**(Slide 1) Lecture 2**

**Muscle physiology**

 **(Slide 2)** Lecture plan:

1. Classification of Synapses.
2. Modern Concepts of Structure of Chemical Synapse and Mechanisms of Signal Transmission at Synapse.
3. Modern Concepts of Mechanisms of Signal Transmission at Synapse.
4. Muscle cell properties.
5. Sequence of signal transmission at neuromuscular synapse.
6. The sequence of events that result in the contraction of an individual muscle fiber.
7. Characteristic Features of Smooth Muscle Tissue.
8. The kinds of muscle contractions.

**(Slide 3)** A synapse is a formation that provides transmission of excitation from one structure to another. In particular, muscle cells can act as another structure. The term “synapse” (from Greek “synapsis” meaning clasp) was proposed by famous English neurophysiologist Charles Sherrington (1897) to denote a hypothetical formation or region specializing in cell-to-cell transmission of signals.

**(Slide 4)** It should be noted that at that time information was believed to be transmitted by bioelectrical impulses, and Sherrington introduced this concept to denote a site of contact between cells for transmission of electrical impulses. First ideas about a probable chemical mechanism of transmission of excitation from nerve to muscle were put forward by French physiologist Claude Bernard (1850, 1856).

**Classification of Synapses**

**(Slide 5)** 1. By localization synapses are divided into central (in the CNS) and peripheral (in the peripheral nervous system and on effector organs).

By contacting structures, central synapses are divided into:

* axoaxonal;
* axosomatic;
* axodendritic;
* somato-dendritic;
* dendrodendritic;
* somato-somatic.

Peripheral synapses are divided into:

* nerve-muscle synapses of skeletal striated muscles;
* nerve-muscle synapses of smooth muscles;
* nerve-muscle synapses of the myocardium;
* synapses of autonomic ganglia;
* neurosecretory synapses.

By transmission mechanism, synapses are divided into chemical and electrical (nexuses of the myocardium, of smooth muscles).

And, finally, by types of processes in postsynaptic formations, synapses are divided into excitatory and inhibitory.

Depending on the chemical compound that participates in synaptic transmission, synapses are divided into cholinergic, adrenergic, serotoninergic, histaminergic, peptidergic, etc.

**Modern Concepts of Structure of Chemical Synapse and Mechanisms of Signal Transmission at Synapse**

**(Slide 6)** Recent electronic microscopic research permitted to distinguish three structural elements at a chemical synapse:

1) presynaptic region (presynaptic terminal);

2) synaptic cleft;

3) postsynaptic region.

**(Slide 7) Presynaptic terminal** is an unmyelinated terminal part of a process of a nerve cell. Presynaptic terminal has a bulb-like configuration with the base facing the membrane of a receiving cell. An essential feature of the presynaptic terminal is existence in it of aggregations of presynaptic vesicles 50 nm in diameter containing neurotransmitter substance (a chemical compound which is a material carrier of a signal to the receiving cell). Neurotransmitter substance may exist in the presynaptic terminal in several forms.

**(Slide 8)** Presynaptic terminal contains proteins (calmodulin and calcineurin) participating in exchange of Ca++ ions. Besides, presynaptic region also contains a number of proteins which, after interaction with Ca++ ions, provide exocytosis of the neurotransmitter into the synaptic cleft (vesicular proteins synaptobrevin and synaptotagmin, and also proteins fixed on the cytoplasmic side of active zones of presynaptic membrane – SNAP-25 and syntaxin). After initiation of exocytosis of the neurotransmitter calcium ions are accumulated by calcium-specific proteins calmodulin and calcineurin and further released into the perisynaptic region by calcium pump.

**(Slide 9)** Neuroransmitters are various chemical compounds classified into several groups. Besides vesicles with the neurotransmitter, presynaptic terminal also contains a large amount of mitochondria and lysosomes which evidences high metabolic activity in these structures. Besides, in this region there were also found precursors to neurotransmitters and products of their metabolism.

**(Slide 10) Synaptic cleft.** The width of synaptic cleft at chemical synapses is from 20 to 50 nm. It contains water, electrolytes, oligosaccharides and enzymes that participate in breakdown of neurotransmitters.

**(Slide 11) Postsynaptic region**. It incorporates the subsynaptic membrane (a part of the postsynaptic membrane carrying special receptors with the affinity to the neurotransmitter, and chemically sensitive ion channels). The postsynaptic membrane proper is a part of the postsynaptic membrane which contains potential-dependent ion channels, and on which postsynaptic potentials are generated. Subsynaptic receptors are classified into ionotropic (ligand-dependent) receptors forming parts of ionic channels on the subsynaptic membrane, and metabotropic receptors that transmit signal into the cell with participation of G-protein and second messengers.

**(Slide 12)** Receptors of the subsynaptic membrane are divided into several groups depending on the neurotransmitter with which they interact:

1) adrenoreceptors interacting with epinephrine (adrenaline) and norepinephrine (noradrenaline);

2) choline receptors interacting with acetylcholine;

3) dopamine receptors interacting with dopamine;

4) serotonin receptors interacting with serotonin;

5) histamine receptors interacting with histamine;

6) opioid receptors interacting with endogenous opiates, enkephalins, endorphins.

**(Slide 13) Modern Concepts of Mechanisms of Signal Transmission at Synapse**

1) Propagation of action potential (AP) along the nerve fiber toward the presynaptic terminal.

2) Increase in the permeability of the presynaptic membrane to Ca++ and influx of Ca++ into the presynaptic region.

3) Migration of vesicles containing active neurotransmitter toward the active zones of presynaptic membrane and release of neurotransmitter into the synaptic cleft by exocytosis.

4) Diffusion of neurotransmitter towards the subsynaptic membrane of the postsynaptic region and its interaction with the corresponding receptors on the sybsynaptic membrane.

**(Slide 14)** Then events may further develop in two ways: 1 – neurotransmitter directly interacts with the receptor with the result of activation of ion channels in the subsynaptic membrane (as at some cholinergic synapses): or 2 – formation of transmitter-receptor complex that changes the configuration of cytoplasmic G-protein of the subsynaptic membrane with subsequent activation of second messengers followed by a chain of biochemical processes that change permeability of ion channels with the result of initiation of local currents and generation of a postsynaptic potential on the postsynaptic membrane.

**(Slide 15)** One of the most common manifestations of excitation in excitable tissues is a change in length, or contraction. An ability of tissue to change its length is based on the property of contractility best expressed in muscle tissue. There are distinguished striated and smooth muscle tissues. Smooth muscle tissue is primarily found in the internal hollow organs: e.g., in the muscle layer of the walls of blood vessels, of digestive tract, urinary bladder, uterus and of some other organs. Striated muscles form the basis of skeletal muscles. A special kind of striated muscle tissue is cardiac muscle.

**(Slide 16)** Any skeletal muscle consists of three types of muscle fibers:

1. Fast phasic muscle fibers called “white” fibers due to a relatively low content of myoglobin pigment;
2. Slow tonic muscle fibers called “red fibers” due to a relatively high content of myoglobin that gives them red coloring;
3. Receptor fibers.

**(Slide 17)** 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 18)** Muscle contraction begins with a nerve impulse that enters the muscle fiber through the neuromuscular junction (or synapse).

**(Slide 19) Neuromuscular Junction\_Animation** (video).

**(Slide 20)** 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.

**(Slide 21)** 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 22)** **T tubulus through which the activation signal for contraction propagates is shown on this slide.**

**(Slide 23) Sliding Filament Theory Of Muscle Contraction Explained** (video).

**(Slide 24 left picture) The sequence of events that result in the contraction of an individual muscle fiber begins** with a signal—the neurotransmitter, acetylcholine—from the motor neuron innervating that fiber. The local membrane of the fiber will depolarize as positively charged sodium ions (Na+) enter, triggering an action potential that spreads to the rest of the membrane which will depolarize, including the T-tubules. This triggers the release of calcium ions (Ca++) from storage in the sarcoplasmic reticulum. The Ca++ then initiates contraction, which is sustained by ATP. As long as Ca++ ions remain in the sarcoplasm to bind to troponin, which keeps the actin-binding sites “unshielded,” and as long as ATP is available to drive the cross-bridge cycling and the pulling of actin strands by myosin, the muscle fiber will continue to shorten to an anatomical limit.

**(Slide 24 right picture)** Muscle contraction usually stops when signaling from the motor neuron ends, which repolarizes the sarcolemma and T-tubules, and closes the voltage-gated calcium channels in the SR. Ca++ ions are then pumped back into the SR, which causes the tropomyosin to reshield (or recover) the binding sites on the actin strands. A muscle also can stop contracting when it runs out of ATP and becomes fatigued.

**(Slide 25)** The contraction of a striated muscle fiber occurs as the sarcomeres, linearly arranged within myofibrils, shorten as myosin heads pull on the actin filaments. The region where thick and thin filaments overlap has a dense appearance, as there is little space between the filaments. This zone where thin and thick filaments overlap is very important to muscle contraction, as it is the site where filament movement starts. Thin filaments, anchored at their ends by the Z-discs, do not extend completely into the central region that only contains thick filaments, anchored at their bases at a spot called the M-line. A myofibril is composed of many sarcomeres running along its length; thus, myofibrils and muscle cells contract as the sarcomeres contract. When signaled by a motor neuron, a skeletal muscle fiber contracts as the thin filaments are pulled and then slide past the thick filaments within the fiber’s sarcomeres. This process is known as the sliding filament model of muscle contraction. The sliding can only occur when myosin-binding sites on the actin filaments are exposed by a series of steps that begins with Ca++ entry into the sarcoplasm.

**(Slide 26)** Tropomyosin is a protein that winds around the chains of the actin filament and covers the myosin-binding sites to prevent actin from binding to myosin. Tropomyosin binds to troponin to form a troponin-tropomyosin complex. The troponin-tropomyosin complex prevents the myosin “heads” from binding to the active sites on the actin microfilaments. Troponin also has a binding site for Ca++ ions.

**(Slide 27)** To initiate muscle contraction, tropomyosin has to expose the myosin-binding site on an actin filament to allow cross-bridge formation between the actin and myosin microfilaments. The first step in the process of contraction is for Ca++ to bind to troponin so that tropomyosin can slide away from the binding sites on the actin strands. This allows the myosin heads to bind to these exposed binding sites and form cross-bridges. The thin filaments are then pulled by the myosin heads to slide past the thick filaments toward the center of the sarcomere. But each head can only pull a very short distance before it has reached its limit and must be “recocked” before it can pull again, a step that requires ATP.

**(Slide 28)** For thin filaments to continue to slide past thick filaments during muscle contraction, myosin heads must pull the actin at the binding sites, detach, re-cock, attach to more binding sites, pull, detach, re-cock, etc. This repeated movement is known as the cross-bridge cycle. This motion of the myosin heads is similar to the oars when an individual rows a boat: The paddle of the oars (the myosin heads) pull, are lifted from the water (detach), repositioned (re-cocked) and then immersed again to pull. Each cycle requires energy, and the action of the myosin heads in the sarcomeres repetitively pulling on the thin filaments also requires energy, which is provided by ATP. Cross-bridge formation occurs when the myosin head attaches to the actin while adenosine diphosphate (ADP) and inorganic phosphate (Pi) are still bound to myosin (**Slide 28 a,b**). Pi is then released, causing myosin to form a stronger attachment to the actin, after which the myosin head moves toward the M-line, pulling the actin along with it. As actin is pulled, the filaments move approximately 10 nm toward the M-line. This movement is called the power stroke, as movement of the thin filament occurs at this step (**Slide 28 c**). In the absence of ATP, the myosin head will not detach from actin. One part of the myosin head attaches to the binding site on the actin, but the head has another binding site for ATP. ATP binding causes the myosin head to detach from the actin (**Slide 28 d**). After this occurs, ATP is converted to ADP and Pi by the intrinsic ATPase activity of myosin. The energy released during ATP hydrolysis changes the angle of the myosin head into a cocked position (**Slide 28 e**). The myosin head is now in position for further movement. When the myosin head is cocked, myosin is in a high-energy configuration. This energy is expended as the myosin head moves through the power stroke, and at the end of the power stroke, the myosin head is in a low-energy position. After the power stroke, ADP is released; however, the formed cross-bridge is still in place, and actin and myosin are bound together. As long as ATP is available, it readily attaches to myosin, the cross-bridge cycle can recur, and muscle contraction can continue.

**Characteristic Features of Smooth Muscle Tissue**

**(Slide 29)** Smooth-muscle cells are distributed within the walls of the internal organs – blood vessels, organs of the digestive tract, urinary bladder, urinary tract, uterus. Smooth-muscle cells have a spindle-like form and are 50-400 microns long and 2-10 microns in diameter and contain only one nucleus. Contractile elements of smooth muscles, like those of striated muscles, are represented by myofilaments, which also contain actin, myosin and regulatory proteins. However, unlike in striated muscles, myofilaments in smooth-muscle tissue are arranged in a random order and do not exhibit a striated pattern. Sarcoplasmic reticulum in smooth muscle cells is poorly developed, and Ca++ ions are stored directly in the cytoplasm of cells. Myosin of smooth-muscle tissue is characterized by low ATPase activity which results in slow sliding of actin and myosin filaments in respect to each other. Due to this, smooth-muscle tissue performs slow, tonic muscular contractions which consume low amount of energy, and fatigue in smooth-muscle tissue develops more slowly than in striated tissue of skeletal muscles. There exist special formations between cells of smooth-muscle tissue called nexuses (electrical synapses), which enable sufficiently rapid propagation of excitation over the tissue in the form of bioelectrical process. It should be added that smooth-muscle cells can shift from relative rest to excitation without any external stimulation, in other words, they possess a property of automaticity.

Comparative characteristics of skeletal and smooth muscles are given in **Slide 30**.

**(Slide 31)** There exist three kinds of muscle contractions:

1. single muscle contraction (a twitch);
2. tetanic muscle contraction (tetanus);
3. tonic muscle contraction.

**(Slide 32)** Tetanic muscle contraction (tetanus) is caused by stimulation of a skeletal muscle with a threshold or suprathreshold electrical stimuli following each other at intervals shorter than duration of a single contraction. Depending on the intervals between stimuli, the result may be either stairway (incomplete) or smooth (flat, complete) tetanus. Incomplete tetanus is obtained when stimuli arrive at intervals that are shorter than duration of a single muscle contraction, but equal or exceed the total duration of the latent period and shortening phase. When electrical stimuli arrive at intervals shorter than the total duration of the latent period and the shortening phase, smooth (flat, complete) tetanus results. The amplitude of complete tetanus exceeds the amplitude of a single muscle contraction and of incomplete tetanus. Further shortening of the interval, or, in other words, increase in frequency of stimulation, results in increase in the amplitude of tetanic contraction.

**(Slide 33)** To help you master the material:

**Kaplan Medical USMLE Step 1 Physiology:** On the website of the department. Pages: 55 – 64.

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

1. Classification of Synapses.

2. Modern Concepts of Structure of Chemical Synapse and Mechanisms of Signal Transmission at Synapse.

3. Modern Concepts of Mechanisms of Signal Transmission at Synapse.

4. Muscle cell properties.

5. Sequence of signal transmission at neuromuscular synapse.

6. The sequence of events that result in the contraction of an individual muscle fiber.

7. Characteristic Features of Smooth Muscle Tissue.

8. The kinds of muscle contractions.

Finish for today

The full lecture is at the indicated website.

**Thank you for attention**