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Physiology #2

مجموعة التفريغ السريع

MSS

Subject: *Physiology #2*

Done by: التفريغ السريع

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Date: *Tuesday, September 24, 2013*

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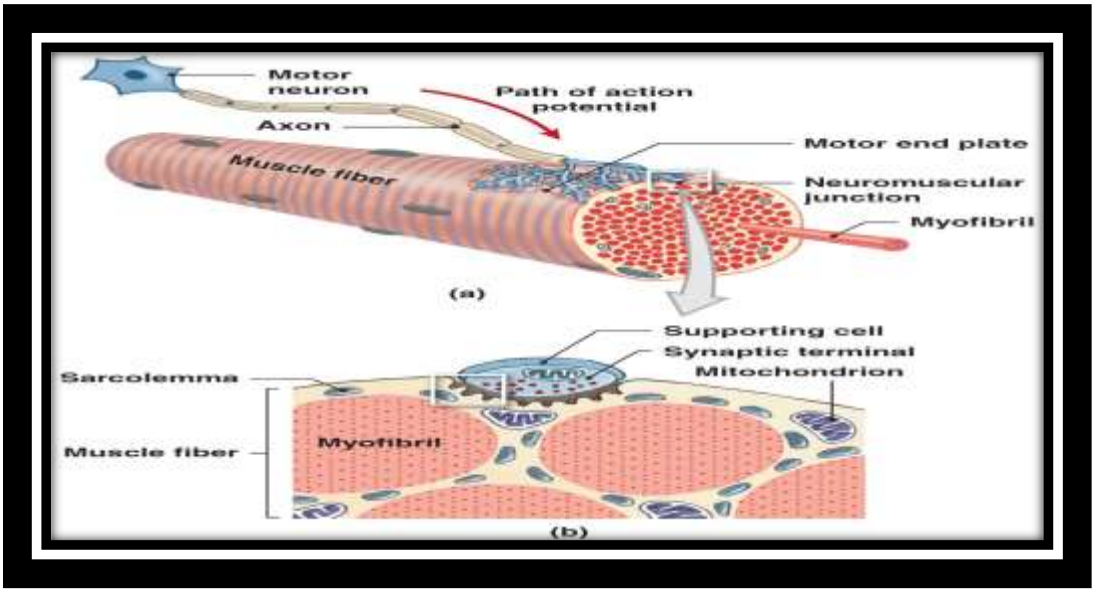
The doctor started by mentioning the headlines of the previous lecture, which are :

-The structure of the skeletal muscle.

-Mechanism of contraction.

*This lecture will talk about the neuromuscular junction



In this figure which represent the muscle fiber ,the fiber is innervated by a large motor neuron and this motor neuron is branched . Many branches enter the muscle fiber.

The neuromuscular junction ; is a structure which helps the stimulus to be transported from the motor end plates to the muscle fiber.

Components of neuromuscular junction:

1- Motor neuron.

2- End plate region; before the ending of a motor neuron .

3- Presynaptic terminal; the last part of a motor neuron , which contains mitochondria for energy and synaptic vesicles . Each synaptic vesicle has approximately 10,000 Acetylcholine "Ach" molecules.

4- Synaptic cleft / gap ; between the presynaptic terminal or end plate region and the muscle sacrolemma. It has the enzyme Cholinesterase - catalyze the hydrolysis of the neurotransmitter acetylcholine, wiki -

5- Postsynaptic membrane ; also called the sacrolemma which is the cell membrane of the muscle. It has Ach receptors and mitochondria to produce energy .

Mechanism of neuromuscular transmission :

The stimulus is transmitted from the motor neuron to the muscle cell by electrical propagation/transmission and an intermediate chemical step . Since the electrical stimulation is very fast , there should be a chemical intermediate step by the presence of acetylcholine which is responsible for a delay of the propagation at the presynaptic terminal . By applying acetylcholine to the postsynaptic membrane it will lead to the contraction of the fiber.

Events during transmission :

-Vesicles are filled with acetylcholine **synthesized** in the presynaptic terminal by the enzyme choline acetyltransferase .

-Ach **storage;** 10,000- 20,000 per synaptic vesicle.

-Action potential reaches the muscle fiber, depolarization of the end plate region (presynaptic terminal) and the **increment of the calcium influx** from the extra cellular fluid to the presynaptic terminal.

- Calcium ions induces the vesicles to fuse with the presynaptic membrane to **empty its contents** to the cleft by **exocytosis.**

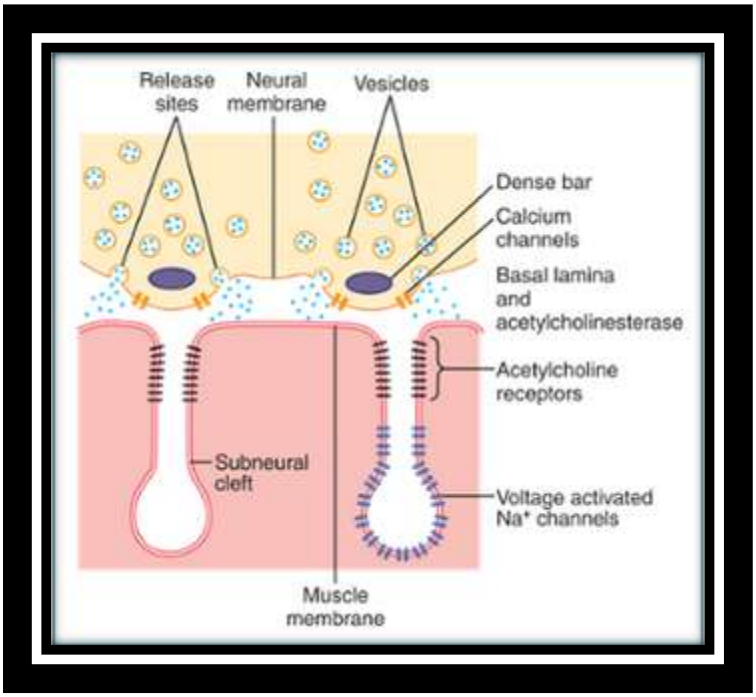
-Acetylcholine molecules start **binding** to the Acetylcholine receptors found on the postsynaptic membrane which will

And this will induce a local depolarization because the influx ion throw the acetylcholine receptors these acetylcholine receptors are small channels gated by acetylcholine binding of 2 acetylcholine to this channel open these channels and allow the influx of sodium to inside of the muscle cell ,hence depolarizing the membrane .

The depolarizing of the membrane we called this end plate potential , the action of acetylcholine this state will not last for ever its only for a very short time a millisecond .. after that the action of acetylcholine will diminished and end up by an enzyme called acetylcholine esterase .

Acetylcholine esterase will break down the acetylcholine into (acetate and choline) , and the choline will reabsorbed to the presynaptic terminal to build acetylcholine again .

We said that the end plate potential is the local depolarization that result from the influx of sodium ion because of the activation of the acetylcholine receptor and this a graded potential means that it is depend on the amount of the acetylcholine released.



this is a presentation of an exocytosis of the synaptic vesicle , the blue dots are acetylcholine molecule and the purple dots are the acetylcholine receptors , binding of the acetylcholine will induce the conformational changes in the channel and open these channels and influx of calcium to the sacroplasm of the muscle fiber .

the acetylcholine receptors is a protein composed of five subunits (2 alpha subunits , 1 beta , 1 gamma , 1 delta) **binding of 2 acetylcholine to each alpha subunit** , so binding of ligand that is acetylcholine cause a conformational changes and open the channel and influx of the calcium into the interior and initiation of what is called end plate potential

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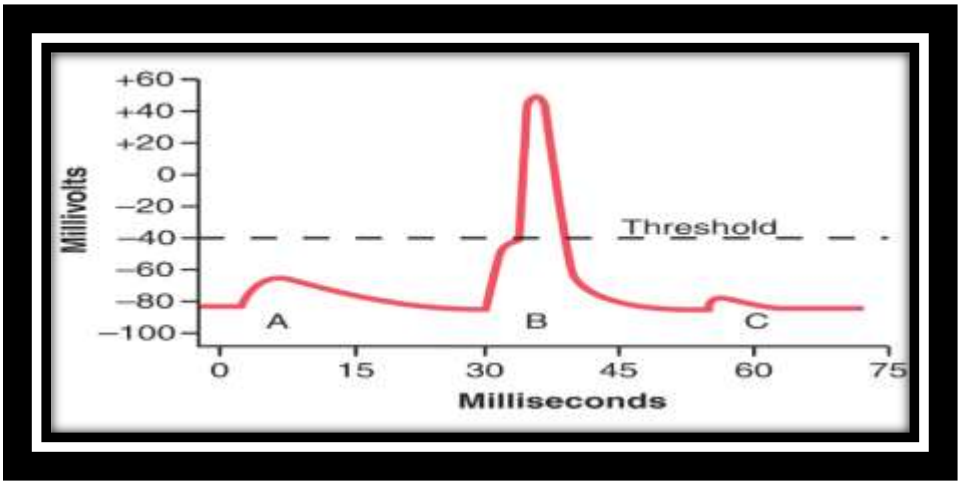
endplate potential and the excitation of the skeletal muscle:

these sequence lead to the formation of this local depolarizion which we call **end plate potential this is usually at the magnitude of (50 – 75) millivolt** .. if u remember when we talked about the action potential and the resting membrane potential of the nerves and the muscle cells , this is like shift in the interior of the cell to this level of charge is more than enough to depolarize the cell membrane because there are sodium channel in the membrane .. these are voltage gated channels which means that these channels sense the changes in voltage .. if there is enough changes in voltage , these channel will open .. sodium channel will open in range of (20-30) millivolt so the local depolarization is great enough to initiate an action potential (it is 50-75 millivolt).

so action potential is **all or none phenomenon** , the local depolarization must reach the **threshold** in order to action potential to take place and as we can see this is more than enough to initiate an action potential in the muscle fiber .



as u can see here is 3 end plate potential , A and C are small end plate potential and they are unable to initiate an end plate potential but D is great enough to initiate an end plate potential .A and C they use a specific drugs to limit the initiation of the action potential at the neuromuscular junction .

Fatigue of the neuromuscular junction :

As we said that the end plate potential is enough to cause an action potential it's about three times greater than needed to initiate an action potential .. and this is called the **safety factor of transmission** , usually an endplate potential is happened due to a stimulus will initiate an action potential but what will happen if the stimulation is at a very high frequency for a long enough duration ? for example 100 hundred times per second for several minutes .

At this time the synaptic vesicle(Ach vesicle) will diminished and depleted and there will be fatigue of the neuromuscular junction after this .. the stimulation will not initiate an action potential and this is what called **fatigue of neuromuscular junction**

.

Acetylcholine formation and release :

The formation of these vesicles takes place in the cell body of neuron usually in the **ventral horn of the spinal cord** , and then these vesicles will be transported through the axon into the synaptic terminal and this process need energy .

These vesicles is around 300,000 vesicles will be synthesis in cell body and transported to the synaptic terminals and then at the synaptic terminals there will be synthesis of acetylcholine by the action of the enzyme acetylcholine transferase from acetate and choline and then filling of these vesicles with acetylcholine then when the action potential reach the synaptic terminals there will be depolarization as we said and this will increase calcium influx to the terminal , calcium will cause the release of these vesicles to the synaptic cleft .

There should be a rapid turnover to these vesicles in order to maintain the excitability of the neuromuscular junction so there are another mechanism to formation of these vesicles like formation from the endosomes or what is called clathrin coated pits from the plasma membrane there are specific contractile protein that produce these vesicles to maintain the functionality of the neuromuscular junction during activation

Here the doctor view an animation to the whole process , but unfortunately I can not find it in the slides . .

Drugs that affect the transmission at the neuromuscular junction:

there are different drugs that can affect this process .....

on Ach release :

1)Ca+2 will enhance the transmission because it is the reason for Ach release .

2) Mg+ and Mn+ will compete for Ca+2 but they did not do the same action so they reduce the amount of Ach that released .

3) Botulin toxin : reduce the exocytosis for Ach release

SO ONLY CA+2 HERE INCREASE ACH RELEASE AND THE OTHERS SUBSATANS BLOCK THE TRANSMISSION

Bind to the receptors:

1) Methacholine, Carbachole and nicotine : all of these produce more transmission than Ach , And the difference between these drugs and Ach is that these drugs are not subjected to the action of acetylcholinesterase ,so the action is longer .

AND at the end there will be kind of **spam** in muscles fibers.

2) D – tubocurare (curare): inhibits transmission by competing with Ach on its receptors, so it will do the opposite action of Ach (block the action of Ach)

Cholinesterase inhibitors:

1) Irreversible – nerve gas and insecticides and diisopropyl flurophosphate : they inhibit acetylcholinesterase and the end result is spam (prolong the action of Ach and more end

plate potential(EPP) , maintain of contraction) (lethal lead to death due to its action on respiratory muscles)

2)Reversible - **neostigmine and physiostigmine**(used as drugs):

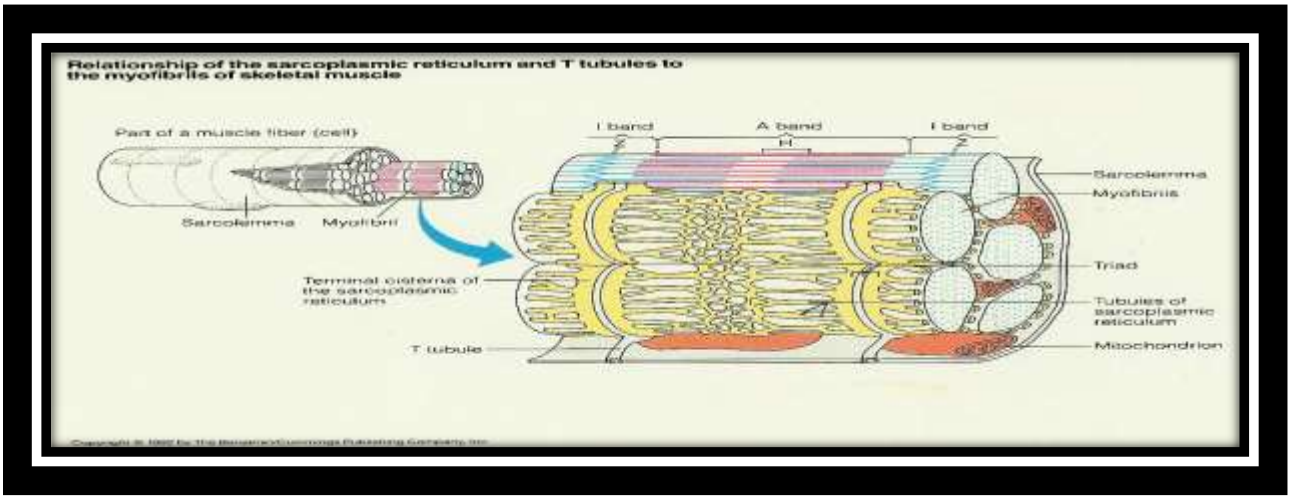
they inhibit the action acetylcholinesterase Reversibly and after specific time they will be released from acetylcholinesterase .

Myasthenia gravis: autoimmune disease where antibodies against the Ach receptors are produced.so the contraction of the muscles will be inhibited and paralysis if the situation is severe .

HOWCAN WE AMELIORATE THIS CONDITION ?

ANS: give neostigmine and physiostigmine (inhibit acetylcholinesterase so more Ach)

The spread of the action potential of the muscle fiber by the way of “transverase tubules”



The action potential arrive to the muscle cell , and the muscle cell unlike the nerve fibers is very large so the action potential cannot penetrate deep to the whole muscle cell .

The t-tubules which are like invagination of the sarcolemma will transfer the action potential to whole muscle cells ,AND these t-tubules will reach from one side from the

plasma membrane to the other side .and there are like cross channel between them to propagate the action potential to every part of the muscle

The action potential in the t-tubules cause release of Ca+2 into the Myoplasm.

And we said that the arrangement of t-tubules with SR (the traid) ,and t-tubules go deep in muscle fibers at the junction between A band and I band of the myofibrils and this arrangement is everywhere in the muscle cell ,so there will an action potential in close proximity to all the myofibrils of the muscle cell inverted by that nerve .

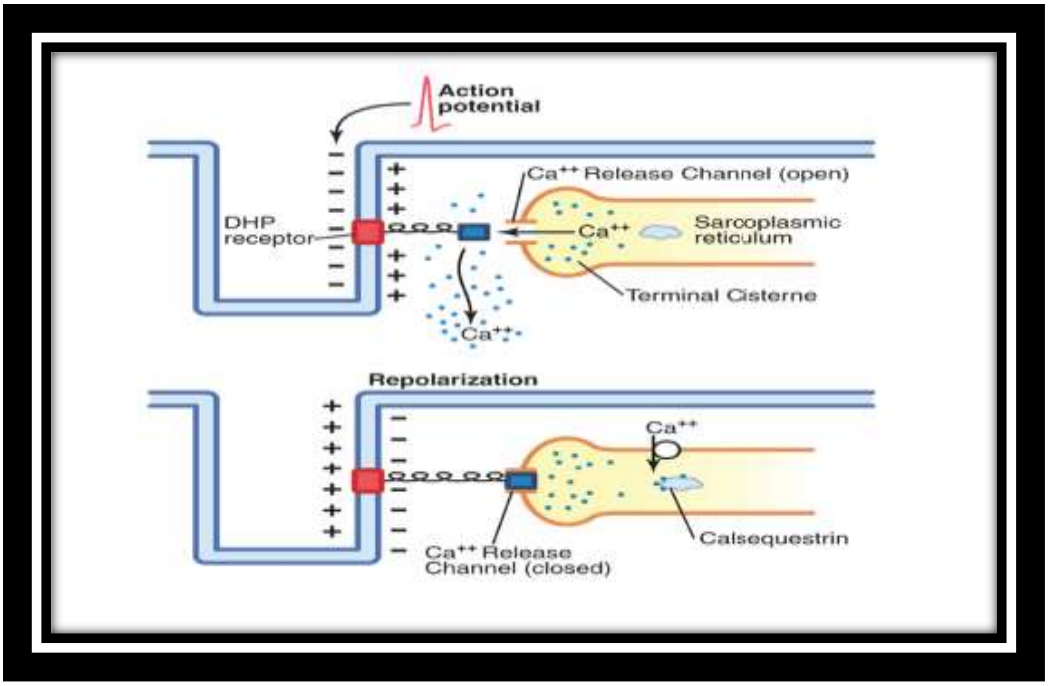
The process by which depolarization of the T-tubule Is converted to an intracellular calcium signal and the Subsequent activation of contraction is called **Excitation-Contraction Coupling**

the release of Ca+2 is the final signal for muscle contraction and this called Excitation-Contraction Coupling.

Release of Ca+2 ions from sarcoplasmic reticulum(SR) :

It starts when the depolarization travelled in T-tubules and then sensed by special sensor called (hydropyridine receptor) a protein located in T-tubules and physically attached to Calicum release channel(rayabdin receptor) so that Ca+2 ions are released from SR .

Calsequestrin : is a protein in SR that augment SR's Ca+2 storage , this protein has has a **low affinity** to allow the release of Ca+2 during stimulation and **high capacity** has the capability to store large amount of Ca+2 leading to increase amount of Ca+2 stored or released .



The terminated of contraction :

By the removal of Ca+2 from the sarcoplasm and this is the action of (SERCA) smooth endoplasmic reticulum Calicium-ATPase which is a pump that move Ca+2 ions from sarcoplasm to SR by ATP hydrolysis as the name implicated (2 Ca+2 ions per one molecule of ATP)

The characteristic of muscle contraction:

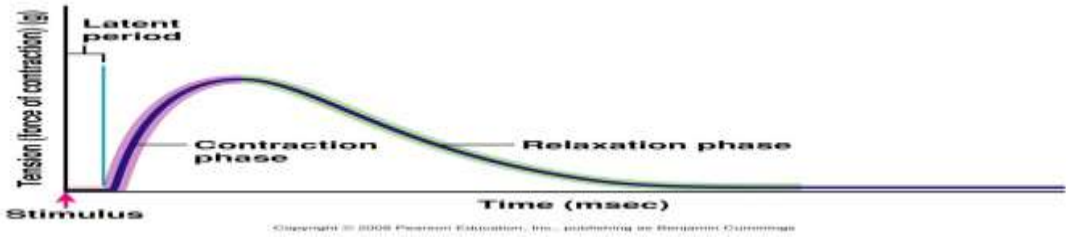
A single action potential whih is stimulation causes single muscle contraction and called twitch

For example(an experiment) if we take a muscle and tie on end to rigid arm and the second end to a transport transducer then stimulate the muscle by an electrode we will record of the twitch (single muscle contraction).

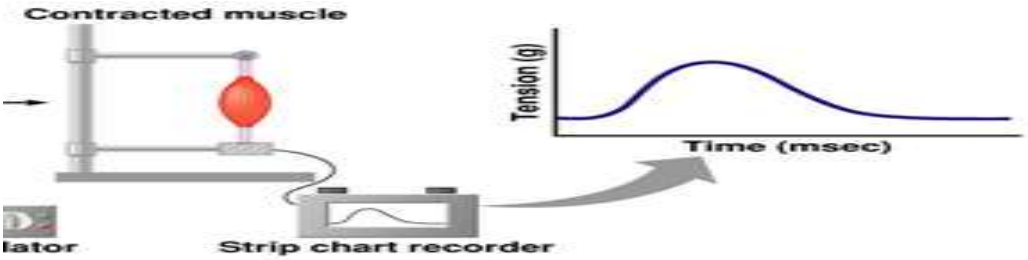
A twitch is composed of three phases **1-elegant phase 2-lizent phase -3 fork phase**

or two phases:

the contraction phase and the relaxation phase .



* duration of relaxation is longer than that of contraction.



** the muscle force depend upon the number of motor units that are activated

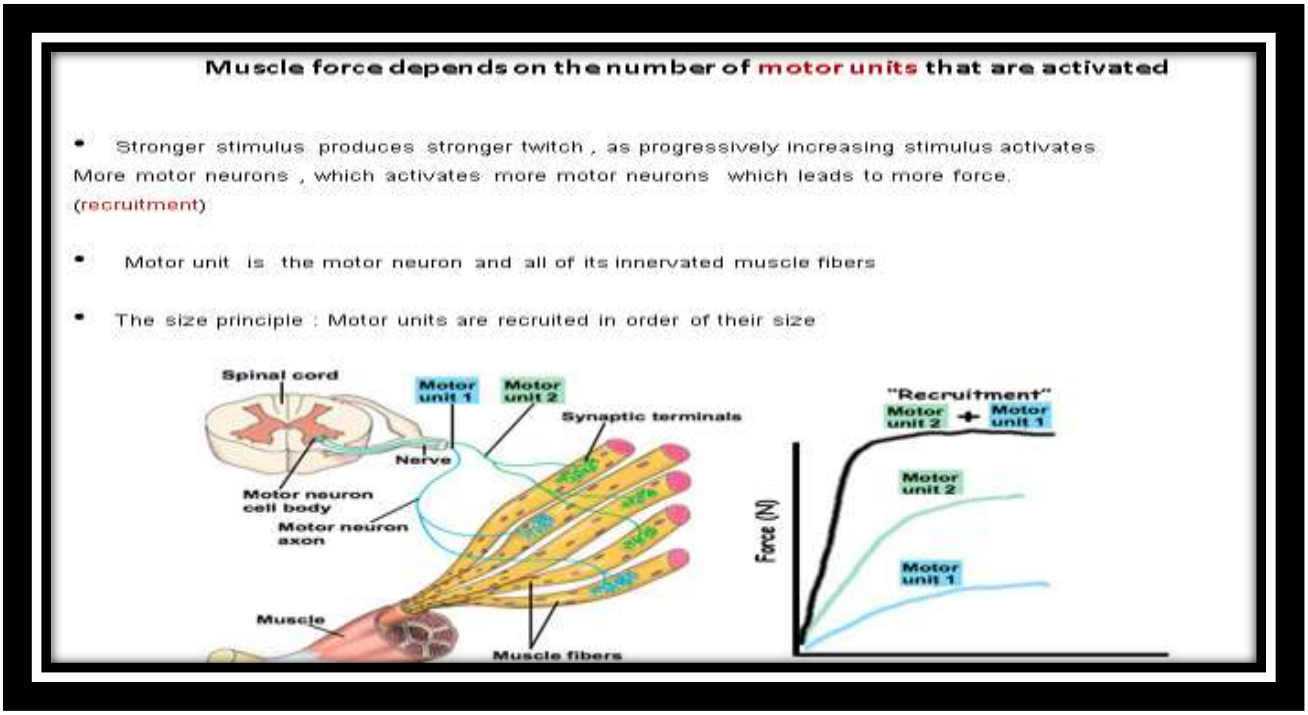
A skeletal muscle is innervated by large myelinated motor neurons of the ventral horn of spinal cord , and each motor neurons composed of many exon that will branch inside the muscle sarcolemma .

Each a motor neuron and all of its innervated muscle fibres is called motor unit, large and small motor unit .

But be attention that each muscle fibre is innervated by single motor neuron, but one motor neuron innervate a lot of muscle fiber.

So if we progressively increase the stimulation we will recruit more motor neuron depending on their size – smaller motor neuron will be stimulated before the large one – this leads to enhance more muscle fibers and this is called recruitment .

Motor 1 innervate 2 muscle fibers and motor 2 innervate 3 muscle fibers if we sitmulate motor #2 we will get more forec than that of motor #1 ,but if you stimulate them together by a third larger stimulus we can even higher force by recruitment.



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