PHYSICAL PROPERTIES AND FUNCTIONS

OF THE BIOLOGICAL MEMBRANE

10.1. STRUCTURE AND PHYSICAL PROPERTIES OF THE BIOLOGICAL MEMBRANE

All biological cells are surrounded by a plasma membrane. In 1972, S. Singer and G. Nicolson proposed the Fluid Mosaic Model of membrane structure. The cytoplasmic membrane consists of phospholipids or glycolipids, cholesterol and protein molecules. Molecules of lipids consist of polar heads (the phosphate radical or glycerol that is soluble in water) and non-polar tails (the fatty acid radical that are insoluble in water) (fig. 10.1). Such molecules are called ***amphiphilic.*** The head of a phospholipid is attracted to water (it is ***hydrophilic***), due to its polar nature. The nonpolar tail is the ***hydrophobic***.

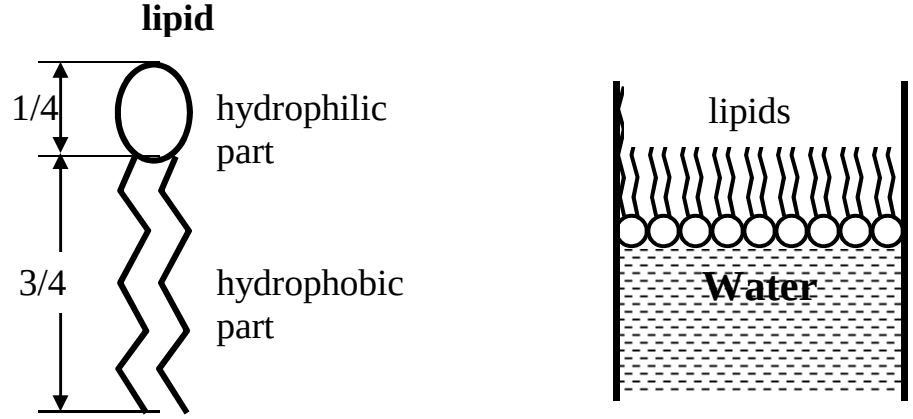

Fig. 10.1. Lipid molecule schematic representation and behavior of lipids on the water surface

Depending on lipid concentration and the lipid type there are some self-organizing structures what lipids assume include ***monolayers, micelles*****, and** ***vesicles***. Self-assembly occurs due to thermodynamics. If the phospholipids are

in water (or other polar solution) the tails will want to be «away» from the solution. They could all go to the top (like oil on water), or they could have the tails point toward each other (fig. 10.2).

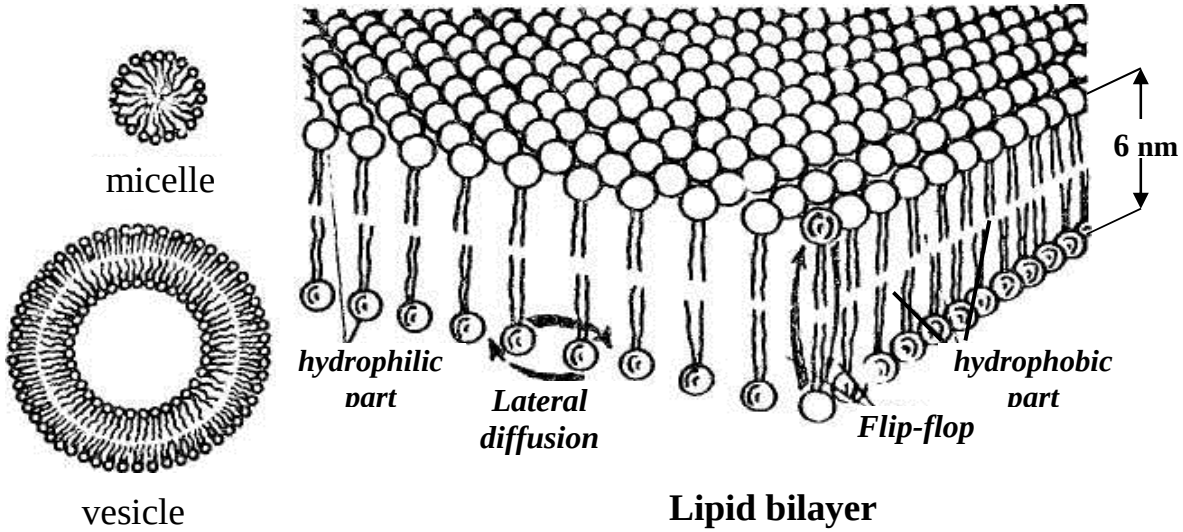

Fig. 10.2. Types of self-organization of lipids in water

The phospholipid bilayer is arranged so that the polar parts of the molecules form the outermost and innermost surface of the membrane while the non-polar parts form the center of the membrane. The lipids of membrane are similar to liquid crystal in which the fluidity and plasticity of liquids referred to symmetry of crystal. The liquid-crystalline properties of membranes are explained by the fact that lipids are in molten state in case of normal blood-heat.

Except lipid molecules plasma membrane contains proteins and carbohydrates. Membrane proteins are divided into two categories, integral and peripheral, depending on their location in the membrane.

Proteins that go through the membrane are called integral or transmembrane proteins. They have hydrophobic (non-polar amino acids with alpha helix coiling) regions within the interior of the membrane and hydrophilic regions at either membrane surface. The interior and exterior «faces» of transmembrane proteins are comprised of different tertiary domains, as is the hydrophobic «core». Some integral proteins become «anchored» within the phospholipid bilayer by covalently bonding to fatty acids. Peripheral proteins are attached to the surface of the membrane, often to the exterior hydrophilic regions of the transmembrane proteins (fig. 10.3). On the interior surface, peripheral proteins typically are held in position by the cytoskeleton. On the exterior, proteins may attach to the extracellular matrix. Peripheral proteins help give animal cell membranes strength.

Usually ***carbohydrates*** are located on the extracellular surface of the plasma membrane. The membrane thickness is 8–9 nm.

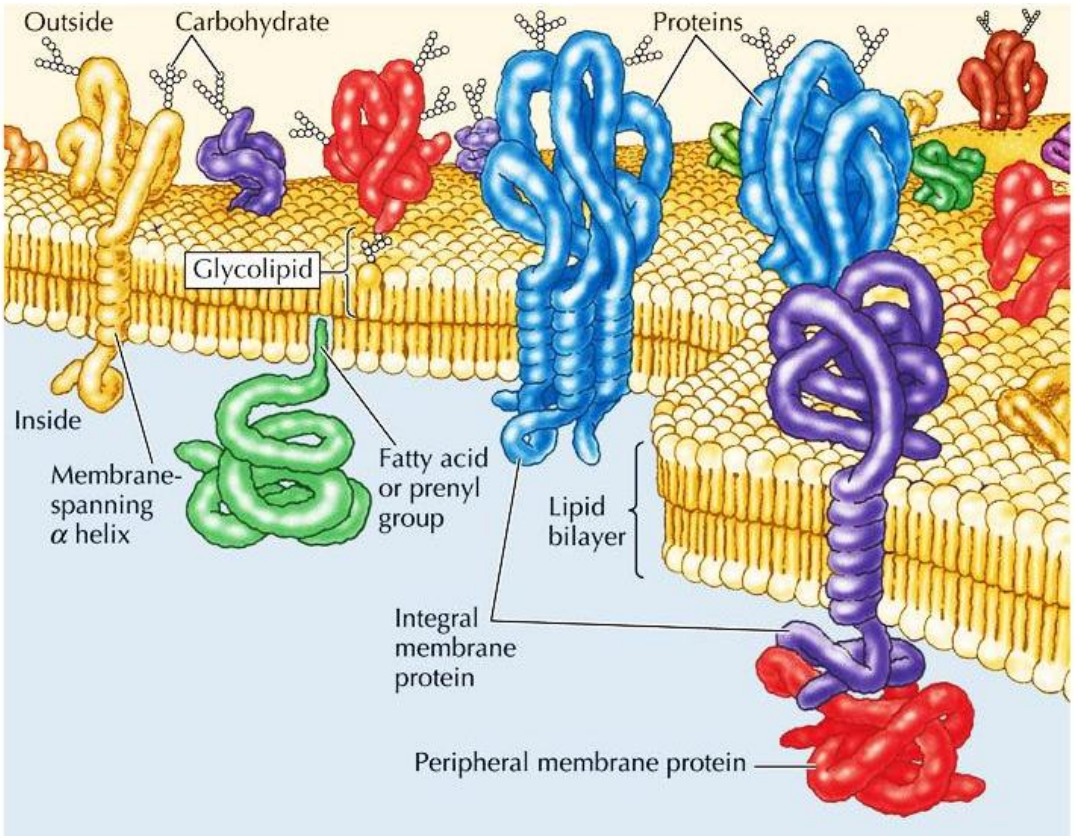

Fig. 10.3. Plasma membrane structure

10.2. TYPES OF LIPIDS AND PROTEINS MOTION IN THE CELL MEMBRANE

The cell membrane is not solid/static/fixed but rather elastic and adaptable to changing needs. Lipids and proteins are in constant thermal motion in the membrane. No strong bonds between neighboring phospholipids, so they fluidly move past one another. The lipids are mobile within their half of the lipid bilayer. Chaotic movements of lipids and proteins along the membrane surface are called ***the lateral diffusion.*** The rate of lipids lateral diffusion is about 5 μm/s. The rate of lateral diffusion of proteins is much less than lipids due to their large mass.

Lipids and proteins are participating in the rotational motion, called ***the rotational diffusion.*** The rotation angular velocity at normal temperatures for phospholipids is high (~ 10^9 rad/s) and for proteins it is much less. For example, for rhodopsin the rotation angular velocity υ is equal to 10^6 rad/s.

The transition of lipids from one membrane monolayer to another (this transition is called ***flip-flop***) is very unlikely and happens very rarely, as in this case, the polar head must pass through the hydrophobic inner region of the membrane, where it is not soluble. The probability of such ***flip-flop*** transitions is 10^{10} times smaller than the probability of lateral diffusion. ***Flip-flop*** movement needs enzymes (flippases) to speed flip-flop.

Protein mobility can vary greatly. Some proteins are free to move. Others may be tethered to structures in the cytoplasm or extracellular spaces, thus restricting their movement. Some types of cell junctions (e. g., tight junctions) can restrict protein movements to a specific membrane domain.

10.3. TRANSPORT OF MOLECULES AND IONS THROUGH THE MEMBRANE

The cytoplasmic membrane is a selectively permeable membrane that determines what goes in and out of the cell (fig. 10.4).

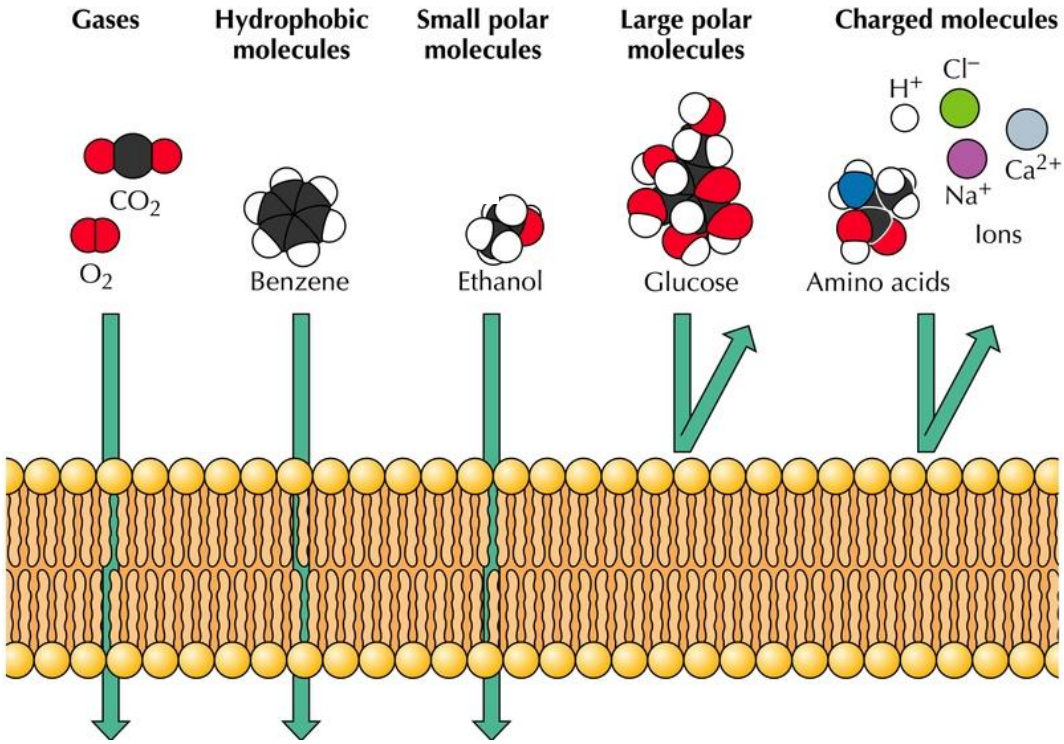

Fig. 10.4. Movement of substances across cell membranes

Water-soluble ions generally pass through small pores in the membrane. All other molecules require carrier molecules to transport them through the membrane. There are two major types of the membrane transport: **passive and active**.

Transport of substances through the membrane is called ***passive*** if it does not expend metabolic energy stored in the cell. Passive transport does not require the electrochemical energy of the hydrolysis ATP — adenosine triphosphate. The main types of the passive transport are the following:

1) simple diffusion through the membrane lipid bilayer;
2) simple diffusion through a protein channels- pores in membrane;
3) facilitated diffusion through the membrane with the help of special carrier molecule.

Diffusion is a spontaneous process of substances penetration from an area of higher concentration to an area of lower concentration due to the energy of

thermal motion. The main driving force for passive transport is the gradient of concentration (more exactly — electrochemical potential gradient) across the membrane.

Simple diffusion through the lipid bilayer

One of the most important factors that determine how rapidly a substance diffuses through the lipid bilayer is the lipid solubility of the substance. Hydrophobic molecules and (at a slow rate) very small uncharged polar molecules can diffuse through the lipid bilayer. For instance, the lipid solubilities of oxygen, nitrogen, carbon dioxide, and alcohols are high, so that all these can dissolve directly in the lipid bilayer and diffuse through the cell membrane. For obvious reasons, the rate of diffusion of these substances through the membrane is directly proportional to their lipid solubility. Especially large amounts of oxygen can be transported in this way; therefore, oxygen is delivered to the interior of the cell almost as though the cell membrane did not exist. Membrane permeability for nonpolar organic compounds is high, since the membrane lipids are well dissolved nonpolar substance. Large polar molecules and ions cannot pass through phospholipid bilayer. One can conclude:

– membrane permeability for the organic molecules decreases when the number of polar groups (hydroxyl, carboxyl and amine) increase;

– membrane permeability for the organic molecules increases when the number of non-polar groups (methyl, ethyl and phenyl) increase.

Simple diffusion through a protein channel

Inorganic polar molecules and ions are insoluble in lipids, so they can pass through the membrane only if there are special channels — pores that exist in the membrane. However, the number of such channels is relatively small, so the membrane permeability for ions and polar compounds is in a hundred times worse than for non-polar compounds.

An ion channel is an integral membrane protein or more typically an assembly of several proteins. The size, shape and charge of each channel acts a ***selective filter*** that allows only certain types of ions to pass. Some types of channel proteins are always open. They allow specific ions to continually pass through the pore's selective filter using the kinetic energy of the ions. Other channel proteins are gated. Access to the ion is governed by «gates», which can be opened or closed by chemical or electrical signals, or mechanical force, depending on the dimensions of channel (fig. 10.5). If the conformational state of protein channels depends on difference in ionic charges on two sides of membrane, the channels are called ***voltage-gated channels.*** If the conformational state depends on binding of specific molecule (ligand) to outer or inner surface of channels, the channels are called ***chemically-gated channels.***

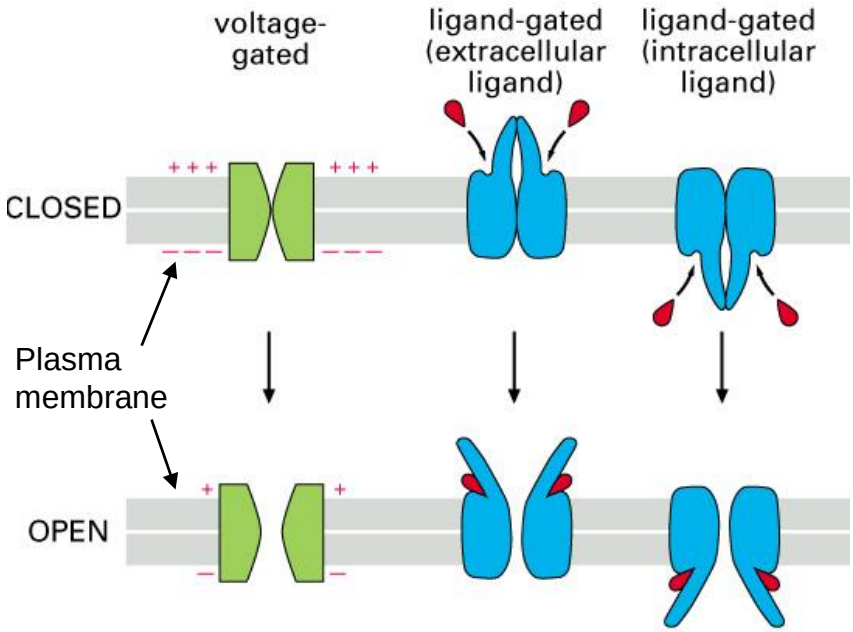

Fig. 10.5. The gating of ion channels

Facilitated diffusion (by carrier molecule)

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

There are two kinds of facilitated diffusion:

1) ***transfer of a substance with a movable carrier*** — a carrier molecule is combined with the transported substance on one side of the membrane, and with it moves through the lipid bilayer to the other side of the membrane;

2) ***relay transfer*** — in this case, the carrier molecules do not make shuttle movements in the membrane and are embedded in the membrane of each other, forming a bridge to it. Capturing a substance transported, extreme carrier molecule transfers it neighboring molecule, and so on «in the relay».

Facilitated diffusion involves proteins known as carriers, which are specific for a certain type of ions and can transport substances in either direction across the membrane. However, unlike channels, they facilitate the movements of solutes across the membrane by physically binding to them on one side of the membrane and releasing them on the other side. The direction of the solute's net movement simply depends on its concentration gradient across the membrane. If the concentration is greater in the cytoplasm, the solute is more likely to bind to the carrier on the cytoplasmic side of the membrane and be released on the extracellular side, and there will be a net movement from inside to outside.

A characteristic feature of carrier-mediated transport is that its rate is saturable. Facilitated diffusion differs from simple diffusion through an open channel in the following importanl way: although the rate of diffusion through

an open channel increases proportionately with the concentration gradient of the diffusing substance, in facilitated diffusion if the concentration gradient of a substance is progressively increased, the rate of transport of the substance will increase up to a certain point and then level off. Further increases in the gradient will produce no additional increase in rate. The reason for this is that there is a limited number of carriers in the membrane. When the concentration of the transported substance is raised high enough, all of the carriers will be in use and the capacity of the transport system will be saturated. This difference between simple diffusion and facilitated diffusion is demonstrated in fig. 10.6, showing that as the concentration gradient of the substance increases, the rate of continues to increase proportionately, but there is limitation of facilitated diffusion to the υ_{max} level.

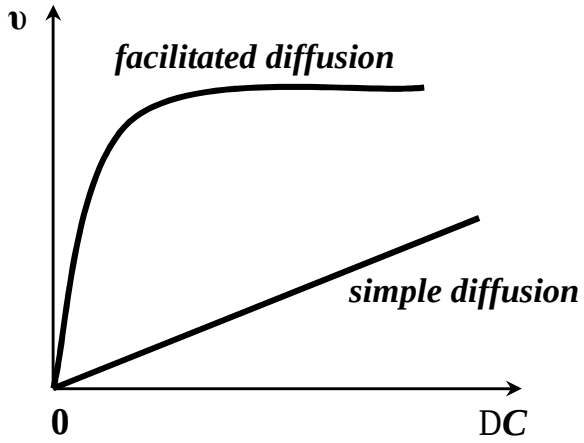

Fig. 10.6. The transfer rate υ dependence on the transported molecule concentration difference Δ*C* across the membrane in simple and facilitated diffusion

Carrier-mediated diffusion has ***three essential characteristics***:

– it is specific, with only certain molecules or ions transported by a given carrier;

– the direction of net movement being determined by the relative concentrations of the transported substance inside and outside the cell;

– it may become saturated if all of the protein carriers are in use.

Among the most important substances that cross cell membranes by facilitated diffusion are glucose and most of the amino acids.

10.4. MATHEMATICAL DESCRIPTION OF THE PASSIVE TRANSPORT

Electrochemical potential is the free energy of one mole of solution. Free energy is the thermodynamic potential, which determines the ability of a physical-chemical system to perform useful work. All useful work that can be done in one mole of a substance is due to decrease of its electrochemical potential. For solutions of substances electrochemical potential can be expressed as

$$\mu = \mu_0 + RT\mathrm{Ln}C + ZF\varphi, \qquad (10.1)$$

μ_0 is the part of chemical potential of one mole of solution which is determined by the energy of chemical bonds of the solute with the solvent; R is the universal gas constant; T is the absolute temperature of the solution; C is the molar concentration of the solute; Z is the electric charge of the dissolved ions, which is expressed in units of electron charge; F is the Faraday number; φ is the electric potential of the solution.

Let's imagine that the membrane separates two solutions of identical composition but different ion concentration (fig. 10.7).

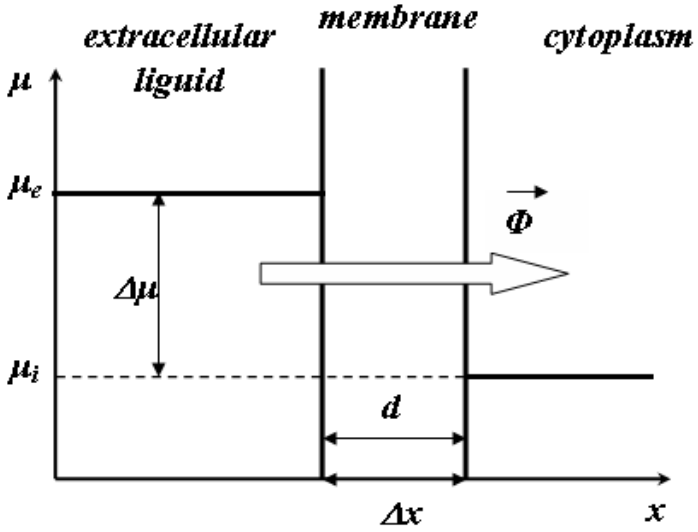

Fig. 10.7. Connection between the diffusion flux direction and the electrochemical potential distribution across the membrane

If the values of electrochemical potential on both sides of the membrane are different $\mu_e \neq \mu_i$, then the system is thermodynamic non-equilibrium. In this case electrochemical potential gradient appears across the membrane: $d\mu/dx = \Delta\mu/d$, where d is the membrane thickness.

The thermodynamic equilibrium of system is characterized by the equality of thermodynamic potentials including electrochemical ones: $\mu_e = \mu_i$. The process of transition from the non-equilibrium to equilibrium state in the case of biological membranes is always accompanied by substance diffusion from the region of greater value of the electrochemical potential into the region with its lower value.

Mathematically, the process of substance transfer is described by the ***Theorell equation*:**

$$\vec{\Phi} = -CU \overrightarrow{\frac{d\mu}{dx}}, \qquad (10.2)$$

where Φ is the diffusion flux density (amount of substance transported through the unit membrane area per second); C is molar concentration of the solution; U is the mobility; $d\mu/dx$ is the electrochemical potential gradient.

Let's find the electrochemical potential gradient $d\mu/dx$. Taking into account that on both sides of biomembranes solvent is always the same — water, so $\mu_{oi} = \mu_{oe} = \text{const}$, one can obtain:

$$\frac{d\mu}{dx} = RT\frac{1}{C}\frac{dC}{dx} + ZF\frac{dj}{dx}. \qquad (10.3)$$

Let's substitute this expression (3) in (1) and write ***Nernst–Planck equation*** describing diffusion of ions across the membrane:

$$\vec{\Phi} = -URT\frac{dC}{dx} - CUZF\frac{dj}{dx}. \qquad (10.4)$$

First summand in this equation describes diffusion which is due to the concentration gradient dC/dx, second summand describes electrodiffusion which is due to electric potential gradient $d\varphi/dx$ through membrane.

In case of the uncharged particles diffusion ($Z = 0$) the second term in the equation (10.4) vanishes and the passive transport of such substances is described by ***Fick Law***:

$$\vec{\Phi} = -D\frac{dC}{dx}, \qquad (10.5)$$

where D is the diffusion coefficient. The diffusion coefficient depends on the mobility of the substance U and the absolute temperature of the medium T:

$$D = URT. \qquad (10.6)$$

It is possible to simplify Fick equation, if concentration gradient is expressed as

$$dC/dx \sim \Delta C/\Delta x = |C_i - C_e|/d, \qquad (10.7)$$

where d is the membrane thickness; C_i and C_e are concentration absolute values on the interior and exterior membrane surfaces:

$$\Phi = p|C_i - C_e|, \qquad (10.8)$$

where coefficient $p = D/d$ is ***permeability coefficient***.

10.5. ACTIVE TRANSPORT OF IONS

Active transport typically moves molecules or ions through a membrane from low their concentration to high in the direction of increasing the electrochemical potential. Passive transport of substances has always gone from the region of large values of the electrochemical potential to the region of its lower values, resulting in electrochemical potential gradient decreases. Active transport of substances is going in the opposite direction and leads to an increase of the electrochemical potential difference on both side of the membrane, so energy is required. Active transport is mediated by carrier proteins that undergo conformational changes in order to move substance across membranes. Many of

the carrier proteins involved in active transport are referred to as pumps. The ATP-dependent pump uses the energy derived from adenosine triphosphate (ATP) hydrolysis to adenosine diphosphate (ADP) and inorganic phosphate (P_i):

$$ATP \rightarrow ADP + P_i + E \ (E = 45 \text{ KJ/mol}).$$

Active transport of substances can be divided into two types:

1) active transport of ions;

2) active transport of organic compounds, mainly amino acids and carbohydrates.

All ATP-dependent pumps (ATPases) share a common feature. They transport substances from the side where they are less concentrated to the side where they are more concentrated by utilizing the free energy associated with ATP hydrolysis. There are several types of ATPases, and they function by distinct mechanisms. The best-studied ATPase is the Na, K-ATPase, also known as the sodium-potassium pump.

The sodium-potassium (Na-K) pump is a transport process that pumps sodium ions out ward through the cell membrane of all cells and at the same time pumps potassium ions from the outside to the inside (fig. 10.8). 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.

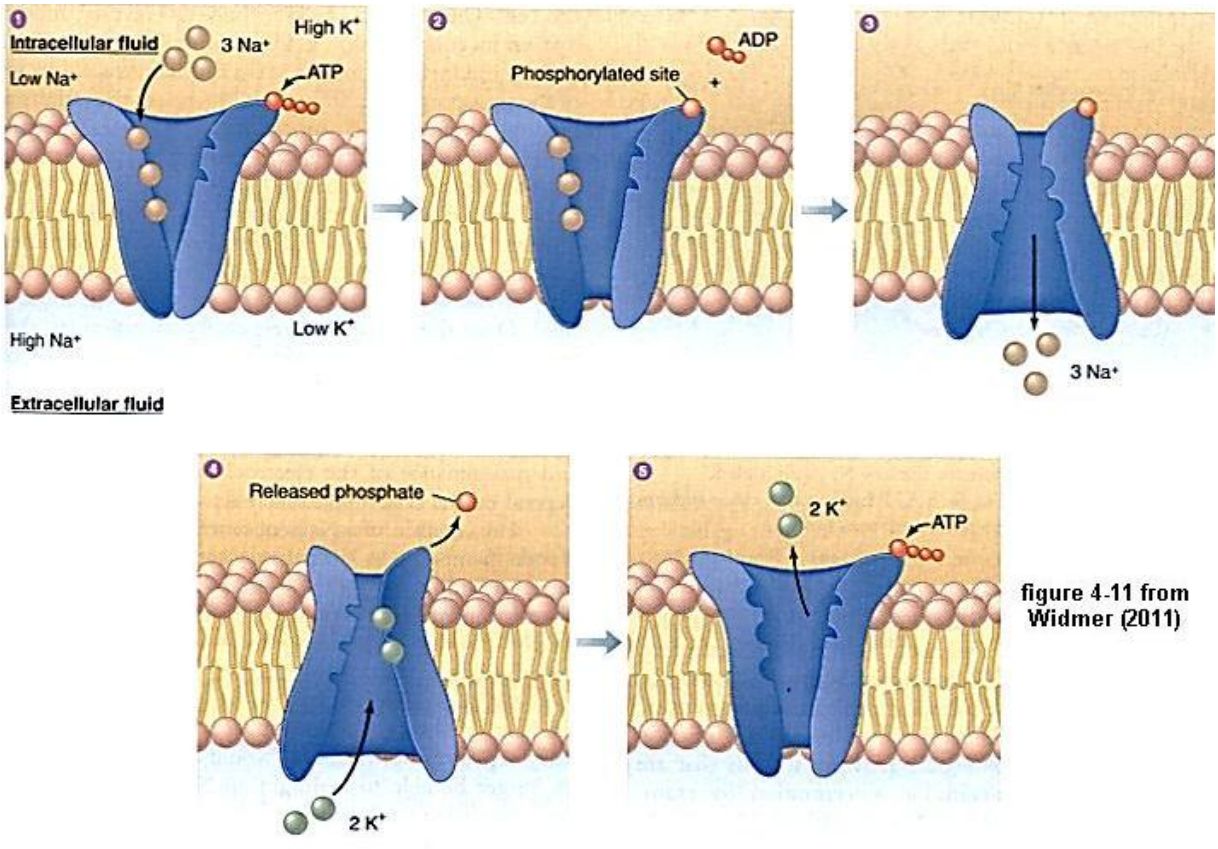

Fig. 10.8. Scheme of the sodium-potassium pump

During one cycle of pumping, the sodium-potassium pump exports three ions of sodium and imports two ions of potassium through the cell membrane.

After binding sodium ions on the interior of the cell, ATP is hydrolyzed and the phosphate is transferred to the pump protein. The phosphorylated protein undergoes a conformational change, delivering the sodium ions to the exterior of the cell and exchanging them for potassium ions. The protein is then dephosphorylated and undergoes an additional conformational change, returning to its original state and delivering the potassium ions to the interior of the cell. The fact that the Na-K pump moves three Na^+ ions to the exterior for every two K^+ ions to the interior means that one positive charge is moved from the interior of the cell to the exterior for each cycle of the pump. This creates positivity outside the cell but leaves a deficit of positive ions inside the cell; that is, it causes ***negativity on the inside***.

***Questions*:**

1. Characterize the cell membrane lipids physical properties. What are cell membrane lipids and proteins functions?
2. Describe types of the lipids and proteins motion in the cell membrane (lateral diffusion, rotational diffusion, flip-flop).
3. What passive transport types across cell membrane are known?
4. Which substances can move across cell membranes? Specify membrane channels properties.
5. What is a facilitated diffusion? Describe facilitated diffusion types.
6. What is the meaning of electrochemical potential? Write the Theorell equation, Nernst-Planck equation and Fick Law. What is the cell membrane permeability?
7. What is the active transport? Explain ions active transport mechanism by the sodium-potassium pump example.

Chapter 11. MEMBRANE POTENTIALS OF THE CELL

The cell membrane acts as a barrier which prevents the intracellular fluid from mixing with the extracellular fluid. These two solutions have different concentrations of their ions. Furthermore, this difference in concentrations leads to a difference in charge of the solutions. This creates a situation whereby one solution is more positive than the other. The membrane potential (φ_m) of an excitable cell is defined as the potential at the inner surface (φ_i) relative to that at the outer (φ_e) surface of the membrane, i. e. $\varphi_m = (\varphi_i) - (\varphi_e)$. This definition is independent of the cause of the potential, and whether the membrane voltage is constant, periodic, or nonperiodic in behavior. If the potential outside is taken to be zero, then the interior resting membrane potential varies from –60 mV to –100 mV depending on the type of cell.

A nerve cell conducts an electrochemical impulse because of membrane potential changes. These changes allow movement of ions through the membrane, setting up currents that flow through the membrane and along the cell. Similar impulses travel along muscle cells before they contract.

11.1. THE NERNST EQUATION

Find the equilibrium membrane potential, which arises due to the diffusion of ions through the cell membrane. Suppose that in a rest the membrane is permeable to one type of ion (K^+). The concentration of potassium ions is higher inside cells than outside due to the active transport of potassium ions. Most cells have potassium-selective ion channel proteins that remain open all the time. There will be net movement of positively-charged potassium ions through these potassium channels with a resulting accumulation of excess negative charge inside of the cell. The outward movement of positively-charged potassium ions is due to its diffusion and continues until enough excess negative charge accumulates inside the cell to form a membrane potential which can balance the difference in concentration of potassium between inside and outside the cell. «Balance» means that the electrical potential that results from the build-up of ionic charge, and which impedes outward diffusion, increases until it is equal in magnitude but opposite in direction to the tendency for outward diffusive movement of potassium. This balance point (the equilibrium state) is characterized by the equality of electrochemical potentials on both sides of the membrane $\mu_e = \mu_i$ and the net transmembrane flux (or current) of K^+ is zero ($\Phi_{K^+} = 0$).

The electrochemical potential inside cell can be written as

$$\mu_i = \mu_{0i} + RT\ln C_i + ZF\varphi_i$$

and the electrochemical potential outside is

$$\mu_e = \mu_{0e} + RT\ln C_e + ZF\varphi_e.$$

The chemical potential of the water is the same on both sides $\mu_{0i} = \mu_{0e}$, and condition of the equilibrium state has the form:

$$RT\ln C_i + ZF\varphi_i = RT\ln C_e + ZF\varphi_e.$$

This equation can be rearranged to give:

$$RT(\varphi_i - \varphi_e) = RT(\ln C_i - \ln C_e).$$

The Nernst equation for equilibrium membrane potential is obtained from the last equation:

$$\varphi_i - \varphi_e = -\frac{RT}{ZF}\ln\frac{C_i}{C_e}, \qquad (11.1)$$

where $\varphi_i - \varphi_e$ is the equilibrium potential for ion; R is the universal gas constant; T is the absolute temperature; Z is the number of elementary charges; F is the Faraday constant; C_e is the extracellular concentration of ion; C_i is the intracellular concentration of ion.

The equilibrium potential for a given ion depends only upon the concentrations on either side of the membrane and the temperature. The Nernst equation is widely used in physiology to relate the concentration of ions on either side of a membrane to the electrical potential difference across the membrane. Usually the outside solution is set as the zero voltage ($\varphi_e = 0$).

Then the difference between the inside voltage and the zero voltage is determined. At physiological temperature, about 29,5 °C, and physiological concentrations (which vary for each ion), the calculated equilibrium potentials are approximately +67 mV for Na^+, +90 mV for K^+, –86 mV for Cl^- and +123 mV for Ca^{2+}.

11.2. RESTING MEMBRANE POTENTIAL

In mammalian cells sodium Na^+, potassium K^+ and chloride Cl^- ions play large roles for the resting membrane potential. The resting membrane potential is determined by the equilibrium potentials for every ion to which the membrane is permeable, weighted by the permeability (*P*), via the Goldman–Hodgkin–Katz voltage equation:

$$\varphi_m = -\frac{RT}{F}\ln\frac{P_{\mathrm{K}}C_i(\mathrm{K}^+)+P_{\mathrm{Na}}C_i(\mathrm{Na}^+)+P_{\mathrm{Cl}}C_e(\mathrm{Cl}^-)}{P_{\mathrm{K}}C_e(\mathrm{K}^+)+P_{\mathrm{Na}}C_e(\mathrm{Na}^+)+P_{\mathrm{Cl}}C_i(\mathrm{Cl}^-)}, \qquad (11.2)$$

where *R*, *T*, and *F* are as above; P_{K}, P_{Na}, P_{Cl} are the membrane permeabilites for K^+, Na^+, Cl^- ions, respectively; $C_e(K^+)$, $C_e(Na^+)$, $C_e(Cl^-)$ are the extracellular concentrations for K^+, Na^+, Cl^- ions, respectively; $C_i(K^+)$, $C_i(Na^+)$, $C_i(Cl^-)$ are the intracellular concentrations for K^+, Na^+, Cl^- ions, respectively. If the permeabilities of Na^+ and Cl^- are zero, the membrane potential reduces to the Nernst potential for K^+ (as $P_{K^+} = P_{\mathrm{tot}}$). Usually, under resting conditions $P_{\mathrm{Na+}}$ and $P_{\mathrm{Cl-}}$ are not zero, but they are much smaller than $P_{\mathrm{K+}}$, which renders φ_m close to the equilibrium potential for potassium. Normally, permeability values are reported as relative permeabilities with P_{K} having the reference value of one (because in most cells at rest P_{K} is larger than P_{Na} and P_{Cl}). Hodgkin and Katz experimentally found that for the giant axon of squid the attitude of the membrane permeability for K^+, Na^+ and Cl^- ions in a rest is P_{K}: P_{Na} : P_{Cl} = 1 : 0,04 : 0,45. Medical conditions such as hyperkalemia in which blood serum potassium (which governs $[K^+]_e$) is changed are very dangerous since they offset the equilibrium potential for potassium, thus affecting resting membrane potential φ_m. This may cause arrhythmias and cardiac arrest.

Because the electric field in the resting cell is zero, there is no net charge in the fluid. Positive ions are neutralized by negative ions everywhere except at the membrane. A layer of charge on each surface generates an electric field within the membrane and a potential difference across it. Measurements with a microelectrode show that the potential within the cell is about 60–100 mV less than outside. If the potential outside is taken to be zero, then the interior resting potential is (–60) – (–100) mV. If the potential drops 80 mV and if the membrane thickness is 8 nm, then the electric field within the membrane is assumed to be constant:

$$E = \frac{\varphi_0}{d} = \frac{80\,\mathrm{mV}}{8\,\mathrm{nm}} = \frac{80\cdot10^{-2}\,\mathrm{V}}{8\cdot10^{-9}\,\mathrm{m}} = 10^7\,\frac{\mathrm{V}}{\mathrm{m}}. \qquad (11.3)$$

11.3. ACTION POTENTIAL IN EXCITABLE CELLS

All cells exhibit a potential difference across the cell membrane. Nerve cells and muscle cells are excitable. They have the ability to generate and propagate electrical signals. The origin of the membrane potential is the same in nerve cells as in muscle cells. In both cell types, the membrane generates an impulse as a consequence of excitation. This impulse propagates in both cell types in the same manner.

An action potential is the brief reversal in the potential difference across a plasma membrane (as of a nerve cell or muscle fiber) that occurs when a cell has been activated by a stimulus (fig. 11.1).

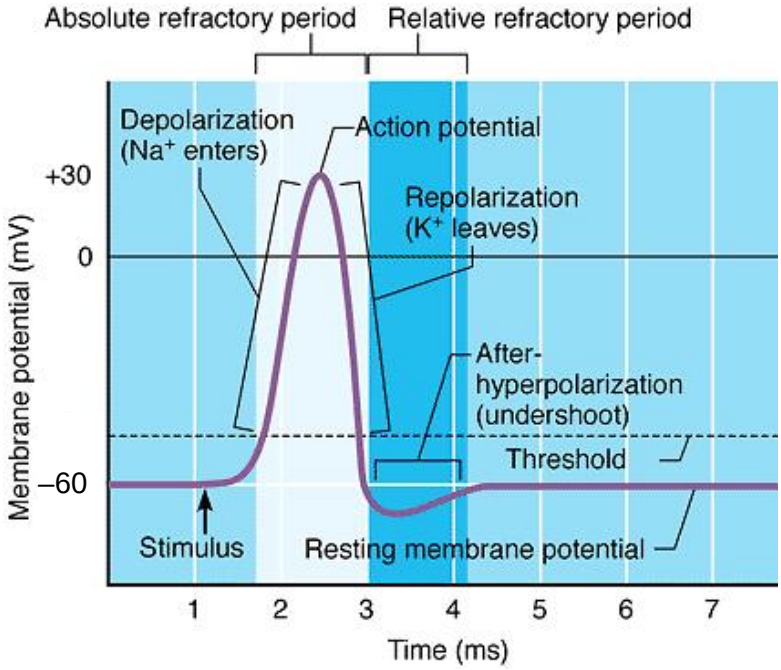

Fig. 11.1. Schematic representation of an action potential in an excitable cell

The course of the action potential can be divided into five parts: the rising phase, the peak phase, the falling phase, the undershoot phase, and finally the refractory period. When the excitable cell membrane is stimulated so that the membrane potential rises and reaches the threshold, the sodium and potassium ionic permeabilities of the membrane change. The sodium ion permeability increases very rapidly at first, allowing sodium ions to flow from outside to inside, making the inside more positive. During the rising phase the membrane potential φ_m depolarizes (becomes more positive). The sharp rise in membrane potential and sodium permeability correspond to the rising phase of the action potential. Hodgkin and Katz experimentally found that for the giant axon of squid the attitude of the membrane permeability for K^+, Na^+ and Cl^- ions during the rising phase is $P_K : P_{Na} : P_{Cl} = 1 : 20 : 0{,}45$.

The point at which depolarization stops is called the peak phase. At the peak of the action potential, the sodium permeability is maximized and

the membrane potential is nearly equal to the sodium equilibrium voltage φ_{Na}. At this stage, the membrane potential reaches a maximum.

Subsequent to this, there is a falling phase. The same raised voltage that opened the sodium channels initially also slowly shuts them off, by closing their pores; the sodium channels become inactivated. This lowers the membrane's permeability to sodium, driving the membrane potential back down. At the same time, the raised voltage opens voltage-sensitive potassium channels; the increase in the membrane's potassium permeability drives the membrane potential φ_m towards the potassium equilibrium voltage φ_K. The efflux of potassium ions decreases the membrane potential thus returning the membrane potential to its resting value or hyperpolarizes the cell. Combined, these changes in sodium and potassium permeability cause the membrane potential φ_m to drop quickly, repolarizing the membrane and producing the «falling phase» of the action potential.

The raised voltage opened many more potassium channels than usual, and these do not close right away when the membrane returns to its normal resting voltage. The potassium permeability of the membrane is transiently unusually high, driving the membrane potential φ_m even closer to the potassium equilibrium voltage φ_K. Hence, there is an undershoot, a hyperpolarization, that persists until the membrane potassium permeability returns to its usual value. The undershoot phase is the point during which the membrane potential becomes temporarily more negatively charged than when at rest. While at rest, following activation, the Na-K pump restores the ion concentrations inside and outside the membrane to their original values.

Each action potential is followed by a refractory period, which can be divided into an absolute refractory period, during which it is impossible to evoke another action potential, and then a relative refractory period, during which a stronger-than-usual stimulus is required. These two refractory periods are caused by changes in the state of sodium and potassium channel molecules. When closing after an action potential, sodium channels enter an «inactivated state», in which they cannot be made to open regardless of the membrane potential — this gives rise to the absolute refractory period. Even after a sufficient number of sodium channels have transitioned back to their resting state, it frequently happens that a fraction of potassium channels remains open, making it difficult for the membrane potential to depolarize, and thereby giving rise to the relative refractory period. Because the density and subtypes of potassium channels may differ greatly between different types of neurons, the duration of the relative refractory period is highly variable.

Duration of the depolarization is small in any cases. For nerve cells and muscle cells this duration is 0,5–1 ms. Duration of the repolarization depends essentially on the type of cells: for the nerve cells and skeletal muscle cells duration of the repolarization is 0,5–10 ms, for the heart muscle cells — about 300 ms.

The action potential amplitude is equal to the sum of absolute values of the resting potential φ_0 and the maximum achieved membrane potential φ_{max} and is ~90–120 mV:

$$\varphi_a = \varphi_{max} - \varphi_0 = \varphi_{max} + |\varphi_0|. \quad (11.4)$$

Currents produced by the opening of voltage-gated channels in the course of an action potential are typically significantly larger than the initial stimulating current. Thus the amplitude, duration, and shape of the action potential are largely determined by the properties of the excitable membrane and not the amplitude or duration of the stimulus. The action potentials are generated anew along excitable stretches of membrane and propagate without decay.

11.4. PROPAGATION OF ACTION POTENTIAL ALONG AN UNMYELINATED AXON

The nerve cell may be divided on the basis of its structure and function into three main parts:

– the cell *body*, also called the soma;
– numerous short processes of the *soma*, called the *dendrites*;
– the single long nerve fiber, the *axon*.

The long nerve fiber, the *axon*, transfers the signal from the cell body to another nerve or to a muscle cell. The long cylindrical axon has properties that are in some ways similar to those of an electric cable. Its diameter may range from less than one micrometer (1 μm) to as much as 1mm for the giant axon of " a squid; in humans the upper limit is about 20 μm. Pulses travel along it with speeds ranging from 0.6 to 100 m s^{-1}, depending, among other things, on the diameter of the axon. The axon core may be surrounded by either a membrane (for an unmyelinated fiber) or a much thicker sheath of fatty material (myelin) that is wound on like tape.

Let's consider the action potential propagation along unmyelinated axon. At resting potential there is positive charge on the outside of axon membrane and negative charge on the inside, with high sodium ion concentration outside and high potassium ion concentration inside (fig. 11.2).

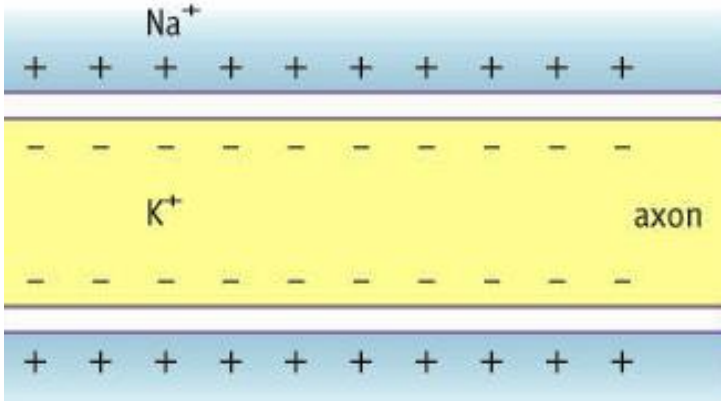

Fig. 11.2. Unmyelinated axon in a rest. There is no net transport of the ion through the membrane

If the membrane stimulus is insufficient to cause the membrane potential to reach the threshold, then the membrane will not activate. The response of the membrane to this kind of stimulus is essentially passive. If the excitatory stimulus is strong enough, the membrane potential reaches the threshold, and the membrane produces a characteristic electric impulse, the nerve impulse. This potential response follows a characteristic form regardless of the strength of the transthreshold stimulus. When stimulated, voltage-dependent sodium ion channels open, and sodium ions flow into the axon, depolarizing the membrane. The potential difference ($\varphi_{max} - \varphi_0$) between excited and unexcited regions of an axon would cause small currents, called local circuit currents, to flow between them in such a direction that they stimulate the unexcited region (fig. 11.3).

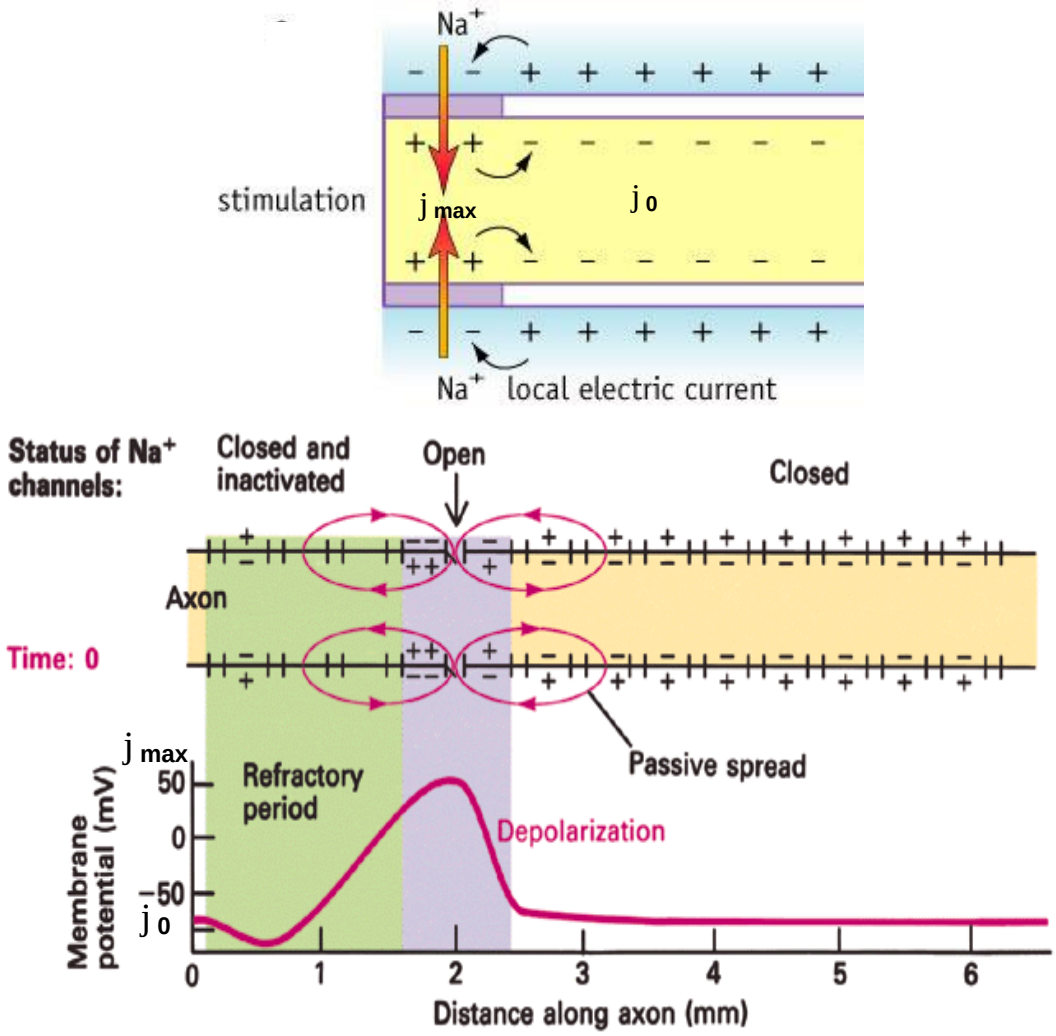

Fig. 11.3. The propagation of action potential along an unmyelinated axon

Meanwhile, in the earlier excited region potassium ions leave the axon, repolarizing the membrane. The currents flowing inwards at a point on the axon during an action potential spread out along the axon, and depolarize the adjacent sections of its membrane (fig. 11.4). The action potential generated at the axon propagates as a wave along the axon.

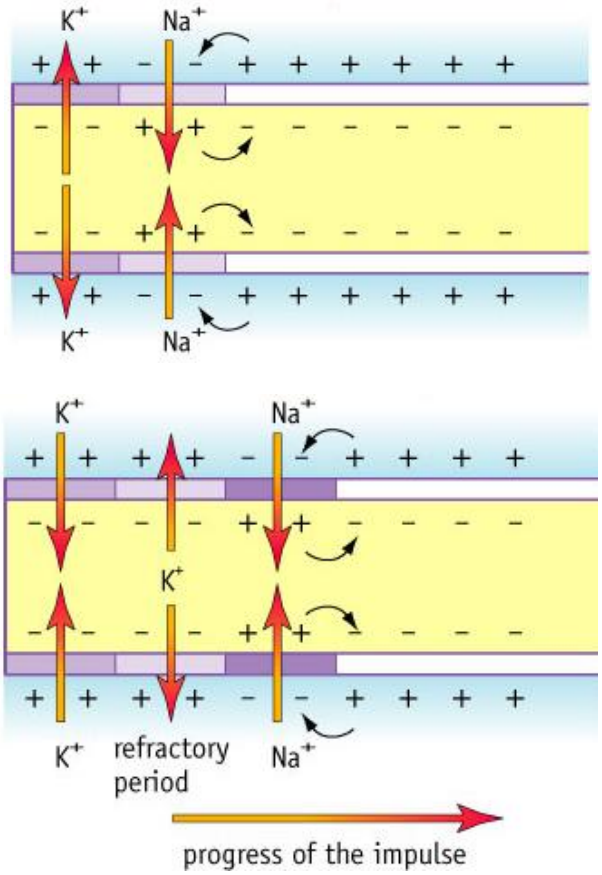

Fig. 11.4. The propagation of action potential along an unmyelinated axon

An important physical property of the axon membrane is the change in sodium conductance due to activation. The higher the maximum value achieved by the sodium conductance, the higher the maximum value of the sodium ion current and the higher the rate of change in the membrane voltage. The result is a higher gradient of voltage, increased local currents, faster excitation, and increased conduction velocity. The decrease in the threshold potential facilitates the triggering of the activation process. Conduction speed can be increased by reducing the internal resistance of the axon. Impulse transmission can be speeded up by increasing the diameter of the axon. However, there are limitations on the size of an axon. Transmission speed can reach 25 m per sec if the diameter of the unmyelinated axon is 1 mm.

11.5. PROPAGATION OF ACTION POTENTIAL ALONG A MYELINATED AXON

The evolutionary need for the fast and efficient propagation of electrical signals in nervous system resulted in appearance of myelin sheaths around neuronal axons. The myelin sheath is not continuous but divided into sections with the size of 2–3 mm, separated at regular intervals by the nodes of Ranvier with the length of 1μm. A typical human nerve might contain twice as many unmyelinated fibers as myelinated. The myelin gives a faster impulse conduction speed for a given axon radius.

A myelinated axon, surrounded by the myelin sheath, can produce a nerve impulse only at the nodes of Ranvier. This myelin sheath makes the axon impermeable to ions so they are unable to diffuse between the tissue fluid and the neurone, so action potentials cannot be generated by the myelinated regions (it acts as an insulator). Action potentials can only be generated at the nodes of Ranvier, so the local currents involved in nerve impulse transmission flow over longer distances. An action potential at one node of Ranvier causes inwards currents that depolarize the membrane at the next node, provoking a new action potential there; the action potential appears to «hop» from node to node. Thus action potential seems to «jump» from node to node, as illustrated in fig. 11.5. Since the intervening parts of the axon membrane do not have to be successively depolarised it takes less time for the action potentials to pass from node to node. This results in nerve impulse transmission that is much faster, the consequence of which is that smaller myelinated nerves can transmit impulses much faster than larger unmyelinated ones (120 m/sec compared to 25 m/sec along unmyelinated axson). Another advantage of this is that energy is saved as sodium potassium pumps are only required at specific points along the axon. Such a propagation is called saltatory conduction. The process of excitation and conduction in myelinated nerve fibers is characterized by its discontinuous and saltatory features.

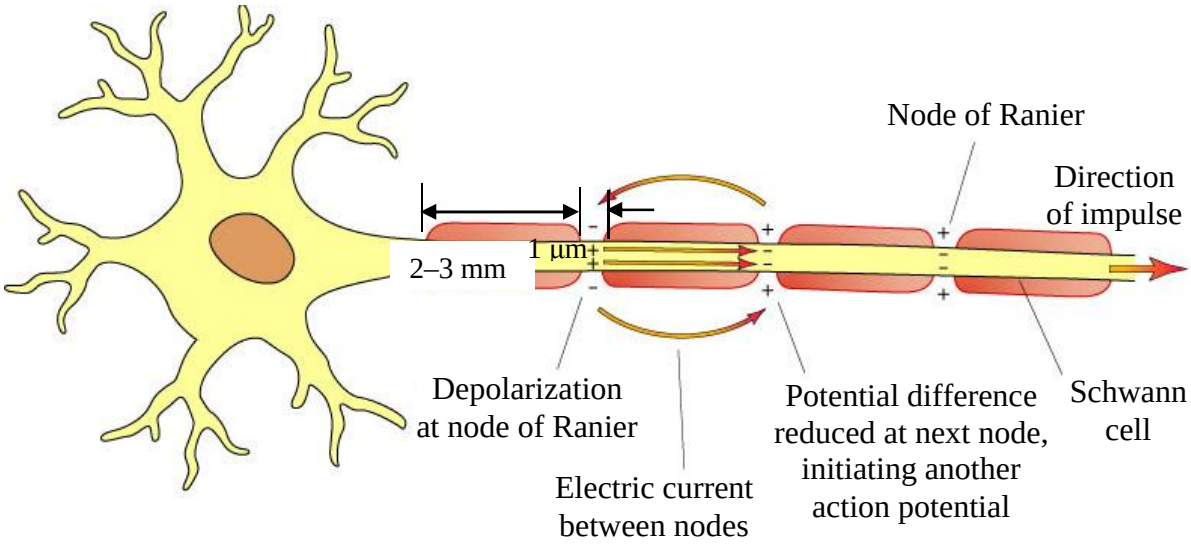

Fig. 11.5. Propagation of action potential along a myelinated axon

The cytoplasm of an axon is electrically conduction and because myelin inhibits charge leakage through the membrane, depolarization at one node of Ranvier is sufficient to elevate the voltage at a neighboring node to the threshold for action potential initiation. Even if one node is damaged, transmission can still effectively bypass that node. Nodes of Ranvier contain a significantly higher density of voltage gated sodium channels than is found in unmyelinated axons (4 orders of magnitude higher).

***Questions*:**

1. How are resting membrane potential generated?
2. Obtain the Nernst Equation.
3. What ions specify the cell membrane potentials? Write the Goldman-Hodgkin-Katz voltage equation. What does the Goldman-Hodgkin-Katz voltage equation describe?
4. What is the condition of cell excitement?
5. What processes occur in cell membrane during action potential generation?
6. Characterize depolarization phase and repolarization one. Give the graph for action potential.
7. What determines the sodium channel permeability?
8. What are the refractory periods? Describe the types and duration of the refractory periods for different cells.
9. Describe the propagation of action potential along an unmyelinated axon.
10. Characterize the propagation of action potential along a myelinated axon.

Chapter 12. ELECTRICAL FIELDS OF THE ORGANS AND TISSUES. METHODS OF THEIR REGISTRATION

12.1. ELECTRICAL FIELD AND ITS CHARACTERISTICS

The fundamental unit of electric charge (e) is the charge carried by the electron and its unit is coulomb. Electron e has the charge magnitude $1{,}6 \times 10^{-19}$ Coulomb (**C**). In nature, the electric charge of any system is always an integral multiple of the least amount of charge. It means that the quantity can take only one of the discrete set of values. The charge, $q = ne$ where n is an integer. Electric charges can neither be created nor destroyed. According to the law of conservation of electric charge, the total charge in an isolated system always remains constant. The total electric charge of a system is equal to the algebraic sum of electric charges located in the system.

When the charges are likely there is a repulsive force between them and, opposite, when the charges are unlikely, there is attractive force between them. The force between two charged bodies was studied by Coulomb in 1785. Coulomb's law states that the force of attraction or repulsion between two point charges is directly proportional to the product of the charges and inversely proportional to the square of the distance between them. The direction of forces is along the line joining the two point charges. Let q_1 and q_2 be two point charges placed in air or vacuum at a distance r apart (fig. 12.1).

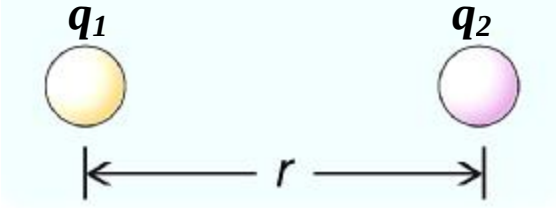

Fig. 12.1. Two point charges q_1 and q_2 placed in air or vacuum at a distance r apart