PHYSIOLOGY TEAM 435

6 Neuromuscular junction

- Very important
- Extra information
- Terms

Today I will do what others won't so, tomorrow
I CAN DO WHAT OTHERS CAN'T !

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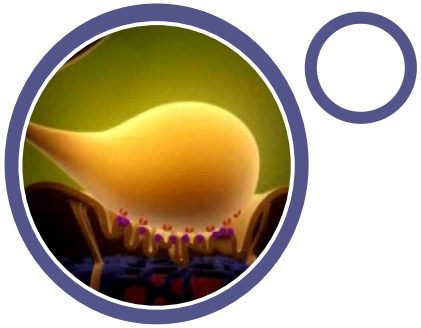
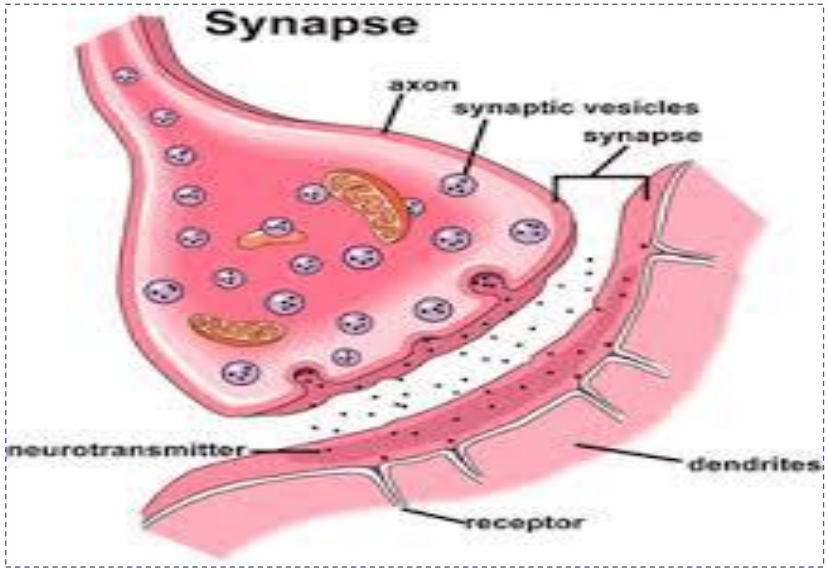
Objectives

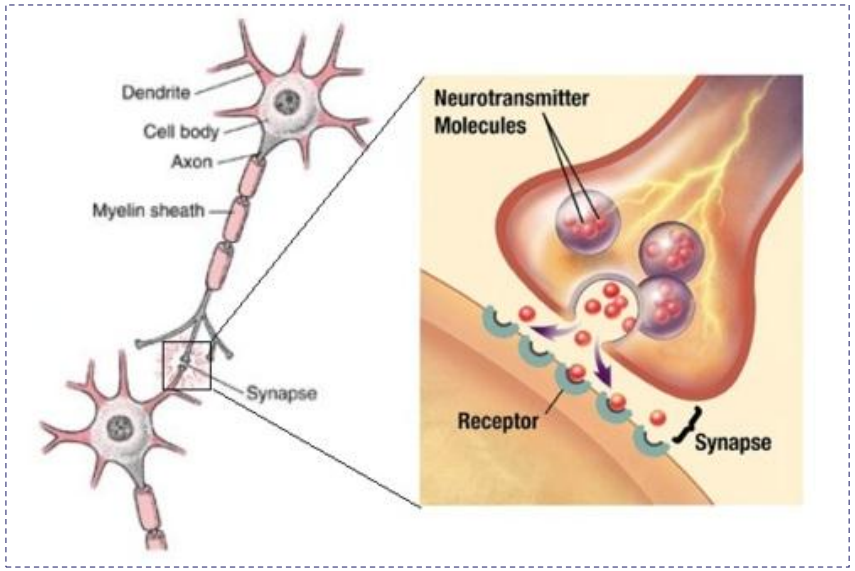
- Describe the anterior horn cell and motor unit .
- Describe and define the structure and function of the neuromuscular junction .
- Describe acetylcholine vesicles , exocytosis , EPP (end-plate potential), acetylcholinesterase , drugs that Inactivate cholinesterase (e.g., neostigmine), Myasthenia Gravis.

Synaptic transmission

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







Video

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Steps involved

Action potential (AP) at the **synaptic knob**

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

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

Neurotransmitter combines with specific receptors on the other membrane

Postsynaptic potential > Action potential will result

Video

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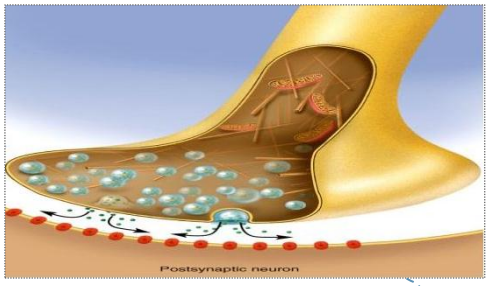
Chemical signals

- One neuron will transmit information to **another neuron** or to a **muscle** or **gland cell** by releasing chemicals called Neurotransmitters.
- The site of this chemical interplay is known as the Synapse.
- An axon terminal (synaptic knob) will abut another cell, a neuron, muscle fiber, or gland cell.
- The site of Transduction : the conversion of an electrical signal into a chemical signal.

- The action potential reaches the axon terminal, then it will carry a massage to muscles " Dear muscles, you have to contract now!"
- At the beginning, this massage 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.
- There are 300,000 vesicle in each axon terminal which contain neurotransmitters such as Acetylcholine.



The nerve will change its shape > loss of meilyn sheath it becomes much wider > knob.

Synaptic knob resembles

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Synaptic transmission

An action potential reaches the **axon terminal** of the **presynaptic cell** and causes voltage gated Ca^{2+}channels to open

Ca^{2+} rushes in, binds to regulatory proteins

Initiates neuromuscular transmission exocytosis

Neuromuscular transmission diffuse across the synaptic cleft and then bind to receptors on the **postsynaptic membrane** and initiate some sort of response on the postsynaptic

Video

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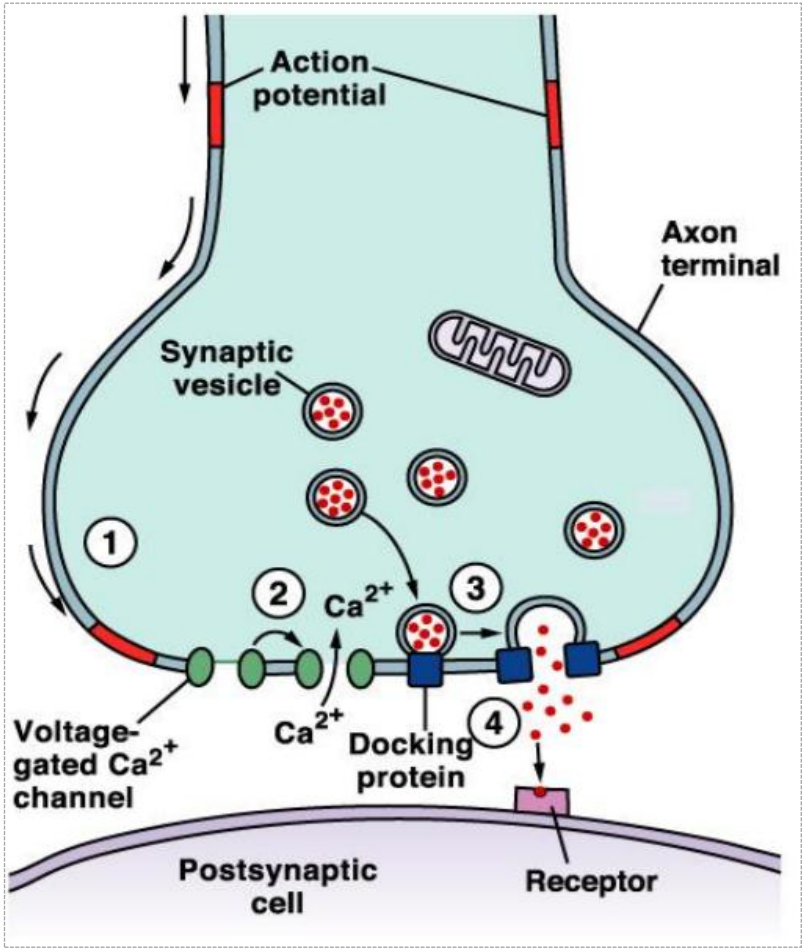
Synaptic transmission



- "Calcium is higher in the ECF than ICF" calcium will enter the cell through :
  [voltage gated Calcium channel].
- Calcium function is to approach vesicles and make them attached to the membrane.

  بعدها تلتصق تماماً ، ثم تنفتح وتفرز ما بجعبتها من مواد كيميائية
  " نسمي عملية الإخراج هنا :Exocytosis"
- "Docking" of vesicles > Exocytosis > the chemical substance will be attached to specific receptors.
- Cleft : يسمّى الفراغ الموجود بين الـ nerve والـ muscle
- This chemical substance that released from vesicles will bind to receptor to produce an action.

The neuromuscular junction consist of :

Axon terminal "synaptic knob"

contains around 300.000 vesicles which contain the neurotransmitter Ach

Synaptic cleft :

- 20-30 nm, it's a space between the axon terminal & the muscle cell membrane.
- Filled with ECF & Ach esterase enzyme " cholinesterase" which can **destroy** Ach.

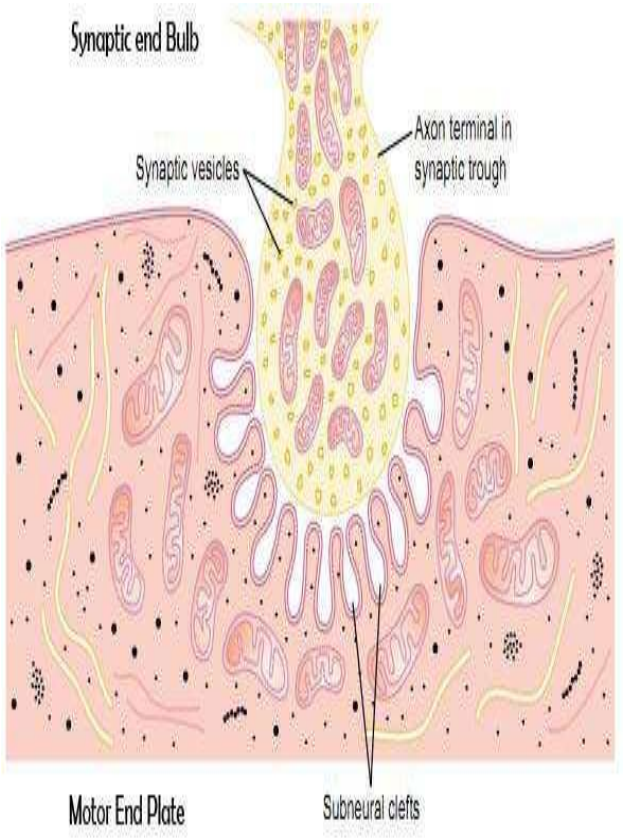
Synaptic gutter
" synaptic trough"

- It Is the muscle cell membrane which is in contact with the nerve terminal.
- It has many folds called **subneural clefts**
- It is greatly increase the surface area.

allowing for accommodation of large numbers of Ach receptors

- Ach receptors are located here.

- Has Ach gated channels "where Ach bind " at motor end plate in post-synaptic membrane.



Cleft : الفراغ الموجود بين الـ nerve والـ muscle يسمّى
Synaptic Gutter : منطقة التعرجات التي تزيد مساحة السطح

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The neuromuscular junction consist of :

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 (acetyle coenzyme A) and choline

Then its 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

Axoplasmic transport "axonal transport" is a cellular process responsible for movement of mitochondria, lipids, synaptic vesicles and other organelles to and from soma through the cytoplasm of its axon (axoplasm).

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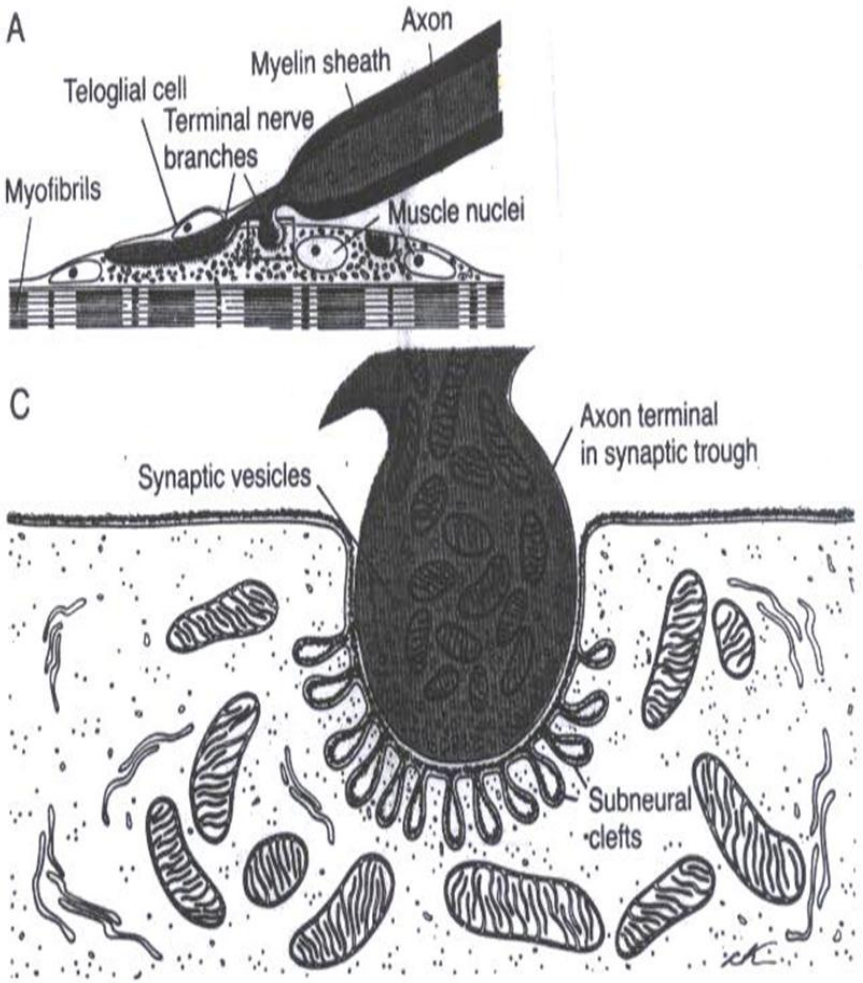
The neuromuscular junction



- The story of neuromuscular transmission:

after activating a motor neuron the Action potential of it will arrive to nerve terminal resulting in opening of calcium channels. then calcium will enter from ECF to ICF. Calcium's entrance will move the vesicles containing the neurotransmitter acetylcholine to cell membrane and exocytose them to synaptic cleft. Acetylcholine will then bind to specific ion channels (nicotinic and muscarinic) those ion channels will open allowing the Na to go in and cause local non-propagated potential (EPP) that will trigger AP that will spread on both sides of muscle .

- Motor end plate area does not obey all-or-none law.

- Motor end plate = neuromuscular junction
- Neuromuscular junction : nerve > motor nerve because it will act on muscles = [Motor-end-plate].
  "The NMJ is the SAME AS MEP"
  تمثّل مكان التقاء motor nerve : مع العضلة

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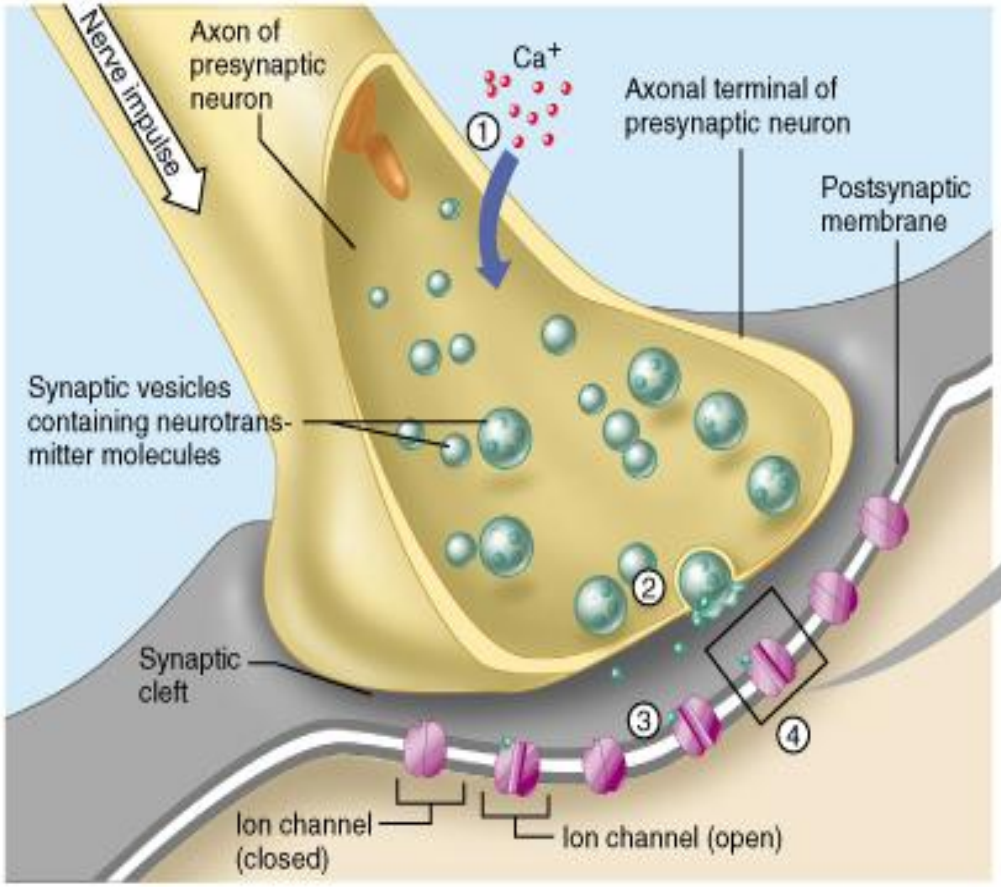
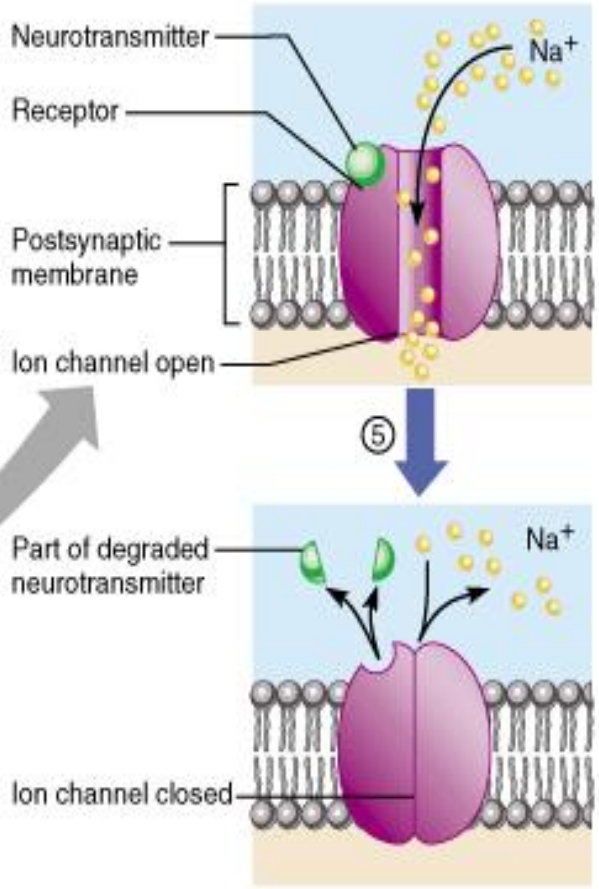
Steps of neuromuscular transmission

1. **AP** reach nerve terminal
2. open **Ca+** channels
3. **Ca+** influx
4. **Ca+** attract vesicles to nerve terminal membrane
5. They rupture& release Ach to synaptic cleft (Ca+ dependent exocytosis)
6. Ach bind to channels then they open
7. Na+ flow to inside
8. Destruction of Ach by Ach esterase enzyme

into choline & acetate go to nerve terminal to be **re-used.**
*The choline is actively reabsorbed into the nerve terminal to be used again to form Ach.

Secretion of acetylcholine (Ach) by nerve terminals : (Ca dependent exocytosis)



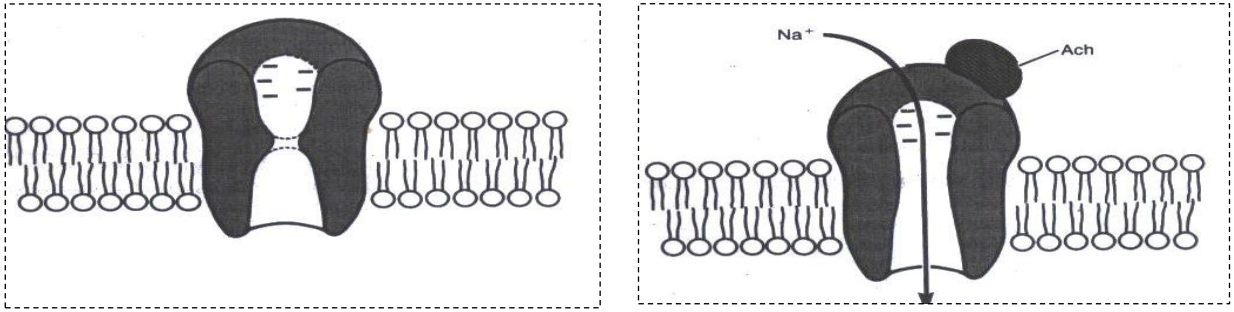


When Ach is released and binds to its receptors , it opens Na ligand channel "Ach الـ تنفتح فقط إذا تم إفراز".

Every millisecond there is a new Ach.
فرضاً : شخص يريد الإمساك بقلم لمدة
ساعة كاملة ، هل نفس الـAch
لأنه يرتبط لمدة أقصاها :millisecondsسيبقى مرتبطاً بالمستقبِل طوال هذه المدة؟ الجواب : لا ،
بالتالي يتغير ويأتي عوضاً عنه Ach
آخر والغرض من ذلك، إذا قرر الشخص ترك القلم مباشرة يحدث ارتخاء للعضلة

Ligand gated

- **Ach** combines with its receptors in the sub-neural clefts.
- This opens sodium channels "Na+ channels" → sodium diffuses into the muscle causing: local non-propagated potential called the "End-Plate Potential (EPP)" [whose value is 50 – 75 mV].
- This EPP triggers a muscle AP "action potential" which spreads down inside the muscle to make it **contract** .



The Acetylcholine channel: left, while in the closed state. Right, after Ach has become attached and a conformational change has opened the channel, allowing excess Na+ to enter the muscle fiber and excite contraction. Note the negative charges at the channel mouth that prevent passage of negative ions.

Video

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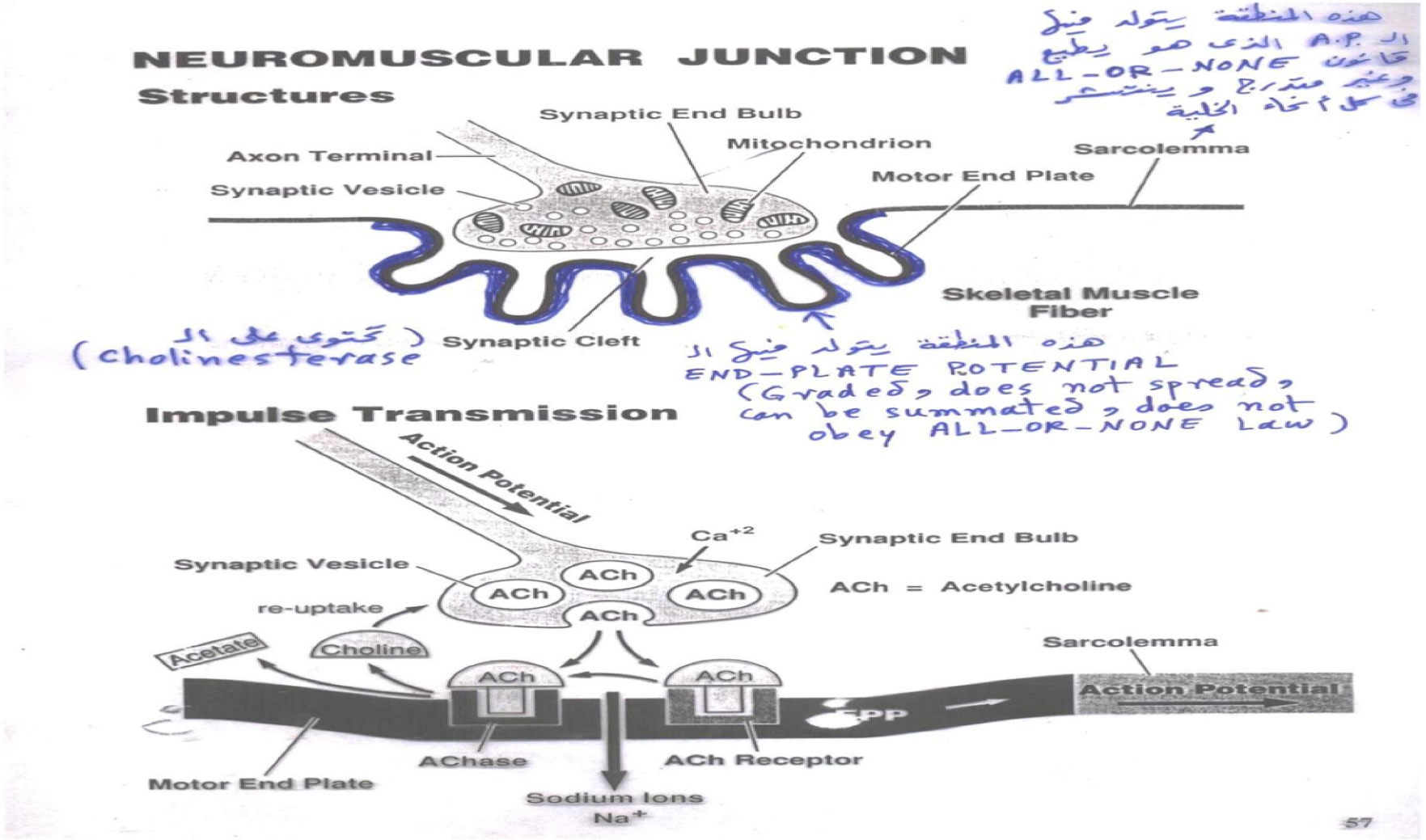

Given by Dr. Manan

في هذه المنطقة :

No action potential. Rather, motor-end plate potential will occur Because AP must be propagated , motor-end-plate potential depend on the amount of Ach and Ach receptors. If Na enters in large amounts AP will occur > propagation > AP يمشي في كل العضلة > يعطي الأوامر للعضلة ولكن لا يعني بالضرورة حدوث الانقباض

Drugs that act on the neuromuscular junction

1. Drugs that act on muscle fiber by Ach like action
2. Drugs that block transmission at neuromuscular junction
3. Drugs that stimulate transmission at neuromuscular junction by inactivation of Ach esterase enzyme

Three ways to make abnormality in the neuromuscular transmission:

- Blocking acetylcholine esterase will cause forever contraction and lead to death > like in the poison gas it is include chemicals which block the acetylcholine esterase for long time, so the muscles will contract for long time so there is no O- exchange and the person will die.
- Blocking of the vesicle released will cause long relaxation > like the mechanism in the Botox .
- Curare > chemical binds to the acetylcholine receptor, so the acetylcholine won't find receptor so there is no motor end potential > which cause relaxation

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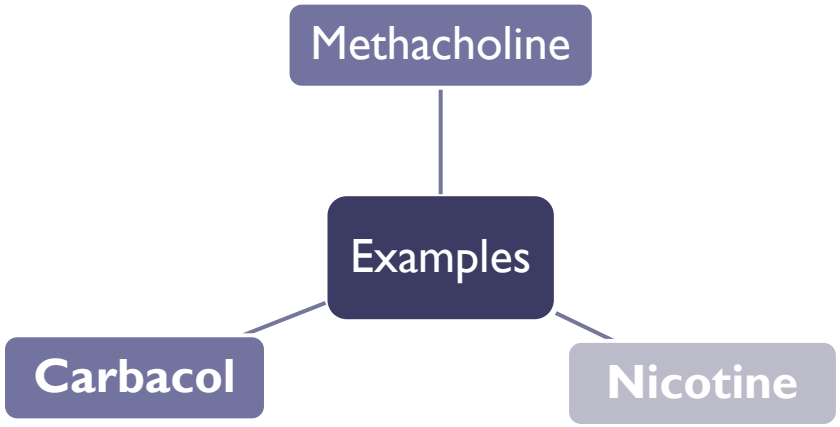
Drugs that act on the neuromuscular junction

1-Drugs that act on muscle fiber by Ach like action: "Agoinst"

They act for minutes or hours, why ?as they DO NOT destructed by Ach esterase enzyme



they work like Ach but with longer duration of action , because they don't have an enzyme that destructs them in contrast Ach has enzyme that destructs it which is Ach esterase.

To remember : Nick use metro rather than car

As we know the muscle fibers have muscarinic receptors , these drugs go and bind to those receptors and stimulate these receptors "as what ach does" their will be depolarization" But these are drugs the body doesn't know them and doesn't't have an enzyme to destruct them ,, so they are kept for a longer time in the synaptic cleft and do their work for a longer time

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Drugs that act on the neuromuscular junction

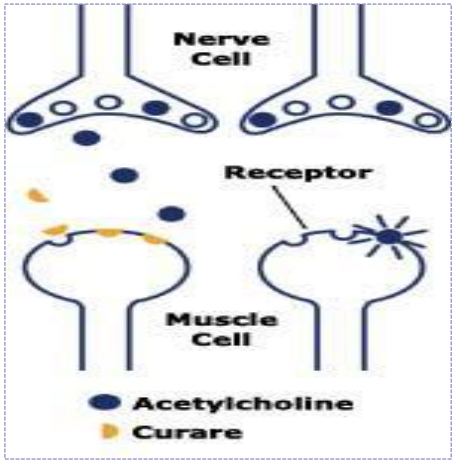
2- Drugs that block transmission at neuromuscular junction :

Act by competitive inhibition to Ach at its receptors and Can Not cause Depolarization.

Examples

- Curare
- Curariform like drugs
  - "having an action like curare"

Remember the word "Rare"



"Curare : Arrow poisons"

There are drugs that resemble Ach, but when they bind to receptors they do not open Na channels > no contraction > relaxation > to be used in surgeries "Anesthesia".
Example : curare.

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Drugs that act on the neuromuscular junction

3- Drugs that stimulate transmission at neuromuscular junction by inactivation of Ach esterase enzyme:-

1- Neostigmine
2- prostigmine
3- physostigmine

→ Inactivates **Ach esterase** enzyme temporarily

To remember :
New professional physician
+ they have the same suffix

Di-isopropyl florophosphate (nerve gas poison)

→ - Inactivates Ach esterase enzyme for days & weeks.
- **Death** because of respiratory muscle spasm

Pharmacological effects : there are drugs that inhibit Ach-esterase > prolonged contraction. > if it is very long it may causes spasm > death.
نفس المبدأ يُستخدم في الغازات السامة فهي تعمل على تعطيلAch-esterase للأبد مما يؤدي للوفاة
So, if we inhibit Ach-esterase for a short time "temporary" > something good
وتعطى هذه الأدوية لمن عندهم نقص في الـ Ach أو خلل في الـ Ach receptors، مثال: **Neostigmine**

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Extra

A famous drug that works on the NMJ:

Botox is a drug made from a toxin produced by the bacterium Clostridium botulinum. It's the same toxin that causes a life-threatening type of food poisoning called botulism. Doctors use it in small doses to Temporary smoothing of facial wrinkles. BOTOX blocks NMJ transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of Ach.

If we want relaxation of the muscle , we don't want it to contract. we use drugs that inhibit the vesicle to be excreted by exocytosis .
An example : Botox.

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Myasthenia Gravis

What is it?	- An autoimmune disorder of adult females. It is a condition causing abnormal weakness of certain muscles. -Body form antibodies against Ach receptors. Patients have 20% of number of Ach receptors . -The EPPs are too small to trigger action potentials & the muscles can not contract.
What does it affect?	- Eyelids. - Extra ocular muscle. - Bulbar muscle. - Proximal limb muscles
Symptoms	**Presents with :** Eyelid drooping **Ptosis /** Impaired speech **Dysarthria** Difficulty in swallowing **Dysphagia** proximal limb weakness in hands and feet.
Treatment	Administration of an inhibitor of acetyl cholinesterase temporarily : Prostigmine / Neostigmine / Tensilon (Edrophonium) is used to test for Myasthenia Gravis "diagnosis" - allowing **more Ach** to remain at the neuromuscular junction to bind to the remained Ach receptors "allow contraction"

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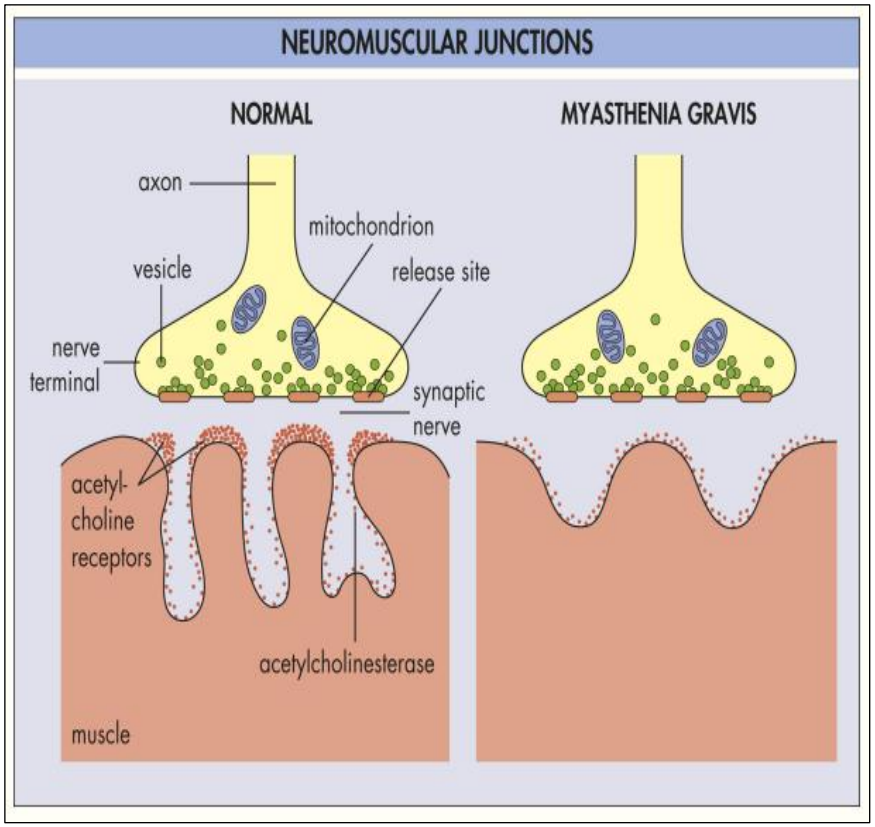
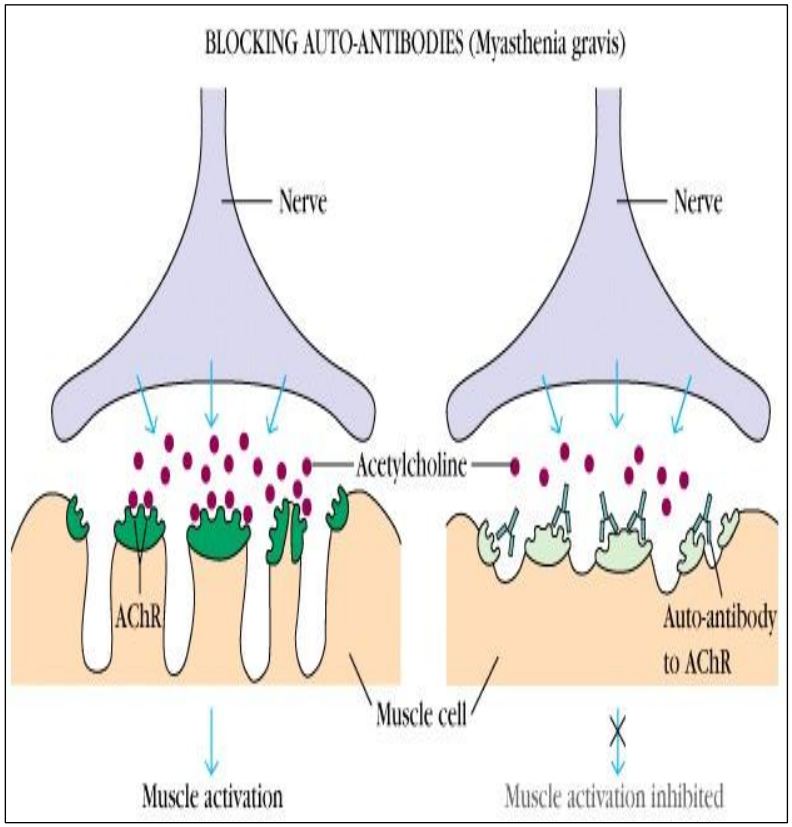
EPPs : End-plate-potential

Myasthenia Gravis





Myasthenia Gravis > disease which need time to appear > it's a autoimmune disorder when the body does not know the receptor and destroy them > the treatment to give the patient drug which block the acetylcholine esterase > to safe the acetylcholine as much as possible.

Myasthenia Gravis
"EXTRA"

Its also known as a rare chronic autoimmune disease marked by muscular weakness without atrophy, and caused by a defect in the action of acetylcholine at neuromuscular junctions.

What's the mechanism of this disease?
Causes muscle paralysis because of the inability of neuromuscular junction to transmit enough signals from nerve fibers to muscle fibers.

The body forms antibodies against Ach receptors. Which means the body is attacking its neuromuscular signals and preventing them from happening. Patients have 20% of number of Ach receptors (because the rest was killed by antibodies formed from the body).

Pathologically:
Antibodies attack the Ach receptors have been found in the blood of most patients presented with this disease.
In which, the patients have developed antibodies that destroy or block their own Ach receptors at the post-synaptic neuromuscular junction.
Thus, the end plate potentials (EPP) that occur in muscle fiber are too weak to initiate the opening of the voltage-gated sodium channels , so the muscle fiber depolarization doesn't occur.

If it was severe enough patient dies of paralysis. In particular, paralysis of respiratory muscles
The disease can be ameliorated for several hours by administrating neostigmine of some anti-choline esterase drugs which allows larger synaptic space .

within minutes those patients can begin to function normally again until a new dose is required a few hours later.

Myasthenia Gravis "EXTRA"

Treatment:

Administration of an inhibitor of acetyl cholinesterase temporarily e.g. prostigmine or neostigmine prevents the breakdown of acetylcholine which is an important chemical that helps the muscles contract.

What does it do exactly?

It allows more Ach to remain at the neuromuscular junction to bind to the remained Ach receptors.& allow contraction.

*These medicines tend to work best in mild myasthenia gravis.

*They can improve muscle contractions and strength in affected muscles.

These treatments can cause side effects, such as stomach cramps and muscle twitching. Other medications may be prescribed to counteract these side effects.

Chronic symptoms frequently require long-term treatment.

If symptoms are mild, some people find that getting plenty of rest helps improve their symptoms without the need for additional treatment. But also, some people prefer treatment.

** And sometimes surgery is advised by removing the thymus (thymectomy).

If it is not clear zoom it :)

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