GENERAL PHYSIOLOGY
(LECTURE 14)

Neuromuscular Junction (NMJ)

By

Dr. Fatma Farrag Ali

Associate Professor of Medical Physiology

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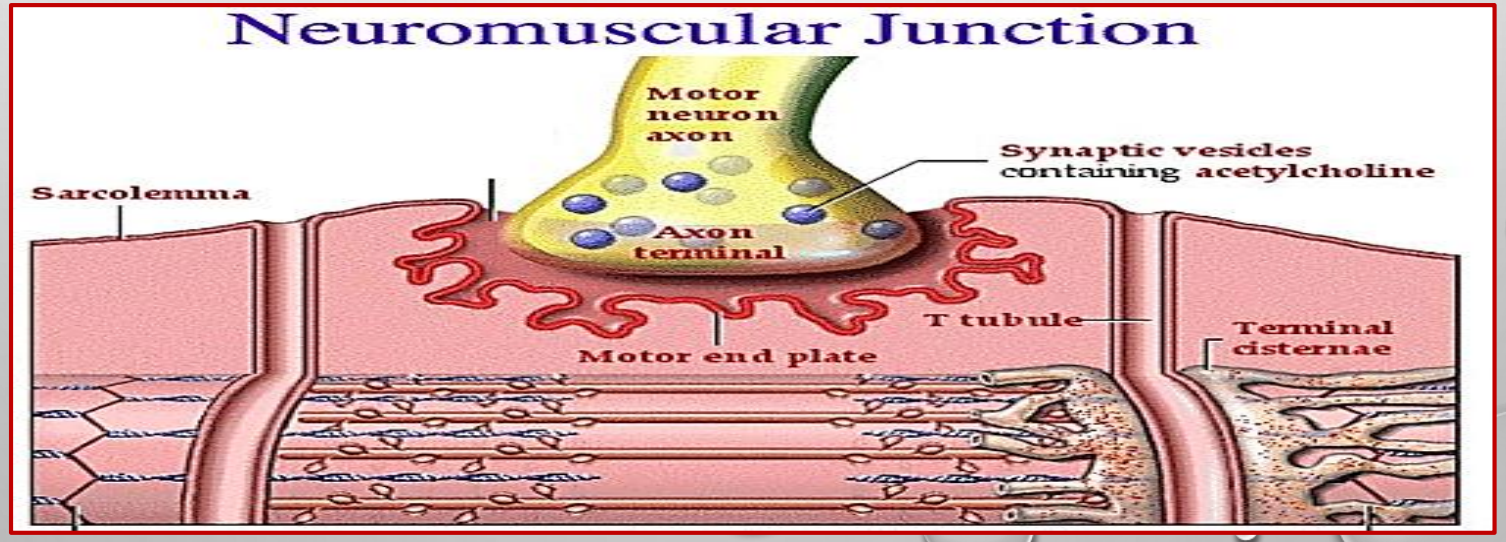
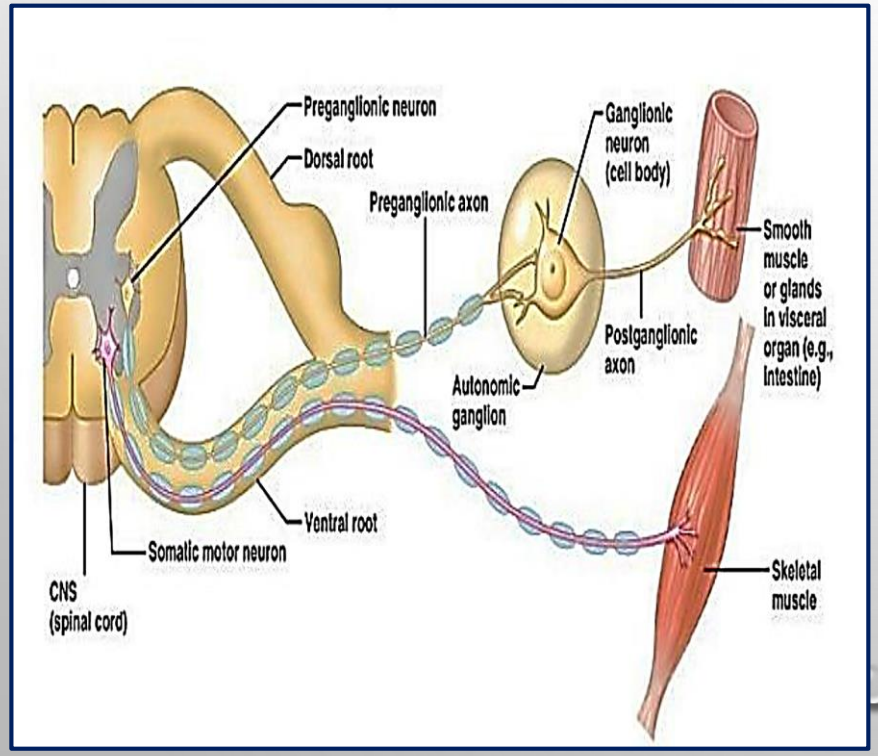
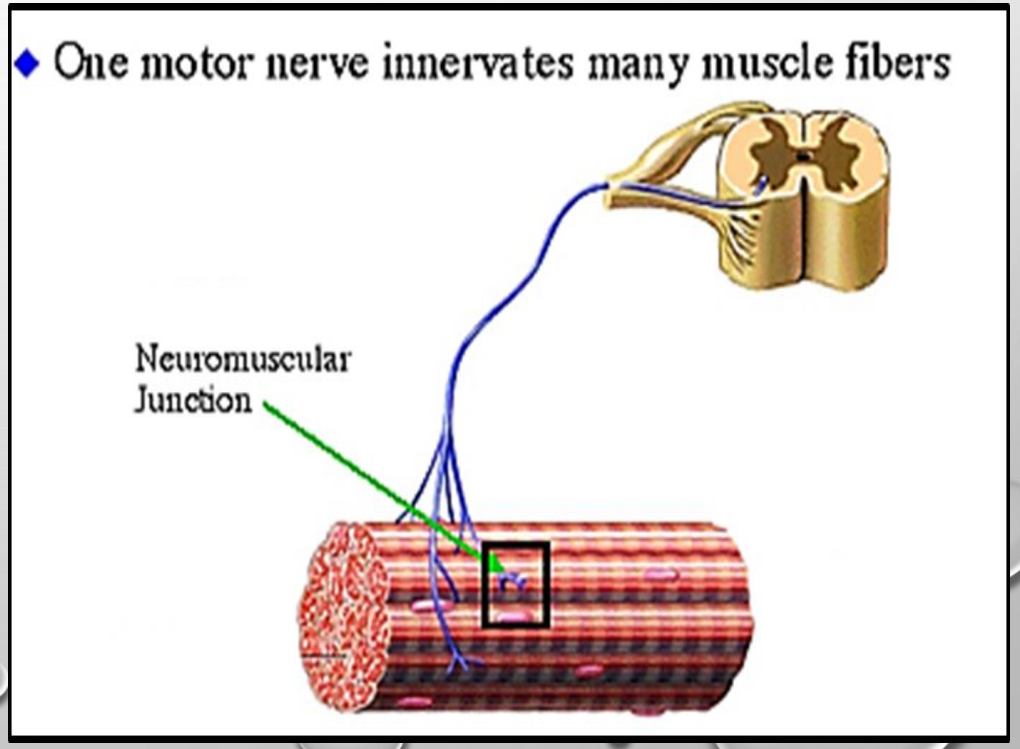


- The skeletal muscle fibers are innervated by large, myelinated nerve fibers (somatic nerves) that originate from large motor neurons in the anterior horns of the spinal cord.

- Each nerve fiber, after entering the muscle belly, normally branches and stimulates from three to several hundred skeletal muscle fibers. Each nerve ending makes a junction, called the **neuromuscular junction**, with the muscle fiber near its midpoint.

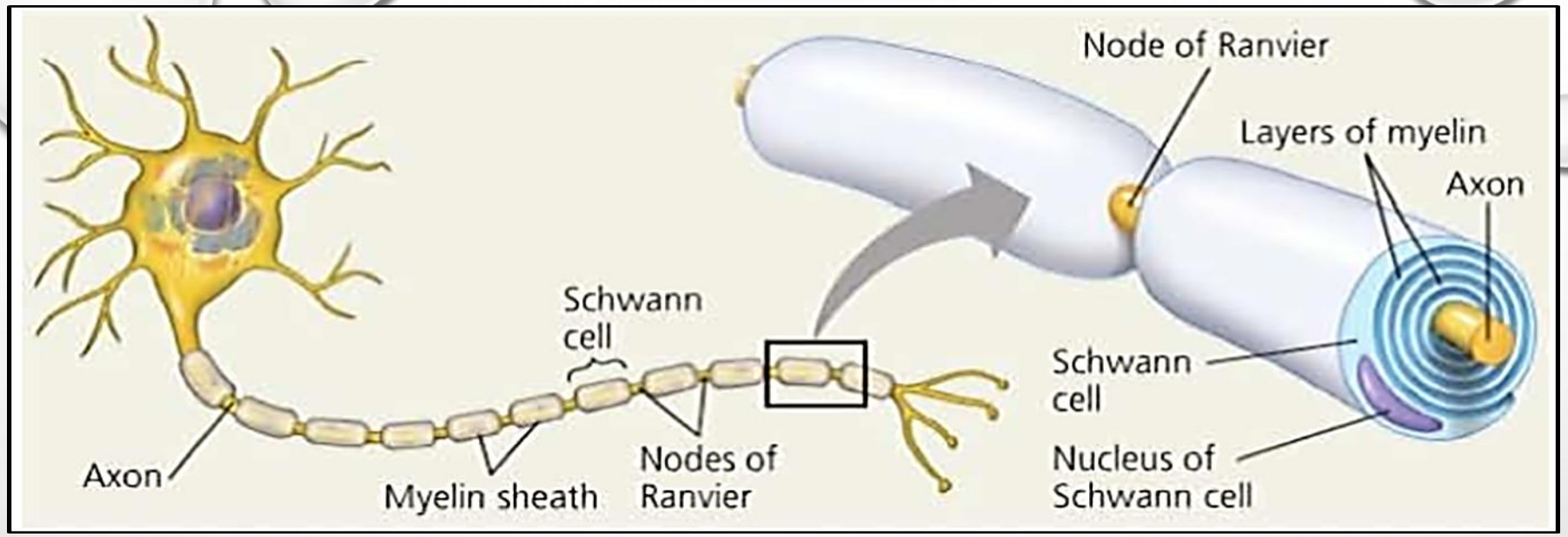


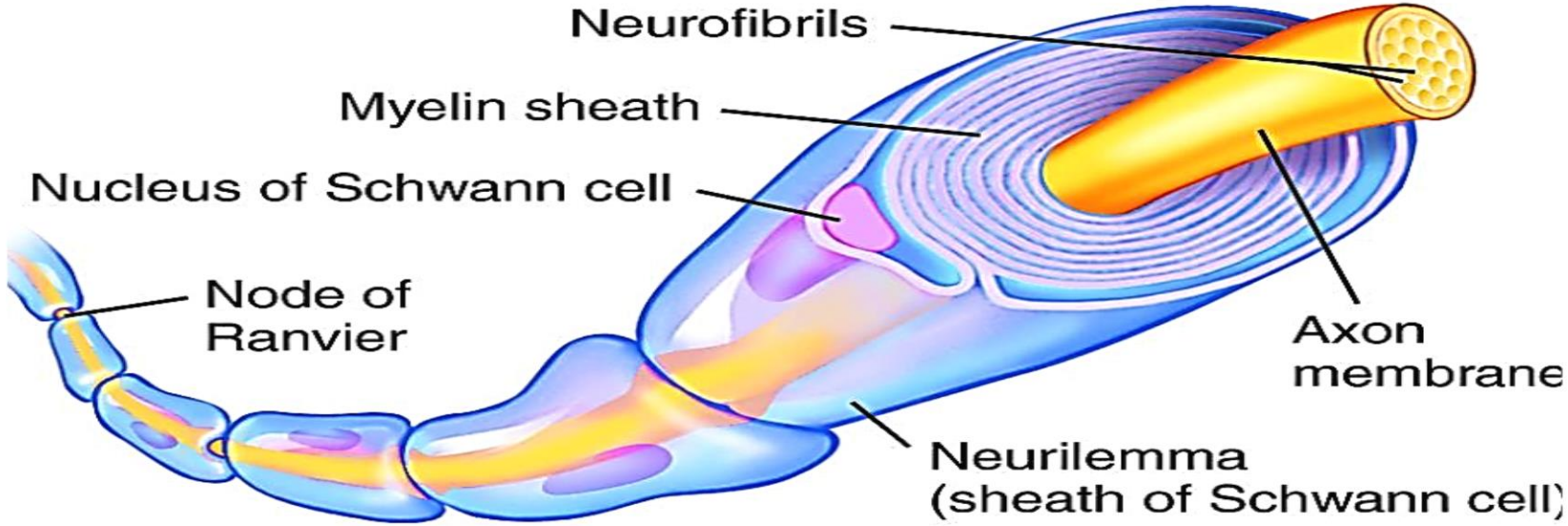


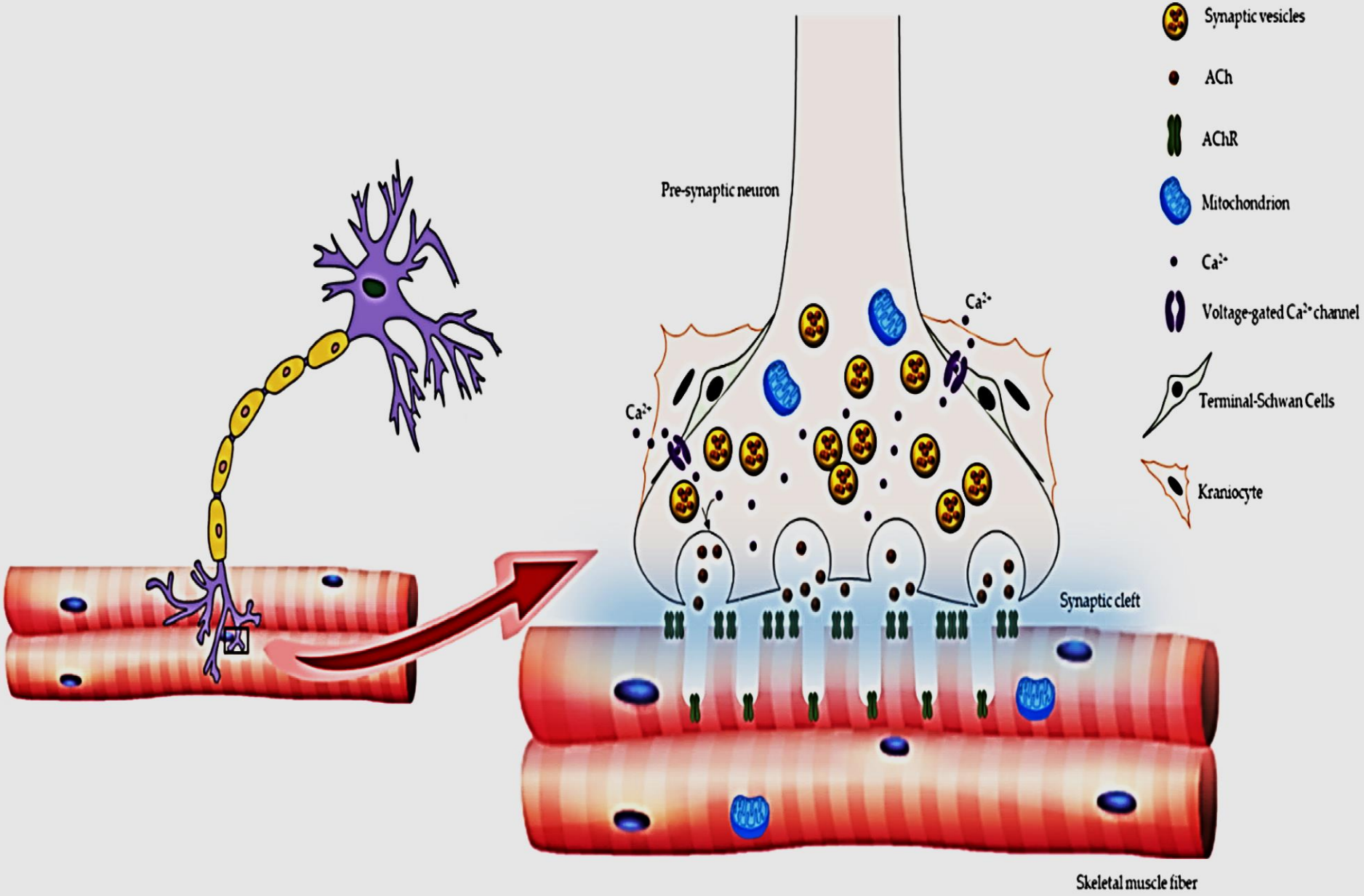
PHYSIOLOGICAL ANATOMY of NEUROMUSCULAR JUNCTION (NMJ) or MOTOR END PLATE (MEP)

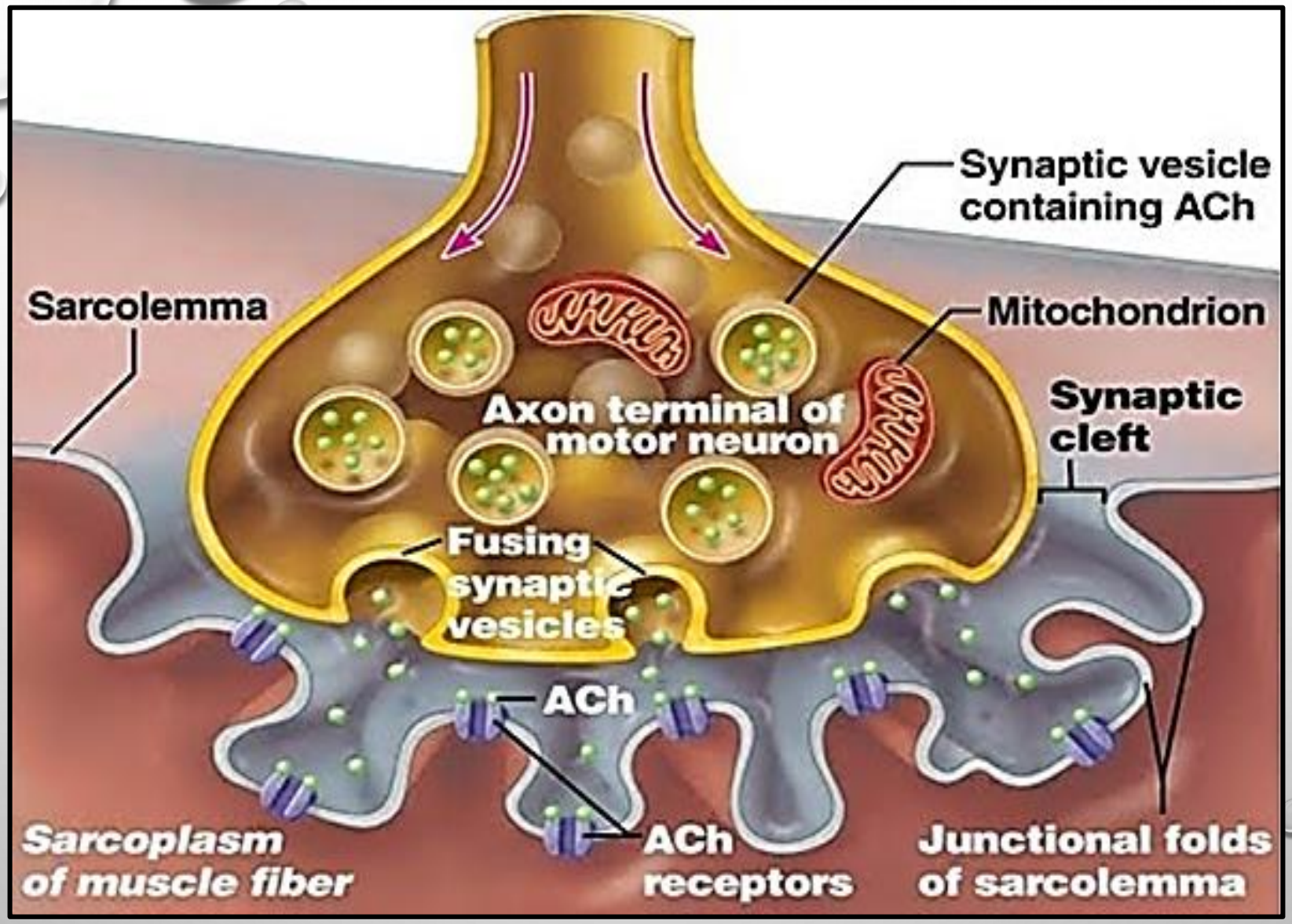
- **NMJ** or **MEP** is the area of **contact** between the nerve fiber and the muscle fiber.
- At the **MEP**, the neurilemma **becomes** continuous with the sarcolemma and the nerve axon **loses** its myelin sheath and breaks into several terminal branches.
- The space between the sole feet and the sarcolemma is called the **synaptic cleft.**
- The **neuron** is **considered** to be the **presynaptic cell** and the **muscle** cell is the **postsynaptic cell.**

- The presynaptic nerve terminal contains **vesicles** that contain the **neurotransmitter**; **acetylcholine (Ach)** and **mitochondria** necessary for its synthesis.
- The sides of the **presynaptic membrane** contain **voltage-gated Ca^{++} channels.**
- **Acetylcholinesterase** (**true**) which degrades ACh into acetate and choline is found in the **synaptic cleft.**
- The **postsynaptic membrane** of the muscle contains numerous **ACh receptors (nicotinic receptors) (ACh ligand - gated ion channels).**


Node of Ranvier
Layers of myelin
Axon
Schwann cell
Schwann cell
Axon
Myelin sheath
Nodes of Ranvier
Nucleus of Schwann cell


Neurofibrils
Myelin sheath
Nucleus of Schwann cell
Node of Ranvier
Axon membrane
Neurilemma (sheath of Schwann cell)


Synaptic vesicles
ACh
AChR
Mitochondrion
Ca2+
Voltage-gated Ca2+ channel
Terminal-Schwan Cells
Kraniocyte
Pre-synaptic neuron
Ca2+
Ca2+
Synaptic cleft
Skeletal muscle fiber

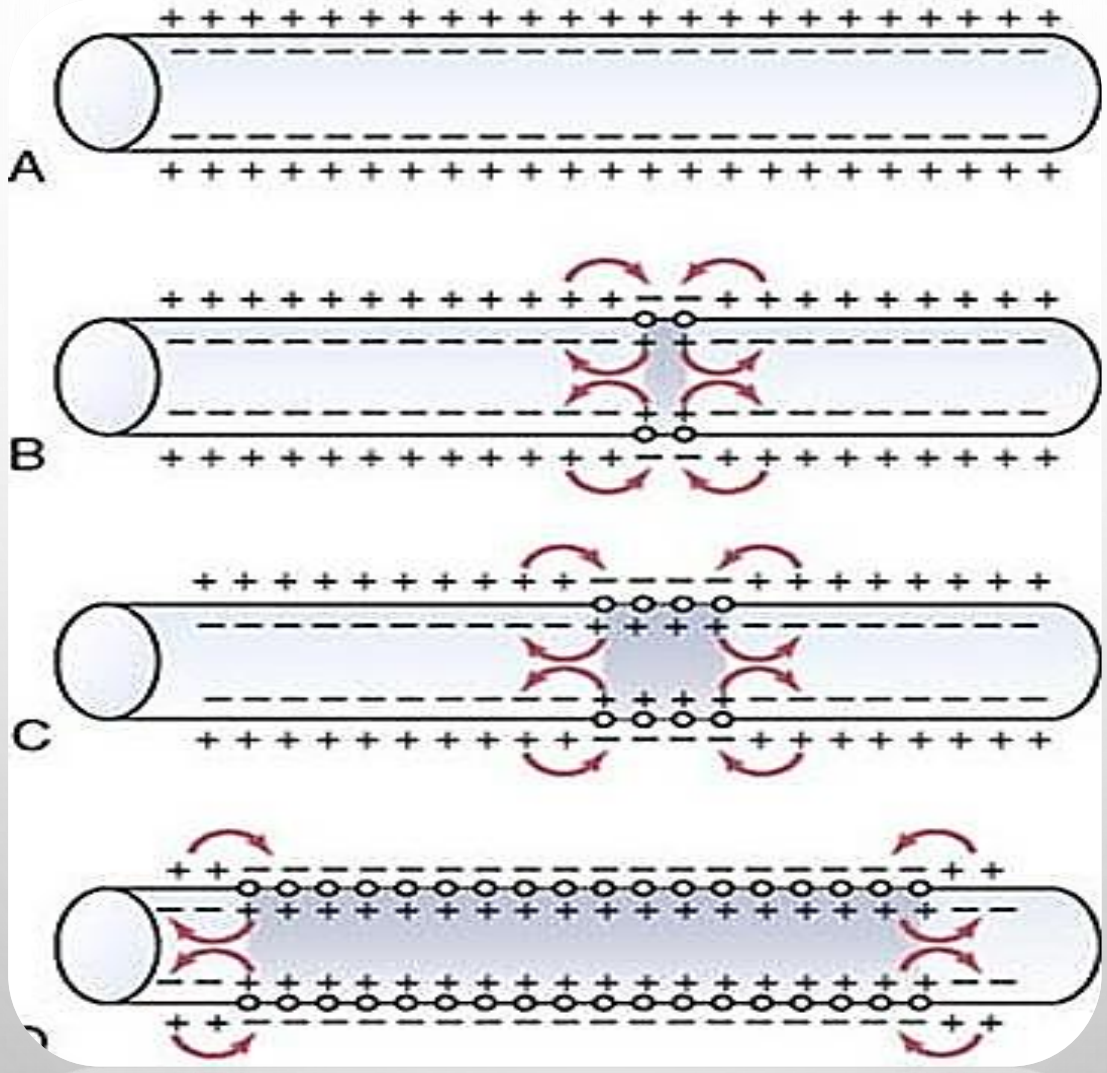

Synaptic vesicle containing ACh
Sarcolemma
Mitochondrion
Axon terminal of motor neuron
Synaptic cleft
Fusing synaptic vesicles
ACh
Sarcoplasm of muscle fiber
ACh receptors
Junctional folds of sarcolemma

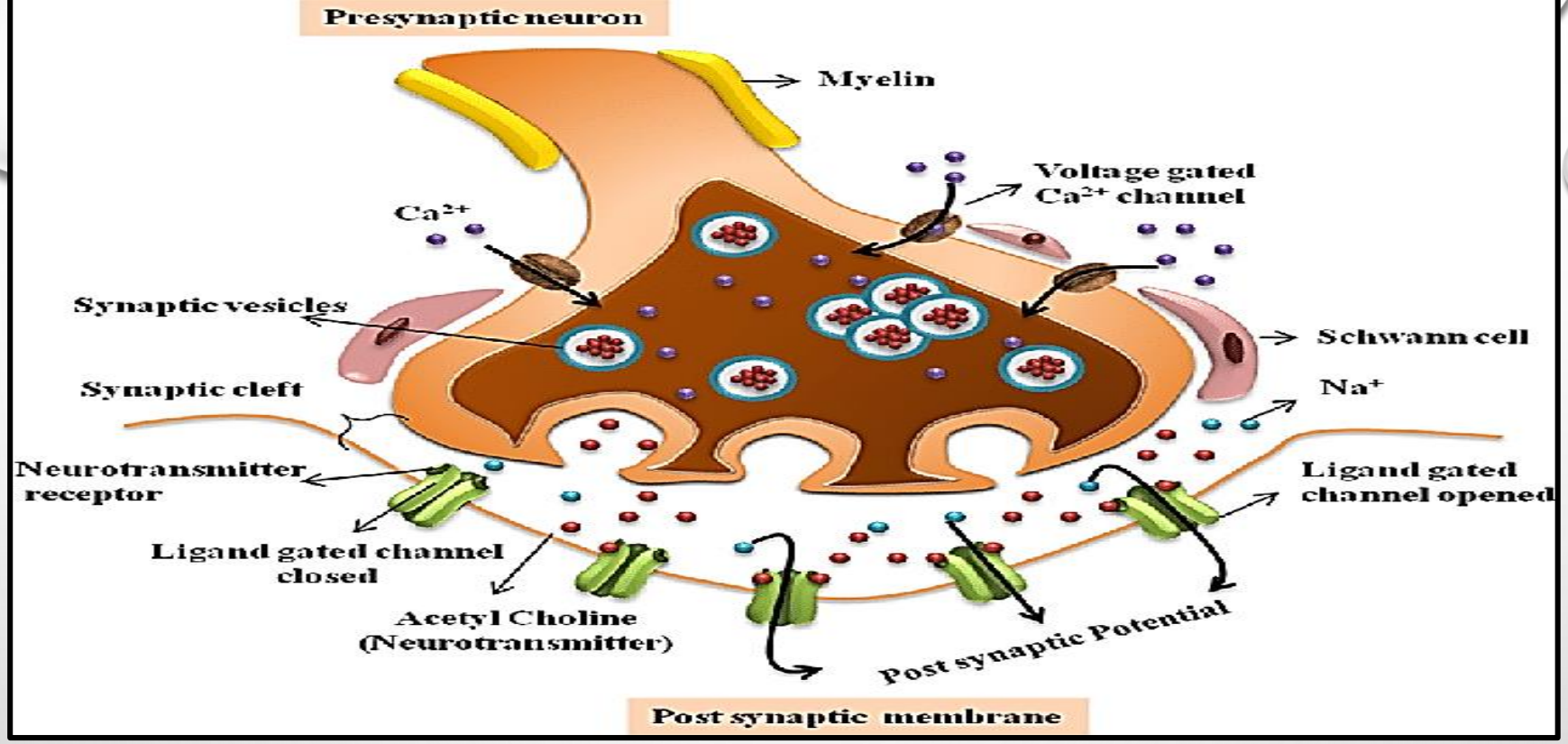
NEUROMUSCULAR TRANSMISSION (NMT)

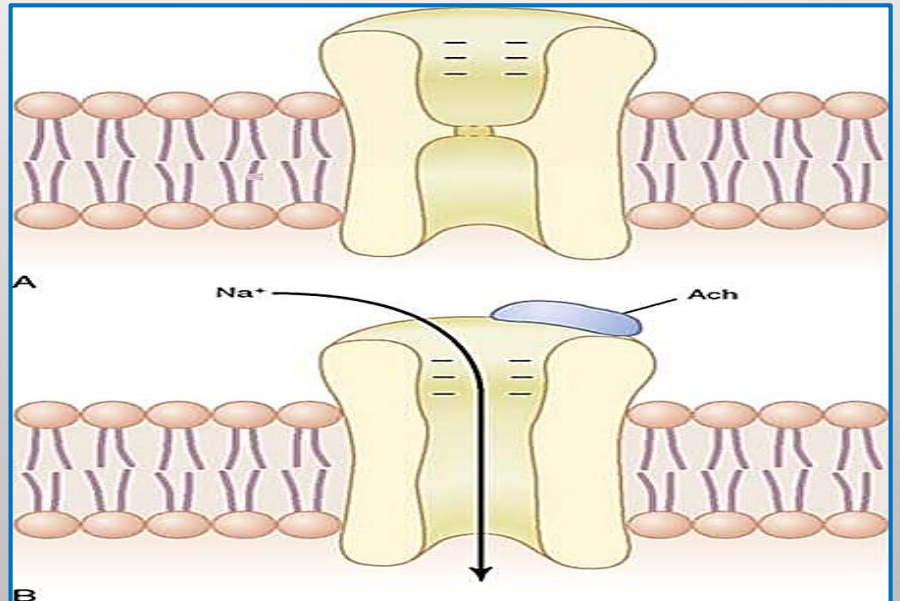
Definition: It means the transmission of the nerve impulse from the nerve to the muscle at the NMJ(MEP)

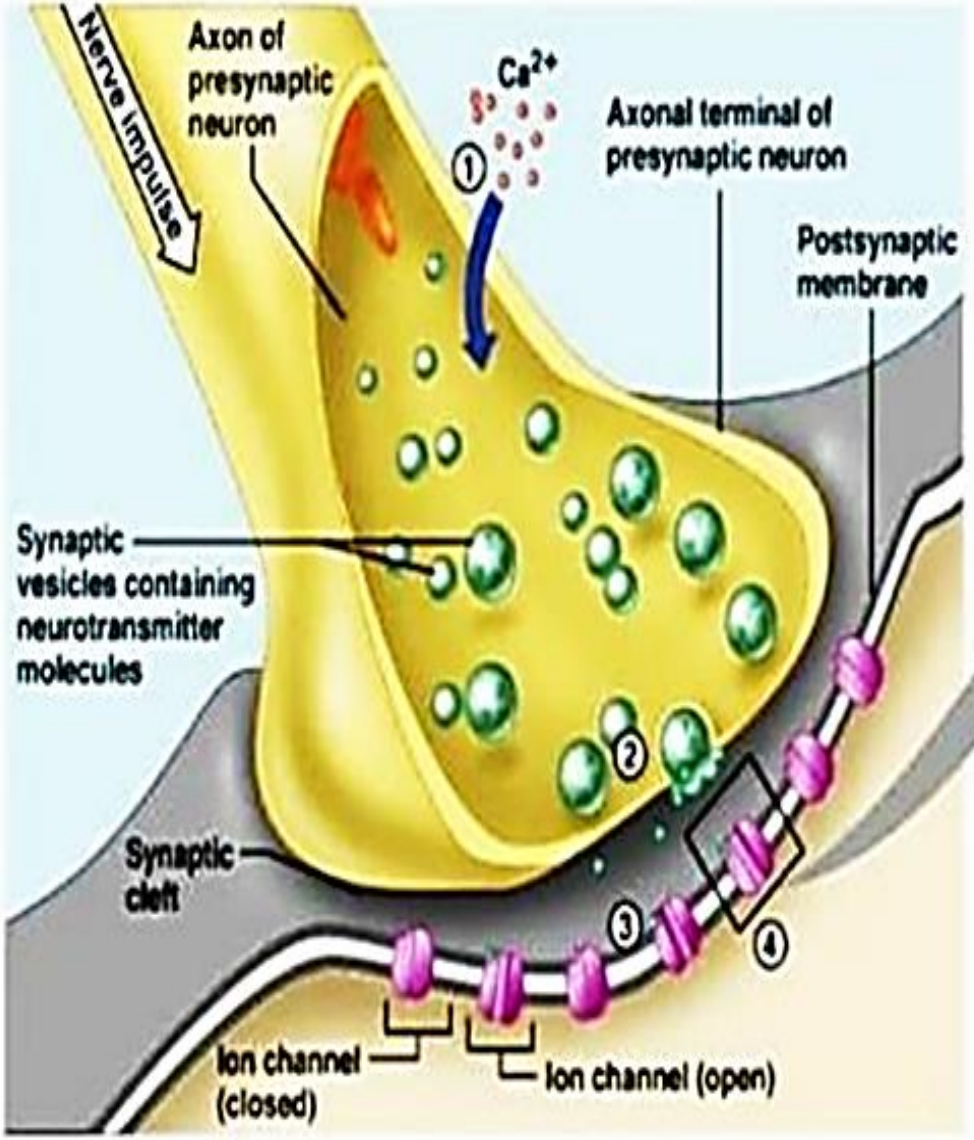
MECHANISM of NMT

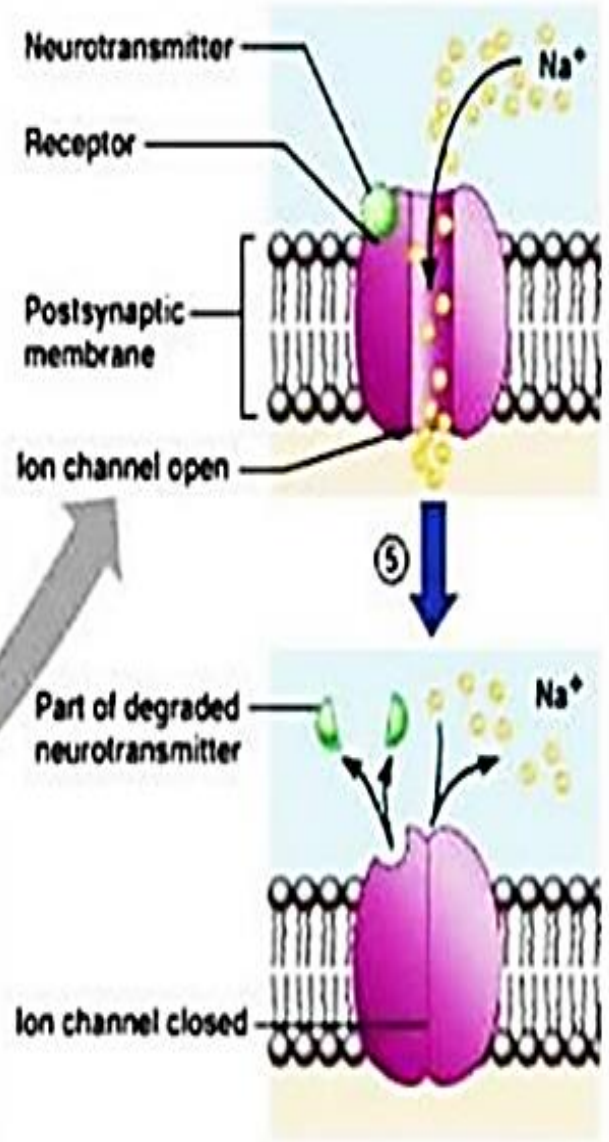
1. The **vesicles** at the axon terminal are loaded with **acetylcholine**.
2. **DEPOLARIZATION** of the nerve terminal at MEP: allows the entry of Ca^{2+} from the extra cellular fluid; ECF (through **voltage gated Ca^{2+} channels**).
3. The influx of Ca^{2+} → **translocation** of the vesicles to the presynaptic membrane → the vesicles contents (ACh) are released by **exocytosis** at the MEP.
4. **ACh crosses** the gap between the nerve terminal and the surface of the muscle (synaptic cleft) and **binds** with its receptors on the surface of the muscle.
5. This binding **increases** the sarcolemmal permeability to **Na^+** → Na^+ **influx** through **ligand-gated channels** → rapid depolarization called **End-Plate Potential** (i.e. **EPP**).
6. When the **EPP reaches the firing level**, an action potential; **AP** is generated at the MEP and **propagates** on either sides of the sarcolemma, as well as to the interior of the muscle fiber along the **T-tubules**.
7. The released Ach is rapidly hydrolyzed by cholinesterase enzyme so that re-excitation of the muscle wouldn't occur. The choline is reabsorbed actively in the nerve terminal to be reused to form new ACh.

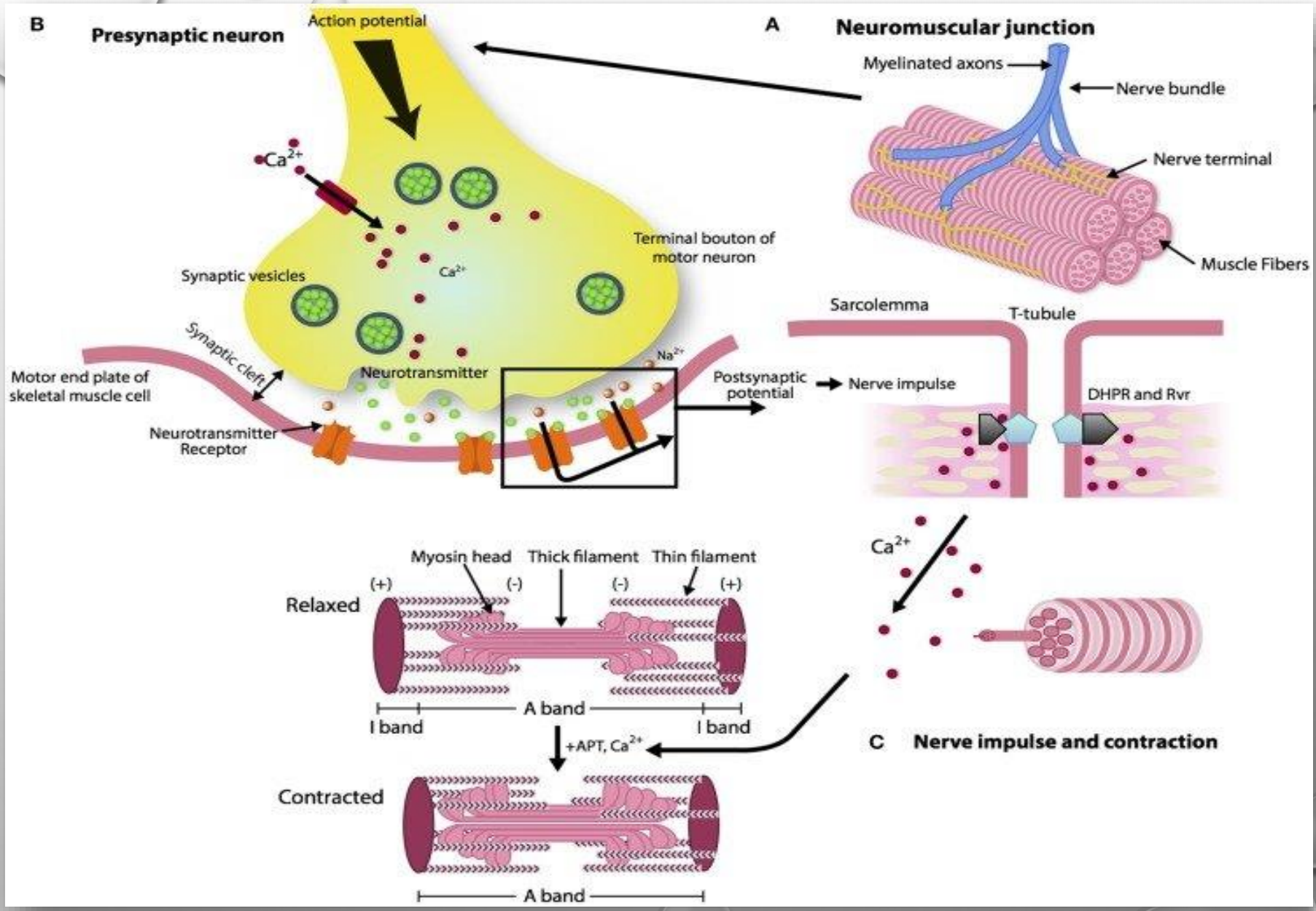

A
B
C


Presynaptic neuron
Myelin
Voltage gated
Ca2+ channel
Ca2+
Synaptic vesicles
Schwann cell
Synaptic cleft
Na+
Neurotransmitter
receptor
Ligand gated
channel opened
Ligand gated channel
closed
Acetyl Choline
(Neurotransmitter)
Post synaptic Potential
Post synaptic membrane


A
Na+
Ach
B


Nerve impulse
Axon of presynaptic neuron
Ca^{2+}
Axonal terminal of presynaptic neuron
Postsynaptic membrane
Synaptic vesicles containing neurotransmitter molecules
Synaptic cleft
Ion channel (closed)
Ion channel (open)
1
2
3
4


Neurotransmitter
Na^+
Receptor
Postsynaptic membrane
Ion channel open
5
Part of degraded neurotransmitter
Na^+
Ion channel closed

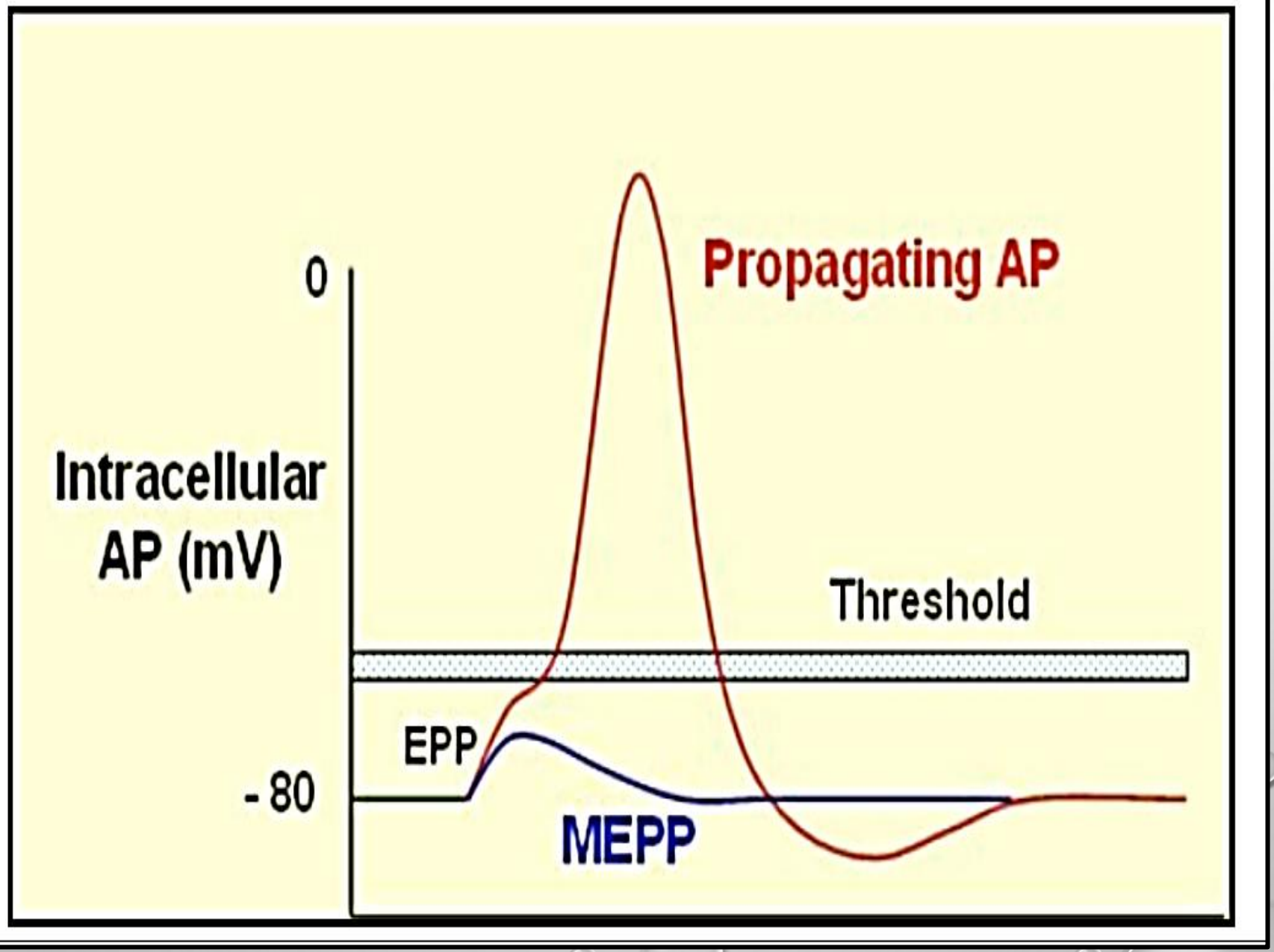

B
Presynaptic neuron
Action potential
Ca^{2+}
Synaptic vesicles
Ca^{2+}
Terminal bouton of motor neuron
Synaptic cleft
Motor end plate of skeletal muscle cell
Neurotransmitter
Na^{2+}
Neurotransmitter Receptor
Postsynaptic potential
Nerve impulse
A
Neuromuscular junction
Myelinated axons
Nerve bundle
Nerve terminal
Muscle Fibers
Sarcolemma
T-tubule
DHPR and Rvr
Ca^{2+}
Myosin head
Thick filament
Thin filament
Relaxed
(+)
(-)
(-)
(+)
A band
I band
I band
+APT, Ca^{2+}
Contracted
A band
C
Nerve impulse and contraction

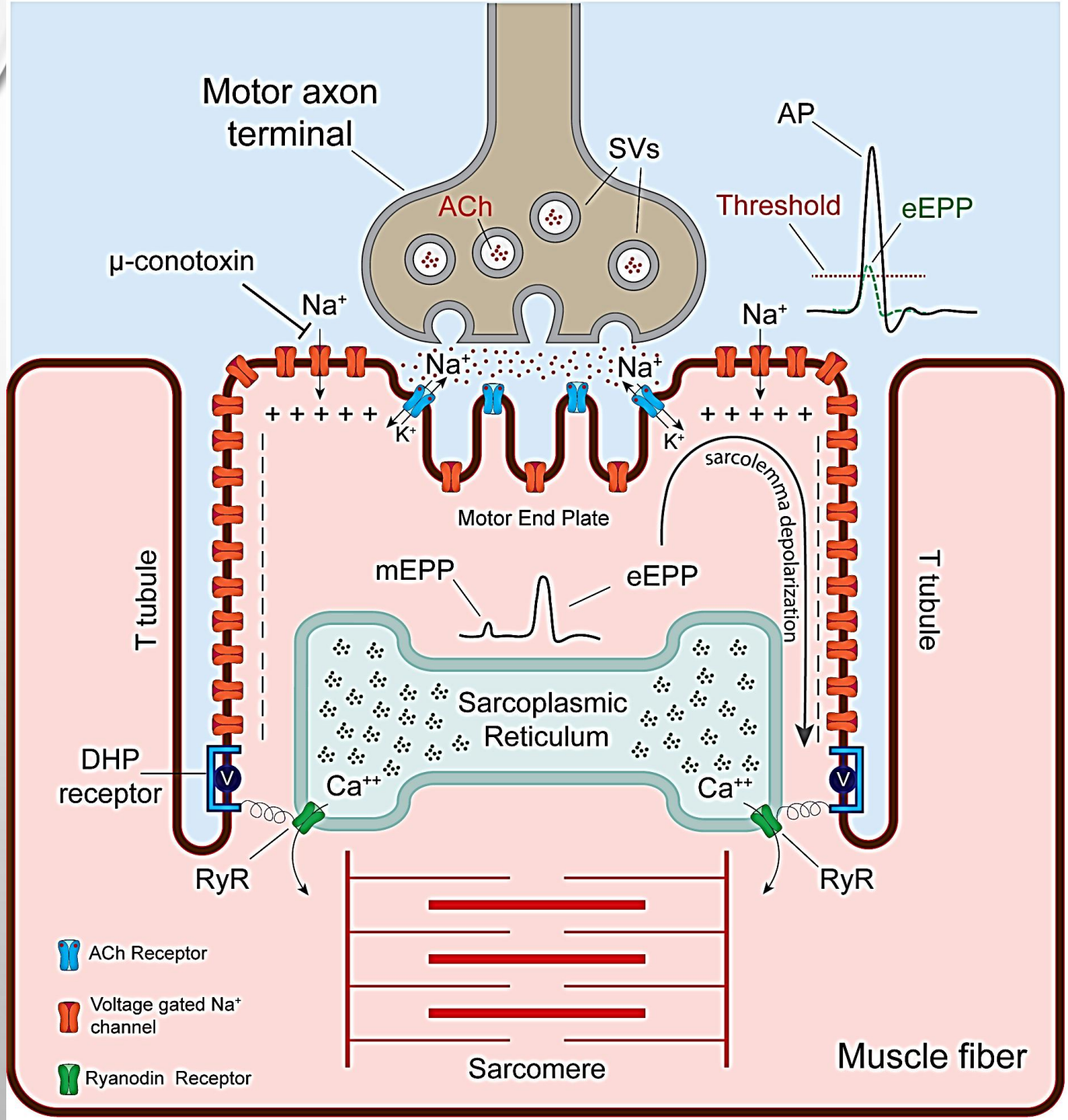
END PLATE POTENTIAL (EPP)

- **Definition:** It is a process of **Partial Depolarization** at the MEP caused by **ACh release** due to a **nerve impulse** in the motor nerve.
- Its **amplitude** is **Directly proportional** to the **amount** of **ACh** released.

MINIATURE END PLATE POTENTIAL (MEPP)

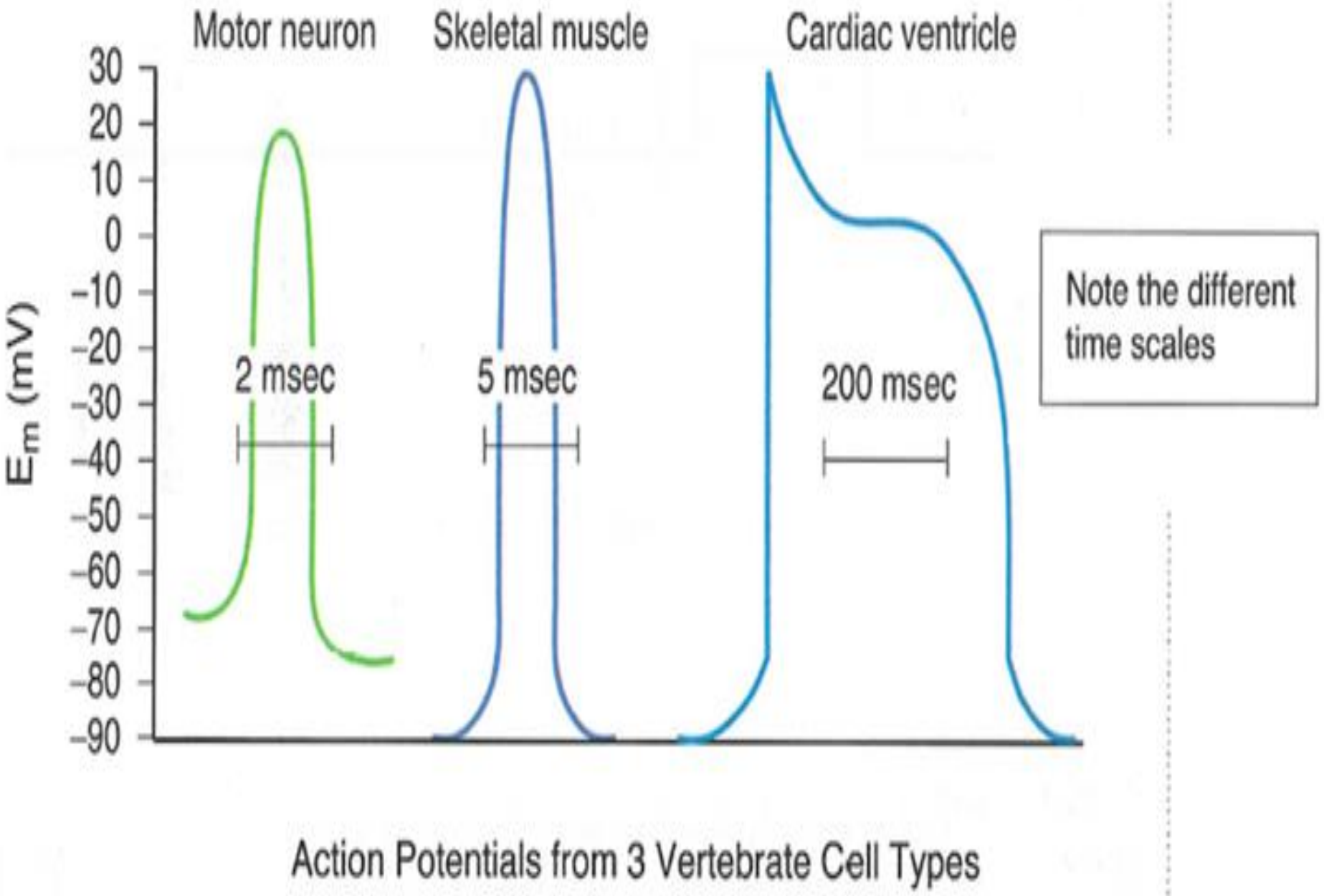
- It is a process of **Partial Depolarization** at the MEP **Due to:**
- **Release of ONE or Single Ach vesicle** → producing **0.4 mV** depolarization of skeletal muscle end plate region **called MEPP.**
- MEPPs occur **spontaneously** at NMJ and are thought to be **due to unstimulated exocytosis of single ACh vesicle.**


0
Propagating AP
Intracellular
AP (mV)
Threshold
EPP
- 80
MEPP


Motor axon terminal
SVs
ACh
AP
Threshold
eEPP
μ-conotoxin
Na+
Na+
Na+
Na+
K+
K+
sarcolemma depolarization
Motor End Plate
mEPP
eEPP
T tubule
T tubule
Sarcoplasmic Reticulum
DHP receptor
Ca++
Ca++
RyR
RyR
ACh Receptor
Voltage gated Na+ channel
Ryanodin Receptor
Sarcomere
Muscle fiber

SKELETAL MUSCLE AP

The skeletal muscle action potential is **similar** to the motor neuron action potential **except** that it is **longer** in duration; about 5 ms and velocity of conduction is slower; 3-5 m/second).



Action Potentials from 3 Vertebrate Cell Types

PROPERTIES OF NEUROMUSCULAR TRANSMISSION

1. **UNIDIRECTIONAL:** from the nerve to the muscle and never the reverse (not in opposite direction).
2. **IT HAS A DELAY OF 0.5 ms (millisecond):** It represents the time needed for the release of ACh, passage of ACh across synaptic cleft and its combination with nicotinic receptors in muscle until the buildup of the EPP.
3. **EASILY FATIGUED:** by repeated stimulation due to the depletion of ACh.

4. Drugs affecting NMT

Drugs that stimulate NMT: e.g.

- **Neostigmine** and **physostigmine (serine)** → **reversible** anti-acetylcholinesterase.
- **"Nerve" gas poison** → irreversible anti-acetylcholinesterase.

Drugs that block NMT: e.g.

Curare → block nicotinic channels from opening→ **flaccid paralysis**.

These agents are used for relaxing skeletal muscle during surgical procedures **(Skeletal muscle relaxants).**

MYATHENIA GRAVIS

- It a disease characterized by **marked progressive weakness and easy fatigability** of muscles.
- It is **an autoimmune disease** that affects **females** more than males.
- It is due to the formation of **autoantibodies** that **lead to:**
  - **Destruction of ACh receptors** at MEP → decreased the response to ACh.
  - If the disease is intense enough, the patient dies of paralysis. In particular, paralysis of respiratory muscles.

Treatment:

By **Reversible choline esterase inhibitors or anticholine esterase**,

e.g. Prostigmine or **neostigmine** → preserve ACh → **better** NMT thus helps initiation of muscle contraction.

SARCOTUBULAR SYSTEM

It is a system of tubules located in sarcoplasm of muscle fibers.

It is formed of a **T-tubular system** and the **sarcoplasmic reticulum (SR)**.

(1)THE T-TUBULAR (transverse tubules) SYSTEM:

- It is an **internal invagination** of the cell membrane.
- It is present at the **junction** of the dark (A) and light (I) bands in the skeletal muscles.
- The **space** between the two layers of the membrane is an **extension of the extracellular space**.

Function:

Rapid conduction of the action potential from the surface of the muscle to all muscle fibrils (myofibrils) inside.

(2) THE SACROPLASMIC RETICULUM (SR):

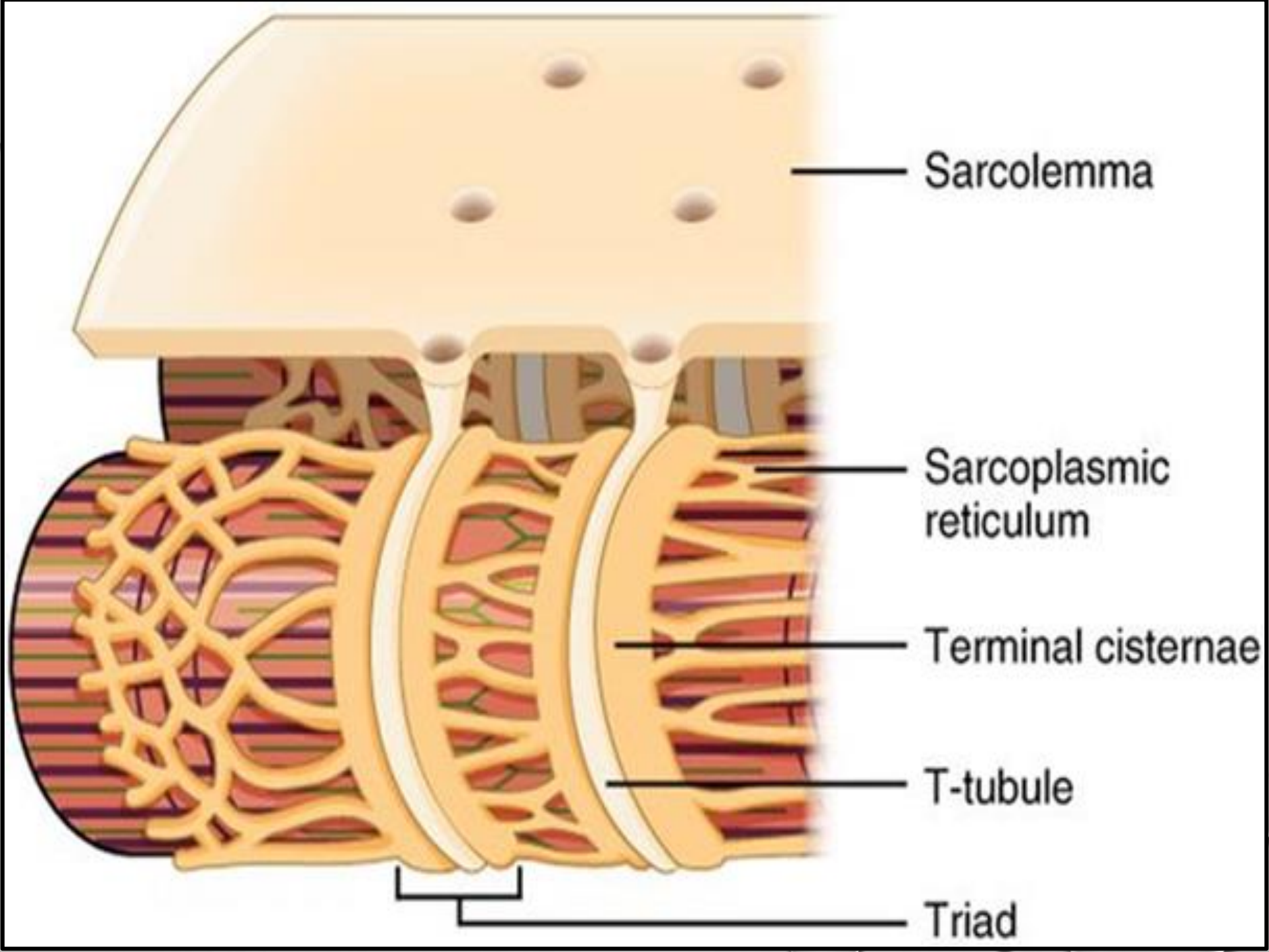
It forms:

- Long **longitudinal tubules** that run parallel to and surround the myofibrils.
- It ends in Large chambers (dilatations) called **terminal cisterns**.

Function:

The sarcoplasmic reticulum (particularly terminal cisterns) is concerned with **Ca^{+} storage and release** which play an essential role in muscle contraction.

The arrangement of the **T-tubules with the terminal cisterns** one on either sides is called **Triad.**


Sarcolemma
Sarcoplasmic reticulum
Terminal cisternae
T-tubule
Triad


THANK YOU