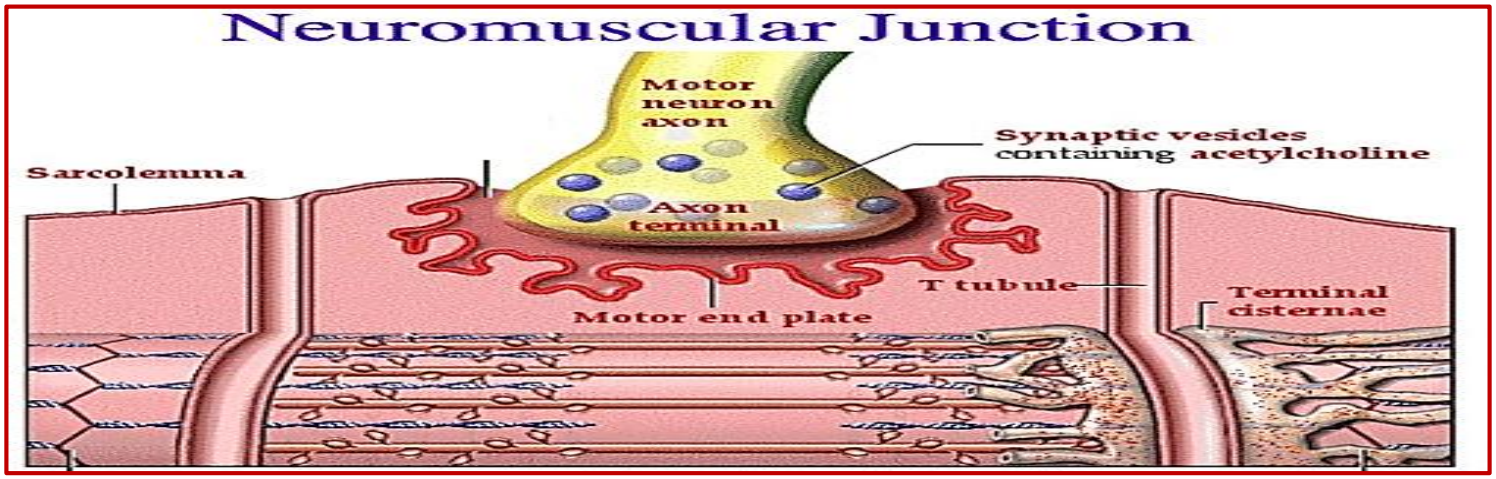
1ST YEAR MEDICAL STUDENTS
PHYSIOLOGY (LECTURE 14)
NEUROMUSCULAR JUNCTION (NMJ)



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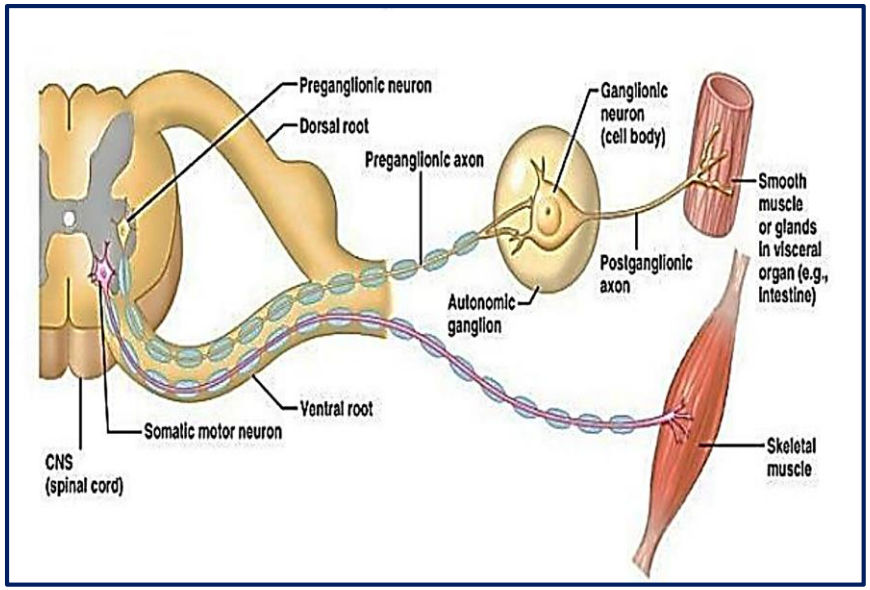
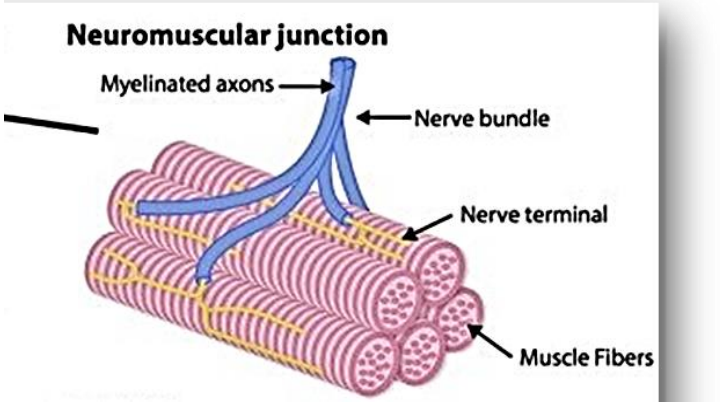
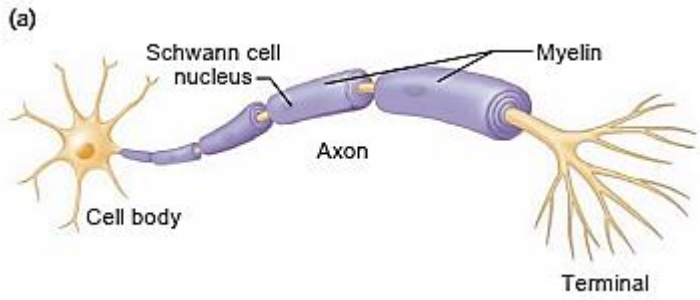
- **Stimulation of the neurons to a skeletal muscle is the only mechanism by which action potentials are initiated in this type of muscle**.
- **The neurons whose axons innervate skeletal muscle fibers are known as motor neurons (or somatic efferent neurons)**, and their cell bodies are located in the brainstem and the spinal cord.
- **The axons of motor neurons are myelinated** and are the **largest-diameter axons in the body**. They are therefore able to **propagate action potentials at high velocities**, allowing signals from the central nervous system to travel to skeletal muscle fibers with minimal delay.
- **Upon reaching a muscle, the axon of a motor neuron divides into many branches, each branch forming a single junction with a muscle fiber called neuromuscular junction (NMJ)**.
- **A single motor neuron innervates many muscle fibers**, but each muscle fiber is controlled by a branch from only one motor neuron.
- **A motor neuron plus the muscle fibers it innervates is called a motor unit**.

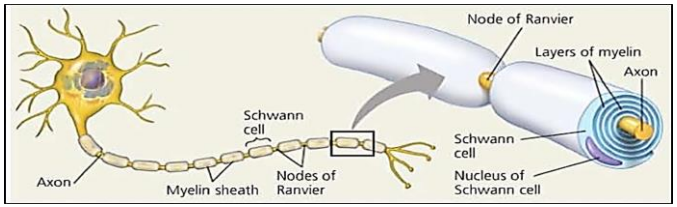

Preganglionic neuron
Dorsal root
Preganglionic axon
Ganglionic neuron (cell body)
Smooth muscle or glands in visceral organ (e.g., intestine)
Postganglionic axon
Autonomic ganglion
Ventral root
Somatic motor neuron
CNS (spinal cord)
Skeletal muscle


Neuromuscular junction
Myelinated axons
Nerve bundle
Nerve terminal
Muscle Fibers


(a)
Schwann cell nucleus
Myelin
Axon
Cell body
Terminal

PHYSIOLOGICAL ANATOMY of NEUROMUSCULAR JUNCTION (NMJ)

- **NMJ** is the area of **contact** and **communication** between the somatic motor nerve fiber and the skeletal muscle fiber.
- **NMJ is a specialized chemical synapse.**
- At the **NMJ**, The myelin sheath surrounding the axon of each motor neuron ends near the surface of a muscle fiber, and the axon divides into a number of short processes that lie embedded in grooves on the muscle fiber surface.
- The **region of the muscle fiber plasma membrane that lies directly under the terminal portion of the axon is known as the motor end plate (MEP)**.
- The space separating the axon terminal and the MEP is called the **synaptic cleft.**
- The **neuron** is **considered** to be the **presynaptic cell** and the **muscle** cell is the **postsynaptic cell.**



- The presynaptic axon terminal contains **vesicles** that contain the **neurotransmitter**; **acetylcholine (ACh)**.
- The sides of the **presynaptic membrane** contain **voltage-gated Ca^{2+} channels.**
- ACh is rapidly broken down by **acetylcholinesterase enzyme** which degrades it into acetate and choline.
- The **postsynaptic membrane** of the muscle contains numerous **ACh receptors (nicotinic receptors) (ligand - gated nicotinic receptors).**

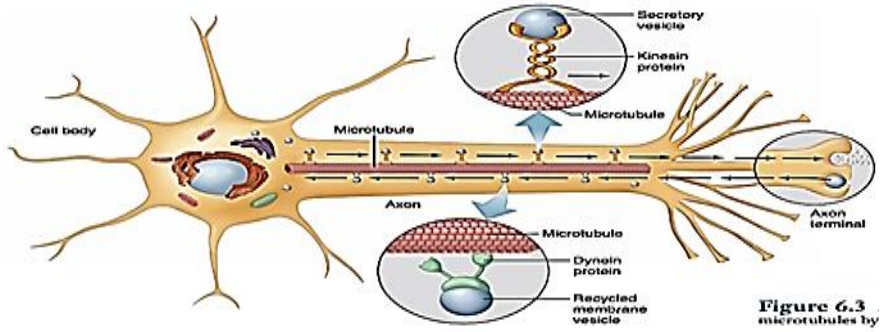
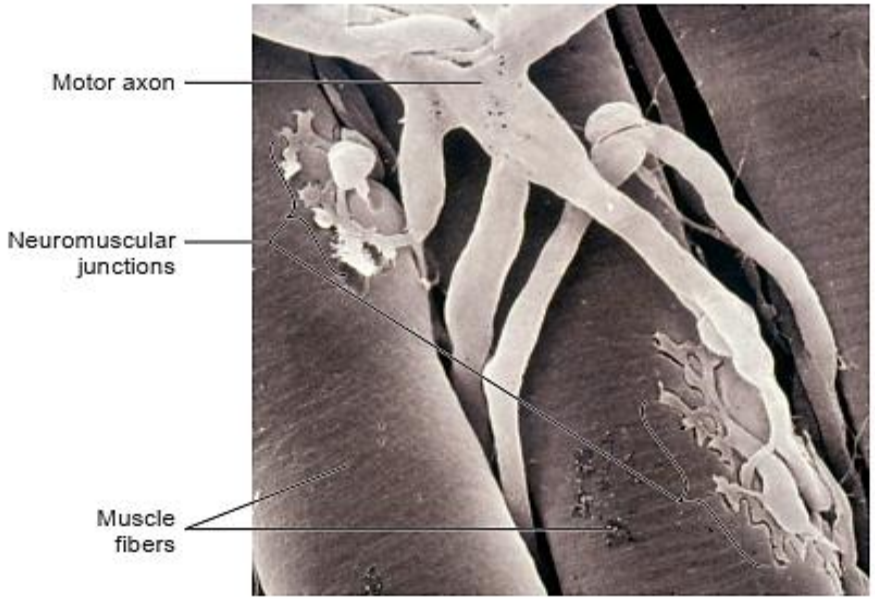
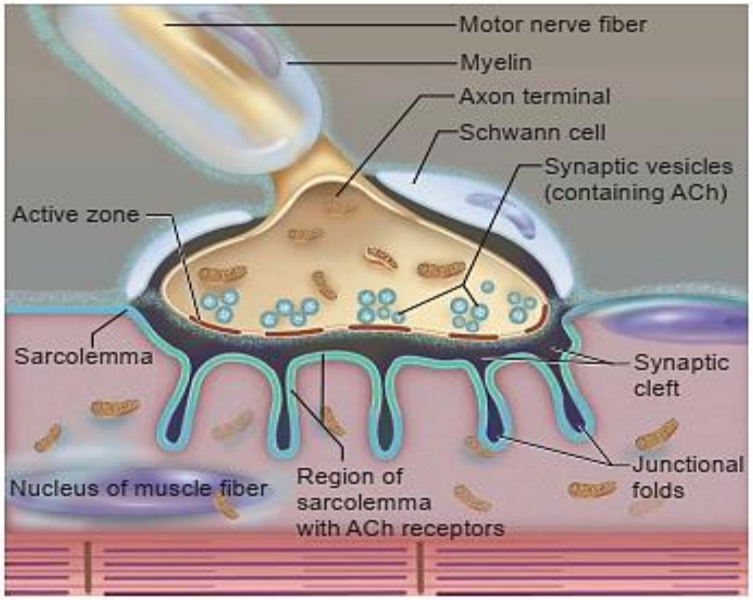


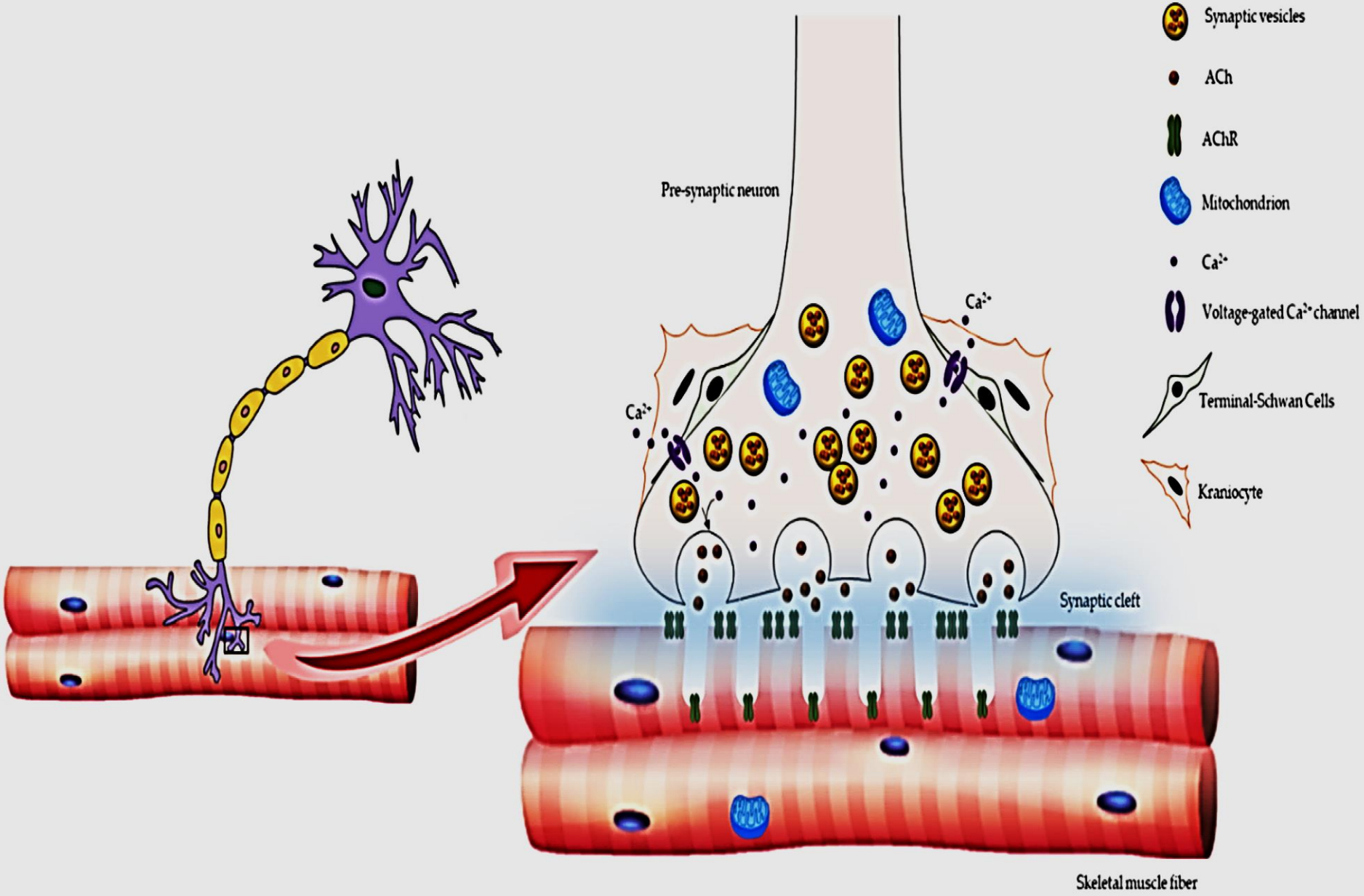
Figure 6.3


Motor axon
Neuromuscular junctions
Muscle fibers

(a)


Motor nerve fiber
Myelin
Axon terminal
Schwann cell
Synaptic vesicles (containing ACh)
Active zone
Sarcolemma
Synaptic cleft
Junctional folds
Nucleus of muscle fiber
Region of sarcolemma with ACh receptors

(b)


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

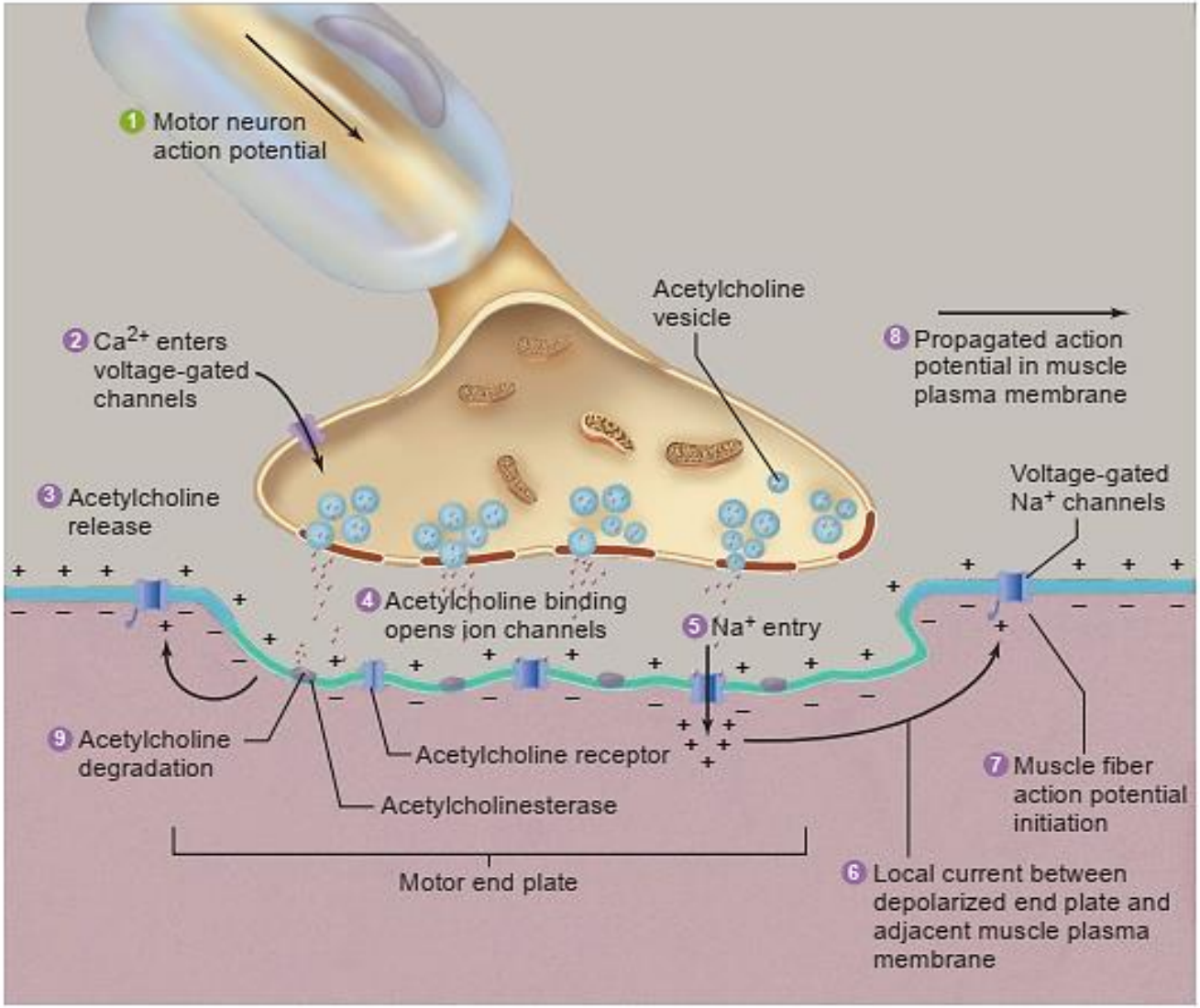
NEUROMUSCULAR TRANSMISSION (NMT)

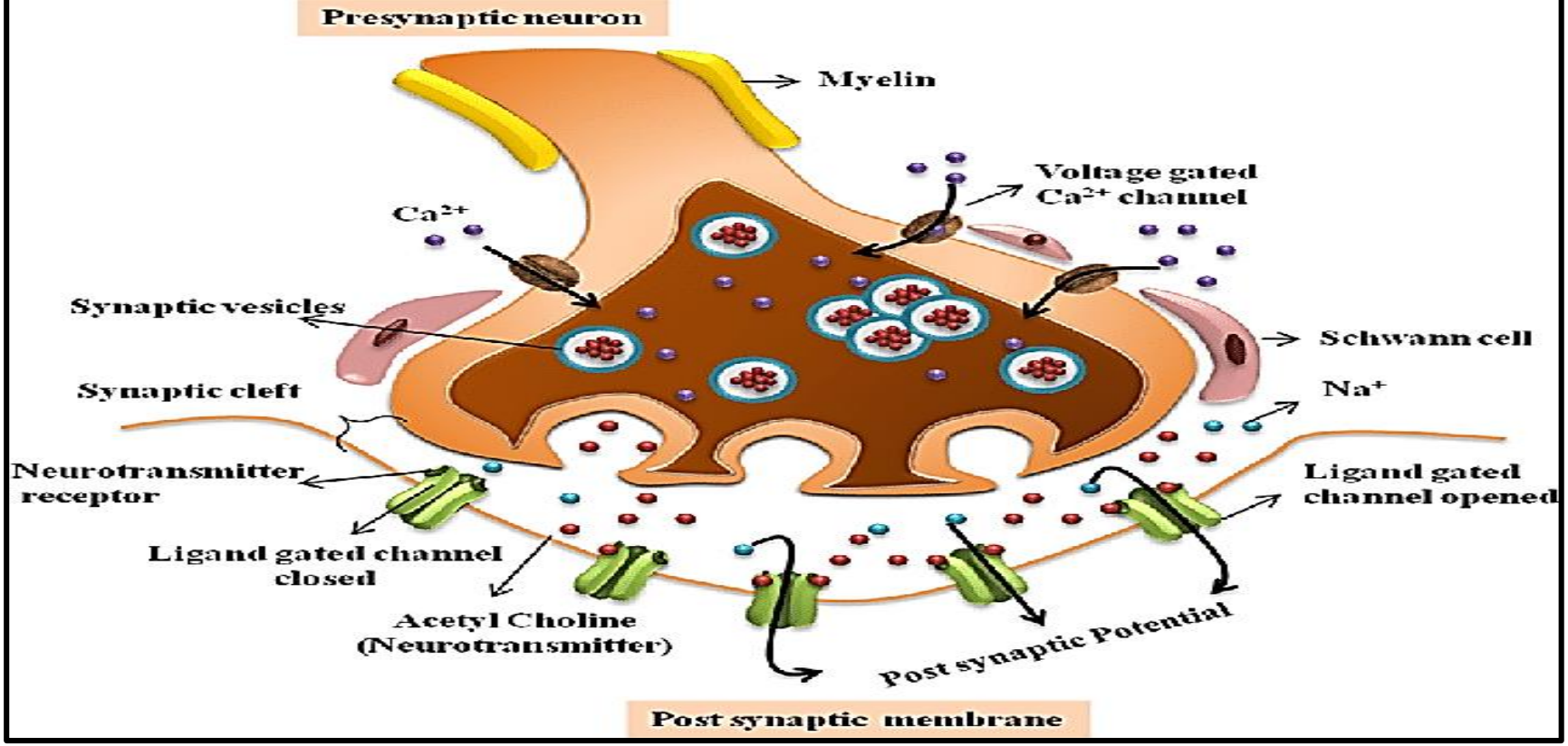
Definition: **It is the transmission of the nerve impulse (AP) from the somatic motor nerve to the skeletal muscle at the NMJ.**

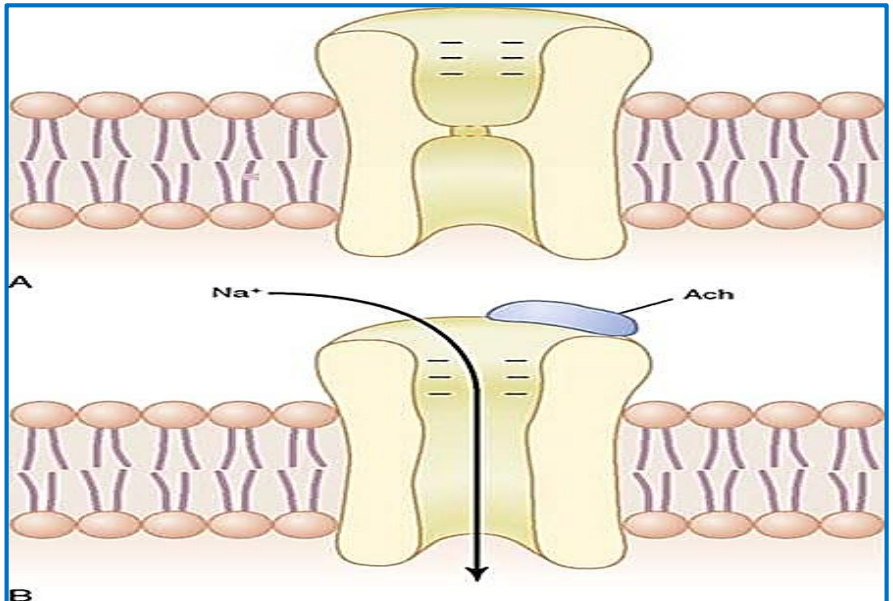
MECHANISM OF NEUROMUSCULAR TRANSMISSION

1. The **vesicles** at the axon terminal are loaded with **acetylcholine (ACh)**.
2. **DEPOLARIZATION** of the nerve terminal 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**.
4. **ACh crosses** synaptic cleft and **binds** with its receptors (nicotinic receptors) on the surface of the muscle.
5. The binding of ACh to its receptors opens an ion channel in each receptor protein → **ligand-gated channels → Na^{+} influx** → local depolarization at MEP called **End-Plate Potential (EPP)**.
6. When the **EPP reaches the threshold potential**, 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. Choline is then transported back into the axon terminals, where it is reused in the synthesis of new ACh.
8. **ACh bound to receptors is in equilibrium with free ACh in the synaptic cleft**.
9. **As the concentration of free ACh decreases because of its breakdown by acetylcholinesterase, less ACh is available to bind to the receptors.**
10. **When the receptors no longer contain bound ACh, the ion (Na^+)channels close.** The depolarized end plate (EPP) returns to its resting potential and can respond to the subsequent arrival of ACh released by another neuron action potential.


1 Motor neuron action potential
Acetylcholine vesicle
2 Ca^{2+} enters voltage-gated channels
8 Propagated action potential in muscle plasma membrane
Voltage-gated Na^+ channels
3 Acetylcholine release
4 Acetylcholine binding opens ion channels
5 Na^+ entry
9 Acetylcholine degradation
Acetylcholine receptor
Acetylcholinesterase
7 Muscle fiber action potential initiation
Motor end plate
6 Local current between depolarized end plate and adjacent muscle plasma membrane


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

END PLATE POTENTIAL (EPP)

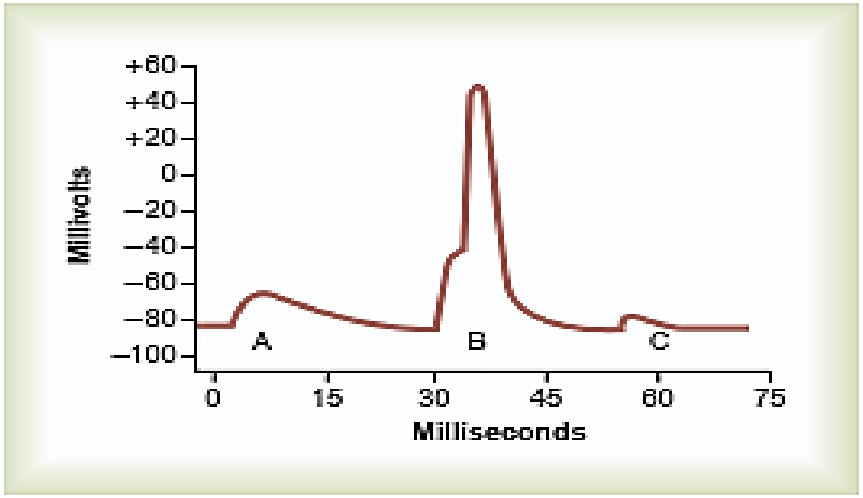
- **Definition:** It is a **Partial Local Depolarization** at the MEP caused by **ACh release** due to a **nerve impulse** in the somatic motor nerve.
- Its **amplitude** is **directly proportional** to the **amount** of **ACh** released.

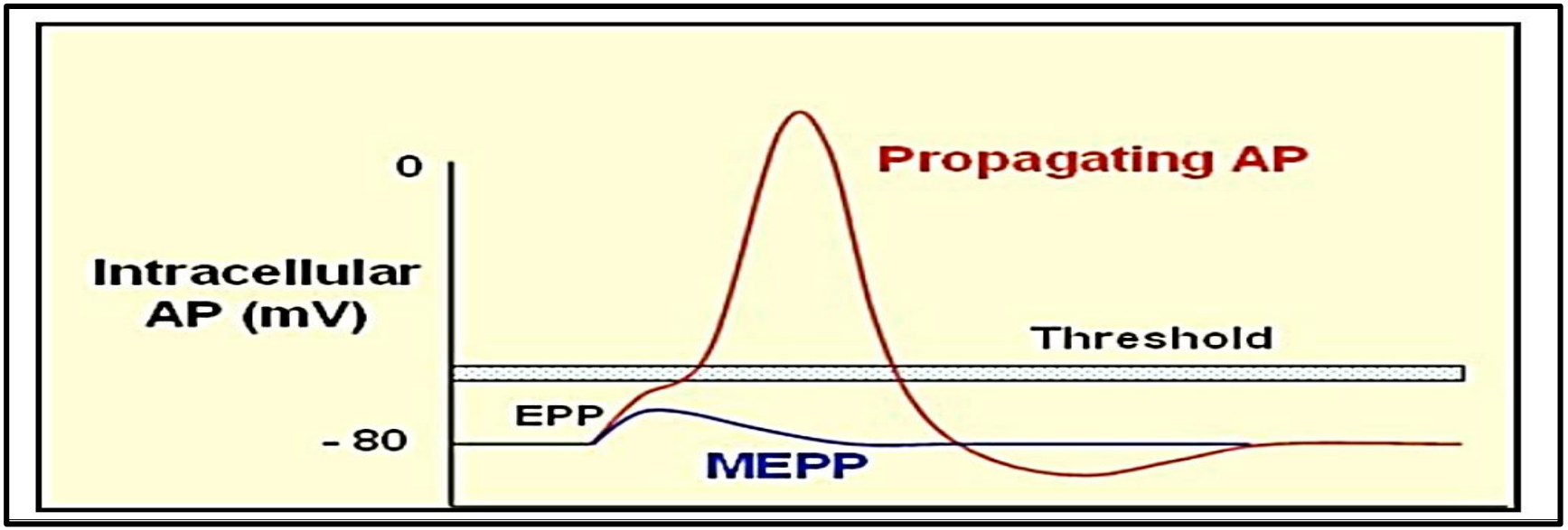
Differences Between EPP and Neuronal Action Potential

	EPP	Neuronal AP
Cause	Produced by **a ligand-gated channel**.	Caused by **voltage-gated channels**.
Depolarization	Rapid depolarization, to a threshold potential → AP	Rapid depolarization, to a potential of +30 or +40 mV
Ion Channels Involved	A single, large **channel for Na^+** carries the charge during an endplate potential.	**Multiple ion channels** are involved in a neuronal action potential, which is **mainly produced by Na^+ influx**.
Repolarization	**Passive**	**increased K^+ conductance (outflow)** is responsible

MINIATURE END PLATE POTENTIAL (MEPP)

- It is a **Partial Local 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.**


+60
+40
+20
0
−20
−40
−60
−80
−100
Millivolts
A
B
C
0
15
30
45
60
75
Milliseconds


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

PROPERTIES OF NEUROMUSCULAR TRANSMISSION

1. **UNIDIRECTIONAL:** from the somatic motor nerve to the skeletal 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

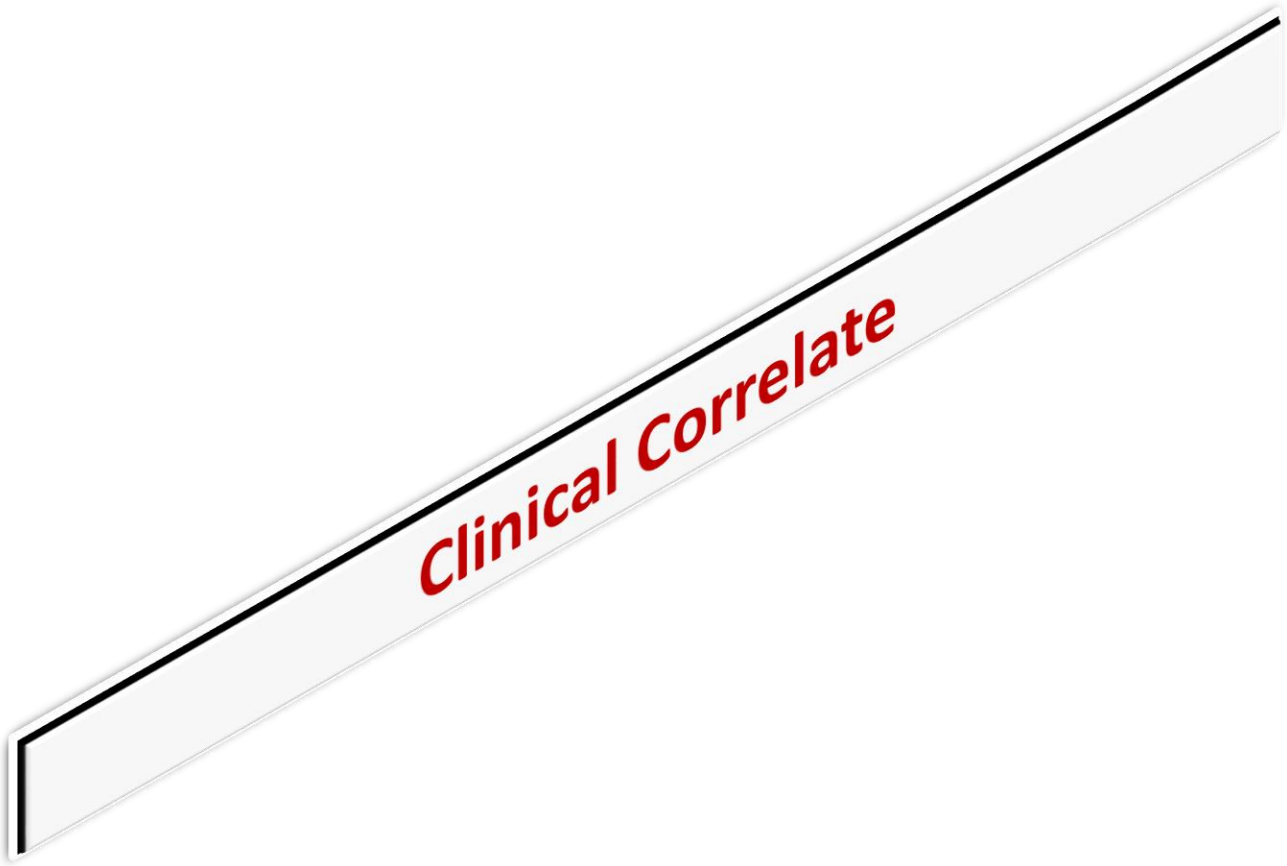
Drugs that stimulate NMT: e.g.

Neostigmine → **reversible** anti-acetylcholinesterase **(cholinesterase inhibitors)**.

Drugs that block NMT: e.g.

Curare:

- Blocks nicotinic channels from opening and is resistant to destruction by acetylcholinesterase.
- When a receptor is occupied by curare, ACh can't bind to the receptor→ Therefore, although the motor neurons still conduct normal action potentials and release ACh, there is no resulting EPP in the motor end plate and no contraction.
- These agents are used for relaxing skeletal muscle during surgical procedures **(Skeletal muscle relaxants).**


Clinical Correlate

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** → decrease the response to ACh.
- A myasthenic crisis is a medical emergency. In a crisis, muscles of respiration are weakened, making breathing difficult.
- **Treatment**:
  - **Reversible cholinesterase inhibitors:**

    e.g. Prostigmine or **neostigmine** → Preserves ACh → **Better** NMT thus helps initiation of muscle contraction.
  - **Immunosuppressive drugs** such as corticosteroids.


Thank you