**(Slide 1) Lecture 1**

**Physiology of excitable tissues**

**(Slide 2)** Lecture plan:

1. Excitability and excitation.
2. Membrane and ionic mechanisms of membrane potential.
3. Action potential and its phases.
4. Physiological properties of skeletal and smooth muscles.
5. Muscle contraction mechanism.
6. Mechanisms and laws of conducting excitement along nerve fibers.
7. Physiology of the neuromuscular synapse.

**(Slide 3)** 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 4)** The main manifestations of life.

**(Slide 5)** Varieties of biological reactions.

**(Slide 6)** Types of excitable tissues.

**(Slide 7)** The following properties are inherent in excitable tissues.

**(Slide 8)** Cell membrane structure (video).

**(Slide 9) 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 10)** 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 11)** 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 12)** The Sodium-Potassium Pump (video).

**(Slide 13)** 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 14)** 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 15)** 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 16)** 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 17)** **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 18)** **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 19)** **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 20)** In the body, there are three types of muscle: skeletal (striated), smooth, and cardiac.

Skeletal muscle, attached to bones, is responsible for skeletal movements. The peripheral portion of the central nervous system (CNS) controls the skeletal muscles. Thus, these muscles are under conscious, or voluntary, control. The basic unit is the muscle fiber with many nuclei. These muscle fibers are striated (having transverse streaks) and each acts independently of neighboring muscle fibers.

Smooth muscle, found in the walls of the hollow internal organs such as blood vessels, the gastrointestinal tract, bladder, and uterus, is under control of the autonomic nervous system. Smooth muscle cannot be controlled consciously and thus acts involuntarily. The non-striated (smooth) muscle cell is spindle-shaped and has one central nucleus. Smooth muscle contracts slowly and rhythmically.

Cardiac muscle, found in the walls of the heart, is also under control of the autonomic nervous system. The cardiac muscle cell has one central nucleus, like smooth muscle, but it also is striated, like skeletal muscle. The cardiac muscle cell is rectangular in shape. The contraction of cardiac muscle is involuntary, strong, and rhythmical.

Smooth and cardiac muscle will be discussed in detail with respect to their appropriate systems. This unit mainly covers the skeletal muscular system.

**(Slide 21)** All muscle cells share several properties: contractility, excitability, extensibility, and elasticity:

**Excitability** is the ability to respond to a stimulus, which may be delivered from a motor neuron or a hormone.

**Contractility** is the ability of muscle cells to forcefully shorten. For instance, in order to flex (decrease the angle of a joint) your elbow you need to contract (shorten) the biceps brachii and other elbow flexor muscles in the anterior arm. Notice that in order to extend your elbow, the posterior arm extensor muscles need to contract. Thus, muscles can only pull, never push.

**Extensibility** is the ability of a muscle to be stretched. For instance, let's reconsider our elbow flexing motion we discussed earlier. In order to be able to flex the elbow, the elbow extensor muscles must extend in order to allow flexion to occur. Lack of extensibility is known as spasticity.

**Elasticity** is the ability to recoil or bounce back to the muscle's original length after being stretched.

**(Slide 22)** Muscle contraction begins with a nerve impulse that enters the muscle fiber through the neuromuscular junction (or synapse).

**(Slide 23) Neuromuscular Junction\_Animation** (video).

**Additionally**

The following list presents an overview of the sequence of events involved in the contraction cycle of skeletal muscle:

1. The action potential travels down the neuron to the presynaptic axon terminal.

2. Voltage-dependent calcium channels open and Ca2+ ions flow from the extracellular fluid into the presynaptic neuron’s cytosol.

3. The influx of Ca2+ causes neurotransmitter (acetylcholine)-containing vesicles to dock and fuse to the presynaptic neuron’s cell membrane.

4. Vesicle membrane fusion with the nerve cell membrane results in the emptying of the neurotransmitter into the synaptic cleft; this process is called exocytosis.

5. Acetylcholine diffuses into the synaptic cleft and binds to the nicotinic acetylcholine receptors in the motor end-plate.

6. The nicotinic acetylcholine receptors are ligand-gated cation channels, and open when bound to acetylcholine.

7. The receptors open, allowing sodium ions to flow into the muscle’s cytosol.

8. The electrochemical gradient across the muscle plasma membrane causes a local depolarization of the motor end-plate.

9. The receptors open, allowing sodium ions to flow into and potassium ions to flow out of the muscle’s cytosol.

10. The electrochemical gradient across the muscle plasma membrane (more sodium moves in than potassium out) causes a local depolarization of the motor end-plate.

11. This depolarization initiates an action potential on the muscle fiber cell membrane (sarcolemma) that travels across the surface of the muscle fiber.

12. The action potentials travel from the surface of the muscle cell along the membrane of T tubules that penetrate into the cytosol of the cell.

13. Action potentials along the T tubules cause voltage-dependent calcium release channels in the sarcoplasmic reticulum to open, and release Ca2+ ions from their storage place in the cisternae.

14. Ca2+ ions diffuse through the cytoplasm where they bind to troponin, ultimately allowing myosin to interact with actin in the sarcomere; this sequence of events is called excitation-contraction coupling.

15. As long as ATP and some other nutrients are available, the mechanical events of contraction occur.

16. Meanwhile, back at the neuromuscular junction, acetylcholine has moved off of the acetylcholine receptor and is degraded by the enzyme acetylcholinesterase (into choline and acetate groups), causing termination of the signal.

17. The choline is recycled back into the presynaptic terminal, where it is used to synthesize new acetylcholine molecules.

**(Slide 24)** Thus, the nerve impulse causes muscle contraction.

**(Slide 25) Sliding Filament Theory Of Muscle Contraction Explained** (video).

**Additionally**

Sequence of events in the muscle fiber contraction-relaxation cycle:

1. The arrival of the action potential along the nerve fiber to the myoneural synapse.

2. Synaptic activation of muscle fibers.

3. The emergence of an action potential and its conduction along the cell membrane and deep into the fiber along the T-tubules.

4. Release of Ca2 + ions from the lateral cisterns of the sarcoplasmic reticulum, its diffusion to myofibrils.

5. Conformation of the troponin-tropomyosin complex.

6. Contact of transverse bridges of myosin with actin.

7. Releasing ATP Energy.

8. Slip of actin and myosin filaments, resulting in shortening of the myofibril.

9. Calcium pump activation.

10. Decrease in the concentration of free Ca2 + ions in the sarcoplasm.

11. Relaxation of myofibrils.

**(Slide )** Mechanisms of electrical phenomena in tissue are used in dentistry.

Electroodontodiagnostics is a method of dental research based on determining the threshold excitation of pain and tactile receptors of the tooth pulp when an electric current passes through it. The process of studying the electrical excitability of teeth is called electroodontometry. The current generated by the electroodontodiagnostics apparatus and used for the lectroodontometry is called the diagnostic current. It should be emphasized that electroodontodiagnostics gives an idea not so much about the state of the tooth pulp itself, but rather characterizes the integrity and functionality of its sensitive nervous apparatus. As you know, with various pathological processes in the hard tissues and pulp of the tooth, not only the histological structure and hemodynamic processes in the pulp change, but also dystrophic processes occur in the nerve receptors, which is manifested by a change in their electrical excitability. At the same time, it should be remembered that changes in lectroodontometry indicators can occur in various pathological conditions of the periodontal tissues and sensory nerves of the maxillofacial region.

**(Slide )** Normally, the pulp of the tooth reacts to the electric current passing through it with minor pain sensations, a tingling sensation, a feeling of a slight shock, a weak electric shock, etc. The high sensitivity of the pulp to the action of stimuli is explained by the large number of sensory nerve endings located in the subodontoblastic plexus of Rashkov, the odontoblastic layer, and predentin.

Tooth caries, as the process progresses and the carious cavity deepens, causes the development of changes in the pulp, leading to a decrease in the sensitivity of nerve receptors: deposition of replacement dentin, changes in the layer of odontoblasts, initial dystrophic processes in the nerve elements. The listed phenomena can gradually lead to a slight decrease in the EOM indicators.

**Thank you for attention**