Garbuzova V.Yu., Obukhova O.A.

The General and Cellular Basis of Medical Physiology

CONTENTS

1 PHYSIOLOGY AS A SCIENCE

Physiology (*physis* – nature, *logos* – science) – is the science about general laws of functioning of living organisms and their parts.

There are many different species of living organisms in the nature, which functioning is significantly different. Therefore, the physiology is divided into several independent sciences: plant physiology, physiology of microorganisms, animal physiology and human physiology (fig. 1.1). The object of the study of human physiology is the human body, features of functioning of which depends on how healthy or sick this organism. So human physiology can be divided into 2 sciences: normal and pathological.

Physiology studies the vital functions of a healthy human body and pathological - sick.

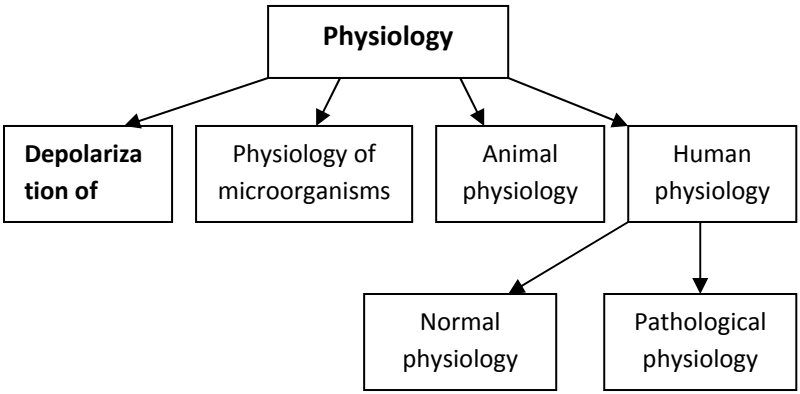


Figure 1.1 – Areas of physiology

Link normal physiology with other sciences

Physiological patterns of functioning of living organisms based on data about macro-and microscopic structure of organs

and tissues, biochemical and biophysical processes that are carried out in cells, tissues and organs.

In the structures of the body are carried out physical and chemical processes that are the subject of study of biophysics and biochemistry. Physical and chemical processes are the basis of the functions that they study physiology (fig. 1.2). Therefore, to clarify the physiological mechanisms is based on the anatomy, histology, biochemistry, biophysics and other disciplines. Physiology synthesizes the knowledge of other disciplines, combining them into a unified system of knowledge about the body. On the other hand, the physiology is the basis for the study of other health sciences such as pathophysiology and clinical disciplines. Revealing the basic mechanisms that ensure the existence of the whole organism and its interaction with the environment, physiology makes it possible to determine the causes, conditions and nature of violations of these mechanisms under conditions of disease. It helps to identify ways and means of influence on the body, which allow normalizing impaired function, restoring health.

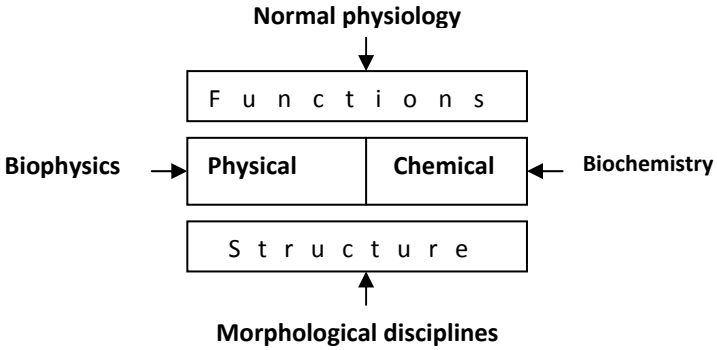


Figure 1.2 – Link normal physiology with other sciences

The value of normal physiology

A general theoretical importance of physiology is that man (even an average) was always curious to know how to work her heart, how she breathes, how digested nutrients and how energy is produced. Answers to these questions gave her physiology. In medicine, physiology general theoretical significance lies in the fact that it is the basis for the study of other disciplines (such as pathophysiology).

1. The practical significance. Physiology is one of the most important disciplines in the preparation of a doctor. Most diseases are manifested primarily by the dysfunction, because without knowledge about the functioning of a healthy body can not diagnose illness, identify ways of treatment, preventive measures, to correct and prevent disease.

2. The work of physician assesses the severity of illness by the largest deviation from the normal physiological functions. Physiological research is the basis of clinical diagnosis, an important method of evaluating the effectiveness of treatment and disease prognosis. Studying the functions of various organs and systems allow to simulate these functions using the devices and machines (apparatus of artificial respiration and blood circulation, the apparatus for hemodialysis, apparatus for defibrillation, the device for hyperbaric oxygenation, etc.).

Basic concepts of normal physiology

1. **Function** – is a form of living structure.

For example, the function of muscle tissue is contraction, function of nervous tissue - the generation of impulses, etc.

2. **The functional unit** – is the smallest group of cells, united to perform a specific function (nephron, motor unit, etc.).

The value of functional units:

• provide continuous operation without fatigue (until some functional units are working, the rest - rest. In this mode of authority may work for a long time, without fatigue);

• changes in the intensity of the function being performed, depending on the needs of the body (the work involved different numbers of functional units);
• provide compensation for damage (intact functional units are beginning to work actively).

3. Physiological systems - the union of the organs for a specified function (blood system, circulatory system, the system of external respiration, etc.). The physiological system is the concept of sustainable. Once disturbed the functioning of one of the bodies, which is part of the system is disturbed or even impossible the functioning of the system.

4. Operating System - a temporary union of the organs and physiological systems for biologically useful effect to the body (gas transportation system - combining the systems of blood, circulatory, respiratory; excretory system - combining the systems of external respiration, digestion, kidneys, skin, etc.; thermoregulatory system - combining the systems of external respiration, circulation, skin, muscles, etc.). A functional system is a dynamic concept. Once achieved the desired result and the biological needs of the body is satisfied, the functional system breaks down.

5. A functional state - the state of biological structures and functions of the organism as a whole at a particular time (fig. 1.3).

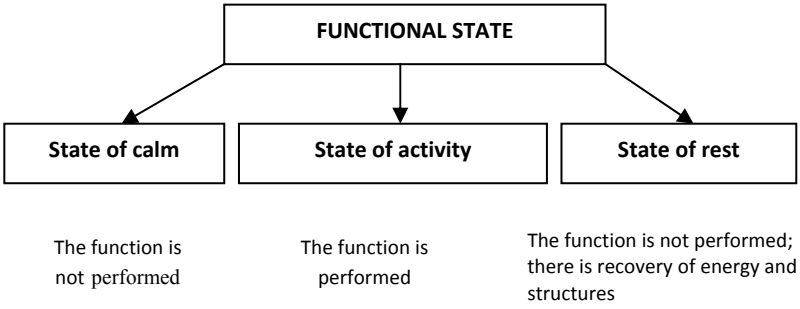


Figure 1.3 – Functional state of biological structures

The concept of a function at different levels of biological organization

Function – is a form of activity which is typical for a living structure.

Elementary structure of a living organism is a cell. So, actually, physiological functions begin from the cellular level. However, the term "function" is often used when dealing with the activities of those structures that make up the cell.

The basic level of biological organization:

1) pre cell 2) cell 3) tissue; 4) organ, 5) system, 6) the body as a whole.

Pre cell (subcellular) level – is a level of structures that make up the cell. This level, in turn, has the following hierarchy:

1 *Micromolecular level* form electrolytes (Na^+, K^+, Ca^{2+}, Cl^-, HCO^-, SO^{2-}, PO^{3-}, etc.), water, microelements (Cu, Fe, Zn, Mn, Co, Mo, Se, etc.), simple organic compounds (monosaccharides , amino acids, lipids, nitrogenous bases, etc.).

2*Macromolecular level* is form proteins, nucleic acids, polysaccharides.

The role of these substances is studied in detail in the course of physical and colloid chemistry, biochemistry.

3 *Supramolecular level* is forms membranes, ribosomes, chromatin, microtubules and microfilaments.

The role of these components of the cells studied in detail in the histology course

4 *Organoid level* is represented by cellular organoids - mitochondria, Golgi apparatus, endoplasmic reticulum, lysosomes, nucleus, and others.

Cellular level. It is at this level begins to realize the concept of "function".

Elementary cell function:
1) Generation and conduction of electrical impulses (neurons, muscle cells, some types of secretory cells).
2) Contraction (muscle cells, endotheliocytes).
3) Migration and mobility (leukocytes).
4) Endocytosis.
5) Exocytosis.
6) Division.
7) Transportation substances.
8) Biochemical work (hepatocytes, adipocytes, leukocytes).

Tissue level. There are four types of the tissue in the organism: nervous, muscular, epithelial, connective. Details of their functions are studied in the course of histology, we note only the basic.

The functions of nervous tissue:

1. Generation and conduction of the electrical impulses.
2. The formation of signaling substances (neurotransmitters, neuromodulators, neurohormones).

The function of muscle tissue is contraction.

The functions of epithelial tissue:

1) Barrier function. Separation of environments is by establishing barriers of epithelial cells connected by close contacts (such as between the epithelial cells of the mucous membrane of the stomach, intestines).
2) Transport function. Oxygen and carbon dioxide is transported throughout the lung epithelium. A gut epithelium absorbs amino acids, glucose and other substances.
3) Secretory function. Epithelial cells make exocytosis of the mucus, which is formed, for example, by the special mucous cells of the epithelium of the stomach, genital tract, epithelial cells of intestines, trachea, bronchi, and proteins (hormones, enzymes, growth factors) that are formed by

the endocrine cells.

4) Endocytosis. Most epithelial cells are able to absorb cholesterol and lipoproteins, transferrin by the way of the receptor-mediated endocytosis. Renal tubular epithelium is involved in pinocytosis.
5) Protective. Epithelial tissue protects the body from damaging action of physical and chemical environmental factors.

The functions of connective tissue:

1) Trophic. Ensuring the supply of elements of the parenchyma.
2) Protective. Connective tissue is involved in the creation of biological barriers, phagocytosis, reaction of cell and humoral immunity.
3) Support. Connective tissue forms the stroma for histological elements of the parenchyma, provides strength of the skin, forms capsules of the organs and can withstand significant mechanical loads.

Organ level includes separate organs: heart, blood vessels, kidneys, lungs, stomach and others.

The system level consists with physiological systems: blood, circulatory, respiratory, digestive, selection, reproduction, nervous system, musculoskeletal and endocrine. The functions of these organs and physiological systems will be the subject of detailed study in the physiology course.

The organism level as a whole. At this level characteristic functions is that ensure the interaction of the organism with the environment. The most important among them are:

1) Functions that ensure receipt of information about environment;

2) Functions that provide analysis of this information;
3) Functions that provide behavioral reactions that underlie in the base of adaptation to environmental conditions.

Basic functional properties of the body:

1 Metabolism and energy between the organism and the surrounding environment is a phenomenon that is the basis of life. In detail this property of the organism being studied in the course of biochemistry.

2 Self-regulation – is the body's ability to carry out the regulation of physiological functions.
There are two mechanisms of regulation of functions:
• nerve (by means of the nervous system);
• humoral (by means of chemicals dissolved in body fluids).

3 Homeostasis – is the constancy of internal environment.

In 1878 Bernard C. proposed postulate that all life processes have only one purpose - to maintain the sustainability of living conditions in our domestic environment. In 1929 William Cannon launched the term "homeostasis". Translated from the Greek *homois* - like, the same; *stasis* - a condition, fixity.

The normal life and activity of cells in multicellular organisms requires the sustainability of the conditions of the internal environment, the environment surrounding the cell (blood, lymph, interstitial fluid).

The need for sustainable living conditions was, in fact, the factor that caused the association of individual cells in multicellular organisms.

This association had a number of consequences for cells. On the one hand, the body created for the cells optimal conditions for existence - homeostasis, which has played a

positive role with regard to the possibility of survival. On the other hand, the cell itself was forced to accept a share of care to establish homeostasis for the entire organism. This led to the specialization of cells and, thus, the loss of their "freedom."

The main parameters of homeostasis:

- Constancy of body temperature (thermal homeostasis).
- Sustainability of osmotic pressure (osmotic homeostasis).
- Sustainability of the ion (ion homeostasis).
- Sustainability indicators of acid-base balance (acid-base homeostasis).
- Sustainability of the water in the body.
- Sustainability gas composition (gas homeostasis).
- Sustainability of the chemical composition (chemical homeostasis).
- Sustainability antigenic structure (antigenic homeostasis).

4 Adaptation – is adaptation of an organism to environmental conditions.

The purpose of adaptation – is maintaining homeostasis of the organism in an environment that is constantly changing.
By the mechanism are distinguished:

- Immediate adaptation;
- Long-term adaptation.

Immediate adaptation is very fast due by the mechanisms and structures that exist at this time. For example, the vessels are narrowed at low temperatures, heart rate increases during the exercise.

Long-term adaptation is carried out gradually by increasing the number of structures involved in adaptation. For example, regular physical exercise increases skeletal muscles mass, the number of red blood cells are increasing during the stay in the mountains.

5 Growth, development, and reproduction
This physiological property provides self-healing and self-reproduction of organisms.

An irritability - the ability of biological structures to move from a state of calm in the active state under the influence of various factors (irritants).

Irritant – is a factor that causes the transition of the biological structure from physiological rest in active status.

Classification of the irritants:

- By the nature of power:
  - Physical;
  - Chemical;
  - Biological;
  - Social.
- By the biological features:
  - Adequate – stimuli to which the biological structure is adapted. For example, a light to the eye, the sound to the ear;
  - Inadequate – stimuli to action of which biological structures are not adapted. For example, the effect of mechanical factors (impact) on the receptors of the eye, the effect of chemicals on tactile skin receptors.
- By the power, the intensity of the action:
  - sub-threshold - stimuli that do not cause biological reactions;
  - threshold – stimuli that are beginning to cause a biological response;
  - suprathreshold – stimuli whose power exceeds the power threshold stimuli.

Irritation – the process of effect of the stimulus on the biological structure.

The biological response – a response of biological structures to the action of the stimulus.

There are such types of biological reactions:

• Local (biological reaction that occurs at the site of irritation and does not extend to adjacent biological structures);

• Common (biological response that extends to adjacent structures).

A common biological response called *excitation*.

Excitability – is ability of biological structures to excitation.

Excitable structures – is structure which is characterized by excitability.

In excitable structures include:

1) Nerve cells and nerve fibers;
2) Muscle fibers;
3) Some types of glandular cells.

The laws of the irritation

I The law of power relations (the law of power)

If is greater power of the stimulus, then is greater (up to certain limits) biological response.

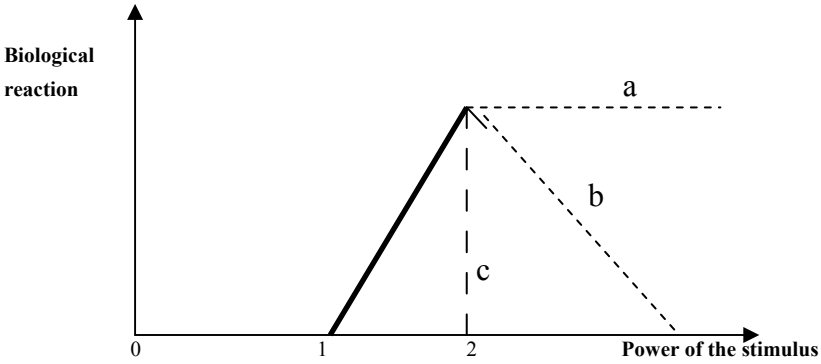


Figure 1.4 – The law of power relations

0 - 1 – subthreshold is range of the powers.

1 - the minimum stimulus power, able to cause minimal reaction - irritation

threshold.
For excitable structures characteristic of this pattern: the smaller the threshold of irritation, the greater excitability of the structure and vice versa.
1 - 2 – submaximal range of the powers, which employs law of thepower relations.
2 - maximum power of the stimulus can cause the biggest reaction.
2 - ∞ – supermaximum range of the powers.
In this range of powers available such variants of the answer of the biological structures:
a - stored maximum response;
b - the intensity of biological response is reduced;
c - the biological structure is destroyed, any response is absent.

II The law "All or Nothing"

On the effect of subthreshold stimulus biological structure does not answer ("nothing"). On the effect of stimulus of the threshold power occurs once the maximum response ("all"). Further increase in stimulus force did not cause increased biological response.

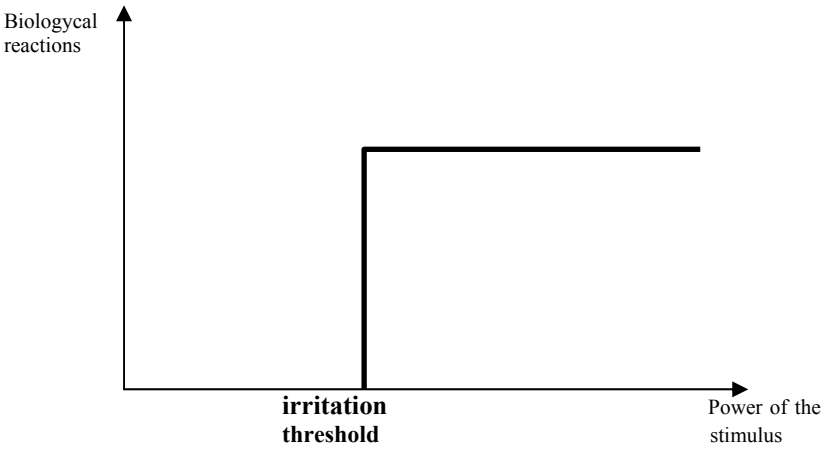


Figure 1.5 – The Law of "All or Nothing"

III The law of duration of the stimulation (the law "Power of Time")

The greater power of the stimulus, the less time is needed so that there was a biological reaction.

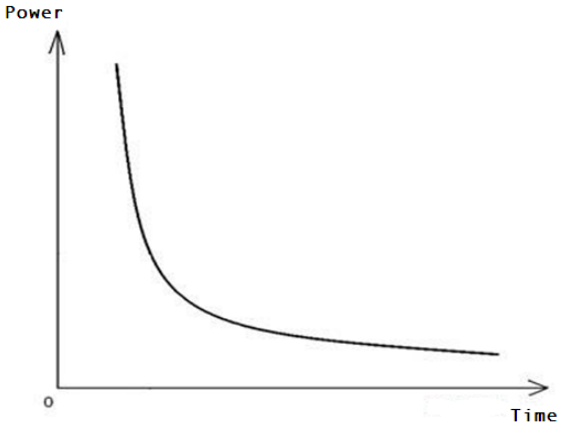


Figure1.6 – The law of "Power of Time"

2 PHYSIOLOGY OF THE CELL. FUNCTIONAL PROPERTIES OF CELL MEMBRANES

The cell is an elementary biological unit. The cell level provides an independent existence and implementation of all major biological functions. Most of the physiological processes in the cell occurring involve the cell membrane. Membranes perform the following functions in the cell:

- Structural. Create the structure of cells and their organoids.
- Isolation. Provide selective permeability of cells to substances.
- Create a gradient of concentration of substances between the structures and environment that surrounds them.
- Regulate the activity of processes that occur in specific structures and cells in general.

Cell membrane (plasmolemma) – is a membrane that separates contents of cells from the extracellular fluid. Its thickness is 7.5 - 10 mkm.

Structure of cell membrane

Modern model of the cell membrane is a liquid-mosaic model, proposed in 1972 by Singer and Nicholson (fig. 2.1). The authors of model called the membrane "lipid sea, where protein icebergs float."

So, according to the mosaic model membrane consists of the following components:

- Lipid component (42%);
- Protein component (55%);
- Carbohydrate component (3%).

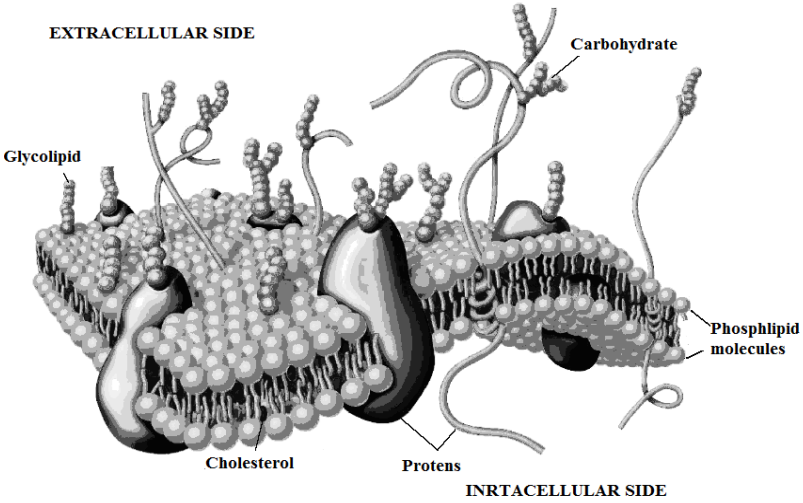


Figure 2.1 – Liquid-mosaic model of cell membrane

Lipid component is based membrane. It performs two main functions:

- barrier function (separation of intracellular contents of cells from their microenvironment, transport of substances);
- matrix function (is the matrix in which there are many membrane proteins).

Lipid film is a double layer of lipids, the so-called bilayer, represented by phospholipids and cholesterol.

Phospholipids molecule is consisting of hydrophilic heads and hydrophobic tails (fig. 2.2). The head is ¼ of molecules of phospholipids. It can be negatively charged or neutral (often neutral, as neutral head easily packed in a film, and negative repel). The structure of the head is including the nitrogen base and phosphoric acid. Tails constitute ¾ of the length of phospholipids. One molecule of phospholipids has two tails. The composition of tails are higher fatty acids – saturated (palmitic, stearic) and unsaturated (linoleic, linolenic,

arachidonic).

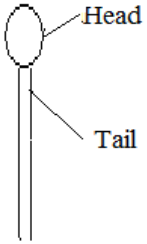


Figure 2.2 – Schematic representation of the phospholipids molecule

Phospholipids' film – is a liquid, which for normal functioning must have a certain viscosity. Normally, the membrane viscosity is the viscosity of olive oil. Normal viscosity is provided by certain ratio of saturated and unsaturated fatty acids: saturated increase viscosity while unsaturated – reduce viscosity.

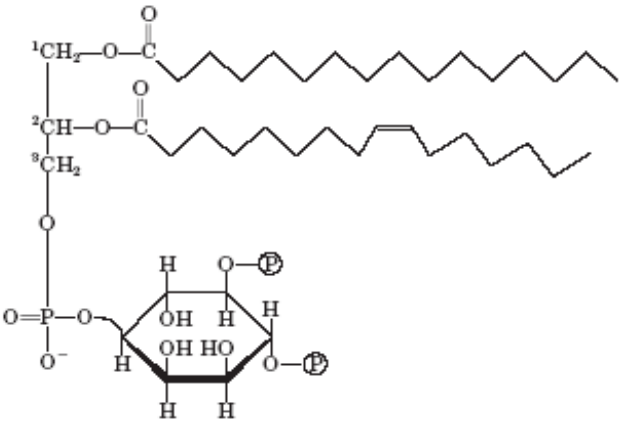


Figure 2.3 – Formula of the phospholipids

Phospholipids within the cell membrane are not rigidly

fixed. They move or within one monolayer (lateral diffusion), or from one monolayer to another (flip-flop).

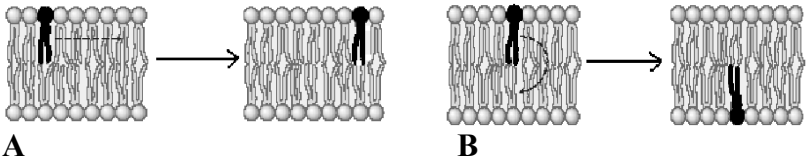


Figure 2.4 – Types of movements in membrane phospholipids: A - lateral diffusion, B - flip-flop.

Cholesterol - monatomic alcohol, derivative of the cyclopentanperhydrofenantren. Its molecule doesn't contain any long straight chains, but consists of 4 rings (fig. 2.5). Cholesterol molecule, like other lipid molecules have polar and non-polar parts so well embedded in the lipid cell membrane ensembles. Plasma membranes contain a significant amount of cholesterol. For example, in plasma membranes of liver cells it constitute about 30% of membrane lipids

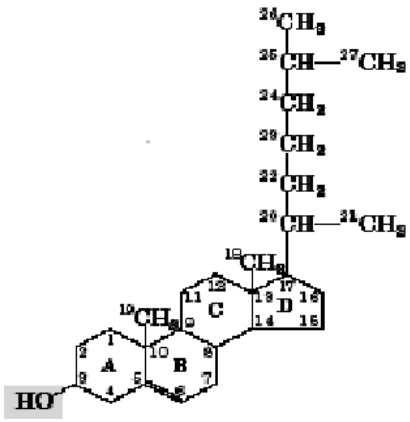


Figure 2.5 – Formula of the Cholesterol

The values of cholesterol for membrane function are very versatile.

- Cholesterol regulates the aggregate state of the bilipid film. If the density of the cell membrane increases, it dilutes it. If the membrane becomes liquid, it rather makes it denser.
- Cholesterol is a membrane damper. Lipid bilayer chains are in state order so random movements of one of them are inevitably transmitted to the others. Cholesterol arranged between phospholipids, blocks this transfer, so co-operative movements quickly decay and the order in membrane is stored.
- Cholesterol provides membrane electroisolation properties.

Protein component. Molecules of the membrane proteins are floating in the lipid membrane matrix like icebergs. They are divided into 2 groups:

1) Integral proteins - are proteins that pass through the membrane (by chemical structure is mainly glycoproteins).

2) Peripheral proteins – are proteins that do not penetrate inside the membrane but attached to its inner or outer surface.

Functions of membrane proteins:

- Transport. Implementation of the transport of substances through the membrane is provided by the protein-channels, proteins-carriers and protein-pumps;
- Catalytic. Catalysis of biochemical reactions is performed usually by the peripheral proteins: endoenzymes, which act on the inner surface of the membrane and ectoenzymes which act on its outer surface;
- Receptor. It is based on specific interactions of membrane proteins with different ligands: mediators, biologically active substances, hormones, immunoglobulins,

complement components, etc.;

- Antigenic. Lies in the implementation of immune reactions;
- Structural. Proteins provide the support of the some structures in the cells. For example, spectrin, glycophorin et al.;
- Implementation of intercellular interactions is provided by adhesive proteins, integrin, selectin et al.

Carbohydrate component of cell membranes is represented by glycocalyx which is composed of carbohydrate residues of membrane glycoproteins and glycolipids and extracellular proteoglycans. Glycocalyx thickness is about 50 nm. Carbohydrates of the glycocalyx have a large number of anionic groups which determines their basic functions.

Functions of glycocalyx:

- Creates a negative charge outside the cell. There are repulsive forces between cells that are in fluid (e.g. blood) with this charge , and they do not stick to each other;
- Provides the intercellular interaction. In tissues glycocalyx of one cell can merge with another glycocalyx, forming intercellular contacts;
- Deposition of extracellular cations includes Ca^{2+}. Thanks to polyanionic nature of the glycocalyx, it can bind large amounts of Ca^{2+} and thus serve its depot.

The main differences between the chemical composition of the cell content and extracellular fluid

There are significant differences in chemical composition of intracellular environment and extracellular fluids. These differences are reflected in Table 2.1.

Table 2.1

	Extracellular fluid	Intracellular fluid
Na^+	142 mEq/L	10 mEq/L
K^+	4 mEq/L	140 mEq/L
Ca^{2+}	2,4 mEq/L	0,0001 mEq/L
Mg^{2+}	1,2 mEq/L	58 mEq/L
Cl^-	103 mEq/L	4 mEq/ L
HCO_3^-	28 mEq/L	10 mEq/L
PO_4^{3-}	4 mEq/L	75 mEq/L
SO_4^{2-}	1 mEq/L	2 mEq/L
Proteins	5 mEq/L	40 mEq/L
Glucose	90 mg%	from 0 to 20 mg%
Amino acids	30 mg%	200 mg%
pO_2	35 mm Hg	20 mm Hg
pCO_2	46 mm Hg	50 mm Hg
pH	7,4	7,0

There is a constant exchange through the cell membrane of substances between the intracellular and extracellular sectors. The basis of this exchange is the mechanisms of transport of substances through the cell membrane.

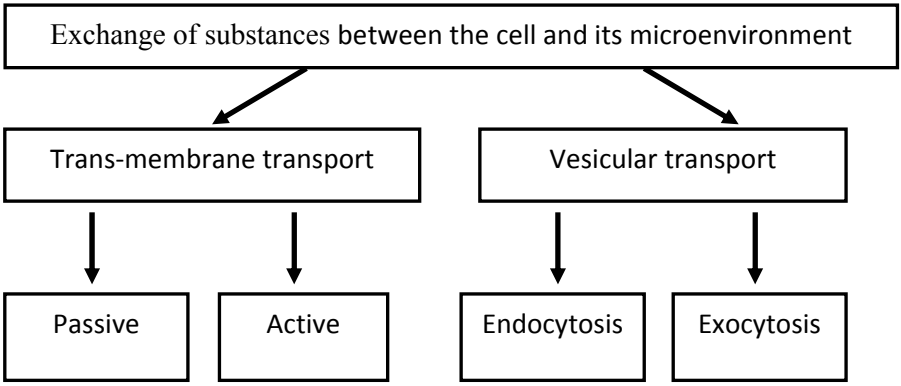


Figure 2.6 – Exchange of substances between the cell and its microenvironment

Vesicular transport – is a transport of substances by the vesicles. Depending on the direction there are of two kinds:

- • endocytosis (transport in the cell);
- • exocytosis (transport out of the cells).

There are two types of endocytosis:

- Phagocytosis (absorption of solids);
- Pinocytosis (absorption of liquids in the form of drops).

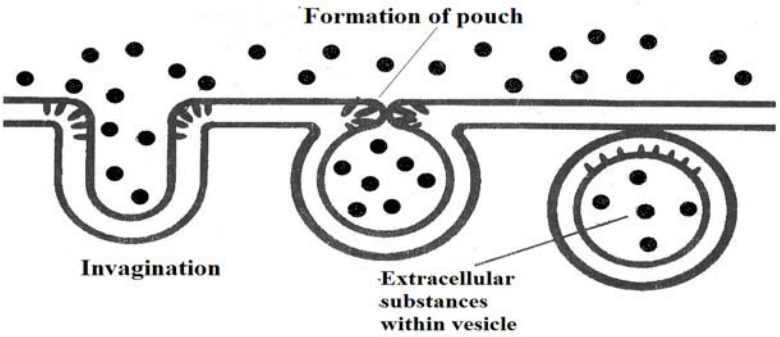


Figure 2.7 – Endocytosis

A substance that is close to the surface of the cell membrane is absorbed in it. Then the membrane is drawn inward and its edges merge. As a result, is formed endocytosis vesicle that breaks away from the membrane and migrates into the cell (fig. 2.7). Often endocytosis vesicles cluster together in one big vesicle and merge with lysosomes containing enzymes for digestion of substances that are transported. Hydrolysis products are used by cells for their own needs. The first two stages of endocytosis occur without energy consumption while the following require ATP energy.

Most cells synthesize macromolecules (hormones, blood proteins, enzymes) "for export". In addition, in the process of metabolism metabolites are formed. Elimination of these secretions and excretions by means of vesicles is called exocytosis.

There are two types of exocytosis:

- Secretion (discharge from the cells of hormones, proteins, enzymes);
- Excretion (discharge from the cell metabolic products).

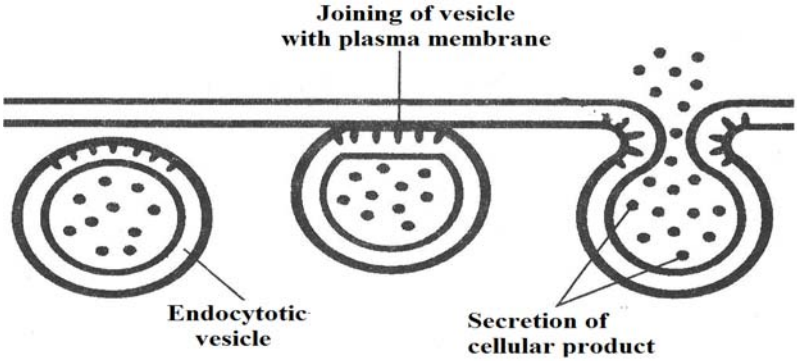


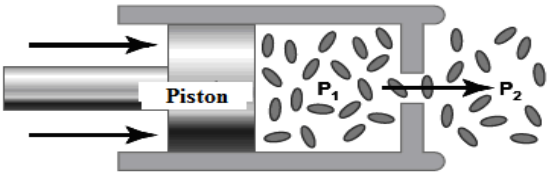
Figure 2.8 – Exocytosis

Exocytosis vesicles approach the inner surface of the cell membrane and contact with it by using special proteins. Shell of the vesicle merges with the membrane and its contents placed in the extracellular space (fig. 2.8).

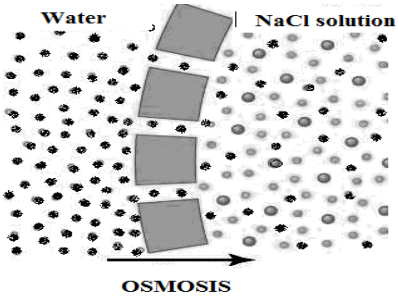
Transmembrane transport - a transport of substances through the membrane and through all its layers.
Transmembrane transport is of two kinds:

- • passive;
- • active.

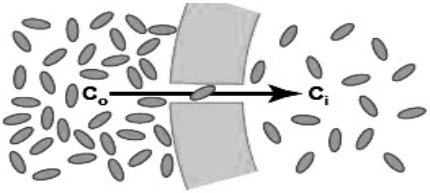
Passive transport – is a form of transport carried out according to the gradients that exist in the cell.
There are 3 types of passive transport:
• **filtering** (transport by hydrostatic pressure gradient).



• **osmosis** (transport by osmotic pressure gradient)



• **diffusion** (transport by the concentration gradient, electric charges, etc.).



The main diffusion is lightweight and simple.

Simple diffusion – diffusion without using carriers. It may be through lipid bilayer and through the protein-channels.

Fat-soluble compounds (alcohols, oxygen, carbon dioxide, nitrogen) and water well diffuse through lipid bilayer. Water is not fat-soluble compound but it is well diffuses through the lipid film because its molecule has a small size and high kinetic energy. The intensity of diffusion of water across

cell membranes is very high. For example, through the erythrocyte membrane every second diffuses into both sides the volume of water that is 100 times greater the volume of the erythrocyte. Transport of water through the lipid bilayer is due to "the theory of temporary voids." According to it by the constant movement of tails of phospholipids in the membrane formed temporary voids through which water molecules pass.

NB: fat-soluble compounds whose diameter is greater than the diameter of water molecules and ions are not well diffused through the lipid bilayer. With increasing size of molecule diffusion ability of the substance decreases sharply. Thus, the diameter of a molecule of glucose is greater than the diameter of water molecules in 3 times and the rate of diffusion of glucose is less than that of water in 100 thousand times. Ions are practically not diffused through the lipid bilayer as in the aquatic environment having the hydration shell, which significantly increases their diameter. The presence of the charge of ions prevents diffusion; this charge interacts with the electric charge of the polar heads of phospholipids.

There are protein-channels for the transport of ions in membrane (integral proteins embedded in the membrane).

Protein-channels have the following properties:

1) Selectivity – the ability to selectively pass through a certain compounds. Depending on the characteristics of the protein-channels, they are not selective (can pass different compounds) and selective (mostly miss one type of molecules). Selectivity of the channel may be absolute when the channel passes through one type of molecule and relative when the channel can pass through some other types of molecules. The selected channels are sodium, potassium, calcium, chloride and some other channels.

2) Presence and condition of gate mechanisms. Condition

of the channel depends on condition of the gate of the channel (gate closed - closed channel, gate opened - opened channel). The basis of opening and closing of the channel is a conformational change of the protein molecule. The reason for these changes can be two types of regulatory influences (electrical potential and chemicals). According to this we can distinguished two types of control of condition of the gates.

1 Potential dependent mechanism. Condition of the portal mechanism of the channel is controlled by the membrane electric potential. For example, when the nerve fiber membrane has a charge of -90 mV, sodium and potassium channels are closed and when this charge begins to decrease, the channels open (fig.2.9).

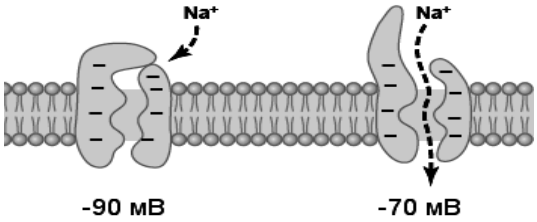


Figure 2.9 – Potential dependent mechanism of control of the gate

Channels in which the state of the gate depends on the potential of the membrane are called potential dependent channels

2 Ligand dependent mechanism. Condition of portal mechanism of the channel is controlled by certain chemical compounds – ligands.
During the interaction of the channel with chemical changes conformation of protein and the channel opens. For example, during the interaction of acetylcholine with sodium channels in muscle fibers, these channels are opened (fig. 2.10).

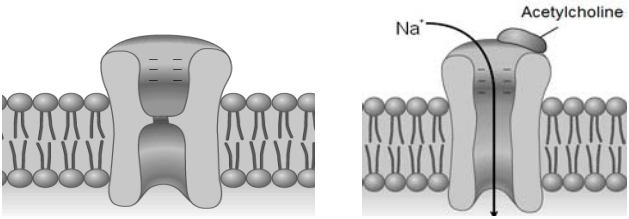


Figure 2.10 – Ligand dependent mechanism of control of the gate

Channels in which the state of the gate depends on the presence of certain chemicals are called ligand dependent (chemo-sensitive).

3 Kinetics of the channels is characterized by the speed of the passage of substances through the channel. Depending on these characteristics the channels are divided into fast and slow channels.

Facilitated diffusion - the movement of compounds within their concentration gradient with the participation of protein-carriers. The intensity of the facilitated diffusion is limited by the number of molecules of protein-carriers and kinetics of their binding with substances that are transferred (fig. 2.11).

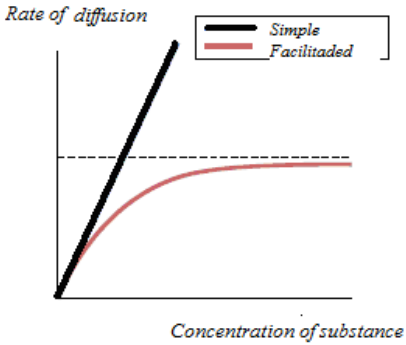


Figure 2.11 – Dependence of the intensity of the facilitated diffusion of number of protein carriers

Stages of facilitated diffusion:

• Specific binding molecule of the substance with the protein-carrier;

• Conformational changes of protein-carrier;

As a result of these changes disrupted communication of molecules with place of the binding occurs and compounds move freely on the other side of the membrane (fig. 2.12).

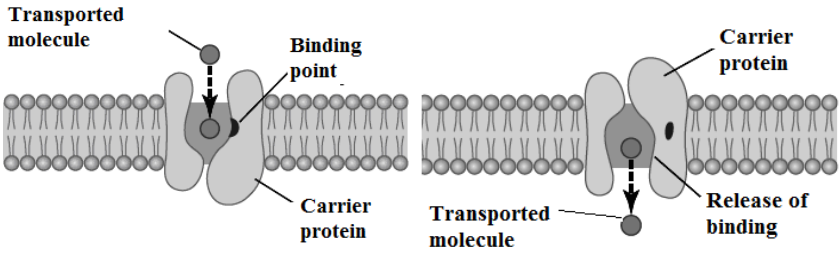


Figure 2.12 – The mechanism of facilitated diffusion

Glucose and most amino acids are transported by the mechanism of facilitated diffusion

Factors affecting the intensity of diffusion of substances through the cell membrane

1 Factors associated with the membrane through which the diffusion are:

a) Membrane permeability for some substance - speed of diffusion of the substance through the unit of area of membrane per unit of difference of concentration of substance (in the absence of electrical gradient or pressure gradients).

Membrane permeability depends on:

• Membrane thickness (the thicker the membrane the lower the permeability);

• Physical-chemical condition of the lipid membrane layer. This condition is determined by the chemical

composition of lipids of the membrane: saturated and unsaturated fatty acids. Unsaturated fatty acids provide the membrane liquid condition and increase permeability. Physical-chemical condition of the membrane is very sensitive to the temperature. When there is hypothermia, the membrane becomes "hardened" and their permeability decreases and vice versa.

• The number of protein-channels and protein-carriers per unit of area of membrane and their functional status (closed or open them);

b) the total area of the membrane through which the diffusion takes place.

2 Factors associated with qualities and condition of substance which diffuses through the membrane:

a) Solubility in lipids;

b) Temperature;

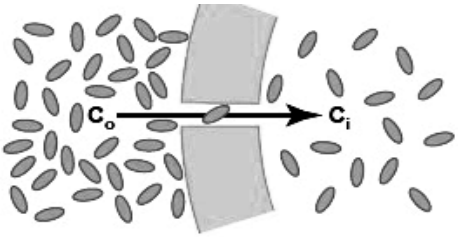
c) The presence of electric charge;

d) Molecular weight.

Influence of molecular weight on the speed of diffusion is ambiguous. If is higher the molecular of weight substances, then is the greater the velocity of the molecules and the greater the intensity of diffusion. On the other hand, increasing the diameter of molecules complicates the diffusion through protein channels (if the diameter of the molecule is larger than the diameter of the channel, diffusion through the channel stops).

3 Factors that drives the diffusion.

- Concentration gradient on both sides of the membrane;



The intensity of the diffusion of the substances is described by the Fick's equation

$$\frac{dm}{dt} = D \cdot \frac{S}{l} \cdot (C_1 - C_2)$$

$\frac{dm}{dt}$ - intensity of the diffusion ;

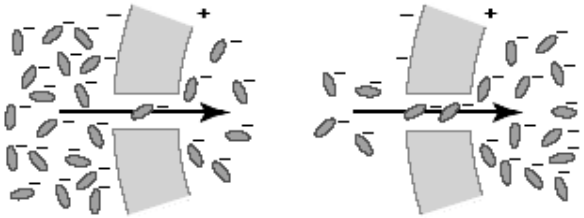
D – coefficient of the diffusion;

S – surface area of membrane through which the diffusion occurs;

l - membrane thickness;

C_1-C_2 – difference in concentrations of substances on both sides of the membrane;

- electric gradient;



- Gradient of hydrostatic pressure. Transport of substances which is by the gradient of hydrostatic pressure is called filtering. Since the pressure in the middle of the cell and extracellular environment is almost the same, filtering does not play an essential role in transport of substances through the cell membrane but is essential when it comes about the transport

through the vascular wall;

- Osmotic pressure gradient. This gradient is of great importance for the transport of solvents, especially water. Transportation for the osmotic pressure gradient is called osmosis.

Active transport – is a form of transport carried out against the existing gradients (concentration, electrical charge, pressure).

Depending on the source of energy used to carry out an active transport, it is divided into primary and secondary.

Primary active transport – is a mechanism of active transport that uses the energy of ATP or other macroergic compounds. It is through protein-pumps.

Each protein-pump consists of two components:

- protein-carrier which binds to a substance and transports it through the membrane;
- protein-enzyme - ATPase which can liberate energy of ATP and use it for conformational changes of the protein-carrier.

Examples of primary active transport is the Na^+-K^+-pump, Ca^{2+}-pump and H^+-pump. Consider the principle of the pump on the example of Na^+-K^+-pump.

Sodium-potassium pump – is a protein that carries Na^+ transport out of cells and K^+ transport in the cell. This mechanism operates in all cells.

Na^+-K^+-pump consists of two subunits: large (100 000) and small (55 000). Large subunit has 3 receptor site for binding of Na^+ ions on the inner surface of the membrane, 2 receptor binding sites of K^+ ions on the outer surface of the membrane and ATPase on the inner surface. Once the binding of 3 Na^+ ions and 2 K^+ ions occurs, the inner part begins the ATPase activity. The energy is released when ATP splitting goes to the

conformational changes of the protein-transporter and Na^+ is released from cells and K^+ goes into the cell (fig. 2.13).

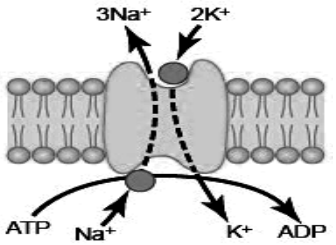


Figure 2.13 – Sodium-potassium pump

The value of Na +-K + - pump:

1 Provides a difference of the concentrations of Na^+ and K^+ in the cell and extracellular environment.

2 Creates an electric potential on the cell membrane. Electrogenesis of the pump associated with the unequal transfer of charge during its work (3 positive charges (3 Na^+) taken out with cells, and made 2 (2 K^+)). For one cycle of the pump cell loses one positive charge.

3 Compliance the sustainability of the cell's volume. How this pump would do not worked, the majority of cells would be edematous.

Secondary active transport (cotransport) – is a mechanism of active transport which directly uses the energy of concentration gradient of certain ions (usually ions Na^+) to transport substances. This gradient in turn creates primary active transport mechanisms and therefore also depends on the energy of ATP.

Secondary active transport is divided into two types:

• symport (transport of two substances in one direction);

• antyport (transport of substances in opposite directions).

Secondary active transport is carried out by specific protein-

carriers.

Symport. Consider the mechanism of symport on example of the sodium cotransport of the glucose. Protein-carrier which carries out this transport has two specific binding sites – for Na^+ and glucose. When one Na^+ ion and one molecule of glucose join, protein undergoes conformational changes resulting in Na^+ and glucose finding them in the cell (Fig. 2.14).

By the same mechanism occurs sodium cotransport of the amino acids occurs. There are 5 types of protein-carriers for transport of amino acids. Sodium cotransport of the glucose and amino acids is particularly intense in epithelial cells of intestinal and renal tubular epithelium.

In addition to these mechanisms of the cotransport in the cells, other forms of symport spread. For example, Na^+-K^+-Cl^- cotransport, K^+-Cl^- cotransport. In some cells there is a symport of ions of iodine, iron and urate ions.

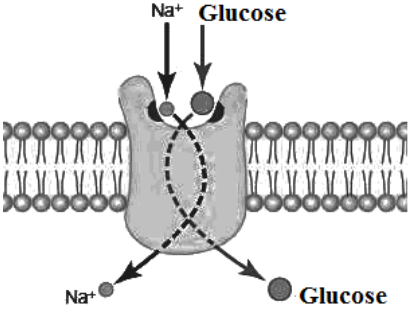


Figure 2.14 – Mechanism of the symport

Antyport (ion exchange mechanism). Consider a mechanism of antyport on the example of Na^+-Ca^{2+} exchange mechanism that is in almost of all cells. Protein-carrier which carries out this transport has two specific binding sites - on the outer surface for Na^+ and on the inside – for Ca^{2+}. When these ions join, protein undergoes conformational changes resulting

to the Na^+ to be placed in the cell and Ca^{2+} - outside the cell (fig. 2.15).

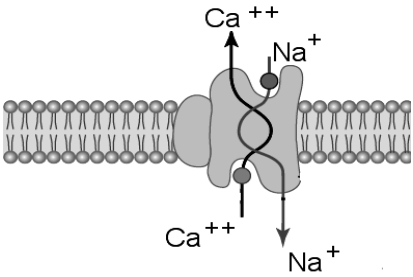


Figure 2.15 – Mechanism of the antyport

By the same mechanism, Na^+-H^+ exchange mechanism occurs which is in renal tubular epithelial cells, and Na^+-K^+, Ca^{2+}-Mg^{2+}, Cl^--HCO_{3-}, Cl^--SO_4^{2-} - exchange mechanisms.

3 RESTING POTENTIAL OF THE NERVOUS FIBRES AND MUSCLE FIBERS

There is a difference of electric potentials between the inner and outer surfaces of the plasma membrane of all cells. It is called the membrane potential and in excitable cells – resting potential.

Membrane potential (MP) – is a trans-membrane potential difference that exists between the inner and outer surfaces of the plasma membrane.

Resting potential (RP) – is a membrane potential of excitable cells that are at rest. In other words, RP – is a special case of membrane potential.

Methods of registering of the RP

Registration of RP is engaged by the electrodes. There are two methods of registering RP depending on their location.

I. *Intracellular removal of RP*. Carried is out by means of a glass electrode and a tip diameter of which is less than 1 mkm. Such electrodes pierce the cell membrane and enter in the cytoplasm. At the time of puncture the membrane potential difference is recorded by the device (voltmeter) (fig. 3.1).

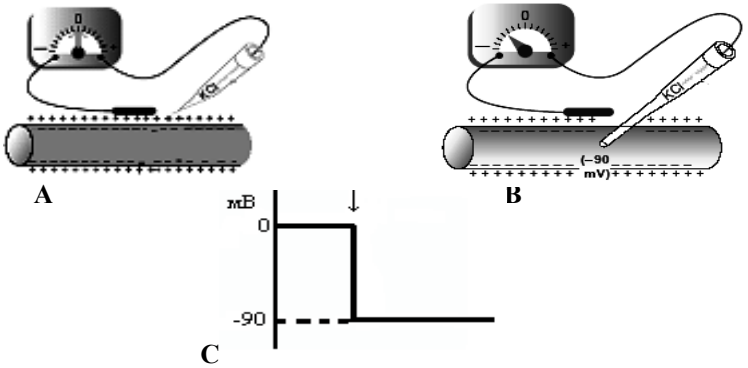


Figure 3.1 – Registration of intracellular membrane potential: A – before, B - after the entering of electrodes in the cell; C – recording of RP on the oscillograph.

II *Extracellular removal of RP*. Both electrodes are placed outside the cell in this method. The named method allows to register the potential damage and potential difference between intact and damaged areas of tissue. The damaged area is depolarized with respect to the area of intact (fig. 3.2).

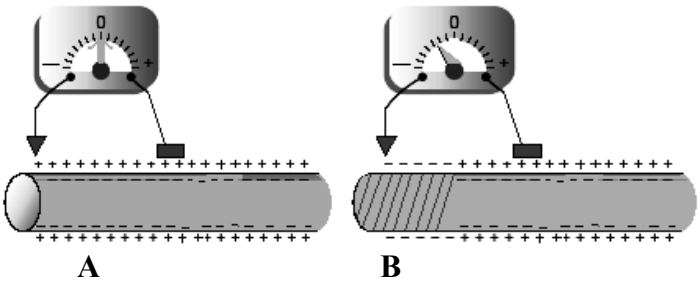


Figure 3.2 – Extracellular registration of membrane potential: A – intact nerve fiber, B - nerve fiber of the damaged area (shaded)

The main physical characteristics of the RP

1) *Polarity*. The inner surface of the membrane resting potential is electronegative with respect to "zero" of the Earth. In other words, the outer surface of the membrane is charged positively and the inner surface of the membrane - negatively.
2) *Sustainability of magnitude*. Value of the RP for particular structures (nerve fiber, muscle cells, neurons) is constant.
3) *Absolute value*. RP has the following values for different body structures: nerve fibers are -90 mV, skeletal muscle fibers are -90 mV, smooth muscles are -50-60 mV, and neurons of the central nervous system are -40-60 mV.

Under the influence of some factors the absolute value of RP is subjected to some changes. There are two types of changes the value of the RP - depolarization and hyperpolarization (fig.3.3).

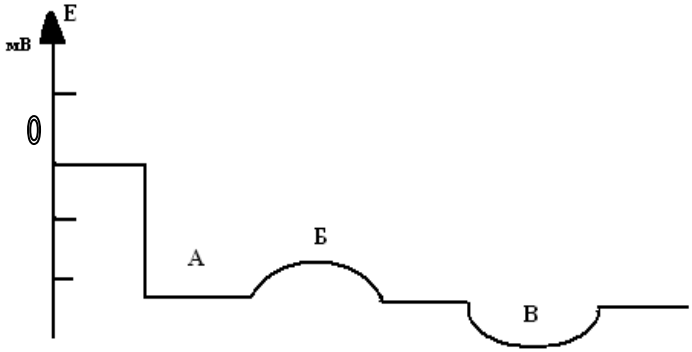


Figure 3.3 – Changes in the absolute value of the RP: A – resting potential; B – depolarization;C – hyperpolarization

Membrane *depolarization* – is a decrease and *hyperpolarization* - increasing the absolute value of the RP.

Ionic mechanisms for the origin of resting potential

The first hypothesis about ionic mechanisms of the origin of the membrane potential was proposed in 1896 by a representative of the Ukrainian school of physiologists Chagovets V.Y., who was the head of the physiology department at Kiev University of St. Vladimir.

Today, it is finally proved that the occurrence of membrane potential is associated with the diffusion of ions. To understand the phenomenon, imagine a cell in which the cytoplasm is replaced by the electrolyte solution, which consists of small particles of cations (e.g. potassium ions) and anions of larger particles (e.g. protein). Small particles of cations can easily diffuse through the pores of the membrane while the cell membrane is impermeable to anions. Place a cell filled with this electrolyte in an environment where it is missing or its concentration is much smaller than in the cell.

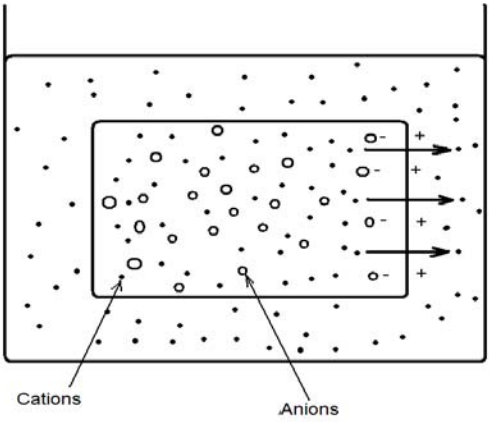


Figure 3.4 – Experience, which explains the ionic mechanisms of the RP.

In this case the share of cations (K^+) under the laws of diffusion will leave the cells in the environment by the concentration gradient and anions will remain in the cell because the membrane is impermeable to them. The transition of the cations from cells in the extracellular environment leads to what is on the inner surface of the membrane and creates an excess of K^+ ions ("+"sign appears), on the outer surface exactly the same number of anions increases (sign "-"). In other words, difference of the potential (i.e. the membrane potential) arises between the inner and outer surfaces of the membrane.

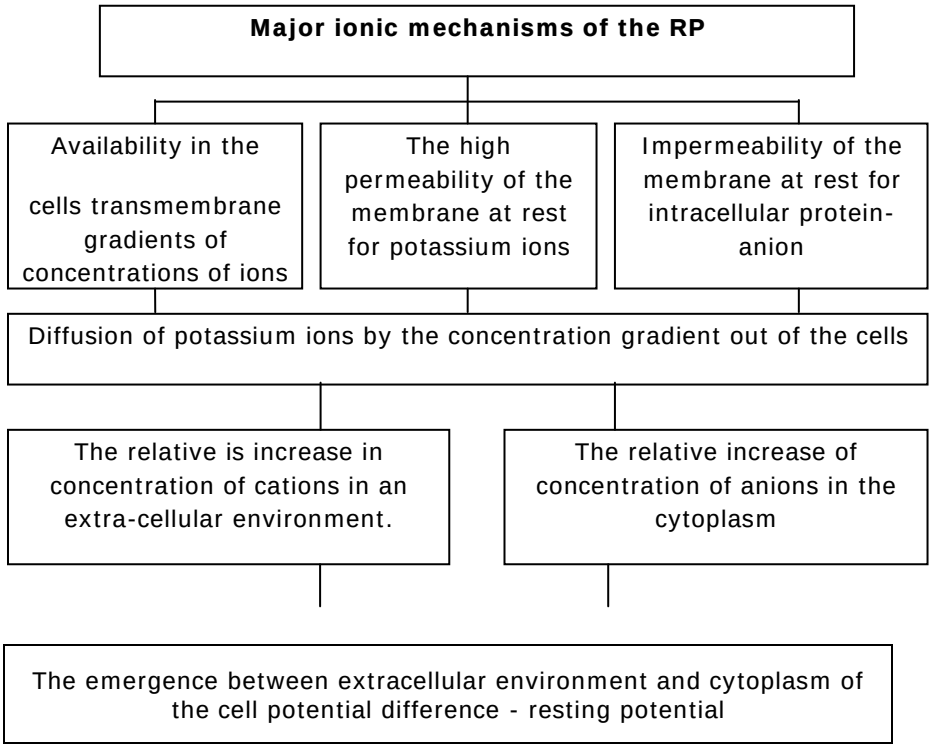


Figure 3.5 – Scheme, which explains the ionic mechanisms of the RP

How long will continue diffusion of cations continue from cells in the extracellular environment?

The fact that the positive charge is created on the outer surface of the membrane will prevent further diffusion of K^+ ions by the concentration gradient. Potassium will go into a cell by the electric gradient (negatively charged membrane from the inside and positively charged from outside). Finally, at the certain membrane potential state of the equilibrium reached. This means that the number of K^+ ions which comes from the cell by concentration gradient is equal to the number of K^+ ions

which enters the cell by the electrical gradient. Membrane potential value at which occur states of equilibrium is called the equilibrium potential for this ion.

Thus, the *equilibrium potential* - a level of electrical membrane potential at which ion diffusion by concentration gradient is balanced by the oppositely directed diffusion of this ion by the electric gradient. Or, in other words, it is a level of electric potential on the membrane that completely stops the flow of ion diffusion by concentration gradient.

Size equilibrium potential calculated by the Nernst's formula, which after the series of transformations takes the form:

$$E = -61 \cdot \lg \frac{[K^+]\, i}{[K^+]\, o},$$

E – equilibrium potential (Nernst's potential);

$[K^+]$i, $[K^+]$o –concentration of potassium ion inside and outside the cell respectively

Substituting in the Nernst's formula the value of the concentration of K^+ ions inside the cell (140 mEq/L) and in the extracellular environment (4 mEq/L), we obtain the value of potassium equilibrium potential which is equal to – 94 mV.

If there are not one but several types of ions in the cell (e.g. potassium, sodium, chlorine) that penetrate through the membrane, the membrane potential value is calculated by the Goldmann-Hodgkin-Katz formula :

$$E = -6{,}1 \cdot \lg \frac{[K^+]_i \cdot P_K + [Na^+]_i \cdot P_{Na} + [Cl^-]_0 \cdot P_{Cl}}{[K^+]_0 \cdot P_K + [Na^+]_0 \cdot P_{Na} + [Cl^-]_i \cdot P_{Cl}},$$

P – membrane permeability to this ion.

Resting potential of nerve and skeletal fibers

Intracellular removal of membrane potential of the large nerve and skeletal muscle fibers suggests that the resting potential in these structures is equal to -90 mV. This level of resting potential is explained by the existence of basic and additional factors that affect the membrane potential in these structures.

Basic factors:

1 Difference of concentrations of K^+ ions in the cytoplasm and in the extracellular fluid. Thus, in the cytoplasm of nerve fiber, the content of K^+ ions is in 35 times higher than in the extracellular environment.

2 High membrane permeability to K^+ ions, low permeability to Na^+ ions and impermeability to intracellular proteins – anions.

That K^+ ions and cell membrane permeability characteristics determine the value of resting potential. This becomes evident by the fact that the resting potential of nerve and skeletal muscle fibers (-90 mV) is very close to the value of the potassium equilibrium potential (-94 mV).

Additional factors:

1) A passive entry of Na^+ ions into the cell. Although at the state of rest, membrane permeability to Na^+ ions is many times smaller than for K^+ ions (about 100), there is a growing diffusion of Na^+ into the cell. It is due on one hand that very large electrochemical gradient for the Na^+ ions is aimed into the cell (concentration of Na^+ outside the cell is 10 times higher than inside, in addition, Na^+ ions are trying to enter the cell, inside which the "-") and on the other hand - the presence of proteins in the cell membrane allow the Na+ to pass through when the cell is at rest. These proteins are called "potassium-sodium leakage channels." They are non-selective ion channels through which ions diffuse through the membrane which is at rest. These proteins are much easier to pass through K+ ions

channels than Na^+ (approximately 100).

Permanent passive entry of Na^+ into the cell reduces its membrane potential, therefore its value is actually smaller than the potassium equilibrium potential.

Calculations by Goldmann-Hodgkin-Katz formula show that the existing entrance of Na^+ into the cell resting potential would be equal to -86 mV but actually it is -90 mV. Why? This explains the following additional factors that affect the RP.

2) Working of the Na^+, K^+-pump.

Na^+, K^+-pump – a cell membrane proteins that carry out active transport of Na^+ and K^+ against their concentration gradients. Operation of this pump has two consequences:

• maintained concentration gradient of Na^+ and K^+ on the both sides of the membrane despite the passive input of Na^+ and K^+ out of cells;

• Makes an immediate impact on the value of the RP due electro genesis of pump. For one cycle of working of the pump is unequal exchange of Na^+ and K^+ (three ions of Na^+ is removed from the cell, and only 2 ions of K^+ come into the cell), resulting to the slight hyperpolarization of the membrane and also the resting potential of nerve and skeletal muscle fibers is -90 mV but not -86 mV as should be expected from calculations performed by the Goldmann-Hodgkin-Katz formula.

The physiological importance of resting potential

The presence of the RP on the membrane of cells determines their rice such as anxiety, i.e. the ability to be excited in response to stimulus.

In terms of electrophysiology, this means that the presence of RP is a prerequisite for the emergence of the action potential (AP).

Changes of RP in terms of pathology

The pathology changes of the RP of the excitable cells most often caused by these violations:

1) Changes of extracellular concentration of K^+ ions.

There are two variants of violations:

• hyperkalemia. K^+ ions enter into the cell and membrane depolarization is developing;

• hypokalemia. In this case, by contrast, K^+ ions go out of cells leading to membrane hyperpolarization.

2) Changes in intracellular concentrations of K^+ ions at:

• enhanced breakdown of proteins (catabolism increase speed). In this case, by reducing the concentration of intracellular protein results to a decrease in intracellular concentrations of K^+ ions which leads to depolarization of the membrane;

• enhanced protein synthesis (anabolic increase speed). Thus, in contrast, increased protein content within the cell is accompanied by an increase of intracellular concentration of K^+ ions. This causes the hyperpolarization of the membrane.

3) Increased cell membrane permeability to Na ions$^+$.

A similar situation occurs when:

• There is damage of cell membranes (violation of its barrier function);

• Appearance (adsorption) of new proteins or other compounds that are passed through Na^+ ions (e.g., adsorption complexes of antigen + antibody, antibiotics – ionophors).

4) Violation of Na^+-K^+-pumps.

The most common cause of such violations is the lack of ATP. During the disorders of function Na^+-K^+-pump decreases the RP due to passive Na^+ entering into the cell.

Regardless of the reason for the change of the RP in terms of pathology (depolarization or hyperpolarization) leads to a steady decrease of excitability of cell which manifested a wide range of disorders of the nervous system, heart, skeletal muscles and organs, which include the smooth muscles.

4 ACTION POTENTIAL

The action potential (AP) – is a rapid change of membrane potential that occurs in excitable structures in response to stimulus.

Actually the ability to generate the AP is the main feature which distinguishes the excitable structures (nerve, muscle and some types of secretory cells) from others.

Structure of the AP

AP of large nerve fibers during intracellular removal has the form shown below fig. 4.1.

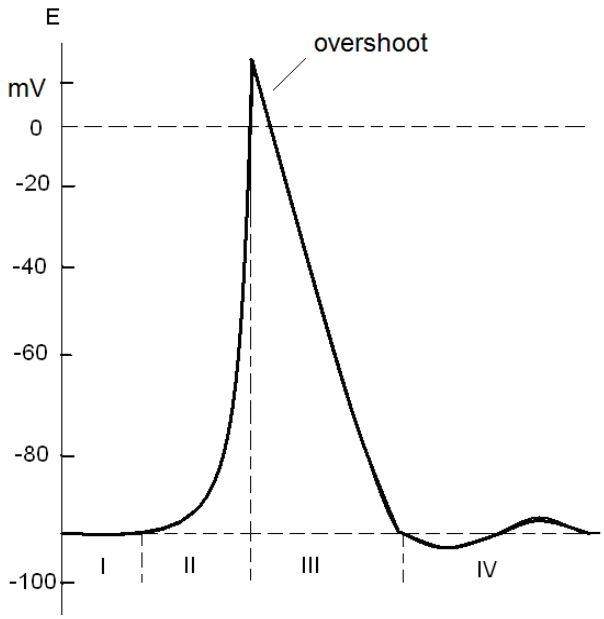


Figure 4.1 – Action Potential at intracellular removal: I – phase of rest; II - phase of depolarization, III – phase of repolarization, IV – phase of the after potential

There are such phases of the AP:

1) Phase of the rest. It is represented by the resting potential. Development of the AP is impossible without resting potential.

2) Phase of depolarization (upward phase). It is very fast (0.1 ms) change of membrane potential is from -90 mV to + 35 mV. In large nerve fibers positive values of the AP are called overshoot. There is no overshoot in small nerve fibers and neurons.

3) Phase of repolarization (downward phase). This is the phase of the restoration of the negative charge on the inner surface of the membrane. Its duration exceeds the duration of depolarization phase.

4) Phase of after potential. Membrane potential for some time deviates from the level of RP after the AP. There are traces of depolarization and traces of hyperpolarization. After potential amplitude never exceeds 15-20% to that of AP.

The main physical characteristics of AP

1) Polarity of the AP. AP is electropositive on the inner surface of the membrane, and on external - electronegative in respect to "zero" of the Earth. In other words, during the development of AP, it is the potential reversion that changes the polarity of charge on the inner and outer surfaces of the membrane (Fig. 4.2).

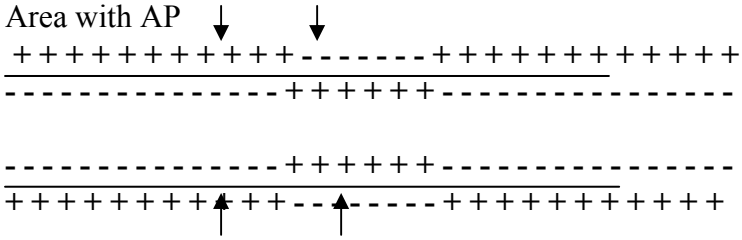


Figure 4.2 – reversion of membrane potential during the AP

2) Value of membrane potential on the top of the AP (value of the overshoot). This value is from +30 to +40 mV in large nerve and skeletal muscle fibers.

3) The amplitude of the AP. It is the distance from the resting potential level to the highest point of the overshoot. This figure is 110 - 130 mV in large nerve and skeletal muscle fibers.

4) Duration of the AP. This characteristic of the AP is significantly different in different types of excitable structures. Thus, in large nerve and skeletal muscle fibers, this figure is 0,5 – 5 ms, whereas in cardiac muscle fibers it is 300 ms.

5) Wavelength of the AP. AP is able to spread throughout the nerve and muscle fibers and its wave length is 0.1 to 5 cm in different structures.

6) Speed distribution of the AP. Depending on the type of fibers, the figure is 0.5 - 120 m / sec.

The main physiological characteristics of the AP

1. Obeys the law of "all or nothing." This means that:
   - AP occurs when the stimulus, the power which is no less than certain thresholds;
   - Physical characteristics of the AP (amplitude, duration, shape) do not depend on the power of stimulus.
2. Ability to auto spread along the cell membrane without damping, i.e. without changing their physical characteristics.
3. AP is accompanied with the refractory period.
4. AP is not capable of summation, i.e., to overlap.

Ionic mechanisms of the AP

The emergence of AP is associated with the existence in the plasma membrane of cells of two types of protein channels.

Let us make a brief discussion on their characteristics.

I Voltage-gated sodium channel proteins

These channels have two properties: selectivity and electrical excitability.

Selectivity – the ability of the channel to allow only Na^+ ions to pass through, therefore these channels are called sodium.

Electrical excitability – the ability of the channel opened and closed in response to changes of the membrane potential (hence the name – voltage-gated).

Na^+ channel consists of two parts:

1) Actually a transport system – a protein that transmits the Na^+ ions through itself.

2) Gate – part of the channel, which defines its opening and closing condition.

Voltage-gated sodium channel has two gates:

• *Activation* (fast). They are located on the outer surface of the protein-channel, have the ability to rapidly open and close;

• *Inactivation* (slow). They are on the inner surface of the protein-channel and are characterized by being slow to open and close.

There are three functional states of the voltage-gated sodium channels (fig. 4.3).

• *State of the rest*. Activation gates are closed, inactivation - open. Channel is impenetrable for Na^+ ions. The channel is in this state when the membrane potential is -90 mV (resting potential level).

• *Activated state*. Both gates (activation and inactivation) are opened, causing the channel to be penetrable for Na^+ ions. These ions pass from outside into the cell by the concentration gradient by simple diffusion mechanism. The reason for opening of the activation gate is due to changes in membrane

potential from -90 mV to +35 mV (depolarization).

• *Inactivated state*. Activation gates are open, inactivated - closed. Channel in impenetrable for Na^+ ions. This state occurs because of changes of the membrane potential from -90 mV to +35 mV. Conformational changes of protein-channel result in depolarization leading not only to the rapid opening of the activation gate but also to the closing of the inactivation gates. However, the latter is much slower

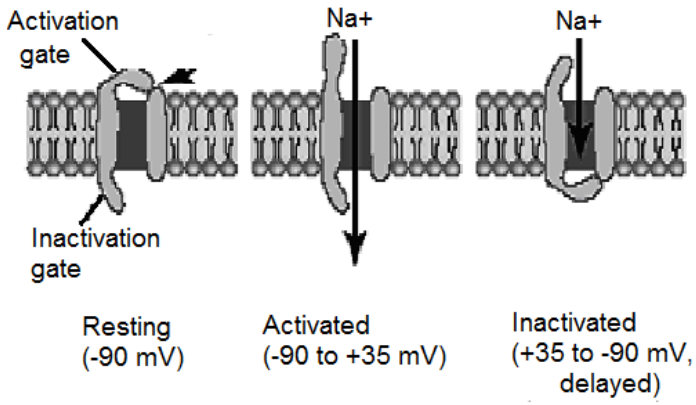


Figure 4.3 – Voltage-gated sodium channels

II Voltage-gated potassium channels

They have the same properties as the sodium channels - selectivity and electrical excitability.

K^+ - channel consists of two parts:

1) Its own transport system - a protein that transmits the K^+ ions through itself;

2) Gate. Unlike sodium channels, there is one gate in the potassium channels located on the inside of the membrane.

There are two functional states of potassium channels (fig.

4.4):

• *State of rest*. Gates are closed. Channel is impermeable for K^+ ions. The channel is in this state when the membrane potential is -90 mV.

• *Active state*. Gates are open. Channel is permeable to K^+ ions. This state occurs during changing the membrane potential from -90 to +35 mV as a result of conformational changes in protein-channel. As these changes occur slowly, then the gate opens slowly.

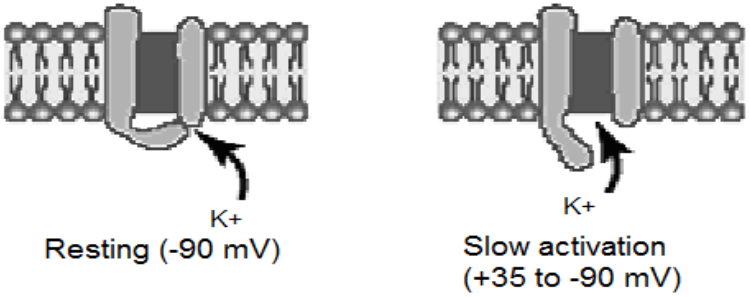


Figure 4.4 – Voltage-gated potassium channel

Thus, there are two main differences of the potassium channels:

- Potassium channels are not inactivated because they have no inactivation gates;
- Opening and closing of potassium channels is slow.

Given the structure and functional characteristics of ion channels consider the origin of the major phases of AP: depolarization and repolarization.

Phase of depolarization

The main mechanism of its occurrence is a sudden 500 – 5000 fold increase in the permeability of the cell membrane for Na^+ ions; resulting ions enter in the cell by the electrochemical gradient (input sodium current) causing a rapid depolarization. Molecular basis of such sharp increase of membrane permeability is the switchover of voltage-gated sodium channels in the activated state. The reason for this is the opening of activation (fast) gate channel caused by membrane depolarization to a critical level equal to -70 -50 mV. This membrane depolarization to a critical level is due to effects on cell stimuli that can cause excitement. Schematically, the mechanism of depolarization phase of AP is shown in fig. 4.5.

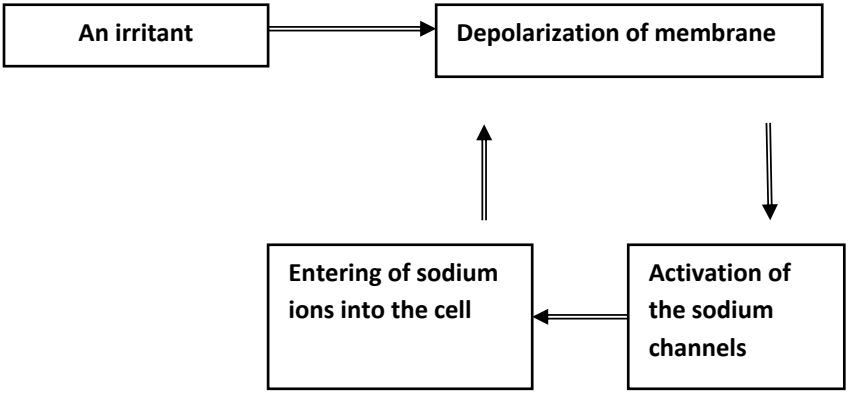


Figure 4.5 – Mechanism of depolarization phase of AP

The basis of rapid depolarization is the principle of positive feedback, which is important in initiation of the physiological processes. Thus, membrane depolarization induces the activation of sodium channels, which increases the

entry of Na^+ ions into the cell. This, in turn increases the membrane depolarization which increases the number of activated sodium channels, etc.

Which value of the potential will depolarization occur? Theoretically it is possible to obtain a value equal to the sodium equilibrium potential. Calculations by formula of Nernst show that it is 70 mV. In fact, the depolarization reaches a level of only 35 mV. Why? This is because of the events that lead to the development of the next phase of AP.

Phase of repolarization

In its development there are two important events:

1) Inactivation of voltage-gated sodium channels.

Inactivation (slow) gates of sodium channels begin to close after 0,1 ms from the onset of development of the AP hence the membrane permeability for Na^+ sharply decreases . The reason for the closure of inactivation gates (like the opening of activation) is membrane depolarization. But other than fast activation gate, inactivation closes slowly, so their complete closure occurs only after 0.1 msec.

Inactivation of sodium channels explains the fact that membrane depolarization does not reach the level of sodium equilibrium potential during the AP.

2) Activation voltage-gated potassium channels.

Simultaneously with the beginning of inactivation of sodium channels, i.e. 0.1 ms, gates of voltage-gated potassium channels begin to open, which increases the permeability of the membrane to K^+ ions. The reason for opening the gates of the potassium channel is protein-channel conformational changes in feed caused by depolarization. As these changes occur slowly, the opening of potassium channels is delayed by 0,1

ms. K^+ ions go out of the cell by the electrochemical gradient (output potassium current) as a result of opening of the potassium channels – the result is a gradual recovery of membrane potential, i.e., repolarization.

Once the membrane potential reaches the level of resting potential (-90 mV), such changes occur in the channels:

• Activation gate closes quickly in sodium channel, and inactivation – opens slowly. Channel goes into the rest state;

• Gate in the potassium channels slowly closes and repolarization stops. However, since the closure of potassium channels is slow, the output of K^+ from the cells continues for some time and after reaching the level of resting potential. This, in particular, is explained by the emergence of trace hyperpolarization when the membrane potential can approach to the value of potassium equilibrium potential (-94 mV).

The physiological importance of the AP

Series of the AP (impulses), which are distributed along the cell membrane, are "signals" that provide the transmission of information along nerve and muscle fibers.

Methods of registration of the AP

I Intracellular removal of the AP.

Microelectrodes enter into the cell and record the classic form of the AP which is presented in fig. 4.1.

II Extracellular removal of the AP.

Carried out by means of electrodes placed outside the cell. There are two methods of the extracellular registration of the AP:

1 Bipolar removal – registration of the two-phase AP.

allows you to record the AP which extends along the intact nerve fibers (fig. 4.6).

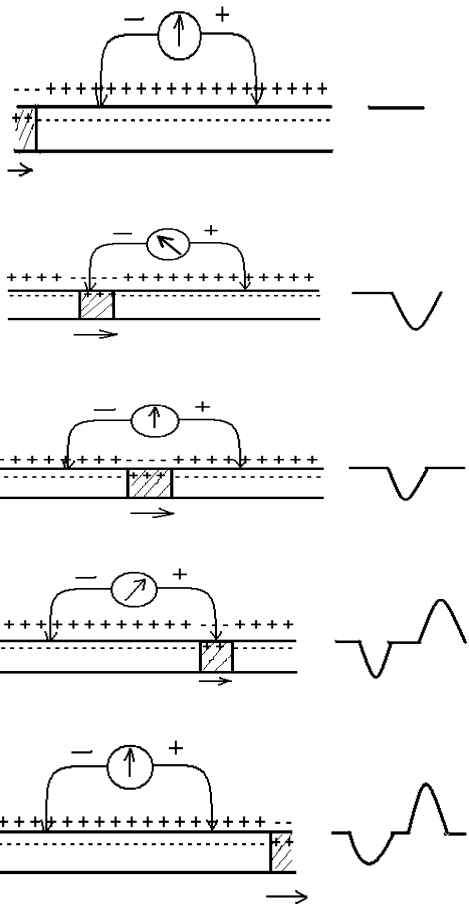


Figure 4.6 – Registration of the two-phase PD using extracellular electrodes. Shaded areas of fiber depolarization. Arrow indicated the direction of distribution of the AP

2 Unipolar removal - the registration of the single-phase of AP. Allows you to record the AP in violation of it (fig. 4.7).

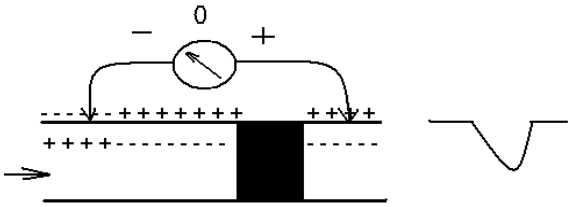


Figure 4.7 – Registration of the single-phase AP using extracellular electrodes. Black shows the damaged portion of fiber through which the AP is not performed. Arrow indicated the direction of distribution of the AP.

Causes and conditions of the AP

AP is caused by interaction of stimulus with the exciting cell. The stimulus is actually the cause of the AP in this interaction, and the properties of cells determine the conditions of its occurrence.

By origin of irritants that can cause the AP, stimuli can be divided into 2 groups:

1) Physical stimuli:
   - Electric current;
   - Mechanical factors (pressure, vibration, stretching).

2) Chemical stimuli:
   - Neurotransmitters;
   - Chemical compounds specific to certain types of chemoreceptor (carbon dioxide, hydrogen ions).

A common feature of all irritants that can cause the AP is that they all lead to the development of cell membrane depolarization.

The main characteristic of cells that determines the conditions of the AP is its excitability.

5. EXCITABILITY

Excitability of cells and tissues is a basic function of life. Also known as irritability, it is the ability of cells to respond to stimuli. Excitability is necessary for the functioning of nerves, muscles, and hormones, among other things. The basis for the excitability of cells is their ion distribution, and the distribution of ions and molecules is determined by transport mechanisms associated with their plasma membrane structure. This structure permits and regulates various forms of ionic and molecular transport mechanisms associated with their plasma membrane structure.

Parameters that determine the excitability of cells

The value of the resting potential. It directly affects the number of inactivated sodium channels. If the AP is more positive, the growing number of inactivated sodium channels. Upon reaching the resting potential of -50 mV level in mammalian cells 100% sodium channels are inactivated and are no stimulus dear forces can not cause AP. Since the value of the AP determined by the concentration of K^+ ions, it is these ions played a leading role when it comes to the above parameter excitability.

The critical level of depolarization. This value of the membrane potential in achieving which is arises of AP. Not every membrane depolarization is causes of AP, but only that reaches a critical value. In large nerve fibers is an average – 65 mV.

The difference between the critical level of depolarization (Ecr) and AP (E_{AP}) is called the threshold potential or threshold depolarization (V) (Fig.5.1).

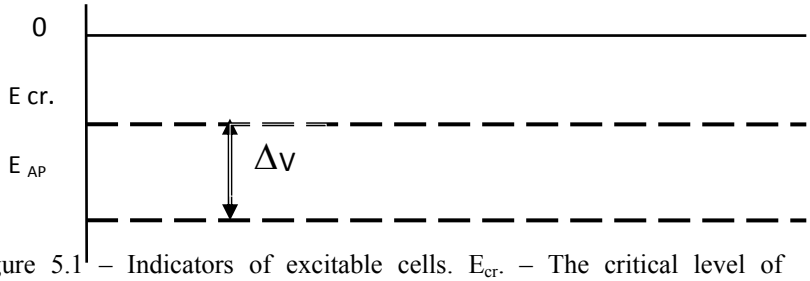


Figure 5.1 – Indicators of excitable cells. $E_{cr.}$ – The critical level of depolarization, E_{AP} - the level of the resting potential, ΔV - threshold potential (threshold depolarization).

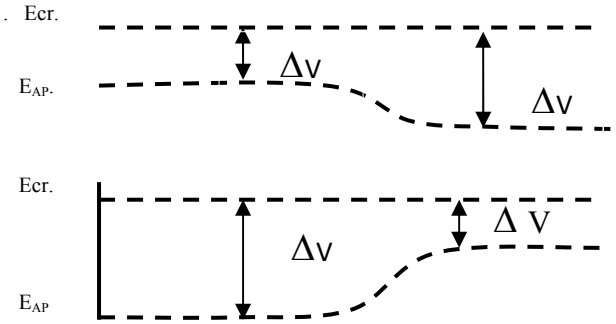
$$Ecr - Erp = \Delta V$$

In this case, ΔV = -65 - (-90) = 25 mV.

The main factor that determines the critical level of depolarization is the extracellular concentration of Ca^{2+}.

With increasing concentration of Ecr is more positive, and thus increases the threshold depolarization (ΔV). Reducing the extracellular Ca^{2+} concentration causes the opposite effect – Ecr approaching the level of AP, respectively, ΔV is decreases.

Based on the value of the options considered, there are four changes in excitability (Fig. 5.2)



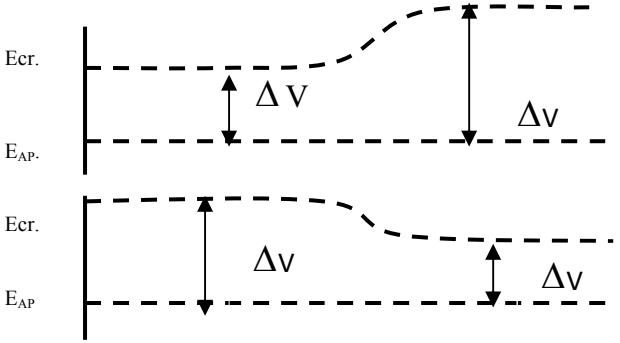


Figure 5.2 – Variants of changes of cell excitability

Changes in excitability during excitation

During and immediately after the excitation cell excitability changes so that there are two periods: the period of absolute and relative refractory period (Fig. 5.3).

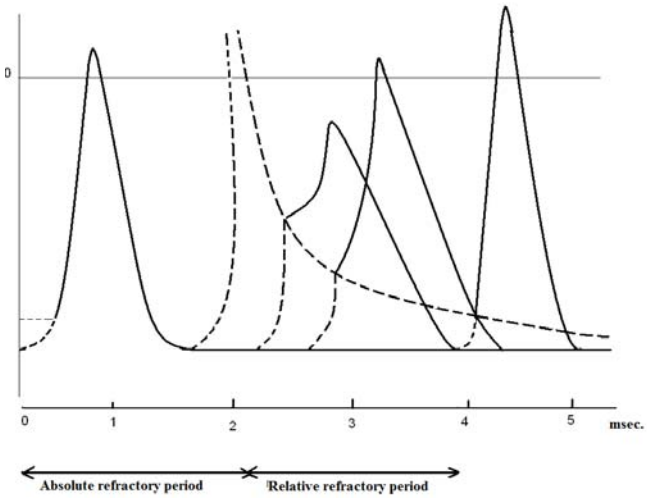


Figure 5.3 - Periods of absolute and relative refractory

1. Period of absolute refractory. The duration of this period for large nerve fibers - from early AP and for some time after its completion, approximately 2 msec. During this period, the cell is not exciting – no stimulus is can not cause AP.

The existence of absolute refractory is because in this period all sodium channels are in the inactivated state. To excitability recovered necessary transition of sodium channels inactivated state to the resting state. This is achieved by closing and opening of the activation gate inactivated protein channels. Since the first closed quickly, and the second opened slowly, even when a membrane potential of -90 mV level of excitability for some time is not restored. Therefore, the length of the absolute refractory is longer duration of AP. The period of absolute refractory is determines the maximum number of AP, which may occur in the nerve fiber for 1 sec. If not myelinated nerve fibers of the length of this period is 2 ms, then 1 : 0, 002 = 500 pulses / sec. In myelinated fibers, where is the duration of the absolute refractory is 0.4 msec – 1: 0.0004 = 2500 imp / sec.

First attention to the various ability excitable structures played a different number of stimuli turned N.E. Vvedensky (1901). Thus, the frequency of discharge of motor nerve fibers with random movements typically is less than 50 per second. While in sensory nerve fibers (e.g., auditory or optic nerve) with a strong stimulation it can reach 1000 per second or more. The maximum number of action potentials ("maximum rhythm"), which is capable of exciting the structure generated for 1 second in accordance with the rhythm of stimulation, N.E. Vvedensky proposed as indicator of lability tissue. Today it is clear that the maximum rhythm nerve impulses and muscle fibers determined by the rate of change of ionic conductivity processes that underlie the absolute and relative refractory.

2. **Relative refractory period.** Occurs immediately after the absolute refractory period and is 1/2 -1/4 of its length.

It is characterized by two features:

a) Increasing the threshold depolarization. This means that during the period in AP may occur, but under the influence of stimuli greater force than usual;

b) AP which occurs during this period is characterized by changes in shape – reduced amplitude and steepness of the rise, increasing the duration.

The possibility of AP during the relative refractory is because at this time a number of sodium channels has regained its initial state (state of rest), but a significant number of them is still in the inactivated state. In addition, potassium channels are not fully closed, so potassium current output prevents AP that appears in response to a strong stimulus to the relative refractory period.

The role of different ions in the development of electrophysiological phenomena in cells

As follows from the above, the leading role in the development of membrane potentials in excitable cells by three ions: K^+, Na^+, Ca^{2+}.

I. K^+ ions. They determine the level of membrane potential. They are also important in the development of AP, causing phase of repolarization.

II. Na^+ ions. They are the major ions that determine the development of AP (phase depolarization). At the same time affect the final value of MP (passive entrance of Na^+ ions into the cell).

III. Ca^{2+} ions. Determine the value of the critical level of depolarization.

Changes in excitability in terms of pathology and effects of pharmacological agents

Consider some of the main cause's excitability disorders:

I. *Violation of the ionic composition of extracellular fluid:*

1. Changing the concentration of K^+ ions:

a) Hyperkalemia (*hyper*- high; *kalium*, potassium; *-emia*, "in the blood") Generates a depolarization of cell membranes (K^+ entrance into the cell).

Depending on the concentration of K^+ ions is the following violations excitability. If extracellular K^+ ions content increases from 4 to 8 mEq/L, then by a small membrane depolarization threshold potential decreases and as a result, excitability increases. If the concentration of K^+ ions in the extracellular fluid becomes higher than 8 mEq/L, whereas due to the increased number of inactivated sodium channel excitability decreases (relative refractory period). If the concentration of K^+ ions reaches 35 mEq/L or more, resulting in a significant membrane depolarization all sodium channels are in the inactivated state. Cell completely loses its excitability (absolute refractory period);

b) Hypokalemia Causes hyperpolarization of the membrane (K^+ ions out of cells) resulting threshold potential increases and decreases excitability.

2. Changing the concentration of Na^+ ions:

a) Hyponatremia (Hypo = low; natraemia = sodium in blood).

In the situation *in vivo*, this leads to an increase in excitability through osmotic mechanisms. The essence of the following: reducing the extracellular concentration of Na^+ ions

→ decrease of osmotic pressure in the extracellular medium (P_{osm}→) transition of water into the cells (cellular edema→) decrease intracellular K^+ ions (effect of divorce) → reduce MP → reduction of potential threshold → increase of excitability.

In vivo, when replacing Na^+ ions in the environment to other ions to maintain P_{osm} AP does not occur, because it develops phase depolarization.

b) Hypernatremia.

Effect is on excitability through the osmotic mechanisms. This developing phenomenon is similar to hyponatremia, only in the opposite direction (see above). As a result, potential thresholds increase excitability decreases.

3. Changing the concentration of Ca^{2+} ions:

a) Hypocalcemia. It is approaching a critical level of depolarization (E_{cr}) to the MP. This threshold potential decreases and increases excitability. If E_{cr} becomes equal to MP, the action potential in nerve fibers occur suddenly, that without the stimulus - develops tetany syndrome (sudden muscle contractions - seizures);

b) Hypercalcemia. It is caused distancing from the E_{cr} level of MP leads to an increase in the threshold potential and reduced excitability.

II. *Damage of cells.*

Always is accompanied by sustained depolarization of the membrane (loss of MP). The bases of this are the following mechanisms:

a) Increased cell membrane permeability to ions Na^+ ions (breach the barrier function of membranes);
b) Violation of Na^+-K^+-pump;
c) Increased breakdown of intracellular proteins.

III. *Effects of specific ion channel blockers.*

Today in experimental trials is using agents that selectively violate conductance ion channels. They are called channel blockers. By blocking sodium channels are tetrodotoxin and batrahotoxin – venom of some species of fishes that bind to the outer part of the sodium channel, resulting in open activation gate becomes impossible and AP does not occur.

By blocking potassium channels are tetraethylammonium. It binds to the protein channel, slow opening gates, resulting in increasing the duration of the repolarization phase only AP and periods of absolute and relative refractoriness.

IV. *Local anesthetics*.

These are substances that are used in medicine as local anesthetics (Novocain, Procaine, and others). These drugs make it difficult or even stop the spread of AP along nerve fibers.

6. ELECTRIC CURRENT AS REASONS EXCITATION OF THE NERVOUS AND MUSCLE FIBERS

Among the stimuli that can cause AP, is the most important electrical current.

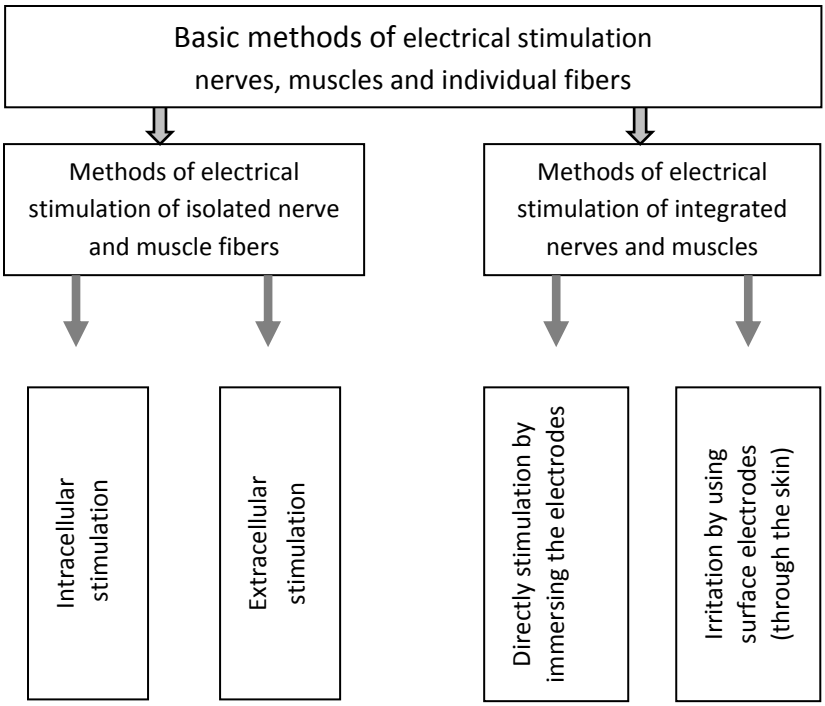


Рисунок 6.1 – Основні методи електричної стимуляції нервових і м'язових волокон

The basis of this electric current is it's the ability to cause membrane depolarization to or above the threshold. This depolarization got called stimulation, and the electrical current acting as a stimulus.

Parameters of electric current that determine its ability to cause excitation

1. The output direction of the current.

According to the law of the polar stimulation (Pfluger, 1859) during stimulation of nerve or muscle direct current stimulation (AP) occurs at the time of direct current circuit only when the cathode ("-"), and at the time of opening - just under the anode ('+') .

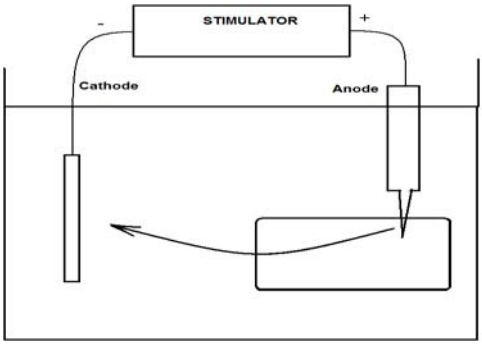


Figure 6.2 – Electrical stimulation by using extracellular electrodes

In intracellular summarizing of excitation current (AP) occurs only when the anode is located inside the cell and cathode - outside.

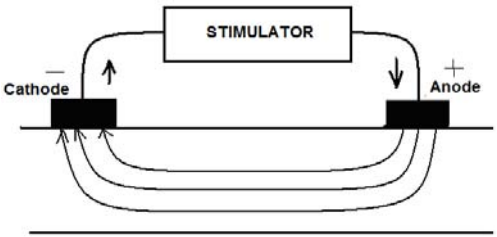


Figure 6.3 – Intracellular electrical stimulation

2. **Threshold or above threshold strength (amplitude) of the electric pulse.**

Excitation is occurs only when the cell is fed electrical pulse of sufficient amplitude – threshold or above threshold.

Threshold power (or threshold voltage) of electric current is used as a measure of excitability of nerves and muscles.

There is such a pattern: the higher excitability of these structures, the lower the threshold force of the current, and vice versa.

3. **Threshold and above threshold duration of electric pulse.**

In order for to cause excitement, an electrical impulse is to be sufficient (threshold or above threshold) duration.

Between the threshold force and threshold of electric current electrical pulse duration is the reciprocal dependence. In the physiology is it won the called of the "law of hyperbole" or curve "power – time."

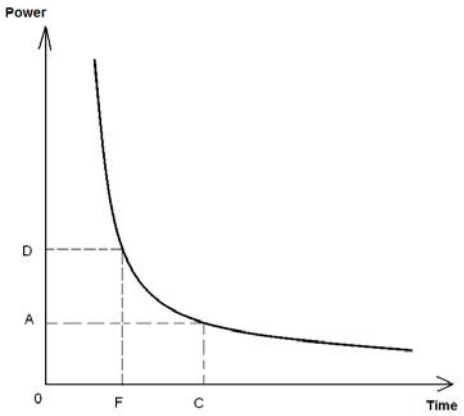


Figure 6.4 - Curve "power-time"

Analyzing the relationship "force - time" are the following

indicators:

a) Rheobase (OA) - Minimum direct current power, can cause excitability (threshold stimulation);

b) Useful time (OS) – the smallest time at which an electrical stimulus must act largest one rheobase in order to induce arousal;

c) Chronaxie (OF) - the smallest time during which an electrical stimulus must act largest two rheobase to cause excitement.

This figure is easier to determine than the useful time, so practice using research rheobase and chronaxie.

Threshold or above threshold is steepness of increase electrical pulse.

If the increase in power electrical pulse is slow (small slope), the ability of electric current to cause arousal decreases and, finally, can even disappear. This phenomenon was called accommodation.

Parameters of cell which are important for the emergence of excitation in it

1. Passive electrical membrane parameters:

a) The membrane capacity (C);

b) The membrane resistance (R).

The plasma membrane of living cells has properties of capacitor. Facing it – external and internal membrane surfaces and dielectric - lipid layer, this has a significant resistance. Due to the presence of membrane channels through which ions can pass, the resistance of this layer is not equal to infinity. So imagine the cell membrane as a capacitor in parallel with the included resistance, which can occur due to withdrawal charges.

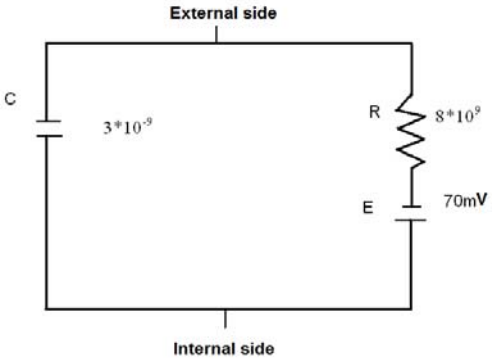


Figure 6.5 - Passive electrical parameters of cell

If the lower the CR product, then the easier for a given power of electric current excitation occurs, and vice versa.

2. Parameters of membrane excitability:

a) The value of the resting potential;

b) The critical level of depolarization.

The difference between these parameters – is threshold potential or threshold depolarization.

Potentials that are occur at the cell membrane during its electrical stimulation

I. Passive potentials.

They are also called electrotonic or electrotones.

They are caused by their own electrical impulses.

1. In passive potentials are:

Cathelectrotonic potential (CETP). This is change in potential at the cathode region. Since the cathode – electrode is the sign "-", then on the outer surface of the membrane is reduced positive charge and developing depolarization.

Anelectrotonic potential (AETP). This is change in potential at

the anode region. Since the anode is an electrode with a "+", then on the outer surface of the membrane increases the positive charge, i.e. there hyperpolarization.

The value of electrotonic potentials determined by passive membrane electrical properties: capacity and resistance.

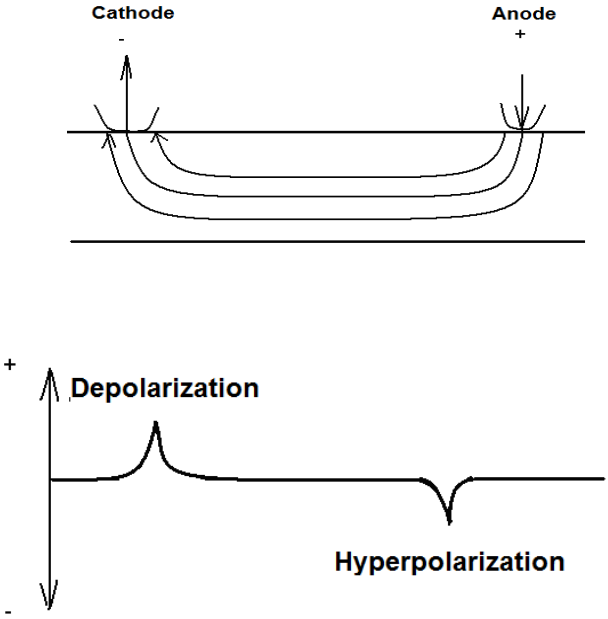


Figure 6.6 – Passive electrical potentials

II. Active potentials.

These potentials are related to changes in cell membrane permeability to ions when the electric current. Potential refers to the active local response and action potential (AP).

1. Local response (local excitation). This additional active membrane depolarization does not reach a critical level.

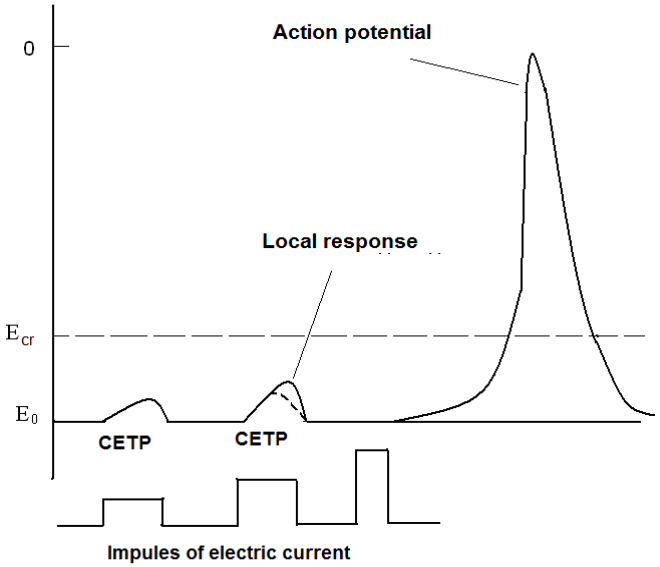


Figure 6.7 - Development of active potentials caused by of electric current pulses

Local response is occurs only in the area cathode. Its cause is CETP. The main mechanism of local responses – is opening appropriate number of Na-channels and Na^+ entry into the cell. However, the number of open Na-channels at the same time is not sufficient to ensure that there was an AP. Further depolarization inhibited Na-inactivation and activation of potassium channels.

The first signs of local responses are detected by current action, the force of which is 50 – 75% of the threshold. By increasing the strength of electric current is an increase the value of the local response.

1. The action potential (excitation that extends).

Once the local response to depolarization is reaches a critical level, there is AP – local excitation turns into excitation

that apply.

Thus, the mechanisms of membrane depolarization to a critical level is the amount KETP (passive potential changes) and local response (active depolarization).

Table 6.1

Comparative characteristic of local response and action potential

Local response	Action potential
Conforms to law of power relations	Obeys the law of "all or nothing"
Local excitation, which does not cover (extends to long distances with attenuation)	This excitation, which extends to long distances without attenuation
During a local response excitability increases	During AP is occurs reflexively
Chance of summation of local responses	APs are not added

The changes in excitability of nerve and muscle fibers, caused by electric current

It's described a few physiological phenomena, the main feature of which is changing the critical level of depolarization during the electric current on the cell.

1. *Cathodic depression*.

As noted, under the cathode is occurs CETP and local response. When a local response reaches a critical level of depolarization is occurs AP. If subthreshold membrane depolarization sufficiently long, there is a phenomenon cathodic depression (Fig. 6.8).

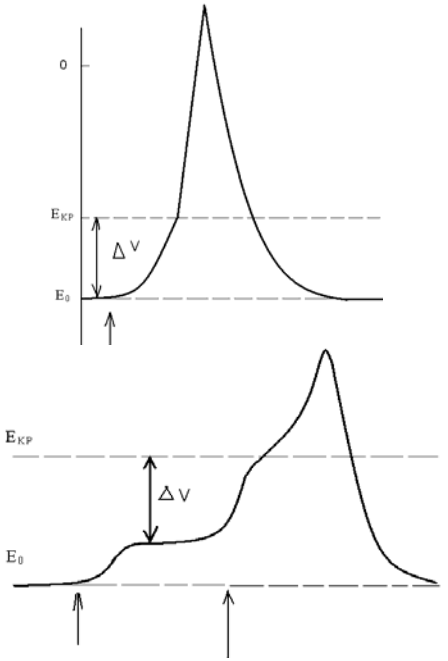


Figure 6.8 – Cathodic depression.

It is characterized by:

• Long-term increase in membrane potential (subthreshold depolarization) (E_0);
• increase the critical level of depolarization ($E_{cr.}$);
• Increase the threshold depolarization (ΔV);
• Reduction of excitability;
• Changes in action potential shape – is reducing the steepness of its rise and amplitude.

The basic mechanism of the phenomenon is that in the long depolarization increases the number of inactivated sodium channels and potassium activated.

It is believed that cathodic depolarization phenomenon is the basis of presynaptic inhibition and observed in the CNS.

2. The anode-unlocking excitement.

The essence of this phenomenon is the occurrence of PD under the anode at the time of electric current.

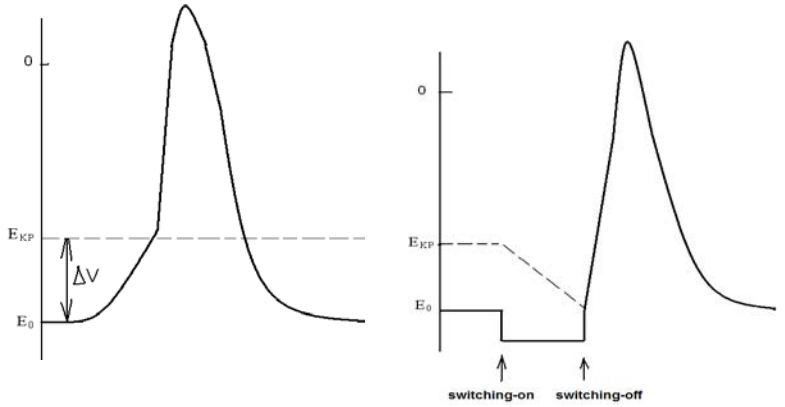


Figure 6.9 – The anode-unlocking excitement

For the given phenomenon is characterized by:

• Reducing the critical level of depolarization ($E_{cr.}$);

• Reducing the threshold depolarization (ΔV) to the level of the resting potential (E_0);

• Increasing the steepness of rise and amplitude of the action potential.

It is believed that the membrane hyperpolarization that is occurs under the anode, the number of inactivated sodium channels (at E_0 certain number of them, though small, but it is).

3. Accommodation.

The essence of this phenomenon is to increase the threshold depolarization when steepness is decrease and increase electric pulse. Thus, the threshold amperage increases

with decreasing steepness of its growth, but at a certain minimum steepness of the response to an electrical stimulus in general disappears.

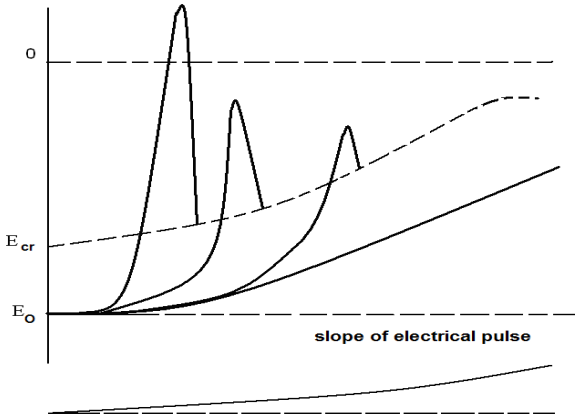


Figure 6.10 - The phenomenon of accommodation.

Signs of accommodation are:

• Increase critical level of depolarization;

• reducing the steepness and amplitude of the action potential;

• With a minimum increase in the steepness of the impulse ("critical slope") PD does not occur.

The main mechanism of accommodation is that the slow increase in steepness the current time to non activated sodium channels and potassium, even before the depolarization reaches a critical level.

7. MECHANISMS CONDUCTING EXCITATION (AP) ALONG NERVE AND MUSCLE FIBERS

The mechanism of spread AP along the membrane

The basis of the spread AP in nerve and muscle fibers are local electric currents that occur between depolarized area fibers and not polarized (quiet) portions of the membrane (Fig.7.1).

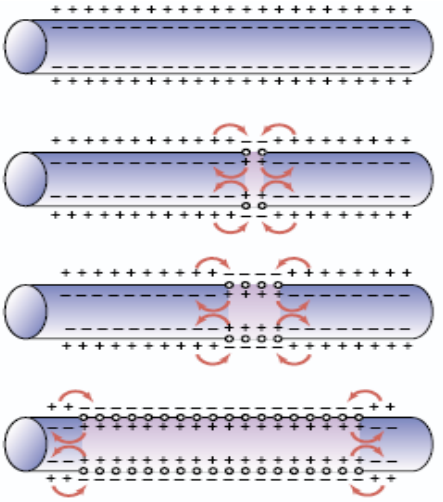


Figure 7.1 - Mechanism of spread AP along nerve fibers. The arrows show the local currents.

Local current, there is the original direction of the "quiet" section of fiber, which means that it, causes depolarization of the membrane. The latter is revealed KETP development and local response. If the total depolarization (CETP + local response) reaches a critical level, there is a AP. And then all over again: local current appears between depolarized area fiber, which has just emerged AP, and

subsequent nearby is the "quiet" area. Thus, the impulse (AP) propagates along the fiber.
Depolarization of "quiet" membrane to threshold occurs at a distance of 1-3 mm from the place of occurrence of AP.

Factors that determine rate of AP conducting

Factors that are important for conduction of excitation in nerve and muscle fibers can be divided into two groups: physical and physiological.

1. Physical Factors:

a) The resistance of the environment that surrounds the fiber.

If the area of the nerve fibers placed in an environment where no ions, i.e. an environment that has a high resistance (e.g. sucrose solution), the conduction of excitation through this section ceases completely. It is immediately restored if the two areas separated by electrolyte fibers connecting metal conductor;

b) The resistance of the internal environment of the fiber. It is defined axoplasm resistance per unit length (longitudinal resistance). This resistance depends on the cross section, and hence the diameter of the fiber. If there are larger diameter of the fiber, then the lower longitudinal resistance and the higher the rate of AP conducting. The opposite pattern is observed with decreasing fiber diameter;

c) The passive electrical parameters of the membrane fibers - capacity and resistance.

In myelinized nerve fibers myelin is an excellent isolator, so the impedance of the membrane AP is very high and can spread through the covered areas of myelin fibers

II. Physiological factors:

a) The amplitude of the AP (E_{AP}), which the power of the excitation pulses. The higher the E_{AP}, the greater the distance from the site of depolarization can be extended local currents.

E_{AP} is determined by the power input sodium current, which in turn depends on the concentration of Na^+ in the extracellular environment while the number of open sodium channels, slew rate of inactivation of sodium channels and activation of potassium;

b) Fiber excitability. The integral indicator of this property, as already noted, is the threshold depolarization (ΔV). All factors that increase ΔV reduce the rate of carrying pulses, up to a total blockade.

To characterize the physiological factors that determine the speed of propagation of AP along nerve fibers were introduced index factor reliability (FR).

$$FR = \frac{E_{AP}}{\Delta V}$$

The higher the FR, the greater the speed conducting pulse, and vice versa. Normally for nerve fibers FR = 5-6. If FR is less than 1, then conducting AP through this site is fully stopped (block conducting). From the formula shows that FR is reduced if reduced or E_{AP} ΔV increases.

Laws of conducting impulses along nerve and muscle fibers.

Conducting impulses along fibers obeys the following laws.

1. Anatomical and physiological continuity of fibers. There is a prerequisite conducting excitement. Violation of anatomical continuity occurs when nerve section or injury. In violation of physiological continuity understand changes in functional characteristics of nerve fibers that Conducting impulses determined - reduction factor of safety (e.g. drying nerve).

2. Bilateral conducting. AP spread to both sides of the place of origin of excitation, as well as branching nerve fibers. If irritate nerve electric current area, the pulses propagate in both afferent and efferent directions.

3. Isolated conducting. In peripheral nerve impulses spread on each fiber separately, i.e. not moving from one fiber to parallel along located. Consequently, the pulses have an effect only on those cells contacted the end of the nerve fibers. This fact is important in view of the fact that each peripheral nerve contains a large number of nerve fibers - motor, sensory, autonomic – that innervate different in structure and function of cells and tissues.

4. Nondecremental conducting that is conducting no damping, in which the AP does not change its characteristics during spread in fiber.

5. The pulse does not cause fatigue fibers – not relative fatigue nerve.

The energy ensuring the conduction of impulses by nerves

During AP Na^+ ions enter into the cell and K^+ out of it. This should cause an increase in intracellular concentrations of Na^+ and K^+ decrease, i.e. reducing the concentration gradient of these ions. But while AP single movement of ions across the membrane are so small that changes in their concentration in the cell immaterial – they can not even register.

Another matter when it comes to conducting impulses along nerve fibers along which passes from 100 thousand to 50 million pulses per hour. At this time, the concentration gradients of Na^+ and K^+ are significantly reduced. To prevent this from happening, you need to restore those gradients, which are Na^+, K^+ - pump whose work requires energy. In general, the gross energy of nerve fibers at works Na^+, K^+ - pumps relatively small. Thus, 1 g of nerve in the frog secretes at maximum stimulation of only 20-100% more heat than the rest.

It is much smaller when compared with the excitation of muscles.

This circumstance actually explains the relatively fatigue of nerve.

"Saltatory" Conduction in Myelinated Fibers

Even though almost no ions can flow through the thick myelin sheaths of myelinated nerves, they can flow with ease through the nodes of Ranvier. Therefore, action potentials occur *only at the nodes.* Yet the action potentials are conducted from node to node, as shown in Figure 7.2; this is called *saltatory conduction.* That is, electrical current flows through the surrounding extracellular fluid outside the myelin sheath as well as through the axoplasm inside the axon from node to node, exciting successive nodes one after another.Thus, the nerve impulse jumps down the fiber, which is the origin of the term "saltatory."

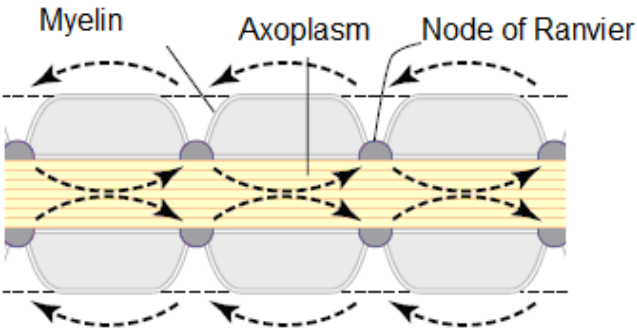


Figure 7.2 – Saltatory conduction along a myelinated axon. Flow of electrical current from node to node is illustrated by the arrows.

Saltatory conduction is of value for two reasons. First, by causing the depolarization process to jump long intervals along the axis of the nerve fiber, this mechanism increases the

velocity of nerve transmission in myelinated fibers as much as 5- to 50-fold. Second, saltatory conduction conserves energy for the axon because only the nodes depolarize, allowing perhaps 100 times less loss of ions than would otherwise be necessary, and therefore requiring little metabolism for reestablishing the sodium and potassium concentration differences across the membrane after a series of nerve impulses.

Still another feature of saltatory conduction in large myelinated fibers is the following: The excellent insulation afforded by the myelin membrane and the 50-fold decrease in membrane capacitance allow repolarization to occur with very little transfer of ions.

Total AP of the nerve trunk

If you allocate from a separate AP nerve fibers, the amplitude and other characteristics AP are not dependent on the strength of stimulation - the law of "all or nothing". If the electric potentials aside from the nerve, which is composed of a large number of nerve fibers in this case manifested power law relationship: an increase in strength of the stimulus (electric current) amplitude registered potentials also increased, but to a certain maximum value and then remains constant regardless of further increase in strength irritation.

This is because the electric response of a nerve is the sum of the responses of its individual fibers connected in parallel. Irritation thresholds of individual fibers differ from one another. At low excitation power of the stimulus occurs in most excitable nerve fibers. Increasing stimulus leads to an increase in the number of excited fibers. Therefore, the total response to touch stimulation increases until all fibers are not involved in the reaction.

If the electrodes through which irritate and record the

total potential of the nerve placed at a sufficiently large distance from each other (10-20cm), you'll find several "peaks" of the total potential (Fig. 7.3).

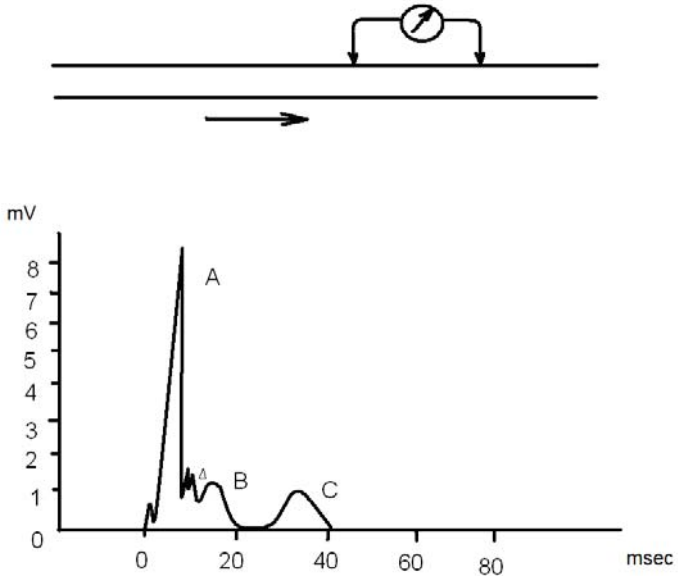


Figure 7.3 - Registration of the total capacity of the nerve trunk

The appearance of waves A, B, C, is due to the fact that the rate conducting impulses in individual nerve fibers is different (see below).

The clinic is widely used registration, the total AP large trunks and skeletal muscles in their natural activity in the body. These methods are called *electroneurography* and *electromyography.*

Classification of nerve fibers

The most widespread got two classifications are listed in Table. 7.1 and 7.2.

Table 7.1

Classification of nerve fibers by Erlanger and Gasser

Type of fiber	Function	Average diameter, μm	Average rate of carrying, m/sec
Aα	Primary afferent fibers of muscle spindles, motor fibers of skeletal muscle	15	100 (70-120)
Aβ	Skin afferents of touch and pressure	8	50 (30-70)
Aγ	Motor fibers of muscle spindles	5	20 (15-30)
AΔ	Skin afferents of temperature and pain	<3	15 (12-30)
B	Sympathetic preganglionic fibers	3	7(3-15)
C	Skin afferents of pain, sympathetic postganglionic fibers (non myelinated)	1	1 (0.5-2)

Table 7.2

Classification of sensory nerve fibers by Lloyd and Hunt

Group	Function	Average diameter, μm	Average rate of carrying, m/sec
I	Primary afferents of muscular spindles and afferents of tendon organs	13	75
II	Skin afferents from mechanoreceptors	9	55
III	Muscle afferents of deep pressure	3	11
IV	Non myelinated afferents of pain	1	1

The main causes and mechanisms of disorders conducting impulses along nerve fibers

I. Violation of anatomical continuity: the intersection of nerve, its injury.

II. Violation of of physiological continuity: change physiological characteristics of nerve fibers conducting pulses are determined (reduction factor of safety).

The basis of physiological violations of continuity may be based on the following mechanisms:

1. Reducing the amplitude of AP. This can happen for example when:

• By reducing the extracellular concentration of Na^+ ions;

• Action of blockers of sodium channel (tetrodotoxin);

• The actions of local anesthetics (substances that slow activation gate opening sodium channels and accelerate the inactivation of sodium and potassium opening.

2. The decrease excitability of nerve fibers. This can happen for example when:

• hyperkalemia;

• local increase in extracellular K^+ concentration in tissues when cells are damaged;

• hypokalemia;

• hypercalcemia;

• membrane is damaged;

• the actions of local anesthetics (shifting the critical level of depolarization by increasing the number of inactivated sodium channels).

III. Violation of energy supply of nerve fibers.

These disorders are the most common cause of disorders of conduction of nerve fibers. Hypoxia, starvation, vitamin deficiencies, toxins, poisons, are disrupting energy metabolism, leading to disorders of Na^+, K^+-pumps. This is causes a steady depolarization of the membrane and, consequently, reduce the excitability of nerve fibers.

IV. Demyelization of nerve fibers.

Myelin destruction and violation of its formation is the cause of decrease in the rate conducting pulses. The most common causes of these changes are:

• Disruption of Schwann cells and loss (hereditary and acquired defects);

• Violations of biochemical processes that provide chemical synthesis of myelin components (e.g., diabetic neuropathy);

• Destruction of myelin by autoimmune mechanisms (e.g., auto allergic diseases).

8. CONDUCTION OF EXCITATION THROUGH NEUROMUSCULAR SYNAPSE

The concept of synapses

Information in the form of impulses (AP) is spreads along nerve fibers eventually have to get to the cells in which it is intended.

Transmission of information from nerve fibers by means of cell-cell contacts, which conducts excitation in the cell that it perceives, called synapses.

Depending on the mechanism of transmission of nerve fibers per cell synapses are divided into chemical and electrical.

Table 8.1

Comparative characteristics of chemical and electrical synapses

Electrical synapse	***Chemical synapse***
The synaptic cleft is 2-4 nm	The synaptic cleft is 10-20 nm
Are functioning without chemicals	Information transfer is carried out by chemicals
Synaptic delay is absent	Synaptic delay is 0.2-0.5 msec
Excitation is conducted on both sides	Excitation is conducted in the same direction
Conducted only excitation	Conducted excitation and inhibition
Almost did not undergo modulation	are subject for modulation
Almost sensitive to temperature changes	Sensitive to changes of temperature

Most of the synapses in the human body is the mechanism chemical functioning.

Chemical synapse consists of:

1. Presynaptic membrane of the nerve fiber ending.
2. Postsynaptic cell membrane, perceiving the excitement.
3. Synaptic cleft - narrow space between the pre-and postsynaptic membranes.

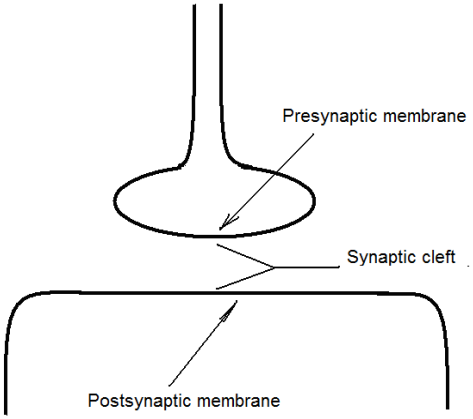


Figure 8.1 – Scheme of the chemical synapse

The mechanism of chemical synapse function can be represented by the following sequence of events:

1. Conduction of impulses (AP) along nerve fibers to nerve endings - presynaptic membrane.
2. Releasing nerve endings in the synoptic cleft mediator.

   Neurotransmitter – a chemical compound that is released nerve endings in the synoptic cleft in response to stimulation. These substances are mediators between the nerve endings and cells.
3. Effect of mediator on the postsynaptic membrane. The interaction with specific neurotransmitter receptors for him postsynaptic membrane.
4. Electrophysiological effects of interactions with

neurotransmitter receptors in the postsynaptic membrane.

There are 2 versions of these effects:

- Postsynaptic membrane depolarization, which may lead to AP. Chemical synapses of this type are called excitatory;
- Hyperpolarization of the postsynaptic membrane, which hinders the emergence of AP. Synapses of this type are called inhibitory.

Basic regularities of excitation through the chemical synapses

1. *Conducting unilateralism.* Unlike the nerve fibers which conduct is bilateral, chemical synapse signal is always transmitted from presynaptic to postsynaptic membrane. That synapse functions like a valve.
2. *A small rate of carrying.* Compared to the nerve fibers synapse through the excitation conducted with a relatively small velocity.
3. *Conducting of each signal coming.*
4. *Rapid fatigue*. Unlike the nerve fibers which practically do not tired to synapses characteristic rapid fatigue.

Structural and functional organization of neuromuscular synapses

Neuromuscular synapse is a synapse between the axons of motor neurons, whose body is in the anterior horns of the spinal cord and lumbar-striated skeletal muscle fibers.

Each nerve fiber branches out many times and may have synapses with many muscle fibers – from 3 to several hundred. Typically, each muscle fiber forms a single synapse nerve endings located in the middle – about the same distance from both ends of the muscle fibers.

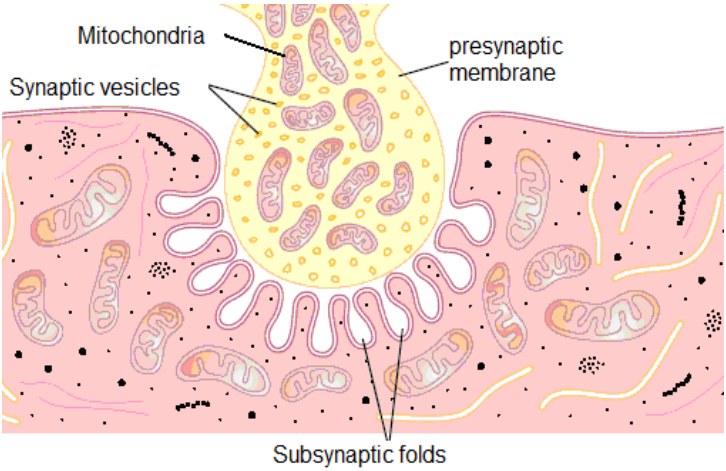


Figure 8.2 - Structural elements of the neuromuscular synapse

The set of all elements of the neuromuscular synapse is called the motor end-plate or end-plate. The structural elements of the end-plate are:

1. Presynaptic part.

The formed nervous terminal that is free from myelin nerve endings of the motor nerve. Each nerve fiber due to the fact that it is at the end of a branched, has a large number of terminals.

Nerve terminals immersed into the muscle fiber, but while it remains on the outside of its plasma membrane.

Nerve terminal structural elements are:

- Plasma membrane;
- Acsoplasm. Contains ions (ion composition is the same as in the nerve fiber), organic compounds (precursors of neurotransmitter, enzymes, its synthesis);
- Synaptic vesicles (vesicles). This structure with a diameter of 40-50 nm is containing neurotransmitter acetylcholine. In one nerve terminal contains about 300 thousand of these

vesicles;

- Dense bodies. This formation which are attached microfilaments engaged exocytosis (release content vesicle outside);
- Mitochondria.

Externally terminal plate is covered by one or more Schwann cells, which provide end-plate relative isolation from the surrounding fluid.

1. *Postsynaptic part.*

The formed plasmatic membrane of muscle fibers, which creates a lot of numerous folds (subsynaptyc fold), which greatly increases the total area of the postsynaptic membrane. At the beginning of each fold in the membrane is embedded proteins specific to perceive the action of neurotransmitter - acetylcholine. It should be noted that dense clusters of cells and synoptic vesicles located just opposite outfall folds.

2. *Synaptic gap.*

This is the distance between the presynaptic and postsynaptic membranes, which is 20-30 nm and full basal membrane consisting of thin layer reticular fibers. These fibers form a sponge-like structure which diffuses through the extracellular fluid and neurotransmitter that is released into the synaptic cleft. In the basement membrane matrix has a large number of acetylcholinesterase molecules – an enzyme that breaks down acetylcholine.

The concept of axon transport

Functioning of synapses is closely related to axon transport.

Axon transport – is a transport of substances and certain organelles in axons from the body of the neuron to the nerve endings and vice versa.

Types of axon transport:

- Rapid axon transport. This transport from the body of the neuron to the nerve endings. It is performed at a speed of 5-15 mm/h. with the participation of neurophibril and micro tubules require energy of ATP and Ca^{2+} ions.
- Slow axon transport. This is transport from the body of the neuron to the nerve endings. It is performed at a speed of 1-3 mm/day, does not require energy.
- Axon retrograde transport. This is transport of substances from nerve endings to the body of the neuron. It is performed at a speed of 2.5-7.5 mm/h. (approximately 2 times slower than the rapid axon transport).

Values of axon transport:

1. The required for the functioning of synapses. From the body of the neuron to the nerve terminals transported:
   - enzymes synthesis of neurotransmitters;
   - empty synaptic vesicles are formed in the Golgi apparatus;
   - mitochondria, the energy are required for synaptic process.
2. Provides trophic nervous. Nerve effect on metabolism in the tissue that innervates. This phenomenon is called trophic nervous. It is believed that by of axon vehicle transported substances – regulators of metabolism in peripheral cells.
3. Affect the functioning of the body of the neuron. Axon Retrograde transport provides admission to the body of the neuron factors that regulate this process of protein synthesis. If the cut axon is in the body of the neuron developing destructive changes, which are called chromatolisis.
4. Participates in the development of certain diseases. Thus, retrograde transport provides admission to the body of the neuron certain types of viruses and bacterial toxins that

matters in the pathogenesis of poliomyelitis virus, tetanus.

The mechanism of functioning of neuromuscular synapses

Transmission of information through the neuromuscular synapse is associated with the following sequential events:

1. **Synthesis of acetylcholine (ACh).**
It is carried out in the cytosol of the nerve terminal.

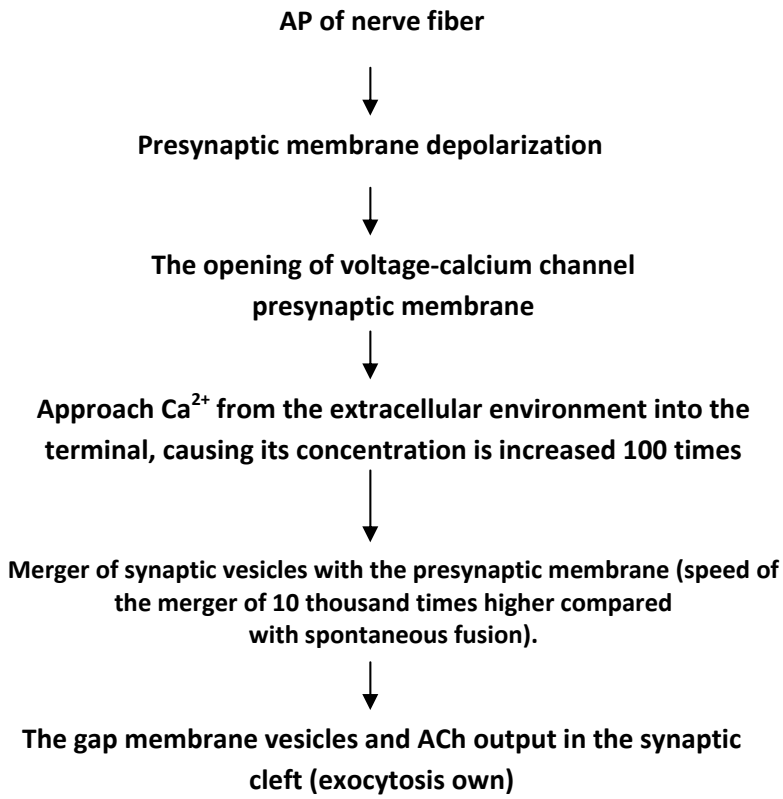
$$Acetyl - CoA + Choline \xrightarrow[transferase]{acetylcholine} ACh + CoA$$

2. **Depositing ACh.**
ACh is transported into the synoptic vesicles where it is stored in a highly concentrated form. Each vesicle contains about 10 thousand molecules of ACh.

3. **The release of ACh in the synaptic cleft.**
There is spontaneous and induced action potential release.

Spontaneous release is characterized in that at rest some random synaptic vesicles fuse with the presynaptic membrane and releases ACh, which are contained in the synaptic cleft. Each vesicle releases a certain amount of ACh, which is called "quantum". The result of the spontaneous release of ACh is the emergence of the postsynaptic membrane so-called miniature end-plate potentials.

The basic mechanism that has functional significance is the release of ACh induced by action potentials. This mechanism can be represented by the following scheme:



4. The action of acetylcholine on the postsynaptic membrane.

Enter into in the synaptic cleft ACh is interacts with acetylcholine receptors in the postsynaptic membrane, which are in the outfalls subsynaptychnyh folds.

Acetylcholine receptor is an ion channel gate which opens acetylcholine (chemo-sensitive channel). This receptor is composed of five protein subunits that form tube shaped channel that passes through the plasma membrane.

At rest, the channel is closed. Once connected to the acetylcholine receptor, protein conformational changes occur

that lead to the discovery channel. Open acetylcholine channel has a diameter of 0.65 nm, which enables him to pass through positively charged ions Na^+, K^+, Ca^{2+}. Negative ions (e.g. Cl^-) do not pass through the canal since its beginning has a charge "-". Leading physiological importance Na^+ is entry through the channel in the muscle fiber, since there is a very large electrochemical gradient for all ions.

Enter into Na^+ from the synaptic cleft in the muscle fiber through the acetylcholine receptor channel leads to a local depolarization of the postsynaptic membrane, causing end-plate potential (EPP). If the EPP reaches a critical level, there is causes AP, which extends on both sides of the muscle fiber. Normally, the EPP is 3-4 times higher than for the occurrence of AP.

Thus, the effect of ACh on the postsynaptic membrane can be represented by the following scheme:

Interaction of acetylcholine ACh receptor-channel

▼

Conformational change in the receptor protein

▼

Opening acetylcholine channel

▼

Enter into Na^+ in muscle fiber

▼

Local postsynaptic depolarization membrane - the emergence of EPP

▼

The emergence of AP

▼

The spread of AP in muscle fiber

When spontaneous ACh quanta allocation changes in membrane potential postsynaptic membrane is negligible. They are called miniature end-plate potentials. Their amplitude is about 1 mV, and the duration of several milliseconds. Naturally, these potentials can not cause the development of AP.

If synaptic cell released ACh a lot it has a few hundred milliseconds and membrane that was originally depolarized gradually repolarized despite the constant presence of ACh. Receptors become refractory to ACh, i.e. inactivated. Loss of sensitivity to the action of neurotransmitter receptors is known as desensitization.

5. Completing of ACh.

Normally, the effect of ACh on the postsynaptic membrane continues to 1-2 msec. Why? This is explained by two factors:

a) Most of ACh subject hydrolytic cleavage, which is the enzyme cholinesterase in sympathetic matrix slit.

$$ACh + H_2O \xrightarrow{holynsterase} Choline + Acetate$$

b) Smaller part of ACh diffuses from the synaptic cleft into the surrounding tissue, and the blood, which is also subject to hydrolysis with plasma choline esterase.

6. Recycling hydrolysis products of ACh and ratio of the number synaptic vesicles.

Hydrolysis products ACh-choline and acetate are reabsorbed from the synaptic cleft into nerve terminals. So they re-used for the synthesis of ACh.

After the release of ACh synaptic vesicle membrane becomes part of the presynaptic membrane. A few seconds after starting endocytosis: from the presynaptic membrane

retraction mechanism of forming "edging" vesicles. Involvement of the membrane due to reduced protein attached to the inner surface of the membrane. "Edging" vesicles fuse that leads to the formation of tanks. Gradually, from cisterns begin gemmating synaptic vesicles that are filled acetylcholine.

Pathophysiological aspects of neuromuscular transmission

Violations of transmission of impulses from nerve to muscle called the blockade of neuromuscular transmission. Its reason:

1. Mechanical damage to the nerves which leads to:
- Violation of AP to the nerve terminal – is disrupted nerve impulse activity;
- Disorders axon plasma transport – is not disturbed nerve impulse activity.

2. Toxins and poisons:
- Botulinum toxin - endotoxin *Clostridium botulinum*;
- Snake venom - bunharotoxin;
- Curare - extract that is obtained from the plant *Strychnos* i *Chondodendron*, growing in South America (the poison used since ancient times, such as for the treatment of Indians arrows);
- Insecticides - substances used to combat insects. It organophosphorus compounds: trichlorfon, dichlorvos, karbofos and others;
- Chemical warfare agents: sarin, soman.

Pharmacological preparations that are used for therapeutic and preventive purposes. (See below).

1. Hereditary factors.

An example is the disease *Myasthenia gravis*. The disease occurs with a frequency of 1:20 000. It is manifested by muscle weakness and fatigue due to violation of

neuromuscular transmission.

Basic mechanisms of blockade of neuromuscular transmission:

1. Violation conducting excitement to the presynaptic nerve endings. (See above).
2. Violation axon plasma transport, which can be caused by:

- Mechanical damage to the nerve (in the experiment using the intersection nerve - innervations);
- Breach of micro tubules (in the experiment of inducing some poisons - colchicine, vinblastine);
- Deficiency of energy necessary for rapid aksonnoho transport. There is speculation that this mechanism is important for the development of nerve disorders in beriberi (hypovitaminosis B1) and alcohol intoxication (alcoholic polyneuritis).

3. Violations of ACh synthesis and deposition in nerve terminals. The reasons which may include:

- Lack of initial products ACh synthesis - acetyl-CoA and choline. Lack acetyl-CoA may be associated with disorders of glucose catabolic transformations (e.g., beriberi). Lack choline may be associated with disturbances of its revenues in the nerve cells of the blood of its seizure disorder from the synaptic cleft;
- Deficiency or breach of enzyme activity holinachetyltransferase;
- Lack of synaptic vesicles. Its cause may be a violation of vesicle formation in the Golgi apparatus of the body of the neuron, their transport to nerve terminals, impaired formation of vesicles with the presynaptic membrane.
- Violations of ACh transport into synaptic vesicles axoplasm.

4. Violation release of ACh in the synaptic cleft.

- *In vitro* simulated removal of Ca^{2+} ions from solution or making a solution Mg^{2+} or Mn^{2+}, which are competitors of

Ca^{2+}.

- *In vitro* release of ACh gives botulinum toxin that blocks voltage-calcium channels, which leads to frustration exocytosis.

5. Violation of acetylcholine receptors postsynaptic membrane.

- Reducing the number of acetylcholine receptors. For example, Myasthenia gravis patients are autoantibodies against these receptors. Originally receptors are blocked, and then destroyed;
- Blockade of acetylcholine receptors. It may be irreversible (action α-buntrotoxin) and reversible (EPP).curare action);
- Inactivation (desensitization) of acetylcholine receptors. This condition is characterized by the fact that in the synaptic cleft is sufficient acetylcholine receptors but insensitive to it. It may be prolonged depolarization in the postsynaptic membrane, which is the result of prolonged exposure ACh this mechanism blockade typical of organophosphorus compounds – choline esterase inhibitors (insecticides, chemical warfare compounds).

6. Violation of energy metabolism. Given these disorders suffer all processes that require energy, such as:

- Conduct AP to presynaptic membrane;
- Synthesis and the formation of enzymes, vesicles, mitochondria;
- Rapid axon transport;
- Transport of ACh into synaptic vesicles axoplasm;
- ACh exocytosis;
- Endocytosis (neoplasm of synaptic vesicles with the presynaptic membrane);
- Rapture nerve terminals ACh hydrolysis products (choline and acetate).

Regardless of the causes and mechanisms of clinically blockade of neuromuscular transmission is muscle weakness, muscle fatigue, muscle paralysis. The most severe manifestation is peripheral respiratory arrest, which is an associated violations decrease respiratory muscle.

Pharmacological aspects of neuromuscular transmission

Purpose of treatment often falls interfere with the mechanisms of neuromuscular transmission by medicines.

There are two groups of preparations that affect this process:

1. **Muscle relaxants.** These are substances that are used during anesthesia to prevent reflex contraction of skeletal muscles.

On the mechanism of action are distinguished:

- Depolarizing muscle relaxants (succinyl, choline, ditylinum) – causing prolonged depolarization of the postsynaptic membrane, resulting in a growing inactivation (desensitization) of acetylcholine receptors and neuromuscular blockade;
- Non depolarizing muscle relaxants (Tubocurarin, Diplasinum, Mellictinum) – block acetylcholine receptors, resulting in the ACh can not cause AP.

2. **Choline esterase inhibitors – is medications of achetylholinesterase.** These medications reverse (Physostigmine, Proserin) and irreversible (Phosphacolum) action. These medications activate other choline esterase; increase the content of ACh in the synaptic cleft. They are used in infants, as well as antagonists of acetylcholine receptor blockers, such termination will not depolarizing muscle relaxants after surgery.

9 CONTRACTION OF SKELETAL MUSCLE

Human interaction with the environment can not be made without reducing its muscles. Movements that occur at the same time required to perform simple manipulations, as well as expression of thoughts and feelings through speech, writing, facial expressions, gestures.
About 50 per cent of the body is skeletal muscle, and perhaps another 10 per cent is smooth and cardiac muscle.

Physiologic Anatomy of Skeletal Muscle

Muscle fiber, as each cell has a membrane - sarcolemma, endoplasmic reticulum - sarcoplasmic reticulum, mitochondria, sarcoplasm. His special feature is the presence of myofibrils. Myofibrils consist of bundles of "threads" - myofilaments (thin – actin filaments and thick - Myosin filaments) (fig. 9.1).

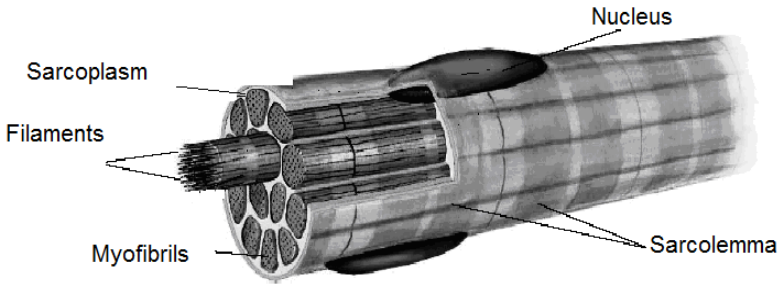


Figure 9.1 - Structure of the muscle fiber

Myofibrils Z-plates divided into several parts - a compartment called a sarcomere. That is sarcomere the portion of the myofibril (or of the whole muscle fiber) that lies between two successive Z discs is called a *sarcomere*. In a relaxed muscle sarcomere length is 2.0 – 2 .5 micrometers.

With the light microscope in sarcomere distinguish light and dark bands. Such cross-striations of myofibrils caused by a special mutual arrangementand of actin and myosin filaments. At the center of each sarcomere have thousands of "thick" myosin filaments with a diameter of about 10 nm. Bundle of myosin filaments in the center of sarcomere looks in the light microscope a dark stripe. Due to the properties of double refraction (anisotropy), this area of sarcomere is called anisotropic disk (A-disk). In the center of A-CD is the area in which no overlapping actin and myosin filaments, which consists only of myosin filaments. This section of the A-disk called H-zone. In the center of H-zones are distinguished thin dark M-line, to which are attached "thick" myosin filaments. At the ends of sarcomere posted "thin" actin filaments, which are attached to the Z-plates. In the light microscope, these areas of myofibrils appear bright bands are called isotropic disks (I disk).

It is from such alternation of light and dark bands in the sarcomere myofibrils of cardiac and skeletal muscle appear their striated appearance.

Sarcomere structure is schematically shown in Fig. 9.2.

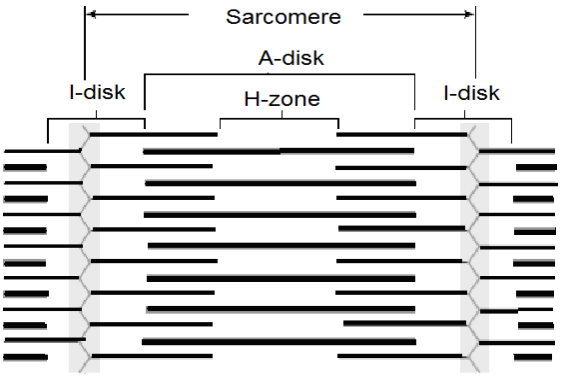


Figure 9.2 – Structure of the sarcomere

Molecular mechanisms of muscle contraction

Molecular mechanisms of muscle contraction explains the theory of Huxley-Hanson – the theory of "sliding" myofibrils (Huxley H.E., Hanson J., 1954)

The main provisions of this theory:

1 Contraction of myofibrils is due to contraction of a large number of sarcomere.

2 During the contraction the length of "thin" actin and "thick" myosin filaments does not change.

3 The process of contraction is a result of sliding actin filaments along myosin filaments.

4 The process of muscle contraction requires energy of ATP.

During muscle contraction under a light microscope observed the following changes:

- reduced length of the sarcomere;
- reduced length of I-dsiks;
- reduced length of the H-zone;
- length of the A-disks does not change.

During muscle relaxations opposite changes occur:

- increasing sarcomere length;
- increasing the length of I-disks;
- increasing the length of H-zone;
- length of the A-disks does not change.

To review the current state of the theory of contraction we need to determine molecular structure of actin and myosin filaments.

The structure of actin and myosin filaments

Myosin filaments – are thick filaments length of 1.6

micrometers. They consist of a protein myosin (molecular weight 500 000).

Myosin molecule consists of two heavy (molecular weight 200 000) and four small (molecular weight 20,000) polypeptide chains. Two heavy chains are combined in a spiral (the so-called "tail" of the molecule). At the end the heavy chains twist and with light make up two heads. Thus, the myosin molecule isolated tail and two heads (fig. 9.3).

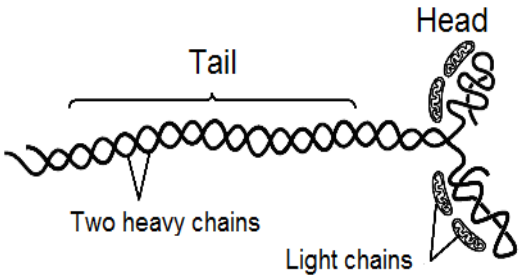


Figure 9.3 - Structure of the myosin molecules

The *myosin filament* is made up of 200 or more individual myosin molecules

Myosin molecules intertwine their tails and form so-called core filaments, from which cross-bridges depart, consisting of head and neck (Fig. 9.4).

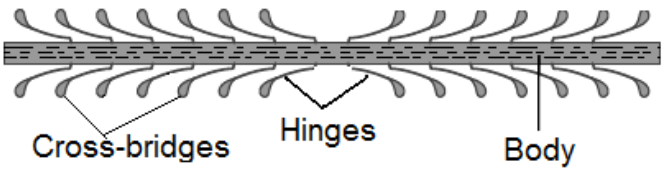


Figure 9.4 – Structure of the myosin filaments

Properties of cross-bridges:

1 Head can bind to actin filaments active centers.

2 Heads have ATPase-activity (ATPase enzyme is activated by actin in the presence of Mg2 + ions and hydrolyze ATP to ADP and inorganic phosphate $P_н$ with release of energy).

3 Heads can bend at the junction of the neck. This place is a kind of hinge mechanism. Bending, head moves associated actin filaments along myosin core.

Actin filaments – are long thin filaments 1 mm and a thickness 7.5 nm. They consist of three proteins:
- Actin;
- Tropomyosin;
- Troponin.

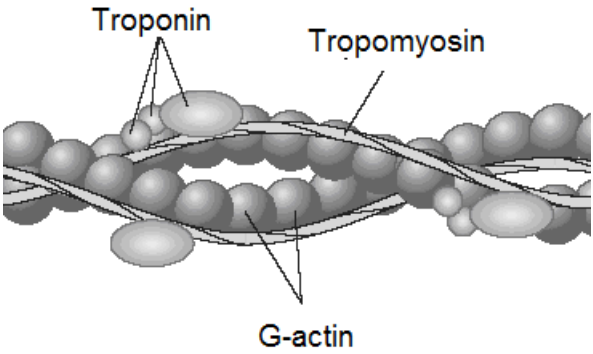


Figure 9.5 – Structure of the actin filaments

Actin is the basis of actin filaments. Two filaments of actin-polymer (F-actin) twisted into double helix. Each F-actin filament is composed of many molecules of actin-monomer (G-actin), whose molecular weight is 42 000. In fact, the F-actin filament resembles a necklace, where beads - G-actin molecule. Each G-actin molecule contains an active center for binding to myosin (binding through ADP, which is actually a bridge between actin and myosin).

Tropomyosin - fibrous protein (molecular weight 70 000, length 40 nm), entangled in a spiral with two F-actin filaments. At rest, when muscle fibers are relaxed, tropomyosin is located so that closes the active centers of actin (one tropomyosin molecule covers seven active centers) and the interaction between myosin heads and active centers of actin is not possible (Fig. 9.6 A). Thus, tropomyosin plays a role of protein that is a blocker of actin active centers.

Troponin - globular protein that consists of three subunits:

• Troponin I - has a high affinity for actin;
• Troponin T - has a high affinity for tropomyosin;
• Troponin C - has a high affinity for Ca^{2+} ions.

Troponin is a protein that regulates the interaction of tropomyosin with actin.

When the concentration of Ca^{2+} ions in the cytoplasm is low, placing troponin such that tropomyosin blocks the active centers of actin. The contraction is not possible (fig. 9.6 A).

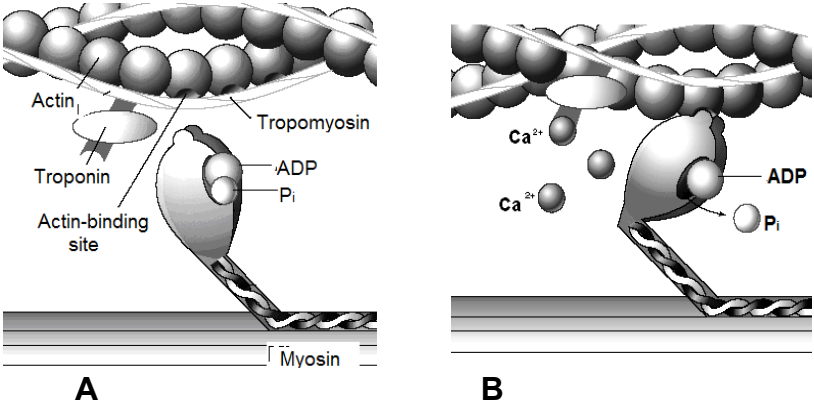


Figure 9.6

With increasing concentration of Ca^{2+} ions in the sarcoplasm of muscle fibers, these ions interact with troponin C

(One troponin molecule binds four Ca^{2+} ions). As a result of this interaction changes conformation of troponin, tropomyosin plunges deep into actin fltament and active centers of actin exempt. The contraction is possible (Fig. 9.6 B).

Molecular mechanisms of muscle contraction

With increasing concentration of Ca^{2+} ions in the sarcoplasm of muscle fibers Ca^{2+} interacts with troponin C and tropomyosin liberates active centers of actin (Fig. 9.6 B). Myosin heads interact with ATP, hydrolyze it to ADP and (Pn) with the release of energy. Products of hydrolysis (ADP and Ph) while remaining bound to myosin heads that need to connect the head to the active center of actin (ADP plays the role of a bridge between actin and myosin). Released energy is accumulated in the hinged mechanism of neck of the cross-bridge (as the spring that is stretched). Head is in the perpendicular position to the actin filaments and interacts with the active center (Fig. 9.7).

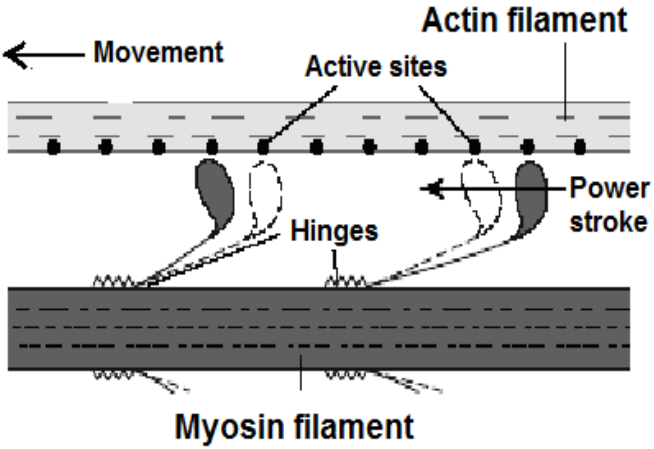


Figure 9.7 – Mechanism of sliding actin filaments

The binding the head with active center causes the head to bend in the neck due to previously accumulated energy stretching (as contraction of pre-stretched spring). This head, bending, entails actin filaments attached and displaces it by about myosin filaments (Fig. 9.7).

In the head, that bended, the molecule ATP replaces ADP and Pn, so the connection between it and the active center of actin destroyed. Once the head was splitting from the active center, ATP is hydrolyzed to ADP and Ph, and the released energy due to head unbendings (as a stretched spring), becomes perpendicular and communicates with the next center of actin. The above cycle is repeated again and again (Fig. 8.9).

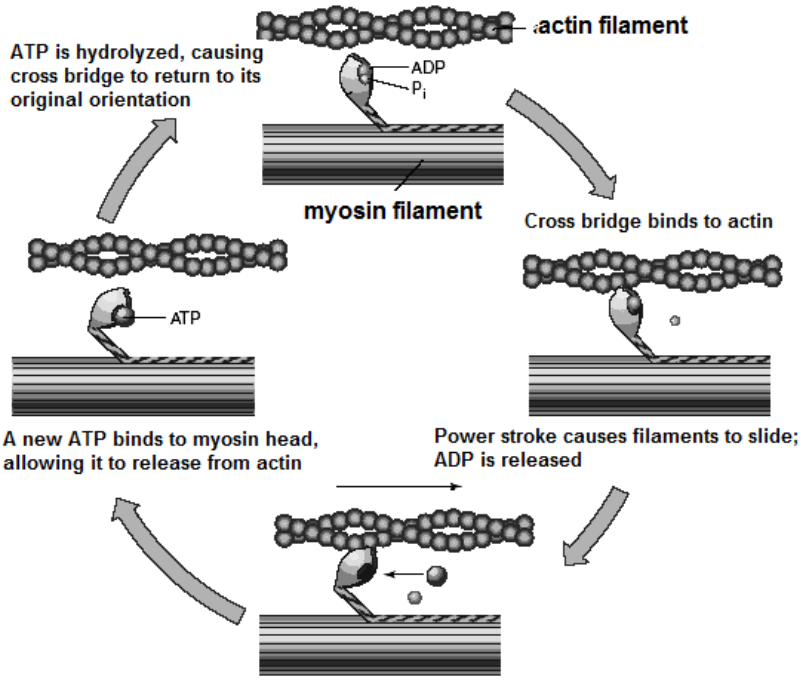


Figure 9.8 – Cross-bridge cycle that causes sliding of the filaments and muscle contraction.

Actin filaments move along miosyn filaments to the center of sarcomere. The described principle of cross-bridge was named – the principle of "paddles". Its basis consists of two cyclical processes:

• Creation and destruction aktomiosyn complexes;

• Bending and unbending heads of cross-bridges.

The movement of a large number of heads creates combined efforts (a kind of "pull"), which promotes actin filament to the middle of sarcomere. With a "stroke" sarcomere is reduced by 1% of its length.

When it comes to reducing sarcomere, you should keep in mind the following:

• Cross-bridges opposite parts miosyn filaments have a different orientation direction. Therefore, the bending-unbending of heads the actin filaments from the various Z-plates of sarcomere move towards each other and the sarcomere length while decreasing;

• Bending-unbending of the heads occurs asynchronously, independently of each other (one bent, unbent the other). If is greater the synchrony of this process, then is greater force contraction. In other words, the greater the number of contacts of cross bridges with actin at each given time, the greater the force contraction.

Stages of muscle contraction

The process of contraction of skeletal muscle is triggered by an impulse that arises in the α motoneurons of anterior horn of the spinal cord.

Reduction process consists of four main stages:

Stage 1. – **Excitation of the membrane of muscle fibers and spread the AP along membrane.**

Terminal nerve fibers that innervate the muscle releases neurotransmitter acetylcholine, which occurs under the

influence of end-plate potential. This AP applies to the membrane of muscle fibers in both directions.

Characteristics of PD, which occurs in skeletal myocytes:

- RP = - 80 -90 mV;
- AP duration = 1.5 ms;
- propagation velocity = 3-5 m / sec.

Stage 2. - Electromechanical coupling.

Electromechanical coupling (coupling between excitation and contraction) – is a transmission signal about contraction from sarcolemma to myofibrils. That transition process of excitation of the membrane of muscle fibers in contraction of myofibrils.

In coupling involved three types of structures:

1. A lateral T-tubules – in tussus ception of sarcolemma placed perpendicular to sarcolemma and to myofibrils. In the middle of the T-tubules contained liquid, this is identical to the composition of the extracellular liquid. In mammals, one sarcomere accounts for two T-tubules at the end miosyn filaments. Membranes of T-tubules able to provide the AP that comes to them on sarcolemma.
2. Terminal tanks - is enhanced part of sarcoplasmic reticulum (SPR), which contact with T-tubules.

3 Longitudinal rolls - is stretched across the membrane components of the SPR.

Terminal cisterns and longitudinal tubules are not connected with the extracellular environment. Their main function is deposit of $Ca2^{+}$ ions.

One transverse T-tubule and two adjacent tanks called *triad* (Fig. 9.9).

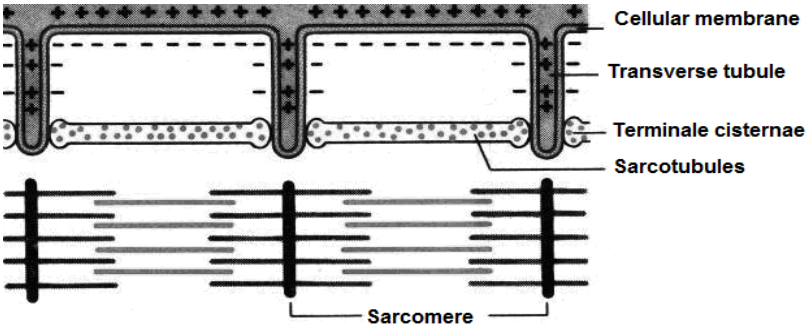


Figure 9.9 – Transverse (T) tubule-sarcoplasmic reticulum system.

Electromechanical coupling is as follows:

1) Conduction of excitation in the T-system. AP extends from sarcolemma on the membrane of T-tubules, which leads to depolarization of the membrane. In places of contact T-tubules with terminal tanks depolarization is transmitted to membrane of SPR.

2) The release of Ca^{2+} ions from the terminal tanks and longitudinal T-tubules in sarcoplasm. SPR membrane depolarization is caused by the rapid opening of Ca-channel membrane tanks and longitudinal tubules. Through open Ca-channels ions of Ca^{2+} by concentration gradient quickly out from the structures of SPR in sarcoplasm.

3) Effects of Ca^{2+} ions to the myofibrils. Due to the Ca^{2+} ions from the SPR concentration of this ion in the sarcoplasm increases of 100 - 1000 times (in the resting Ca^{2+} concentration in the sarcoplasm is 10^{-8} M, and during the reduction of - 10^{-6} – 10^{-5} M). Ca^{2+} interacts with troponin C and tropomyosin releases active centers of actin.

Stage 3. – Actually contraction.

With the opening of the actin active centers begins the process of contraction - sliding actin filaments along miosyn filaments to the center of sarcomere with using ATP.

Stage 4. – Relaxation.
The process of relaxation of myofibrils associated with the restoration tropomiosyn block of actin active centers. This occurs with decreasing concentrations of Ca^{2+} ions in the sarcoplasm to the original level (10^{-8}M). This process is associated with the following mechanisms:

• Jobs Ca-pump SPR membranes. Ca-pumps - the proteins that are embedded in the membrane of SPR and have ATPase activity. Increasing concentrations of Ca^{2+} during contraction to 10^{-6}–10^{-5} M results an activation of Ca-pumps, which are beginning to active transport of Ca^{2+} ions against the concentration gradient from the sarcoplasm in to the SPR. There is binding of Ca^{2+} with Calsequestrin (protein of SPR). Reducing the concentration of Ca^{2+} in the sarcoplasm causes change in conformation of Tropinin and recovery of tropomiosyn blocks. Active centers of actin can not interact with myosin heads, and the contraction stops.

Energy supply of muscle contraction

The process of muscle contraction is energy-dependent process. ATP in muscle fibers used in such processes:

• the work of Na-K-pumps of sarcolemma (Na-K-ATPase). This mechanism provides the excitability of muscle fibers, supported resting potential;

• spatial movement of myosin cross-bridges (myosin heads containing the enzyme ATPase). This is ensured, in fact, the process of contraction - sliding actin filaments along miosyn filaments;

• the work of Ca-pump of SPR (Ca-ATPase). This mechanism provides a process of relaxation of muscle fibers.

Structures that use ATP is sarcolemma, myofibrils, SPR.

Sources of ATP in myocytes are:

• creatinephosphate (CP). This macroergic compound concentration in the cell which is 30 mmol/L.

$$CF + ADP \longrightarrow C + ATP.$$

This reaction provides a rapid replenishment of ATP. Number of creatinephosphate in the cell is small, so by this source the muscle can be contraction during 7-8 seconds;

• anaerobic (anoxic) oxidation of glycogen and glucose (Glycogenolysis and glycolysis). This path provides a contraction of muscle up to 1 minute;

• aerobic oxidation of carbohydrates, fats, amino acids. Oxidation reactions occur in mitochondria, require a large amount of oxygen. This is path provides prolonged contraction of muscles and are a major source of ATP.

The concept of motor unit

The structural unit of muscle is the muscle fiber. Functional unit of muscle called the motor (motor) units.

Motor unit consists with α - motoneurons of anterior horn of spinal cord and all the muscle fibers innervated by this neuron. Excitation of motoneurons is a simultaneous contraction of all motor units.

Classification of motor units:

- *By function.*

On this basis distinguish fast and slow motor units. For fast motor units is characterized by very rapid and strong contraction. They provide short-distance running (sprinters), different types of jumps. For the slow motor units are typical slow but prolonged contractions. They provide long-distance running (stayyery), maintaining body posture. Comparative characteristics of fast and slow motor units are shown in the table. 9.1.

Table 9.1

Comparative characteristics of fast and slow motor units

Fast motor units	Slow motor units
Contain little myoglobin (so-called white muscle)	Contains a lot of myoglobin (the so-called red muscle)
They consist of long muscle fibers in size	They consist of short muscle fibers in size
The main source of energy - and anaerobic glycolysis glycogenolysis	The main source of energy, aerobic oxidation of carbohydrates and fats
They contain few mitochondria	Contain many mitochondria
Have relatively poor blood supply	Have a good blood supply
Very well developed SPR	SPR developed worse

- *By the structure.*

On this basis distinguish small and large motor units. The structure of small motor units is a small number of muscle fibers. For example, in laryngeal muscle motor units consisting of 2-3 muscle fibers, in the muscles of the face - 10-12. Typically, small motor units are excited weak nerve incentives, since the excitability of neurons is high. The grand muscle units is a lot of muscle fibers. For example, in muscles of limbs and trunk of their number reaches several hundreds. Large motor units are excited stronger incentives compared to small, because the excitability of nerve fibers is lower.

Physiological characteristics of muscle contraction

1 Load

Depending on the type of load there are 2 contraction models of isolated muscle:

• isotonic contraction. This type of contraction occurs when the muscle moves the cargo. One end of the muscle fixed, the other - free, bound with a cargo;
• isometric contraction. This type of contraction occurs when both ends of the muscle fixed (Table 9.2).

Table 9.2

Comparative characteristics of contraction regimes

isotonic contraction	isometric contraction
During the contraction decreases the length of muscle	During the contraction of muscle length does not change
Muscle tension does not change	Muscle tension increases
Running external work (moving cargo in space)	Exterior work not implemented

When the issue is not isolated muscle, but the muscle that functions in the body, then distinguish the following types of contraction:

• axotonical contraction. This is type of contraction, in which both reduces the length of muscle and increasing its tension. This type of reduction provides a dynamic moving body in space and some of its parts in respect to each other;

• isometric contraction. This is type of contraction, in which muscle tension increases without changing their length. This static type of contraction provides the contraction to support the posture of the body.

2 Power

The power developed by muscle during contraction is the sum of the powers of individual muscle fibers.

There are maximum and absolute power of contraction.

The maximum power in the isotonic mode is determined by the maximum weight of cargo, which raises the muscle during the contraction, in isometric mode - load, which develops muscle.

Maximum power is expressed in kg.
The maximum power depends on the structure of muscle, its functional state. For example, dog jaw muscles can lift cargo, 8.3 times greater than its mass.
However, the maximum force does not allow comparing the strength of various muscles. This is another indicator.
Absolute power of contraction – is the ratio of maximum isometric contraction power to physiological cross-sectional area of muscle.
Absolute power is expressed in kg/cm2.
Physiological cross-section of a muscle is cross-sectional area of fibers that make up this muscle.
As is known, distinguish parallel-fibrous, fusiform, cirrus muscles (Fig. 9.10).

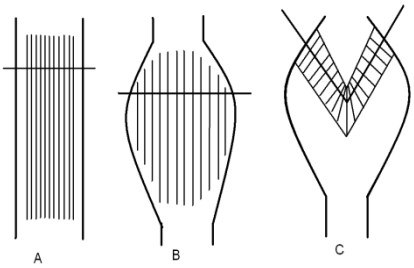


Figure 9.10 - Type of structure of different muscles: A - muscle fibers with parallel arrangement; B - fusiform muscles; C - cirrus muscles

Physiological cross-section coincides with the geometric only parallel-fibrous muscles. In the fusiform, and especially in cirrus it is much larger than the geometric.

Muscles of the oblique arrangement of fibers have a greater physiological cross-section and thus more power.

The absolute power of some muscles is shown in the table. 9.3.

Table 9.3

Name of muscle	Absolute power kg/sm^2
Human calf muscle	5,9
Flexing muscle shoulder	8,1
Masticator muscles	10,0
Biceps	11,4
Triceps	16,8
Smooth muscle	1,0

Factors that determine the power of muscle contraction:

1. At the molecular level power of contraction is determined by the number of complexes formed between myosin heads and actin filaments active centers.

In turn, the number of formed actomyosin complexes depends on:

• Outgoing sarcomere length.

The maximum power of contraction is the muscle developing at sarcomere length of 2.0 - 2.25 microns. It is at such length the number of actomyosin complexes are greatest (Fig. 9.11 A).

If sarcomere length is less than 2.0 microns, the actin filaments are coming one after another and prevent the formation actomyosin complexes.

If sarcomere length greater than 2.25 microns, the zone of overlap actin filaments and miosyn filaments decreases, thus decreasing the number of myosin heads that can attach to the active centers of actin (Fig. 9.11 B, C).

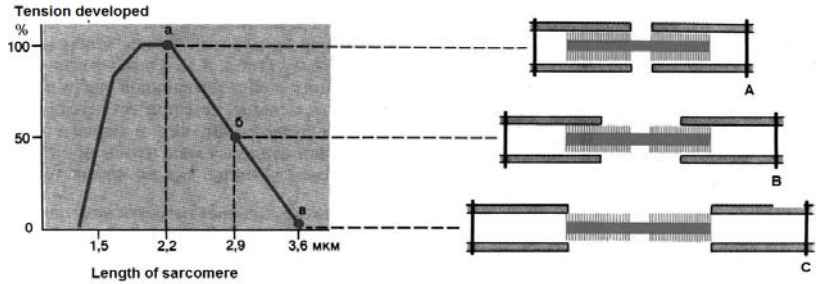


Figure 9.11 - Relation between sarcomere length and the number of actomyosin complexes

• Quantities of open active centers of actin filaments, which is determined by the concentration of Ca^{2+} ions in the sarcoplasm.

More Ca^{2+} ions, the more complexes formed between troponin C and Ca^{2+}, more open active actin centers, more actomyosin complexes formed and more power of contraction.

• Opportunities heads cyclically disconnect from one active site and join another. This possibility depends on the presence of ATP.

Thus, the main factors that determine the power of contraction at the molecular level, is the original length of the sarcomere, the concentration of Ca^{2+} ions in the sarcoplasm, the presence of ATP.

II At the cellular level power of contraction depends on the number of myofibrils in the muscle fiber. If is more myofibrils, then is greater power of contraction.

With enhanced muscle work is occur hypertrophy, characterized by an increasing number of myofibrils and increases the power of contraction.

The mechanism of hypertrophy explains F. Meyersona theory according to which, with enhanced working muscle consumes more ATP, as a result of hydrolysis by ADP is formed. ADP is a regulator of transcription in the nucleus. With intensification the processes of transcription and

translation increased biosynthesis of structural proteins, a growing number of myofibrils.

III On the organ level rise the power of contraction is caused by the phenomena of spatial and frequency summation.

Spatial summation - is the increase a power of muscle contraction by the involvement in the process of more motor units. With weak incentives are contract only small motor units of muscle. With increasing stimulus intensity, more motor units begin to engage in the contraction process. If is more motor units excited, then is greater power of contraction in total muscle.

Frequency summation (tetanisation) – is increase of power of muscle contraction by increasing the frequency of stimulation. With increasing stimulation frequency to 50 pulses per second, the power of muscle contraction increases 3 – 4 times.

3 Duration

By the duration the contraction are rare and titanium.

Isolated contraction occurs under the condition where one muscle fiber affects one stimulus.

There ate three phases in single muscle contraction (Fig. 9.12):

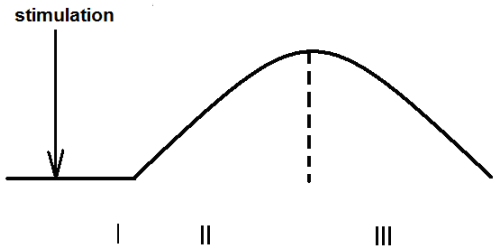


Figure 9.12 – Single contraction curve: I - latent period; II - the period of contraction, III- the period of relaxation.

I phase - latency period (time from start of the stimulus to the contraction of muscles), which lasts on average 15 ms;
II phase – the period of contraction (gradual increase in muscle tension), which lasts on average 50 ms;
III phase - the period of relaxation (the gradual reduction of muscle tension), which lasts an average of 50 ms.
Tetanic contraction (tetanus) – long and strong muscle contractions associated with increased frequency of stimulation. For the occurrence of tetanus each successive stimulus must act on the muscle, which has not finished a cycle of contraction-relaxation.

The basis of tetanus is the phenomenon of summation (imposing a contraction on the other). To place summation, it is necessary that the interval between incentives was no less than the refractory period of muscle fibers.

Depending on the frequency of stimulation distinguishes two types of tetanus: 1) *serrated,* occurs at low frequency stimulation (5-50 Hz) when every to account for the phase relaxation of the previous contraction;

2) *smooth (solid),* occurs when high frequency stimulation (50 Hz) when every successive incentive to account for the contraction phase of the previous phase of contraction (Figure 9.13).

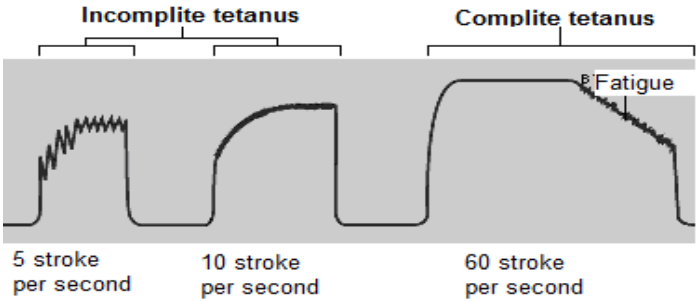


Figure 9.13 - Types of tetanus

During the tetanus increased power of muscle contraction. The reason of this is the growth of the concentration of Ca^{2+} ions in the sarcoplasm, because during the relaxation he fails to return into the SPR.
It should be remembered that during the tetanus consist contractile responses, but not AP (fig.9.14).

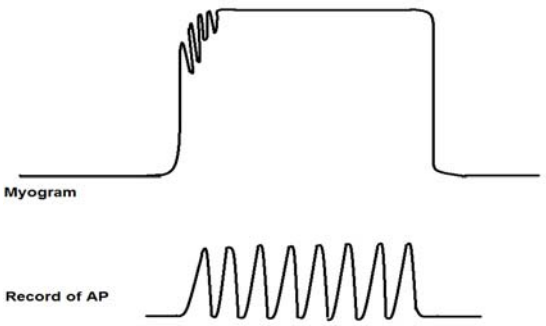


Figure 9.14 - Registering the amplitude of contractions and AP

4 Speed

Speed of muscle contraction is determined by two factors:
• type of motor units (fast or slow).
Fast motor units are characterized by very rapid and strong contraction, and slow - slow, but long. This is because the maximum speed of sarcomere shortening (no load) is equal to the maximum speed of sliding actin filaments and miosyn filaments a relative one. The more cross bridges break down of ATP and interact with actin, the greater the speed of sliding. Myosin has a low ATPase activity in slow motor units, so the process takes place in them slowly;
• the load on it.
Speed of contraction is inversely proportional to the load on the muscles. Graphically this pattern is called the curve "load speed" or "power-velocity" (Hill's curve).

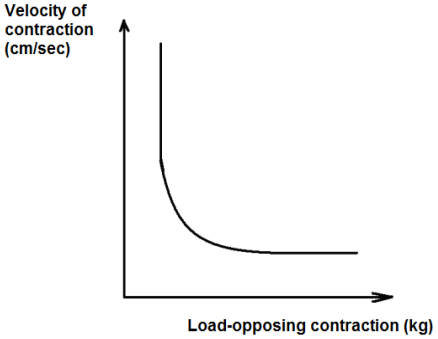


Figure 9.15 – Relation of load to velocity of contraction in a skeletal muscle

5 Work

The work of muscle measured by the product of weigh of the lifted load on the size of shortening of the muscle. There are 2 types of muscle's work:

- External (dynamic);
- Internal (static).

Outdoor work – is a work of moving cargo body or its parts in space. She is performed in experimental conditions in isotonic mode of contraction, in a body at axotonical contraction.

Outdoor work depends on factors such as:

1) Speed of the contraction. The maximum external work performed at medium speed (the law of the medium speeds);
2) Load. The maximum external work performed at medium load (the law of the medium load).

Static work - a work in which muscle fibers develop tension, but not change its length. It is in isometric mode (for example, work with containment of the cargo). Inner work is associated with the processes developing in the same muscle fiber (mechanical work to overcome friction, osmotic work on moving ions, etc.) 6.

6. Fatigue

Fatigue - temporary reduction in muscle performance that occurs as a result of the work and disappears after rest. Fatigue finds himself by the reducing of the contraction power (amplitude), increasing latency period and duration of relaxation phase.

Factors that cause fatigue:

I) At the cellular level (in conditions in vitro in isolated muscles):

• reduction of inventories of ATP (occurs due to decreased glycogen reserves, interruption resynthesis of ATP and creatinephosphate);

• accumulation of metabolic products. Acidic metabolic products (lactic acid, pyruvic acid, phosphoric acid, etc.) is diffuse into the around cell space and reduce the excitability of muscle fibers, inhibit glycolysis and ATP formation, competitively bind to troponin C, displacing calcium.

It should be noted that isolated skeletal muscle fatigue in his direct irritation is the laboratory phenomenon. In a body to muscle constantly enters the blood, which supplies the necessary nutrients and takes away the metabolic products. Therefore, in vivo the fatigue of the motor apparatus during prolonged work develops more difficult and depends on other factors.

II) On the organ level (in the in vivo condition):

• Fatigue related motor nerve centers;

• Fatigue of the neuro-muscular synapses.

Proof that the lower efficiency of muscles primarily is concerned with the fatigue of nerve centers, there are Sechenov's experiments in which he proved that rehabilitation of human hands tired muscles faster if other hand or muscles of lower extremities work in the rest period. Sechenov I.M. called this relaxation as active.

Proved that the muscles that perform static work, tired

faster than muscles that perform dynamic work. For example, a person is harder to stand than to walk.

To study muscle fatigue in humans in laboratory conditions using ergographs – devices to record mehanohramms with rhythmic movements that are performed by the muscle group. The simplest is Moss's ergograph. The device records the amplitude of finger movements, to which is attached cargo. Record fatigue curve called ergogramme (fig.9.16).

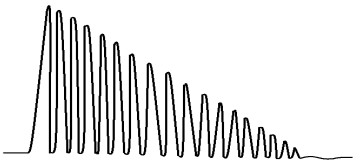


Figure 9.16 – Ergogramme recorded on Moss's ergometer

There are ergographs that capture certain human movements. Thus, in clinical widely used bicycle ergograph (bicycle ergometer). The patient moves the foot pedal device with a specific resistance movement. Special sensors register the motion parameters and indicators respiratory, circulatory and ECG. Bicycle ergometer determines the functionality of the human body.

10 PHYSIOLOGY OF SMOOTH MUSCLE

Smooth muscle consists of multiple layers of spindle-shaped cells. It is involved in the function of many organs (stomach, intestine, gall bladder, urinary bladder, uterus, bronchi, eyes, etc.) and the blood vessels, where it plays an important role in circulatory control. Smooth muscle contains a special type of F-actin- tropomyosin and myosin II filaments, but lacks troponin and myofibrils (Fig. 10.1). Furthermore, it has no distinct tubular system and no sarcomeres (nonstriated). It is therefore called smooth muscle because of this lack of striation. Smooth muscle filaments form a loose contractile apparatus arranged approximately longitudinally within the cell and attached to discoid plaques, which also provide a mechanical means for cell–cell binding of smooth muscle. Smooth muscle can shorten much more than striated muscle.

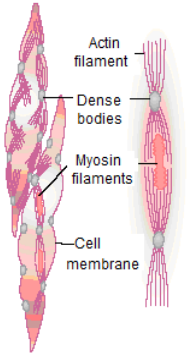


Figure 10.1 – Structure of smooth muscle.

The actin filaments are organized through attachment to the dense bodies that contain a-actinin, a Z-band protein in skeletal muscle. Thus, it is assumed that the dense bodies function as Z-lines. The ratio of thin to thick filaments is much higher in smooth muscle (~15:1) than in skeletal muscle (~6:1).

Smooth muscle is rich in intermediate filaments that contain two specific proteins, desmin and vimentin.

Smooth muscle fibers are much smaller (2-10 m in diameter) than skeletal muscle fibers (10-100 m). It is customary to classify smooth muscle as single-unit and multi-unit smooth muscle (Fig. 10.2). The fibers are assembled in different ways. The muscle fibers making up the single-unit muscle are gathered into dense sheets or bands. Though the fibers run roughly parallel, they are densely and irregularly packed together, most often so that the narrower portion of one fiber lies against the wider portion of its neighbor. These fibers have connections, the plasma membranes of two neighboring fibers form gap junctions that act as low resistance pathway for the rapid spread of electrical signals throughout the tissue. Most smooth muscles—including those in the digestive tract and uterus—are single-unit. The multi-unit smooth muscle fibers have no interconnecting bridges. They are mingled with connective tissue fibers. Examples of multiunit smooth muscles are the arrector pili muscles in the skin and the ciliary muscles attached to the lens of the eye.

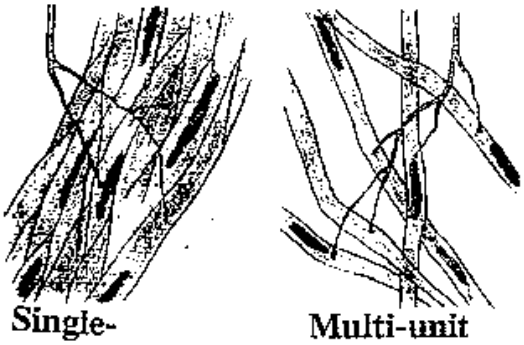


Figure 10.2 – Single-unit and multi-unit smooth muscle.

Excitation-contraction coupling

A smooth muscle is excited by external stimuli, which causes contraction, like skeletal occurs in 4 stages:

Stage 1. Inducing stimuli.

In skeletal muscle there is only one initiator reduction - an electrical nerve impulse. The smooth muscle of the initiators can be 5:

- nerve stimulation;
- hormonal stimulation;
- mechanical stretching of muscle fibers;
- changes in the chemical composition of interstitial fluid;
- spontaneous initiation.

The principle reason for the different types of initiation is the existence of the smooth muscle membrane proteins of different types of protein-receptors.

The common feature of initiating factors is that they are due to different mechanisms leading to increased intracellular concentrations of Ca^{2+} ions. Ca^{2+} ions in the smooth muscles perform two important functions: taking part in the generation of action potential and ensure the reduction.

Consider the basic mechanisms of initiation of smooth muscle contraction.

The nervous stimulation.

Smooth muscles have sympathetic and parasympathetic innervations. Pulses on fibers of the autonomic nervous systems are going to the nerve endings, which have numerous varicose that store neurotransmitter. In smooth muscle there issued neuromuscular synapses, so excited autonomic fibers neurotransmitter is released at the cell surface. Distance diffusion of neurotransmitter is higher than in skeletal muscle, so the latency period greater response.

Neurotransmitter is interacts with receptor of smooth

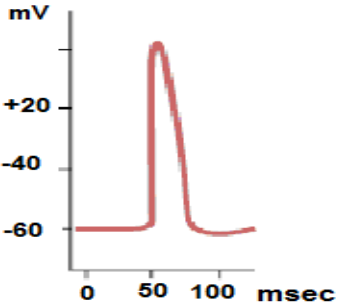
muscle cells (SMC). In the membrane of smooth muscle cells have two types of receptors: excitable (their activation leads to reduction) and inhibitory (their activation leads to relaxation).

The value of the membrane potential of smooth muscle is varies depending on the type of fiber and functional status. In normal resting membrane smoothly muscle cells has the potential -50-60 mV.

The emergence of AP is caused by the entrance of Ca^{2+} ions into the cell (instead of Na^{+}-ions, as in skeletal muscles) through Ca^{2+}-voltage-channels in the membrane of SMC is much more than Na^{+}-ions. Ca^{2+}-channels more slowly than Na^{+}-channels, because steepness of increase in smooth muscle cell action potential is less.

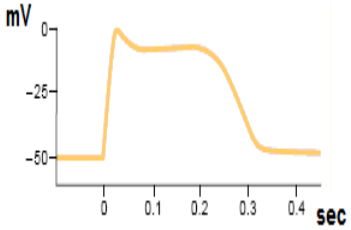
In the SMC are appearing two types of AP.

1. Spike-potential.



Duration 10 - 50 msec

2. Plateau.



Duration to 0,3 sec.(300 msec)

Figure 10.3 – Types AP of smooth muscle cells

The action potential extends along the membrane and through Nexus passes on neighboring cells.

1. Hormonal stimulation.

Among the major humoral factors that cause contraction of smooth muscle is norepinephrine, epinephrine, serotonin, histamine, angiotensin, vasopressin, oxytocin.

There are three mechanisms of hormonal stimulation of SMC:

- Hormone is interacts with the receptor which leads to conformational changes in the protein receptor and opening of calcium channels. Initial depolarization is develops due to the entrance Na^+ i Ca^{2+} ions in the SMC. The initial depolarization is causes the opening of Ca^{2+}voltage- channels, massive Ca^{2+} ions entry into the cell and the emergence of AP. This mechanism is similar to the stimulation of nerve stimulation. It is quite rare.
- Hormone is interacts with the receptor, which leads to the opening of chemo-sensitive, and then potential-dependent calcium channels and entry of Ca^{2+} ions into the cell. There is a depolarization, which does not reach a critical level and AP does not occur. This mechanism is the most common.
- Hormone is interacts with the receptor, which leads to the formation of secondary mediators (messengers) and phosphorylation of protein Ca-channels of sarcoplasmic reticulum, the opening of these channels and release of Ca^{2+} from SPR. This mechanism takes place in the context of SMC, which is moderately developed SPR, as most of MMC reticulum poorly developed and is only 2% of the volume of the cytoplasm.

2. Mechanical stretching of smooth muscle.

When stretching visceral SMC they have a spontaneous action potential that causes contractions. This potential is the result of a combination of slow waves of depolarization (Fig. 10.4) and reduction of negative value of the potential arising

from the tension.

3. Spontaneous contractions.

Such action potential generated in some so-called pacemaker SMC and applies them to all other SMC. The basis of the action potential generation is slow undulating rhythmic changes in membrane potential (called pacemakers wave). When this wave reaches the level is -35, there is one or more AP, which is transmitted to neighboring cells. There is a hypothesis that the cause pacemaker waves are rhythmic changes in the permeability of ion channels or activity of Na-K pump.

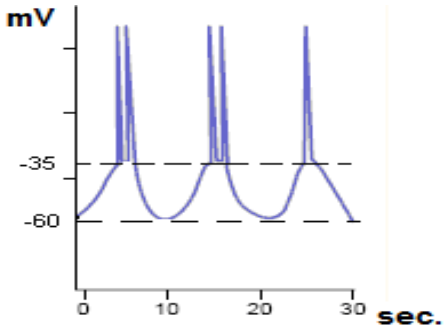


Figure 10.4 – Wavelike changes in smooth muscle membrane potential and action potential generation.

4. The changes the chemical composition of tissue fluid.

There are many local chemical factors that affect the processes of reduction, relaxation SMC. These are including a lack of oxygen, excess CO_2, excess acidic foods and H^+ ions.

Very important of this mechanism is initiating contraction in the regulation of local blood circulation. These factors of feedback are causes relaxation of SMC followed vasodilatation. The impact of these factors on the functioning of SMC is detailed study to date pathophysiology.

Stage 2. Linking between stimulus and contraction.

Linking between stimulus and contraction is achieved by Ca^{2+} ions. The main source of Ca^{2+} is extracellular environment. There is a large concentration gradient of ions between the extracellular and intracellular fluid (inside the cell – 10^{-7} M, outside the cell - 10^{-3}M). Calcium is enters to the SMC due to opening of Ca^{2+}voltage-channels during the action potential (nerve stimulation and mechanical stretch), or potential dependent (chemo sensitive) Ca^{2+}-channels without the development of AP (hormonal stimulation and the action of certain chemicals). SPR values as a source of intracellular Ca^{2+} ions is small, as SPR in smooth muscle is rudimentary and only 2 - 7% of the volume of the cytoplasm.

Further action Ca^{2+} ions as a regulator of muscle contraction in smooth muscle is significantly different from that of skeletal muscle. In SMC is missing troponin mechanism of regulation rates (no protein troponin). However, this mechanism is another protein that can bind Ca^{2+}-calmodulin. This process occurs as follows. Ca^{2+} ions are bind to calmodulin and to form a complex that activates the enzyme myosin kinase. Myosin kinase phosphorylates (adds phosphoric acid) light chains of myosin heads. Phosphorylated myosin heads are acquire the ability to form complexes with actin filaments (dephosphorylated head lose that ability).

Stage 3. The actual contraction.

Molecular mechanisms of reduction are the same as in skeletal muscle – actin filaments are slide along myosin.

The main difference between the actual processes of reduction SMC is that the cycle of formation latch-bridge – its cleavage - the formation of a new bridge in smooth muscle is much higher (10 – 300 times) than in skeletal muscle fibers. This means that the duration of each newly formed latch-bridge

in SMC more as compared to skeletal muscle fibers. This is due to lower activity of ATP-ase proteins. Low rate of formation of new latch-bridges causes a number of functional characteristics of smooth muscle. These are:

- Cycle duration of contraction-relaxation in SMC to 30 times greater than in skeletal muscle. Smooth muscle may be able to reduce hours and days, the so-called state of prolonged muscle tone.
- The maximum power reduction of SMC, is calculated per unit area of cross section even slightly higher when compared with skeletal muscle (smooth muscle – 4-6 kg/cm^2, 3-4 kg/cm^2).
- Speed reduction is much less than in skeletal muscle.
- Use less ATP.
- Have a low fatigue.

Step 4 – relaxation.

This stage is associated with the removal of Ca^{2+} ions from the cell. When the concentration of Ca^{2+} is reduced to the initial level of 10^{-7}, enzyme myosin phosphotase is activated. It is dephosphoryliated myosin heads which lose the ability to interact with actin.

The following mechanisms for removing Ca^{2+} from SMC:

• Most importantly, the work of Ca^{2+}-pump the plasma membrane, which removes Ca^{2+} in the extracellular environment;

• Na^{+}-Ca^{2+} antiport.