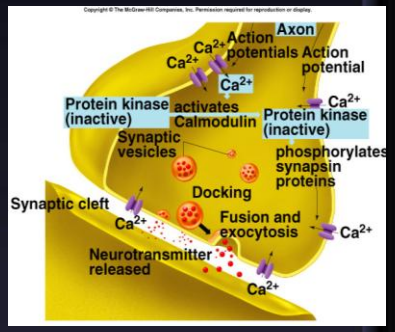
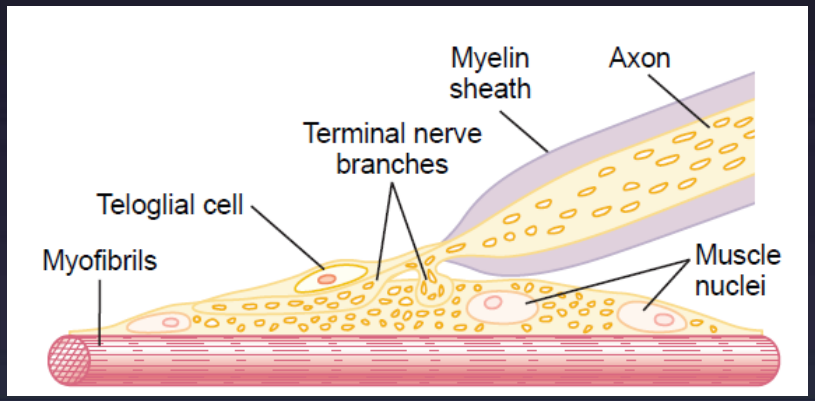

بسم الله الرحمن الرحيم

Nerve & Muscle

NEUROMUSCULAR TRANSMISSION

The Motor End Plate





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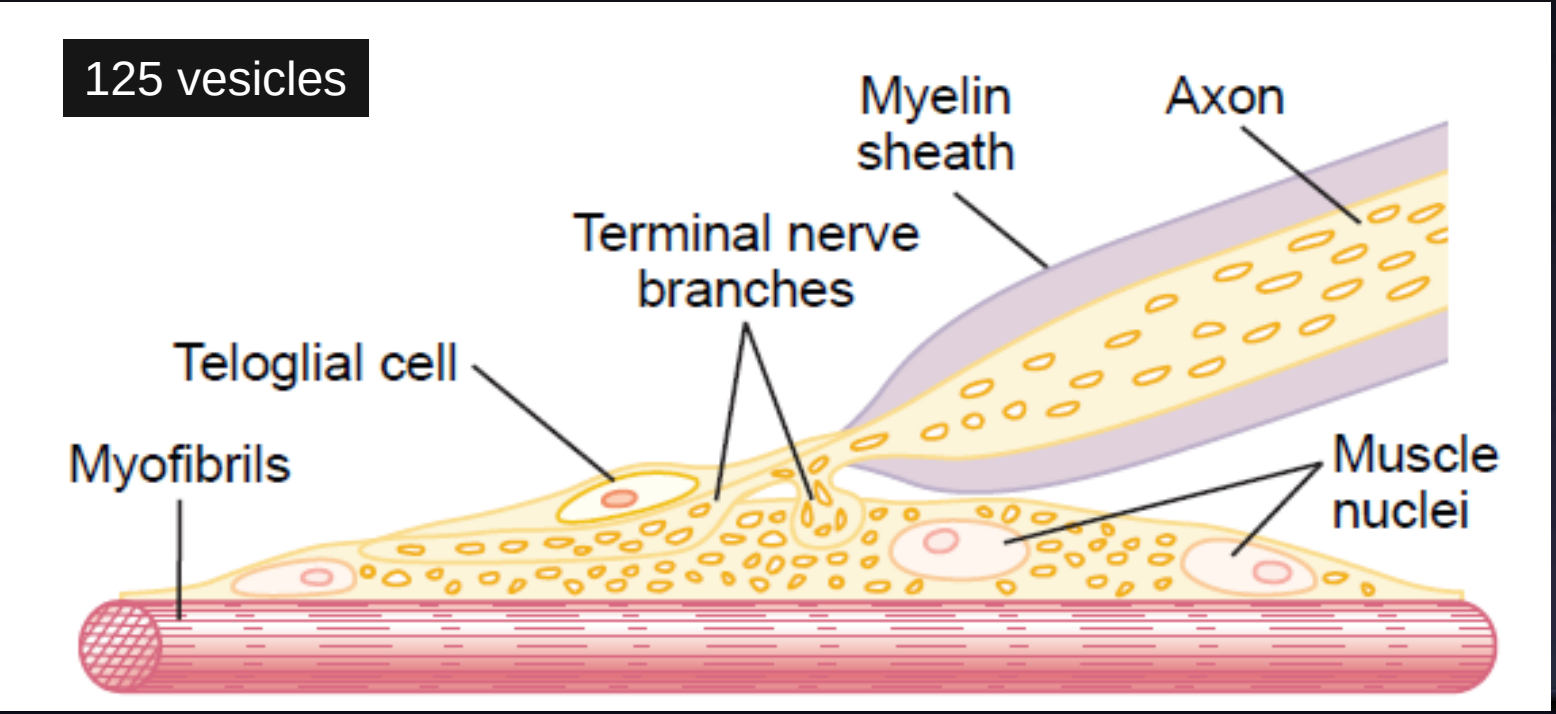
Objectives

At the end of this lecture you should be able to describe:

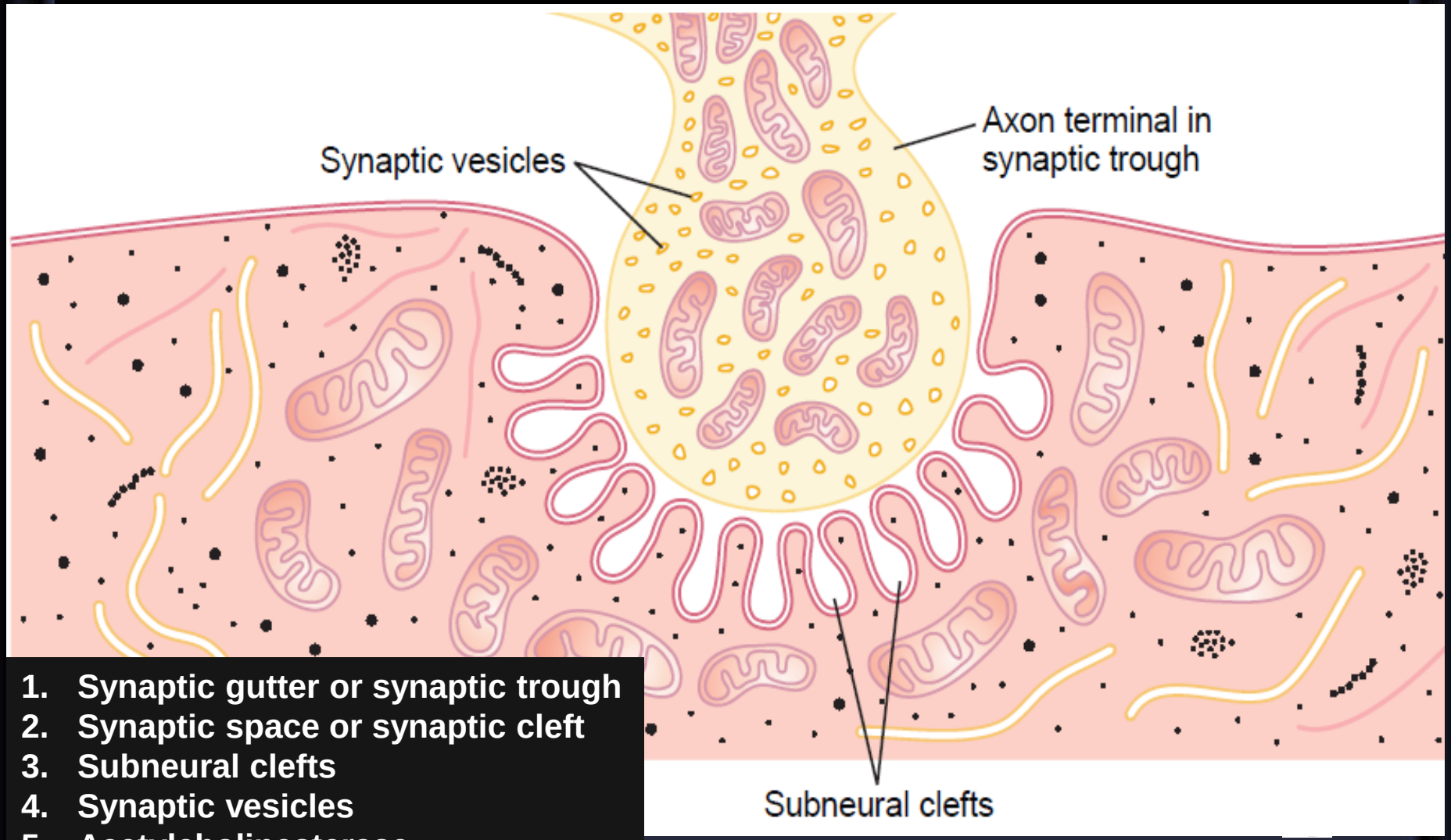
1. ***Physiologic Anatomy of NMJ***
2. ***End Plate Potential and Action Potential***
3. ***Events at the neuromuscular junction***
4. ***NM transmission in smooth & Cardiac Muscles***
5. ***Drugs affecting NM transmission***
6. ***Neuromuscular disorders (MG & LEMS)***

MOTOR END PLATE

The nerve fiber forms a complex of branching nerve terminals that invaginate into the surface of the muscle fiber but lie outside the muscle fiber plasma membrane. The entire structure is called the motor end plate.

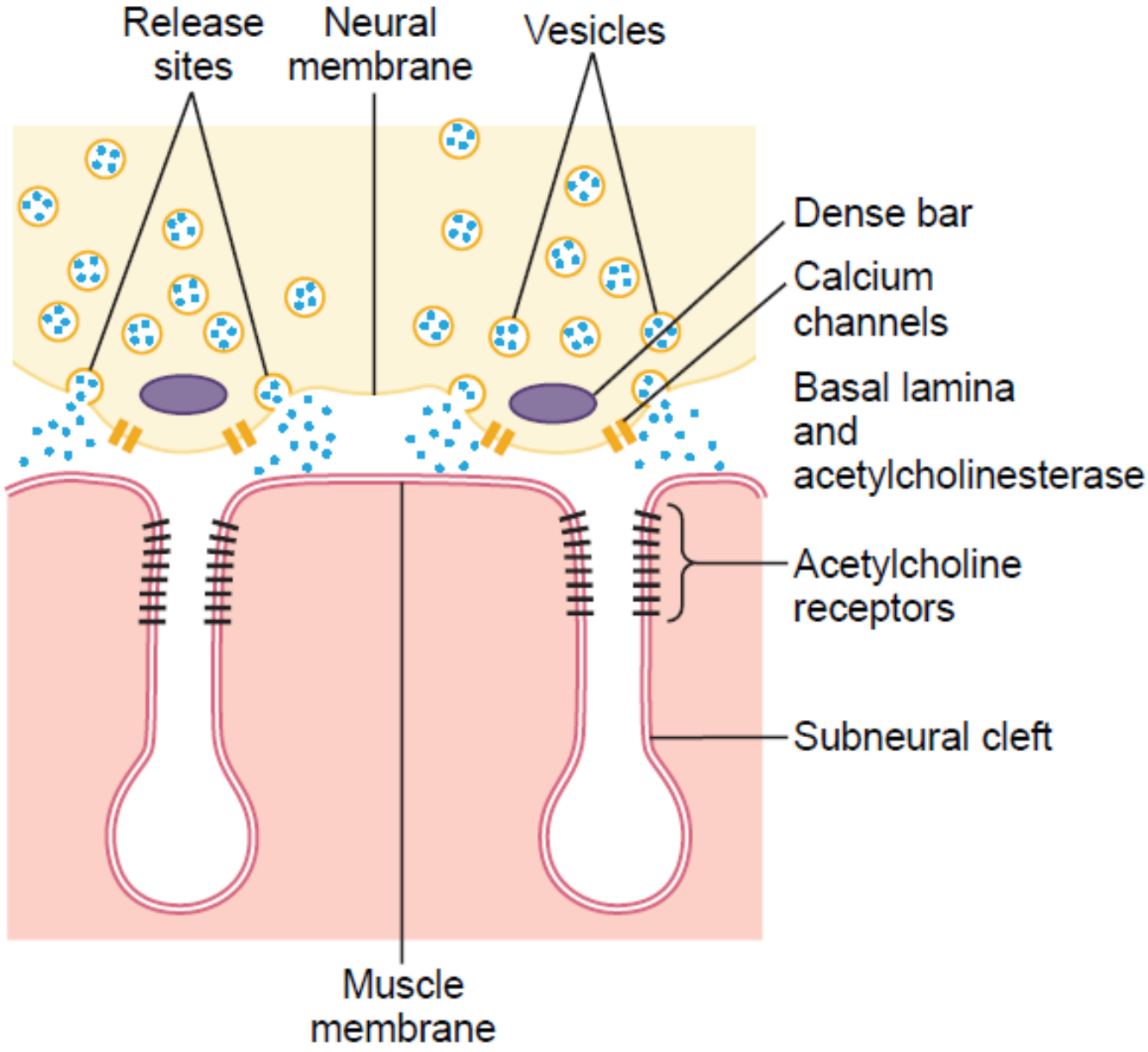


contact point between a single axon terminal and the muscle fiber membrane



1. Synaptic gutter or synaptic trough
2. Synaptic space or synaptic cleft
3. Subneural clefts
4. Synaptic vesicles
5. Acetylcholinesterase

1. *Voltage gated calcium channels*
2. *Acetylcholine-gated ion channels*



Release of acetylcholine from synaptic vesicles at the neural membrane of the neuromuscular junction

RELEASE OF ACETYLCHOLINE AT NMJ

MW: 275,000 two alpha proteins and one beta, delta, and gamma proteins

A: Closed state.
B: After acetylcholine (Ach) has become attached and a conformational change has opened the channel

Fate of Ach
Acetylcholinesterase (Acetate diffuses out & Choline is used by reuptake)
Takes 5 to 10 milliseconds.

2 Ach bind to alpha unit and activates the opening of ion channels
Repels Neg Ions

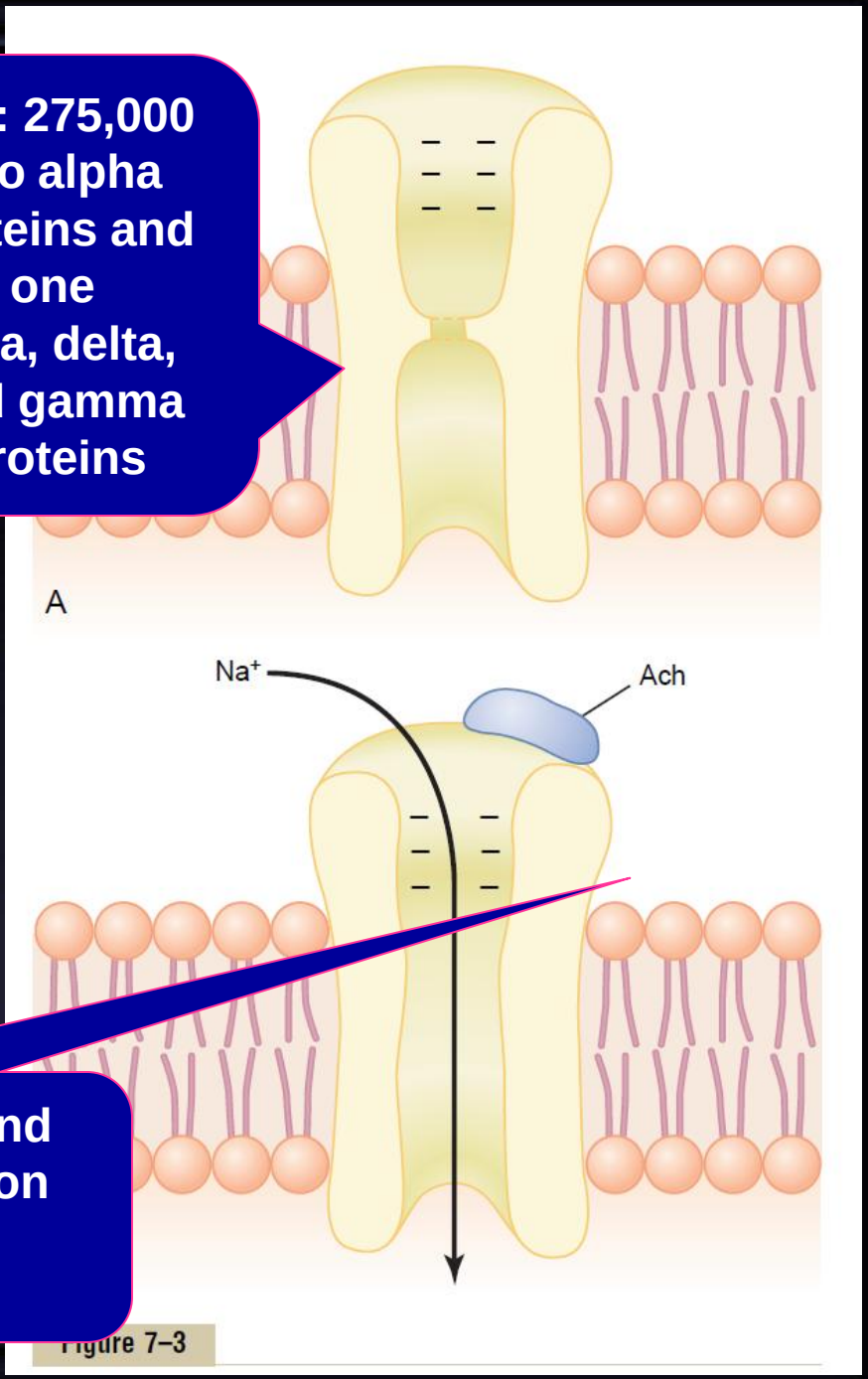


Figure 7–3

300,000 vesicles in single m end plate

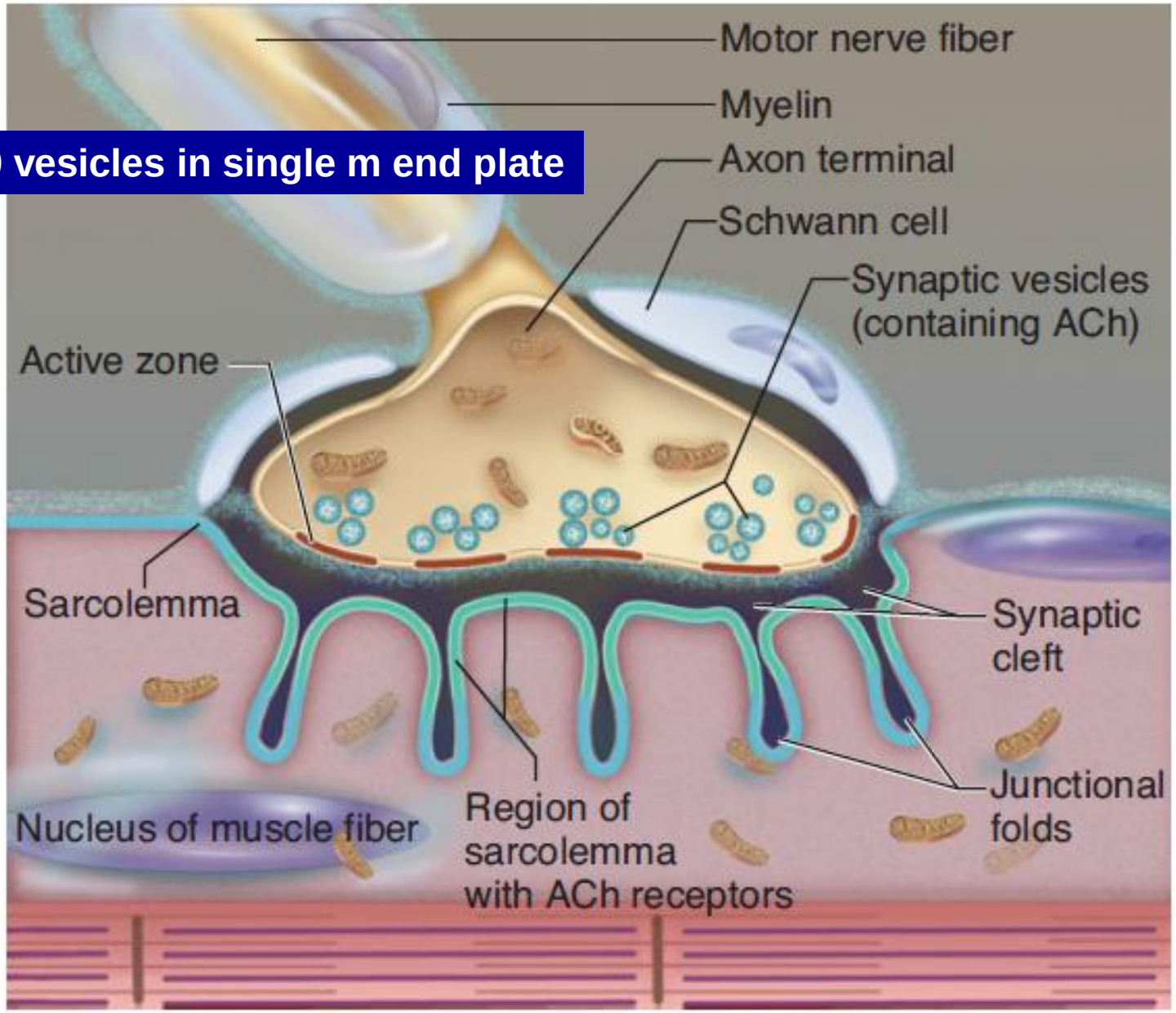


Figure: Structure of a neuromuscular junction

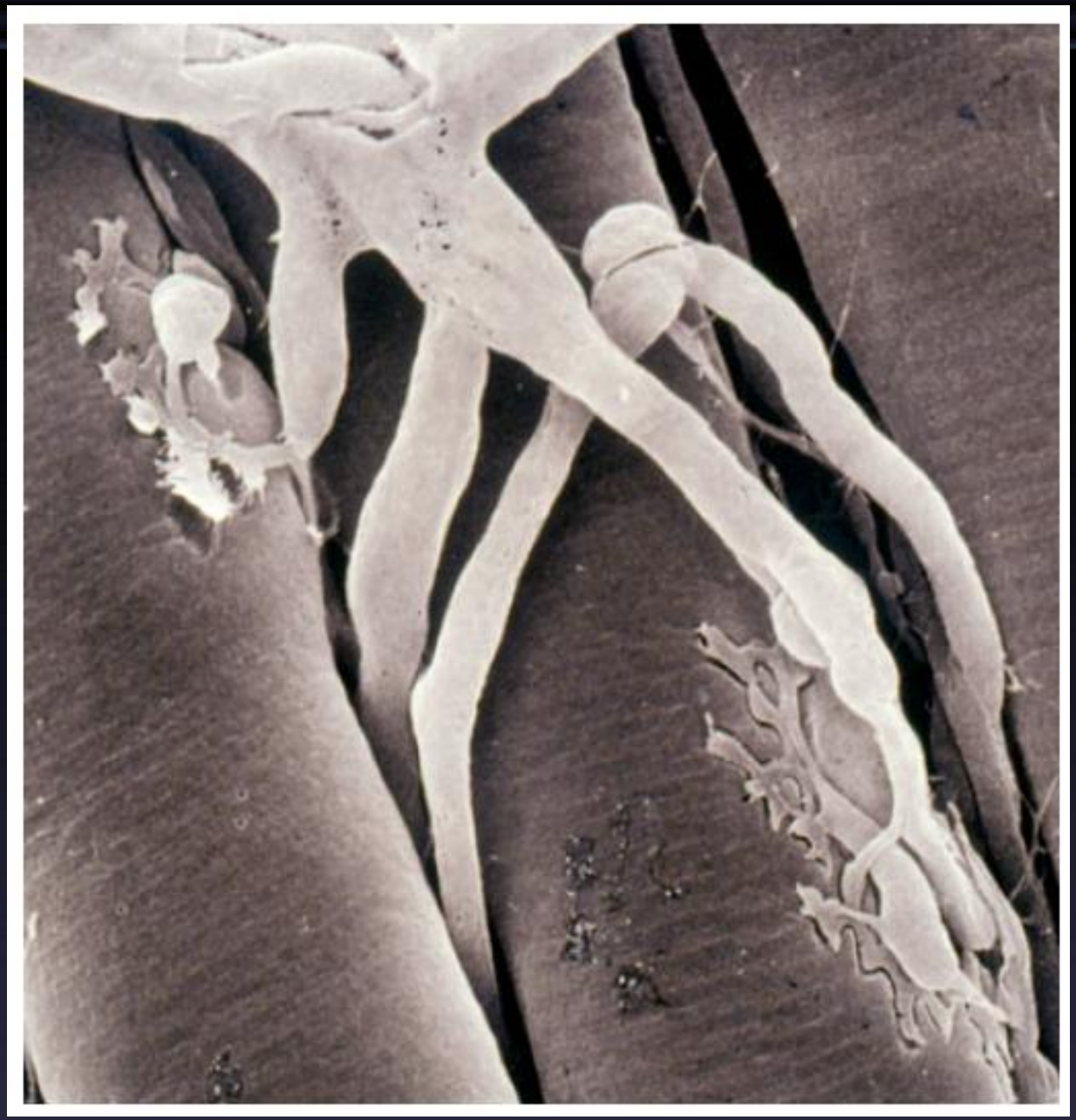
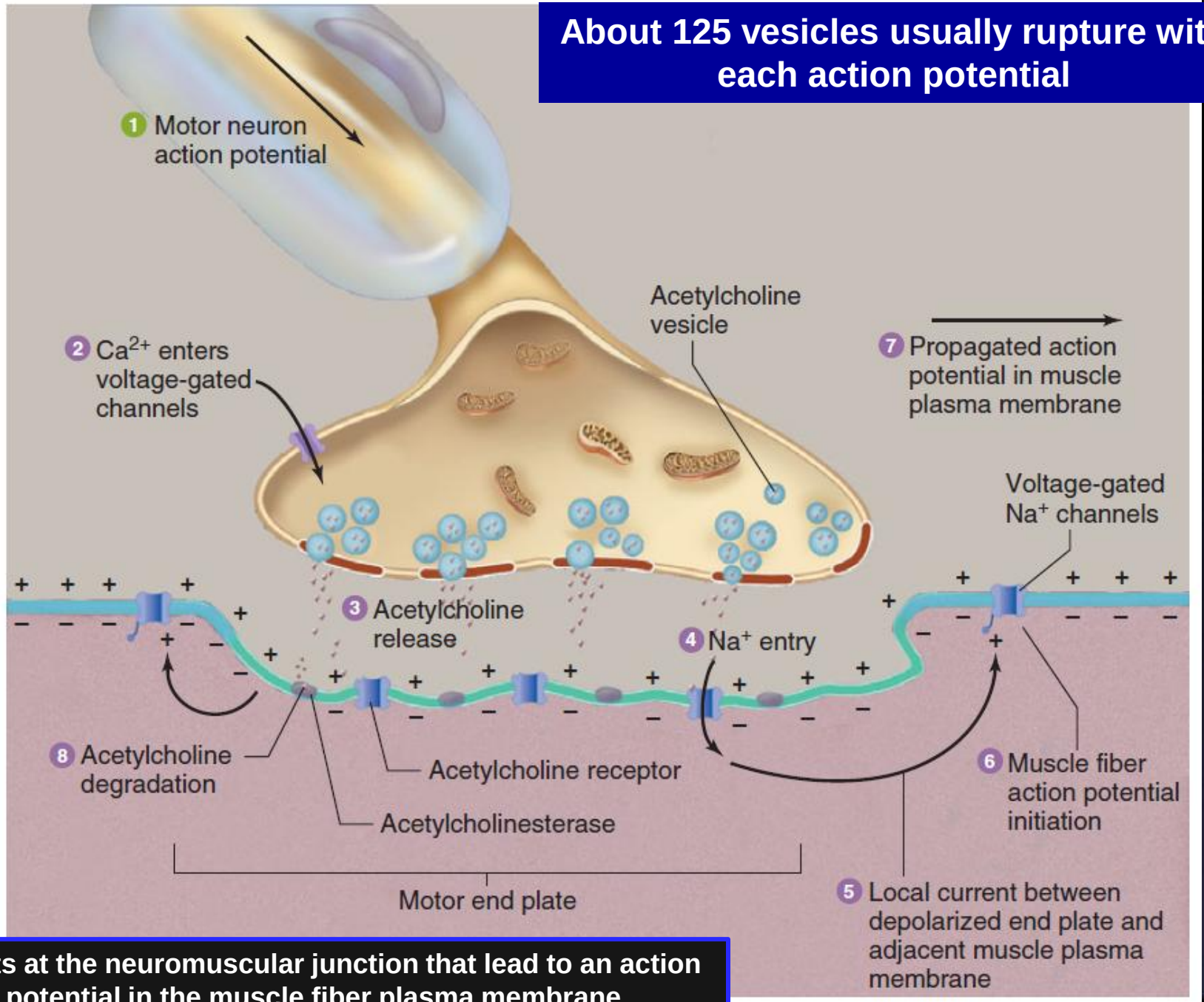


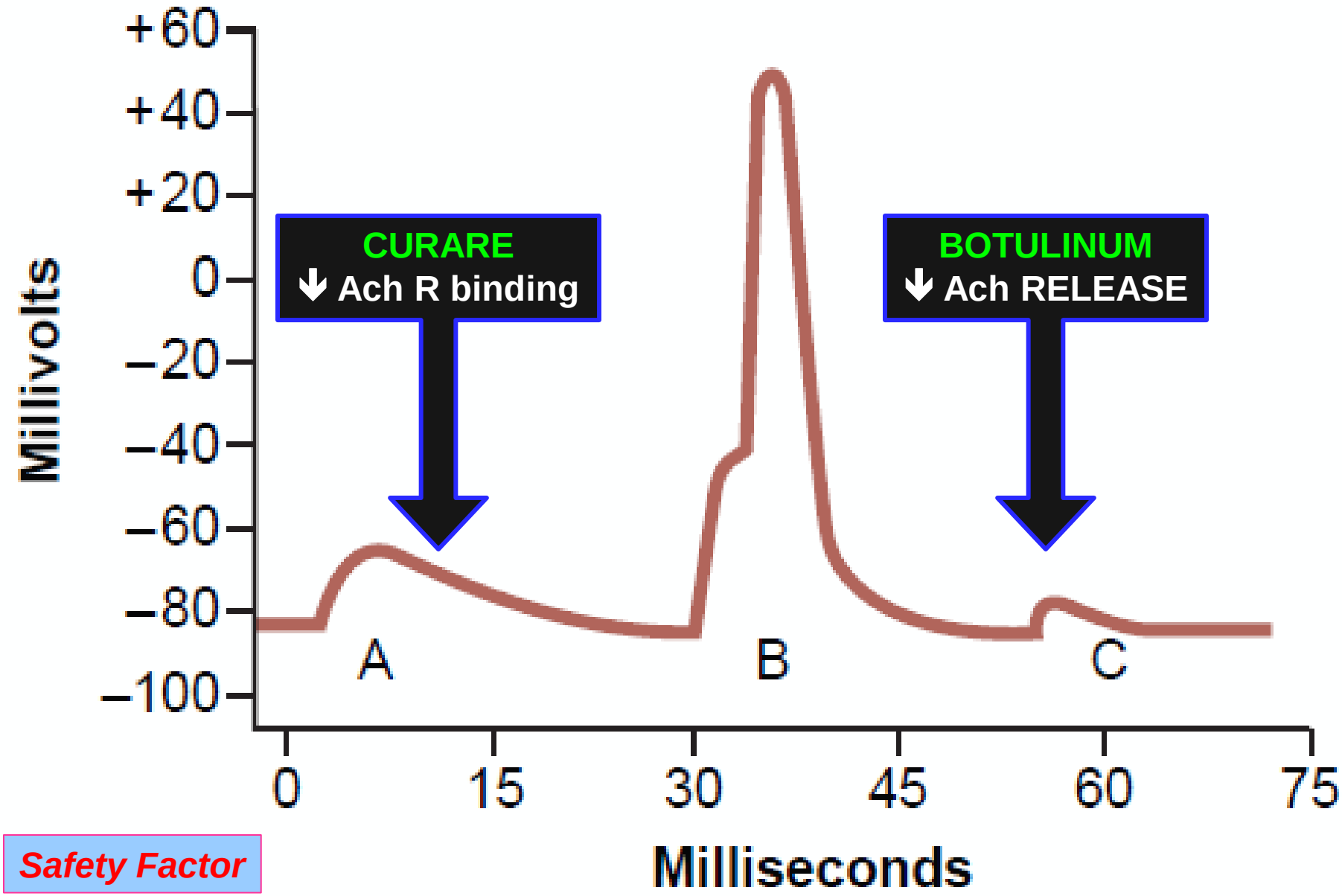
Figure: Electron Mic Structure of a neuromuscular junction

About 125 vesicles usually rupture with each action potential



Events at the neuromuscular junction that lead to an action potential in the muscle fiber plasma membrane

END PLATE POTENTIAL & ACTION POTENTIAL



Safety Factor

Drugs Acting at the Neuromuscular Junction

- **Acetylcholine Like Action.**

  Methacholine, carbachol and nicotine
- **Drugs that Inactivate Acetylcholinesterase**

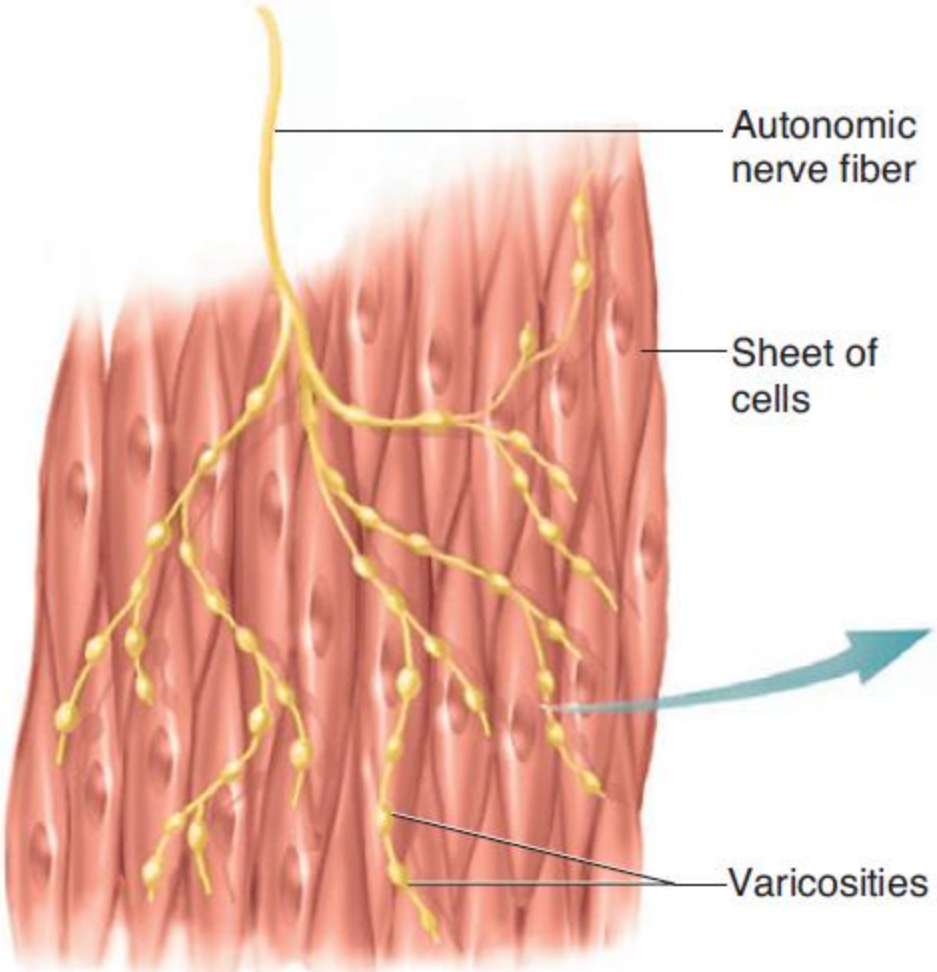
  Neostigmine, physostigmine, and diisopropyl fluorophosphate [“nerve” gas poison]
- **Drugs That Block Transmission at the NMJ**

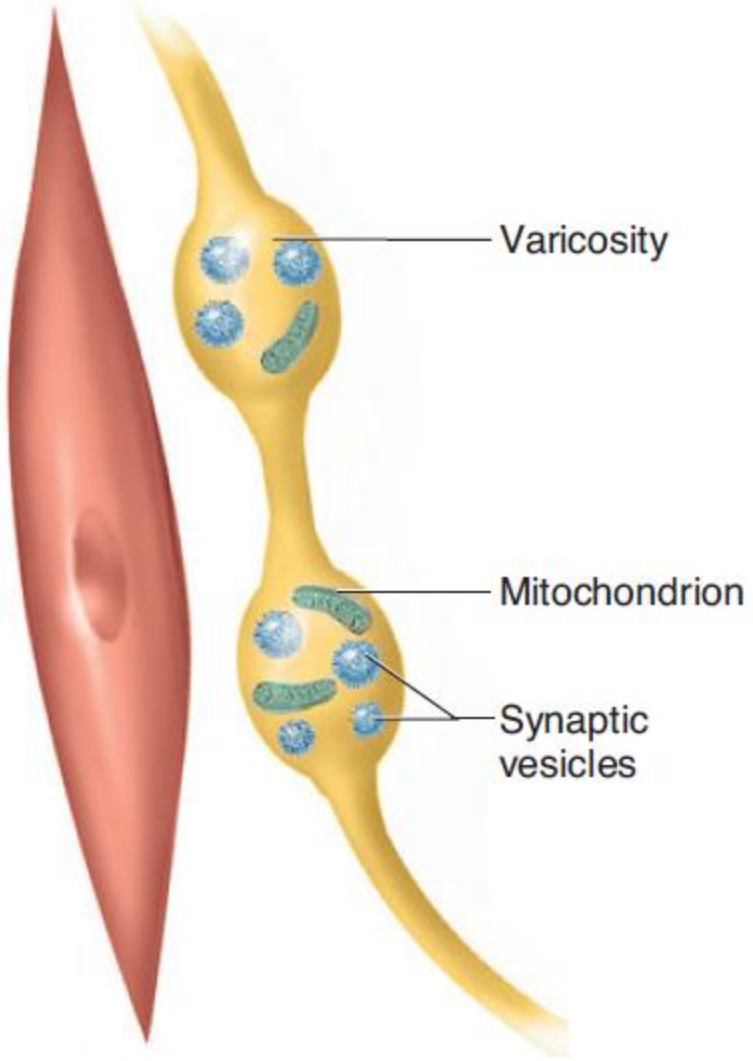
  Curariform drugs

NERVE ENDINGS IN SMOOTH & CARDIAC MUSCLE

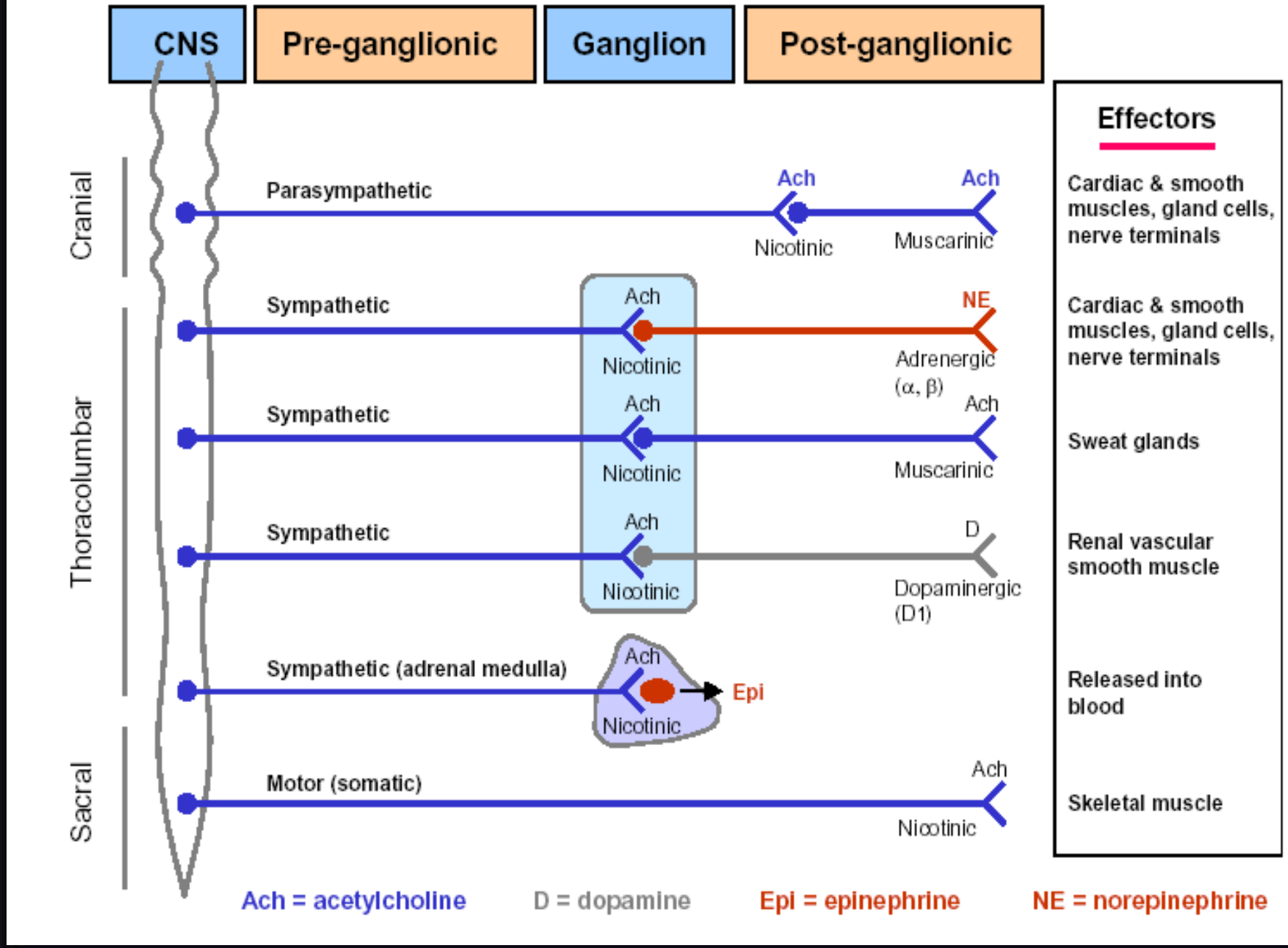
- There are no recognizable end plates or other postsynaptic specializations. The nerve fibers run along the membranes of the muscle cells and sometimes groove their surfaces.
- The multiple branches of the noradrenergic and, presumably, the cholinergic neurons are beaded with enlargements (varicosities) and contain synaptic vesicles
- The type of contact in which a neuron forms a synapse on the surface of another neuron or a smooth muscle cell and then passes on to make similar contacts with other cells is called a **synapse en passant.**

In noradrenergic neurons, the varicosities are about 5 μm apart, with up to 20,000 varicosities per neuron.





excitatory junction potentials (EJPs)
inhibitory junction potentials (IJPs)


CNS
Pre-ganglionic
Ganglion
Post-ganglionic
Cranial
Thoracolumbar
Sacral
Parasympathetic
Ach
Nicotinic
Ach
Muscarinic
Sympathetic
Ach
Nicotinic
NE
Adrenergic
(α, β)
Sympathetic
Ach
Nicotinic
Ach
Muscarinic
Sympathetic
Ach
Nicotinic
D
Dopaminergic
(D1)
Sympathetic (adrenal medulla)
Ach
Nicotinic
Epi
Motor (somatic)
Ach
Nicotinic
Effectors
Cardiac & smooth muscles, gland cells, nerve terminals
Cardiac & smooth muscles, gland cells, nerve terminals
Sweat glands
Renal vascular smooth muscle
Released into blood
Skeletal muscle
Ach = acetylcholine
D = dopamine
Epi = epinephrine
NE = norepinephrine

DENERVATION HYPERSENSITIVITY

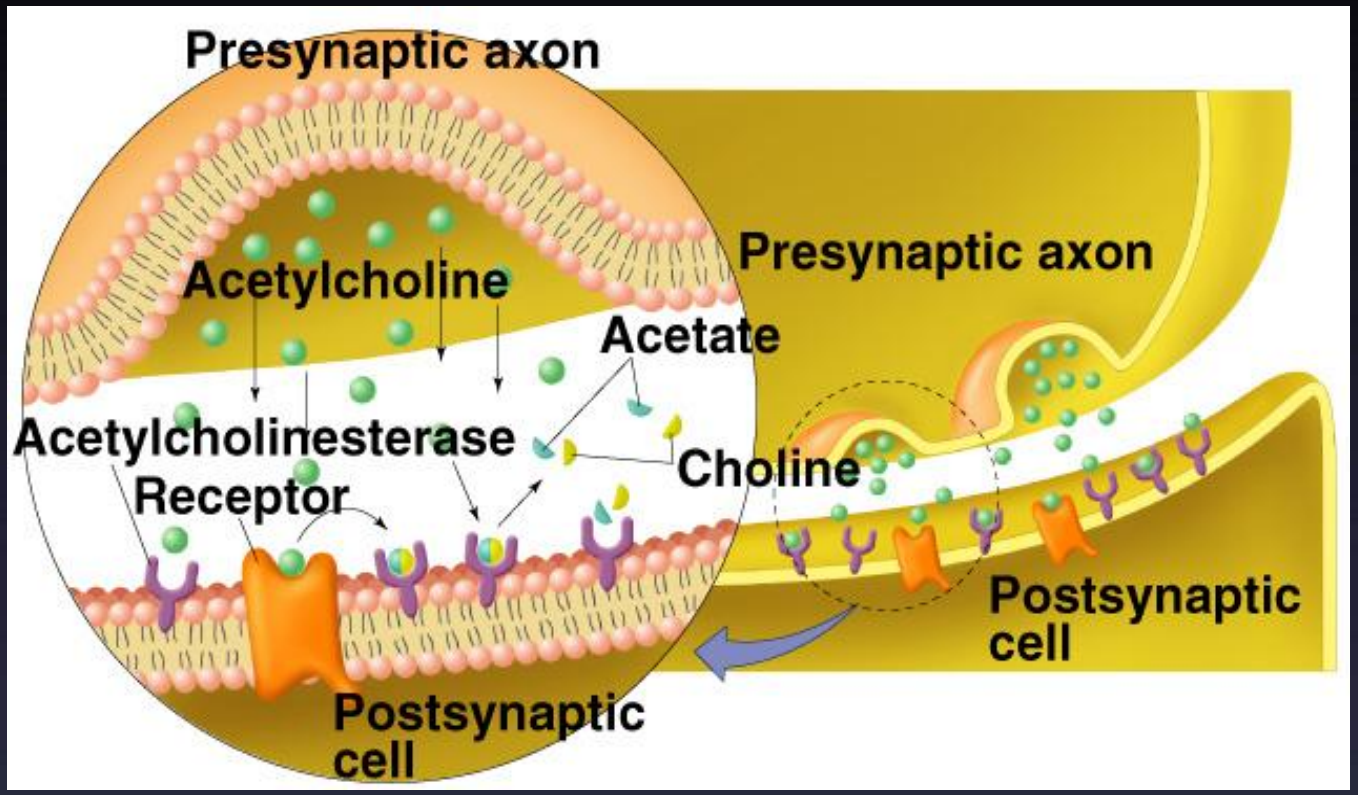
- **Definition:** When the motor nerve to skeletal muscle is cut and allowed to degenerate, the muscle gradually becomes extremely sensitive to acetylcholine.
- **Mechanism:** Normally nictinic R are located only in vicinity of motor end plate while after denervation there is a marked proliferation of nicotinic receptors over a wide region of the neuromuscular junction.
- **Cause:** upregulation of its receptors and lack of reuptake of secreted neurotransmitters.

Acetylcholine (ACh) as NT

- **ACh is both an excitatory and inhibitory NT depending on organ involved.**
  - **Causes the opening of chemical gated ion channels.**
- **Nicotinic ACh receptors:**
  - **Found in autonomic ganglia and skeletal muscle fibers.**
- **Muscarinic ACh receptors:**
  - **Found in the plasma membrane of smooth and cardiac muscle cells, and in cells of particular glands.**

Acetylcholinesterase (AChE)

- **Enzyme that inactivates Ach and is present on postsynaptic membrane or immediately outside the membrane.**
- **Prevents continued stimulation.**



NEUROMUSCULAR DISORDERS

MYASTHENIA GRAVIS:

•It is an NM disorder affecting the NMJ & it is characterized by impaired neuromuscular transmission & muscle weakness.

•Prevalence is 1/20000-30000.

•F/M ratio is 6:4.

•Age: any age

•Most patients have circulating autoantibodies to the postsynaptic nicotinic Ach receptors. A thymoma is found in approx 10% of patients.

•Features : weakness on exertion that improves with rest. Ocular, bulbar & facial muscles are commonly involved-ptosis, reduced facial expression,dysarthria & dysphagia.

•Diagnosis: By clinical features, Neostigmine test and nerve conduction studies (repetitive nerve stimulation RNS)

MYASTHENIA GRAVIS (CONT.)

- **Treatment:**

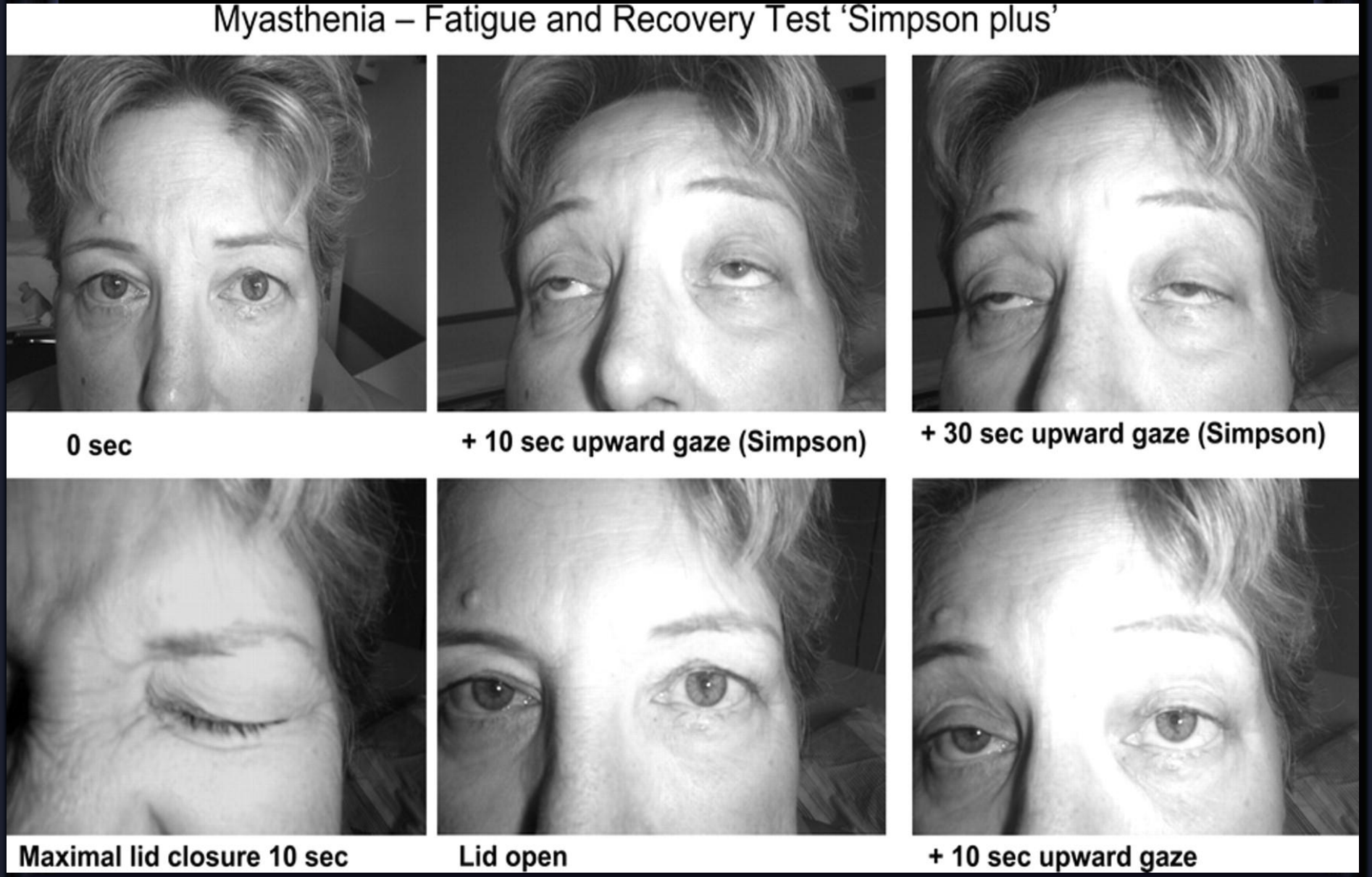
  ***oral anticholinesterases-pyridostigmine**

  ***Immunosupression-corticosteriods or azathioprine**

  ***Thymectomy – young onset, Ab positive pt, thymoma.**

  ***Plasmapheresis .**

MYASTHENIA GRAVIS-Fatigue and Recovery test



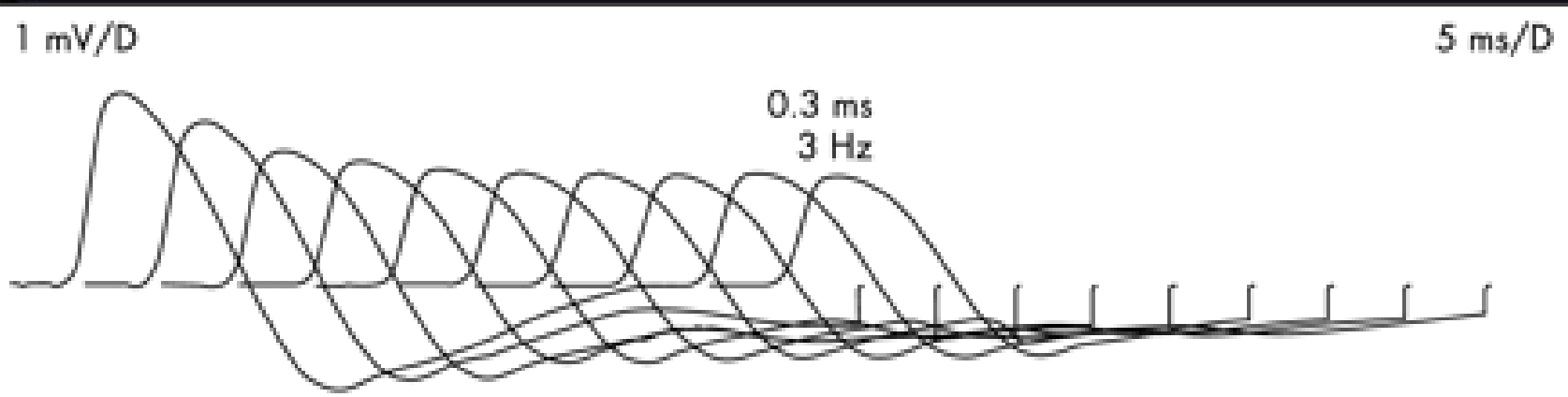
LAMBERT EATON MYASTHENIC SYNDROME (LEMS)

- It is an autoimmune neuromuscular disorder affecting the presynaptic neuromuscular junction.

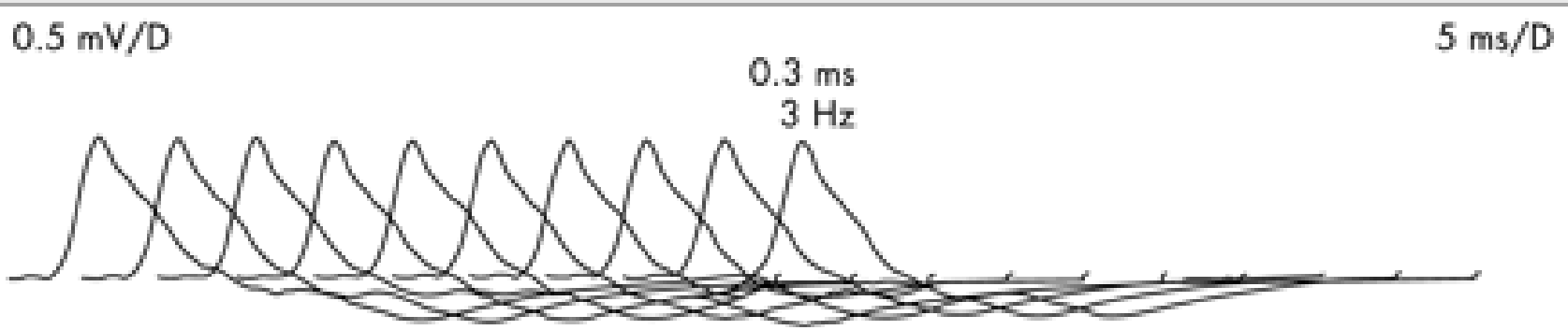
- Muscle weakness in LEMS is caused by auto-antibodies to voltage gated calcium channels at the presynaptic side of the neuromuscular junction leading to a reduction in the amount of acetylcholine released from nerve terminals

- Features: Fatigue, muscle pain and stiffness. The weakness is generally more marked in the lower extremity muscles. Also reduced reflexes, drooping of the eyelids, facial weakness and problems with swallowing. Patients often report a dry mouth, impotence, and constipation.

- Diagnosis: Clinical symptoms, nerve conduction studies (repetitive nerve stimulation RNS) and the presence of auto-antibodies against voltage gated calcium channels.

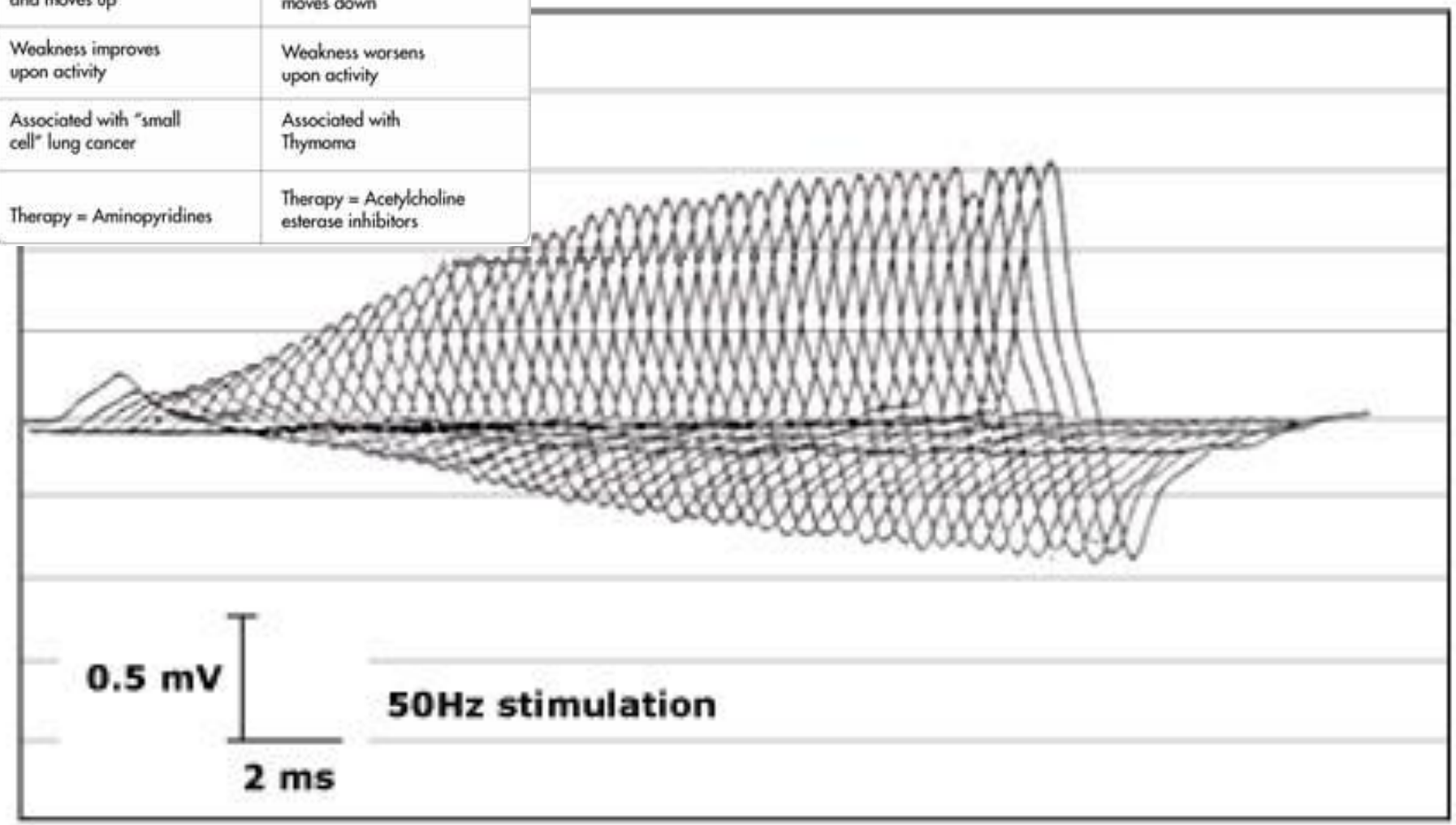


repetitive long thoracic nerve stimulation in Mysthenia Gravis



Normal repetitive long thoracic nerve stimulation

LEMS	Myasthenia-Gravis
Antibodies against the **nerve** where acetylcholine is released	Antibodies against the **muscle receptor** for acetylcholine
Starts at extremities and moves up	Starts at eyes and moves down
Weakness improves upon activity	Weakness worsens upon activity
Associated with "small cell" lung cancer	Associated with Thymoma
Therapy = Aminopyridines	Therapy = Acetylcholine esterase inhibitors



Repetitive long thoracic nerve stimulation in LEMS


THANKS