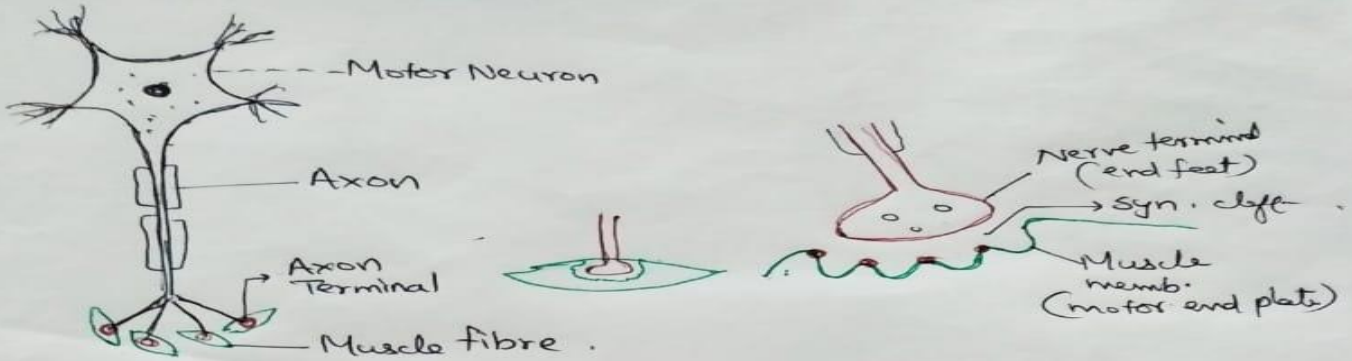
NEUROMUSCULAR JUNCTION



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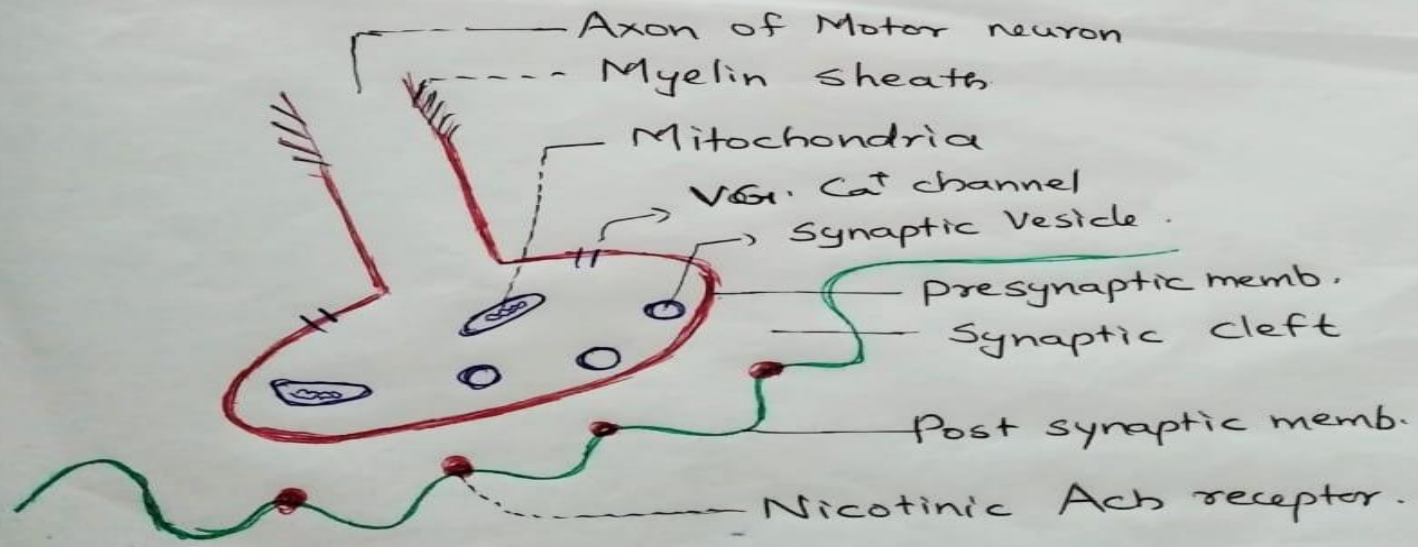

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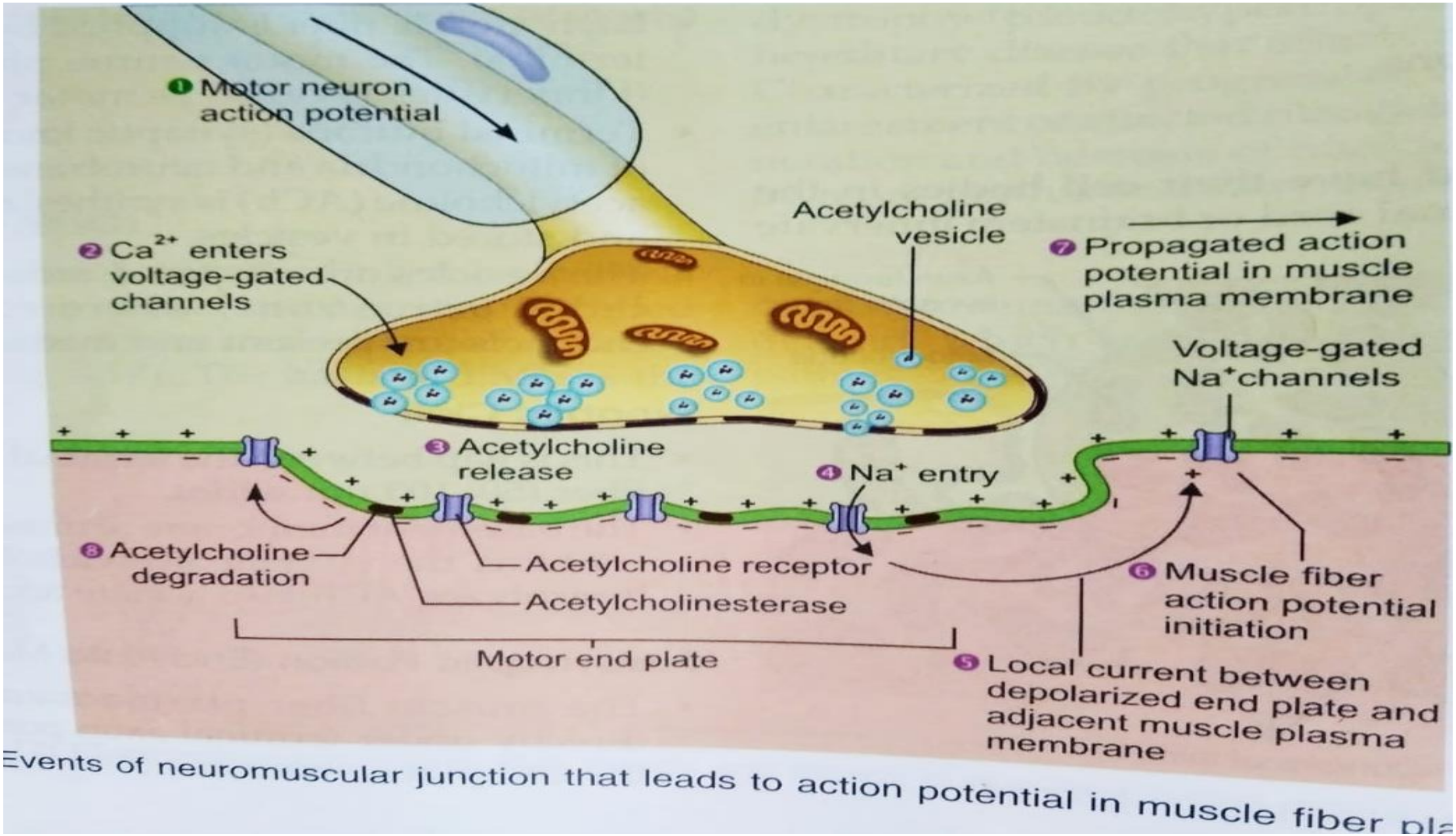

Events of neuromuscular junction that leads to action potential in muscle fiber pla

Neuromuscular junction

- **NMJ** ----Junction b/w a motor neuron and a muscle fibre .
- When impulses transmit from neuron to muscle through NMJ , muscle contracts
- The nerve terminal = end feet - supplies muscle fibre
- Sarcolemma at NMJ is thickened and invaginated – **motor end plate**
- End feet fits into the motor end plate

- NMJ consists of ---- **End feet**

  ---- synaptic cleft

  --- Motor end plate

- **Nerve terminal or end feet**
- It has no myelin sheath , covered by schwann cells
- Protrudes into synaptic gutter or synaptic trough

- Contains V. G Ca+ channels, mitochondria, synaptic vesicles , etc
- Each end feet contains 3 lack vesicles and each vesicle contains 10000 Ach molecules

When 1 AP comes 60 – 100 vesicles rupture

- Ach synthesis --- mitochondria provides energy,
  after synthesis, it is stored in synaptic vesicles..

- Enzyme –choline Acetyl Transferase – helps in synthesis of Ach from choline.

- Synaptic cleft
- Space between presynaptic membrane and post synaptic memb.

  --50nm – 100 nm width
- ECF flows through it.
- (Ach released is about 10 times that required to produce AP in muscle fibre)

Acetyl choline esterase is found-

- **It can destroy excess Ach**, after its action is over

- **Motor end plate**

- Modified part of muscle fibre.

- Invaginated, thickened and form folds (folds– palisades)

- On post syn. memb, many nicotinic Ach receptors are present

- They are **ligand gated Na+ channels**

Events takes place during neuromuscular transmission

- Arrival of impulse at the nerve terminal
- Opening of V.G Ca+ channels and influx of Ca+
- When Ca conc increases , Syn vesicles bind with syn memb & release Ach into synaptic cleft by exocytosis

--Ach binds with Ach receptors present on motor end plate

(Ach receptor = ligand gated Na+ channel)

Ach receptor opens and Na+ influx---causes End Plate Potential **(EPP)**

(((EPP -local potential , non propagative & graded pot

graded potential—its magnitude depends on how many Na enter the muscle, it does not obey all or none law))

- When EPP reaches threshold level (-40 mv), it triggers the opening of V G Na channels on sarcolemma –causing development of AP
- AP spreads through muscle fibre
- By excitation – contraction coupling

  --**Muscle contraction.**
- **Removal of Ach**
- excess Ach is hydrolysed and removed by Ach-esterase
- -**prevents continuous or repititive stimulation of the muscle fibre.**

- Miniature end plate potential (MEPP)
- During rest , there is a release of very small amount of Ach producing small depol in the muscle cell—MEPP
- Its magnitude 0.5 mv
- The MEPP is very minimum & not sufficient to produce EPP
- A large no of MEPP can be summated to produce an AP , when it reaches -50 mv

Drugs that affect NMT

- **Stimulant drugs**

1) Drugs having Ach like action

Methacholine

Carbachol

Nicotine

2) Anticholine esterase

physostigmine

Neostigmine

Diidopropyl flurophosphate

Tensilon

blocking drugs

1) presynaptic blocking drugs

botulinum toxin

2) **post synaptic blocking drugs**

a) by competitive inhibition

D tubocurarine

bungarotoxine

b) **by persistent depolarisation**

decamethonium,succinyl choline

- **Neuromuscular stimulators**
- Drugs having Ach like action
- Carbachol, nicotine etc act like Ach and produce EPP and AP .

  -- contraction occurs
- These drugs are not destroyed by AchEsterase .-their action prolonged

- They cause repeated stimulation and continuous action of muscle and cause a state of **muscle spasm**

- **Drugs that inactivate Ach esterase** (anticholine esterase)
- Neostigmine, physostigmine etc inactivate AchE—
- Then Ach cannot be hydrolysed -- Ach accumulates-
- -repeated stiulation and continuous action of muscle
- -- leads muscle spasm

Neostigmine is used in the treatment of Myasthaenia gravis

- Anticholine esterase---2 types
- Reversible inhibitors---physostigmine, neostigmine
- Irreversible inhibitors—malathion, baygon

- **NM blocking drugs**

--some of them are very useful in surgery, they relax muscles by paralysing them .

This reduces the dose of the anasthaetic agent necessary for surgery

1) **Presynaptic blocking drug**--- botulinum toxin produced by c lo clostridium botulinum

- It **binds with presynaptic membrane** and interrupts the synthesis and release of Ach, --- NMT does not occur – causes muscle paralysis.

Applications 1)---botulinu toxin is used for cosmetic purposes- to relax muscles that cause facial wrinkles

2) In Achalasia cardia --Injection of botulinum toxin into lower oesophageal sphincter relieves muscle spasm

- **Post synaptic blocking drug** - competitive blockers

Eg --- **curare and gallamine**

- It binds with **Ach receptor** and does not allow Ach to bind with it

--(-it competes with Ach to bind with receptor)

Curare –receptor complex cannot open ligand gated Na channel—no EPP or AP ----thus block NMT --it leads **muscle paralysis.**

Since it is competitive, if more Ach is there , it can bind with AchR and thus overcome the block

- Neostigmine is used as an antidot in curare poisoning
- neostigmine is an AchE inhibitor –so destruction of Ach cannot occur –Ach accumulates –it can bind with receptor—NMT occurs

- **Applied physiology** –
- **Curare**—is used in south America , as an arrow poison for hunting animals. When an animal is hit by an arrow poisoned with curare at its tip, the animal gets paralysed and dies of respiratory failure within minutes.
- **Gallamine**—is given before surgery to relax sk muscles– it reduces required dose of general anasthaesia as well as bleeding complications .

- **Drugs block NMT by persistent depolarization**
- Succinyl choline, Decamethonium etc (act in the same manner as large doses of nicotine , carbachol etc)
- They act like Ach and cause EPP & AP , but they are not destroyed by AchE
- Muscle remains in a state of depol for a long time and does not come to repol (Na channels remains open) ,block NMT
- Muscle is refractory to any stimulus ---depolarizing block or persistent depolarization .
- Initially muscle contracts later paralysis
- Succinyl choline is used in anastesia as a muscle relaxant

- **Disorders of NMT**
- Myasthenia gravis
- Rare disease – affecting NMJ – NMJ is unable to transmit signals from Neuron to muscle --muscular weakness and paralysis of involved muscles
- -- autoimmune disease -- circulating antibodies are developed against Ach receptors and destroy some of the receptors -- and NMT does not occur properly
- Changes occur in NMJ

--No of receptors decreases

--Post synaptic folds are flattened

--Synaptic cleft is widened

- Normally on repeated stimulation of the motor nerve , the amount or quanta of Ach released per AP gradually decreases (presynaptic rundown) , but this amount is enough to generate EPP and AP .

- But in MG patients, due to post synaptic changes along with presynaptic rundown, for the successive stimuli—the contractile response decreases—causing muscle fatigue

- The weakness increases during prolonged use of muscle and improves after rest or sleep (that time new Ach will be produced) **therefore patient is better in the morning and weakness towards evening**

- Most commonly affected muscles – extra ocular muscles,facial,swallowing,mastication, pharyngeal and laryngeal
- Drooping of eyelids (weakness of muscles of upper eyelid) is an early and prominent symptom
- In severe cases resp muscle paralysis—leads death

- Treatment–

1) neostigmine --- Ach esterase inhibitor -- Ach accumulates

Ach can bind with available receptors

2) cortisol –suppress antibody production

3) plasmapheresis--- helps to remove autoantibodies

4) thymectomy is done in patients with thymoma

Lambert Eaton Myasthenic syndrome

auto immune disease

Antibodies develop against V G Ca channels

--decrease Ca influx –--- decrease Ach release from nerve endings.

- Muscle weaknes seen in limb muscles

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