النادي الطبي

PHYSIOLOGY
HAYAT BATCH

done by : عبد الودود الخفش + لانا التوتنجي

lecture no: 29

Figure 6-1. Organization of skeletal muscle, from the gross to the molecular level. *F, G, H,* and *I* are cross sections at the levels indic

General physiology
Second semester 2022-2023
Lecture 29
Neuromuscular junction and excitation contraction coupling in skeletal muscle

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Lecture objectives

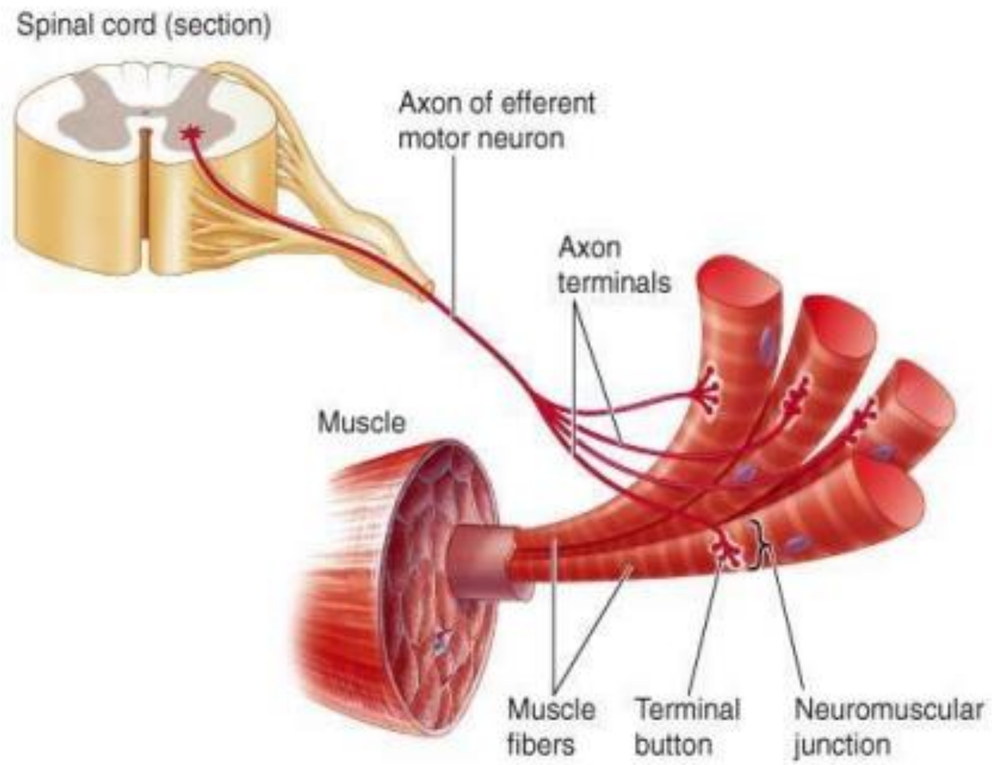
- Define motor units
- Identify the components of the neuromuscular junction and the physiological anatomy of NMJ
- Describe the sequence of events that leads to a propagation of action potential in the skeletal muscle and the neurotransmission across the NMJ
- Identify the neurotransmitter released at the neuromuscular junction , its
- synthesis and degradation
- Identify the cholinergic receptors at the NMJ
- Define the motor end plate potential and identify its characteristics
- Explain how drugs or toxins affect neuromuscular transmission
- Describe the mechanism of excitation contraction coupling in skeletal and cardiac muscles
- Explain the pathophysiology of Myasthenia Gravis and malignant hyperthermia

Innervation of skeletal muscles :The Motor unit

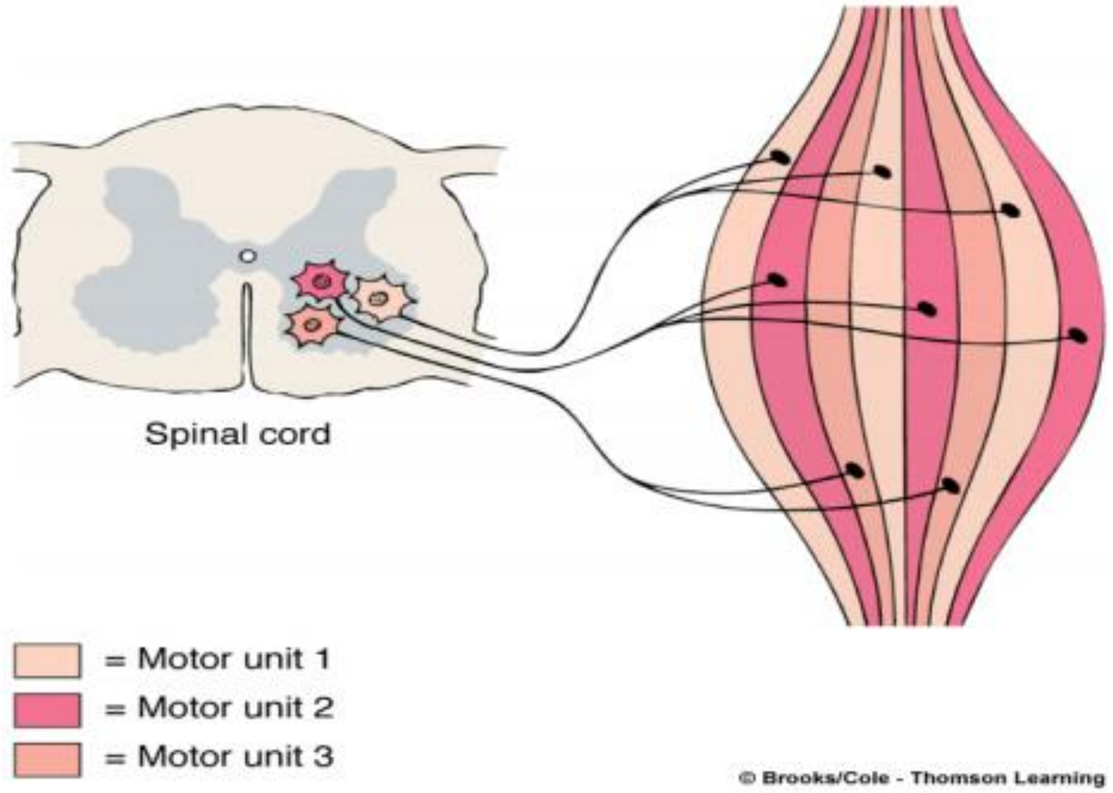
- **Neuromuscular junction :** the synapse between motor neuron and muscle fiber is called the neuromuscular junction

- **Motor neurons :** are the nerves that innervate muscle fibers

- **Motor unit :** single motor neuron and the muscle fibers it innervate



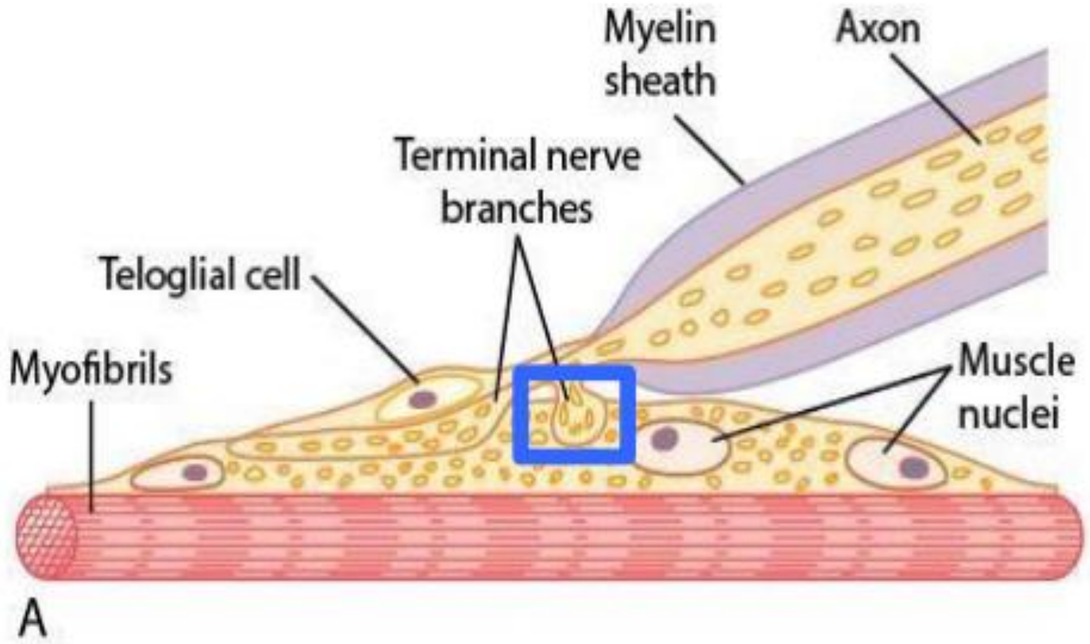
Innervation of skeletal muscles The Motor unit



motor neuron ممكن يغذي أكثر من خلية عضلية... بس ما بصير الخلية العضلية تتغذى من أكثر من Neuron

Component of neuromuscular Junction

- Specialized synapse between a motoneuron and a muscle fiber
- Occurs at a structure on the muscle fiber called the motor end plate *(usually only one per fiber)*
- Teloglia : Parasynaptic Schwann cells (also known as Terminal Schwann cells) are Neuroglia found at the Neuromuscular junction (NMJ)
- Function : synaptogenesis, and nerve regeneration.



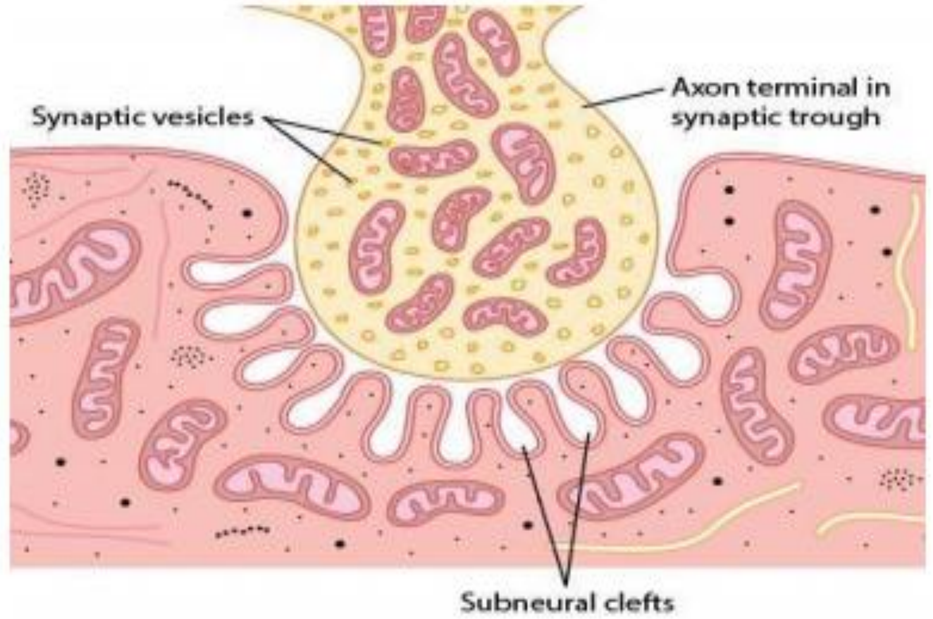
Neuromuscular Junction (cont.)

القاع الي ينغمس فيه ال Neuron

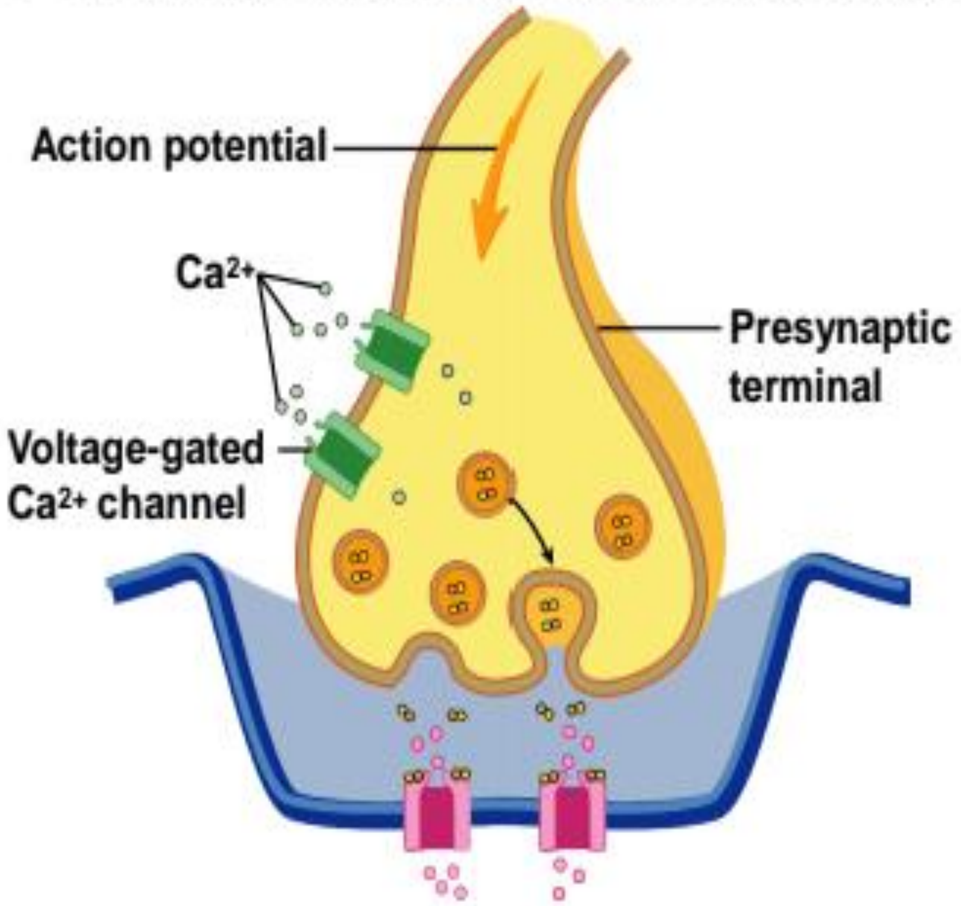
منخفض تعرجات

Synaptic trough: invagination in the motor endplate membrane

- **Synaptic cleft:**
  - 20-30 nm wide
  - contains large quantities of acetylcholinesterase (AChE
- **Subneural clefts:**
  - increases surface area of post-synaptic membrane



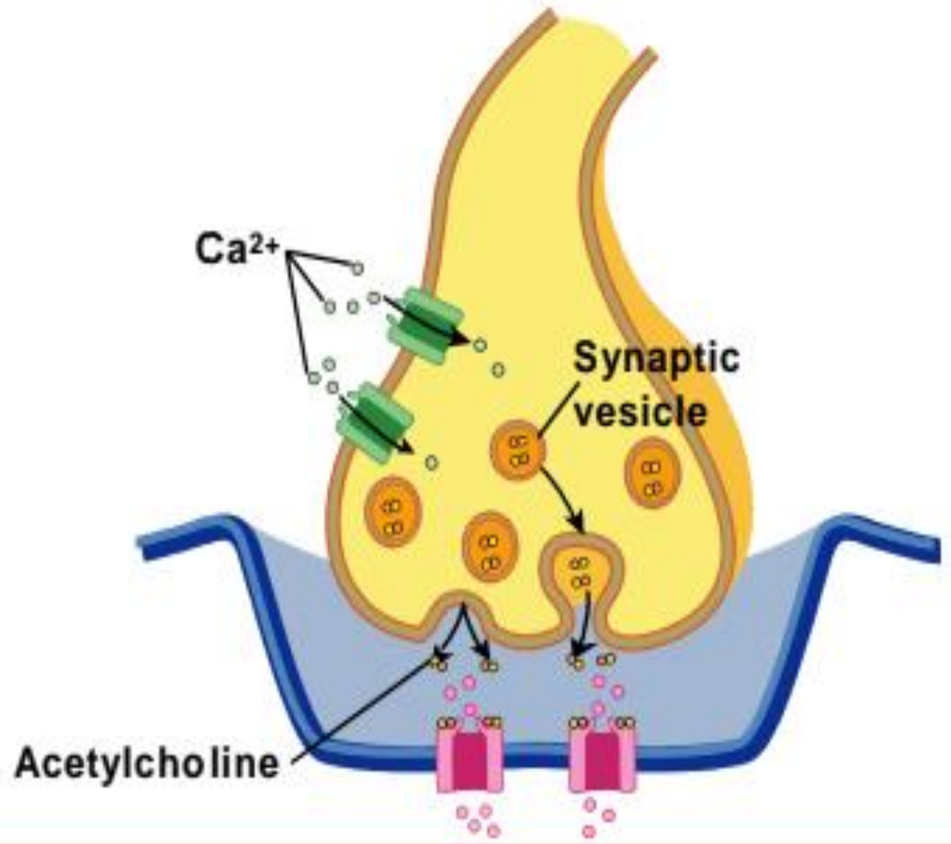
Sequence Of Events At Neuromuscular Junction



Arrival of action potential at the presynaptic terminal causes activation of voltage gated Ca channels and Ca enters presynaptic terminal

Sequence Of Events At Neuromuscular Junction (continued)

The calcium ions, in turn, Activates *Ca2+-calmodulin dependent protein kinase*, which, in turn, phosphorylates *synapsin* proteins that anchor the acetylcholine vesicles to the cytoskeleton of the presynaptic terminal. Leading to exocytosis



Ca2+ influx into the terminal causes release of the neurotransmitter acetylcholine into synaptic cleft , which has been synthesized and stored into synaptic vesicles

The receptor in NMJ is nicotinic Ach.

ACh Release - *details*

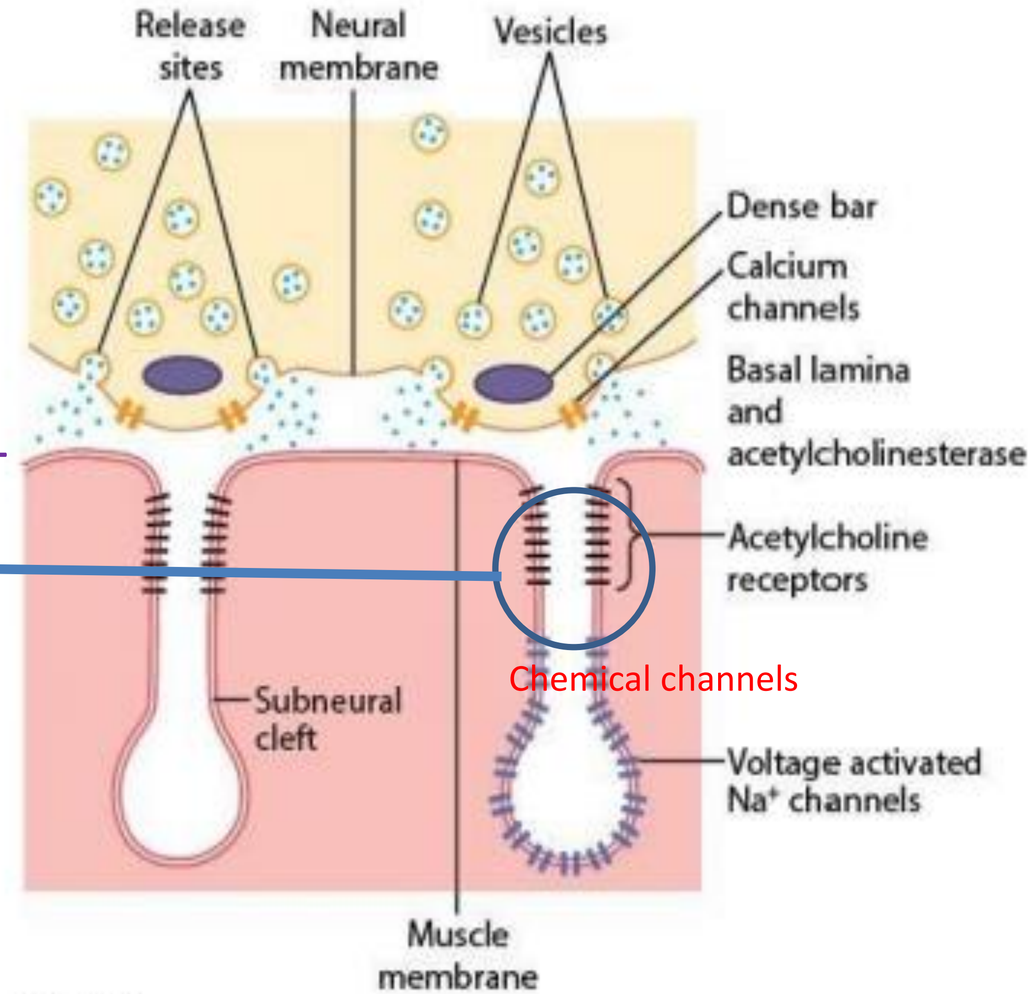


Figure 7-2

These channels let in Na+ ion and causes graded potential

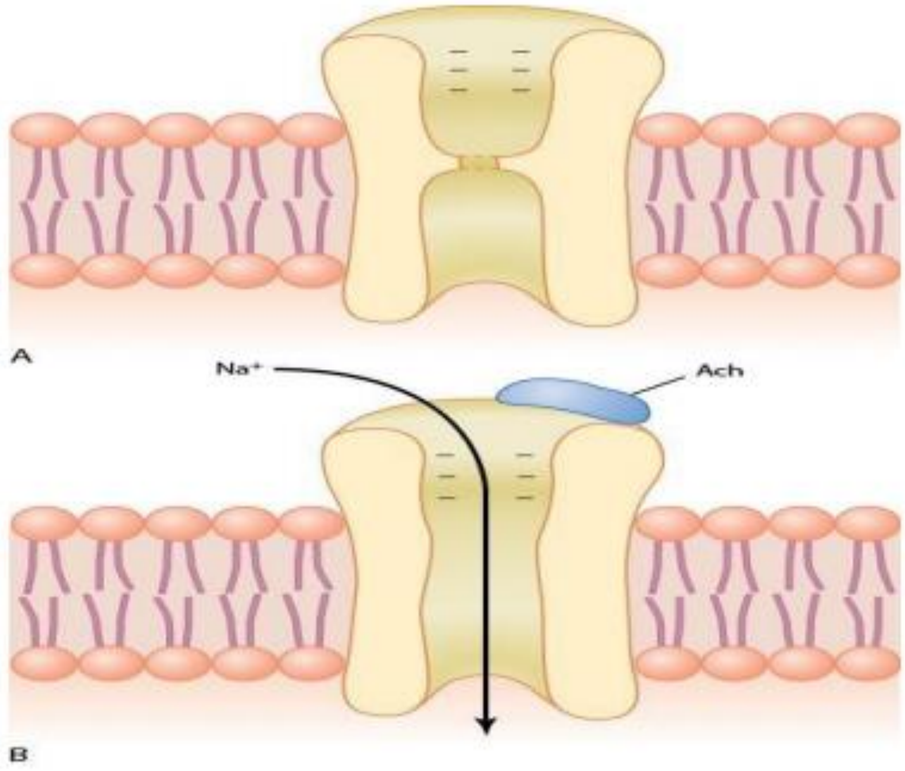
- Ca^{2+} channels are localized around linear structures on the pre-synaptic membrane called dense bars
- Vesicles fuse with the membrane in the region of the dense bars.
- Ach receptors located at top of subneural cleft.
- Voltage gated Na^{+} channels in bottom half of subneural cleft

The graded potential من chemical channels will causes action potential (اذا كان السعة كافية)
عن طريق دخول ايونات الصوديوم من the voltage Na+ channel

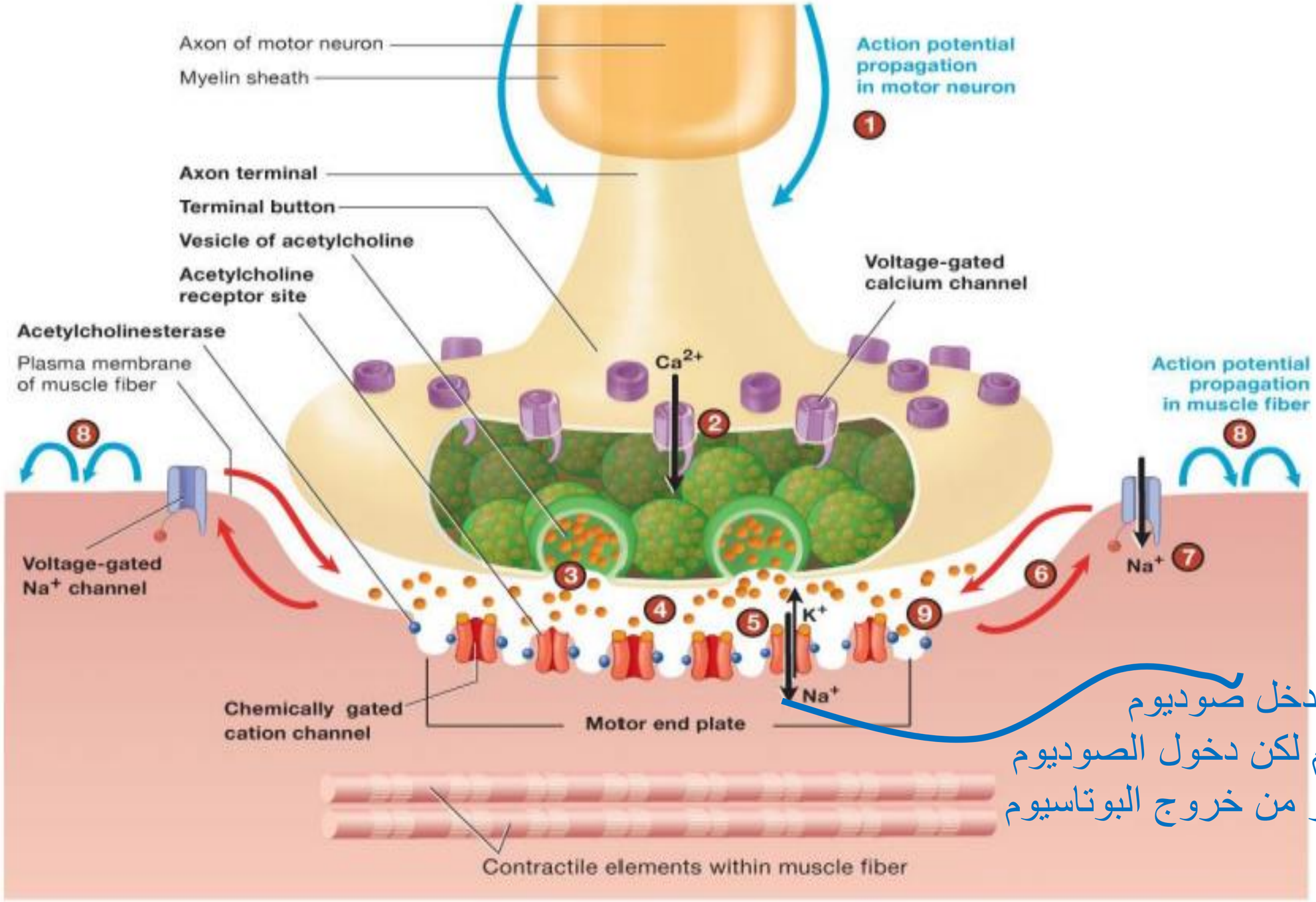
The aim of the synapse is to do localized depolarization which generates the action potential in the muscle cell… when the action potential is generated it will pass through the transverse tubule and release Ca+ ion…. Ca ion fuse with the troponin

Acetylcholine gated channel

Acetylcholine-gated channel. **A,** Closed state.
B, After acetylcholine *(Ach)* has become attached and a conformational
change has opened the channel, allowing sodium ions to enter the muscle fiber and excite contraction. Note the negative charges at the channel mouth that prevent passage of negative ions such as chloride ions.



Summary of events at the neuromuscular junction



هو فعليًا بدخل صوديوم وبوتاسيوم لكن دخول الصوديوم أكثر بكثير من خروج البوتاسيوم

Summary of events at the neuromuscular junction

1. An action potential in a motor neuron is propagated to the terminal button.
2. The presence of an action potential in the terminal button triggers the opening of voltage-gated Ca^{2+} channels and the subsequent entry of Ca^{2+} into the terminal button.
3. Ca^{2+} triggers the release of acetylcholine by exocytosis from a portion of the vesicles.
4. Acetylcholine diffuses across the space separating the nerve and muscle cells and binds with receptor sites specific for it on the motor end plate of the muscle cell membrane.
5. This binding brings about the opening of cation channels, leading to a relatively large movement of Na^{+} into the muscle cell compared to a smaller movement of K^{+} outward.
6. The result is an end-plate potential. Local current flow occurs between the depolarized end plate and adjacent membrane.
7. This local current flow opens voltage-gated Na^{2+} channels in the adjacent membrane.
8. The resultant Na^{2+} entry reduces the potential to threshold, initiating an action potential, which is propagated throughout the muscle fiber
9. Acetylcholine is subsequently destroyed by acetylcholinesterase, an enzyme located on the motor end-plate membrane, terminating the muscle cell's response.

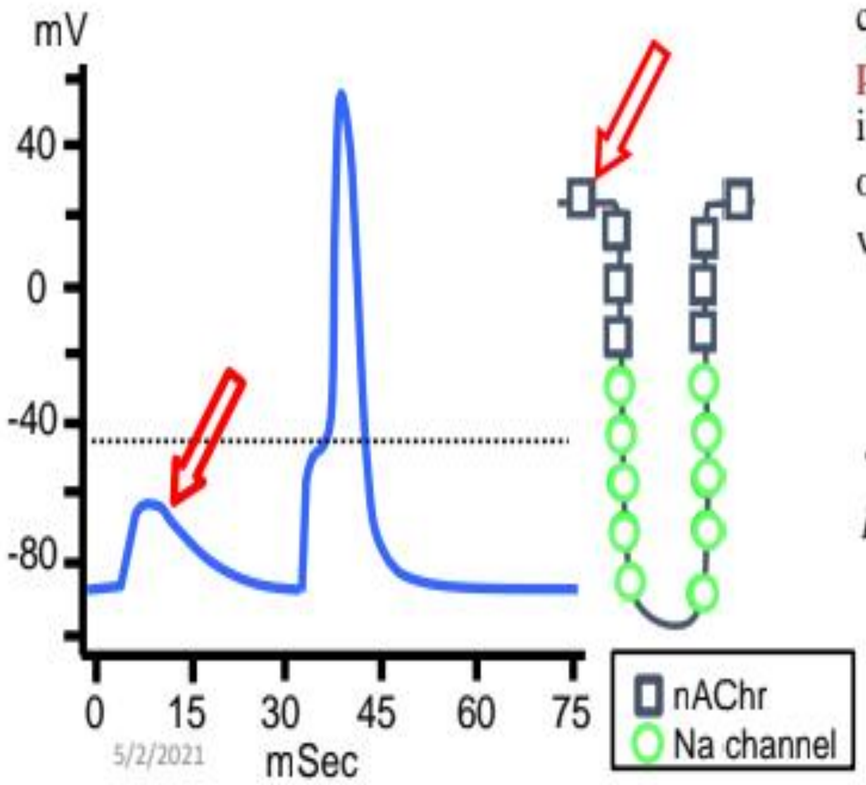
Graded potential

Action potential

هو نفسه EPSP الي اخدناه بمحاضرة 14,15 بس هون غيرو اسمه Neuromuscular junction لانه

End plate potential and action potential at *the motor endplate* .

•ACh released into the neuromuscular junction binds to, and opens, nicotinic ACh receptor channels on the muscle fiber membranes (Na^+, K^+, Ca^{2+}).



•Opening of nACh receptor channels produces an **end plate potential**, which will normally initiate an AP if the local spread of current is sufficient to open voltage sodium channels.

•*What terminates the process?*

acetylcholinesterase

هاد زيه زي ال EPSP الي اخدناه، واخدنا انه في Temporal summation and special summation لكن بدك تنتبه انه ال special summation كان يعتقد انه نزيد ال presynaptic لنفس ال Postsynaptic ، هون مش هيك لانه قلنا كل muscle fiber يشبك فيها motor neuron واحد بالتالي اذا بدك تزيد ال Graded potential بدك تزيد ال frequency

لكن اذا بدك تزيد الforce لانقباض العضلة... We need more motor units

هون فقط Temporal

End plate potential

- When the ion channel on post synaptic membrane opens both Na^+ & K^+ flow down their concentration gradient.
- At resting potential net driving force for Na^+ is much greater than K^+ ,when Ach triggers opening of these channels more Na^+ moves inwards than K^+ out wards, depolarizing the end plate. This potential change is called end plate potential (EPP).
- EPP is not an action potential but it is simply depolarization of specialized motor end plate
- Small quanta (packets) of Ach are released randomly from nerve cell at rest, each producing smallest possible change in membrane potential of motor end plate, the MINIATURE EPP.
- When nerve impulse reaches the ending, the number of quanta release increases by several folds and result in large EPP.
- EPP than spread by local current to adjacent muscle fibers which depolarized to threshold & fire action potential

Drug Effects on End Plate Potential

- Inhibitors -

1. Balk widow spider venom

2.Organophosphates

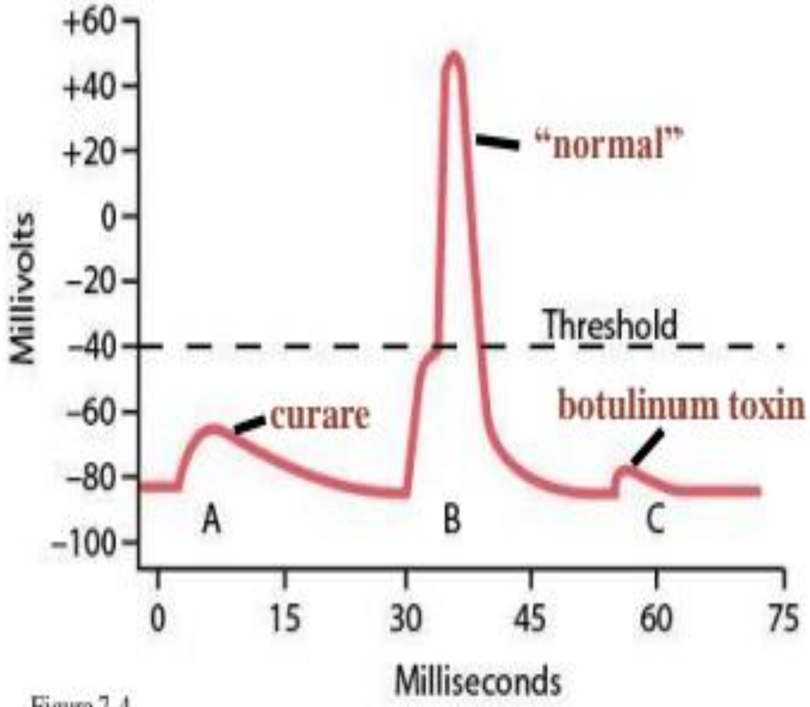


Figure 7-4

Curariform drugs (D-turbocurarine)

- block nicotinic ACh channels by competing for ACh binding site
- reduces amplitude of end plate potential therefore, no AP

Botulinum toxin

- decreases the release of Ach from nerve terminals
- insufficient stimulus to initiate an AP
- Causes muscle paralysis

شلل

Drug Effects on NMJ

- Black widow spider venom . Causes explosive release of Ach at all cholinergic synapses
- Prolonged depolarization May cause respiratory failure
- Organophosphates are used as medications, insecticides, and nerve agents as a weapon.
- Theses substances are anticholinesterase agents thus prolong the action of acetylcholine at cholinergic synapses
- Symptoms of toxicity include :
- increased saliva and tear production, diarrhea, nausea, vomiting, small pupils, sweating, muscle tremors, and confusion.
  - The onset of symptoms is often within minutes, and it can take weeks to disappear

EC Coupling

The junction between two terminal cisternae and a T-tubule

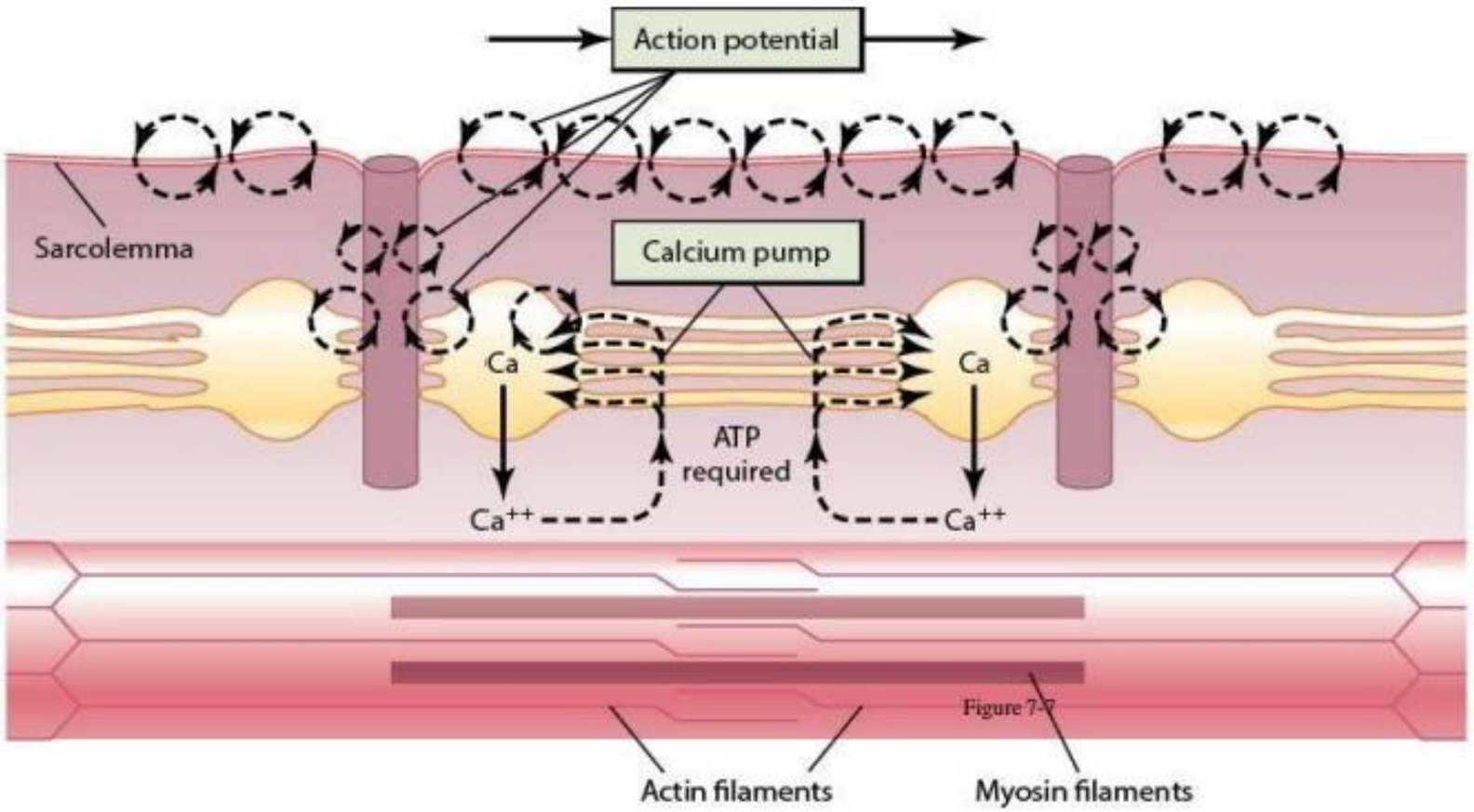


Figure 7-7

Excitation-Contraction Coupling

Transverse tubule / SR System

T-tubules:

- Invaginations of the **sarcolemma** filled with extracellular fluid
- Penetrate the muscle fiber, branch and form networks
- Transmit AP's deep into the muscle fiber

Sarcoplasmic Reticulum:

- terminal cisternae and longitudinal tubules
- **terminal cisternae** form junctional "feet" adjacent to the T-tubule membrane
- intracellular storage compartment for **Ca^{2+}**

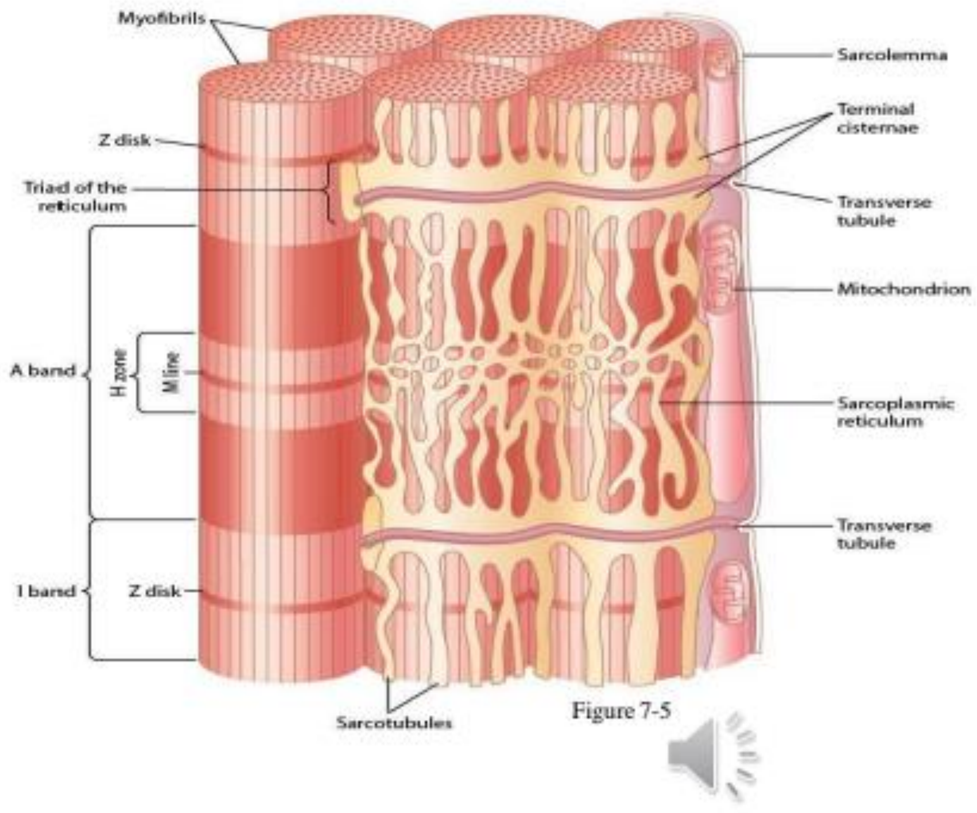
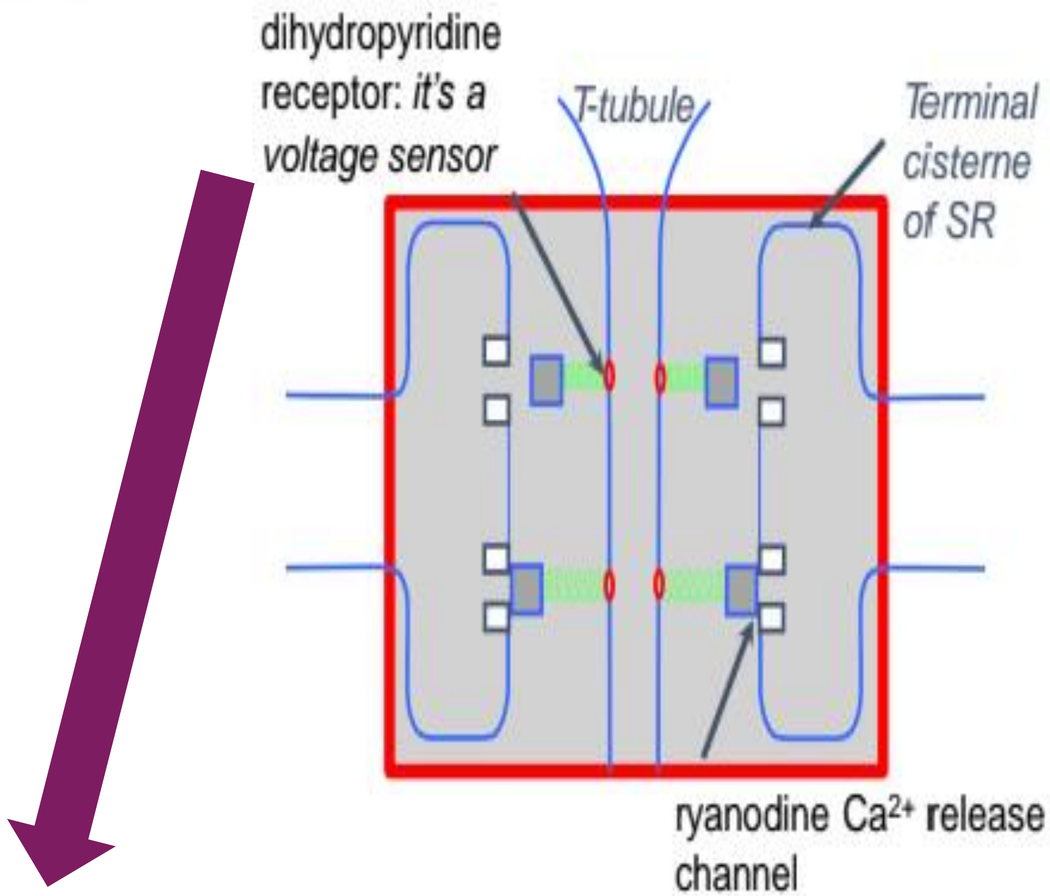


Figure 7-5

EC Coupling -

- *The "Triad" The junction between two terminal cisternae and a T-tubule*



Action potential will activate the dihydropyridine receptor, and this will lead to activation of the Ca+ channels in the sarcoplasmic reticulum and they called ryanodine channels

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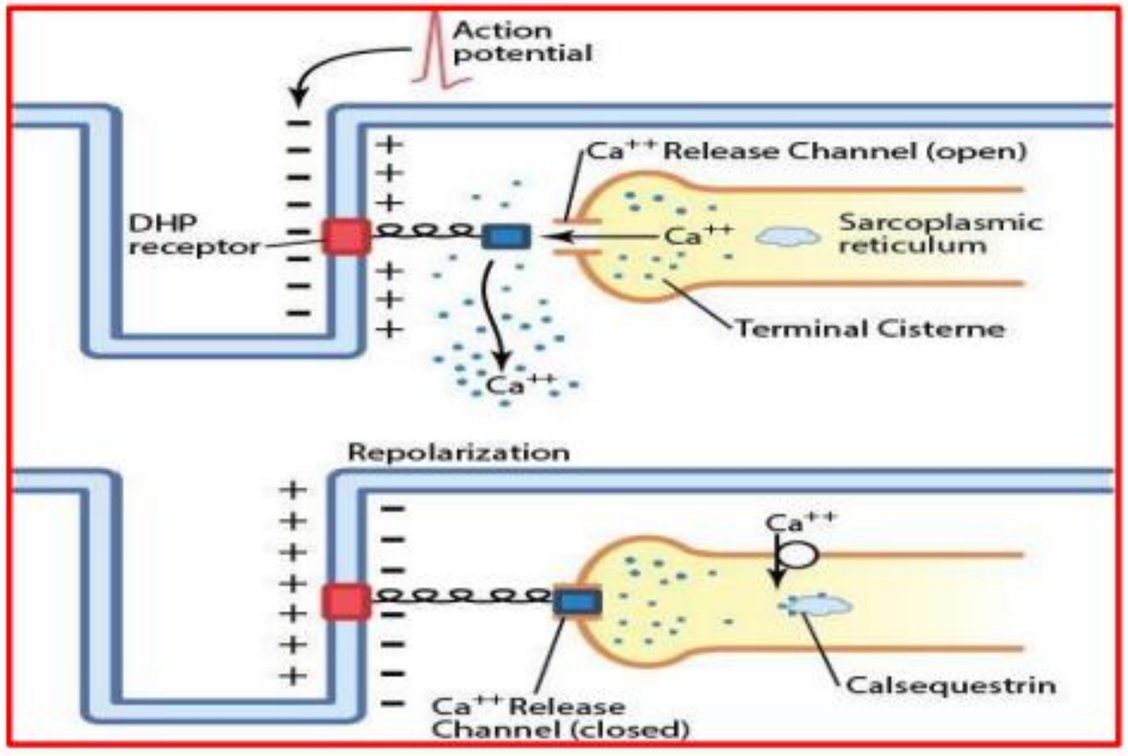
EC Coupling – *Skeletal muscle*

an action potential in the transverse tubule that causes a conformational change in the voltage-sensing dihydropyridine *(DHP)* receptors, opening the Ca++ release channels in the terminal cisternae of the sarcoplasmic reticulum and permitting Ca++ to rapidly diffuse into the sarcoplasm and initiate muscle contraction.

During repolarization *(bottom panel)*, the conformational change in the DHP receptor closes the Ca++ release channels and Ca++ is transported from the sarcoplasm into the sarcoplasmic reticulum by an adenosine triphosphate–dependent calcium pump

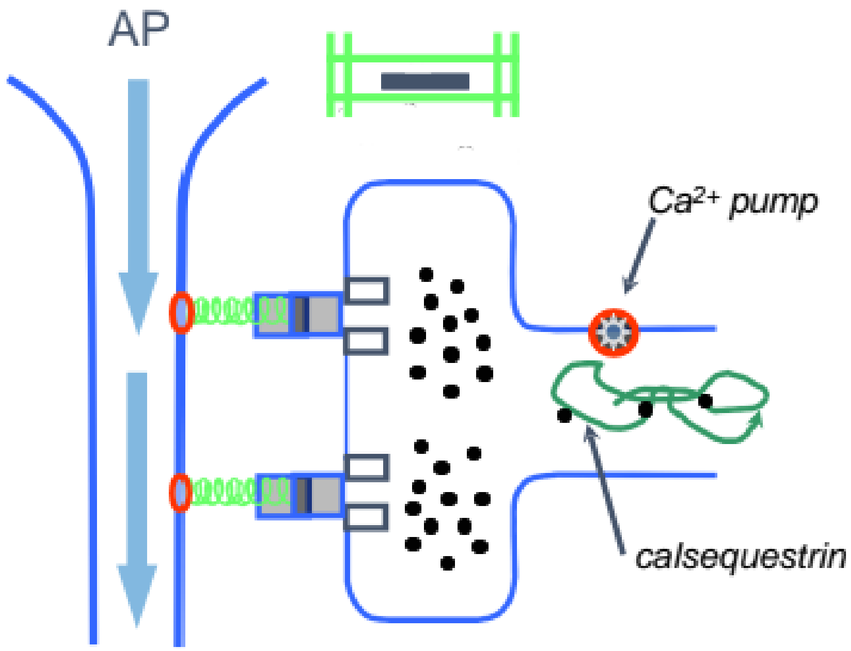


EC Coupling — *how it works*

(skeletal muscle

Sequence of Events:

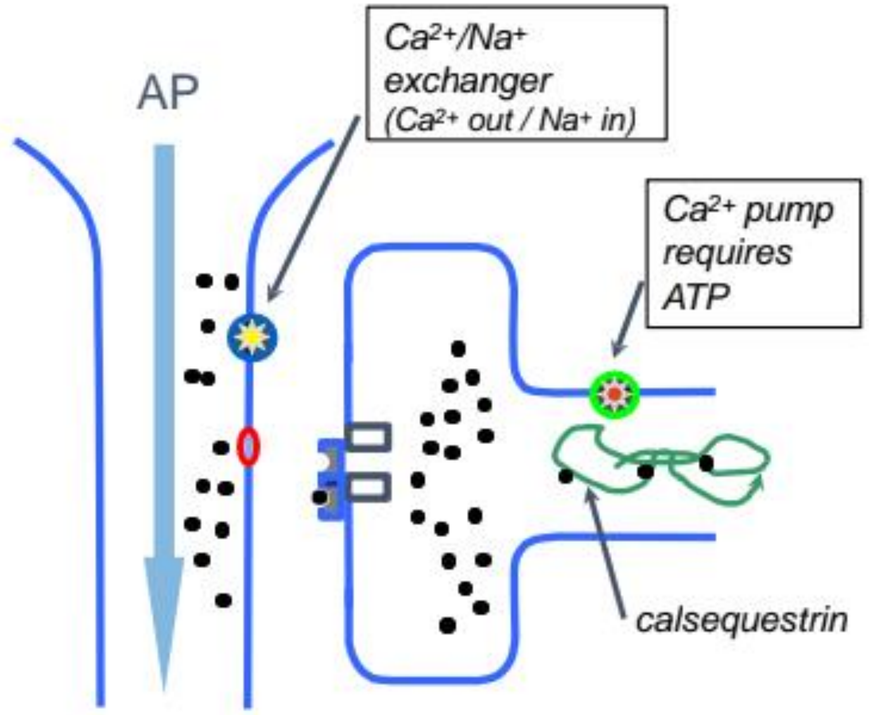
1. AP moves along T-tubule
2. The voltage change is sensed by the DHP receptor
3. is communicated to the ryanodine receptor which opens. ***(VACR)***
4. Contraction occurs
5. Calcium is pumped back into SR. Calcium binds to calsequestrin to facilitate storage.
6. Contraction is terminated.



EC Coupling – *how it works (skeletal muscle)*

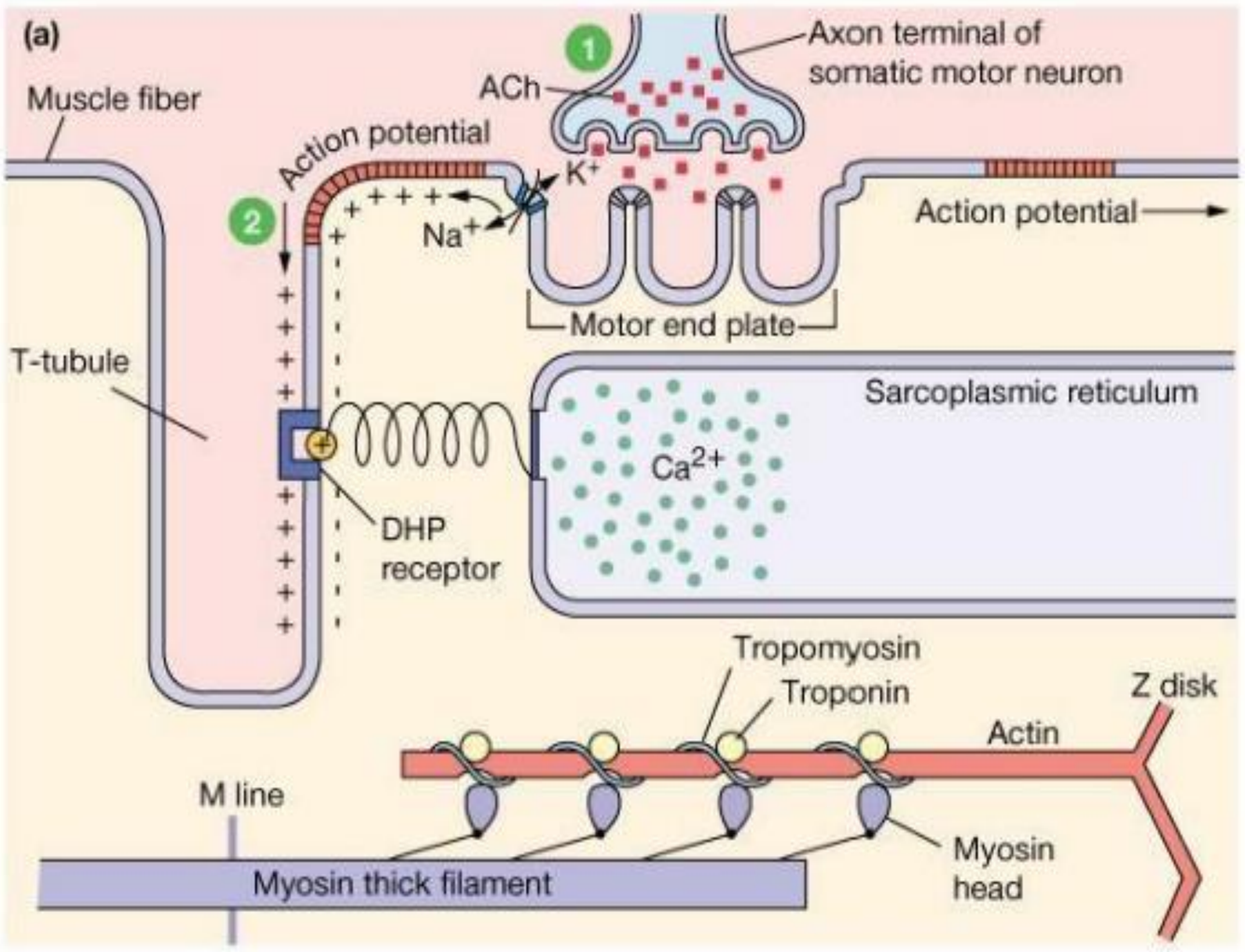
Sequence of Events:

1. AP moves along T-tubule
2. Activation of DHP receptors – voltage sensors that release a small amount of Ca into the fiber.
3. Ca then binds to the ryanodine receptor which opens, releasing a large amount of Ca. *(CACR)*
4. Calcium is pumped (a) back into SR, and (b) back into T tubule.
5. Contraction is terminated.



ملخص لكل ما سبق

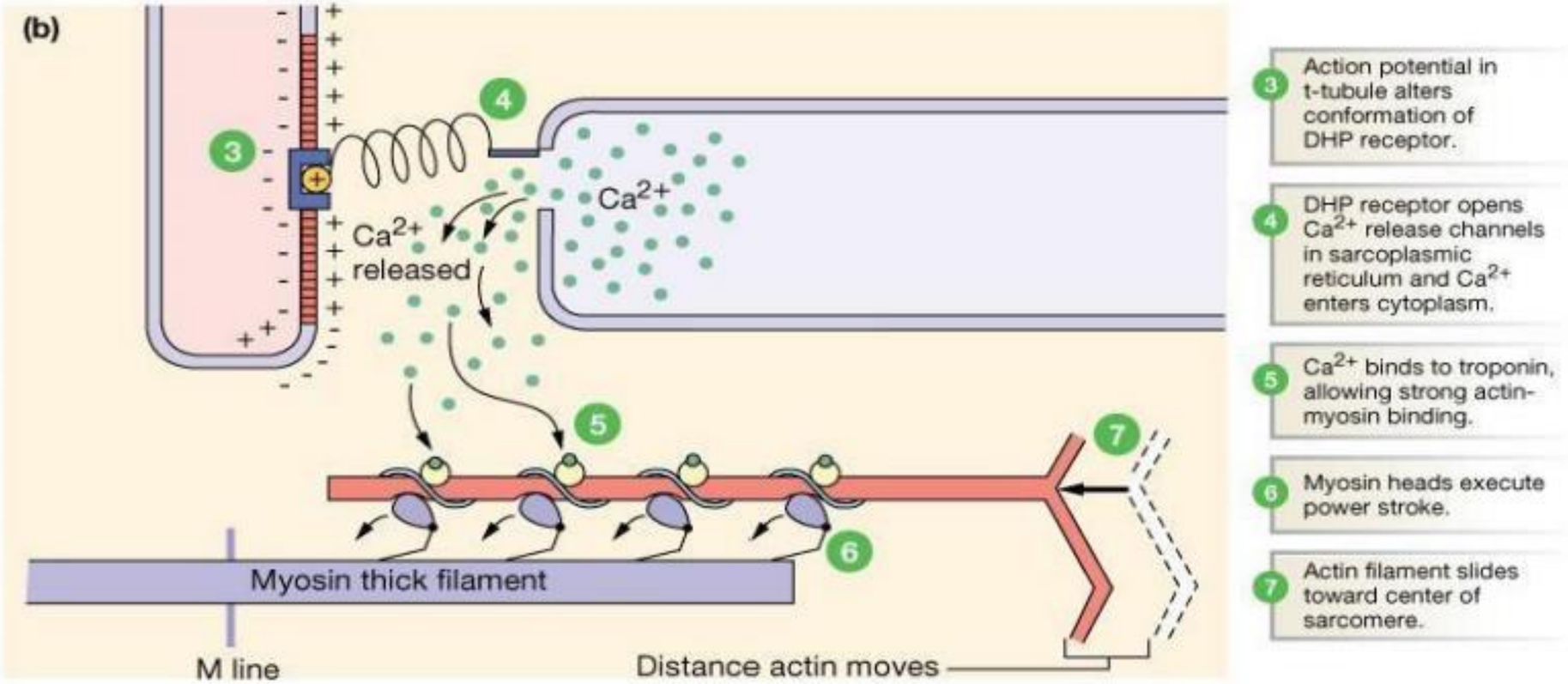
Excitation contraction coupling summary



1. Somatic motor neuron releases ACh at neuro-muscular junction.

2. Net entry of Na^+ through ACh receptor-channel initiates a muscle action potential.

Excitation contraction coupling summary



مو مهم تفاصيل المرض

Myasthenia Gravis

symptoms:

- paralysis - lethal in extreme cases when respiratory muscles are involved
-

Cause:

- autoimmune disease characterized by the presence of antibodies against the nicotinic ACh receptor which damages or destroys them
- weak end plate potentials

Treatment:

- usually ameliorated by anti-AChE (neostigmine)
- increases amount of ACh in nmj

السؤال الي ممكن يجي بالامتحان...

The main primary cause of neuromuscular transmition in myasthenia Gravis is…?

ANS:- distraction / damage of Ach receptors due to autoimmune disease

مو مطلوبة للامتحان

Malignant Hyperthermia

Symptoms:

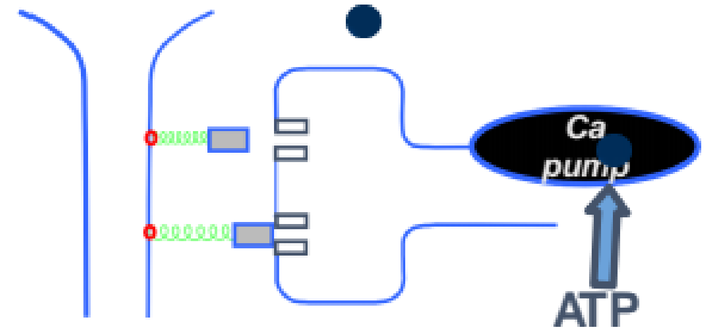
- increased body temperature
- skeletal muscle rigidity
- lactic acidosis *(hypermetabolism)*

Cause:

- triggered by halogenated anesthetics (isoflurane, halothane)
- familial tendency - can be tested for by muscle biopsy
- constant leak of SR Ca^{2+} through ryanodine receptor

Why is so much heat generated?

Ans: our bodies are only about 45% energy efficient, 55% of the energy appears as heat.



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#النادي_الطبي
#معكم_خطوة_بخطوة