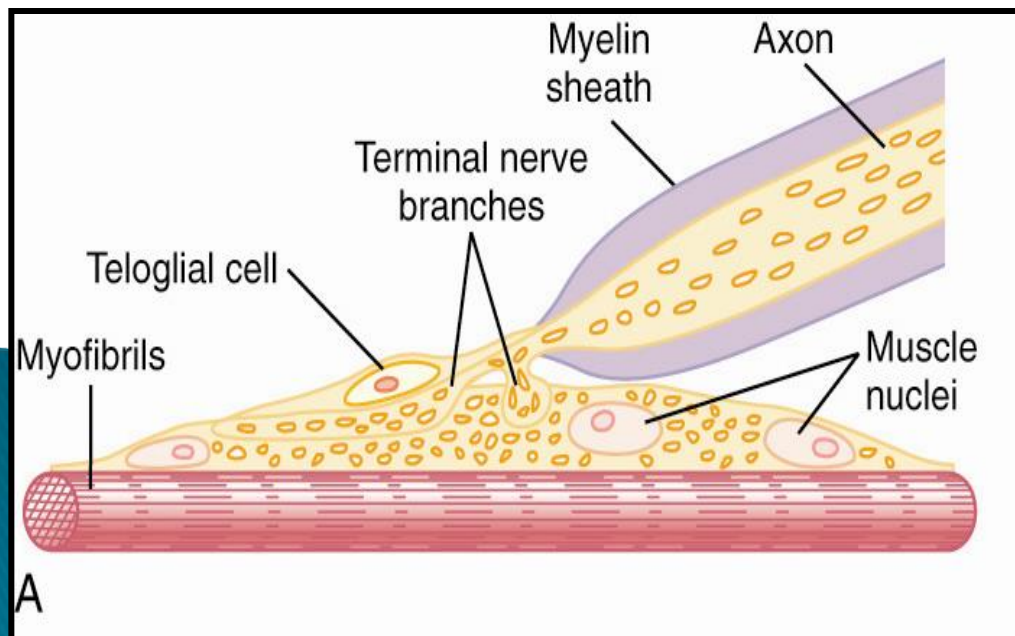


*Nerve -muscle physiology*

# ***Neuro –muscular transmission***



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# *SLO*

- ▶ To Know the structure of N–M junction
- ▶ To Know the events of Transmission
- ▶ To Know Drugs acting at N–M junction
- ▶ To Know Applied aspects of N–M junction

- Skeletal muscles must be stimulated by a nerve to contract (motor neuron)
  - Motor unit
    - One neuron
    - Muscle cells stimulated by that neuron
- 

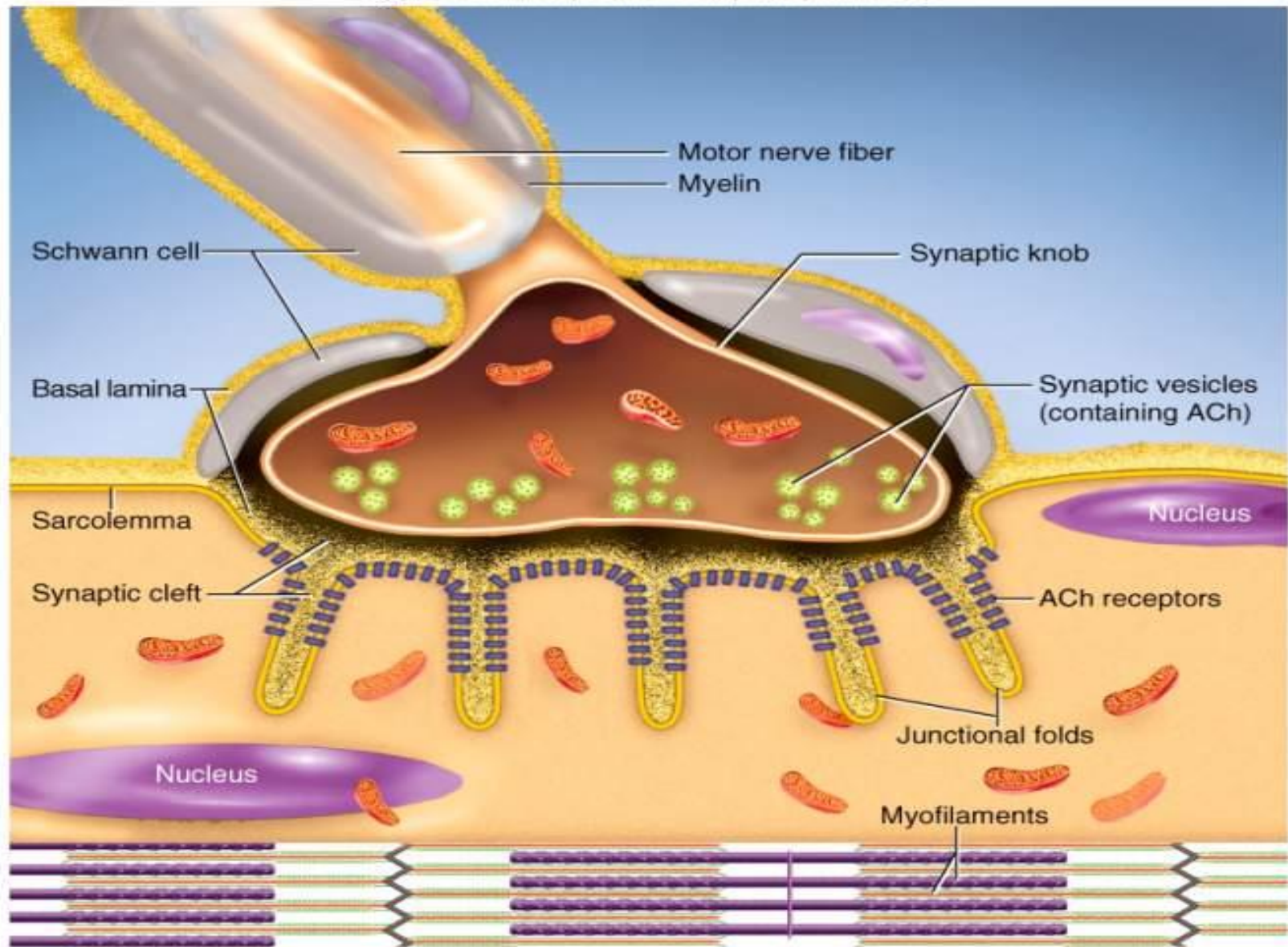
# Neuromuscular junction

Neuromuscular junctions –

- association site of nerve and muscle
- Specialized synapse between a **motor neuron** and a **muscle fiber**
- Occurs at a structure on the muscle fiber called the **motor end plate** (usually only one per fiber)

# The Neuromuscular Junction

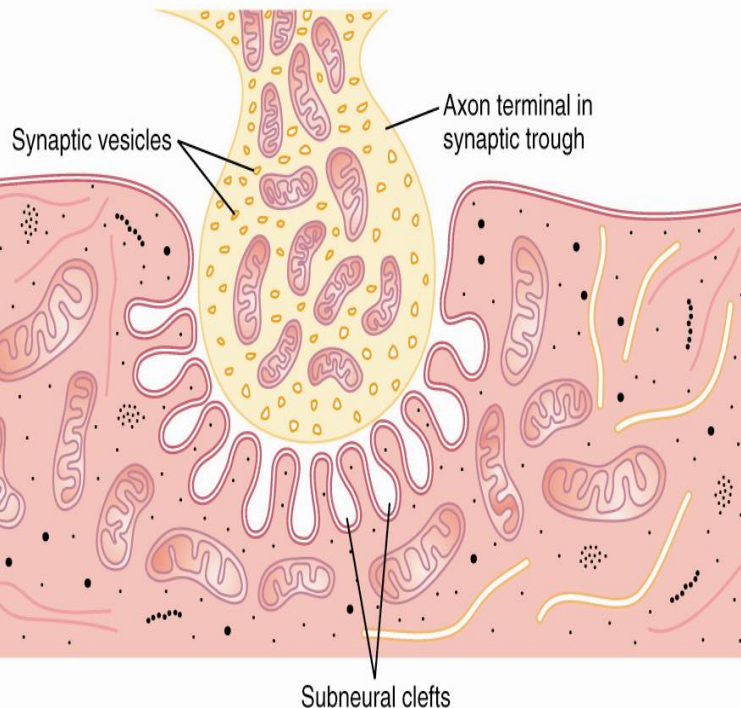
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(b)

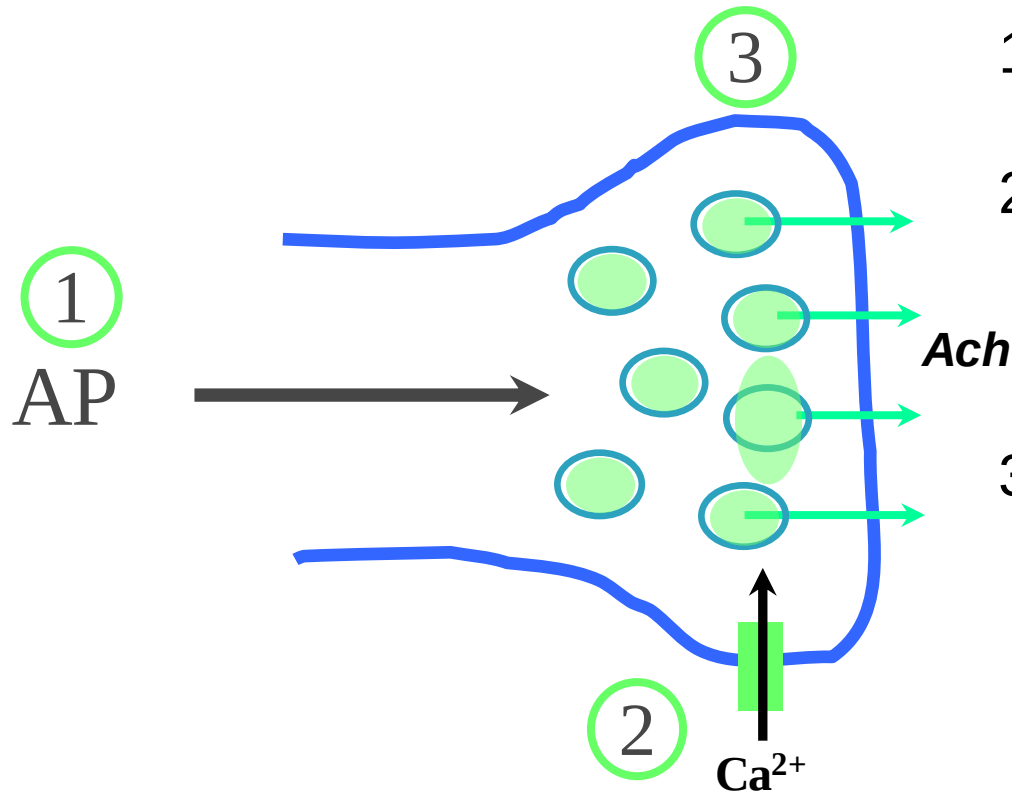
# Neuromuscular Junction

**Synaptic trough:**  
invagination in the  
motor endplate  
membrane



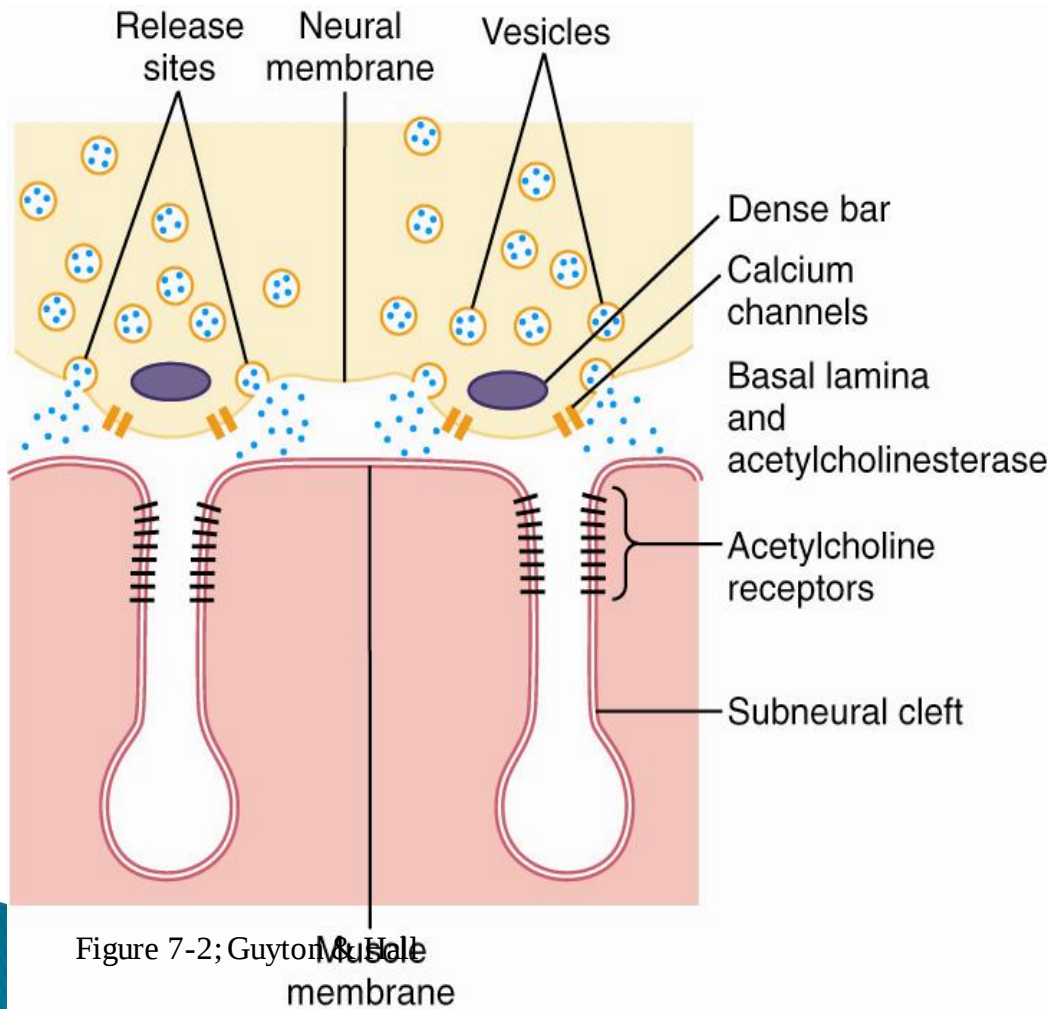
- **Synaptic cleft:**
  - gap between nerve and muscle
  - Nerve and muscle do not make contact
  - Area between nerve and muscle is filled with interstitial fluid
  - 20-30 nm wide
  - contains large quantities of **acetylcholinesterase (AChE)**
- **Subneural clefts:**
  - increase the surface area of the post-synaptic membrane
  - ACh gated channels at tops
  - Voltage gated  $\text{Na}^+$  channel in bottom half

# Events at N-M junction- *ACh Release*



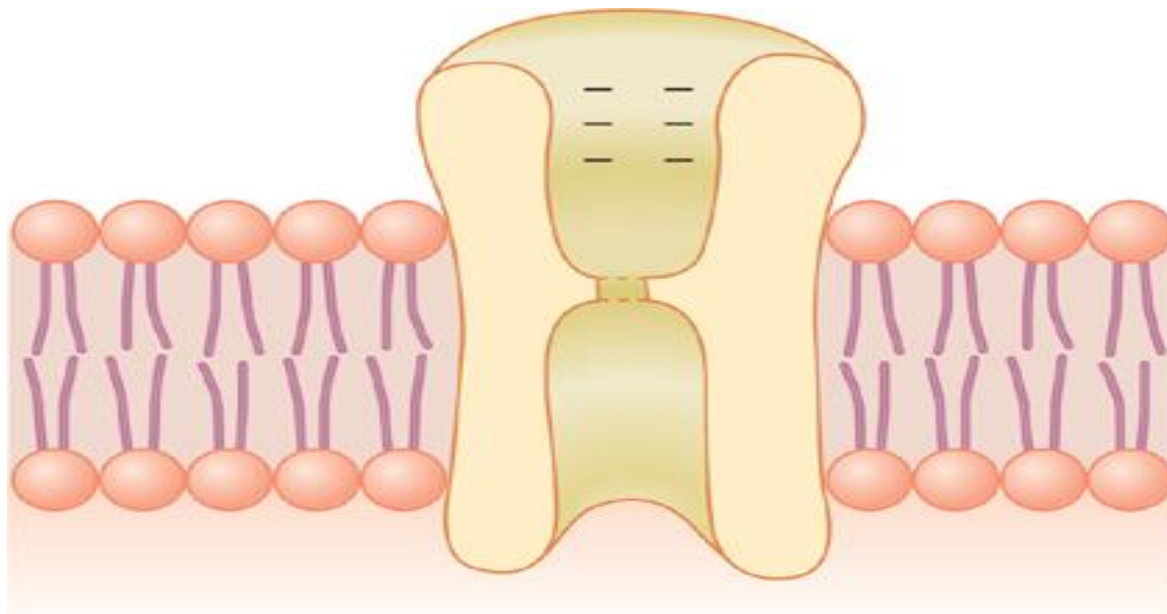
1. AP begins in the ventral horn of spinal cord.
2. Local depolarization at synaptic knob opens voltage-gated  $\text{Ca}^{2+}$  channels.
3. An increase in cytosolic  $\text{Ca}^{2+}$  triggers the fusion of synaptic vesicles with the pre-synaptic membrane and release of ACh (*exocytosis*).

# ACh Release - *details*

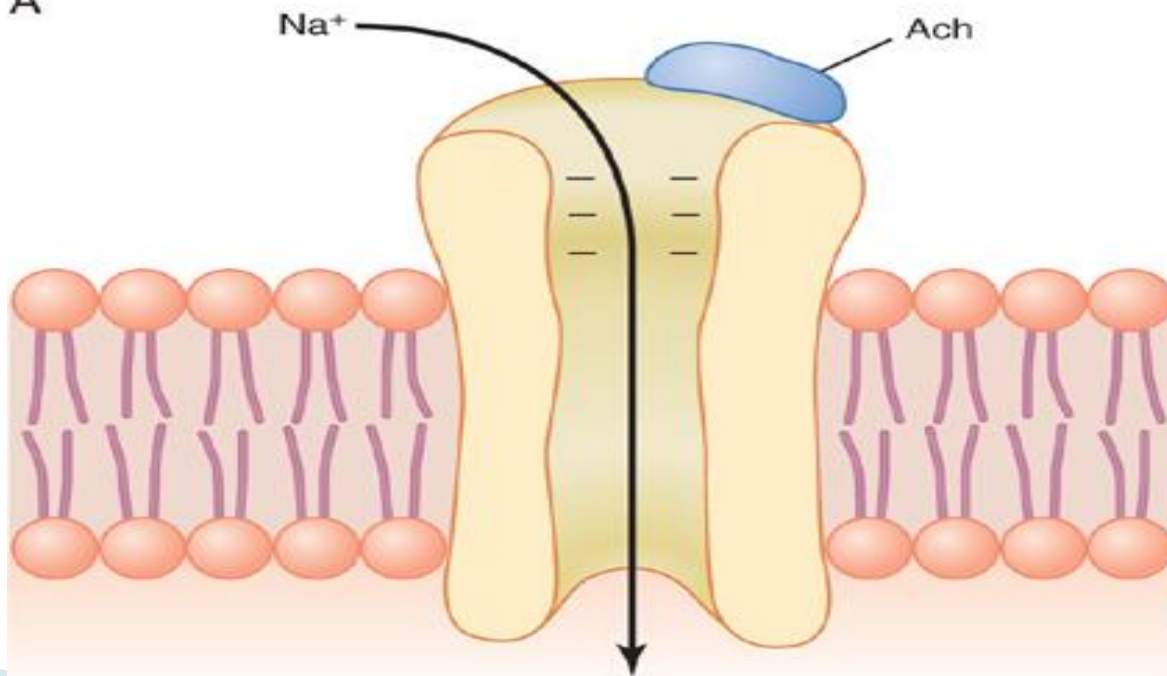


- $\text{Ca}^{2+}$  channels are localized around linear structures on the pre-synaptic membrane called **dense bars**.
- Vesicles fuse with the membrane in the region of the dense bars.
- Ach receptors located at top of subneural cleft.

- ▶ ACh released into the neuromuscular junction binds to, and opens, *nicotinic ACh receptor channels* on the muscle fiber membranes ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ).
- ▶ Opening of nicotinic ACh receptor channels produces an **end plate potential**, which will **normally** initiate an AP if the local spread of current is sufficient to open more and more sodium channels.
- ▶ *Acetylcholinesterase*



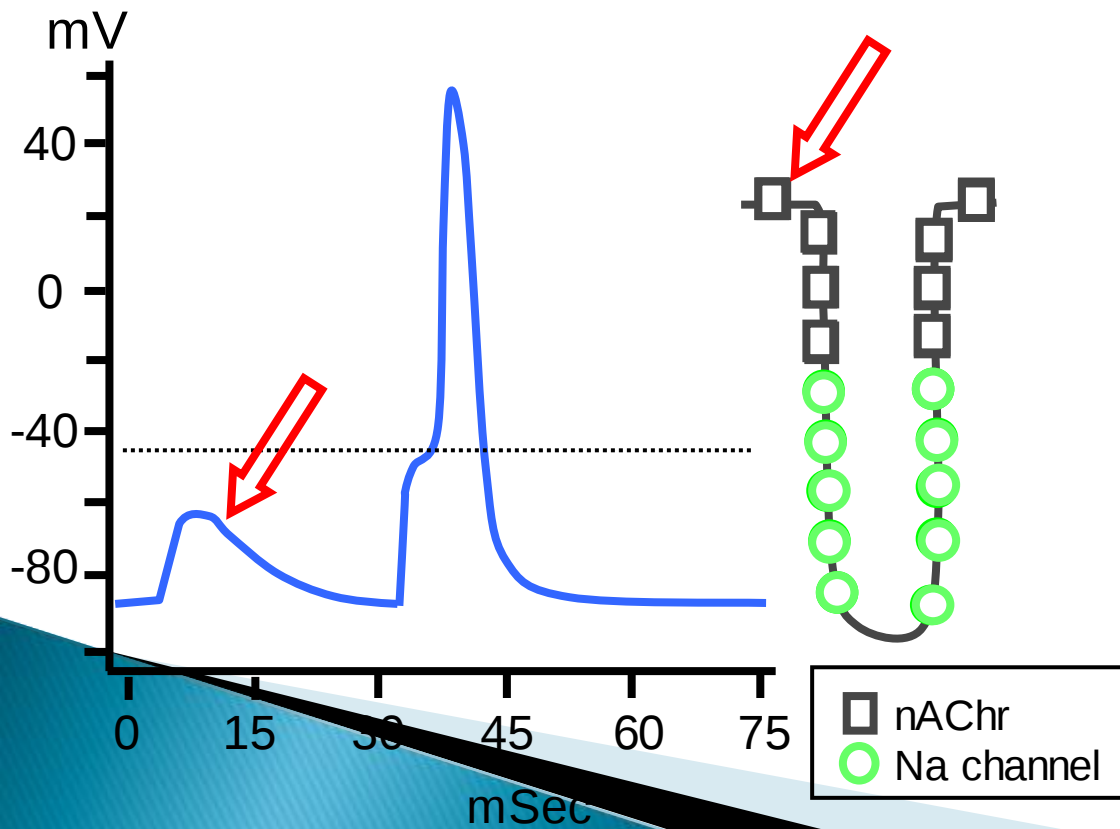
A



B

# End Plate Potential and Action Potential

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



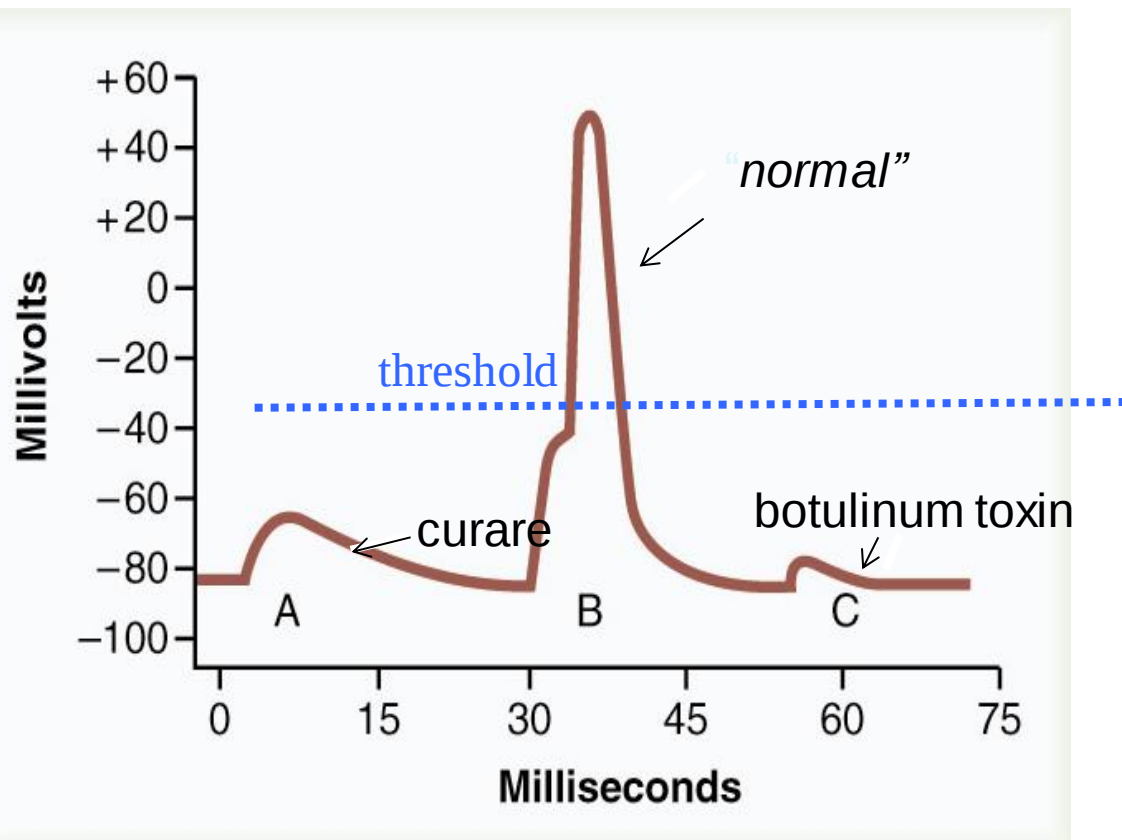
- Opening of nACh receptor channels produces an **end plate potential**, which will **normally** initiate an AP if the local spread of current is sufficient to open more and more sodium channels.

- What terminates the process?*

**Acetylcholinesterase**

# Drug Effects on End Plate Potential

## - *Inhibitors*



### Curariform drugs (D-tubocurarine)

- 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

# Drug Effects on End Plate Potential

## - *Stimulants*

**ACh-like drugs** (*methacholine, carbachol, nicotine*)

- bind and activate nicotinic ACh receptors
- not destroyed by AChE – prolonged effect

**Anti-AChE** (*neostigmine, physostigmine, diisopropyl fluorophosphate or “nerve gas”*)

- block the degradation of ACh
  - prolong its effect
- 

# Myasthenia Gravis

## Incidence:

- 2 per 10,00,000 people / year

## symptoms:

- rapid onset with muscular weakness
- Most commonly affected –extra ocular, facial, mastication muscles.
- 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 destroys them
- weak end plate potentials

## Treatment:

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

# ***Lambert-Eaton Myasthenic Syndrome***

## **Incidence / symptoms:**

- 1 per 100,000 people / year
- 40% also have small cell lung cancer
- muscle weakness/paralysis

## **Cause:**

- LEMS results from an autoimmune attack against **voltage-gated calcium channels** on the presynaptic motor nerve terminal.
- weak end plate potentials

## **Treatment:**

- can be treated with anti-AChE (neostigmine)
- increases amount of ACh in nmj