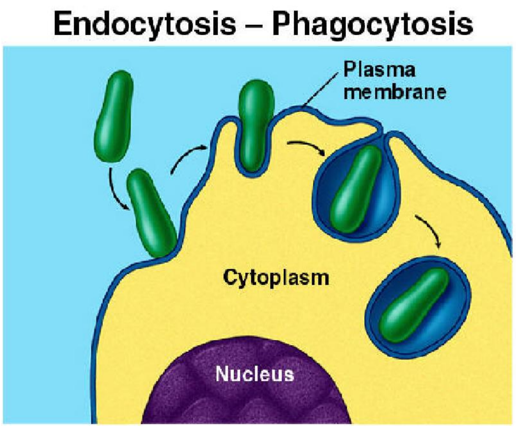
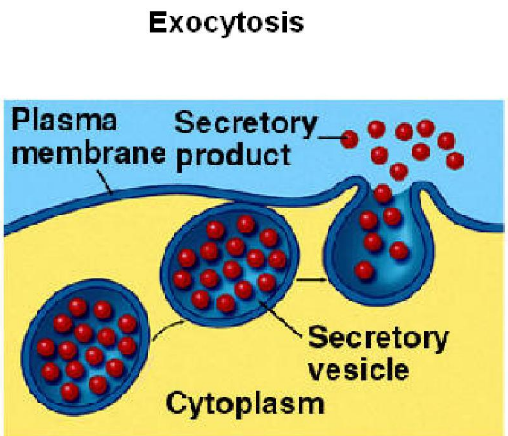
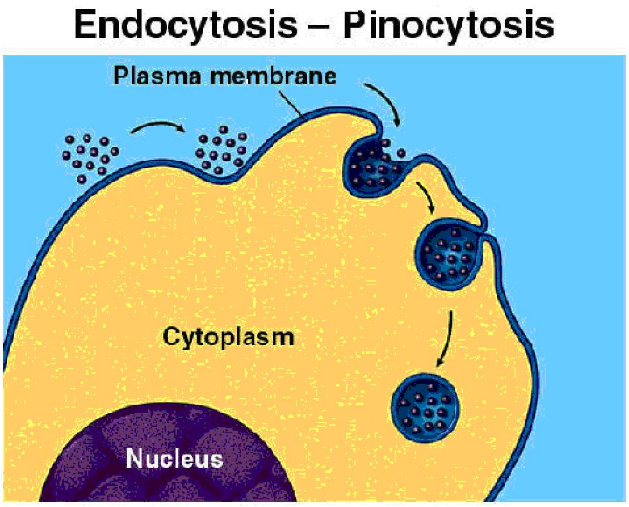


Figure 1.3 Two types of passive molecular transport: Simple diffusion and the much larger facilitated diffusion (C is concentration) (*http*://www.zuniv.net/physiology/book/images)

Endocytosis - An <u>active process</u> of taking in something through a cell membrane, which uses energy (ATP). Phagocytosis - cell eating. Exocytosis - the opposite of endocytosis, is also an active process. Pinocytosis - Cell drinking







. **Figure 1.4**

Active transport - transport proteins within the membrane must use energy (ATP) to move substances either to the inside or outside of the membrane.

The Na^+-K^+-pump

The Na^+-K^+-pump is a transmembrane protein in the cell membrane. The pump contains a channel, which consists of two double subunits: 2 α - and 2 β - subunits; the catalytic subunit (alpha) is an Na^+-K^+-activated ATP- ase and the beta -subunit is a glycoprotein. The pump is a primary active transporter, because it uses the cellular energy of the terminal phosphate bond of ATP. The Na^+-K^+-pump transports 3 Na^+ out of the cell and 2 K^+ into the cell for each ATP hydrolyzed. This is a net movement of positive ions out of the cell, and therefore called an electrogenic transport. The Na^+-K^+-pump is located in the basolateral exit-membrane of the epithelial cell. The primary active ion-transport provides metabolic energy for the secondary water absorption through the luminal membrane. Hereby, the active pump in the exit-membrane drives the luminal transport across the entry membrane. This transport of NaCl and water is surprisingly nearly isotonic.

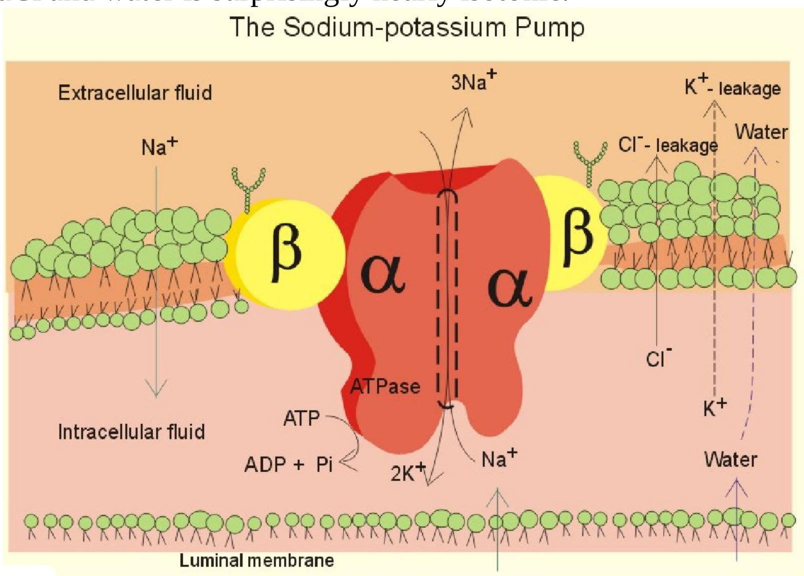
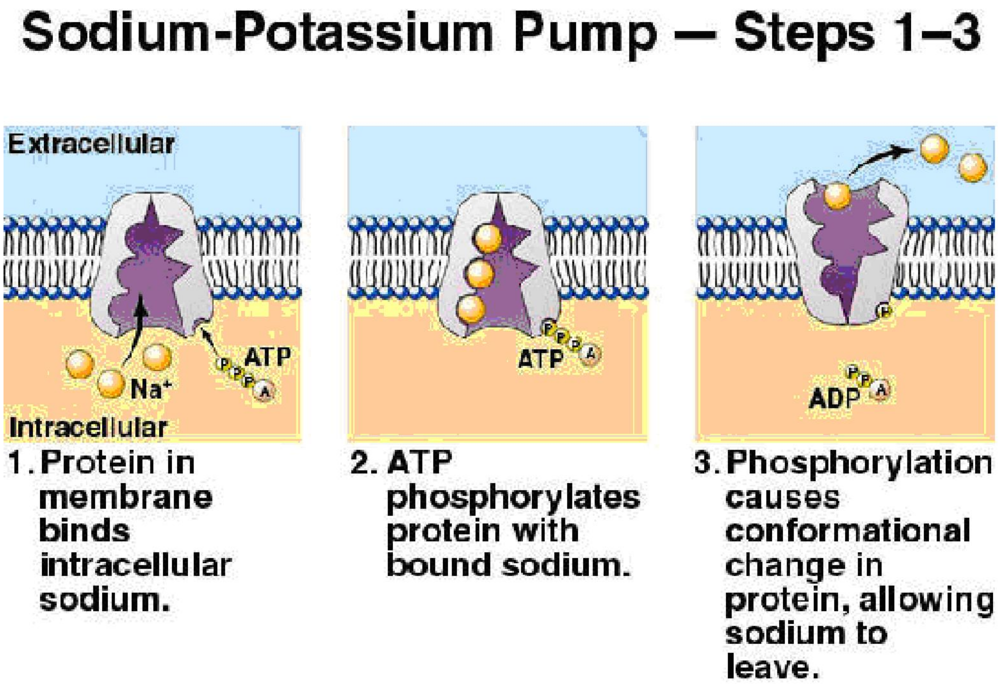


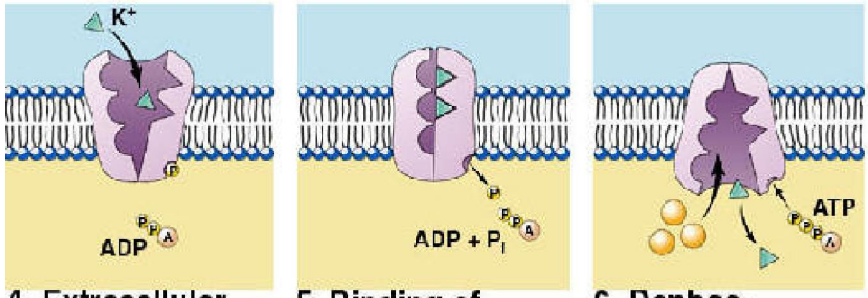
Figure 1.5 (http://www.zuniv.net/physiology/book/images)

The Na^+-K^+-pump builds up a high cellular electrochemical gradient for K^+ and indirectly for Cl^-. The water out flux is coupled to the outward transport of K^+ and Cl^-. The interstitial fluid receives ions and glucose, causing its osmolarity to increase. The osmotic force causes water to enter the interstitial fluid via the cell membranes and the gaps between the cells (tight junctions). This in turn causes the hydrostatic pressure in the interstitial fluid to rise. In a healthy standard person nutrients and oxygen are transported into the cell interior from the extracellular fluid through the cell membrane. The Na^+-K^+-pump is responsible for maintaining the high intracellular [K^+] and the low intracellular [Na^+]. The energy of the terminal phosphate bond of ATP is used to actively extrude Na^+ and pump K^+ into the cell. The membrane also contains many K^+- and Cl^--channels, through which the two ions leak through the cell membrane.

The sodium-potassium pump must break ATP down into ADP in order to pump sodium three ions outside the cell (continued below), while it pumps two potassium ions into the cell. The ATP phosphorylates (adds a phosphate to) the membrane protein as it binds to the sodium and breaks down, and it dephosphorylates the protein as it binds with the potassium. Cellular respiration must occur to add the phosphate back to ADP, thus restoring the ATP. In co transport, one process (the Na-K pump), is coupled with movement of a molecule of sugar (glucose) out of the cell, while allowing sodium to enter through the protein.



Sodium-Potassium Pump – Steps 4–6



4. Extracellular potassium binds to exposed sites.

5. Binding of potassium causes dephosphorylation of protein.

6. Dephosphorylation of protein triggers change back to original conformation, potassium moves into cell, and the cycle repeats.

Resting membrane potentials

A membrane potential difference is conventionally defined as the intracellular minus the extracellular electrical potential. When a microelectrode penetrates a membrane, it records a negative potential with respect to an external reference electrode caused by different permeability of anions and cations. This is the resting membrane potential (RMP). The resting membrane potential is an essential mechanism in storing and processing information in neurons and other cells. Concentration gradients across cell membranes are present for several ions, whereby they diffuse from one location to another. The ion with the highest permeability and concentration gradient, such as the potassium ion, establishes a membrane potential. This potential enhances or inhibits the flux of other ions and the ultimate situation is an electro neutral flux. The chloride ion diffuses extremely rapidly, but otherwise positive ions (cations) diffuse more rapidly than negative ions (anions) through a membrane. However, as an example the permeability for Na^+ is low compared to that of K^+ in neurons.

Resting membrane potentials (RMP) and Equilibrium potentials (V_{Eq}) in different cells.

	RMP (mV)
Skeletal muscle	- 80
Myocardial cells	- 90
Smooth muscle cells	- 40 to –60 (oscillations)
Neurons	- 70