Neuromuscular junction

RIFFAT SULTANA

Neuro muscular junction

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

Motor end plate

- Each terminal branch of nerve fiber(axon terminal) when comes close to the muscle fiber it loses the myelin sheath ,and innervates into the surface fiber,this portion is expanded.This entire structure is called motor end plate .It is covered by one or more schwann cells that insulate it from the surrounding fluid.

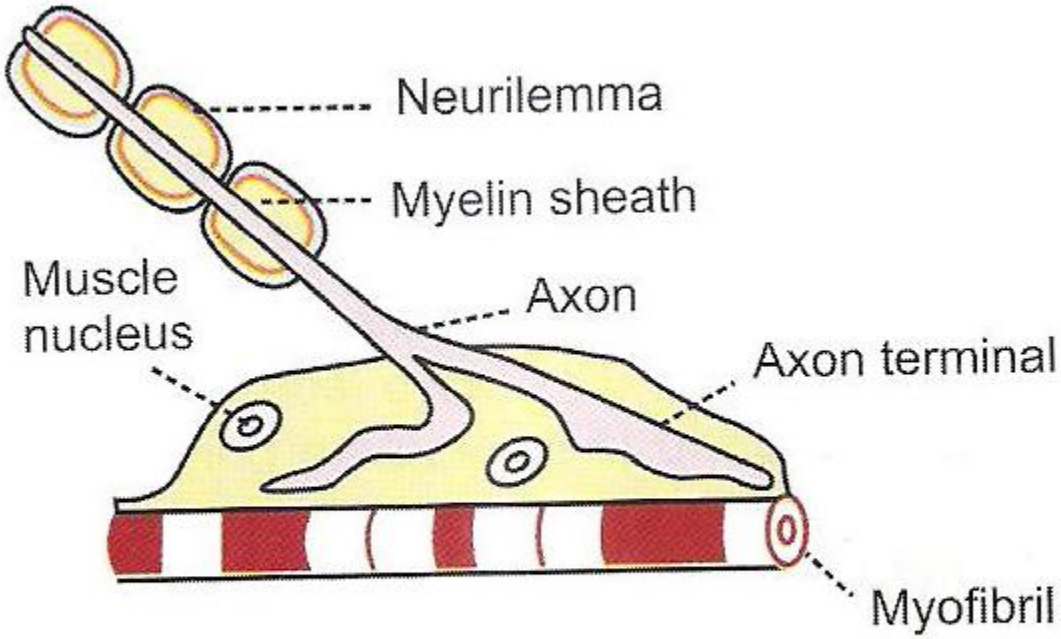


FIGURE 32-1: Longitudinal section of neuromuscular junction

Neuro muscular junction

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

Synaptic gutter or synaptic trough

- The motor end plate invaginates inside the muscle fiber and forms a depression which is known as synaptic trough or synaptic gutter.

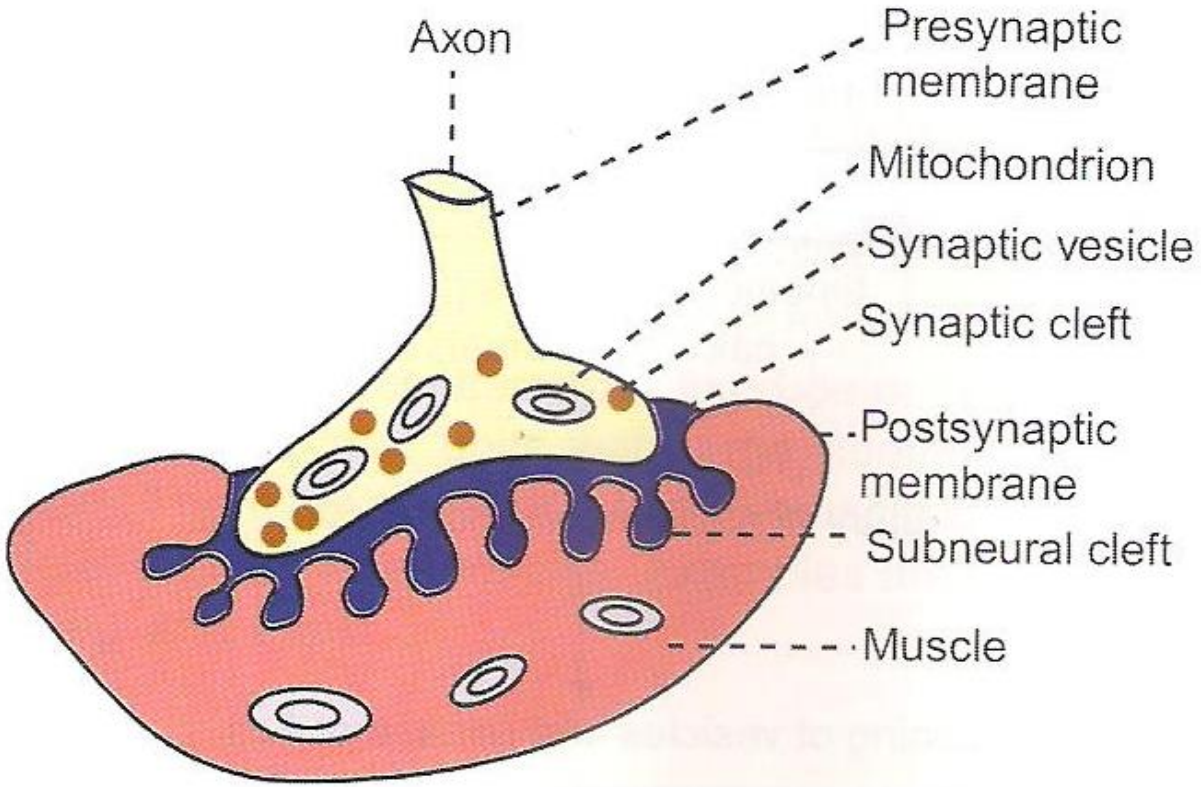


FIGURE 32-2: Structure of neuromuscular junction

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 axon terminal there are many mitochondria that supply the ATP,the energy source that is used for synthesis of the excitatory neurotransmitter Acetylcholine.
- Acetylcholine in turn excites the muscle fiber membrane.
- Acetylcholine is synthesized in the cytoplasm of the terminal but is absorbed into many small vesicles, about 300,000 are normally in the terminals of a single end plate

- 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

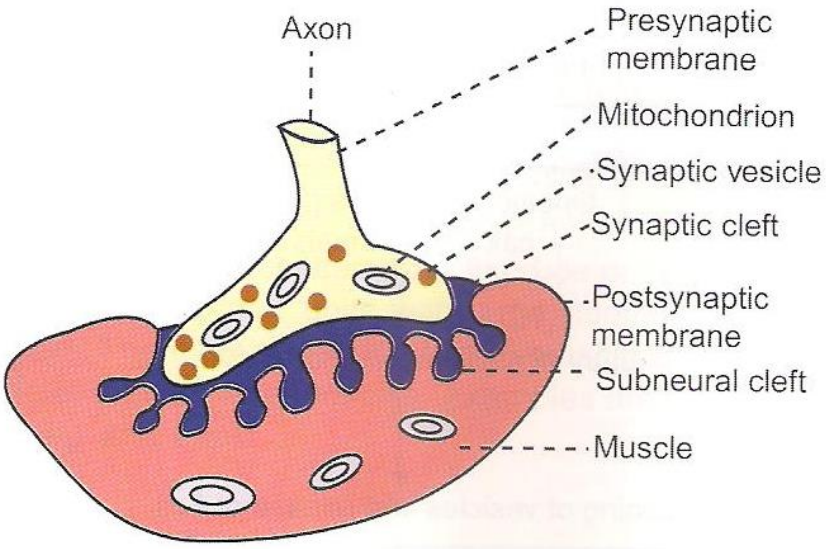
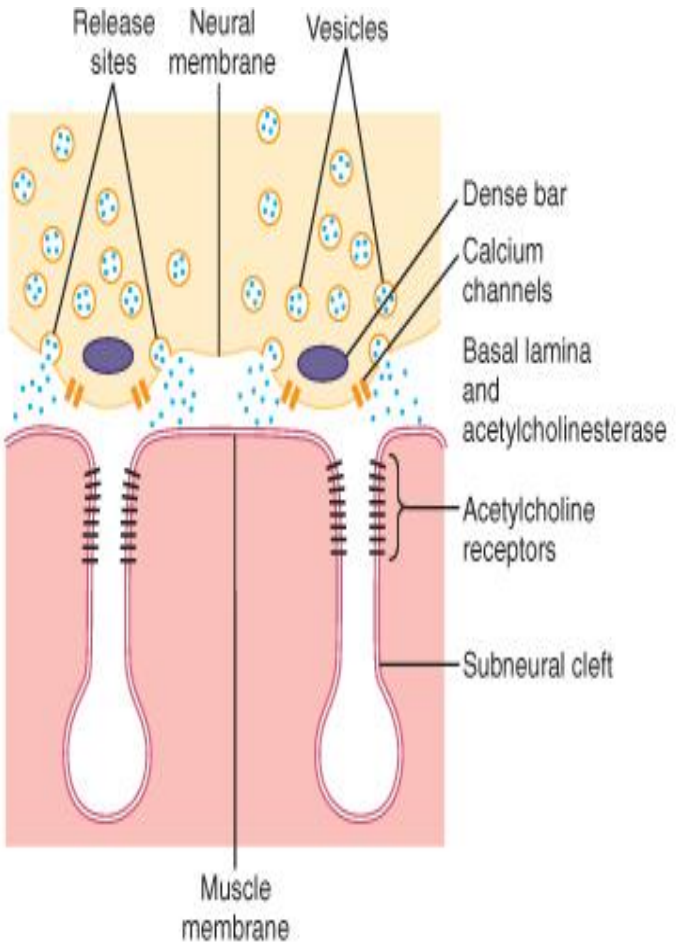


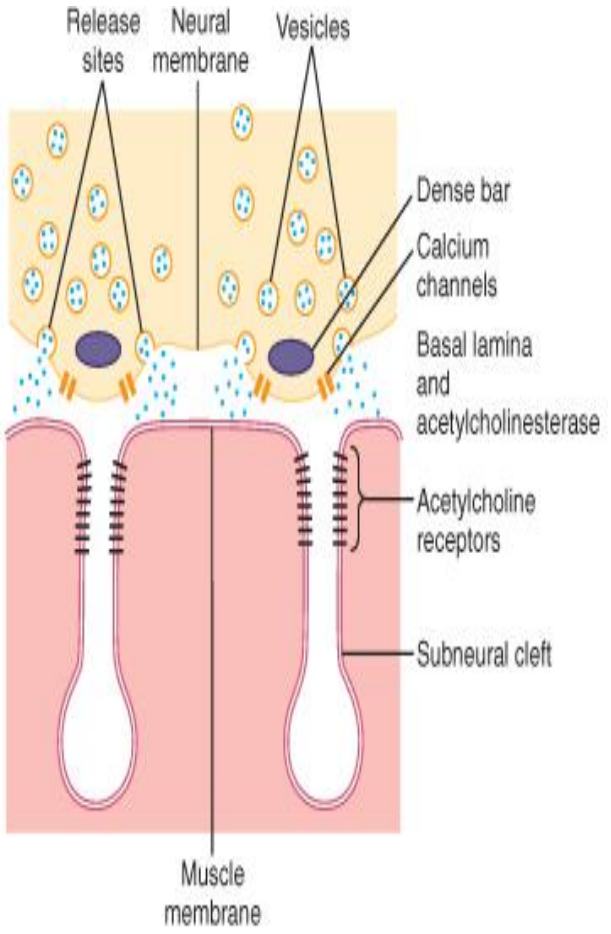
FIGURE 32-2: Structure of neuromuscular junction

RELEASE OF ACETYLCHOLINE

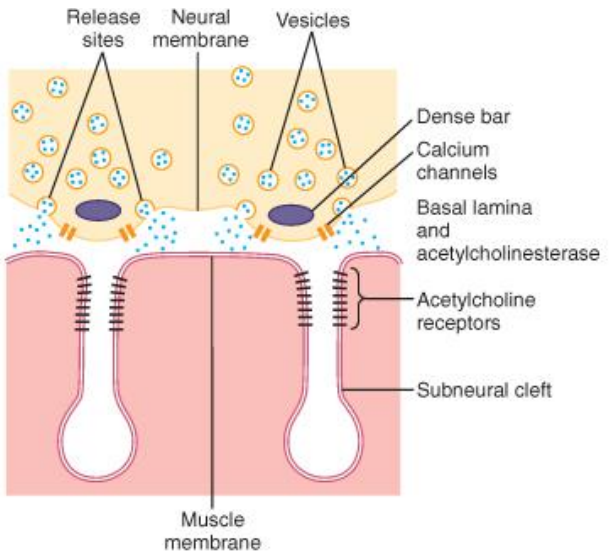
- When a nerve impulse reaches the neuromuscular junction about 125vesicles of acetylcholine are released from the terminal into the synaptic space.



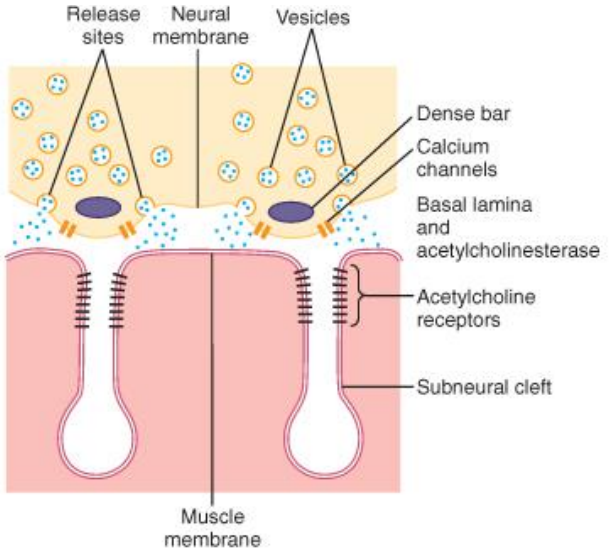
- On the inside of the neural membrane are linear dense bars.
- To each side of each dense bar are protein particles that penetrate the neural membrane these are voltage gated calcium channels

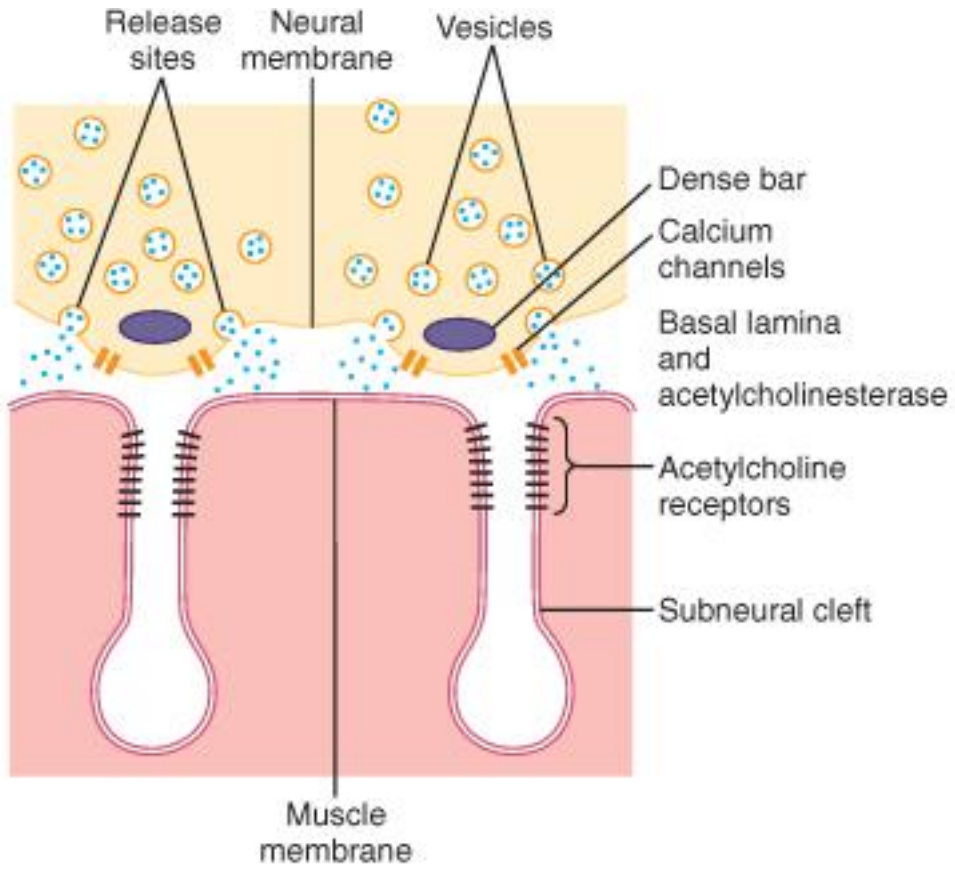


- When the action potential spread over the terminal these channels open and allow calcium ions to diffuse from the synaptic space to the interior of the nerve terminal.
- The Ca ions exert an attractive influence on the acetylcholine vesicles drawing them to the neural membrane adjacent to the dense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



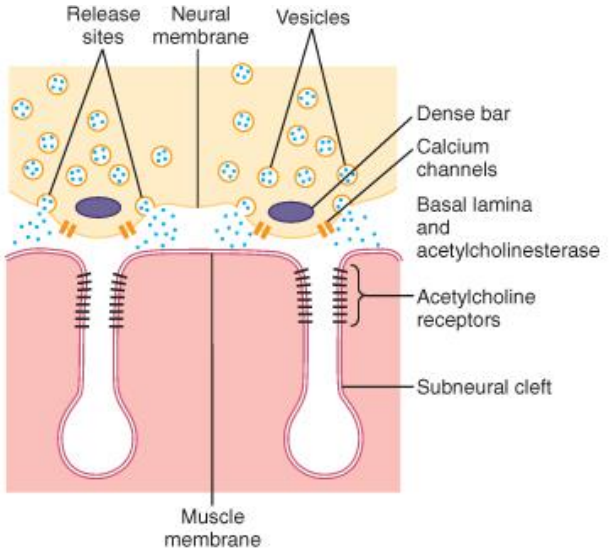
- The vesicles then fuse with the neural membrane and empty their acetylcholine into the synaptic space by the process of Exocytosis.



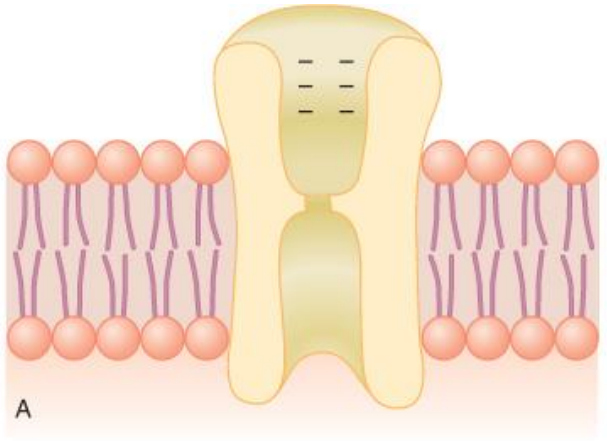


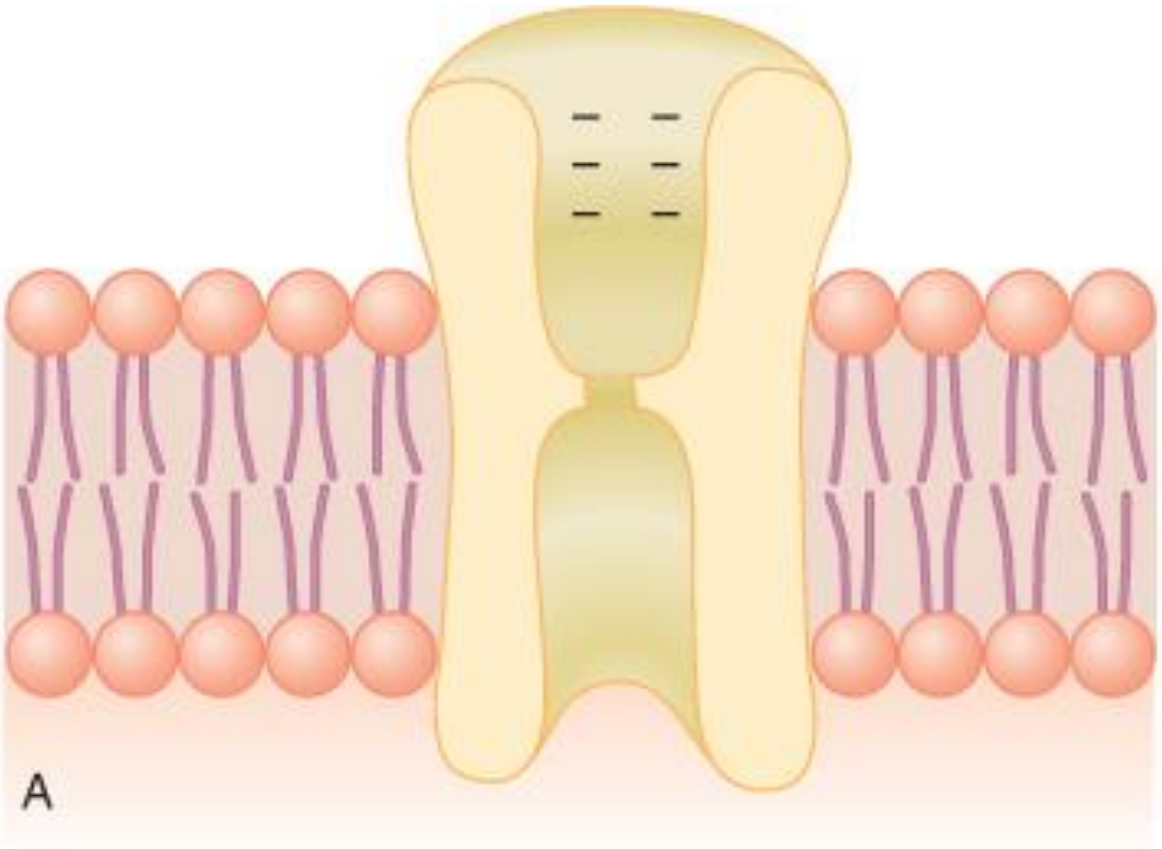
Effect of Acetylcholine on the post synaptic muscle fiber membrane to open the ion channels

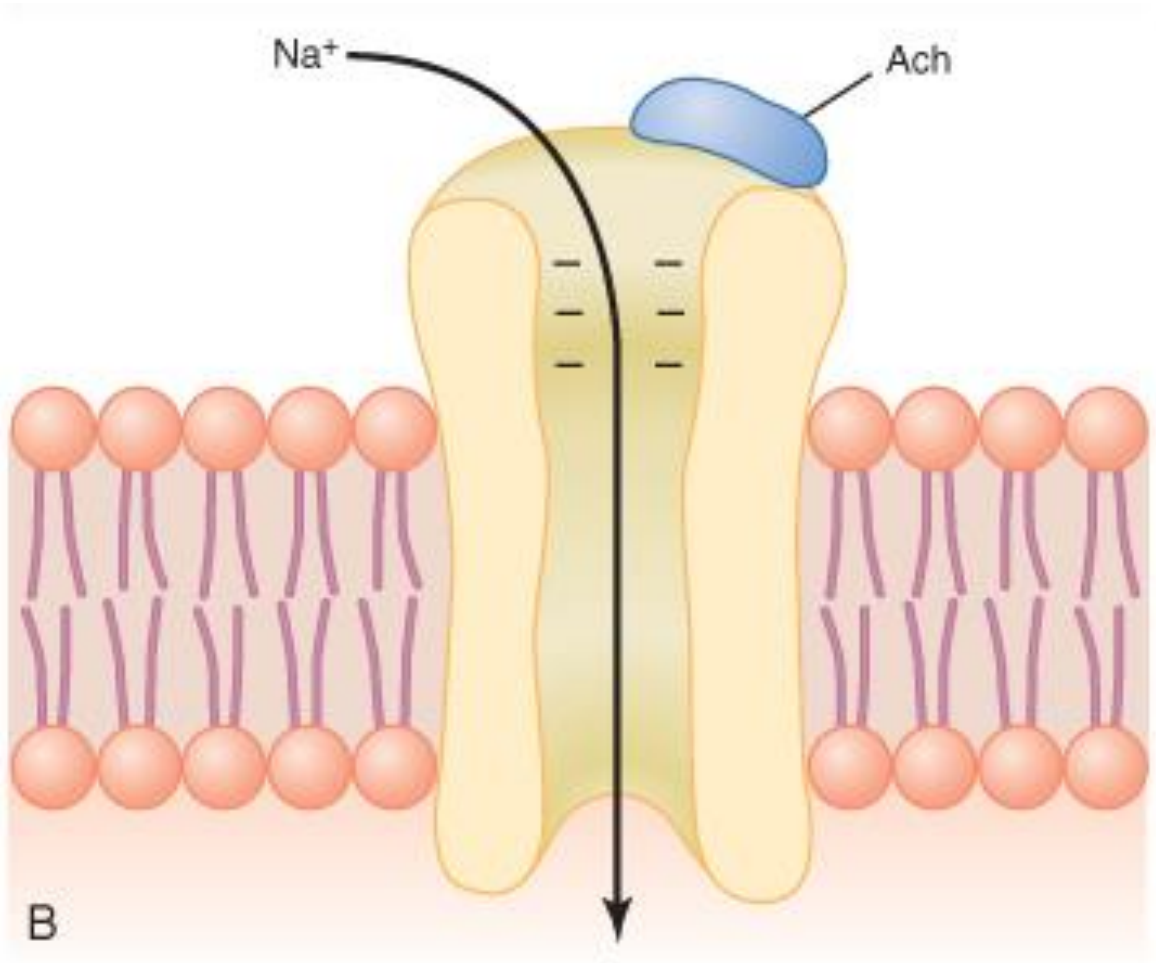
- Actylcholine receptors or acetylcholine gated ion channels are located almost entirely near the mouths of the subneural cleft, where the acetylcholine is emptied into the synaptic space.
- Each receptor is a protein complex that has a total molecular weight of 275000.



- 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 alpha subunit proteins.
- This causes a confirmational change that opens the channels as shown in figure B







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 then any other ions

Principal effect of opening the acetylcholine gated channels

- First there are only two positive ions in large concentration Na ions in the extracellular fluid and K ions in the intracellular fluid.
- The very negative potential on the inside of the muscle membrane -80 to -90 mV,pulls the +ve charged Na+ ions to the inside of the fiber,while simultaneously efflux of the positively charged K ions when they attempt to pass outward.
- This creates a local positive potential charge inside the muscle fiber membrane,called the **end plate potential**.
- This end plate potential initiates an action potential that spreads along the muscle membrane and thus causes muscle contraction.

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 which is attached mainly to the spongy layer of connective tissue that fills the sympathetic space and between the presynaptic nerve terminal and the post synaptic muscle membrane

Destruction of the released Acetylcholine by acetylcholinesterase

- A small amount of acetylcholine diffuses out of the synaptic space and is then no longer available to act on the muscle fiber membrane.
- The short time that the acetylcholine remains in the synaptic space a few milliseconds at most normally is sufficient to excite the muscle fiber

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

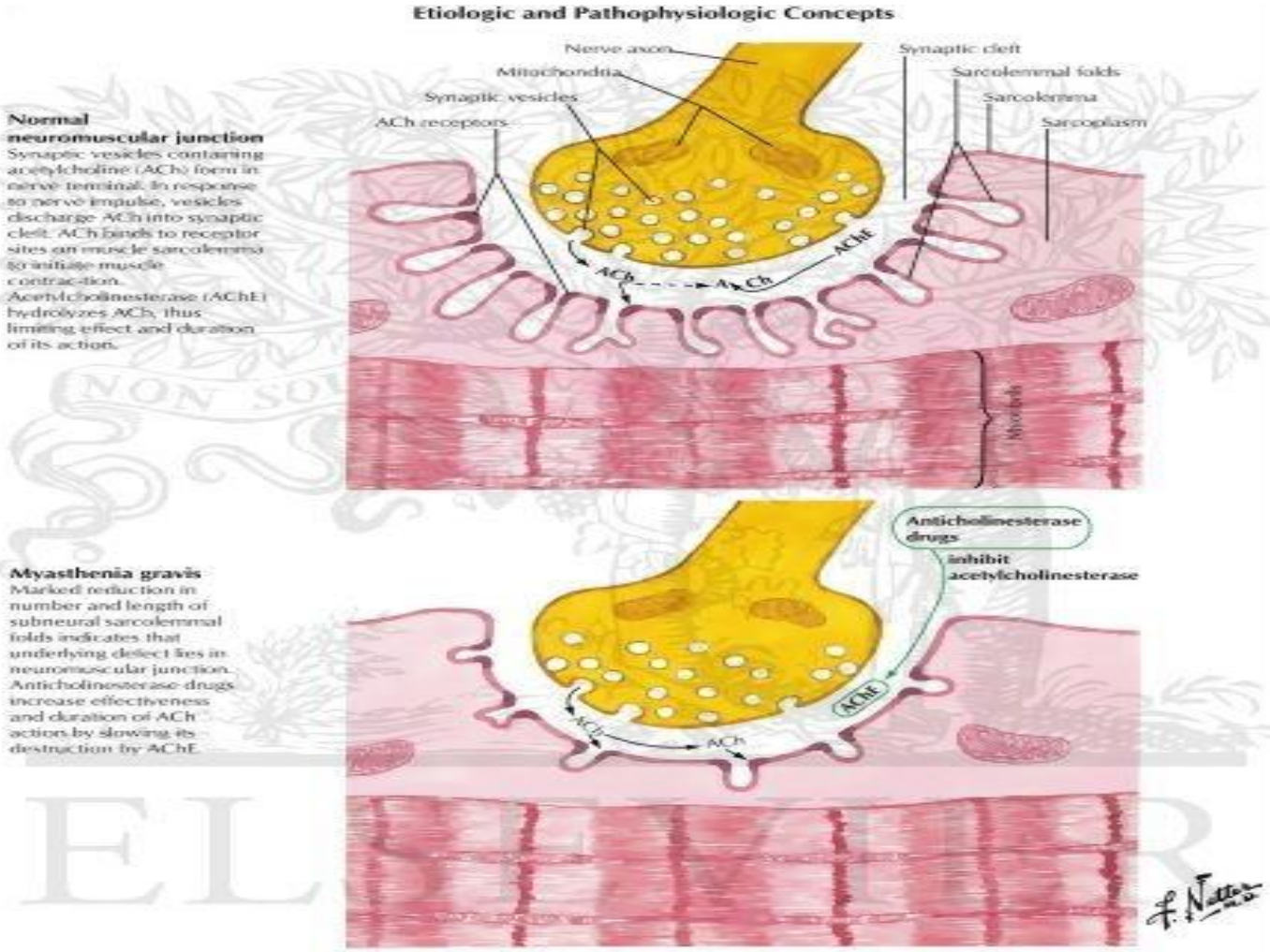
Patho physiology of Mysthenia Gravis

- 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.

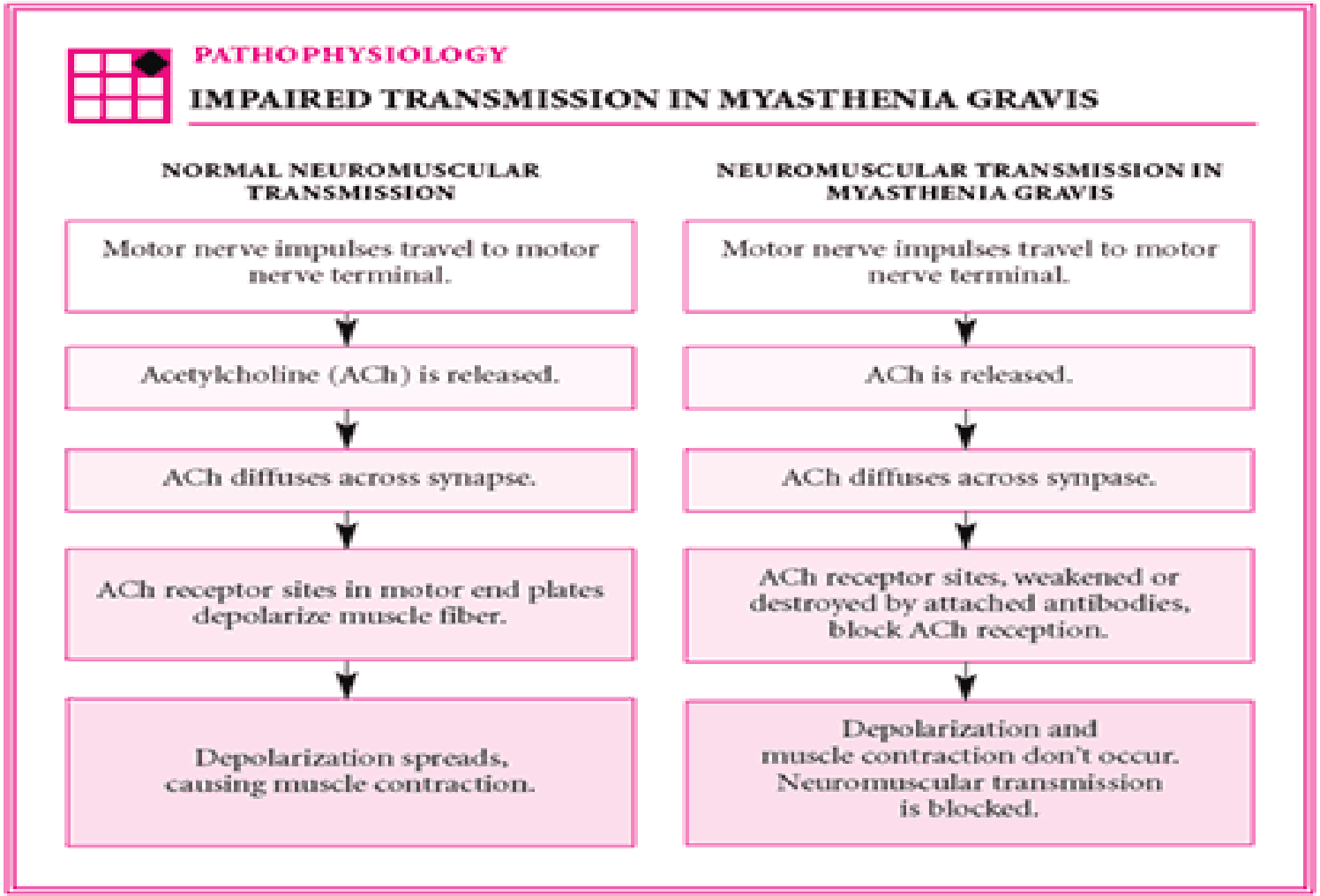
Patho physiology of Mysthenia Gravis

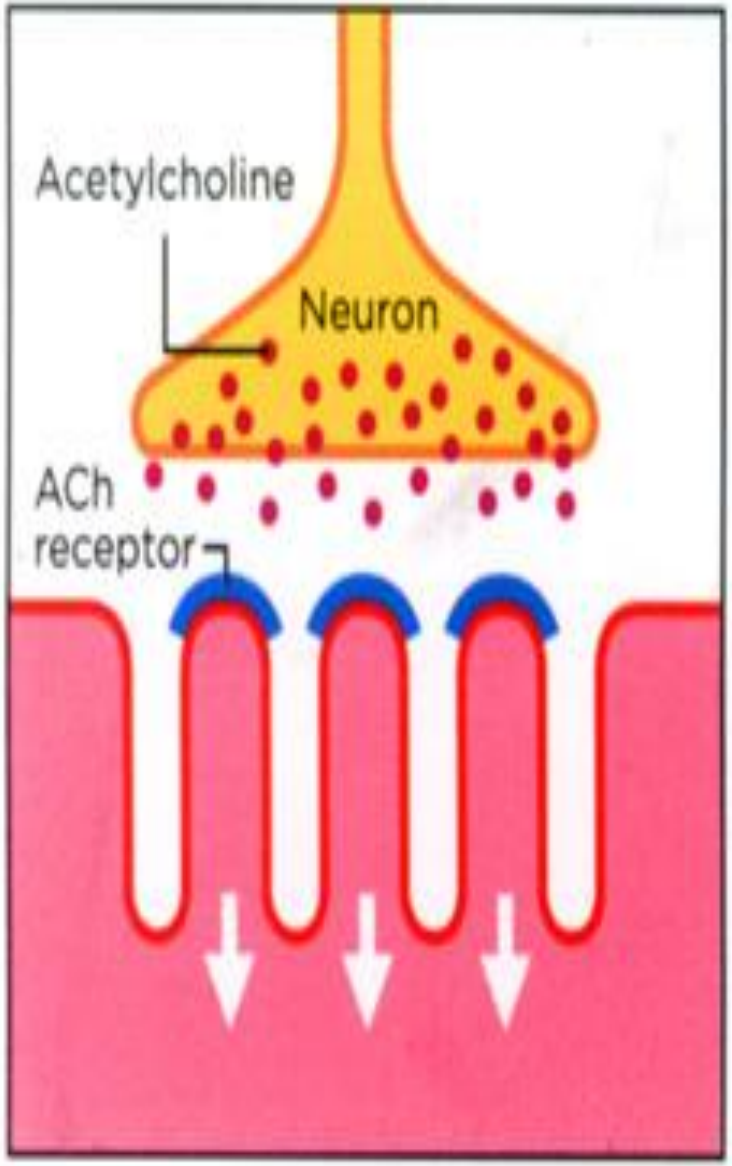
- Mysthenia gravis is a chronic autoimmune disease leading to destruction of the acetylcholine receptors(approximately 70%) on the motor end plate region of muscle cells.
- Acetylcholine release is normal ,the absence of functional receptors on the motor end plate region of the muscle cell means that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

MYSTHENIA GRAVIS

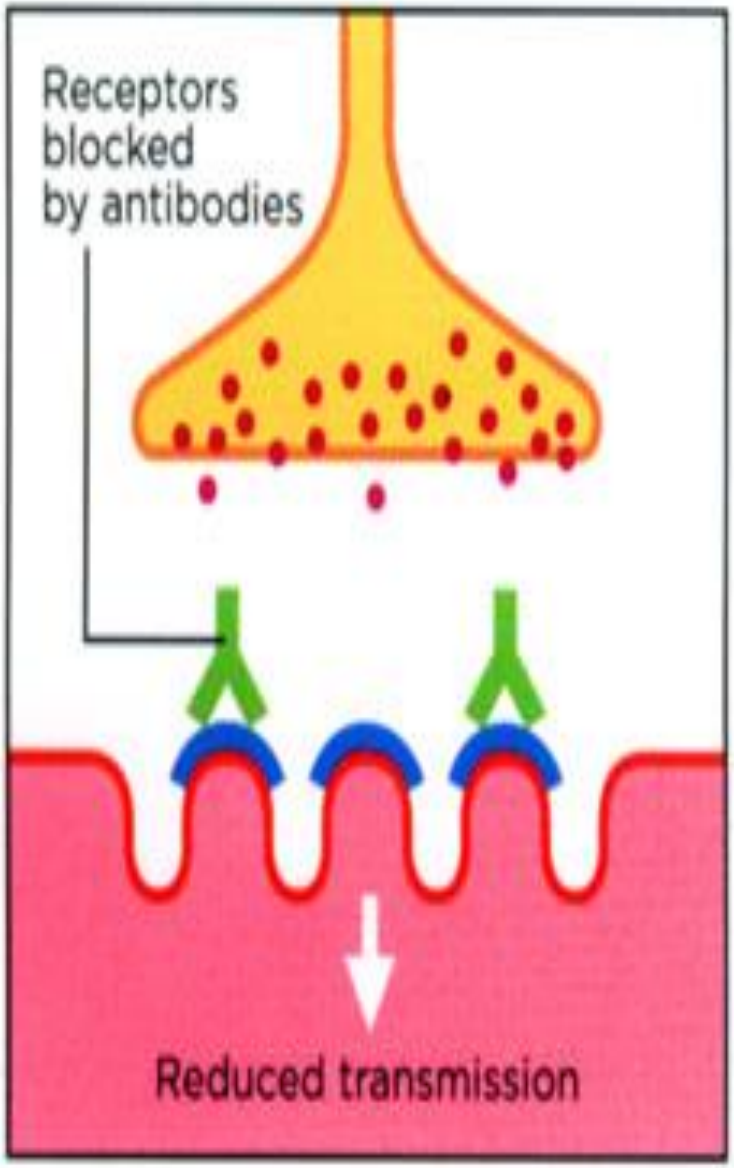


MYSTHENIA GRAVIS

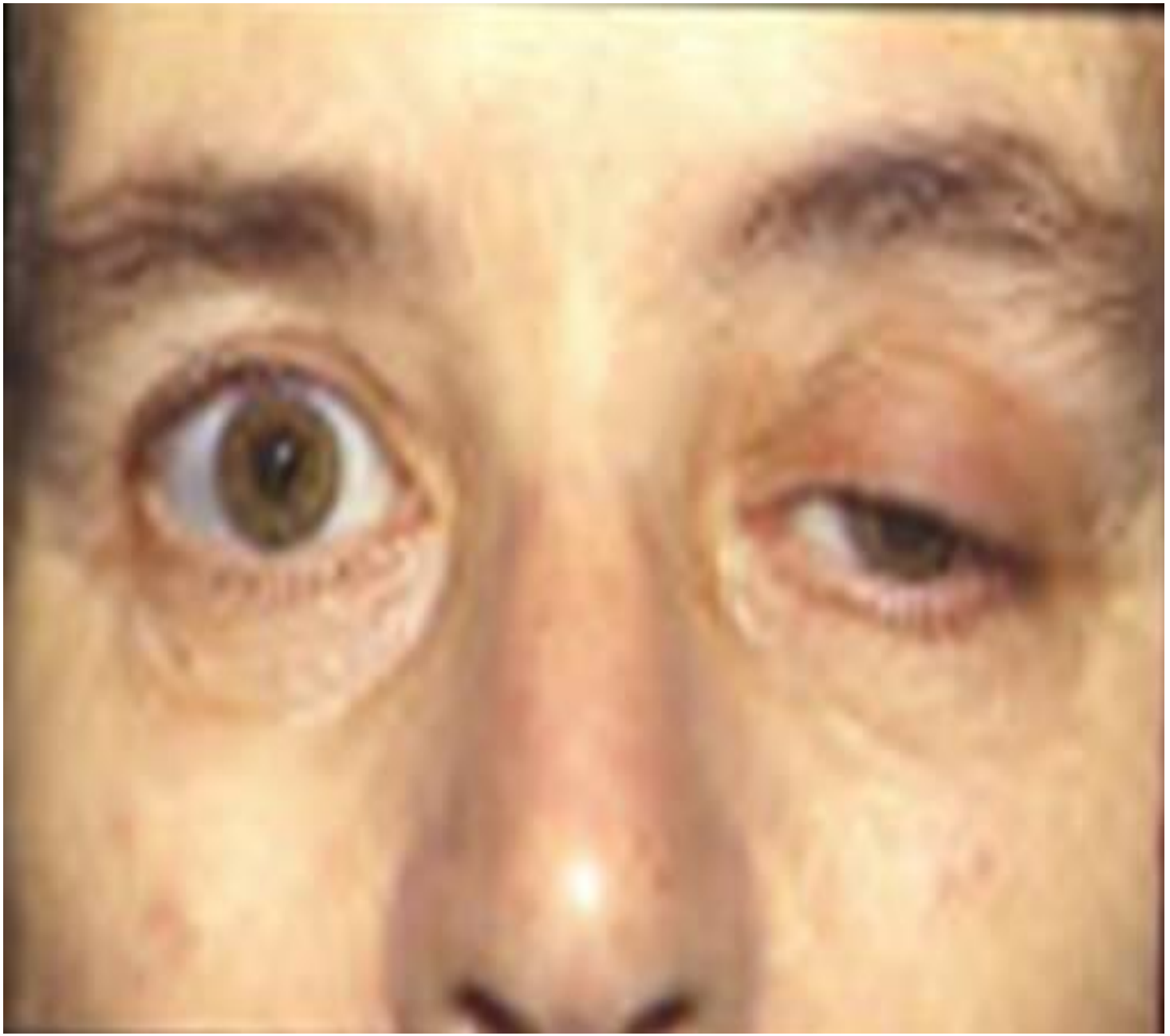




Normal neuromuscular junction



Neuromuscular junction in myasthenia gravis



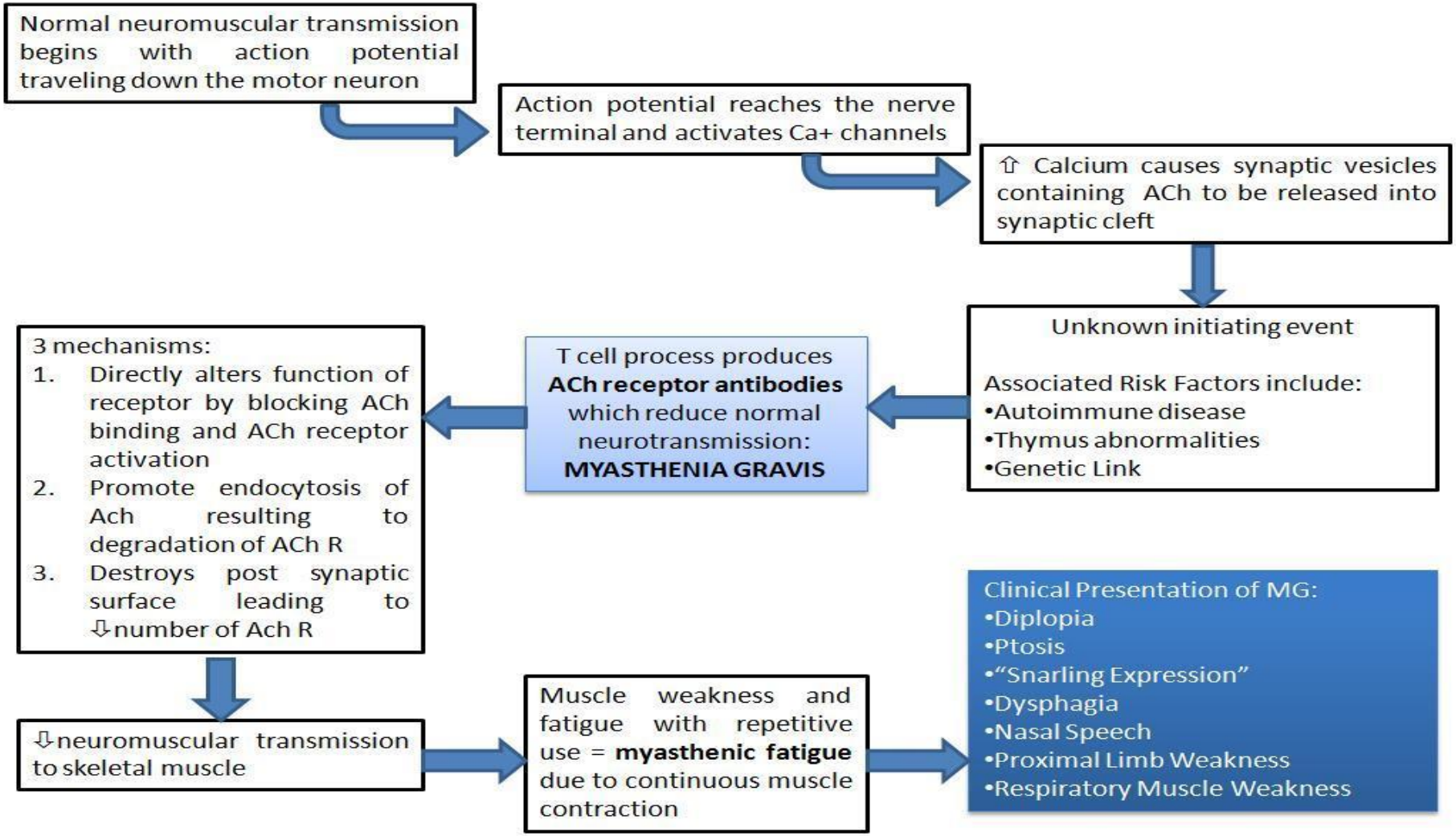
MYSTHENIA GRAVIS

Ptosis (drooping of the eyelid)

A.D.A.M.

MYSTHENIA GRAVIS

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.
- Plasma testing:Presence of antibodies directed against the acetylcholine receptors(normal<0.03mmol/L)

Excitation contraction coupling

- Action potential comes down the neuron---Axon terminal—stimulates Ca to enter axon terminal---Ca causes the vesicles to releases—Acetylcholine—Acetylcholine are ion channels which causes the flow of ions which is responsible for the change in potential.
- When the membrane depolarizes voltage gated Ca channels present in the sarcolemma open up and Ca moves into the sarcoplasm from the extracellular fluid.
- This Ca from the Sarcoplasmic Reticulum stimulates the release of more Calcium called as Calcium induced calcium release(CICR)
- Increased Ca bind to Troponin move the Tropomyosin out of the way thus it help in muscle contraction

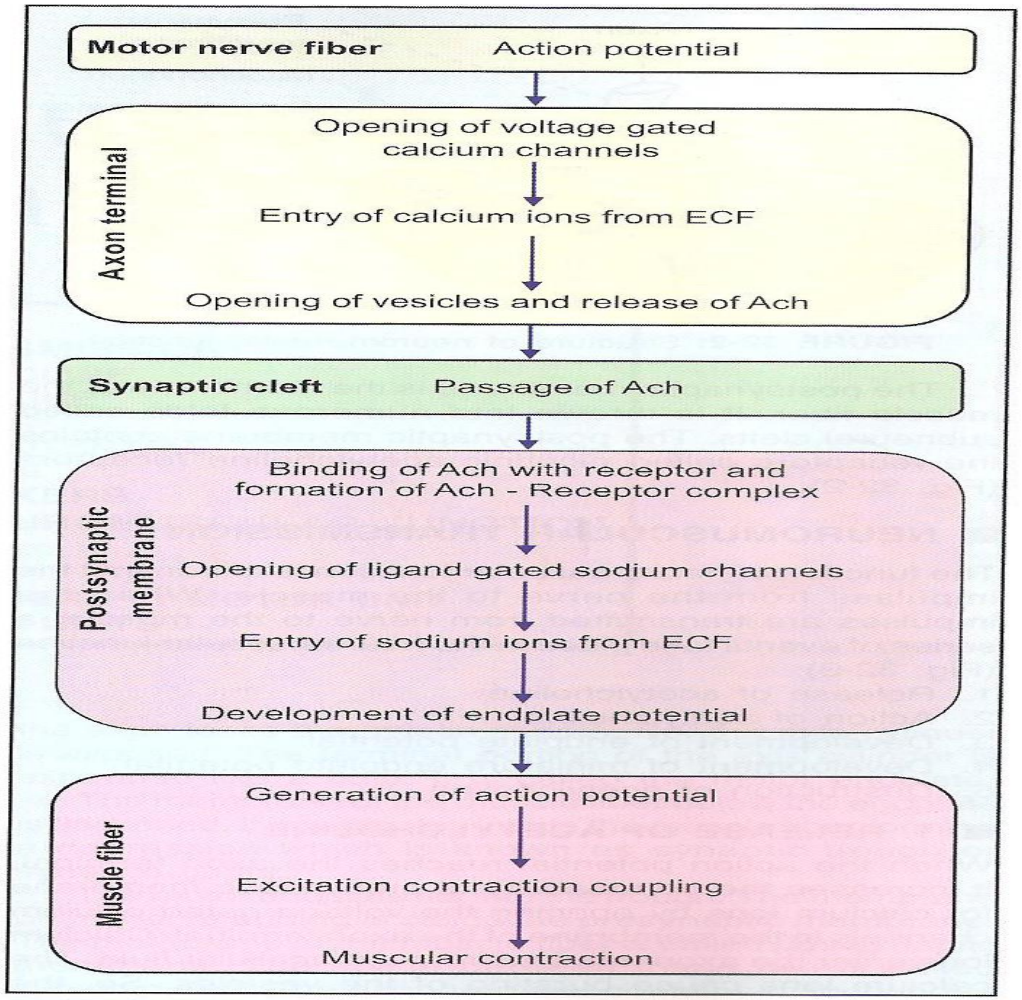


FIGURE 32-3: Sequence of events during neuromuscular transmission. Ach = Acetylcholine. ECF = Extracellular fluid