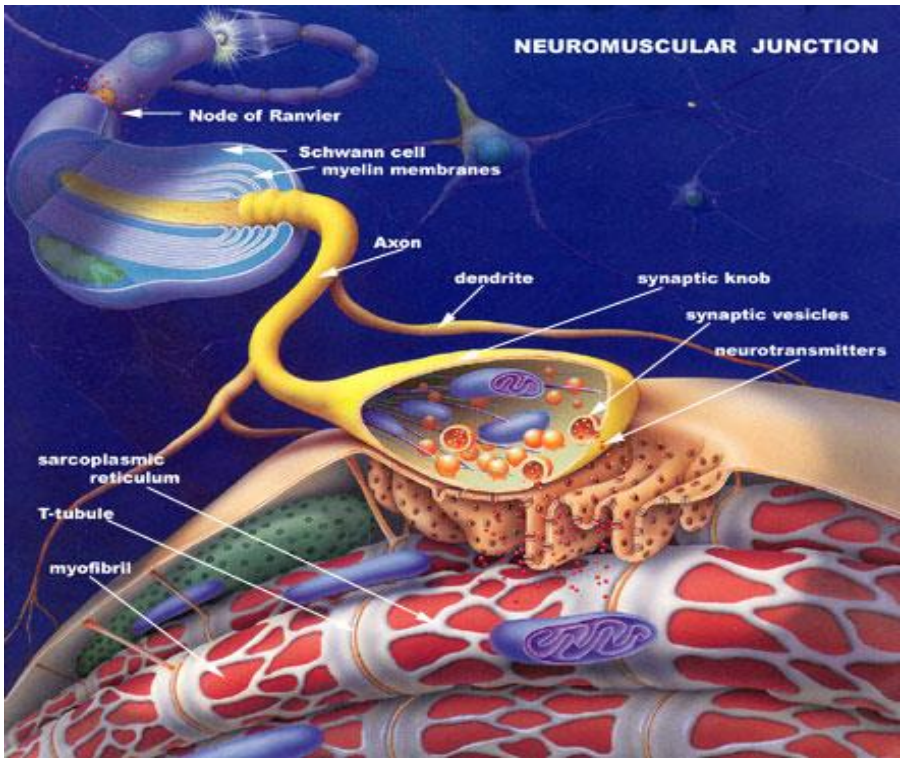
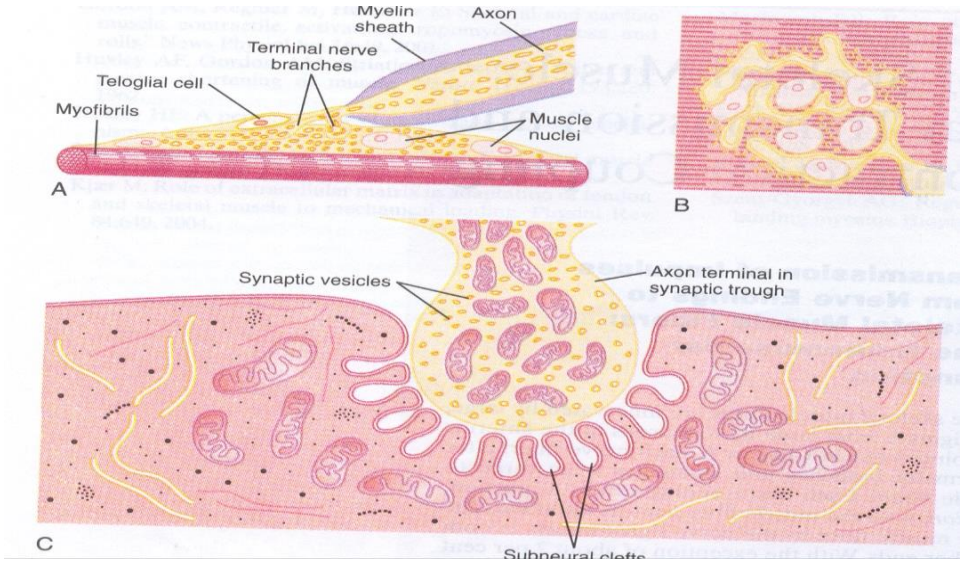
NEUROMUSCULAR JUNCTION – I

Neuromuscular junction

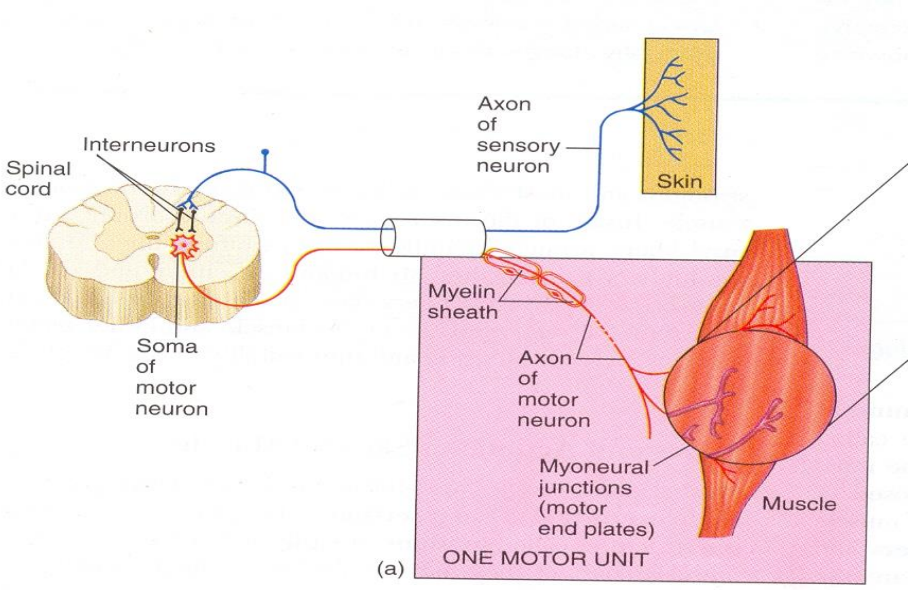


- **The skeletal muscle fibers are innervated by large motor neurons in the anterior horn of spinal cord.**
- **Junction between a motor neuron and a skeletal muscle fibre.**
- **Also called Myoneural junction.**

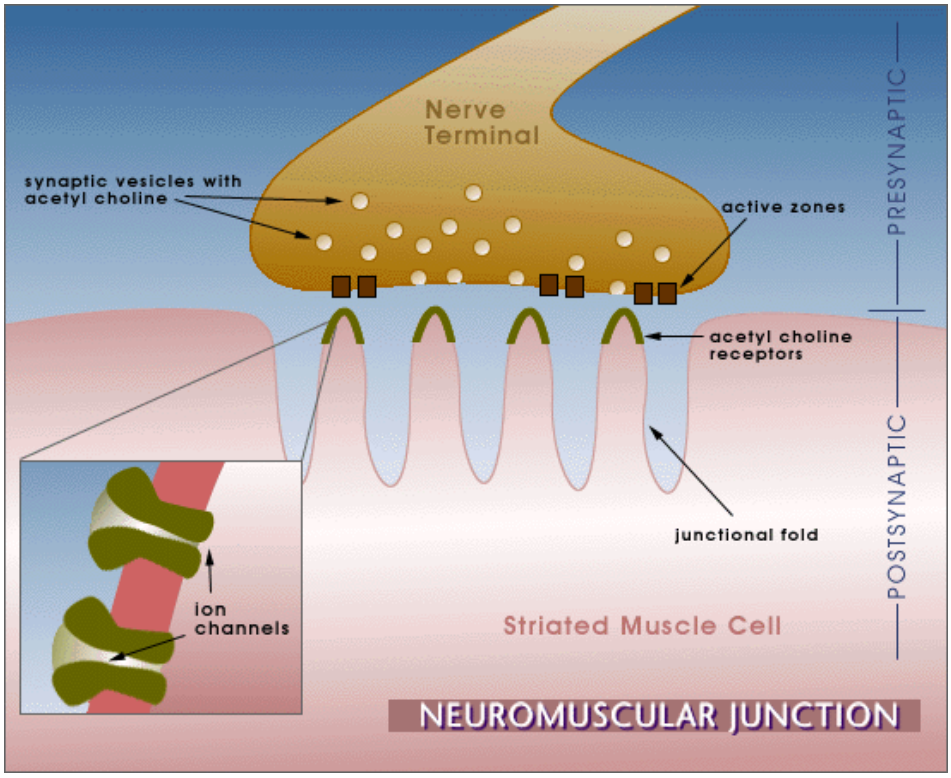
NEUROMUSCULAR JUNCTION



PHYSIOLOGIC ANATOMY

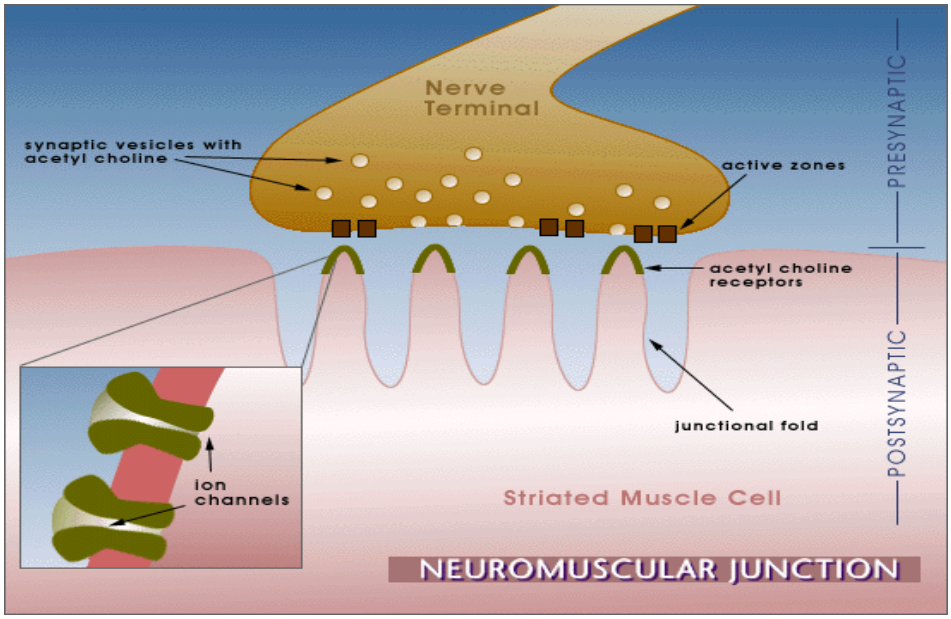


Anatomy of neuromuscular junction



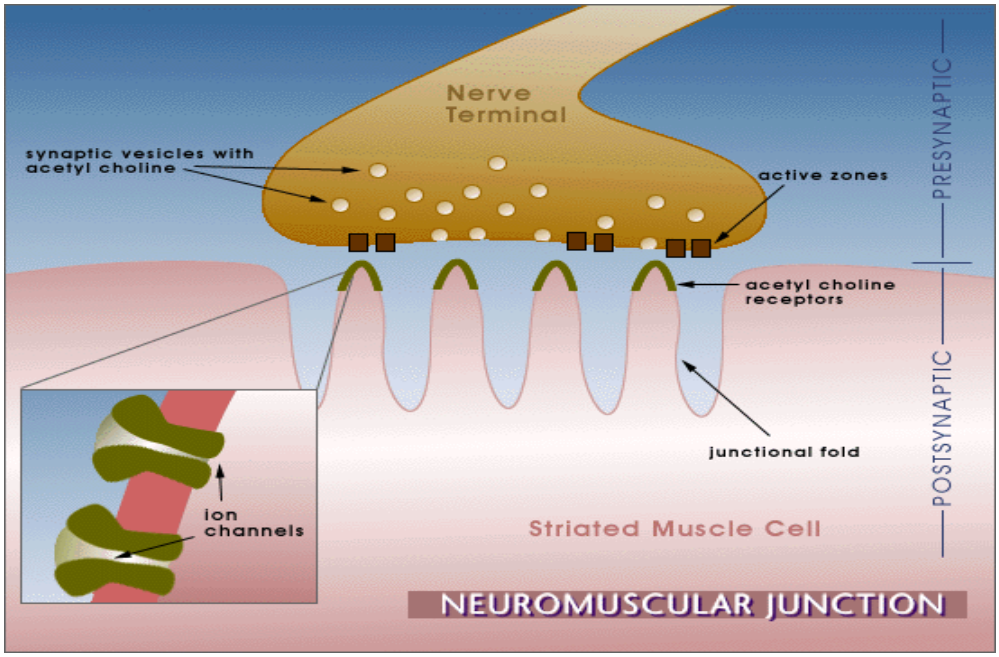
- The nerve fibers form a complex of branching nerve terminals.
- At termination, axon of motor neuron loses myelin sheath and lie outside the muscle fiber membrane.

Anatomy of the neuromuscular junction



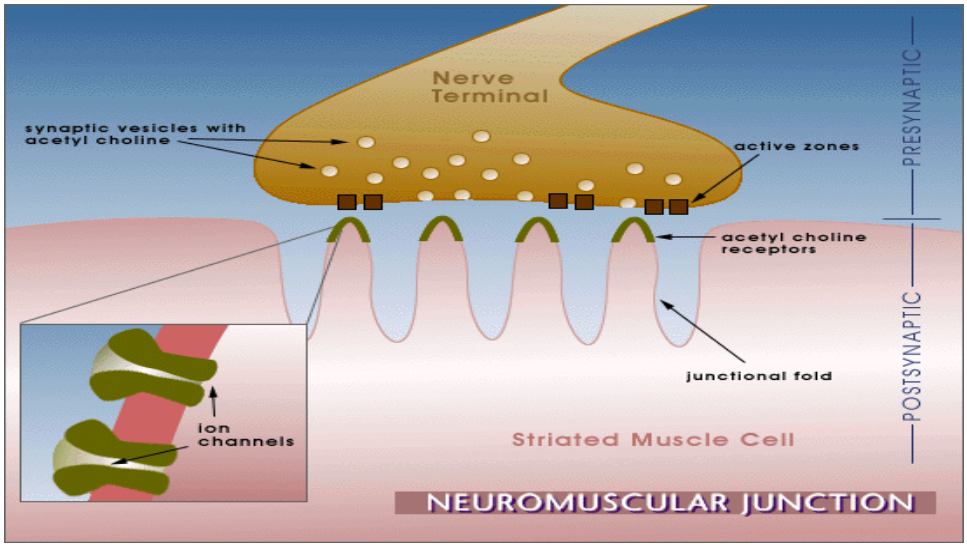
- These terminal branches show dilatation at end called synaptic knob or sole foot or terminal buttons
- Each branch develops contact with a separate muscle fibre

Anatomy of the neuromuscular junction



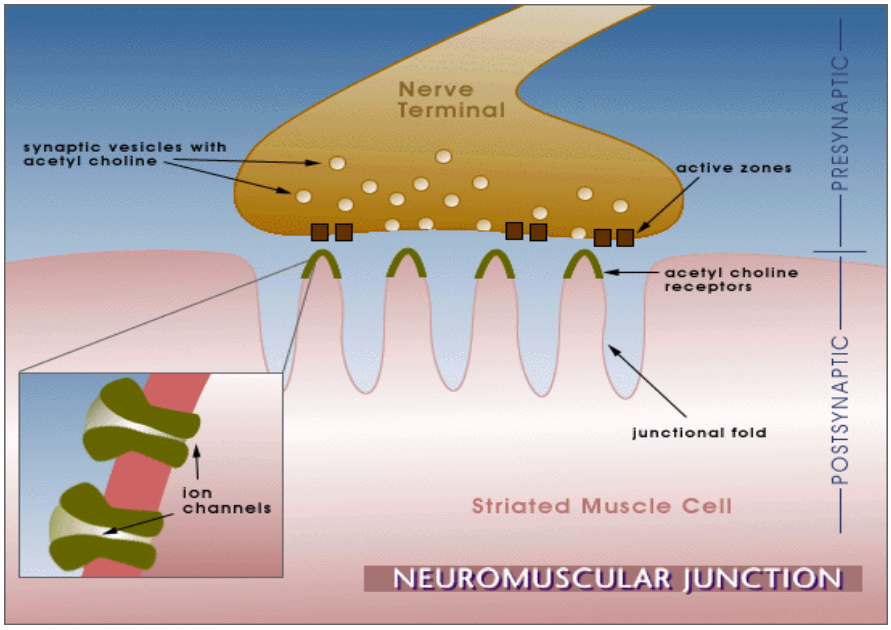
- Presynaptic nerve terminal contains **mitochondria** and **synaptic vesicles** (**3,00,000)** with neurotransmitter **Ach.**
- Vesicles are clustered around specific points called **Active zones or Dense bars,** that contain numerous voltage gated Ca++ channels.

Anatomy of the neuromuscular junction



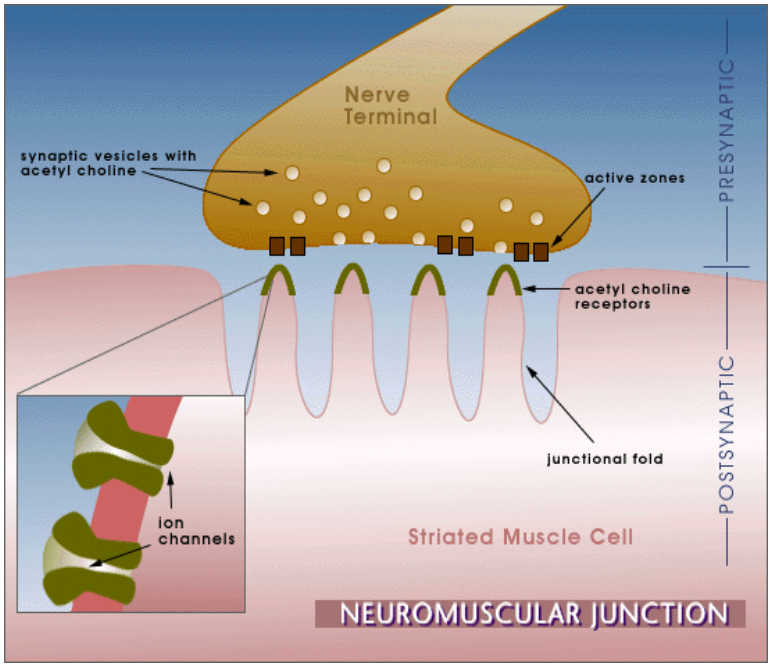
- The space between two membrane called the **synaptic cleft (40-100 nm wide)** filled with ECF
- **Motor end plate** is the thickened part of the muscle membrane (sarcolemma) which makes a close contact with the axon terminal

Anatomy of the neuromuscular junction

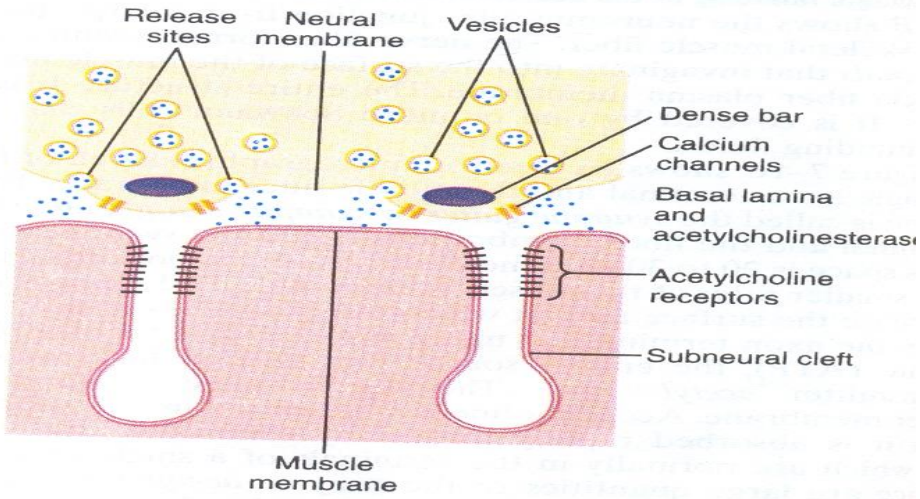


- This shows a small depression called **synaptic gutter or synaptic trough**
- The terminal button fits into the synaptic trough
- Muscle membrane of motor end plate is thrown into folds called **junctional folds** which increase the surface area

Anatomy of the neuromuscular junction



- The **Ach receptors** are found near the mouths of the junctional folds
- Below the junctional folds many voltage gated Na+ channels present
- Acetyl-cholinesterase found in high concentration in synaptic clefts,which hydrolyzes Ach



SECRETION OF ACETYLCHOLINE BY THE NERVE TERMINALS

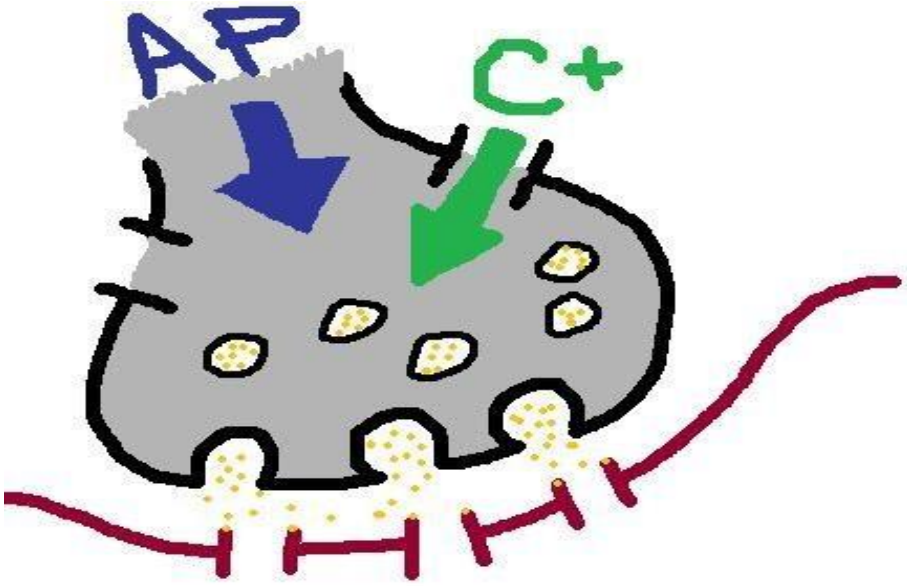
Arrival of AP at axon terminal

Voltage-gated Ca^{++} channels open & Ca^{++} influx

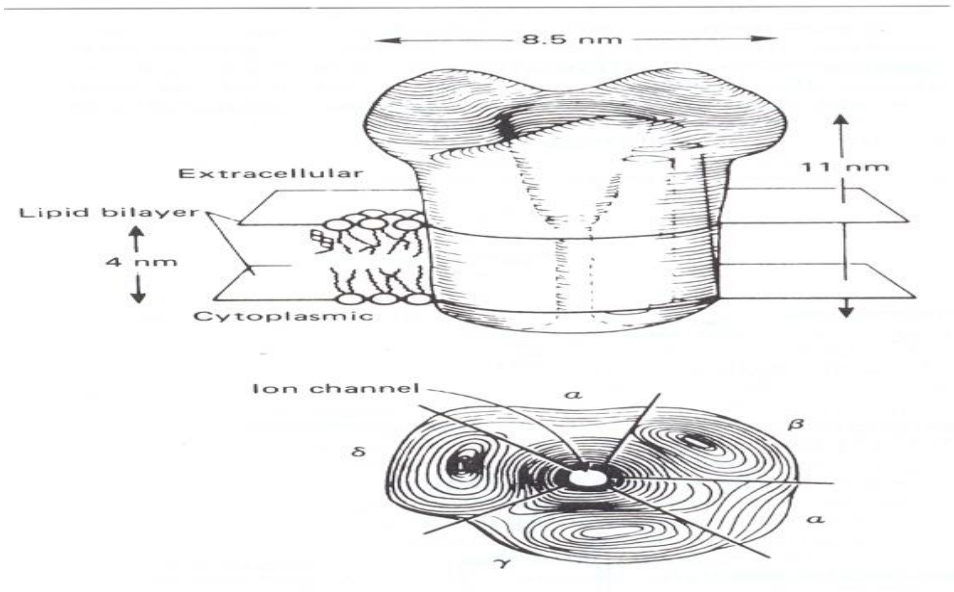
125 vesicles are drawn to presynaptic membrane

Ach vesicles are fused (Synaptobrevin & Syntaxin)

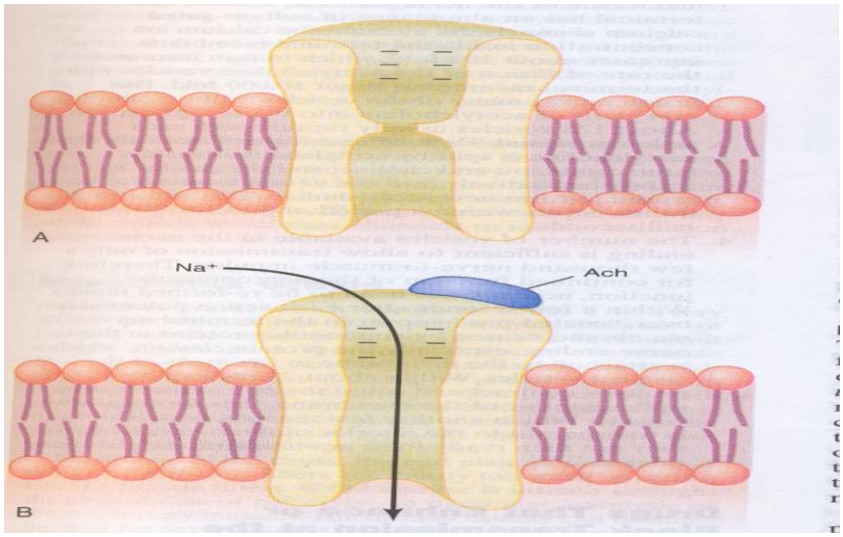
Ach is emptied by exocytosis

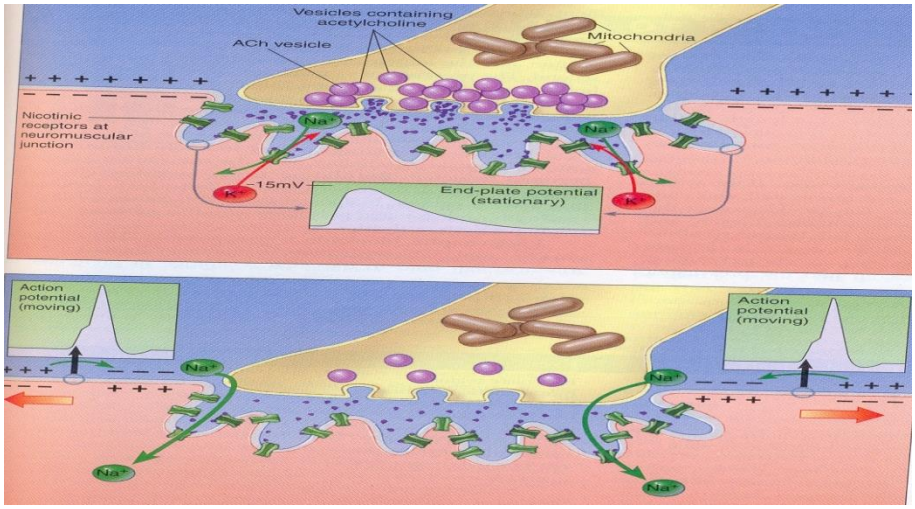


ACETYLCHOLINE CHANNEL (NICOTINIC)



ACETYLCHOLINE CHANNEL





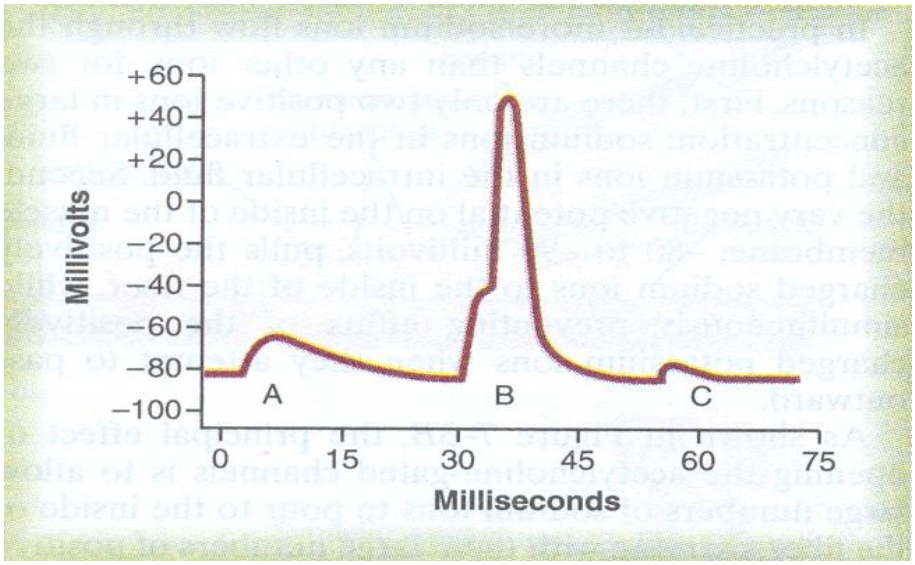
ACETYLCHOLINE GATED ION CHANNELS

- Molecular weight- 2,75,000; Diameter – 0.65 nm
- Each consists of 2α, 1ß, 1γ and 1δ subunits
- It remains constricted until 2 Ach molecules attach to 2 α subunits
- Na^+, K^+ & Ca^{++} move easily creating endplate potential

ENDPLATE POTENTIAL & EXCITATION OF SKELETAL MUSCLE FIBERS

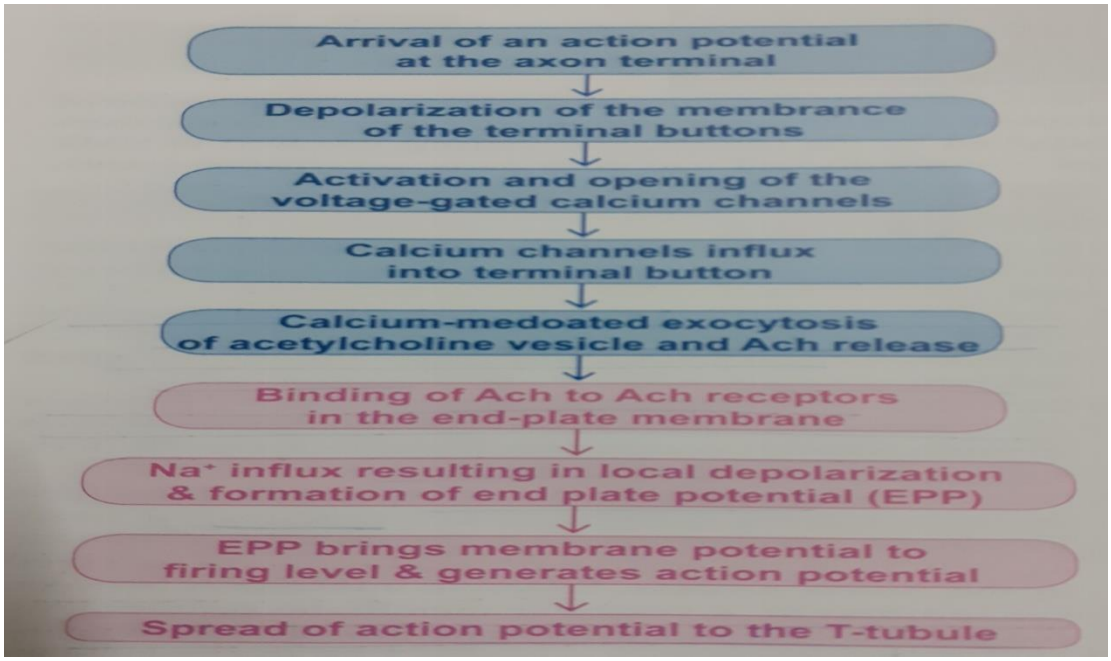
- An average human endplate contains 15-40 million Ach receptors. Each nerve impulse releases 125 vesicles and each vesicle contains 10,000 molecules of Ach.
- Sudden influx of Na^+ causes membrane potential to increase in the positive direction called end plate potential.

ENDPLATE POTENTIAL

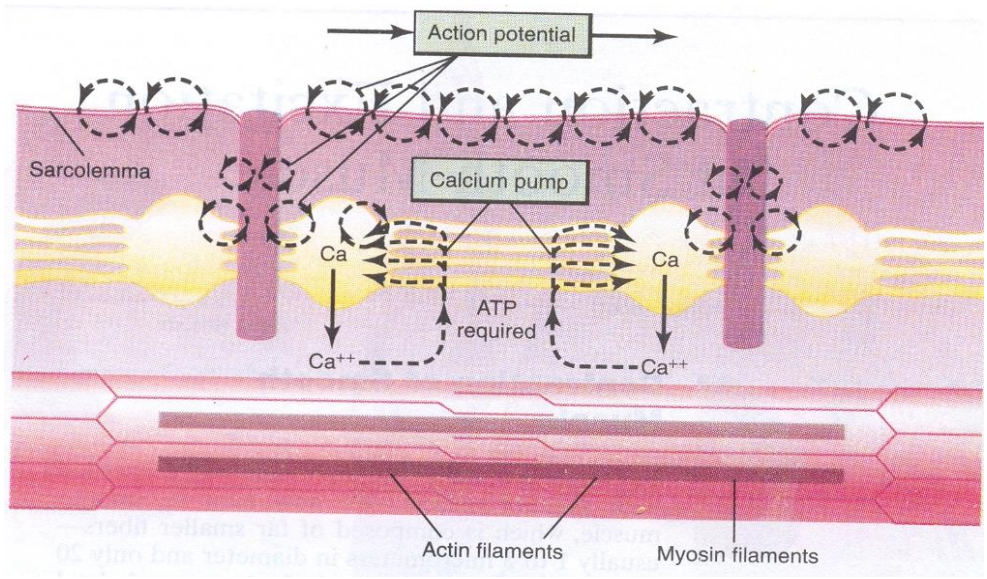


A- Curare C - Botulinum Toxi

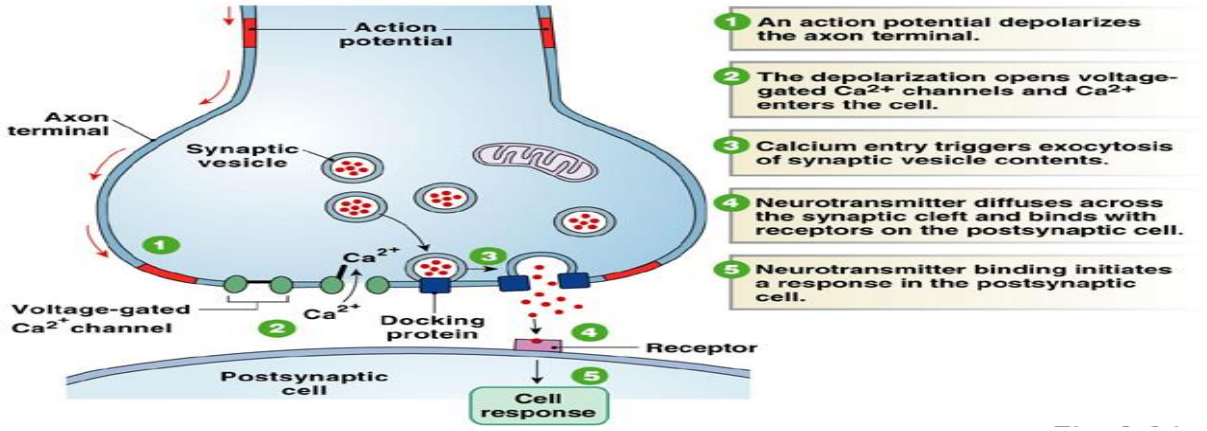
MECHANISM OF NEUROMUSCULAR TRANSMISSION



EXCITATION – CONTRACTION COUPLING



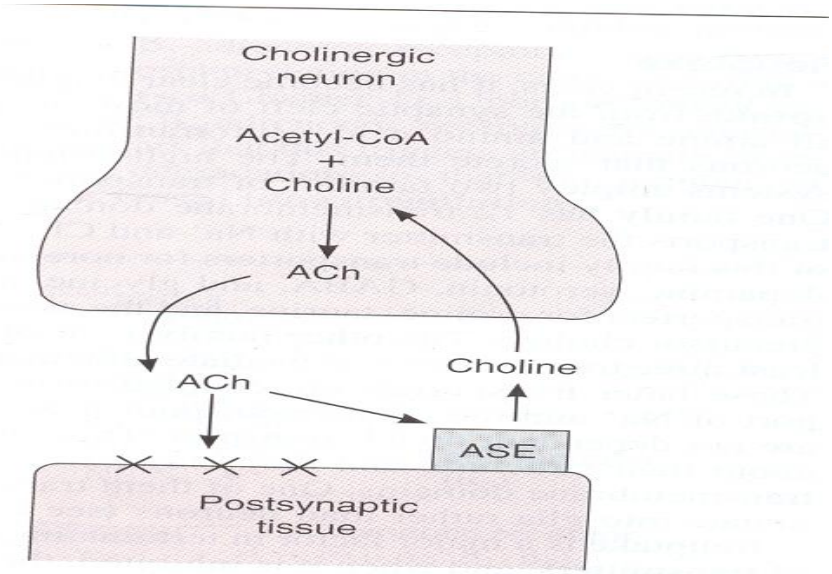
Summary



ACETYLCHOLINE FORMATION AND RELEASE

1. Small vesicles (40 nm in diameter) via streaming in the axoplasm comes to NM junction
2. About 3,00,000 Ach vesicles collect in nerve terminals

SYNTHESIS OF ACETYLCHOLINE



3. Under resting conditions, miniature endplate

potential of 0.5 mV in amplitude is produced

4. When an action potential arrives at the terminal,

it opens Ca^{++} channels - 125 vesicles rupture with each action potential

5. The vesicles are replenished by coated pits with the help of contractile proteins called clathrin

DESTRUCTION OF ACETYLCHOLINE

- It is destroyed by acetylcholine esterase
- A small amount of Ach diffuses out of the

synaptic space and no longer available

BLOCKADE OF NEUROMUSCULAR TRANSMISSION

Neuromuscular transmission is disrupted at different steps by

- Drugs
- Chemicals
- Toxins

Trauma

Types:

- **Presynaptic blockade – impaired Ca^{++} influx**

causing decreased vesicle release

- **Postsynaptic blockade – affects the**

generation of EPP

Presynaptic blockade

- 1. Botulinum toxin
- Clostridium botulinum – Botulism
- Lethal dose for adult human – 2-3µg
- B. toxin inactivates synaptobrevin & syntaxin
- It inhibits the release of Ach from the axon terminals – flaccid paralysis
- Clinical use – Achalasia cardia

2. Hemicholinium

It inhibits choline uptake by the presynaptic terminals

Depletion of Ach

EPP decreases & AP is not formed

Postsynaptic blockade

- Competitive blockers
- Depolarising blockers

1. Competitive blockers

- **They compete with Ach for its receptor sites.**
- **Ion channels are not opened.**
- **Ach fails to bind to its receptors, absence of EPP and lack of muscle contraction.**
- **Eg: Curare & gallamine**

- **Curare : A plant product, arrow head poison for hunting.**
- **Gallamine : It is given before surgery to relax the skeletal muscles.**

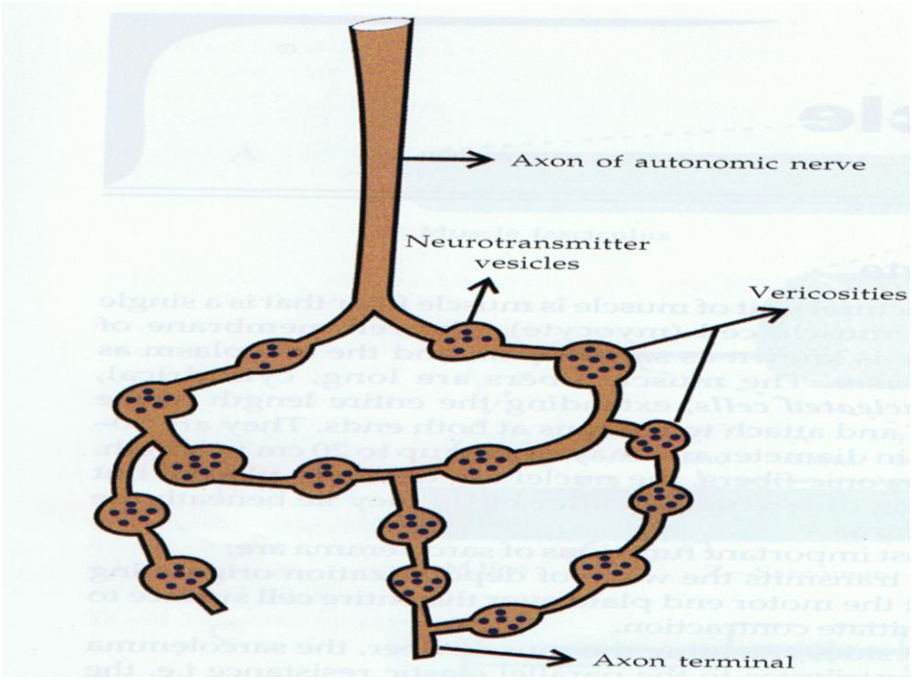
2. Depolarising blockers

- **Succinylcholine & carbamylcholine have biological activity of Ach but not hydrolyzed by AchE.**
- **Ion channels remain open.**
- **Maintained depolarisation keeps the Na^+ channels in an inactivated state.**

b) Irreversible AchE inhibitors

- **Organophosphorus compounds (pesticides like parathion, malathion & baygon)**
- **Nerve gas (Diisopropylflurophosphate) bind to AchE tightly.**
- **No further contraction resulting in death.**

AUTONOMIC NEURONS ON
SMOOTH MUSCLE



MYASTHENIA GRAVIS

- **It is an autoimmune disease characterised by weakness and fatiguability of skeletal muscles.**

- **Etiology: Decline in the no. of available AchR on the motor endplate due to the antibodies against these receptors.**
  The anti AchR antibodies
- **Compete with Ach to bind to AchR producing receptor blockade.**
- **Induce endocytosis of AchR.**
- **Damage the postsynaptic membrane.**
- **Women are affected more than men in a ratio of 3:2.**
- **There is a decremental response to repetitive nerve stimulation in the affected muscle.**
- **Symptoms aggravate towards evening.**
- **The extraocular muscles and the lids are often involved.**
- **Diplopia & ptosis are early symptoms.**

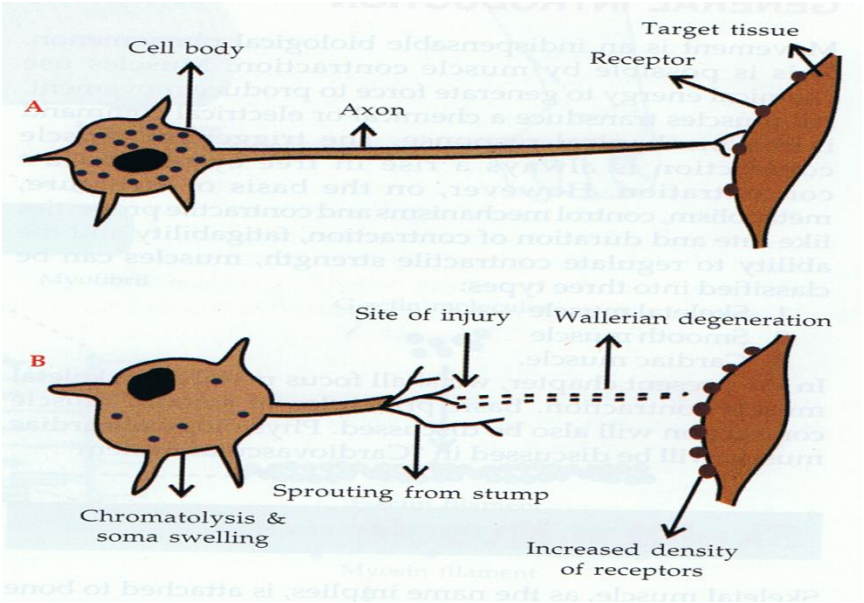
TREATMENT

- **Administration of AchE inhibitors – pyridostigmine & neostigmine.**
- **Thymectomy – blunts down the immune response.**
- **Immunosuppression – glucocorticoids & azathioprine.**
- **Plasmapheresis – removes AchR antibodies from plasma.**

DENERVETION HYPERSENSITIVITY

- **When a neuron is cut, the distal axon degenerates, the target tissue becomes more reactive to NT.**
  The phenomenon of increased responsiveness is known as denervation hypersensitivity.

DENERVATION HYPERSENSITIVITY
FOLLOWING NERVE INJURY



Hypersensitivity occurs due to 3 reasons:

- **Increased no. of receptors at the postsynaptic membrane (upregulation).**
- **Increased responsiveness (sensitivity) of receptors to the chemical.**
- **The reuptake of NT molecules by the presynaptic terminal is decreased.**