Physiology Team Notes 2

Musculoskeletal Block

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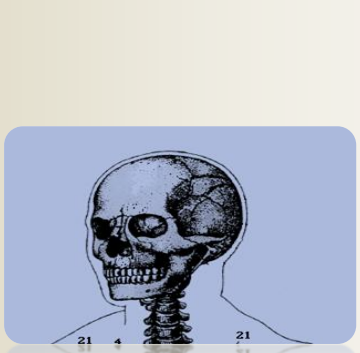

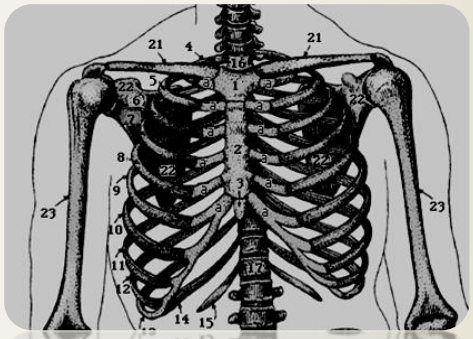

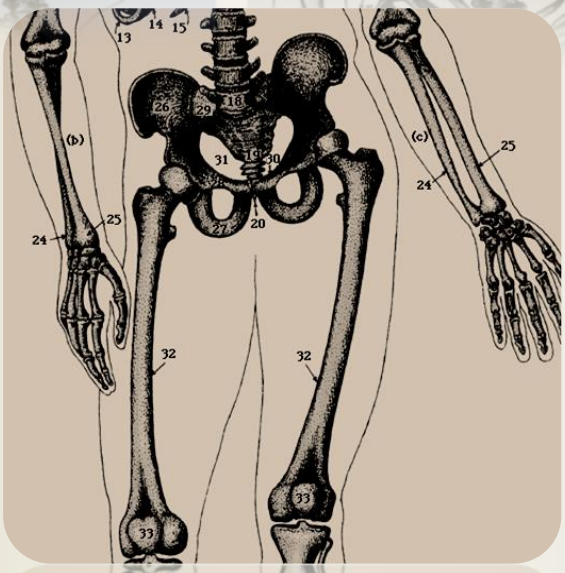

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Student Guide:

1- **The main Source of information here is the slides that was provided by the Doctors.**
2- **Everything written in Pink is from female slides**
3- **These notes for two lectures :-**
    - **Neuromuscular junction**
    - **Muscle contraction**

4- **Anything written in Brown Square is an addition by the team.**

Example : Team Additions

The Neuromuscular Junction

- ✓ Muscle & nerve are called **excitable tissues** because they respond to chemical, mechanical, or electrical stimuli.
- ✓ A stimulus produces change in membrane permeability which lead to movement of ions across the cell membrane, then action potential well result.

Example for chemical stimuli:

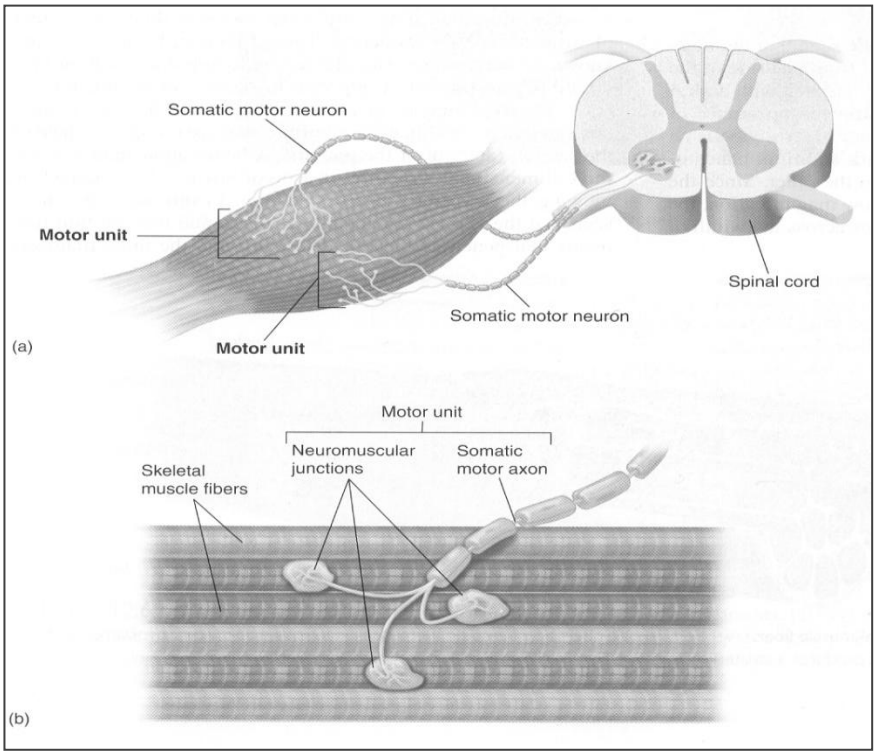
Acetylcholine. When it is released, it attaches to the ACH receptors on the Motor End Plate of the muscle (Which in turn produces the AP which Starts the process of the muscle contraction) .

Example for Electrical stimuli:

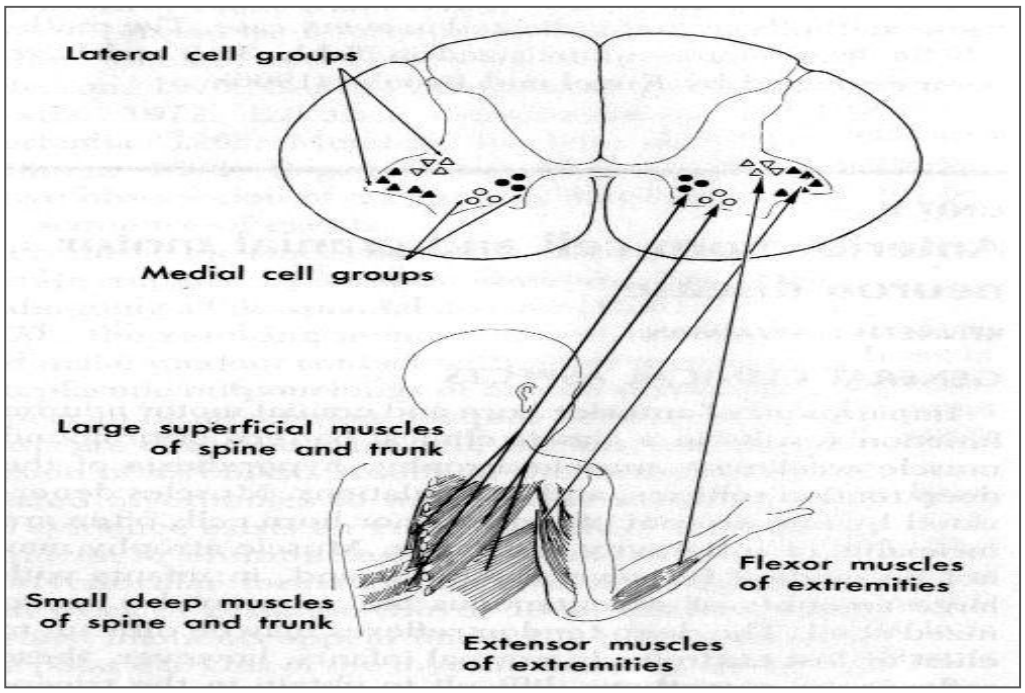
After heart Transplantation, The heart muscles will be shocked with small paddles to restart the heartbeat.

Neurons have :

- Cell body
- Dendrites
- Axon
- Myelin sheath
- Node of ranvier
- Schwan cell

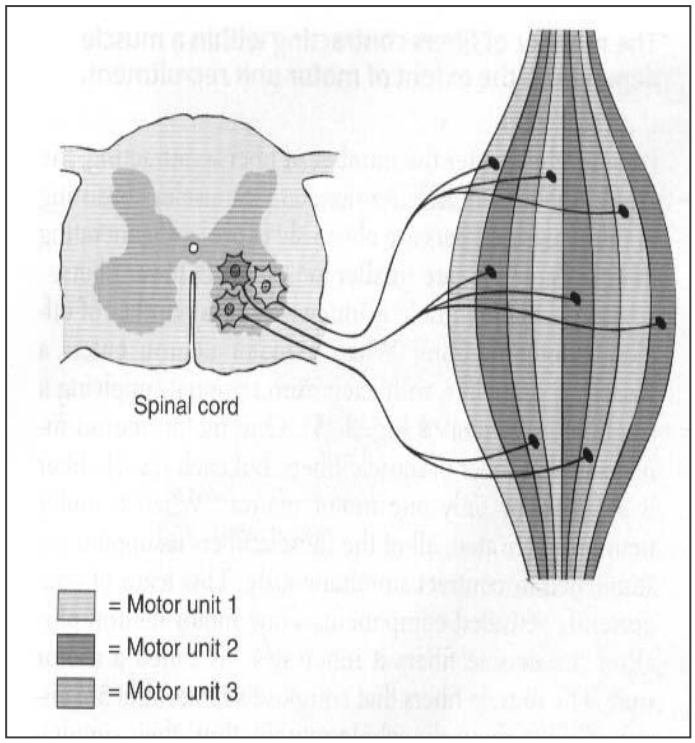


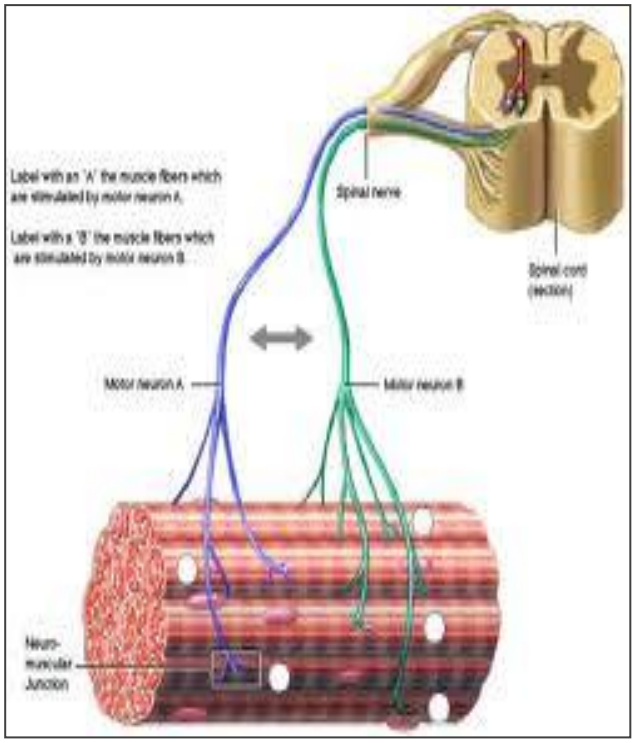
Anterior Horn Cells (Motor Neurons):

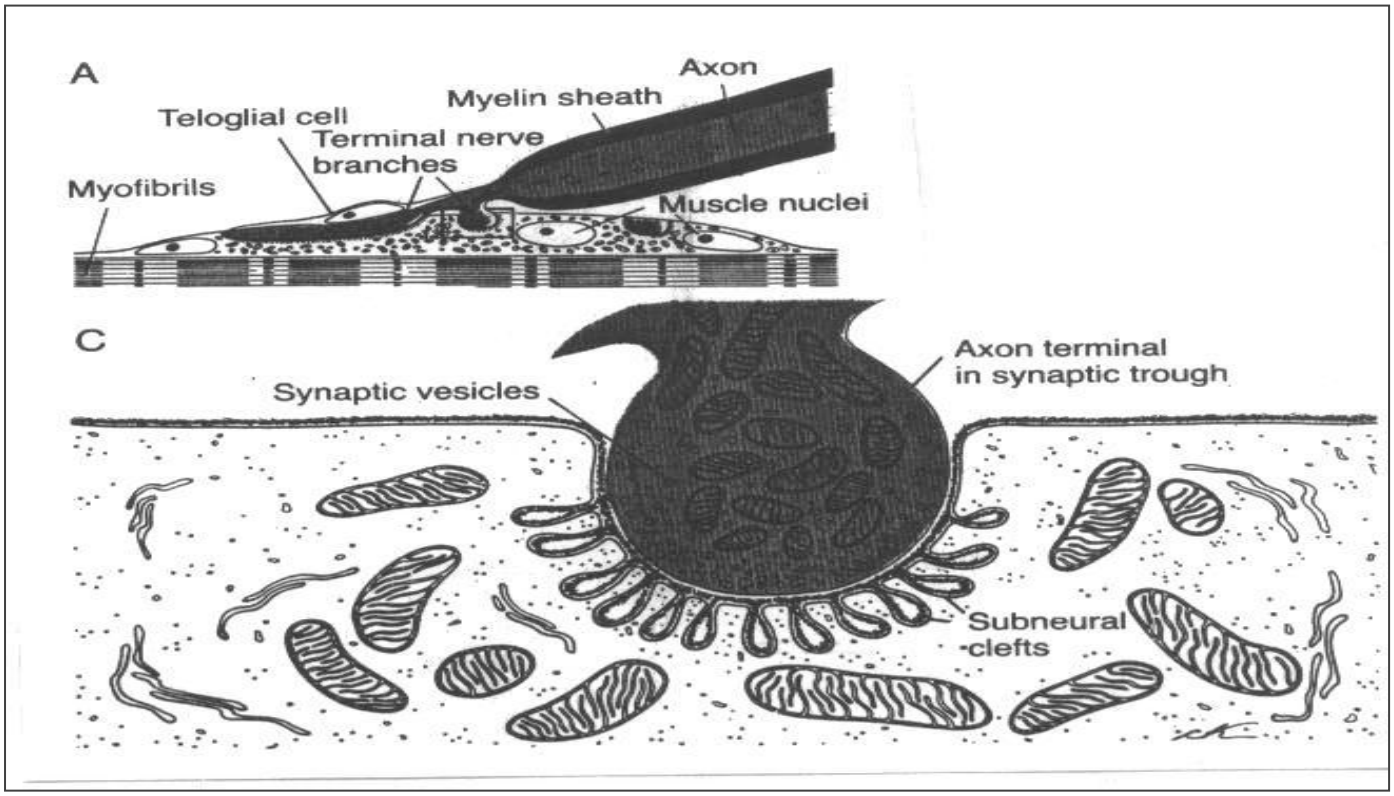


Motor Unit:

It is the motor neuron (Anterior horn Cell) and all the muscle fibers it supplies.







The Neuromuscular junction consists of:

- **Axon Terminal :** contains around 300,000 vesicles which contain the neurotransmitter acetylcholine (Ach).
- **Synaptic Cleft :** 20 – 30 nm (nanometer) space between the axon terminal & the
- **muscle cell membrane:** It contains the enzyme cholinesterase which can destroy Ach .
- **SynapticGutter(SynapticTrough):** It is the muscle cell membrane which is in contact with the nerve terminal . It has many folds called Subneural Clefts , which greatly increase the surface area , allowing for accommodation of large numbers of Ach receptors . Ach receptors are located here .

Neuromuscular junction (NMJ)= the meeting point of the nerve and muscle cell.

ACH-receptors has Na+ channels in it , which do not have a property to induce action potential in subneural cleft .

- The entire structure of axon terminal , synaptic cleft and synaptic gutter is called " **Motor End-Plate** "

- Ach is synthesized locally in the cytoplasm of the nerve terminal , from active acetate (acetyl coenzyme A) and **choline**.

- Then it is rapidly absorbed into the synaptic vesicles and stored there.

- The synaptic vesicles themselves are made by the Golgi Apparatus in the nerve soma (cell-body). Then they are carried by Axoplasmic Transport to the nerve terminal , which contains around 300,000 vesicles.

Synaptic transmission:

Synapse is the junction between two neurones where electrical activity of one neurone is transmitted to the other.

Difference between <u>Synapse</u> and <u>Junction</u>:

Synapse: connection between 2 nerves.

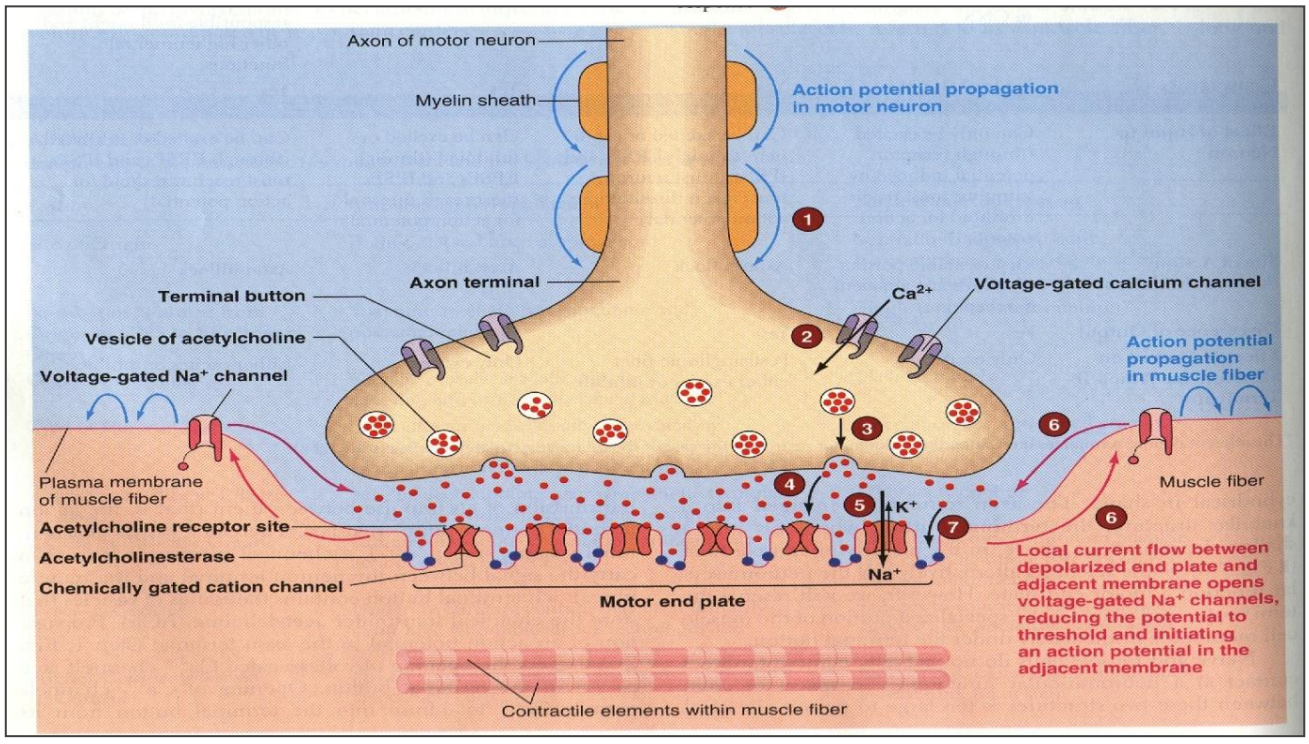
Junction: between Nerve and Muscle.

Synaptic gutter **=** motor end plate

Cell membrane of the muscle fiber (curved area of) **= Synaptic cleft .**

Acetylcholine:

- Ach is synthesized **locally** in the cytoplasm of the nerve terminal , from active acetate (acetyl coenzyme A) and **choline**.
- Then it is rapidly absorbed into the synaptic vesicles and stored there.
- The synaptic vesicles themselves are made by the Golgi Apparatus in the nerve soma(cell-body).
- Then they are carried by Axoplasmic Transport to the nerve terminal , which contains around 300,000 vesicles .
- Each vesicle is then filled with around 10,000 Ach molecules
- When a nerve impulse reaches the nerve terminal ,it **opens calcium channels** ,calcium diffuses from the ECF into the axon terminal Ca++ releases Ach from vesicles by a process **of EXOCYTOSIS**.
- One nerve impulse can release 125 Ach vesicles.
- The quantity of Ach released by one nerve impulse is **more than enough** to produce one End-Plate Potential .



- AP (nerve impulse) reaches the axon terminal by **salutatory transduction (jumping)**
- Diffusing of Ca+ from ECF into the axon terminal happens because calcium in ECF is more than ICF calcium.
- Calcium has a property that stimulates vesicles to be opened and releases ACH.

Ach combines with its receptors in the sub-neural clefts.

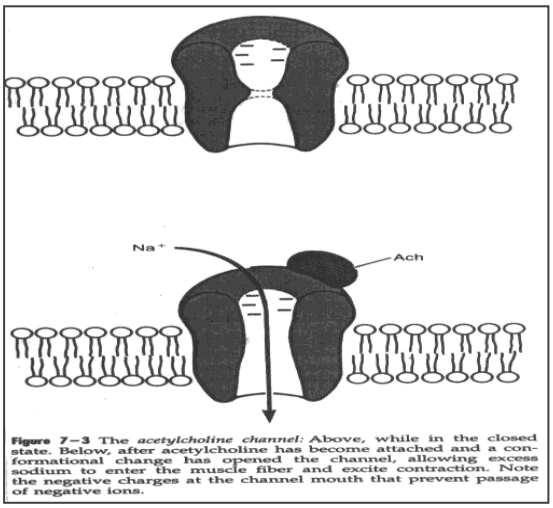


Figure 7–3 The *acetylcholine channel:* Above, while in the closed state. Below, after acetylcholine has become attached and a conformational change has opened the channel, allowing excess sodium to enter the muscle fiber and excite contraction. Note the negative charges at the channel mouth that prevent passage of negative ions.

This opens sodium channels & sodium diffuses into the muscle **causing a local non-propagated potential called the " End-Plate Potential (EPP)"**.

whose value is 50 – 75 mV. This EPP triggers a muscle AP which spreads down inside the muscle to make it contract.

After binding of ACH **, Cholinesterase** starts to destroy ACH to stop contraction process (relaxation) . In order to last the contraction, another nerve impulse (AP) is needed to release more ACH that is not consumed and present in large quantities.

- Action potential cannot jump from the nerve to the muscle because of the synaptic cleft (space in between).
- Electrical change (AP) occurs before mechanical change (contraction).
- Muscle induces its own AP (which is different to that of the nerve AP)
- EPP is a stage between ACH binding to receptors and AP generation.

Q:

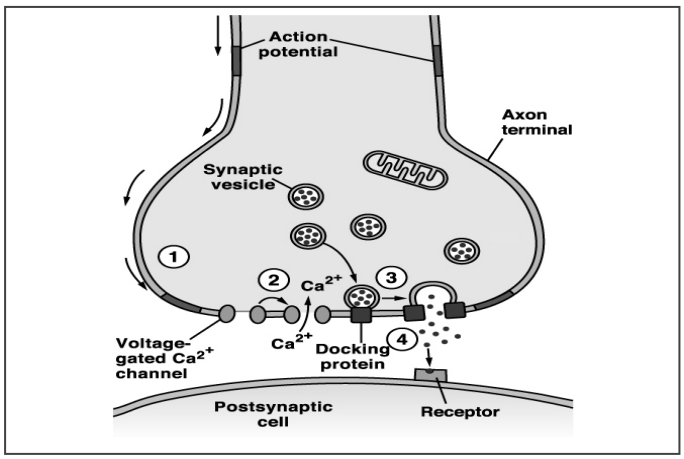
1- When ACH binds to the receptor in muscle, AP is immediately formed (**False**)

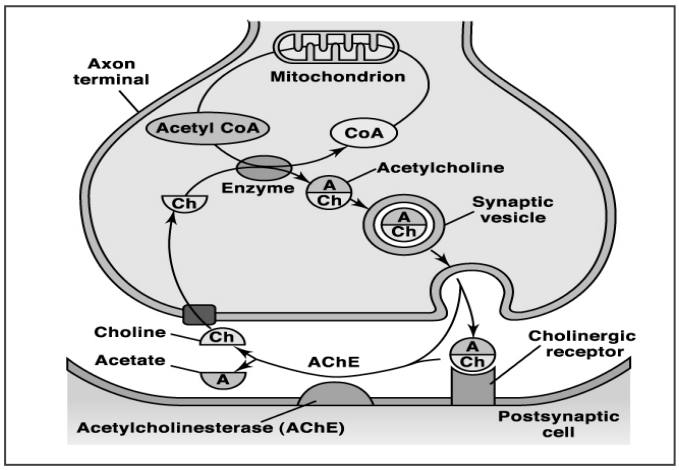
The Truth is that the **EPP** is formed before the AP.

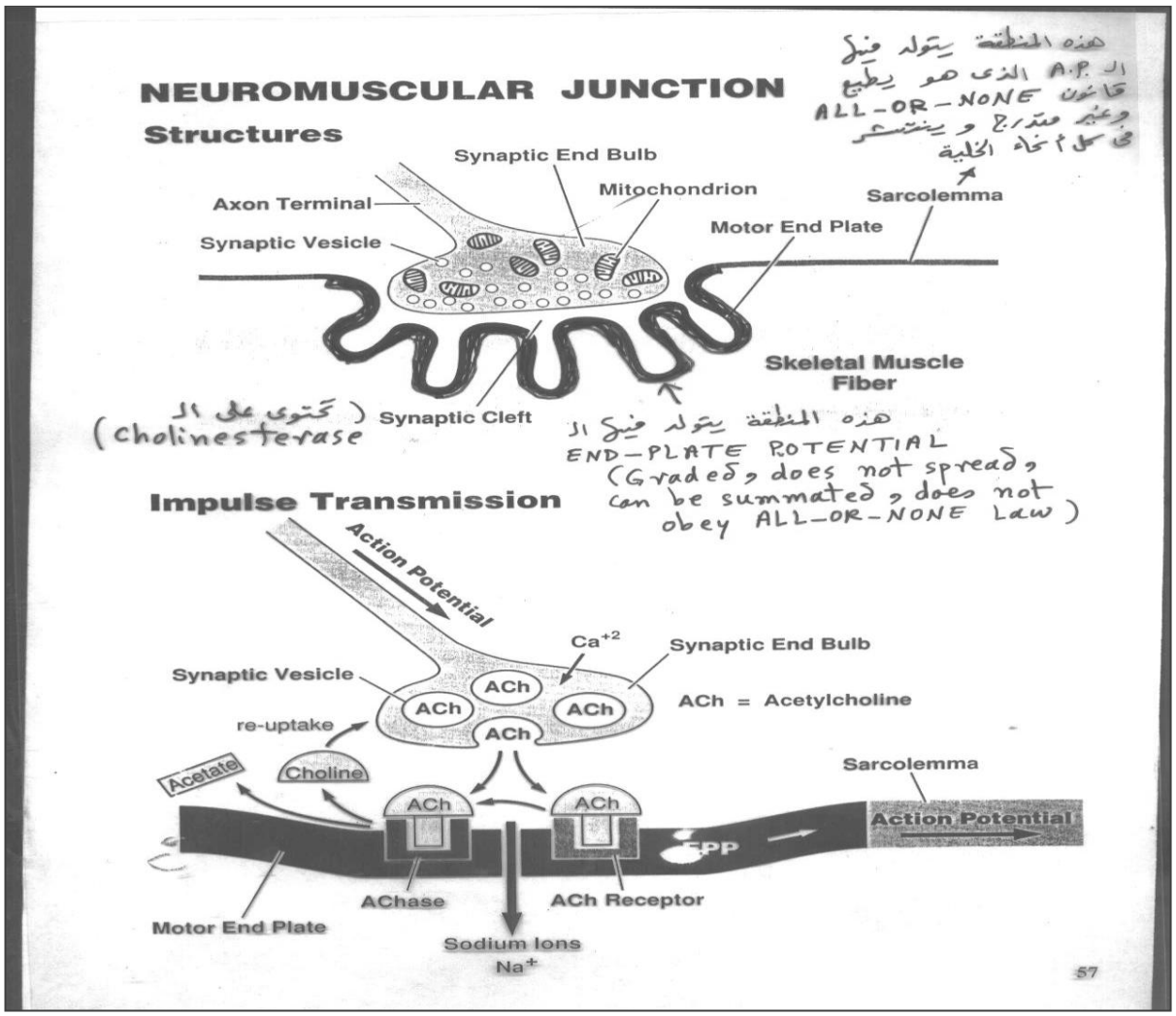
What comes to the mind is ACH binding to receptors to open NA channels to induce AP, but this does not occur, because the property of Sodium channel in Subneural cleft cannot generate AP.

EPP will spread to the sides of cell membrane, which is similar to the nerves as when the electricity reaches Threshold level, Sodium channels (differs from the previous) will be opened and inducing AP.

After ACH acts on the receptors , it is hydrolyzed by the enzyme Acetyl **cholinesterase (cholinesterase)** into Acetate & Choline . The **Choline is actively reabsorbed** into the nerve terminal to be used again to form ACH. This whole process of Ach release, action & destruction takes about 5-10 ms .







Myasthenia Gravis

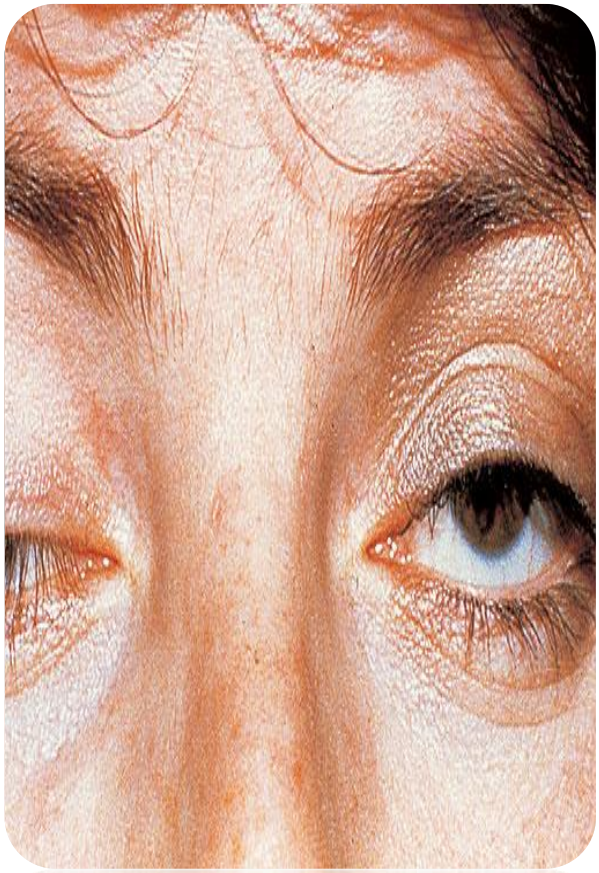
- **<u>Auto-immune disease.</u>**

- Antibodies against Ach receptors destroy many of the receptors >> decreasing the EPP , or even preventing its formation >> weakness or paralysis of muscles (depending on the severity of the disease) .

- Patient may die because of paralysis of respiratory muscles.

- **<u>Treatment</u> :** Anti-cholinesterase drugs .

These drugs deactivate the cholinesterase enzyme (which destroys Ach) and thereby allow relatively large amounts of Ach to accumulate and act on the re-maining healthy receptors >> good EPP is formed >> muscle contraction.



Drugs Acting on the NMJ

- **Drugs that stimulate the muscle cell by Acetylcholine-like action :**
  1- Nicotine**.** **2**- methacholine**.** **3-** carbachol .

- **Drugs that block neuromuscular transmission :**
  Curare and curare-like drugs (curariform drugs) . They have a chemical structure similar to ACH , but cannot stimulate the receptors .
  They occupy acetylcholine receptors and thereby prevent ACH from acting on its receptors >> muscle weakness or paralysis .

Example : Tubocurarine. It is used during some surgical operations.

- Nicotine mimics(يشابه) the action of ACH.
- Curare is a family of drugs that causes paralysis because it prevents ACH from acting. (It is used with patients with chronic epilepsy to stop the muscle spasms but respirators are placed to help the patient breath because it cause paralysis to the muscle) .
- Curare should be used only with patients who have healthy liver, because liver's function is to get rid of toxins since Curare is considered as a toxin.

Anticholinesterase drugs :

e.g. Neostigmine (Prostigmin) , Physostigmine , Pyridostigmine (Mestinon)
Used in treatment of Myasthenia Gravis .
These drugs inactivate the cholinesterase enzyme (which destroys Ach) and thereby allow relatively large amounts of Ach to accumulate and act on the remaining healthy receptors , good EPP is formed muscle contraction .

Prostigmin , Neostigmine are Anticholinesterase, that means they will inactivate Cholinesterase (which destroys ACH) Leading to large amount of ACH.

" **if you inhibit the inhibitor you stimulate !** "

Muscle contraction

The Muscle Action Potential

- **Muscle RMP** = -90 mV (same as in nerves) .
- **Duration of AP** = 1-5 ms (longer duration than nerve AP , which is usually about 1 ms) .
- **Conduction velocity** = 3-5 m/s (slower than big nerves) .

There are 4 important muscle proteins :

- ✓ Two contractile proteins that slide upon each other during contraction
  - **Actin.**
  - **Myosin.**
- ✓ Two regulatory proteins
  - **Troponin** : excitatory to contraction
  - **Tropomyosin :** inhibitory to contraction .

- Each muscle cell (fiber) is 10 -80 micrometer long & is covered by a cell membrane called Sarcolemma.
- Each cell contains between hundreds to thousands Myofibrils.
- Each Myofibril contains 3000 Actin filaments & 1500 Myosin filaments
- Each myofibril is striated consisting of :
  - **Dark Bands** (**A**-bands): consist mainly of **Myosin & Actin**
  - **Light Bands** (**I**-bands): consist of **Actin.**

- The ends of Actin are attached by Z-Discs(**Z**-lines).
- Myofibril lying between two Z-discs is called **Sarcomere** . It is about 2 mcrometers .
- When contraction takes place Actin & Myosin slide upon each other and the distance between two z-discs decreases :
  This is called **Sliding Filament Mechanisms**

Sliding Filament Mechanism (will be discussed later)

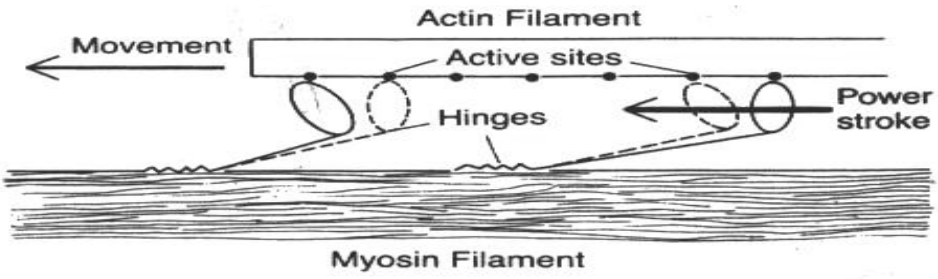


Figure 6–7 The "walk-along" mechanism for contraction of the muscle.

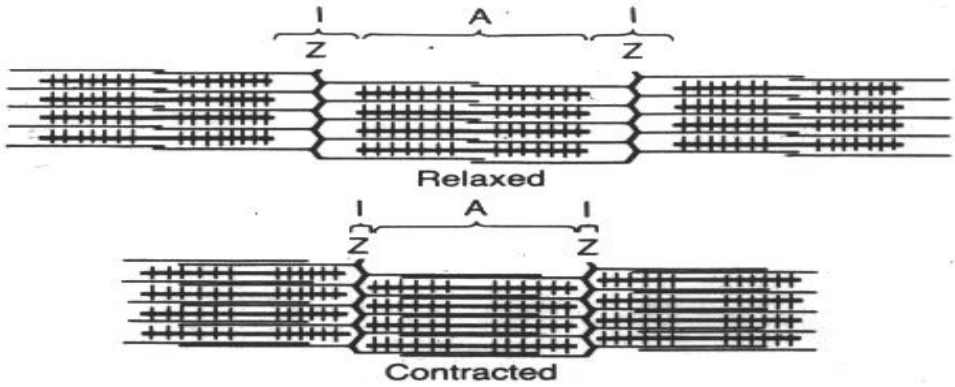


Figure 6–4 The relaxed and contracted states of a myofibril, showing sliding of the actin filaments (black) into the spaces between the myosin filaments (red).

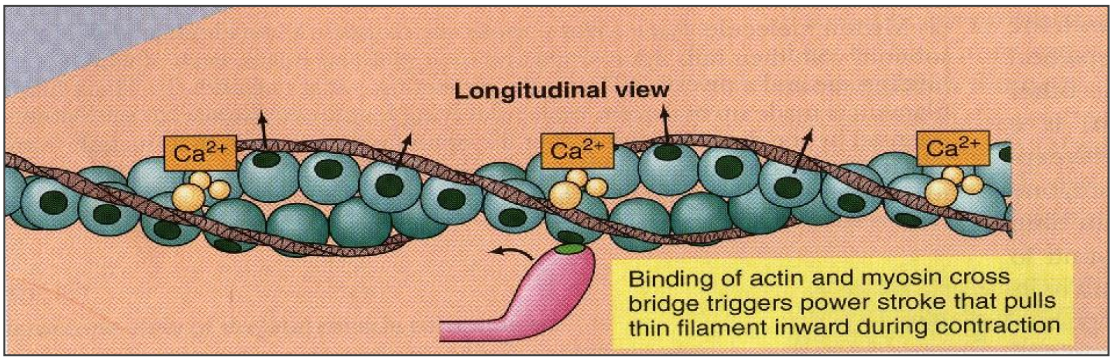
- Actin Filament consists of Globular protein (G-actin) molecules that are attached together to form a chain.

- Each two chains wind together like a double helix.
- Each G-Actin molecule has a binding site for Myosin head (called actin active sites)

- These active sites are covered and hidden from the Myosin head by the inhibitory protein Tropomyosin.

- When Troponin is activated by Ca++ it will move the Tropomyosin away from these sites and expose them for Myosin.

- Then myosin immediately attach to actin active sites.
- when the myosin head attaches to actin it forms a " cross-bridge"



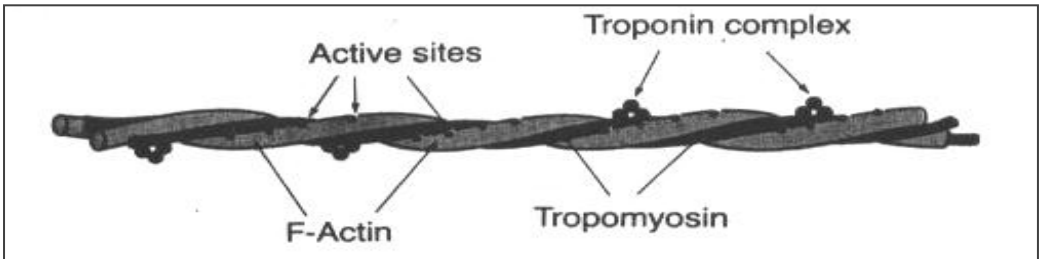


Figure 6–6 The actin filament, composed of two helical strands of F-actin and tropomyosin molecules that fit loosely in the grooves between the actin strands. Attached to one end of each tropomyosin molecule is a troponin complex that initiates contraction.

Myosin

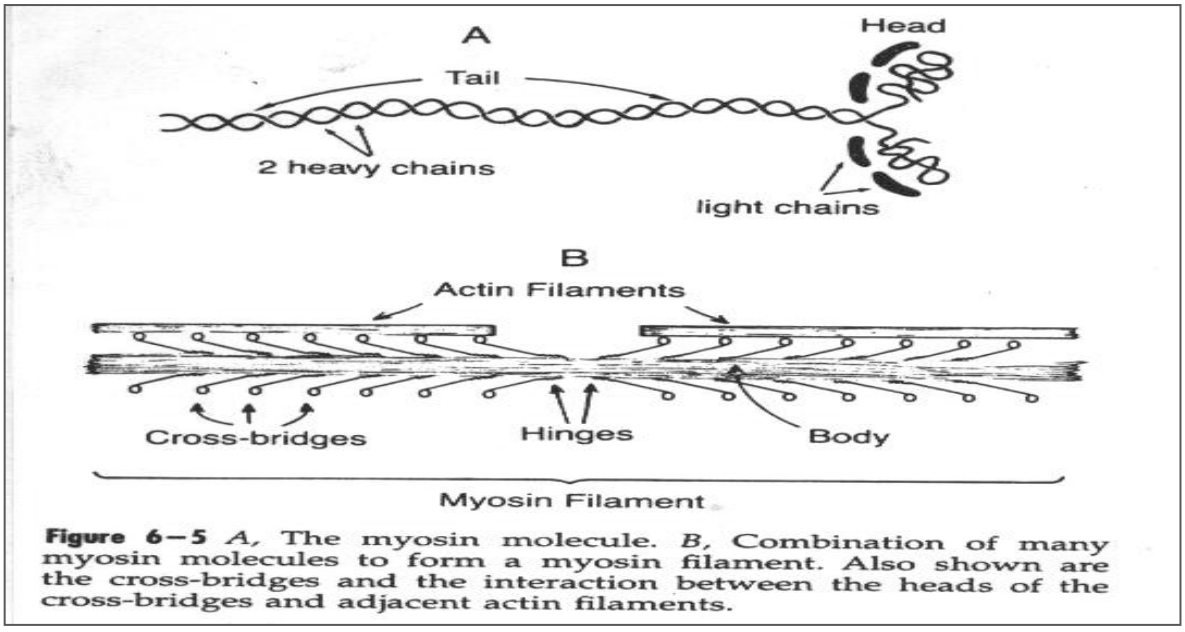


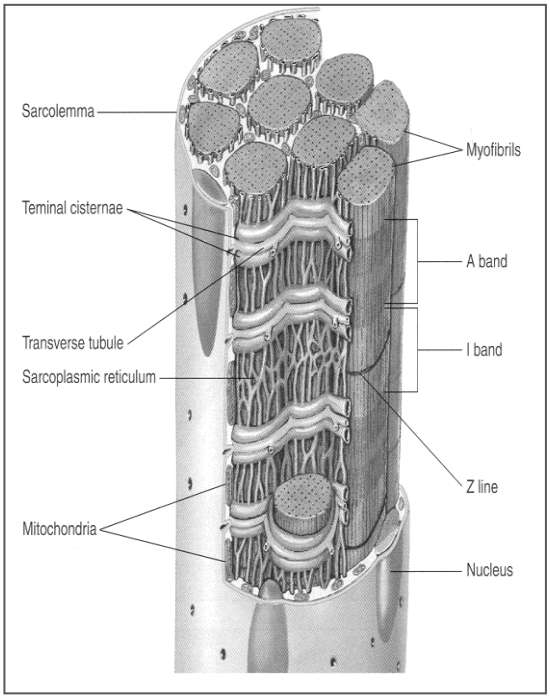
Figure 6–5 *A*, The myosin molecule. *B*, Combination of many myosin molecules to form a myosin filament. Also shown are the cross-bridges and the interaction between the heads of the cross-bridges and adjacent actin filaments.

Each Myosin molecule has :
Head , Hinge (joint) , Tail.

Each myosin head contains :
1) ATP-binding site .
2) ATP-ase enzyme .

Each 200 myosin molecules aggregate to form a myosin filament , from the sides of which project myosin heads in all directions .

- The **EPP** (end-plate potential) triggers a muscle **AP**.
- The **muscle AP spreads** down inside the muscle through the Transverse Tubules (T-tubules)→reach the Sarcoplasmic Reticulum (SR) .



- The muscle AP **opens calcium** channels (in the walls of the SR)→ calcium passively flows out (by concentration gradient) of the SR into muscle cytolasm → Ca++ combines with **Troponin** .

- The **activated troponin** pulls inhibitory protein (**Tropomyosin**) away from the myosin binding sites on actin and once these sites on actin are exposed → myosin heads quickly bind to them.

- This binding activates the enzyme **ATPase in the Myosin Head** →breaks down ATP releasing energy →used in the "Power Stroke " to move the myosin head →leading to pulling & dragging of actin→sliding of actin on myosin.

- Power Stroke : tilting of the cross-bridge head (myosin head) and dragging (pulling) of actin filament.

- **End plate potential leads to opening of ligand-gated channels causing depolarization, until the membrane reaches a certain value of -65 mV.**
- **When it reaches -65 mV the voltage-gated channels open causing an influx of Na leading to further depolarization and AP.**

Muscle contraction:

1) **Simple Muscle Twitch:**

The mechanical response (contraction) to single AP (single stimulus).

2) **Summation Of Contraction:**

- **Spatial Summation:**

The response of single motor unites are added together to produce a strong muscle contraction.

- **Temporal Summation:**

When frequency of stimulation increased (on the same motor unite), the degree of summation increased, producing stronger contraction

Types of muscle contraction:

1- **Isometric Contraction:**

No change in muscle length, but increase in muscle tension (e.g. standing)

2- **Isotonic contraction:**

Constant tension, with change in muscle length (e.g. lifting a loud)

— **When ca is pumped back into sarcoplasmic reticulum >>ca detached from troponin >> tropomyosin return to its original position >> covering active sit on actin >> prevent formation of cross bridge >>relaxation.**

Summary

1. **Muscle AP spreads through T-tubules**
2. **it reaches the sarcoplasmic reticulum where _ opens its Ca++ channels _ calcium diffuses out of the sarcoplasmic reticulum into the cytoplasm _ increased Ca++ concentration in the myofibrillar fluid .**
3. **Ca++ combines with Troponin , activating it**
4. **Troponin pulls away Tropomyosin**
5. **This uncovers the active sites in Actin for Myosin**
6. **Myosin combines with these sites**
7. **This causes breakdown of ATP and release of snergy which will be used in Power Stroke**
8. **Myosin and Actin slide upon each other _ contraction**
9. **A new ATP comes and combines with the Myosin head . This causes detachment of Myosin from Actin .**
10. **ATP is needed for 3 things :**
    a. **Power stroke .**
    b. **Detachment of myosin from actin active sites .**
    c. **Pumping C++ back into the Sarcoplasmic reticulum .**

Important Flashes :

- http://msjensen.cehd.umn.edu/1135/Links/Animations/Flash/0009-swf_function_of_th.swf
- http://msjensen.cehd.umn.edu/1135/Links/Animations/Flash/0010-swf_action_potenti.swf
- http://msjensen.cehd.umn.edu/1135/Links/Animations/Flash/0011-swf_breakdown_of_a.swf