Neuromuscular junction

Neuro muscular junction

- The skeletal muscle fibers are innervated by a large myelinated nerve fiber that originate from large motor neurons in the anterior horns of spinal cord.
- Each nerve fiber before entering the muscle branches and stimulates from three to several hundred muscle fibers

Motor end plate

- Each terminal branch of nerve fiber when comes close to the muscle fiber it loses the myelin sheath and innervates the surface fiber is called motor end plate.

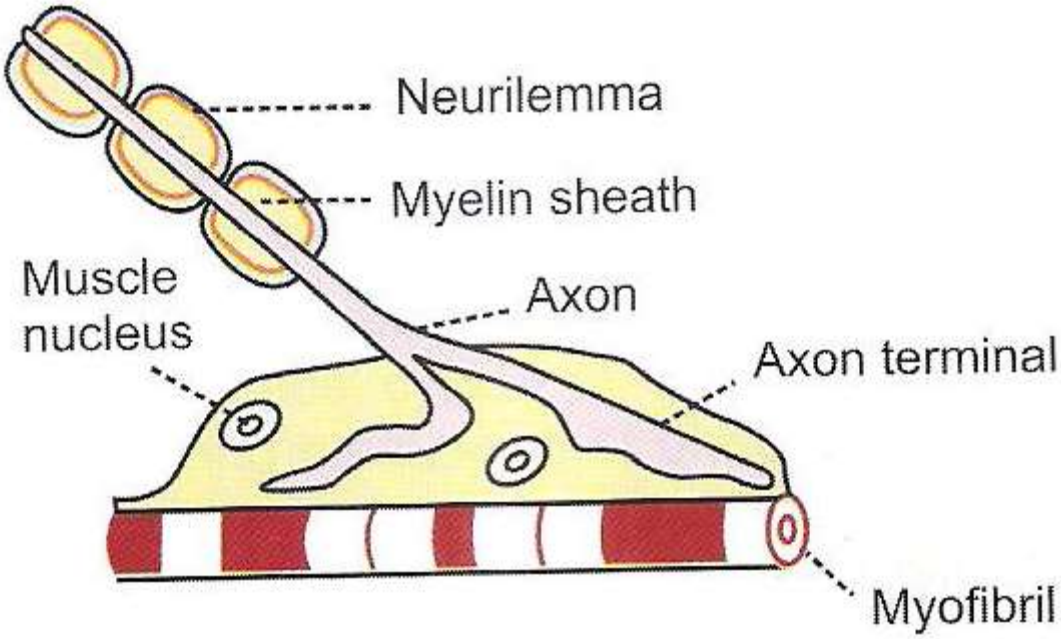


FIGURE 32-1: Longitudinal section of neuromuscular junction

Neuro muscular junction

- Each nerve ending makes a junction called the neuromuscular junction with the muscle fiber near its midpoint.

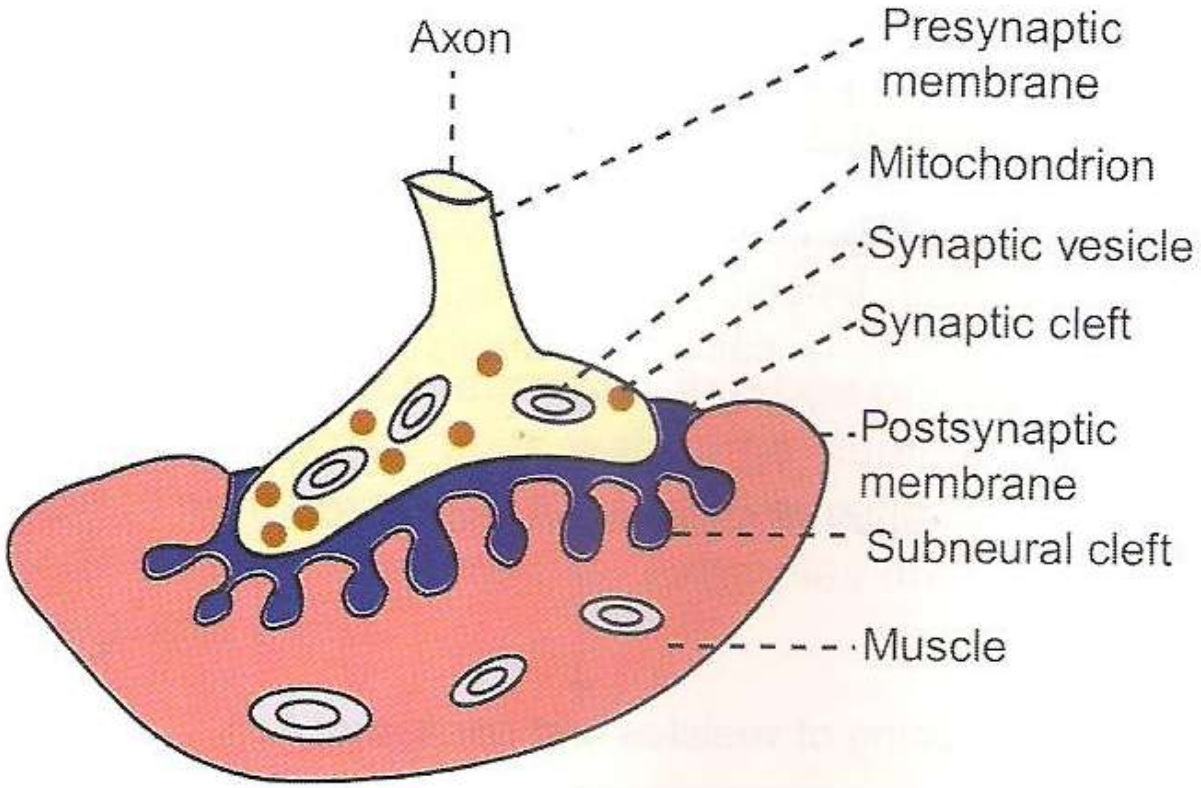


FIGURE 32-2: Structure of neuromuscular junction

Synaptic cleft

- The membrane of the nerve ending is called the presynaptic membrane.
- The membrane of the muscle fiber is called postsynaptic membrane.
- The space between these two is called synaptic cleft.
- The space is 20-30 nanometer wide.
- The axon terminal contain mitochondria and synaptic vesicles.
- The synaptic vesicles contain the neuromuscular substance acetylcholine.

Synaptic cleft

- The acetylcholine is synthesized by mitochondria present in the axon terminal and stored in the vesicle.
- The mitochondria contain ATP which is the source of energy for the synthesis of acetylcholine.

Synaptic cleft

- The synaptic cleft contain layer of spongy reticular matrix, which contain large quantities of acetylcholinesterase.
- Post synaptic membrane is the membrane of the muscle fiber. It is thrown into numerous folds called subneural cleft. The post synaptic membrane contain the receptors called NICOTINE ACETYLCHOLINE RECEPTORS

- In the synaptic space are large quantities of the enzyme acetylcholinesterase which destroy acetylcholine a few milliseconds after it has been released from the synaptic vesicles

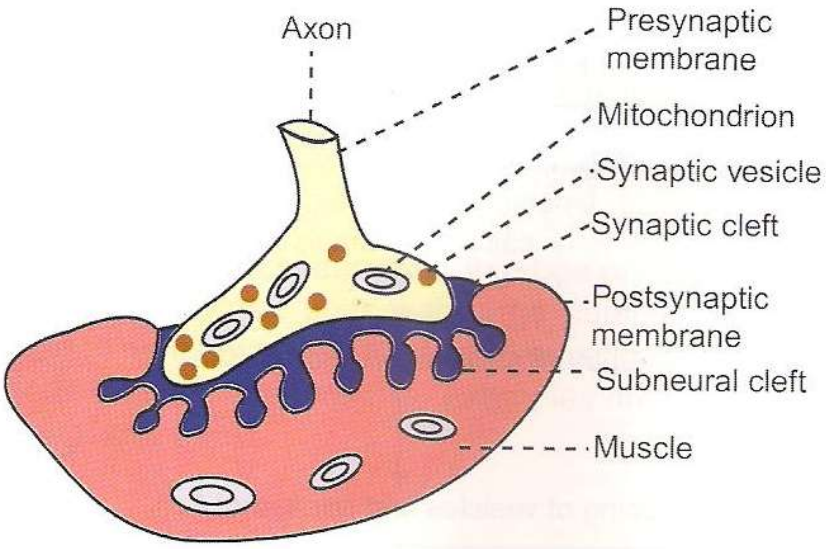
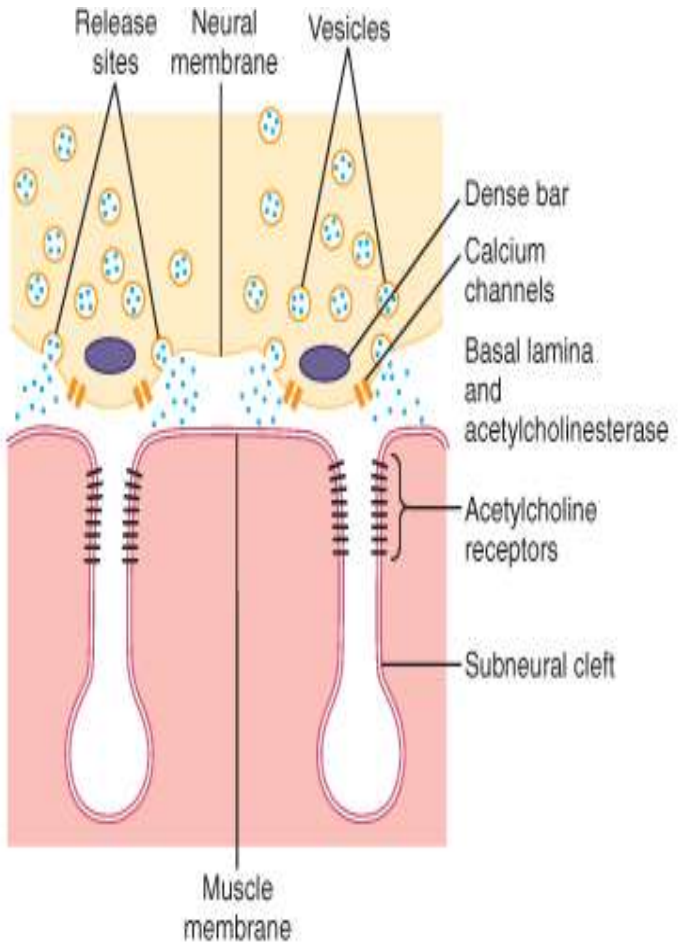


FIGURE 32-2: Structure of neuromuscular junction

RELEASE OF ACETYLCHOLINE

- When a nerve impulse reaches the neuromuscular junction about 125vesicles of acetylcholine are released from the terminal into the synaptic space.



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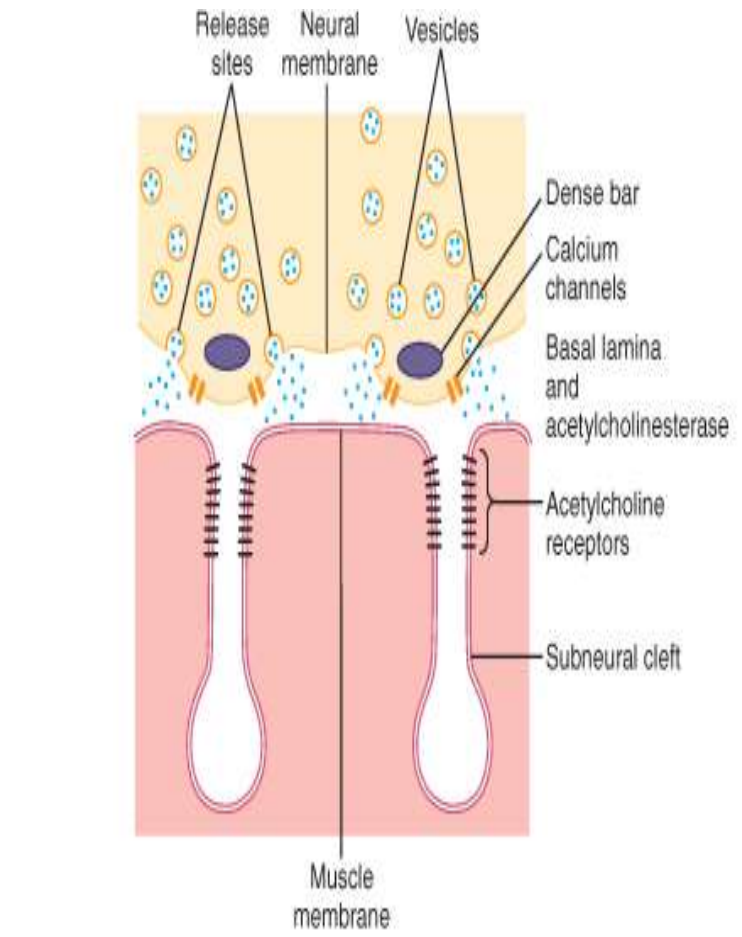
- On the inside of the neural membrane are linear dense bars.
- To each side of each dense bar are protein particles that penetrate the neural membrane these are voltage gated calcium channels



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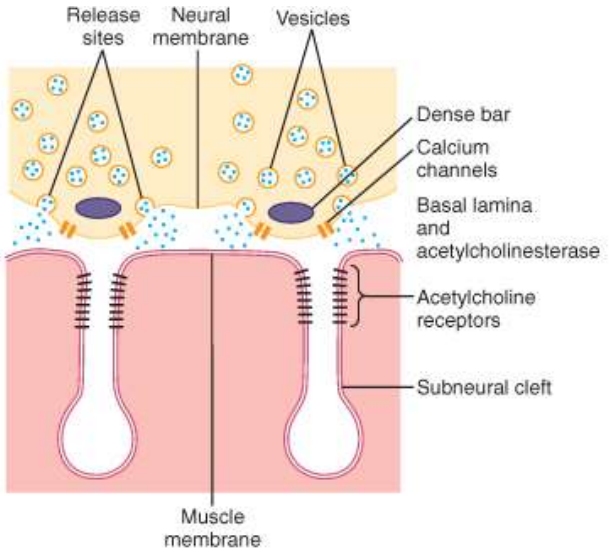
- When the action potential spread over the terminal these channels open and allow calcium ions to diffuse from the synaptic space to the interior of the nerve terminal.
- The Ca ions exert an attractive influence on the acetylcholine vesicles drawing them to the neural membrane adjacent to the dense bars.



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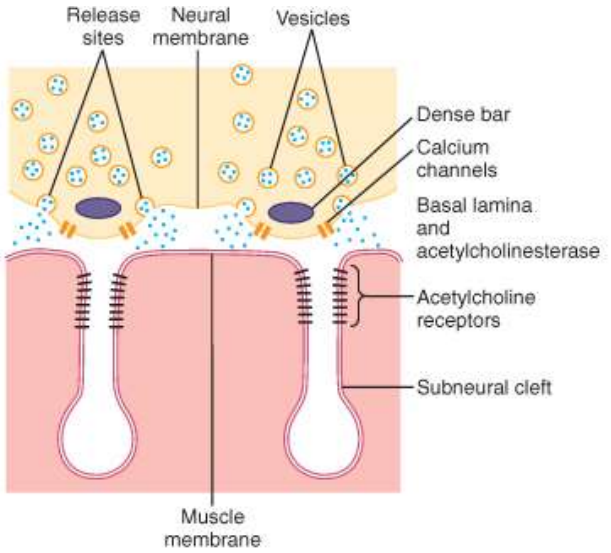
- The vesicles then fuse with the neural membrane and empty their acetylcholine into the synaptic space by the process of Exocytosis.



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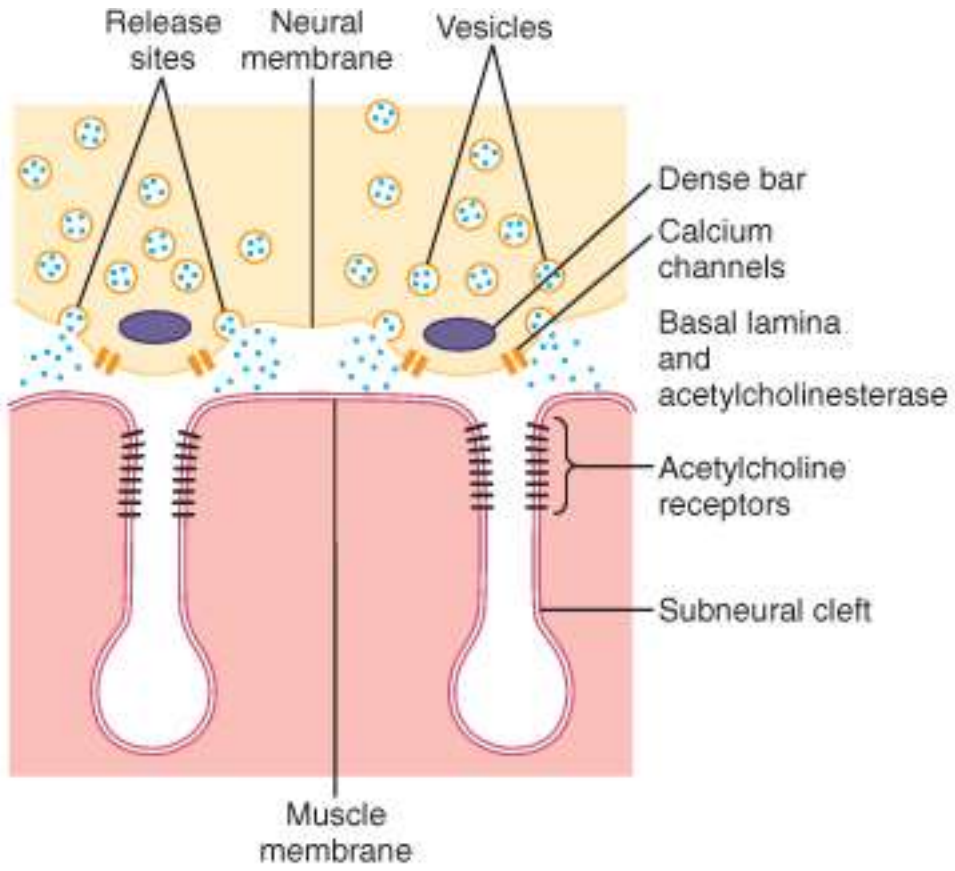

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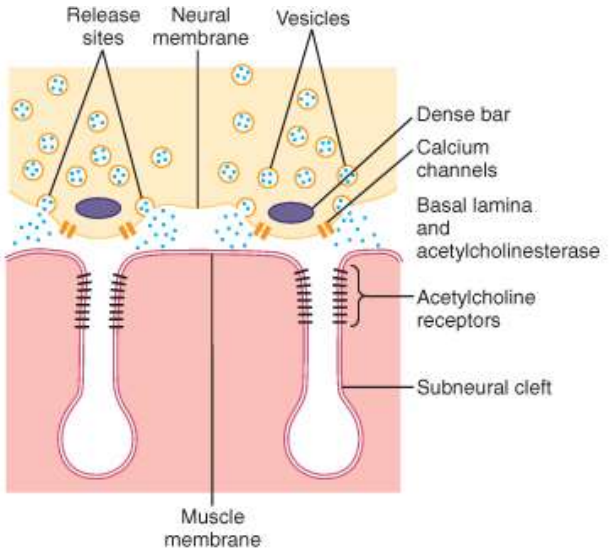
Effect of Acetylcholine on the post synaptic muscle fiber membrane to open the ion channels

- Actylcholine receptors or acetylcholine gated ion channels are located almost entirely near the mouth of the subneural cleft, where the acetylcholine is emptied into the synaptic space.



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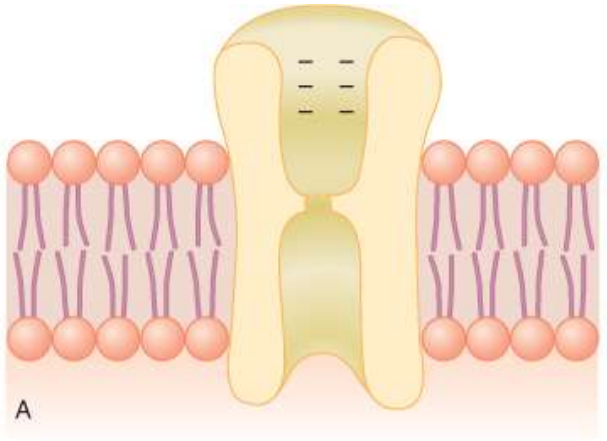
- These protein molecules penetrate all the way through the membrane lying side by side in a circle to form a tubular channel.
- The channel remain constricted as shown in figure A.Until two acetylcholine molecules attach respectively to the two alpha subunit proteins.
- This causes a confirmational change that opens the channels as shown in figure B



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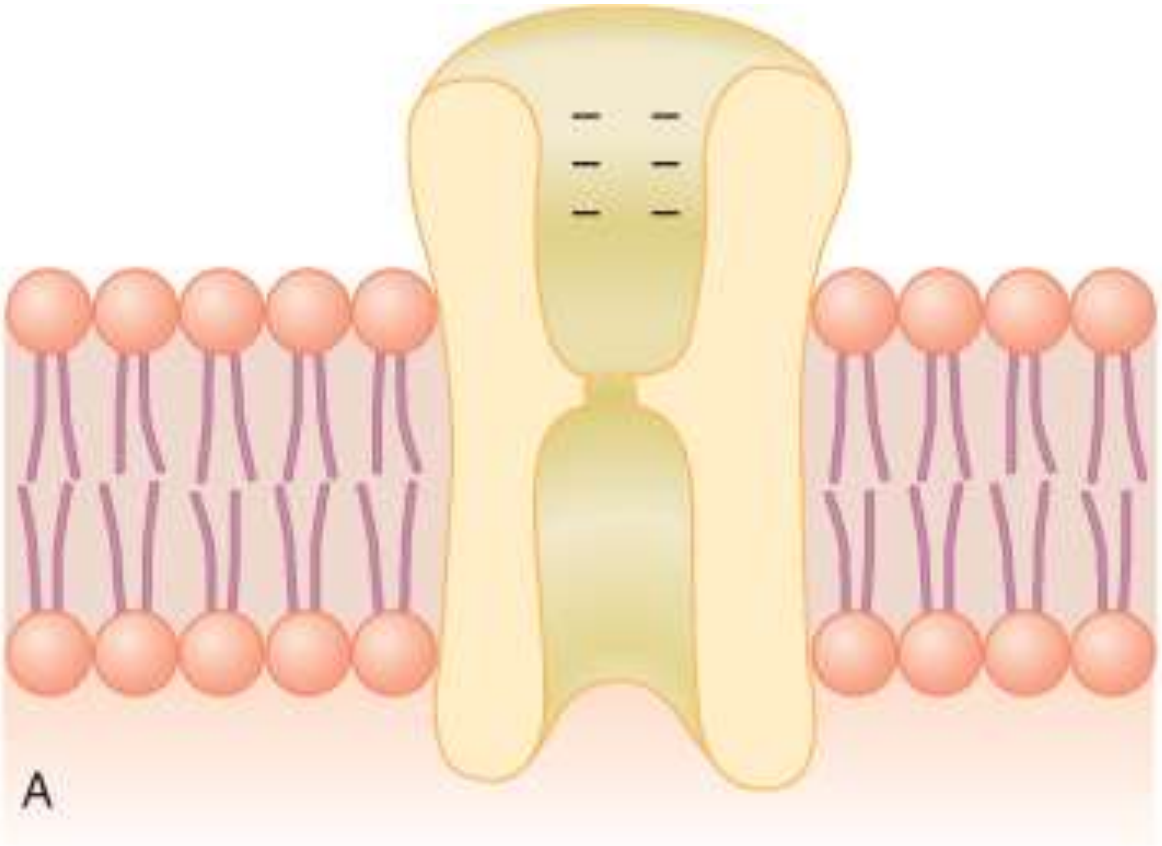

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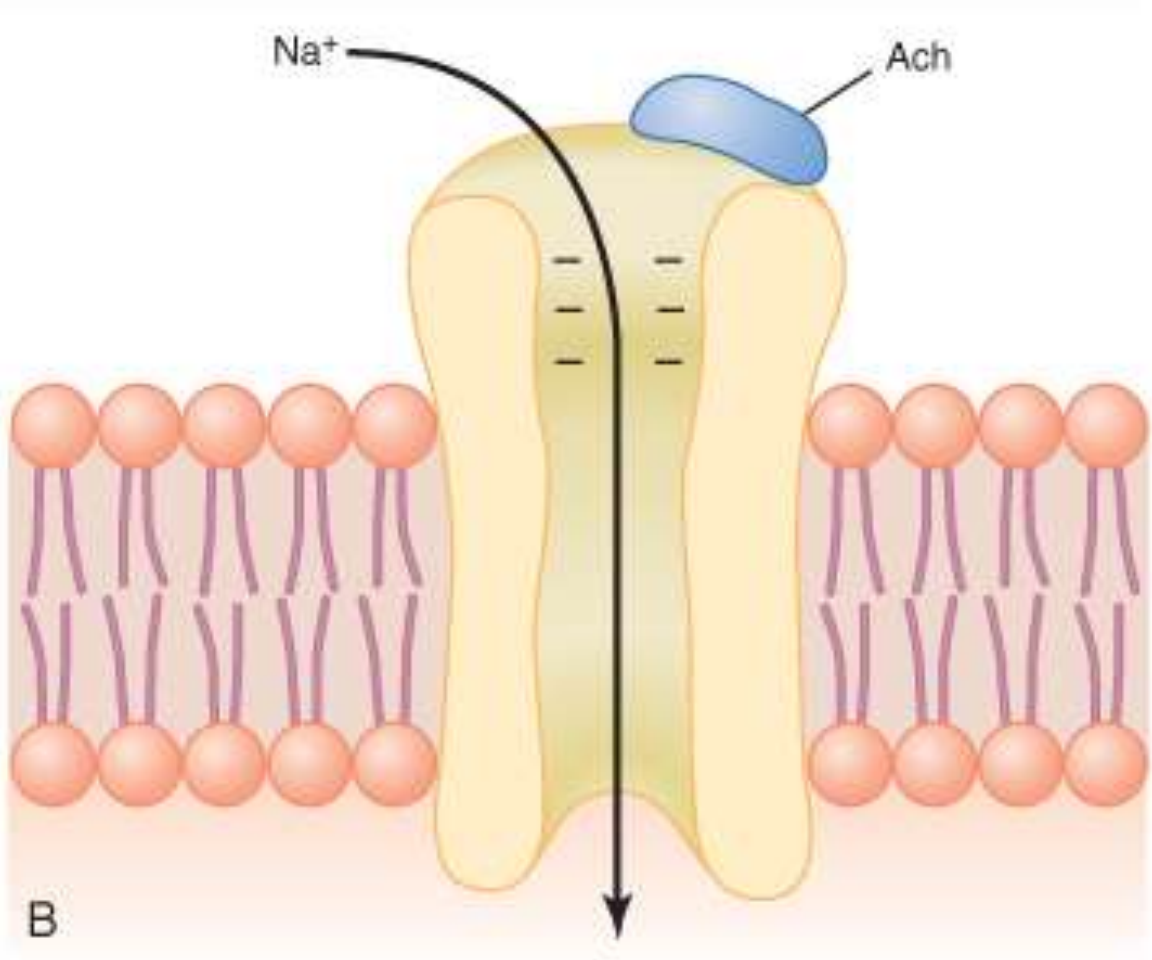

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Effect of Acetylcholine on the post synaptic muscle fiber membrane to open the ion channels

- The opened acetylcholine channels has a diameter of about 0.65nanometer which is large enough to allow Na+,k+,Ca+ to move easily through the opening.
- Cl- ions due to negative charge in the mouth of channels are repelled.
- More Na ions flow through the acetylcholine channels than any other ions

Destruction of the released Acetylcholine by acetylcholinesterase

- The acetylcholine ,once released into the synaptic space, continues to activate the acetylcholine receptors as long as the acetylcholine persists in the space.
- Acetylcholine is removed rapidly by two means.Most of the acetylcholine is destroyed by the enzyme acetylcholinesterase.

- Excitatory inhibitory transmitter at smooth muscle NMJ..
- Acetylcholine.
- Norepinephrine.

Response depend on type of receptors

- Local tissue factors are ….

  lack of oxygen

  excess carbon di oxide

  increase hydrogen ion

  adenosine,lactic acid,increase k,
decrease calcuim and increase body temp.

- Effect of hormones…

  epinephrine/norepinephrine

  acetylecholine

  angiotensin,endothelin

  vasopressin,oxytocin

  serotinin, histamine

- Mechanism of smooth muscle excitation/inhib

Two ways….

1 Na,K,Ca channels.

2 Activate membrane receptor…change in muscle fiber…release of Ca ion

Adenylate cyclase/guanylate cyclase enzyme system for inhibition. Decrease Ca conentrtion.

- 25 years old man presenting with hx of vomiting and diarrhea. Next day he developed diplopia ,ptosis and weakness of his both upper and lower limbs, his neurological examination shows lower motor neurone type weakness….

most likely diagnosis

Neuromuscular blockers

Two types of NMJ Blockers

- Presynaptic Blockers
- Post Synaptic Blockers

Presynaptic blockers

- Presynaptic blockers block release of ACH from nerve terminals. These include botulinium toxin and also deficiency of calcium and excess of magnesium.
- Bangarotoxin in snake

Post-synaptic blockers

Competitive blockers: These compete with ACH to bind with receptors on motor end plate. So the receptors are not available for binding with ACH. These blockers bind with the receptors and don't produce depolarization.

- **Example:** d-tubocurarine. Alkaloid obtained from plant Curare. Leaves of these plants were used by red Indians for application on arrow heads to hunt animals.
- Among synthetic blockers flaxidil used in surgical operations.
- When there is over dosage of these drugs we give Anticholinesterases i.e. Neostigmine, Physostigmine, Diisopropylfluorophosphate.

Drugs That Stimulate the Muscle Fiber by Acetylcholine Like Action

- Many compounds, including
- methacholine, carbachol, and nicotine, have the same effect on the muscle fiber as does acetylcholine.
- These drugs are not destroyed by cholinesterase or are destroyed so slowly that their action often persists for many minutes to several hours.

Drugs That Stimulate the Neuromuscular Junction by inactivating Acetylcholinesterase

- 1. neostigmine,
- 2. physostigmine, and
- 3. diisopropyl fluorophosphate.

- A young lady presenting to neurology clinic ,complaning of fatigue why carrying out her common household activities specially more in the evening ,she is also complaining of some time double vision. Her routine neurological examination was normal except….

Ptosis (drooping of the eyelid)

A.D.A.M.

MYSTHENIA GRAVIS

- Is an autoimmune disease in which antibodies attack the acetylcholine receptors on the motor end plate region of the muscle cell.
- The symptoms are due to both the activation of the acetylcholine receptors and to the disruption of the histology of the motor end plate region

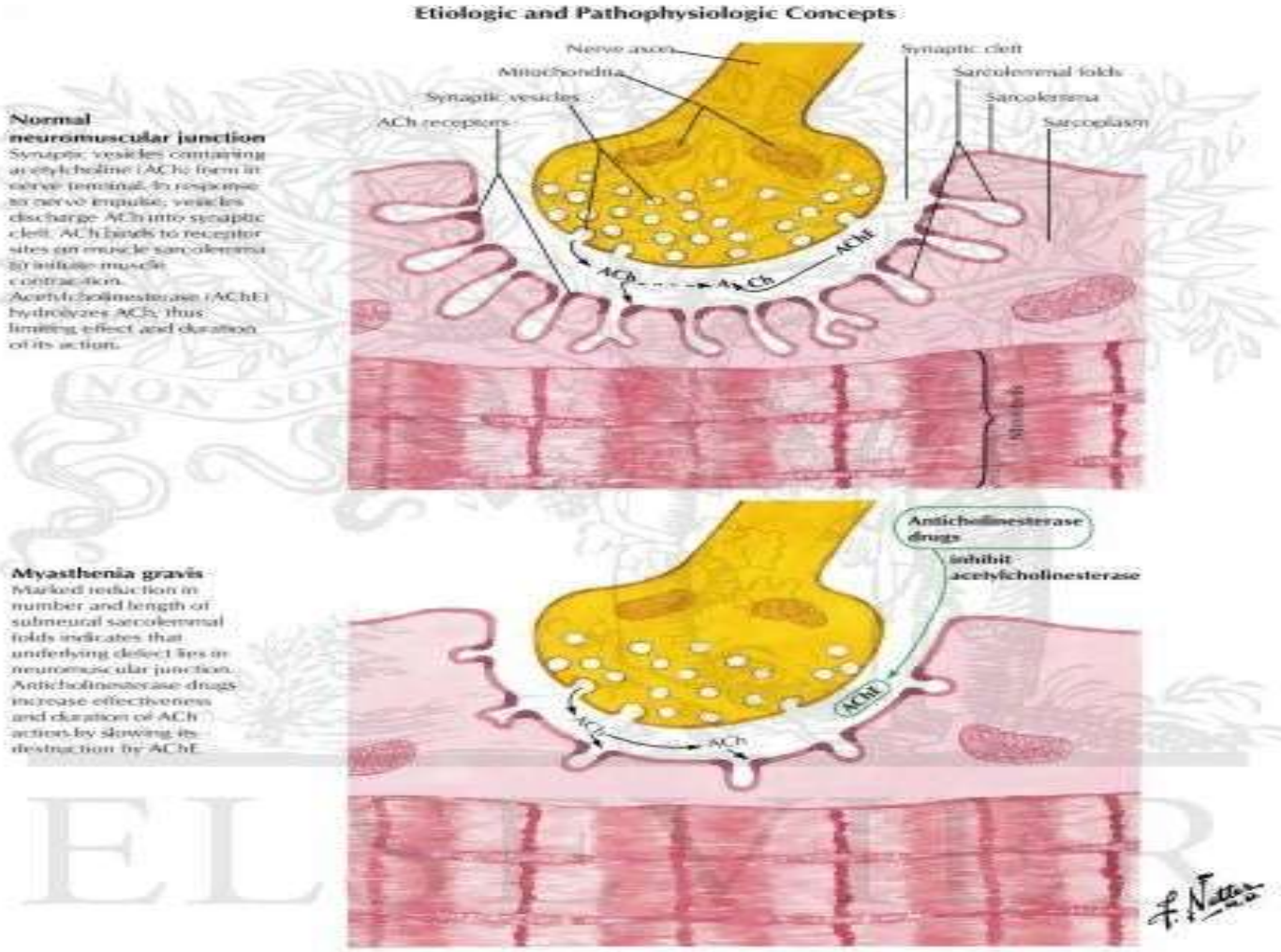
Patho physiology of Mysthenia Gravis

- Neuromuscular transmission requires the release of an appropriate amount of acetylcholine into the synaptic cleft
- The diffusion of the acetylcholine across the cleft
- Binding of the acetylcholine to the receptors opens a channel that is equally selective for Na+ and K+ and there is selective depolarization of the end plate region to -15mV.
- The depolarization generates an action potential that spreads along the skeletal muscle cell, causing the release from the sarcoplasmic reticulum and inducing a contraction.

Patho physiology of Mysthenia Gravis

- Mysthenia gravis is a chronic autoimmune disease leading to destruction of the acetylcholine receptors(approximately 70%) on the motor end plate region of muscle cells.
- Acetylcholine release is normal ,the absence of functional receptors on the motor end plate region of the muscle cell means that biological response is diminished.
- Normally acetylcholine is degraded in the synaptic cleft by the activity of the enzyme acetylcholinesterase

MYSTHENIA GRAVIS



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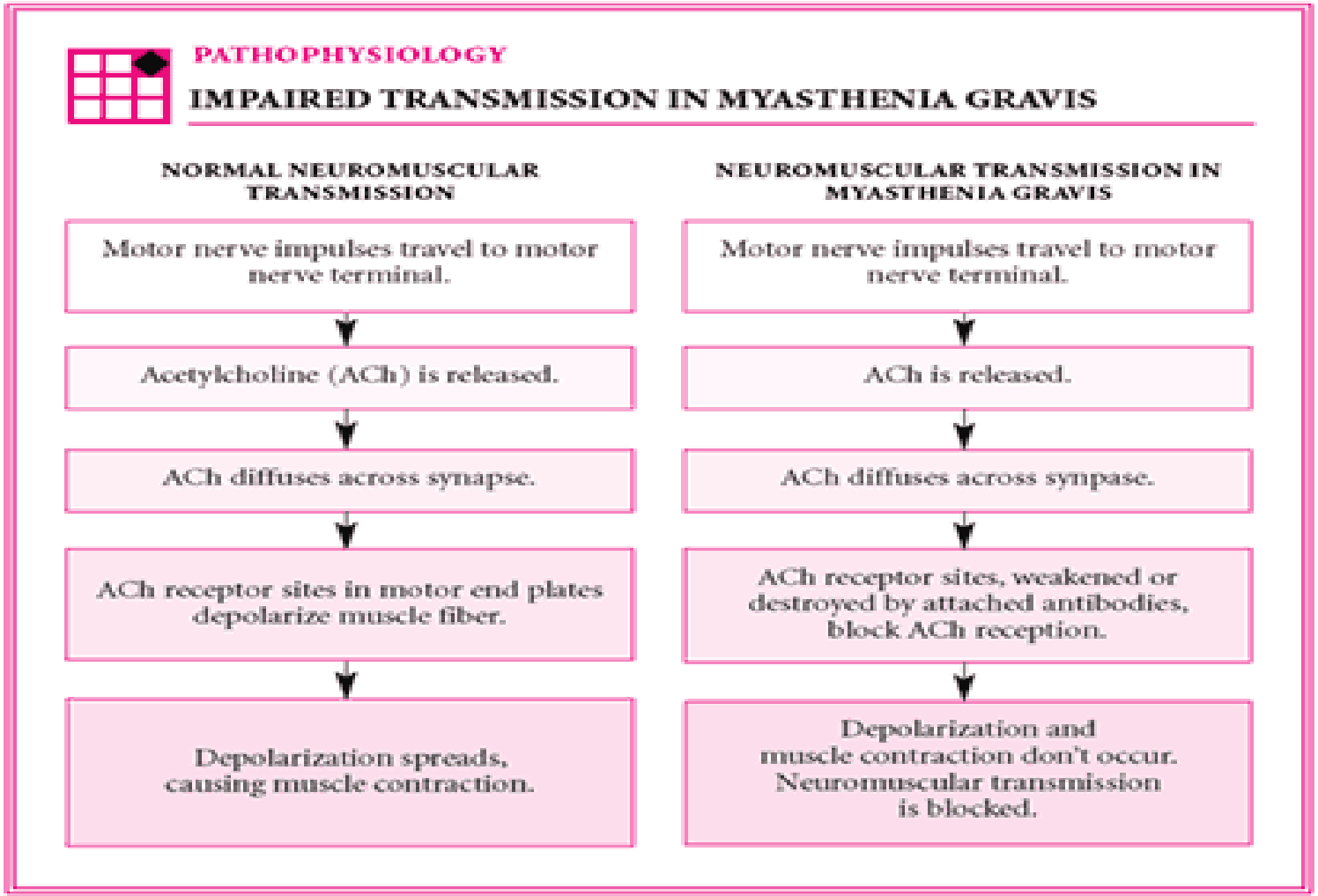
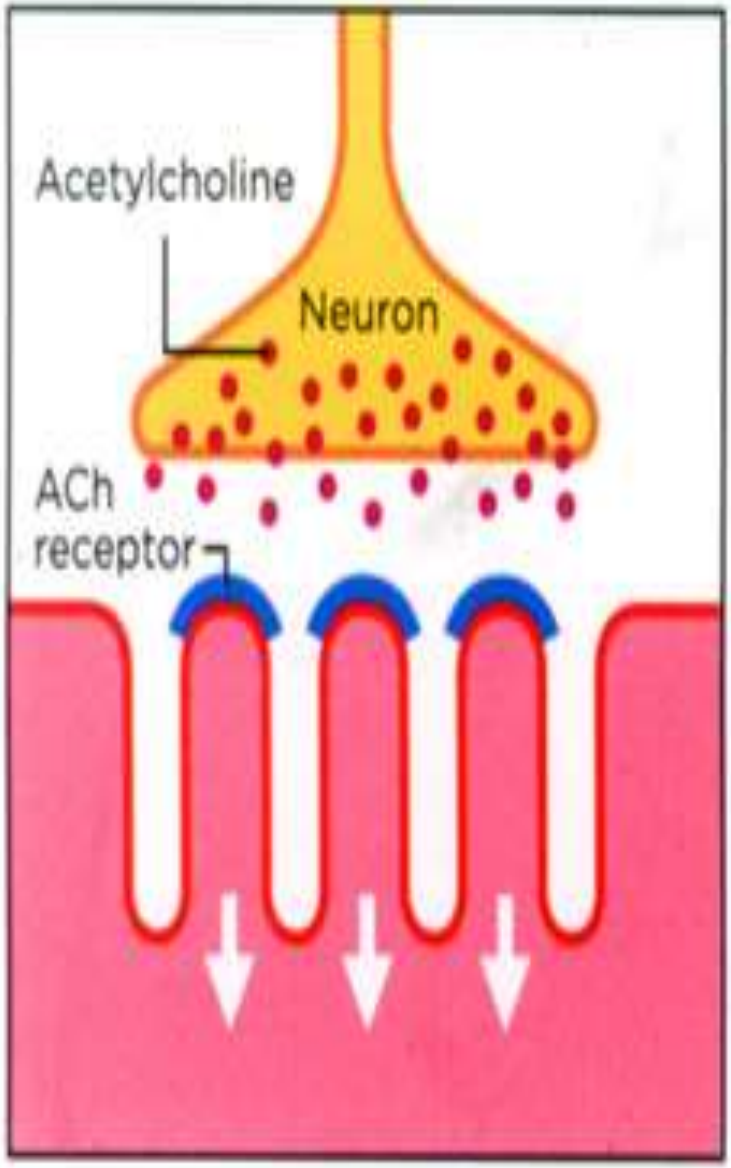
MYSTHENIA GRAVIS

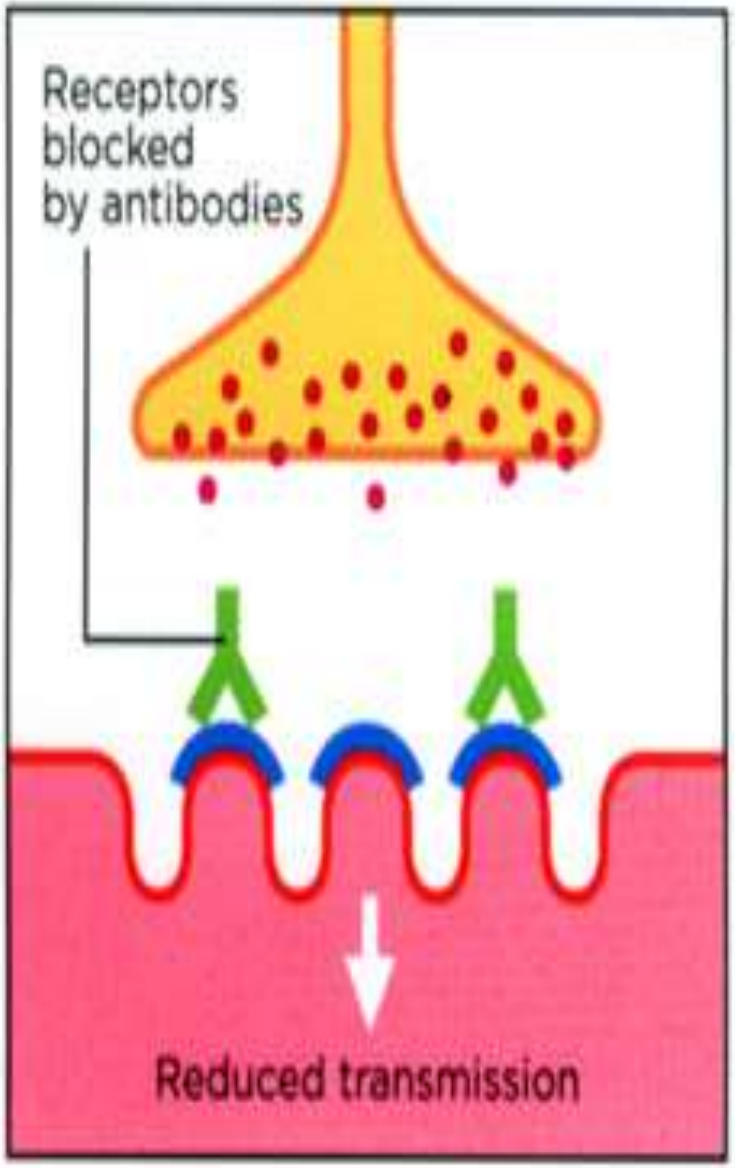


Outcome of mysthenia gravis

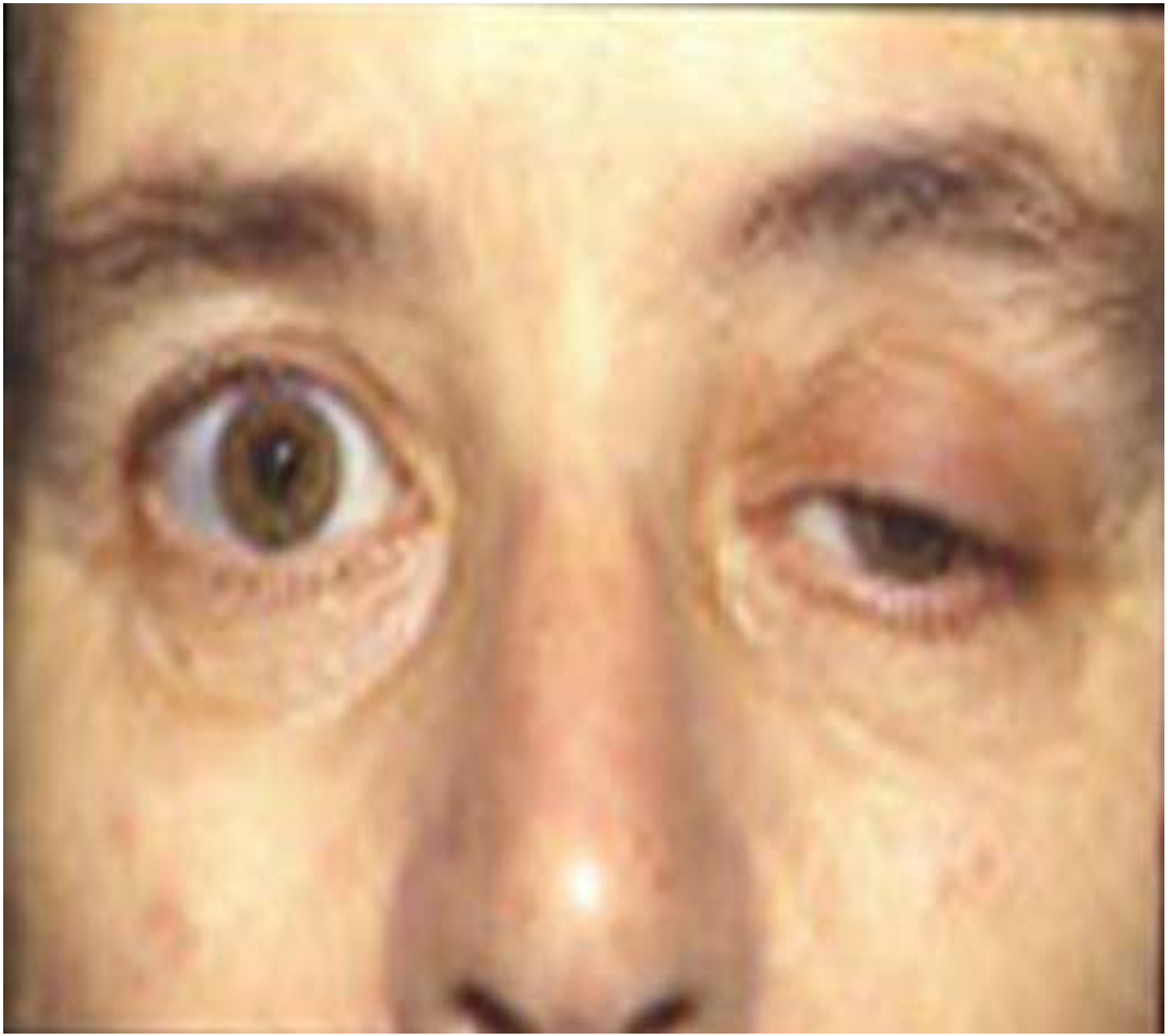
- Symptoms can be diminished by increasing the amount of acetylcholine in the synaptic cleft.
- This is done by administering Pyridostigmine,an acetylcholinesterase inhibitor.
- Blocking the degradation of acetylcholine acts to increase the effective concentration of acetylcholine in the synapse and therefore activates a greater percentage of the remaining functional acetylcholine receptors.
- Plasma testing:Presence of antibodies directed against the acetylcholine receptors(normal<0.03mmol/L)



Normal neuromuscular junction

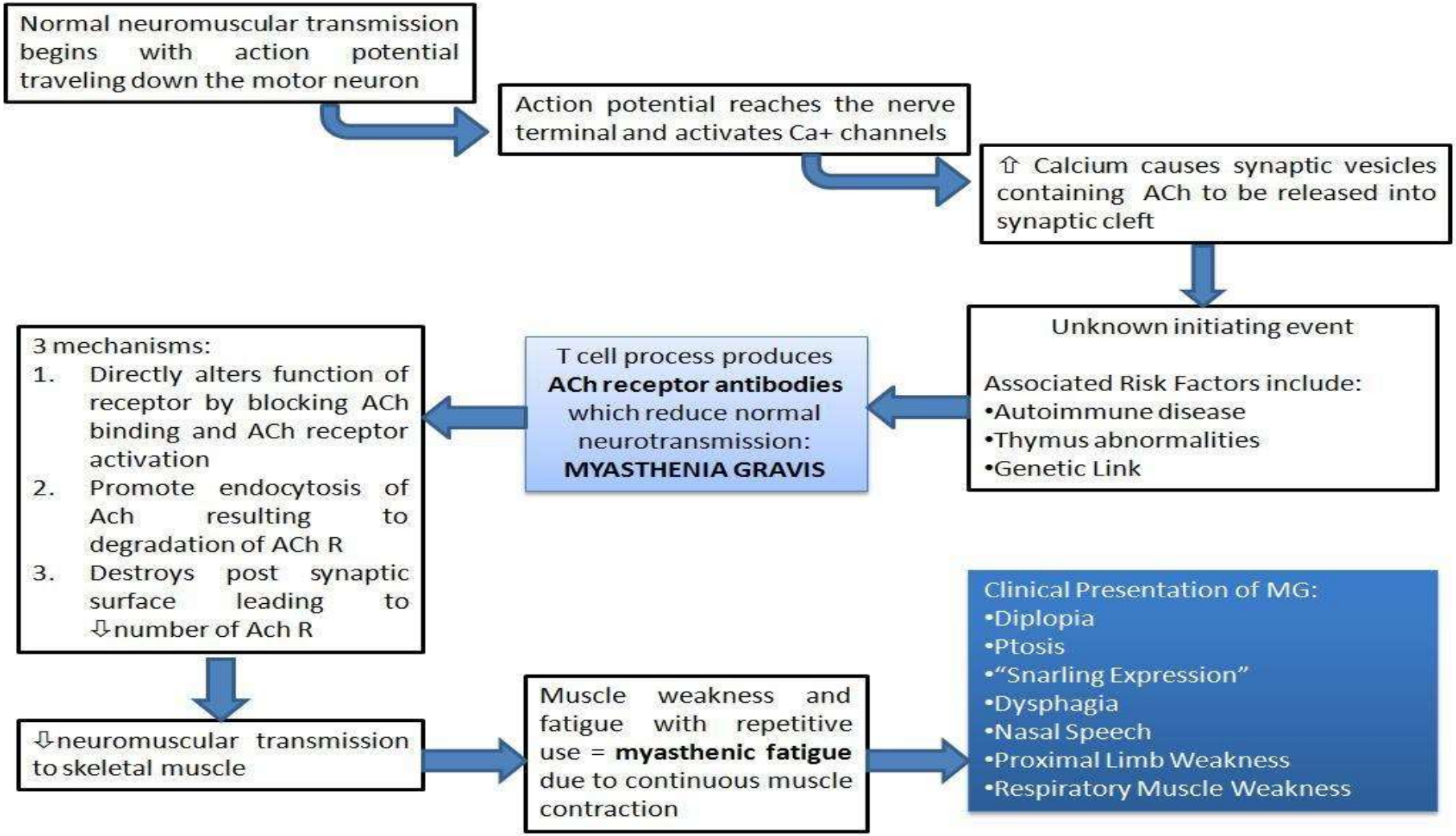


Neuromuscular junction in myasthenia gravis



MYSTHENIA GRAVIS

MYSTHENIA GRAVIS



- MANAGEMENT
- TENSILON TEST

  DRUGS..

- SDL….
- EATON LAMBERT SYNDROME