Neuromuscular Transmission

&

Physiology of muscle contraction

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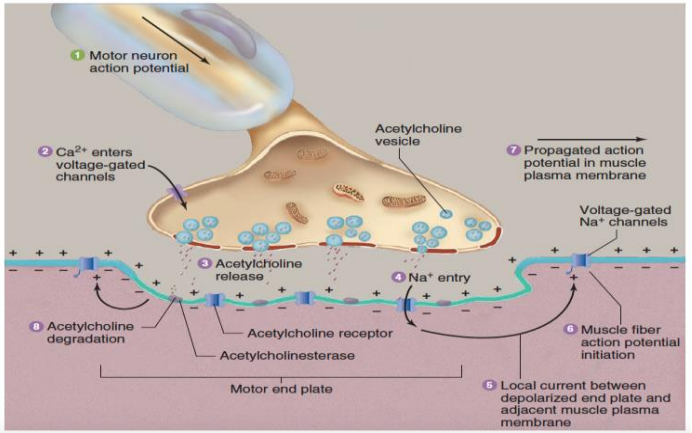
The **Simple Story** of Neuromuscular Transmission

Arrival of Action potential to nerve terminal - after activating the motor neuron - will open calcium channels .. then calcium will enter from ECF to ICF. Calcium will stimulate the releasing of the neurotransmitter Acetylcholine.. Acetylcholine will be released. Acetylcholine will then bind to specific ion channels on the sarcolemma (muscle cell membrane) those ion channels will open allowing the Na & K to go in and out changing the potential of the cell which will start another action potential that will spread on both sides of neuromuscular junction transmitting the impulses...

AS SIMPLE AS THAT, SEE!



The nerves will talk and the muscles will listen.. unfortunately nerves are <u>always</u> talking and muscles are <u>always</u> listening so.. it's **one way** process

Now let's talk scientifically...

Additional Slide

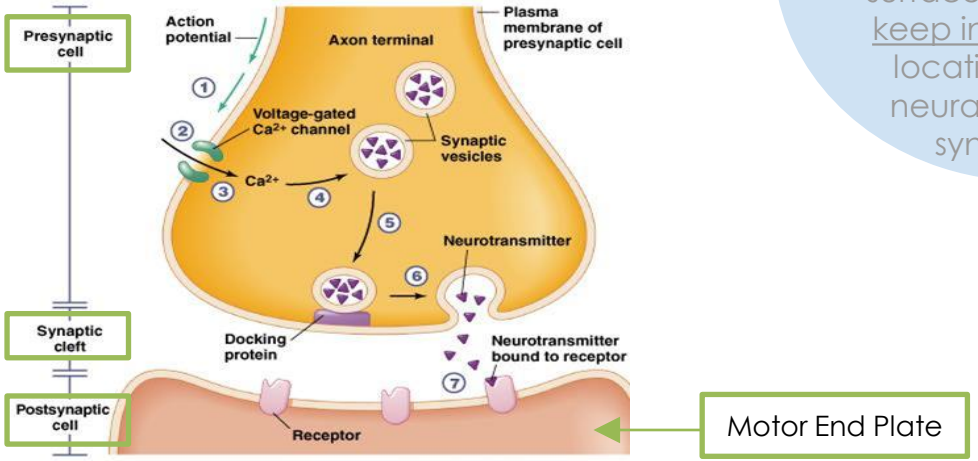
But you should read it for fun and a better understanding..

The Neuromuscular Junction (The Motor End Plate)

The transmission nerve impulse occurs in the neuromuscular junction (NMJ) , it contains three main sites :

- (Presynaptic cell) Terminal end of a motor axon[1]
  (Synaptic cleft) which contains the subneural clefts.
- (Postsynaptic cell) sarcolemma[2]

Synaptic cleft is 20 to 30 nanometers wide & it's located between the terminal end of the axon and the surface of the muscle. keep in mind that the location of the sub neural cleft is in the synaptic cleft



1- Contains **around** 300,000 vesicles which contain the neurotransmitter acetylcholine.
2- Neurotransmitters acetylcholine bind to specific receptors (nicotinic and muscarinic)
once a neurotransmitter has bound with a postsynaptic receptor it is quickly broken down by enzymes .

Acetylcholine (ACH)

How it is stored ?

The vesicles of acetylcholine is formed in the body (soma) of neuron by Golgi apparatus , then it is transported to the terminal end where the the acetylcholine itself is synthesized from active acetate (acetylcoenzyme A)(derivative of acetic acid)and choline .

How it is released?

When an action potential arrives to the axon terminal , the voltage gated calcium channels are activated , thus allowing the diffusion of calcium ions , those calcium ions draw the synaptic vesicles to the membrane of the terminal of the neuron .
finally, ACH contained within the vescles is liberated by exocytosis , about 125 vesicles are release its content into the synaptic cleft.

How it is destructed?

Most of the acetylcholine is destroyed by the enzyme acetylcholinesterase into acetate and choline The Choline is actively reabsorbed into the nerve terminal to be used again to form Ach .

The receptors involved in the motor end plate

1) Receptors in the presynaptic cell

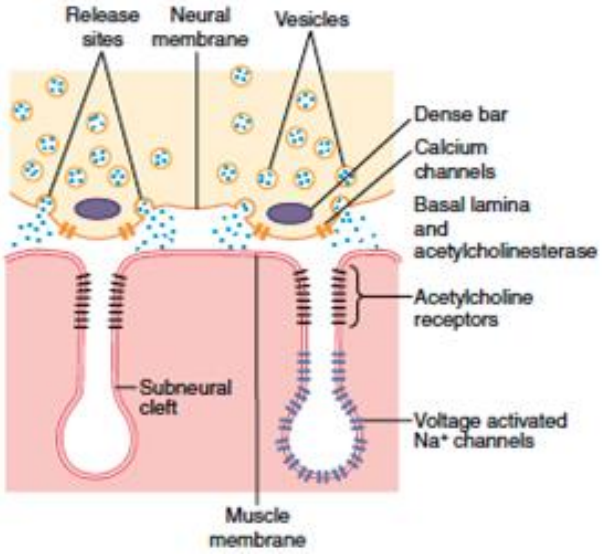
Voltage-gated calcium channels :

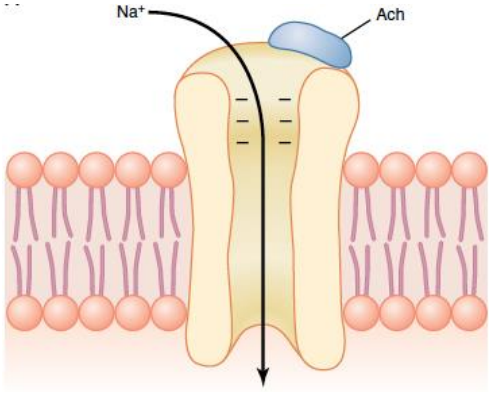
These channels open when the action potential arrive, allowing the influx of calcium that will lead to the release of acetylcholine.

2) Receptors in the postsynaptic cell

Acetylcholine-gated ion channels:

The complex is composed of five subunit proteins, two alpha proteins , single beta, delta, and gamma proteins.





It is very important to distinguish between ligand gated and voltage gated channels

Summary Of The Whole Lecture

(1) Normal neuromuscular transmission begins with AP[1] traveling down the motor neuron

(2) AP reaches the nerve terminal and activates ca++ channels

(3)↑ca++ causes synaptic vesicles containing Ach[2] to be released into the synaptic cleft

(4) Ach binds to AchR[3] on Sarcolemma[4]

(5) AchR channel opens and allows Na+ into muscle[6]

(6) Rising Na+ level generates AP at the end plate

(7) Voltage-gated Na+ channels open and allow more Na+

(8) Muscle AP wish will then lead to muscle contraction

steps of neuromuscular transmission

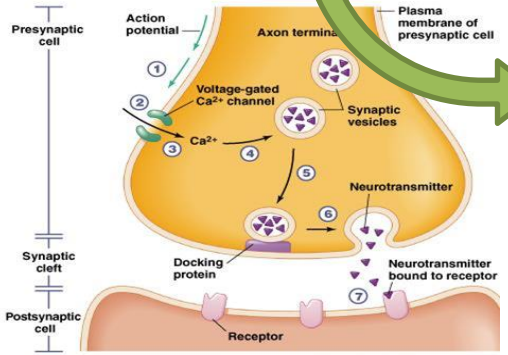
Fate of Ach

Ach diffusion

Followed by rapid decline in Ach levels via :

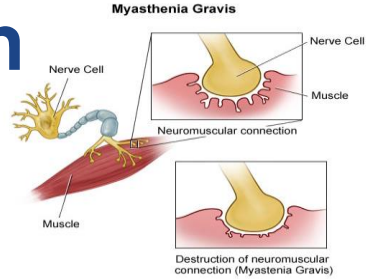
Ach deactivation by AchE[5] within the synaptic cleft

This prevents multiple reactivations of AchR



1- Action Potential
2-Acetylcholine
3-Acetylcholine receptors
4- Muscle plasma membrane
5- Acetylcholinestrase
6 - It opens k+ channels also but it doesn't have much impact

Problems in neuromuscular junction



Myasthenia Gravis:

- Autoimmuneneuromuscular disease.

- Muscle weakness, Due to circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction , Leading to fluctuating muscle weakness and fatigue.

LAMBERT EATON MYASTHENIC SYNDROME :

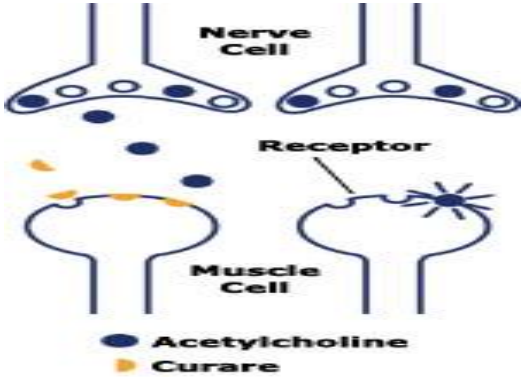
- Autoimmuneneuromuscular disease

- muscle weakness caused by an autoimmine reaction in which auto-antibodies are formed against presynaptic voltage-gated calcium channels , in the presynaptic site of the neuromuscular junction leading to a reduction in the amount of acetylcholine released from nerve terminals .

LEMS	Myasthenia-Gravis
Antibodies against the **nerve** where acetylcholine is released	Antibodies against the **muscle receptor** for acetylcholine
Starts at extremities and moves up	Starts at eyes and moves down
Weakness improves upon activity	Weakness worsens upon activity
Associated with "small cell" lung cancer	Associated with Thymoma
Therapy = Aminopyridines	Therapy = Acetylcholine esterase inhibitors

Drugs that affect neuromuscular transmission

There are two pharmacology lectures about these drugs



Acetylcholinesterase inhibitors: Neostigmine

Curare:

*Arrow poisons

*Competitively and **reversibly** inhibiting Acetylcholine receptors found at the neuromuscular junction

*Anesthesia : is a temporary state consisting of unconsciousness, loss of memory, lack of pain, and muscle relaxation.

DENERVATION HYPERSENSITIVITY

Definition:

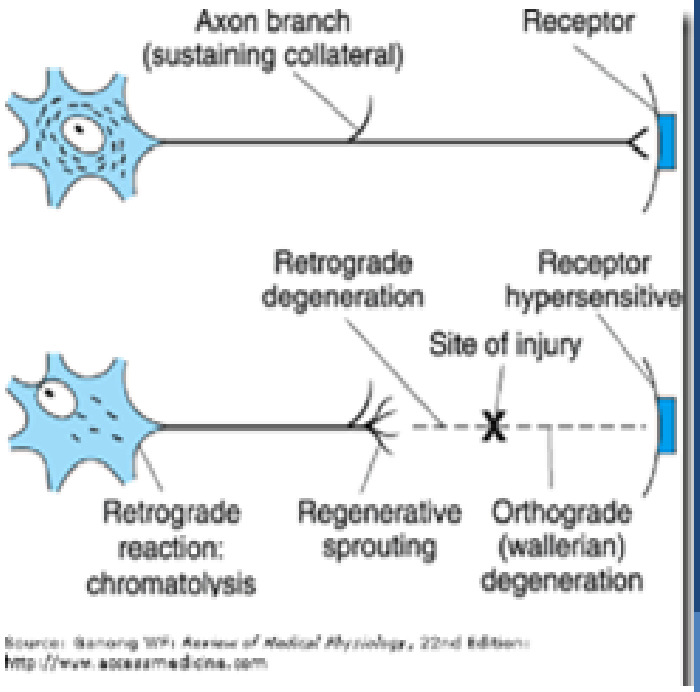
When the motor nerve to skeletal muscle is cut and allowed to degenerate, the muscle gradually becomes extremely sensitive to acetylcholine.

Mechanism:

Normally nicotinic receptor are located only in vicinity of motor end plate while after denervation (cut) there is a marked proliferation of nicotinic receptors over a wide region of the neuromuscular junction.

Cause:

upregulation of its receptors and lack of reuptake of secreted neurotransmitters.



The Muscle Action Potential (AP)

Muscle Resting membrane Potential
=
-90mV
(Same as in nerve)

Duration of action potential
=
1-5ms
(longer than nerve fibre)

Conduction velocity of AP in muscles
=
3-5m/s
(slower than big nerves)

Muscle fibres and myofibril

Muscle

↓

Muscle fascicle
(group of fibres)

↓

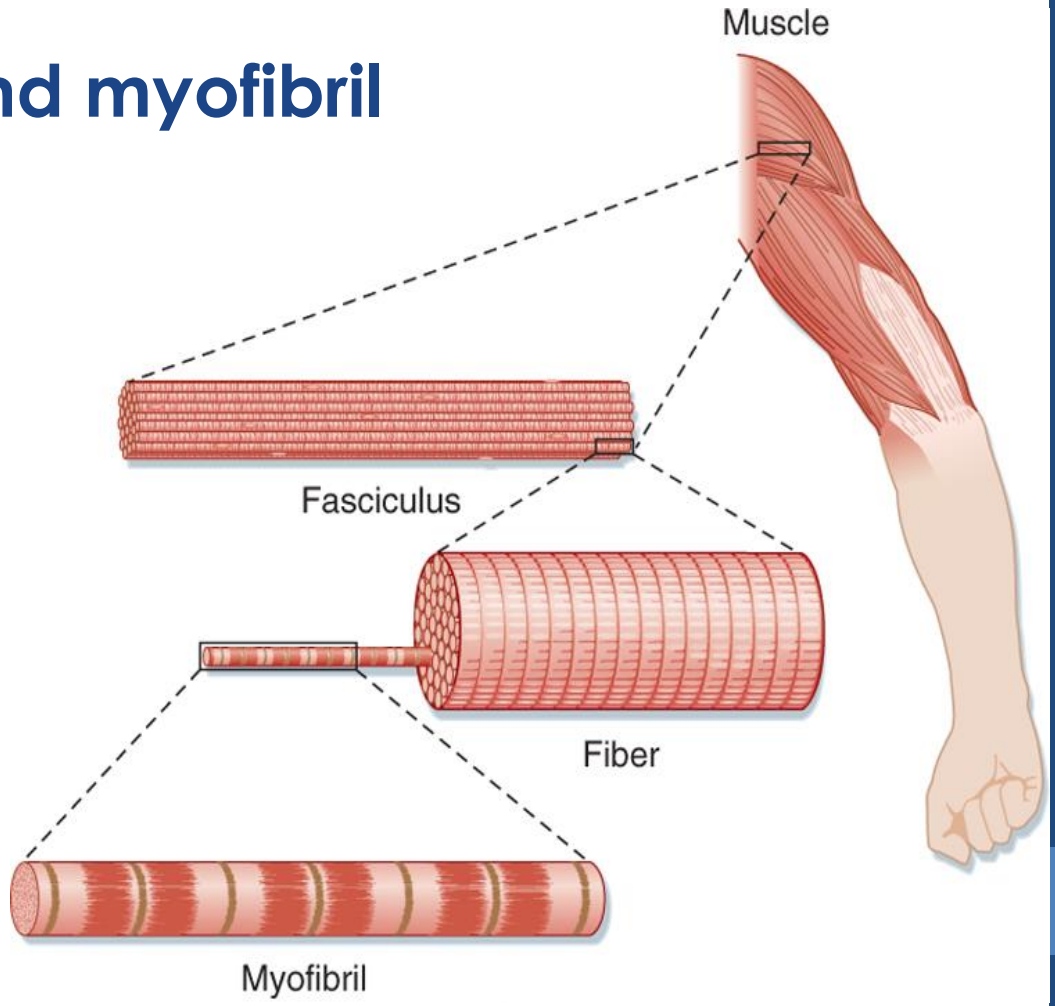
Fibres (covered by sarcolemma)

↓

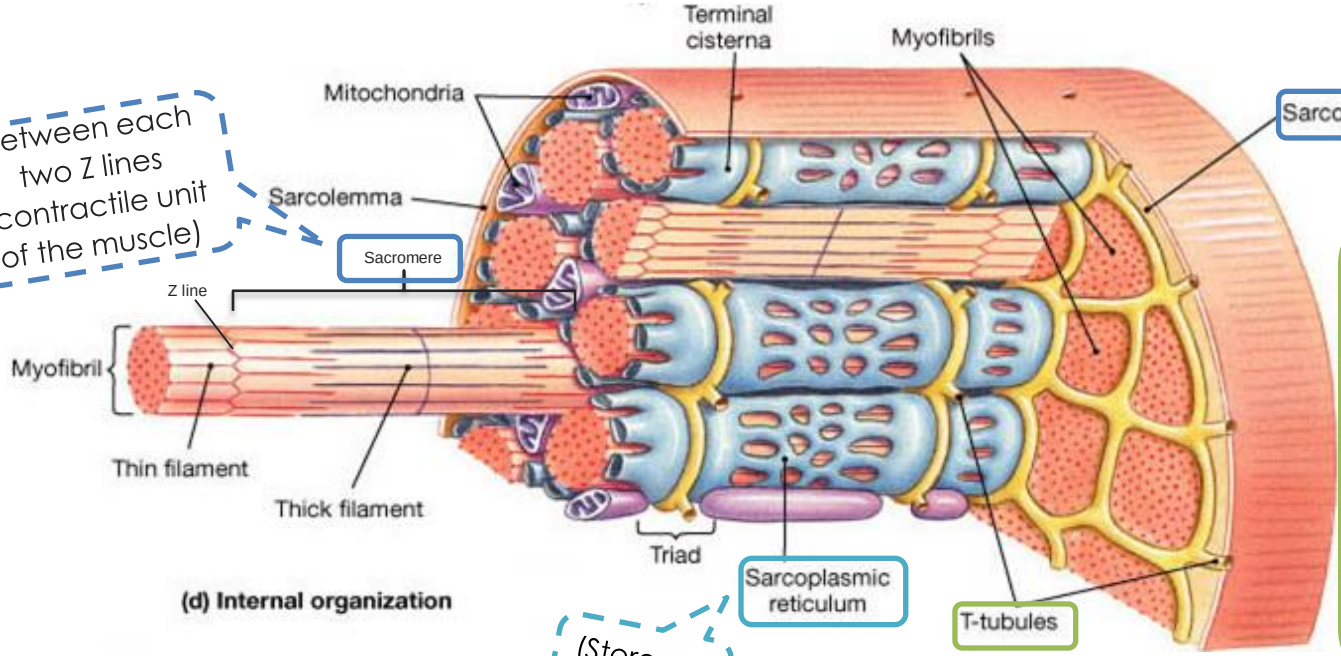
Myofibrils

A band — dA**r**k

I band — **I**ight



What is inside a myofibril?



between each two Z lines (contractile unit of the muscle)

(Store of calcium)

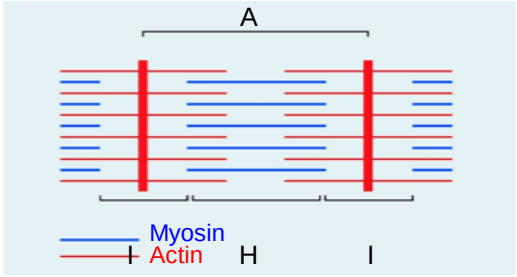
extend from one side of muscle to other

Function:
conduct impulses from the surface of the cell (SARCOLEMMA) down into the cell and, specifically, to another structure in the cell called the SARCOPLASMIC RETICULUM.

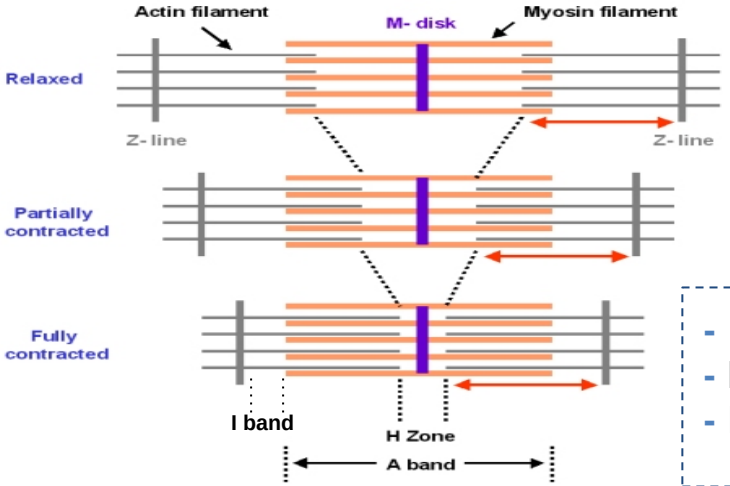
Sliding Filament Mechanism

As we can see inside each sarcomere there are three bands:

1- I Band = Actin only "thin".
2- H Band = Myosin only "thick".
3- A Band = Formed of Actin and myosin filaments .



When contraction takes place in our muscle Actin and myosin slide upon each other " without any change in their length" so the distance between the Z bands(sarcomere) decrease, this process called **Sliding Filament Mechanism (The walk along theory).**



While contraction:

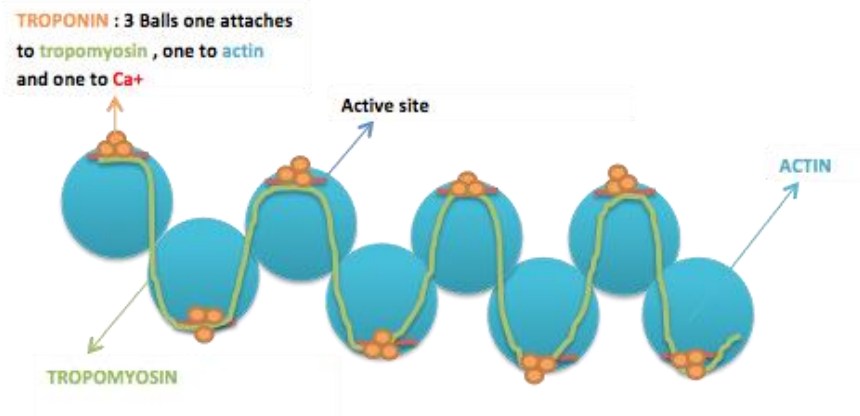
- **A Band** is constant.
- **I Band** shorten.
- **H Band** shorten or even disappear.

Actin filament is thin and when contraction occurs myosin which is the thick filaments pulls the actin to its ward and contraction takes place"
will be discussed in details on coming slides

On molecular level How does the thin and thick filaments look like..

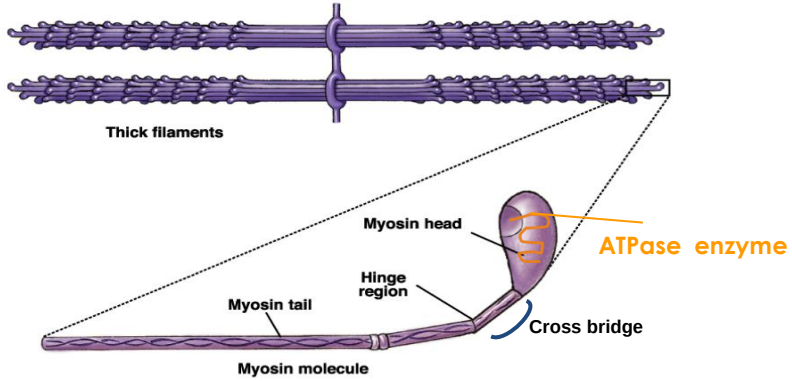
Thin filaments

contains **Actin** , **Tropomyosin** and **Troponin.**



Thick filaments

contains only **Myosin**

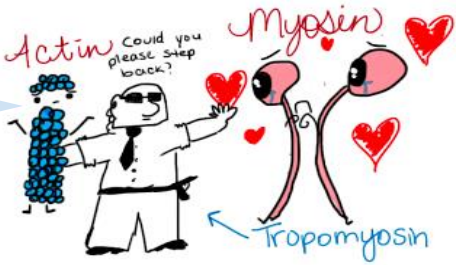


Myosin head contain "2 ears" **2 binding sites**

1- ATP binding site

2- Actin binding site

During relaxation myosin is attracted to actin (As it has a binding site for it)but tropomyosin is attaching to actin and covering the binding site not allowing the myosin to attach to actin.



Muscle Contraction:

1- Acetylcholine released from axon terminal binds to receptors on sarcolemma "discussed in details previously".

2- Spreading of muscle action potential into T-tubules.

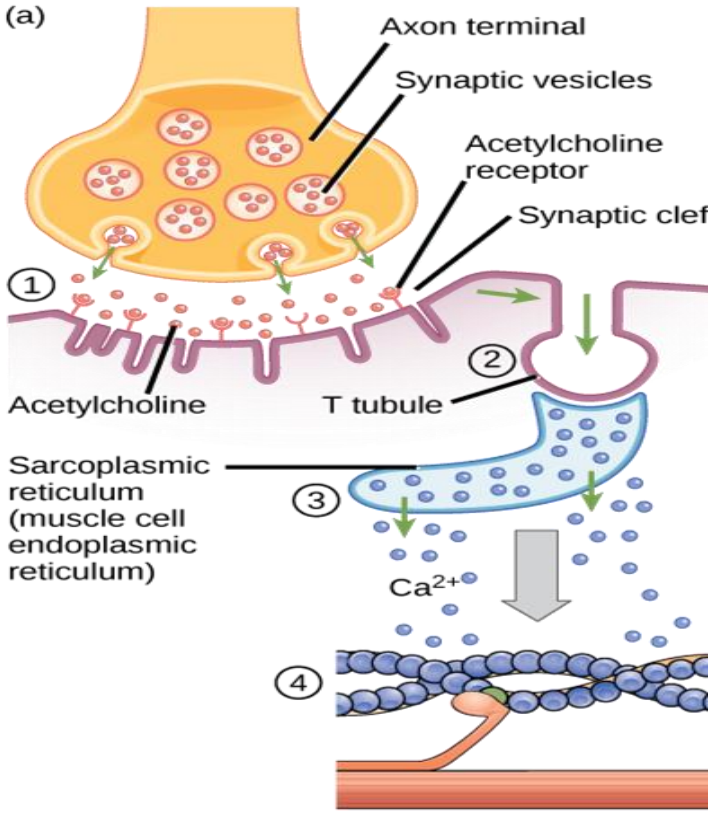
3- Release of calcium (by calcium channels in the walls of the sarcoplasmic reticulum).

* Calcium passively flows out from sarcoplasmic reticulum into the cytoplasm.

** Increased Ca++ concentration in the myofibrillar fluid.

*** Calcium combines (Activate) with **Troponin**. **Troponin** Pull **Tropomyosin** sideway.. Exposing the Active Site on Actin to the Myosin.

4- Myosin Heads with ATP on them, gets attached to Actin Active Site immediately.



Step 3 is the most important step!
Because **calcium is the hero**.
without calcium muscle contraction will never occur

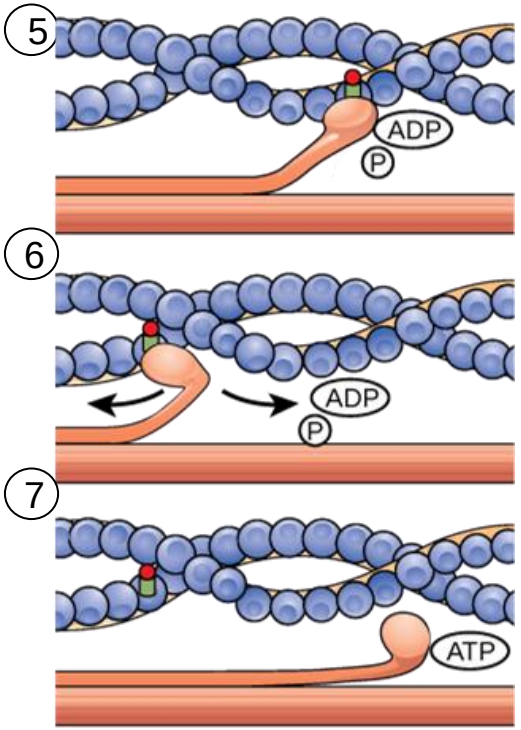
Muscle Contraction: cont.

5- This binding activates the **enzyme ATPase** in the Myosin Head. it cleavages (breaks down) of ATP releasing Energy (**ATP** to **ADP** & **P**) Linkage between Actin & Myosin is broken as new **ATP** binds to Myosin cross bridge > **ATP** Hydrolyzed and cross bridge go back to its Original Conformation.

6- The "**Power Stroke**" means tilting of the cross-bridge head (Myosin Head) and Dragging (Pulling) of Actin filament.

7- When a new **ATP** occupies the vacant site on the Myosin Head, this triggers **detachment** (separation) of Myosin from Actin.

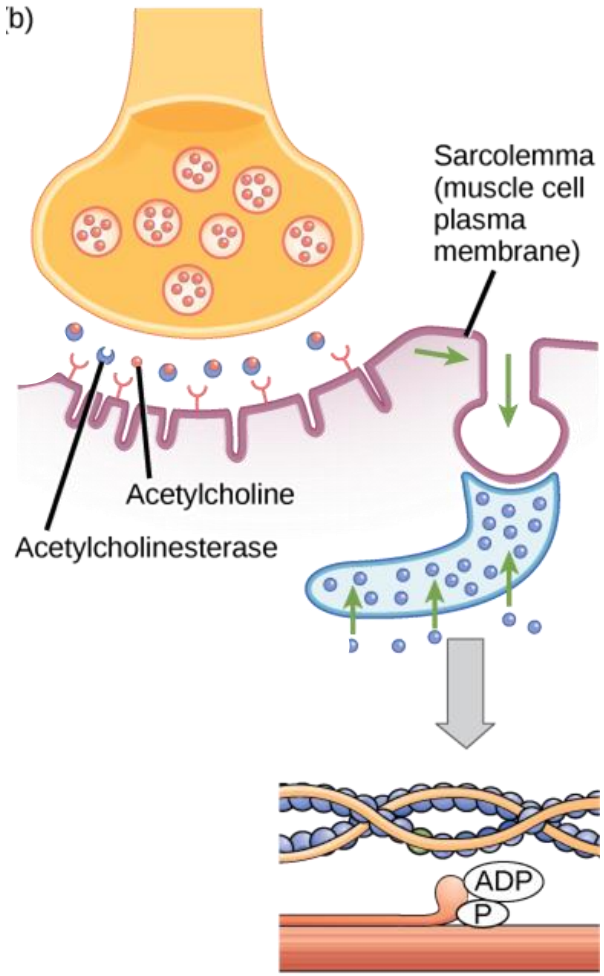
The free Myosin swings back to its original position & attach to another Actin & the cycle repeat itself.



Muscle Relaxation:

* When Ca is Pumped “Actively” back into Sarcoplasmic Reticulum.

* Calcium detached from **Troponin** » **Tropomyosin** returns to its Original Position covering Active Site on Actin and will again prevents attachment between Actin and Myosin thus will cause Relaxation.



YouTube Video explains the muscle contraction process

[Muscle Contraction Process: Molecular Mechanism [3D Animation]]

MCQs

1- the space between the axon terminal & the muscle cell membrane is ??

A - motor end-plate
B - myelin sheath
C - synaptic cleft
D - motor neuron

2 - Synapse is the junction between two neurons where electrical activity of one neuron is transmitted to the other

A -true

B - false

3- synaptic vesicles is filled with Ach molecules ??

A - 100,000

B - 300,00

C - 10,000

D - 20,000

4 -During neuromuscular transmission, the arrival of nerve AP at the synaptic knob leads to which of the following ??

A - Opening of Na channels.
B - Opening of K channels.
C -Opening of Ca channels.

5 - which step of neuromuscular transmission appear after Na permeability increase ??

A - AP spread on the membrane
B - end plate potential develop
C - release of Ach

D - muscle contraction

Answers:
1 - C
2 - A
3 - C
4 - C
5 - B

MCQs

for both lectures
(neuromuscular transmission, physiology of muscle contraction)

1. **During the upstroke "dedepolrization phase" of the nerve action potential**
   A. There is net outward current and the cell interior becomes more negative.
   B. There is net outward current and the cell interior becomes less negative.
   C. There is net inward current and the cell interior becomes more negative.
   D. There is net inward current and the cell interior becomes less negative.

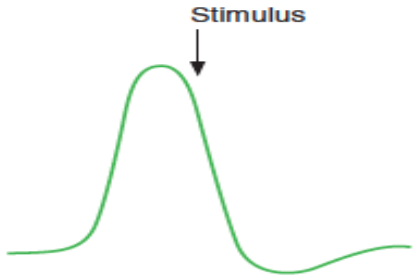
2. **The correct temporal sequence for events at the neuromuscular junction is**
   A. Action potential in the motor nerve;depolarization of the muscle end plate; uptake of Ca2+ into the presynaptic nerve terminal.
   B. Uptake of Ca2+ into the presynaptic terminal;release of acetylcholine (ACh); depolarization of the muscle end plate.
   C. Release of ACh; action potential in the motor nerve; action potential in the muscle
   D. Uptake of Ca2+ into the motor end plate; action potential in the motor end plate;
   E. Action potential in the muscle.

3. **A 42-year-old man with myasthenia gravis notes increased muscle strength when he is treated with an acetylcholinesterase (AChE) inhibitor. The basis for his improvement is increased**

   A. Amount of acetylcholine (ACh) released from motor nerves.
   B. Levels of ACh at the muscle end plates.
   C. Number of ACh receptors on the muscle end plates.
   D. Amount of norepinephrine released from motor nerves.
   E. Synthesis of norepinephrine in motor nerves.

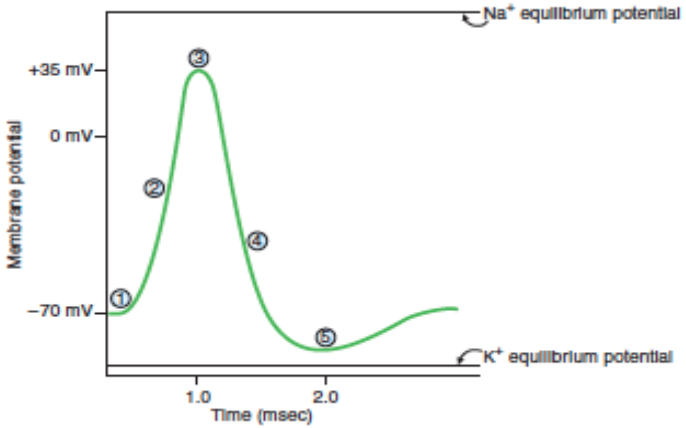
4. **During a nerve action potential, a stimulus is delivered as indicated by the arrow shown in the following figure. In response to the stimulus, a second action potential**

   A. Of smaller magnitude will occur.
   B. Of normal magnitude will occur.
   C. Of normal magnitude will occur, but will be delayed.
   D. Will occur, but will not have an overshoot.
   E. Will not occur.



5. At which labeled point on the action potential is the K+ closest to electrochemical equilibrium?

A. 1
B. 2
C. 3
D. 4
E. 5



6.What process is responsible for the change in membrane potential that occurs between point 1 and point 3?

A. Movement of Na+ into the cell..
B. Movement of Na+ out of the cell.
C. Movement of K+ into the cell.
D. Movement of K+ out of the cell.
E. Activation of the Na+–K+ pump.
F. Inhibition of the Na+–K+ pump.

7. What process is responsible for the change in membrane potential that occurs between point 3 and point 4?

A. Movement of Na+ into the cell.
B. Movement of Na+ out of the cell.
C. Movement of K+ into the cell.
D. Movement of K+ out of the cell.
E. Activation of the Na+–K+ pump.
F. Inhibition of the Na+–K+ pump.

8. At the muscle end plate, acetylcholine (ACh) causes the opening of

A. Na+ channels and depolarization toward the Na+ equilibrium potential
B. K+ channels and depolarization toward the K+ equilibrium potential
C. Ca2+ channels and depolarization toward the Ca2+ equilibrium potential
D. Na+ and K+ channels and depolarization to a value halfway between the Na+ and K+ equilibrium potentials
E. Na+ and K+ channels and hyperpolarization to a value halfway between the Na+ and K+ equilibrium potentials.

9.Which of the following temporal sequences is correct for excitation–contraction coupling in skeletal muscle?

A. Increased intracellular [Ca2+]; action potential in the muscle membrane; cross-bridge formation
B. Action potential in the muscle membrane; depolarization of the T tubules; release of Ca2+ from the sarcoplasmic reticulum (SR)
C. Action potential in the muscle membrane;splitting of adenosine triphosphate (ATP); binding of Ca2+ to troponin C
D. Release of Ca2+ from the SR; depolarization of the T tubules; binding of Ca2+ totroponin C.

10. In skeletal muscle, which of the following events occurs before depolarization of the T tubules in the mechanism of excitation–contraction coupling?

A. Depolarization of the sarcolemmal membrane
B. Opening of Ca2+ release channels on the sarcoplasmic reticulum (SR)
C. Uptake of Ca2+ into the SR by Ca2+-adenosine triphosphatase (ATPase)
D. Binding of Ca2+ to troponin C
E. Binding of actin and myosin

Answers:
1)D
2)B
3)B
4)E
5)E
6)A
7)D
8)D
9)B
10)A

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