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Nerve and muscle physiology

This lecture is divided into two parts , at the beginning we will review some important concepts regarding neurons , excitable tissues and membrane - action potentials , but I went through some details for you to get the full picture ,then we will describe the structure of skeletal muscles at the microscopic level and how contraction takes place.

- This sheet is not enough, refer to the handout and try to understand EVERY SINGLE WORD , also refer to the slides that are only a collection of pictures to visualize what is written here .

* peripheral NS has two divisions :

- **Somatic nervous system** : brings sensations from skin to the CNS, and carries motor impulses to a voluntary muscle (**skeletal muscle**)

- Autonomic nervous system

>> So when we say somatic nerve we mean that this nerve has somatic fibers (axons) that belong to the structure of the somatic nervous system (that its motor neurons innervate skeletal muscles)

- properties of the somatic motor neuron : it has a cell body (soma) in the spinal cord , long axon toward the muscle , and many terminals exist at the level of the muscle , each terminal will synapse with one muscle cell (BUT here we don't call it synapse (that occur between two neurons) , it is called a **neuromuscular junction** . The two are very similar ! A synapse is a junction between a neuron and the next cell , A neuromuscular junction is a kind of synapse , one that occurs between motor neurons and muscle cells .

* A group of axons from different neurons form a cable like structure that is called **a nerve** > so axon is a nerve fiber.

* Axons in somatic motor neurons are myelinated

- How the message is sent from the CNS toward the skeletal muscle in order for it to contract?

We have an action potential development in the motor neuron (efferent neuron) at the **axon hillock** < the junction between the axon and the cell body > that spread along the axon toward the terminals.

* A nerve terminal contains plenty of vesicles that carry the neurotransmitters.

- What is the membrane potential?

Membrane potential refers to the **difference** in charge **between** the inside and outside of a neuron, which is created due to the unequal distribution of ions on both sides of the cell. The term **action potential** refers to the electrical signaling that occurs within neurons.

The plasma membrane separates two compartments, each with different composition because of differences in the permeability of the membrane to different ions.

- Assuming that the membrane is only permeable for potassium, the movement of potassium ions won't stop when the concentrations on

both sides are equal, because during its movement development of a potential across the membrane takes place also. When the **electrochemical equilibrium** is reached the created potential will prevent any net movement (even if the conc. of ions is still high in the ICF and low in the ECF).

Net diffusion::potassium is still moving from outside to inside and from inside to outside, but the difference between these movements is zero.

- Assuming permeability for Na+ only, the inside of the cell becomes positive in respect to the outside due to the movement of sodium ions from the outside towards cytosol.

<u>The Equilibrium Potential for an Ion</u>⇒ the equilibrium resulting from the movement of this specific ion across the membrane, it is measured by Nernest Equation.

$$E = \frac{RT}{ZF} \ln \frac{[C]out}{[C]in}$$

R (Gas Constant) = 8.314472 (J/K·mol)
T (Absolute Temperature) = t °C + 273.15 (°K)
Z (Valence)
F (Faraday's Constant) = 9.6485309×10^4 (C/mol)
[C]out (Outside Concentration, mM)
[C]in (Inside Concentration, mM)

The permeability for only a single ion is only an assumption. In fact, the plasma membrane is usually permeable for both ions e.g. (permeable for Na+ and K). The movement of any ion down its own electrochemical gradient will tend to move the membrane potential towards the equilibrium potential of that ion, BUT the permeability for

one ion is much higher than the other. The potential created by the movement of the ion that the membrane is more permeable to will be closer to the equilibrium potential of that ion .e.g. Na+/K+: the membrane is more permeable to K+ so the potential will be closer to the equilibrium potential of potassium {close to -95 BUT NOT equal to -95}.

<< The more permeable the membrane is for an ion , the more the equilibrium potential of that ion will influence the membrane potential >>

For the whole membrane also, the potential can be calculated according to the permeabilities for all ions using **Goldman Hodgkin katz equation**

$$V_m = \frac{RT}{F} \ln\left(\frac{p_K[K^+]_o + p_{Na}[Na^+]_o + p_{Cl}[Cl^-]_i}{p_K[K^+]_i + p_{Na}[Na^+]_i + p_{Cl}[Cl^-]_o} \right)$$

i = Conc. inside
o = Conc. outside
P = permeability of the membrane to that ion.

* The movement of a negatively charged ion has a reversal effect compared to a positively charged ion, that's why the concentrations are reversed in the equation.

* There are two types of channels that membranes have:

- Chemical (ligand) gated channels, that can be activated by a specific ligand binding.

- Voltage gated channels, that can be activated at certain voltages.

* Membranes of excitable cells (neurons, muscles) have resting membrane potential < under resting conditions >, so they can generate action potential.

* Different cell types have different resting membrane potential values.

Why? It depends on the permeability to Na+, K+ and the presence of the Na+ _ K+ pump.

- Resting membrane potential is NOT static , it can be changed upon stimulation , these changes in the membrane potential are due to changes in permeability of plasma membrane to different ions , this occurs due to control of transport mechanisms .

- The significance of the **resting membrane potential** is that it allows the body's excitable cells (neurons and muscle) to experience rapid changes to perform their proper role. ... For neurons, the firing of an action **potential** allows that cell to communicate with other cells via the release of various neurotransmitters.

- Any change in the ion composition around the plasma membrane will change the resting membrane potential , we can have these

changes to a less negative << depolarization , can be established by activation of Na+ channels >> or to a more negative << hyperpolarization , can be established by activation of K+ channels>>

(Less or more negative inside relative to the outside).

**** DON'T FORGIT: that motor neurons and skeletal muscle cells are bearing only these 2 types of channels which are involved in the electrical activity that we can have.**

Now, what are the phases of action potential?

- **Resting phase**: the normal state when there is no stimulus.

- **Depolarization phase**: upon stimulation, Na+ chemical gated channels (opened by a ligand that is typically a neurotransmitter) and some voltage gated channels open, the flow of Na+ to the inside causes the membrane potential to be less negative, action potential will not be developed until the membrane potential reaches a point at which all Na+ voltage gated channels are activated, this voltage point is called the **threshold point**.

* **All or none principle** is applied here , which states that since the threshold point is reached , AP will fire . So, either the membrane potential reaches the threshold leading to an AP or NO .

* Depolarization phase includes 2 events: first, the change in membrane potential before reaching the threshold point. Second, the firing event which occurs after reaching the threshold point.

* when the membrane potential reaches the threshold , NOT only Na+ channels are activated , but also K+ voltage gated channels are activated . BUT they open slower than Na+ channels.

- **Repolarizing phase** : K+ channels continue opening and they are not fully opened until Na+ channels are completely closed , while these positively charged ions diffuse to the outside of the cell , it returns the inner side of the plasma membrane back to its negative state , that's why it is called **Re**polarization .

- Returning to the resting state:

Repolarization continues until the resting membrane potential is restored, then K+ channels close slowly. This slow closing of K+ channels makes the membrane potential slightly more negative than the resting state . this condition is called **positive after potential** or **after hyperpolarization** or **undershoot . leak channels** and **Na+_K+ pump** work to return to the resting state.

* The depolarization that produces Na+ channels opening , also causes delayed activation of K+ channels and Na+ channel inactivation , leading to repolarization of the membrane potential as the action potential sweeps along the length of the axon. In its wake , the action potential leaves the Na+ channels inactivated and K+ channels activated for a brief time . these transitory changes make it harder for the axon to produce subsequent action potentials during this interval, which is called the refractory period. Thus, the refractory period limits the number of action potentials that a given

nerve cell can produce per unit time. As might be expected, different types of neurons have different maximum rates of action potential firing due to different types and densities of ion channels. The refractoriness of the membrane in the wake of the action potential explains why action potentials do not propagate back toward the point of their initiation as they travel along an axon.

*There are two types of refractory periods , the **absolute refractory period**, which corresponds to depolarization and repolarization, and the relative **refractory period**, which corresponds to hyperpolarization.

- **Absolute**: Is the **period** of **time** during which a second action potential ABSOLUTELY cannot be initiated, no matter how large the applied stimulus is. **Relative**: Is the interval immediately following the **Absolute Refractory Period** during which initiation of a second action potential is INHIBITED, but not impossible. (needs stronger stimulus) .

* Na+ voltage gated channels are found on 3 conformations :

1. Open (during depolarization , its function defines the absolute refractory period) 2. Closed but not capable of opening (during repolarization-falling stage) , which can be opened by a suprathreshold stimulus reflecting the relative refractory period
3.closed and capable of opening .

- Remember that these motor neurons are myelinated , so AP propagate along the axon by saltatory conduction from one node of

Ranvier to the next increasing the conduction velocity of action potentials .

- Not only myelination can influence the velocity of conduction, but also the diameter of nerve fibers , larger fibers conduct impulse with higher velocity .

- What happens at the synapse ?

* Once the impulse reaches the terminals of the presynaptic neuron, the activation of Ca++ channels occurs , allowing the influx of Ca++ into the synaptic knop that triggers the release of neurotransmitters into the synaptic cleft by exocytosis .

* These neurotransmitters bind to a specific receptors on the postsynaptic membrane (on skeletal muscles , the neurotransmitter is Ach that binds to nicotinic receptors). Depending on the type of these ligand gated channels , this will either trigger the activation of Na+ ligand gated channels which allows an influx of Na+ into the postsynaptic membrane that leads to depolarization , this is called **Excitatory Post Synaptic Potential (EPSP)**, these are not action potentials , but small depolarizations (subthreshold potentials). Or it might trigger the activation of K+ ligand gated channels , if present , which allows an efflux of K+ out of the postsynaptic membrane leading to hyperpolarization , this is called **Inhibitory Post Synaptic Potential (IPSP).**

- **Summation** : is the addition of post-synaptic potentials , meaning for example , two depolarizations can sum up to elicit a higher depolarization .

- The two types of summation are :

* **Spatial summation** : which appears when two or more potentials (IPSP/EPSP) are generated from two or more different presynaptic neurons simultaneously at the same postsynaptic membrane . As a result , these two responses will be summed into a final response . It may take place between EPSPs inducing more depolarization , or between IPSPs triggering more hyperpolarization , or between EPSPs and IPSPs .

* **Temporal summation** : which appears when 2 or more potentials are generated from one presynaptic neuron at different times . These potentials are then summed together to induce more depolarization (frequency dependent) .

<< So the chemicals (neurotransmitters) induce depolarizations that if they are subthreshold potentials can be summed to reach the threshold .

* Slide 22 shows different synaptic organizations

- Convergence : means signals from multiple inputs uniting to excite a single neuron . Action potentials converging on the neuron from multiple terminals provide enough spatial summation to bring the neuron to its threshold (but most of the presynaptic neurons are inhibitory neurons , so we need higher inputs from presynaptic

neurons that can cause depolarization to reach the threshold and generate AP at these motor neurons)

- Divergence : one presynaptic neuron that has terminals synapsing with many postsynaptic neurons .

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* The muscle tissue is classified according to its morphology into : striated and unstriated (smooth) muscles , which can be voluntary or involuntary .

- Cardiac muscles are striated involuntary muscles.

- Smooth muscles are unstriated involuntary muscles.

- Skeletal muscles are striated voluntary muscles.

* Remember that the prefixes < **sarco** and **myo >** refer to muscles , so wherever you see them in a word you should immediately think about muscles . For example : Sarcolemma > means the plasma membrane of a muscle cell .

Sarcoplasmic reticulum > means the smooth ER of a muscle cell

Myofiber , myofibrils > mean a muscle cell , organelles inside a muscle cell respectively .

* The muscle cell is called a muscle fiber because it is elongated .

* Slide 2 Shows the origin of skeletal muscles , notice how myoblasts that come from mesenchymal cells fuse together to form one

multinucleated and elongated cell that shows striations (alterations between light and dark areas).

* The fleshy part of the muscle is divided by a connective tissue into bundles , each one is called :a fasciculus or fascicle (plural: fasciculi) ,

and each fascicle is composed of muscle cells , the sarcoplasm of these muscle cells is filled with cylindrical organelles known as myofibrils .

* if we magnify the myofibril, we will see that it is composed of thick and thin filaments (myofilaments) and they are highly organized along the myofibril to form repeating units of sarcomeres (the smallest functional unit in the muscle tissue)

* Under the microscope the sarcomere is composed of :

- **The A band** : composed of thick filaments and some overlapping areas that contain thin filaments , and this band corresponds to the length of the thick filaments . A band means Anisotropic band , iso=similar / so it means dissimilar structures (thick and some overlapping thin filaments)

- **The I band** : composed of thin filaments only . I band means Isotropic band since it has similar structures (only thin filaments)

- **M line** (if 2 dimensions are viewed) / disk (.. 3 dimensions..): located in the middle and holds the thick filaments .

- **H zone** : the area in the middle of the A band where there is no overlapping (consists of thick filaments only).

- Two Z lines / disks : holding the thin filaments .

* A sarcomere is composed of an A band and 2 halves of I bands (The distance between two Z discs).

* The highly organized pattern of contractile proteins in the myofibrils gives striations to the muscle cells so the whole muscle tissue appears striated .

>> Structure of the thick and thin filaments:

* Thick filament is an aggregation between many myosin molecules , each one of them has globular head that is protruding to form what is known as **cross bridge** , and one tail that is alpha helical in shape forming the backbone of the thick filament . The head of a myosin molecule has two binding sites , one binds to actin and the another one is ATP-ase binding site because the process of contraction needs energy .

* Thin filaments are composed of polymerized globular actin molecules (that contain the binding sites of myosin heads) in an alpha helical structure called filamentous actin (F actin) , two strands are twisted to form actin filament that form the backbone of the thin filament , they also have regulatory proteins (a helical protein called tropomyosin, and a three subunits protein called troponin << **subunit C** that interact with calcium , **subunit T** that interact with tropomyosin and **subunit I** that has affinity for actin>>)

* When the muscle is relaxed , myosin heads cant bind to the binding sites in actin filaments because tropomyosin masks these binding sites . During contraction thin filaments slide over the thick filaments moving toward the midline (sliding theory) , this leads to

shortening of the sarcomere and since the myofibril has repeated sarcomere units the whole muscle cell will shorten , but myofilaments (actin and myosin) themselves WILL NOT shorten they only overlap.

* What happens to the bands upon contraction ? (slide 7)

- The A band will NOT shorten since it corresponds to the length of the thick filaments that will not change .

- The I band : thin filaments will slide over thick filaments leading to the shortening of the I band .

- The H zone : will shorten after overlapping .

* Transverse sections are taken at different levels of a sarcomere (slide 6)

- At the zone where you have overlapping , you have thick filaments surrounded by thin filaments . Notice that each thick filament is surrounded by six thin filaments , and each thin filament is

surrounded by three thick filaments , so the ratio of thin to thick filaments is 2:1 .

- At M disc , the thick filaments are inserted together by another protein structures which are holding these thick filaments .

- At the zone where you have no overlap (H zone) , only thick filaments are seen .

* Cross – Binding cycle: (slides 15 , 16).

- The two binding sites have high affinity toward each other ONLY if the head is phosphorylated , otherwise there is no binding , this can be seen obviously in smooth muscles since there is no tropomyosin to cover myosin binding sites on the thin filaments (so we get contraction by phosphorylation of the heads , and relaxation by dephosphorylation). Notice that in skeletal muscles even if the myosin heads are phosphorylated but there is no calcium , binding will not take place .

- When the calcium is present , it binds to the C subunit of troponin molecules leading to a conformational changes that remove tropomyosin from myosin binding sites. At this stage , the head of each myosin unit is bound to an ADP and phosphate molecule , the myosin heads bind to the thin filaments by the newly exposed myosin binding sites , after binding we have head tilting (AKA power

stroke) by which thin filaments are pulled toward the center of the sarcomere , as the myosin units move , the heads release ADP and the phosphate molecule from their sites .

The gliding motion is halted when ATP molecules bind to the myosin heads (detachment process) , thus severing the bonds between myosin and actin . The ATP molecules are now decomposed into

ADP and phosphate molecule , with the energy by this rxn stored in the myosin heads ready to be used in the next cycle of movement .

The myosin heads resume their initial position (energized position) along the actin myofilaments .

- If we have high Ca+2 level , we will have the cycle again and again , but if Ca+2 conc. is decreased ,the heads are energized ready for contraction , but the rate of contraction will be reduced .

- If there is no ATP in the muscle cell , heads cant detach from actin filaments and they are stuck in this position (rigor mortis <muscle stiffness > after few hours of death).

Good luck