Editing file

Neuromuscular transmission

- Red : important
- Black : in male / female slides
- Pink : in female slides only
- Blue : in male slides only
- Green : notes
- Gray : extra
- Guyton

Objective

Know and describe the followings:

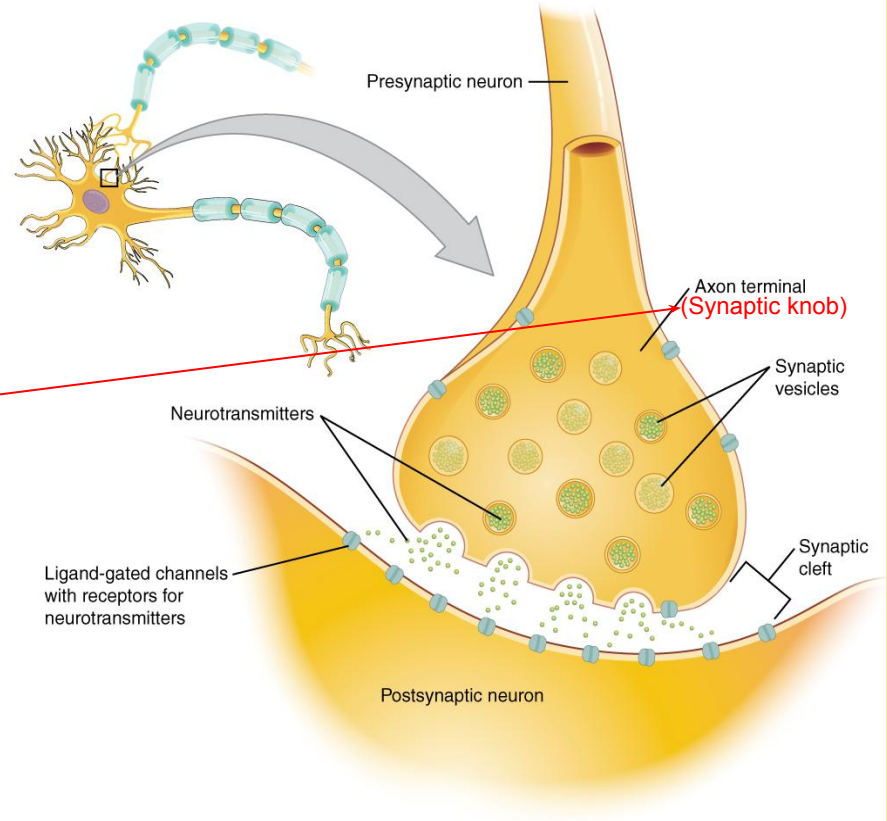
- The physiologic anatomy of the skeletal muscle and NM junction.
- Drugs/ diseases affecting the neuromuscular transmission.

Chemical Signals

Helpful video

One neuron will transmit info by releasing chemicals called neurotransmitters to

- Muscle
  - **The Neuromuscular Junction (NMJ)**
    - What is the purpose of **neuromuscular transmission**? Muscle contraction
- Gland
- Neuron

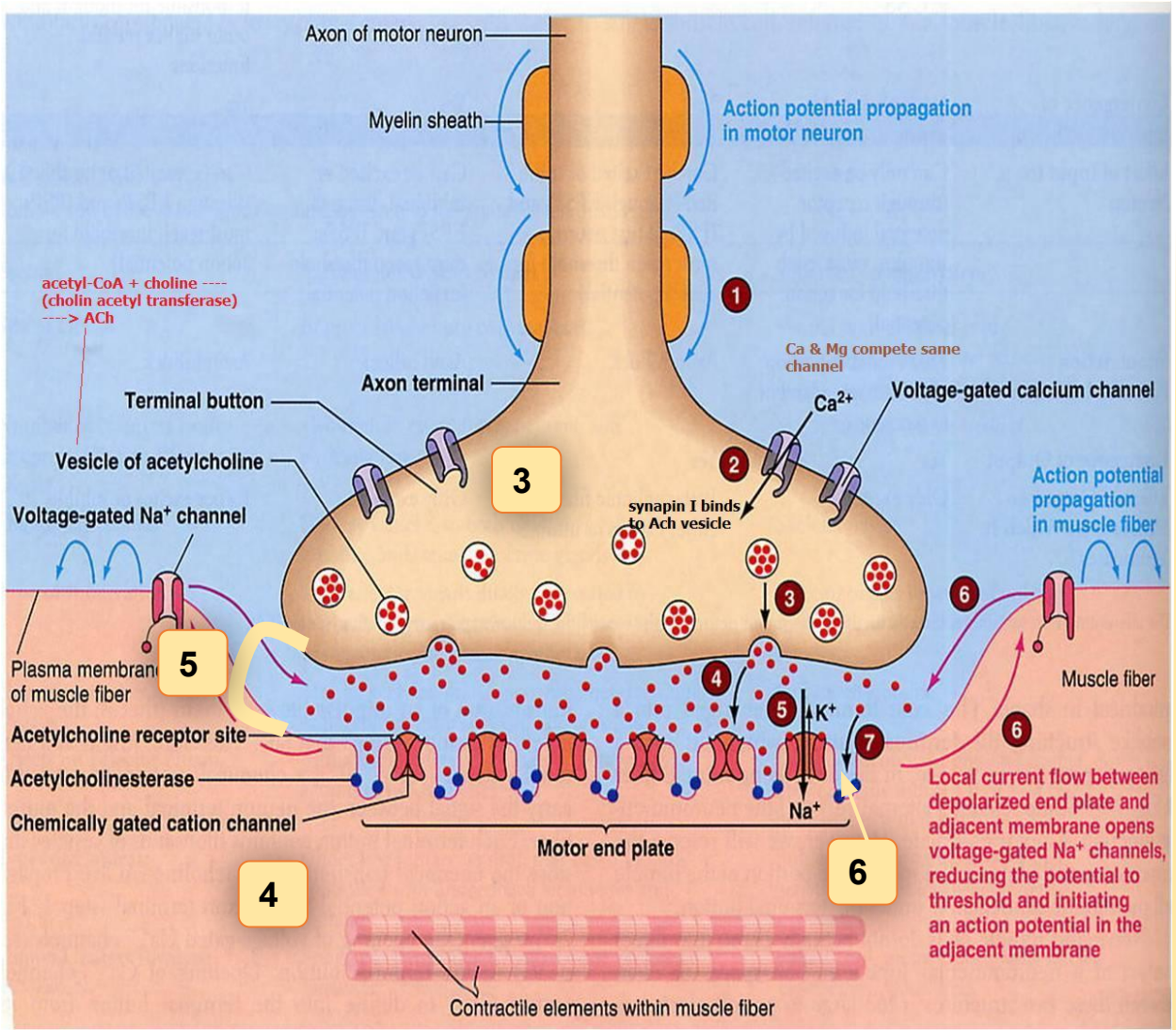


- **synapse** is the site (junction) of this chemical interplay.
- An axon terminal (synaptic knob) will meet another cell, a **neuron** **muscle** fiber, or **gland** cell.

-This is the site of transduction – the conversion of an **electrical** signal into a **chemical** signal.

Physiologic Anatomy of the Neuromuscular Junction (Nerve+Muscle)

1-Motor End Plate (is the area where muscle face nerve ending)
2-Synaptic trough/ gutter {the muscle where it is invaginated (fold within it self) by a nerve terminal and a depression (subneural cleft) is made}
3-Presynaptic terminal (motor nerve ending)
4-Postsynaptic terminal (in muscle)
5-Synaptic space/cleft (between the two ends and it contain ECF)
6-Subneural cleft
7-Acetylcholine (Ach)
8-Synaptic vesicles
9-Acetylcholinesterase (destroy Ach)



dr Mohammed said I'm not asking for the names

The Neuromuscular junction consists of

Motor end plate (موجود في العضلة) composed of : (3)

01 Axon terminal (nerve terminal):

- Contains around **300,000** synaptic vesicles, which contain the neurotransmitter acetylcholine (Ach).
- Each vesicle has **10,000** Ach molecules.

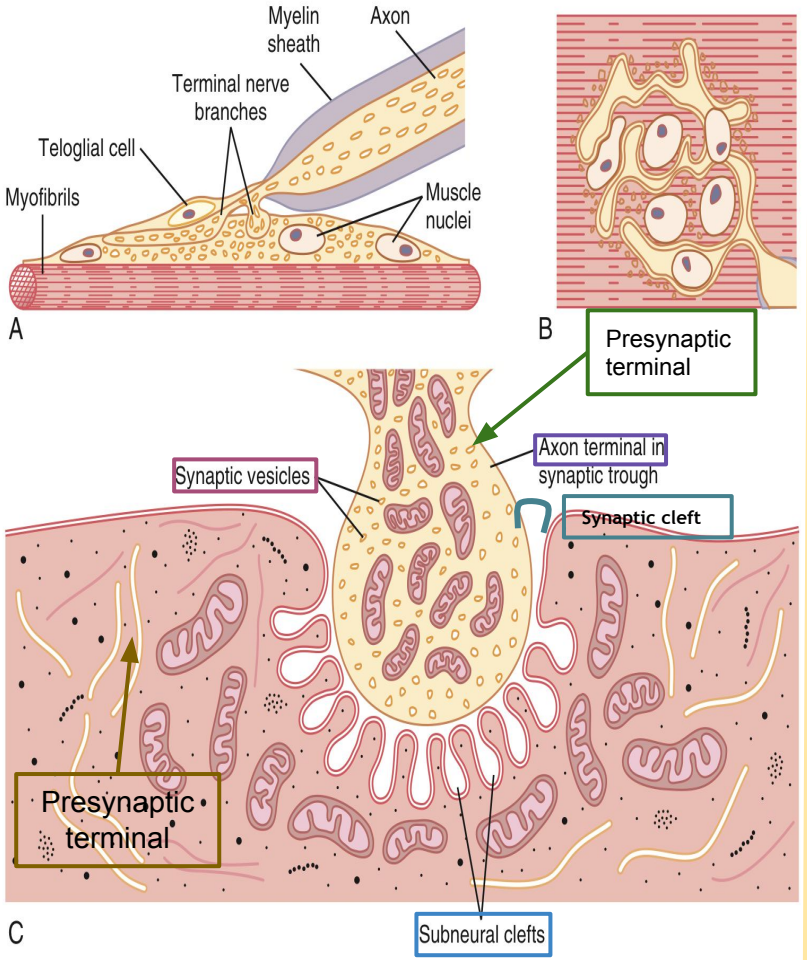
02 Synaptic Cleft:

- **20 - 30 nm (nanometers)**, the space between the axon terminal & the muscle cell membrane.
- It contains ECF & Acetylcholinesterase which can destroy Ach. (will talk more about it later)

03 Synaptic Gutter (Synaptic Trough):

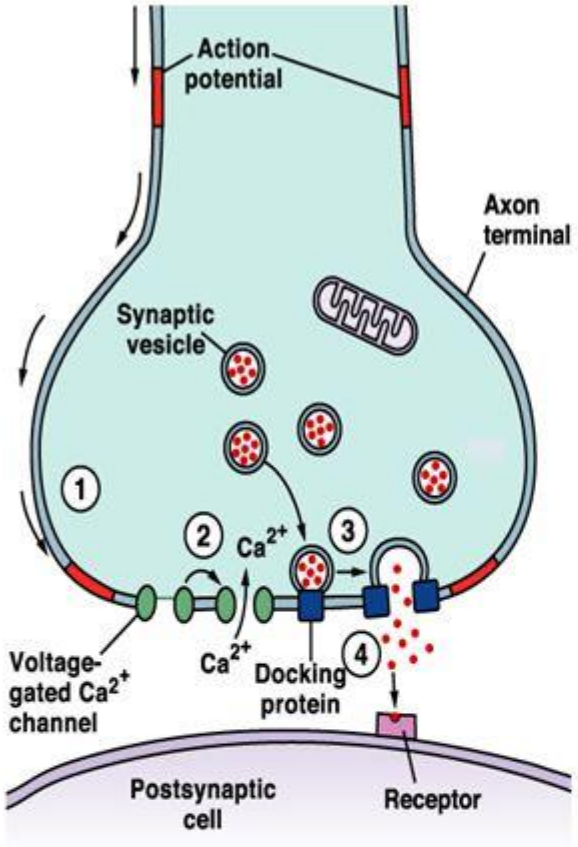
- The muscle cell membrane which is in contact with the nerve terminal.
- It has many folds called Subneural Clefts, Function of Subneural Clefts:

1. Increases surface area.
2. Allows accommodation of large numbers of Ach receptors which are located here.



Acetylcholine

01	**Synthesized:**	• From active acetate (acetyl coenzyme A) +choline.
02	**Synthesis location:**	• In the cytoplasm of the nerve terminal (axon terminal)
03	**Absorption & Storage:**	• Rapidly in synaptic vesicles
04	**Synaptic vesicles synthesis mechanism :**	1. Synthesized by the Golgi Apparatus in the nerve soma (cell-body), 2. Then they are carried by Axoplasmic Transport to the nerve terminal (axon terminal) which contains around 300,000 vesicles .



Secretion of Acetylcholine by the Nerve Terminals:

increases electrical potential in the positive direction as much as 50-75 mV and creates a local EPP.

1

Action potential (AP) at the synaptic knob

:A nerve impulse reaches the *nerve terminal*

2

Ca+ channel open (voltage-gated Ca+ channels) increase Ca+ permeability

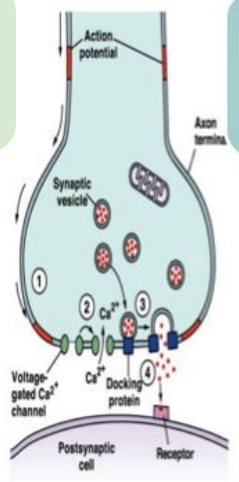
calcium diffuses from the ECF into the axon terminal

This step doesn't need energy because it's with concentration gradient

Ca dependent exocytosis :

Ca attract vesicles to nerve terminal membrane , they rupture & release Ach to synaptic cleft

release of neurotransmitter (NT) (Ach) from synaptic knob to synaptic cleft



2 molecule of Ach combines with specific receptor on the subneural cleft

A small amount diffuses out of the synaptic space.

Important End Note :

- One nerve impulse can release 125 Ach vesicles, which is more than enough to produce one *End Plate Potential.*
- *Action Potential = Muscle Contract*

This opens the Ach gated receptor channels

(Sodium channels)

Conformational change

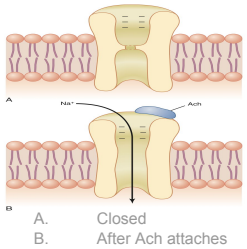
Na flow to inside to diffuse into muscle causing local non-propagated potential (End-Plate Potential)

$Na^+/Ca^+/$ or K^+ ions not negative ions such as Cl^-

Because receptors have a negative charge in its mouth prevent the entering of negative ions

Through;
Acetylcholine-gated channel or Sodium channel (different names in slides and Gyton)
These channels opens and close in response to chemicals (Ach)

The whole mechanism of Ach production, releasing, and destruction takes 5 to 10 minutes.



Destruction of Ach : by Ach esterase enzyme into:

-Choline : reabsorbed in the nerve terminal to form new Ach

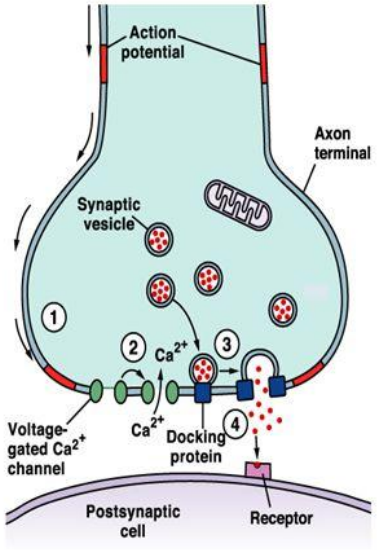
- Acetate : goes to blood

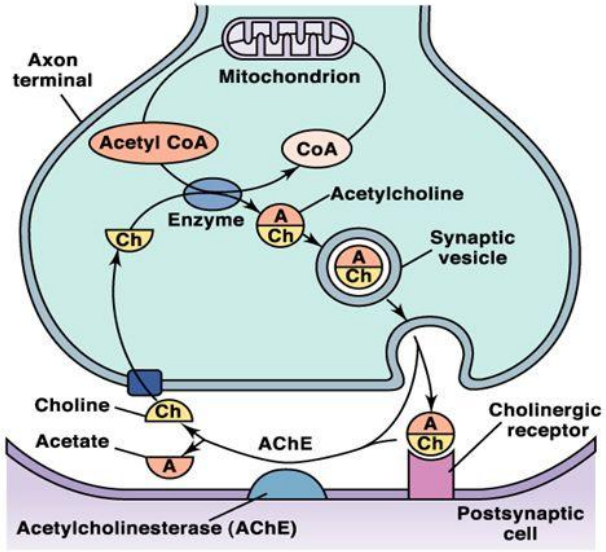
اذا الجسم ما تخلص من ACH
يسبب انقباض مستمر للعضلة

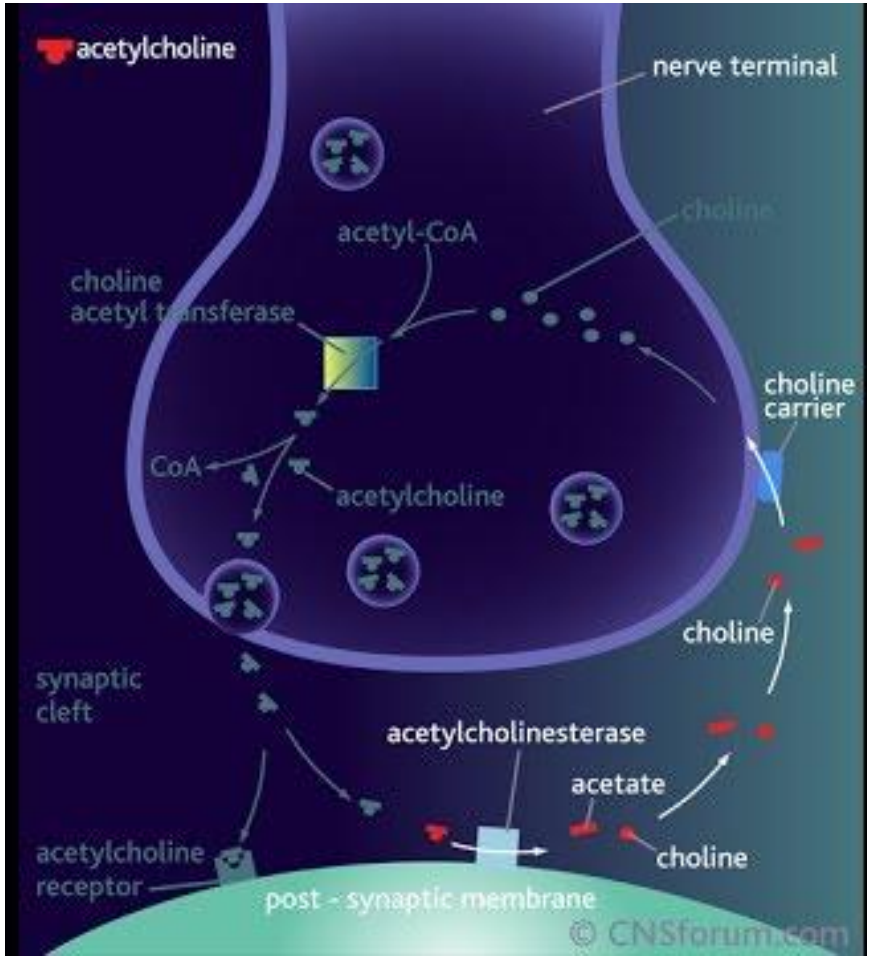
Final step: After Ach acts on the receptors

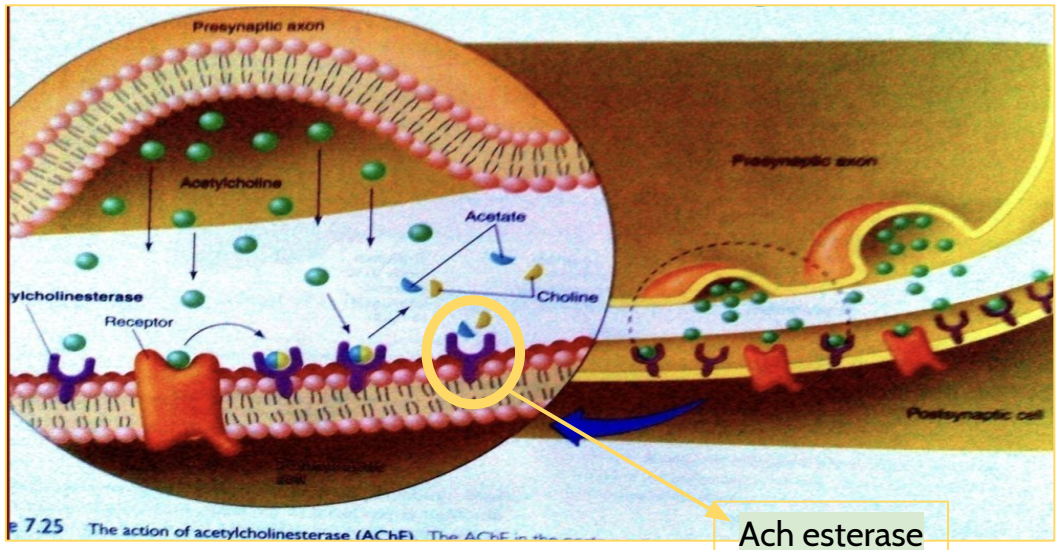
The End-plate potential(EPP) triggers a muscle AP which spreads down inside the muscle to make it contract .

Destruction of Ach

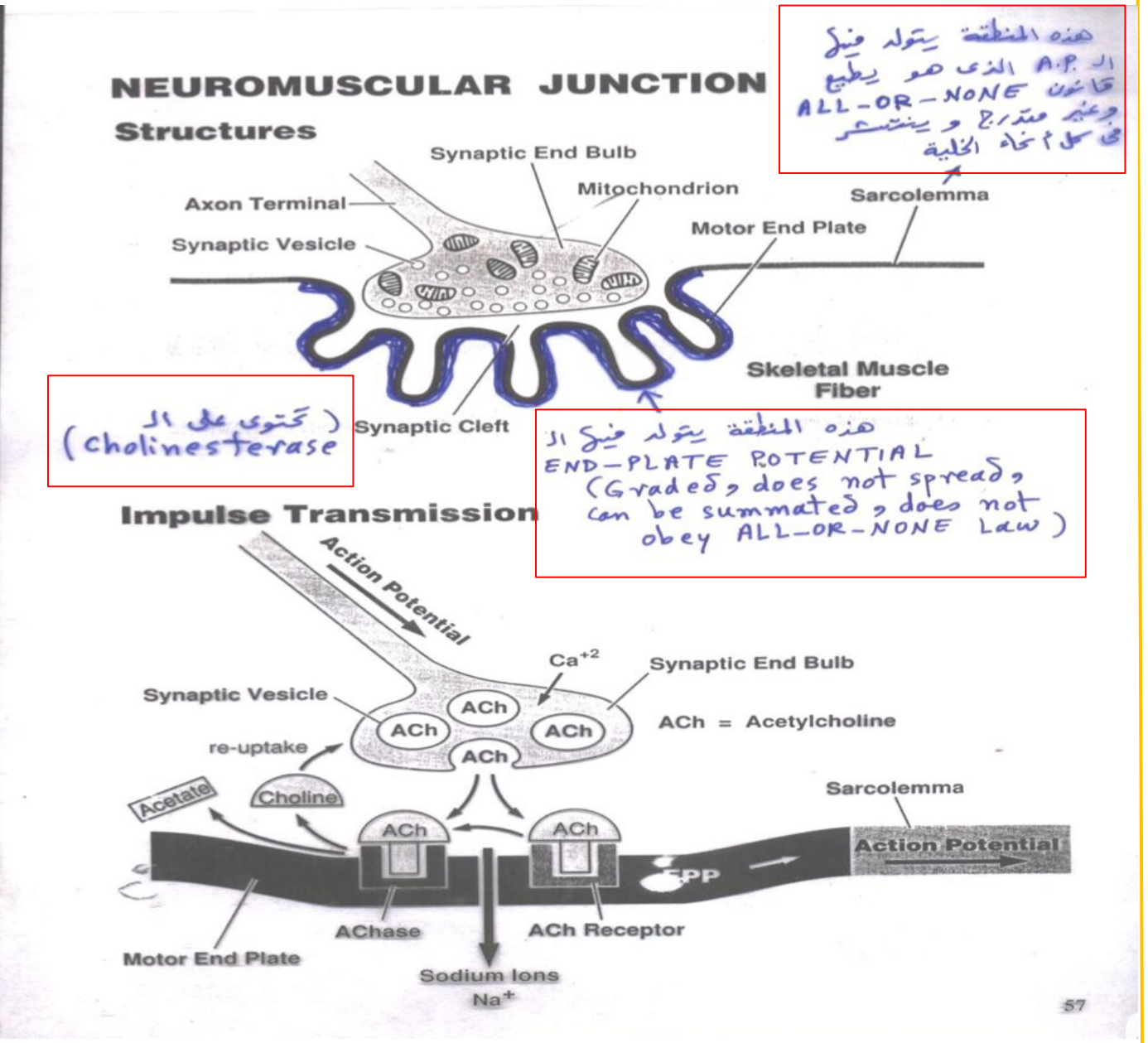








Ach esterase



هذه المنطقة يتولد فيها ال A.P. الذي هو عبارة عن ALL-OR-NONE قانون وغير متدرج و ينتشر في كل أنحاء الخلية

(تحتوي على ال cholinesterase)

هذه المنطقة يتولد فيها ال END-PLATE POTENTIAL (Graded, does not spread, can be summated, does not obey ALL-OR-NONE Law)

Extra information

At the beginning, this message was electrical then it becomes chemical.
Action potential > stimulate releasing of chemical substance > that's why we said "the massage was electrical then it becomes chemical" which called as [Transduction].

- presynaptic cell: an axon terminal (synaptic knob) which contains synaptic vesicles.
- postsynaptic cell: a neuron, muscle fiber, or gland cell.
- end plate potential : Different than action potential in that it is not an all or none response , the more neurotransmitter there is the higher the response, and it may not propagate. If there is sufficient Na influx , it will turn to Action Potential and propagate.

How many mV to reach threshold of muscle ? we need 100 ACH vesicles each one will worth 0.4 mV. So all we need is about 40 mV.

Summary :
AP (nerve) > open calcium voltage gated channels > calcium influx > calcium stimulate ACH vesicles > ACH outflex > 2 ACH molecules open ACH receptor channels > +ve ions influx > local positive potential happens > Na+ voltage gated channels sense the change then open > AP in muscle > contraction

AP and EPP

Action potential	End plate potential
• In neurons and muscle cells • Maintained by voltage-gated Na and K channels • It can propagate • Amplitude may be as high as +50 mV • Follow the all-or-none role • Doesn't produce respond until it reach threshold point • Not graded	• Found only on the postsynaptic membrane of the muscle cell • Caused by the ligand-gated acetylcholine receptor channels • spread along the muscle fiber • Do not follow the all-or-none role • Doesn't need to reach **threshold(is about -40)** to produce respond, any small stimuli will produce respond

Drugs That Enhance or Block Transmission at the Neuromuscular Junction

Drugs That Stimulate the Muscle Fiber by Ach-Like Action	Drugs That Stimulate the NMJ by Inactivating Acetylcholinesterase	
Methacholine Carbachol Nicotine المادة اللي في الدخان	Neostigmine, Physostigmine	Diisopropyl fluorophosphate (nerve gas poison)
They act for minutes or hours (are not destructed by cholinesterase)	inactivate acetylcholinesterase for several hours	inactivates acetylcholinesterase for weeks (can cause death because of respiratory muscle spasm)

Drugs That Enhance or Block Transmission at the Neuromuscular Junction

Drugs That Block and inhibit Transmission at the NMJ	
Botulinum Toxin **Inhibit the contraction**	**Curare & Curariform like-drugs**
Bacterial poison that decreases the quantity of Ach release by the nerve presynaptic terminals. This attack the vesicles that contain Ach so they decrease the quantity of Ach release so the contraction will be weak Dr. Mannan note ; Clinical application —> Botox 	Prevent passage of impulses from the nerve ending into the muscle by blocking the action of Ach on its receptors on MEP No contraction —> شلل act by competitive inhibition to Ach at its receptors & can not cause Depolarization.

Dr. Mohammed note;
Botulinum toxin cause food poisoning.

Clinical Application: Myasthenia Gravis

➢ Autoimmune disease, Occurs in about 1 in every 20,000 persons.

➢ **Cause :**

1-The body forms antibodies against Ach receptors which destroy the receptors leaving only about 20%.

➢ **Mechanism :**

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

➢ **Signs :**

1-Disease of adult females affects eyelid, extra ocular bulbar and proximal limb muscles.
2-Presents with ptosis, dysarthria, dysphagia, and proximal limb weakness in hands & feet.
3-Causes muscle weakness

➢ **Consequences :**

Can lead to paralysis of respiratory muscles which will lead to death.(depending on the severity of the disease)

Treatment:

➢ **1- Anti-cholinesterase drugs** "Example.Neostigmine"

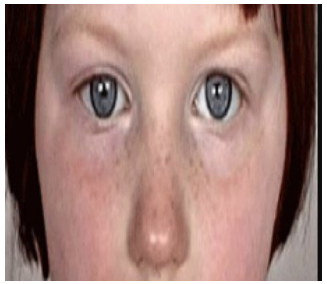
Mechanism : Inactivate Cholinesterase enzyme to allow more Ach to accumulate in the synaptic space and act on the remaining healthy receptors

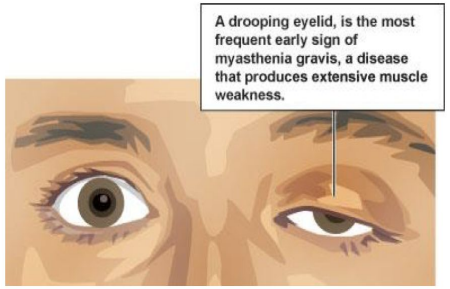
➢ 2- Corticosteroids and immunosuppressant drugs : to inhibit the immune system and limiting antibody production

Remember: AcetylCholinesterase hydrolyzes (breaks, destroys) Ach into choline and acetate.

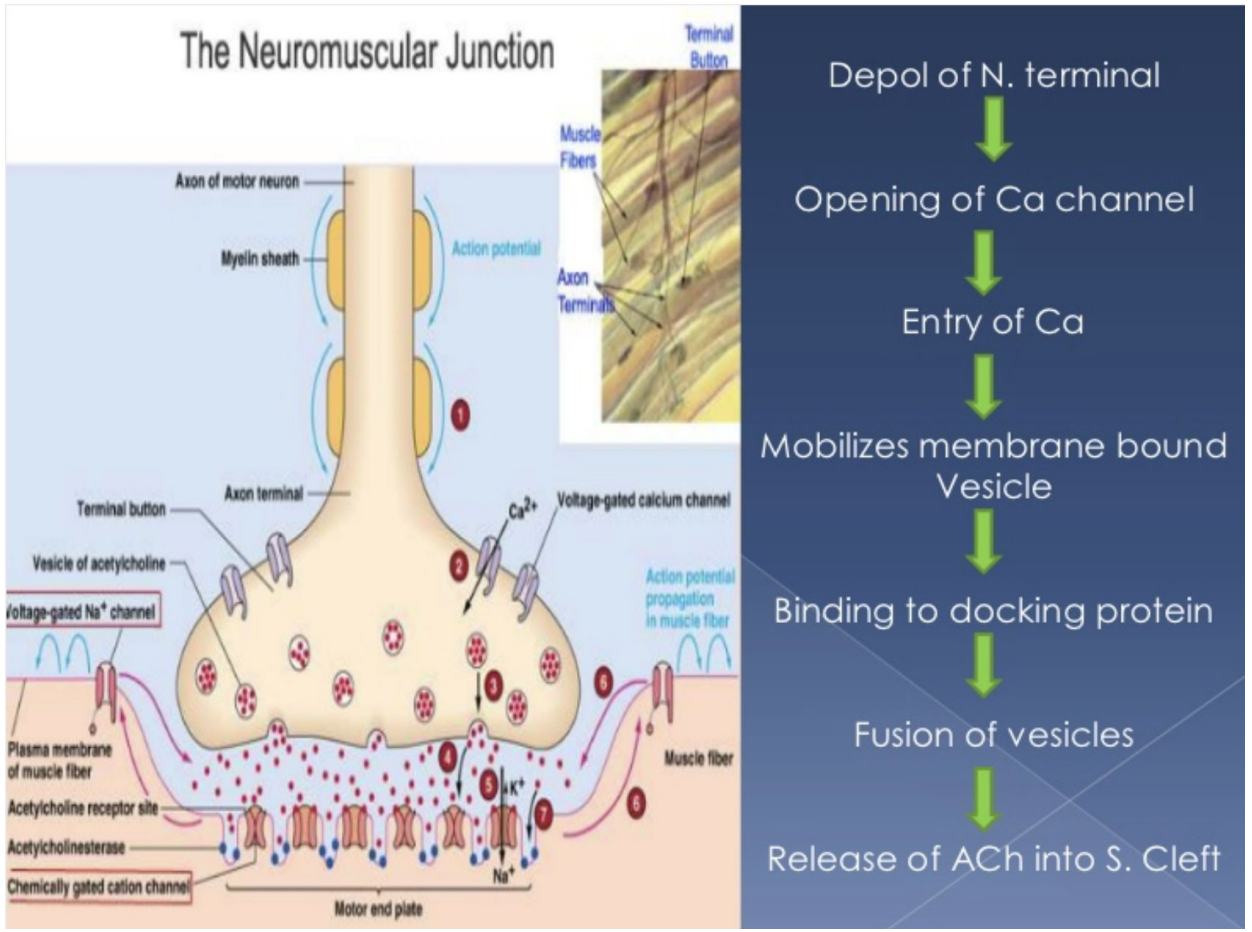
After treatment :

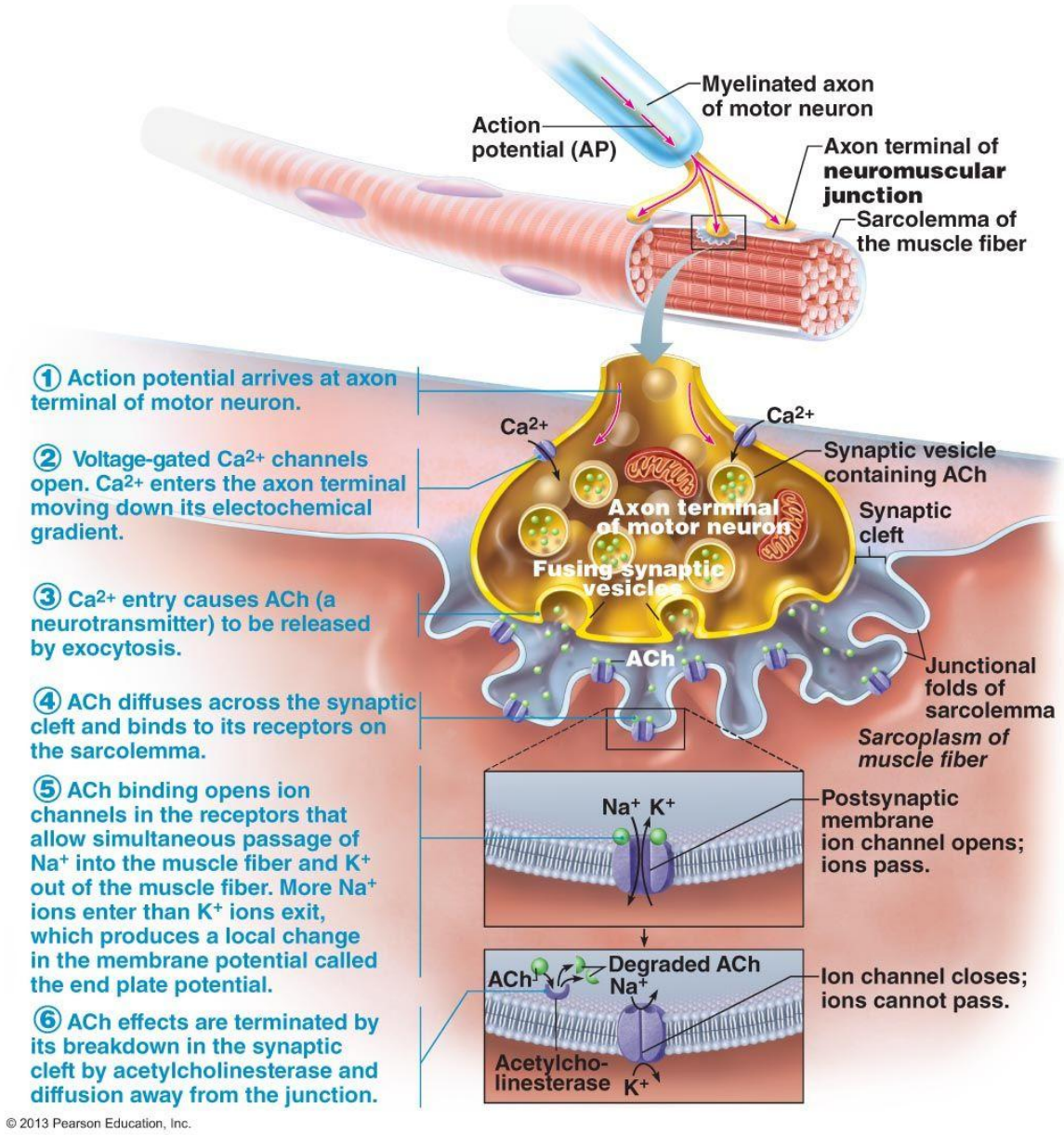
- Good EPP is formed.
- Muscle will Contract.





Summary


The Neuromuscular Junction
Terminal Button
Muscle Fibers
Axon Terminals
Axon of motor neuron
Myelin sheath
Action potential
Axon terminal
Terminal button
Vesicle of acetylcholine
Voltage-gated Na+ channel
Voltage-gated calcium channel
Ca2+
Action potential propagation in muscle fiber
Plasma membrane of muscle fiber
Acetylcholine receptor site
Acetylcholinesterase
Chemically gated cation channel
Muscle fiber
Motor end plate
K+
Na+
Depol of N. terminal
Opening of Ca channel
Entry of Ca
Mobilizes membrane bound Vesicle
Binding to docking protein
Fusion of vesicles
Release of ACh into S. Cleft


Myelinated axon of motor neuron
Action potential (AP)
Axon terminal of neuromuscular junction
Sarcolemma of the muscle fiber
① Action potential arrives at axon terminal of motor neuron.
② Voltage-gated Ca2+ channels open. Ca2+ enters the axon terminal moving down its electochemical gradient.
③ Ca2+ entry causes ACh (a neurotransmitter) to be released by exocytosis.
④ ACh diffuses across the synaptic cleft and binds to its receptors on the sarcolemma.
⑤ ACh binding opens ion channels in the receptors that allow simultaneous passage of Na+ into the muscle fiber and K+ out of the muscle fiber. More Na+ ions enter than K+ ions exit, which produces a local change in the membrane potential called the end plate potential.
⑥ ACh effects are terminated by its breakdown in the synaptic cleft by acetylcholinesterase and diffusion away from the junction.
Ca2+
Ca2+
Synaptic vesicle containing ACh
Axon terminal of motor neuron
Synaptic cleft
Fusing synaptic vesicles
ACh
Junctional folds of sarcolemma
Sarcoplasm of muscle fiber
Na+ K+
Postsynaptic membrane ion channel opens; ions pass.
ACh
Degraded ACh
Na+
Ion channel closes; ions cannot pass.
Acetylcho-linesterase
K+
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Muscle fatigue

From Guyton
(Not include in the slides only for your information)

Muscle fatigue due to;

1- Prolonged and strong contraction
2- increase the rate of depletion of muscle glycogen
3- inability of the contractile and metabolic processes of the muscle fibers to continue supplying the same work output
4- Interruption of blood flow through a contracting muscle (complete muscle fatigue) because the loss of blood (oxygen) supply

Intense prolonged muscle contraction —> diminish in neuromuscular junction —> further diminishing muscle contraction

SAQ

Q1-Synapse between a motor neuron and a muscle cell is a definition of?

Q2- Neurotransmitter released by Ca++ entering neuron at the synaptic knob

Q3- Triggered to open by action potentials; diffuse Ca++ into the synaptic knob of the neuron

Q4- ACh will diffuse through what and bind to chemically gated ion channels on the muscle cell membrane (sarcolemma)

Answers

SAQ1-neuromuscular junction

SAQ2- Acetylcholine

SAQ3- voltage-gated calcium channels

SAQ4- synaptic cleft

Quiz

1) What means of membrane transport is used to release the neurotransmitter into the synaptic cleft?		2)Acetylcholine is recycled from the synaptic cleft as what two components?	
A.	A carrier	A.	Chlorine + Acetyl
B.	A channel	B.	Choline + Acetyl
C.	Exocytosis	C.	Chlorine + Acetate
		D.	Choline + Acetate
3)what is the function of Curare drug		4)Binding of the neurotransmitter to receptors on the motor endplate opens channels that let which ion enter the cell and cause depolarization?	
A.	Bacterial poison that decreases the quantity of Ach release	A.	Sodium ions
B.	block the action of Ach on its receptors on MEP	B.	Calcium ions
C.	inactivate acetylcholinesterase for several hours	C.	Potassium ion
D.	inactivates acetylcholinesterase for weeks		

Answers key: 1)C 2)D 3)B 4)A

Team leaders

- Elaf Almusahel
- Omar Alshenawy

♂ team members

- **Mohammed Alhamad**
- Badr Almuhanna
- Abdulrahman Alhawas
- Meshari Alzeer
- Aued Alanazi
- Omar Alghadir
- Omar Aldosari

♀ team members

- **Noura Almazrou**
- Arwa Al Emam
- Tarfah Alkaltham
- Deema almaziad
- Renad Almutawa
- Rema Almutawa
- Jude alkhalifah
- May Babaeer
- Njoud alali

Thank you

@physiology438

Editing file

Summary file for your revision