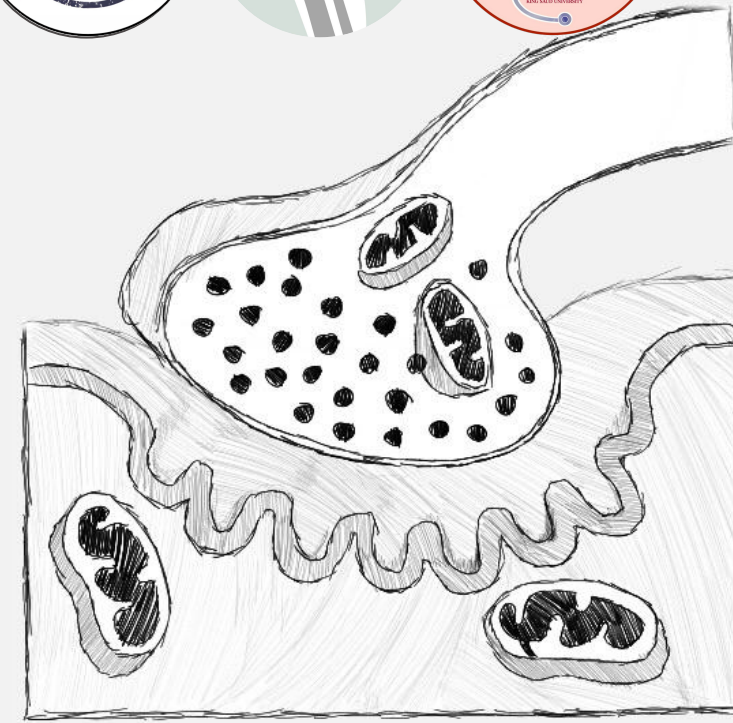
Editing File

Neuromuscular Transmission



Color Index:
-Main Text -Important -Notes
-Boy Slides -Girl Slides -Extra

Ty to Hasan Alsugahyir for sketch (MED445 inshallah) <3

Objectives

01 The physiologic anatomy of the skeletal muscle and NM junction.1

02 The general mechanism of skeletal muscle contraction.

03 Motor End Plate potential and how action potential and excitation-contraction coupling are generated in skeletal muscle.

04 The molecular mechanism of skeletal muscle contraction & relaxation.

05 Sliding filament mechanism.

06 Drugs/ diseases affecting the neuromuscular transmission.

Chemical Signals

Female Slides Only

One neuron will transmit info to another neuron or to a muscle or gland cell by releasing neurotransmitters (chemicals).

Synapse: the site of chemical interplay (where neurons release neurotransmitters to transmit info).

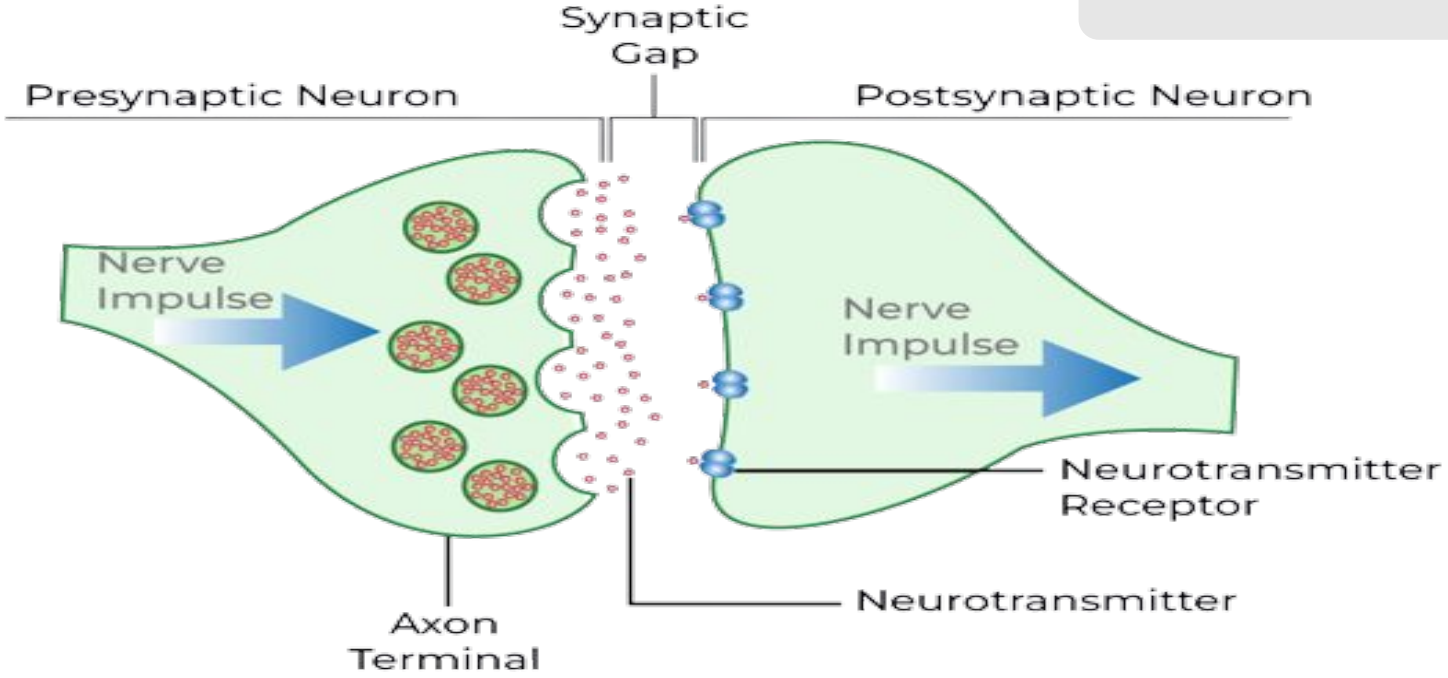
Synaptic knob: axon terminal. (End of neuron)

★ Synaptic knob will abut (be adjacent/next to) another cell, a neuron, muscle fiber, or gland cell.

Transduction: Is the process of conversion of an electrical signal into a chemical signal.

★ Transduction site: synapse

💡Extra Image for clarification

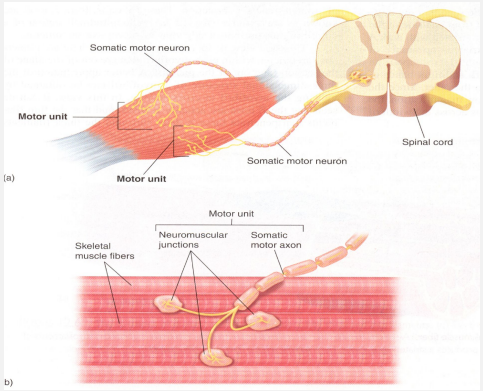


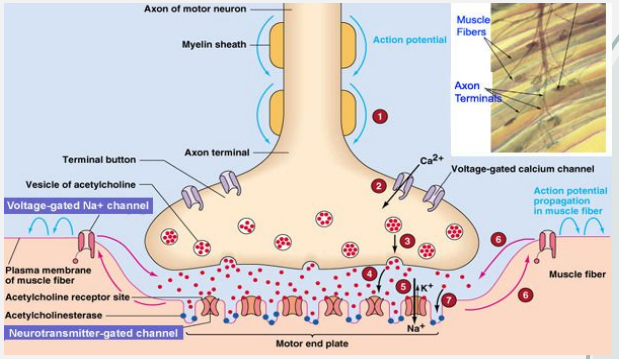
Neuromuscular transmission

Neuromuscular Junction (NMJ) and its components

Transmission of impulses from nerve endings to skeletal muscle fibers occurs via: **neuromuscular junction** (NMJ). Its composed of :

- ★ Motor End Plate (MEP)
- ★ Synaptic space/cleft
- ★ Presynaptic terminal (in neuron)
- ★ Postsynaptic terminal (in muscle)
- ★ Acetylcholine (Ach)
- ★ Synaptic vesicles (Ach vesicle)
- ★ Synaptic trough/gutter
- ★ Subneural cleft
- ★ Acetylcholinesterase
- ★ Ach Receptors





439:
Neuromuscular Junction: a chemical synapse formed by the contact between a motor neuron & a muscle fiber (part of a motor unit).
Motor Unit: motor neuron + muscle fibers it innervates

Female Slides Only

Motor End Plate

Entire structure of axon terminal, synaptic cleft & synaptic gutter

Synaptic Gutter: The muscle's cell membrane which is in contact with the nerve (axon) terminal.

- Has subneural clefts.

Subneural Clefts: many folds in the synaptic gutter.

- Ach receptors are located here.
- Greatly increase surface area → allow accommodation of large numbers of Ach receptors.

Synaptic Cleft: 20 – 30 nm space between axon terminal & muscle cell membrane.

- Contains cholinesterase (enzyme) → can destroy Ach.

Axon terminal: contains around 300,000 vesicles which contain the neurotransmitter acetylcholine (Ach).

Acetylcholine

Female Slides Only

01 Ach synthesized locally in the cytoplasm of the nerve terminal, from active acetate (acetyl coenzyme A) + choline.

02 Then Ach is rapidly absorbed into the synaptic vesicles and stored there.

03 Synaptic vesicles are made by Golgi Apparatus in the nerve soma (cell body).

04 Synaptic vesicles are carried by **axoplasmic transport** to the nerve terminal (contains around 300,000 vesicles).

05 Each vesicle is filled with around 10,000 Ach molecules.

How is ACH released?

- ★ 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.

Effect of Ach on the Postsynaptic Muscle Membrane

Important Slide

01 Ach combines with its receptors in the subneural clefts. Two molecules of Ach must attach to the receptor.

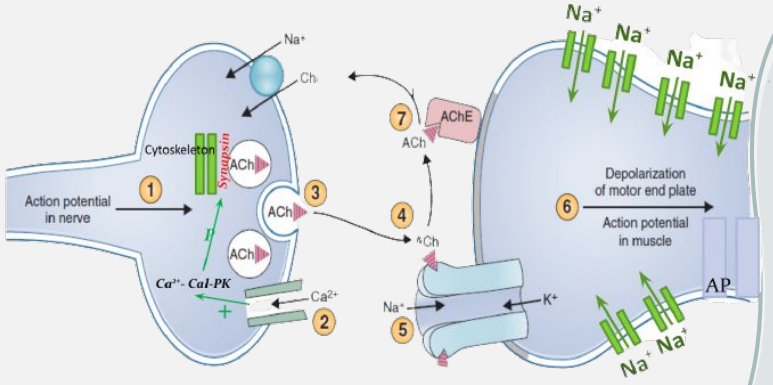
02 Sodium (Ach) channels open → Na^+, Ca^{++}, or K^+ ions to move through easily. But not -ve ions (e.g. Cl^-).

03 Na^+ diffuses into the muscle (More Na^+ ions will pass through which creates a local positive potential change inside the muscle fiber membrane) → End-Plate Potential (EPP - local, non-propagated potential)

04 EPP triggers a muscle AP which spreads down inside the muscle fiber membrane → it contracts.

05 Ach is hydrolyzed by Acetylcholinesterase / cholinesterase (enzyme) into Acetate + Choline.
Choline → is actively reabsorbed into the nerve terminal (used again to form Ach) This whole process of Ach release, action & destruction takes about 5-10 ms .

*When Ach-gated channels open → sudden influx of Na^+ → increase electrical potential in +ve direction (50 -75 mV) → local EPP created → voltage gated Na^+ channels will open.



This slide is a combination of female & male slides but all what is said is important for understanding

Summary of Neuromuscular transmission

01 First we must have AP (cell +inside, -outside) .

02 AP stimulates opening of voltage gated Ca channels (Ca enters the nerve cell). *Normally: Ca is higher in the ECF. => Ca passes from high to low conc.

03 Ca adds wheels to Ach vesicles (docking).

04 Ach vesicles go to synaptic knob, exocytosis happens.

05 Ach binds with its ACH nicotinic receptors on the muscle membrane

01 Conformational changes of Ach receptors => ligand (chemical) gated channels open (receptors open, they have - charge).

02 Na enters the muscle cell (because of - charge of opened receptors). => decreasing negativity

03 now muscle cell is +inside, -outside (EPP happens)

EPP is not AP because:
1-it's not "All or none".
2-it doesn't propagate.
3-summation is possible.
4-it depends on number of opened receptors, number of Na that enters, ...

04 if EPP is big enough => AP transmits through the muscle cell

05 ACH is degraded by acetylcholinesterase. *If we want action to continue, we must have new AP + new Ach.

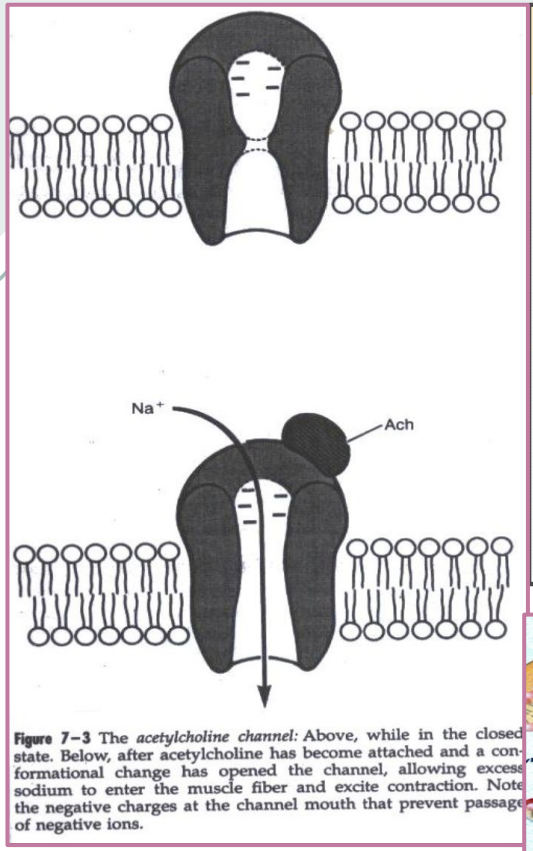


Figure 7–3 The *acetylcholine channel:* Above, while in the closed state. Below, after acetylcholine has become attached and a conformational change has opened the channel, allowing excess sodium to enter the muscle fiber and excite contraction. Note the negative charges at the channel mouth that prevent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

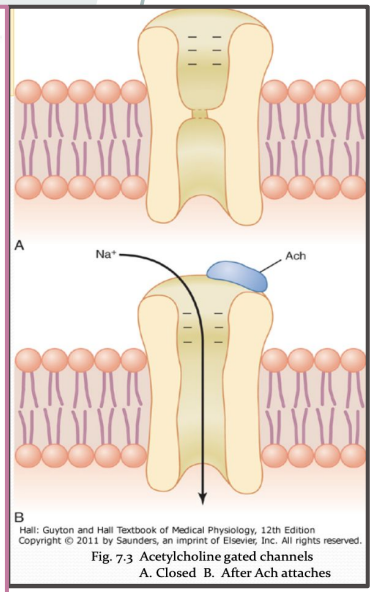
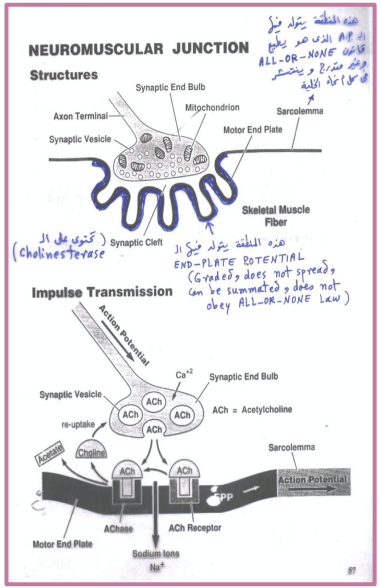
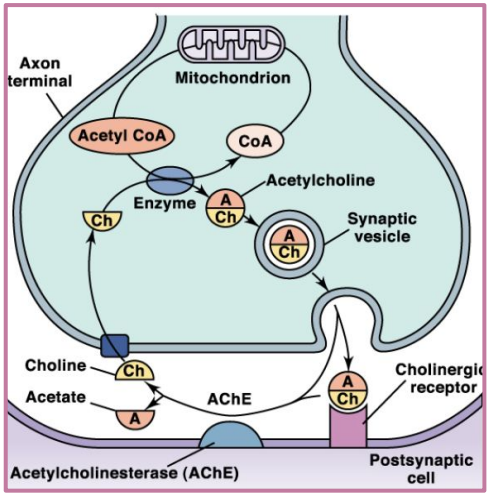
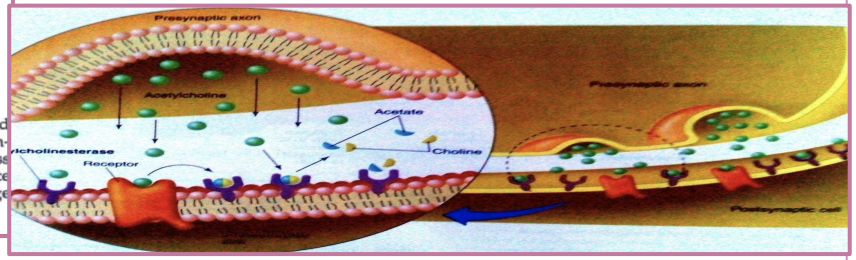
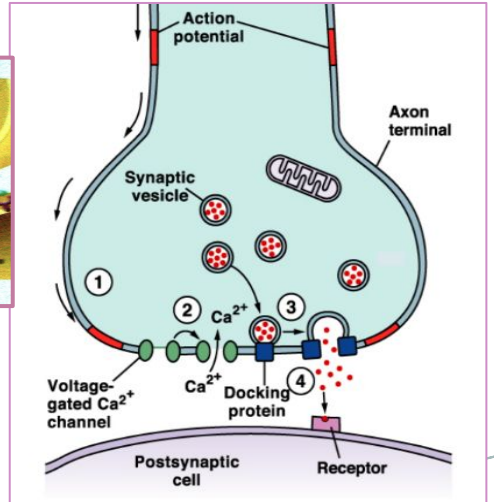


Fig. 7.3 Acetylcholine gated channels
A. Closed B. After Ach attaches







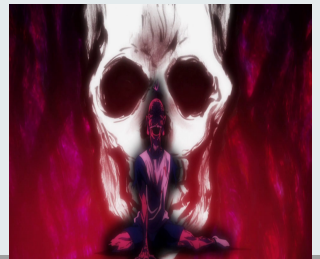


Illustrative pictures from slides

Muscle Action Potential

	Skeletal Muscle	**Large Nerves**
Resting Membrane Potential	-80 to -90 mV	-80 to -90 mV
Duration of the Action Potential	Lasts 1 - 5 msec	Lasts 0.2 - 1 msec
Velocity of Conduction	3 - 5 m/sec	39 - 65 m/sec

ليش العصب أسرع؟ لان فيه Myelin

Drugs that Enhance Transmission at the neuromuscular junction (Cause muscle contraction)	Drugs that Stimulate the muscle fiber by Ach-like action:	Methacholine	- They act for minutes or hours - Not destructed by cholinesterase
		Carbachol	
		Nicotine.	
	Drugs that Stimulate the NMJ by Inactivating Acetylcholinesterase توقف الانزيم الي يكسر Ach. الي هو Acetylcholinesterase	Neostigmine	They inactivate acetylcholinesterase for several hours
		Physostigmine	
		Diisopropyl fluorophosphate (nerve gas poison) 	- They inactivate acetylcholinesterase for weeks - Can cause death because of respiratory muscle spasm - Was used in wars

Drugs that Block Transmission at the neuromuscular junction (Cause muscle Relaxation)	Curare	Prevent passage of impulses from the nerve ending into the muscle by blocking the action of Ach on its receptors on MEP. *act by competitive inhibition to Ach at its receptors & can not cause Depolarization
	Curariform like-drugs	
	Botulinum toxin	Bacterial poison that decreases the quantity of Ach release by the nerve presynaptic terminals. *Females' Dr: Botox (botulinum toxin) prevents Ach release, muscles are relaxed

Myasthenia-Gravis Disease

Definition

- An autoimmune disease /disorder usually in adult females.
- Patients develop antibodies against their own Ach receptors (block/destroy their own ACH receptors) → decreased/unformed EPP → weakness/paralysis of muscles (depends on severity of disease).
- EPP are too small to initiate opening of voltage-gated Na+ channels → no AP → muscles can't contract.
- Occurs in 1/20,000 persons.
- Patients have 20% of Ach receptors.

اذا مثلا الشخص الطبيعي معه 100 بيكون عند الشخص المريض 20

Symptoms

- Ptosis (drooping eyelid)
- Dysarthria (difficulty speaking)
- Dysphagia (difficulty swallowing)
- Proximal limb weakness in hands & feet.

Affects: eyelids - extraocular bulbar - proximal limb muscles.

- Muscle weakness from NMJ inability to transmit enough signals from nerve fibers to muscle fibers.
- Patient may die from respiratory failure (from respiratory muscle paralysis) (Females' DR: laryngeal spasm).

Treatment

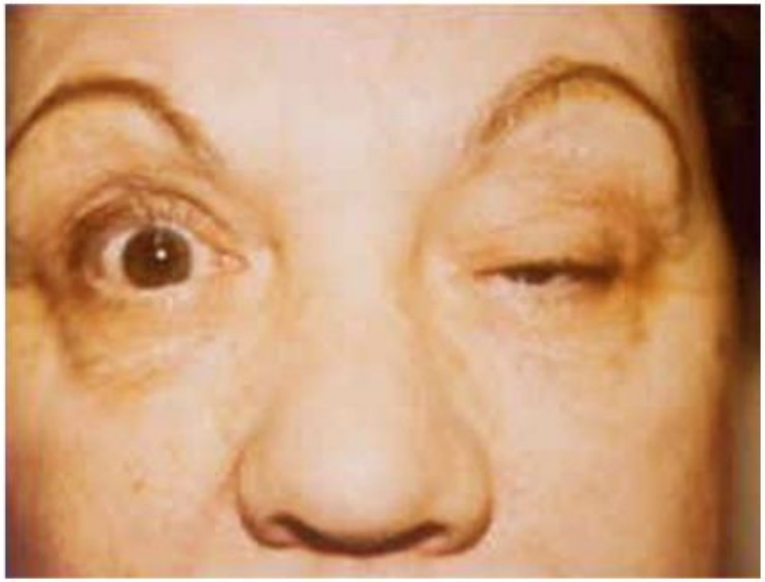
Anti-cholinesterase drugs (eg: Neostigmine)

- These Drugs inactivate cholinesterase (destroy Ach) → allows large amounts of Ach to accumulate in the synaptic space
- → act on remaining healthy receptors → good EPP formed →muscle contraction.
- **Corticosteroids** and **immunosuppressant** drugs inhibit the immune system, limiting antibody production.

عشان نعوض النقص بالرسبتر راح نراكم Ach

Myasthenia-Gravis Disease

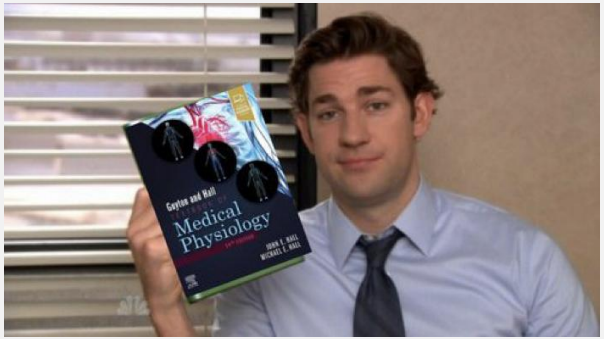
Facial muscle weakness



Ptosis

You can find the pages related to this lecture from (Guyton) here

Note: Guyton has extra information that might not be with us, but if you want to learn more about the topic make sure to check it out :3



Thanks to team 443 <3

MCQs

Q1:1-Transduction is:			
A-conversion of chemical signal to electrical signal	B-transmission of nerve endings to skeletal muscle fiber	C-conversion of electrical signal to chemical signal	D-end of nerve
Q2-One nerve impulse can release:			
A-125 Ach vesicles	B-10,000 Ach vesicles	C-300,000 Ach vesicles	D-100,000 Ach vesicles
Q3-Ach is synthesized by..... in nerve terminal:			
A-cell membrane	B-cytoplasm	C-endoplasmic reticulum	D-golgi apparatus
Q4:Synaptic vesicles are made by:			
A-cell membrane	B-cytoplasm	C-cytoplasm	D-golgi apparatus

Answers:
1.C
2.A
3.B
4.D

SAQs

Q1: What is a Neuromuscular junction?

A1: it is where the transmission of impulses from nerve
endings to skeletal muscle fibers occurs.

Q2: What is the difference between EPP and AP?

A2:EPP: doesn't propagate or spread (is local) - is graded
- can be summated - does not obey ALL-OR-NONE law.
AP: does spread throughout the whole cell - not graded
- obeys ALL-OR-NONE law.

Q3: What is the effect of Ach on the postsynaptic muscle membrane?

A3: slide 8

Ahmad Addas

Nawaf Alshalan

Fawaz Almadi

Khalid Alkanhal

Abdulrahman Khaldi

Khalid Alghamdi

Talal Alrobaian

Abdullah Muhnna

Zyad Alshuhail

Ibrahim Al Bin Ali

physiology.444ksu@gmail.com

Mays Ahmed

Alanoud Alnajawi

Joud Binkhamis

Shaden Alshammari

Lama Almoutairi

Leena Shagrani

Marwah Fal

Rahaf Mohammed

Huda Bassam

Aram Alzahrani

Noor Altalag