**(Slide 1) Lecture 1**

**Physiology of excitable tissues**

**(Slide 2)** Lecture plan:

1. Physiology as a fundamental biomedical science.
2. What is homeostasis?
3. Excitability and excitation.
4. Membrane and ionic mechanisms of membrane potential.
5. Action potential and its phases.
6. Mechanisms of nerve impulse conduction along nerve fibers.

**(Slide 3) Physiology is the science of life.** It is the branch of biology that aims to understand the mechanisms of living things, from the basis of cell function at the ionic and molecular level to the integrated behaviour of the whole body and the influence of the external environment. Research in physiology helps us to understand how the body works in health and how it responds and adapts to the challenges of everyday life; it also helps us to determine what goes wrong in disease, facilitating the development of new treatments and guidelines for maintaining human and animal health. The emphasis on integrating molecular, cellular, systems and whole body function is what distinguishes physiology from the other life sciences.

**(Slide 4)** Types of human physiology:

1. **Cell physiology.** This is the cornerstone of human physiology; it is the study of the functions of cells.
2. **Special physiology.** This is the study of the functions of specific organs. For example, renal physiology is the study of kidney function.
3. **Systemic physiology.** It includes all aspects of the function of the body systems, such as cardiovascular physiology, respiratory physiology, reproductive physiology etc.
4. **Pathophysiology.** It is the study of the effects of diseases on organ or system functions (pathos is the Greek word for disease).

Physiology, together with anatomy, histology, and biochemistry, is one of the most important medical and biological sciences that provide the basis for further medical education.

**(Slide 5)** The word physiology is of Greek origin and consists of two words: “physis” meaning nature and “logos” meaning science, so in the broad sense physiology is a science about nature. In the narrow sense, physiology is a science about functions of a human and animal organism. The term “function” is derived from the Greek word “functio” meaning activity. **A function is a manifestation of vital activity of the whole organism and of its systems, organs and tissues, which provides adaptation of an organism to changing environmental conditions, or changes the environment to the requirements of an organism with the aim of maximal adaptation.** So, the subject of physiology is a function. **For example, the slide shows the functions of the endocrine system and blood.**

**(Slide 6)** Functions can be divided to simple and complex. An example of a simple function is transport of low-molecular substances across the biological membrane. Higher mental functions of a human are examples of complex functions.

**(Slide 7)** Functions can also be classified into inborn and learned (acquired). Examples of inborn functions are numerous unconditioned reflexes inherent to humans: sucking, swallowing, pupillary reflexes. Examples of learned functions are acquired, or conditioned, reflexes: food, defense and other reflexes.

By time of realization, functions can be categorized into static and dynamic. An example of a static slowly-realizing function is muscle tone. An example of a dynamic rapidly-realizing function is a single contraction of a skeletal striated muscle.

You've already seen the video of homeostasis. More information about it.

**(Slide 8)** Maintaining a stable system requires the body to continuously monitor its internal conditions. Though certain physiological systems operate within frequently larger ranges, certain body parameters are tightly controlled homeostatically. For example, body temperature and blood pressure are controlled within a very narrow range. A set point is the physiological value around which the normal range fluctuates. For example, the set point for typical human body temperature is approximately 37°C. Physiological parameters, such as body temperature and blood pressure, tend to fluctuate within a range of a few degrees above and below that point. Receptors located in the body’s key places detect changes from this set point and relay information to the control centers located in the brain. The control centers monitor and send information to effector organs to control the body’s response. If these effectors reverse the original condition, the system is said to be regulated through negative feedback. Control centers in the brain and other parts of the body monitor and react to deviations from this set point using negative feedback. Negative feedback is a mechanism that reverses a deviation from the set point, and in turn, maintains body parameters within their normal range. The maintenance of homeostasis by negative feedback goes on throughout the body at all times and an understanding of negative feedback is thus fundamental to an understanding of human physiology.

**(Slide 9)** A negative feedback system has three basic components: a sensor, control center and an effector. A sensor, also referred to a receptor, monitors a physiological value, which is then reported to the control center. The control center compares the value to the normal range. If the value deviates too much from the set point, then the control center activates an effector. An effector causes a change to reverse the situation and return the value to the normal range. In order to set the system in motion, a stimulus must drive a physiological parameter beyond its normal range (that is, beyond homeostasis). This stimulus is “heard” by a specific sensor. For example, in the control of blood glucose, specific endocrine cells in the pancreas detect excess glucose (the stimulus) in the bloodstream. These pancreatic beta cells respond to the increased level of blood glucose by releasing the hormone (insulin) into the bloodstream. The insulin signals skeletal muscle fibers, fat cells (adipocytes), and liver cells to take up the excess glucose, removing it from the bloodstream. As glucose concentration in the bloodstream drops, the decrease in concentration − the actual negative feedback − is detected by pancreatic alpha cells, and insulin release stops. This prevents blood sugar levels from continuing to drop below the normal range.

And we move on to the main topic – **Physiology of excitable tissues.**

**(Slide 10)** Professor Luigi Galvani at the University of Bologna conducted a series of experiments on a frog preparation at the end of the 18th century, which laid the foundation for research on bioelectric phenomena.

**(Slide 11)** The main manifestations of life.

**(Slide 12)** Varieties of biological reactions.

**(Slide 13)** Types of excitable tissues.

**(Slide 14)** The following properties are inherent in excitable tissues.

**(Slide 15)** Cell membrane structure (video).

**(Slide 16) Distribution of ions between the extra- and intracellular environment in the motor neurons of the spinal cord.** All cells of the body have an electric charge due to the unequal concentration of cations and anions in the outer and inner membrane layers. The inner membrane layer has a negative charge, the outer layer has a positive charge. Sodium is the most abundant cation in the extracellular environment, potassium is the most abundant cation in the intracellular environment. Different concentration of anions and cations is a consequence of the unequal membrane permeability for different ions. The membrane permeability is determined by the presence of ion channels in its composition and the size of the channels. The ionic permeability of the membrane changes when the stimulus acts on the cell. As a result, ions move rapidly across the membrane according to an electrochemical gradient (for example, positive ions move towards an excess negative charge and a lower concentration of this ion). This is the process of excitation.

**(Slide 17)** Passive transport is represented by processes of simple and facilitated [**fəˈsɪlɪteɪted**] diffusion. **Simple diffusion** follows a concentration or electrochemical gradient. This type of diffusion is typical for water and gases dissolved in it, fat-soluble substances, as well as some polar molecules of small size. **Facilitated diffusion** occurs with the participation of carrier proteins or through specialized ion channels.

**(Slide 18)** A change in resting potential or membrane potential underlies the process of arousal. Resting potential is the difference in electrical potentials inside and outside the cell. It is always negative and has constant values for each type of cells. The resting potential for neurons is -70 mV, for muscle fibers it is -90 mV. Negative potential values are determined by the movement of potassium and sodium ions across the cell membrane. Potassium leaves the cell in much larger quantities than sodium enters the cell. The membrane permeability for potassium ions is 25 times higher than for sodium ions. In addition, organic anions cannot escape from the cell due to their large size. Accordingly, more negative ions are inside the cell at rest and more positive ions are outside the cell.

The membrane potential in the state of cell rest remains at the same level. Hence, there is an active mechanism for maintaining the membrane potential. Ion pumps are such mechanisms. For example, the sodium potassium pump is realized by the energy of the adenosine triphosphate molecule.

**(Slide 19)** The Sodium-Potassium Pump (video).

**(Slide 20)** Increasing the permeability of the membrane for sodium ions underlies the excitation of nerve and muscle cells. This increase is carried out due to the opening of additional sodium channels and the appearance of transmembrane currents, which leads to a rapid change in the membrane potential and the appearance of an **action potential**. Thus, the action potential is of a sodium nature in contrast to the resting potential. The excitation process includes the generation of an action potential, its propagation and the specific tissue response to this potential (for example, muscle cell contraction or secretion).

**The action potential threshold** is the potential level at which membrane depolarization triggers the action potential. The action potential threshold is most often minus 50 mV. The difference between the membrane potential and the action potential threshold is called the **critical depolarization level**. The lower the action potential threshold, the lower the critical level of depolarization and the higher the excitability of the cell.

**An action potential is a high-amplitude and rapidly propagating signal across the membrane that provides information transfer.** A typical peak-like potential is when registering an action potential with the following phases:

1. **The depolarization phase** is accompanied by a rapid increase in potential from negative values to a positive peak - overshoot which is about plus 30 mV.

2. **The repolarization phase** is accompanied by the restoration of the initial level of the membrane potential. Trace potentials are distinguished here: trace negativity (hyperpolarization) and trace positivity (depolarization).

The depolarization phase is characterized by the opening of sodium channels. Sodium channels close at their peak and potassium channels open − the process of repolarization begins. The maximum opening of potassium channels occurs at the end of repolarization and trace hyperpolarization occurs. Na+/K+ (sodium/potassium) pump is activated against the background of a slow phase of repolarization (its trace negativity) and returns the membrane potential to its original state.

**(Slide 21)** Refractory is non-excitability. Closed sodium channels do not immediately restore their ability to activate. Accordingly, the cell loses its ability to excite during the entire stage of depolarization of the action potential and partially the phase of depolarization. This is called the **absolute refractory period**. Sodium channels gradually leave the state of inactivation and the cell's excitability is slowly restored. This period is called the **relative refractory period**. But the strength of irritation must be increased during this period in order to excite the cell.

**(Slide 22)** There are two types of stimuli: **adequate and inadequate**. An adequate stimulus can cause irritation in small doses. These are stimuli to the action of which the tissue has adapted in the process of evolution. An inadequate stimulus can cause excitement but more force must be applied. The tissue may be damaged in this case.

**(Slide 23)** There are three laws of irritation of excitable tissues:

1) the law of the force of irritation;

2) the law of the duration of irritation;

3) the law of the gradient of irritation.

**(Slide 24)** **Law forces of irritation** establishes the dependence of the response on the strength of the stimulus. This dependence is not the same for individual cells and for the whole tissue. For single cells, addiction is called all-or-nothing. The nature of the response depends on the sufficient threshold value of the stimulus. When exposed to a subthreshold value of irritation, there will be no response (nothing). When the stimulus reaches the threshold value, a response occurs, it will be the same when the threshold and any suprathreshold value of the stimulus (part of the law is all).

**(Slide 25)** **Law duration of irritation**. The response of the tissue depends on the duration of the stimulation, but is carried out within certain limits and is directly proportional. There is a relationship between the strength of irritation and the duration of its action. This relationship is expressed as a force versus time curve. This curve is called the Goorweg-Weiss-Lapik curve. The curve shows that no matter how strong the stimulus, it must act for a certain period of time. If the time period is short, then the response does not occur. If the stimulus is weak, then no matter how long it acts, no response occurs. The strength of the stimulus gradually increases, and at a certain moment a tissue response occurs. This force reaches a threshold value and is called rheobase (the minimum force of irritation that causes the primary response). The time during which a current equal to the rheobase acts is called useful time.

For an aggregate of cells (for tissue), this dependence is different, the response of the tissue is directly proportional to a certain limit to the strength of the stimulus applied. The increase in the response is due to the fact that the number of structures involved in the response increases.

**(Slide 26)** **Law irritation gradient.** Gradient − this is the steepness of the increase in irritation. The tissue response depends, to a certain extent, on the stimulation gradient. With a strong stimulus, for about the third time the stimulation is applied, the response occurs faster, since it has a stronger gradient. If you gradually increase the threshold of irritation, then the phenomenon of accommodation appears in the tissue. Accommodation is the adaptation of tissue to a stimulus that slowly grows in strength. This phenomenon is associated with the rapid development of Na-channel inactivation. Gradually there is an increase in the threshold of irritation, and the stimulus always remains subthreshold, that is, the threshold of irritation increases.

The laws of irritation of excitable tissues explain the dependence of the response on the parameters of the stimulus and ensure the adaptation of organisms to factors of the external and internal environment.

**(Slide 27)** The principle of propagation of the action potential is associated with the emergence of incoming local currents of sodium ions through the excited section of the membrane, which lead to the excitation of a neighboring inactive section. In this case, local outgoing currents arise in neighboring inactive areas of the nerve or muscle fiber, causing a redistribution of charges on the membrane and depolarization already in these areas. As soon as depolarization in these areas reaches a threshold level, sodium channels open in them, and an action potential arises. In other words, the conduction of PD in unmyelinated fibers is associated with its constant occurrence in adjacent membrane regions. The propagation of excitement occurs without a decrease in the speed and amplitude of the action potential.

**(Slide 28)** The rate of conduction of the action potential depends on how quickly and how far from the active site the membrane depolarizes to a threshold level when local currents flow. This, in turn, depends on the magnitude of the incoming ionic current and the cable properties of the fiber. The magnitude of the incoming current is determined by the density of the sodium channels of the membrane, and the cable properties are determined by the specific resistance of the membrane and axoplasm, as well as by the fiber diameter. The thicker the nerve fiber, the further the depolarization will propagate from the active site, respectively, the higher the propagation rate of the action potential will be.

**(Slide 29)** To help you master the material:

**Kaplan Medical USMLE Step 1 Physiology:** On the website of the department. Pages: 19 – 36.

Questions that we will analyze for a lesson on this topic:

1. Concepts of excitability and irritability.
2. Excitable and non-excitable tissues.
3. Resting membrane potential: its scheme, parameters, mechanism of formation.
4. Action potential: concept, scheme of action potential (phase), its parameters, mechanism of occurrence.
5. The recovery period.
6. Mechanisms of nerve impulse conduction along nerve fibers.

**Thank you for attention**