DRUGS ACTING ON NMJ

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LEARNING OUTCOMES

By the end of the lecture, students will be able to…

1. list the drugs/agents that influence the neurotransmission at the neuromuscular junction
2. list the types of neuromuscular blockers
3. describe the pharmacological profile of drugs acting on the neuromuscular junction.
4. describe the basis of the use of acetylcholinesterase inhibitors in myasthenia gravis and reversal of the effects of muscle relaxants

OUTLINE….

A. Neuromuscular Junction

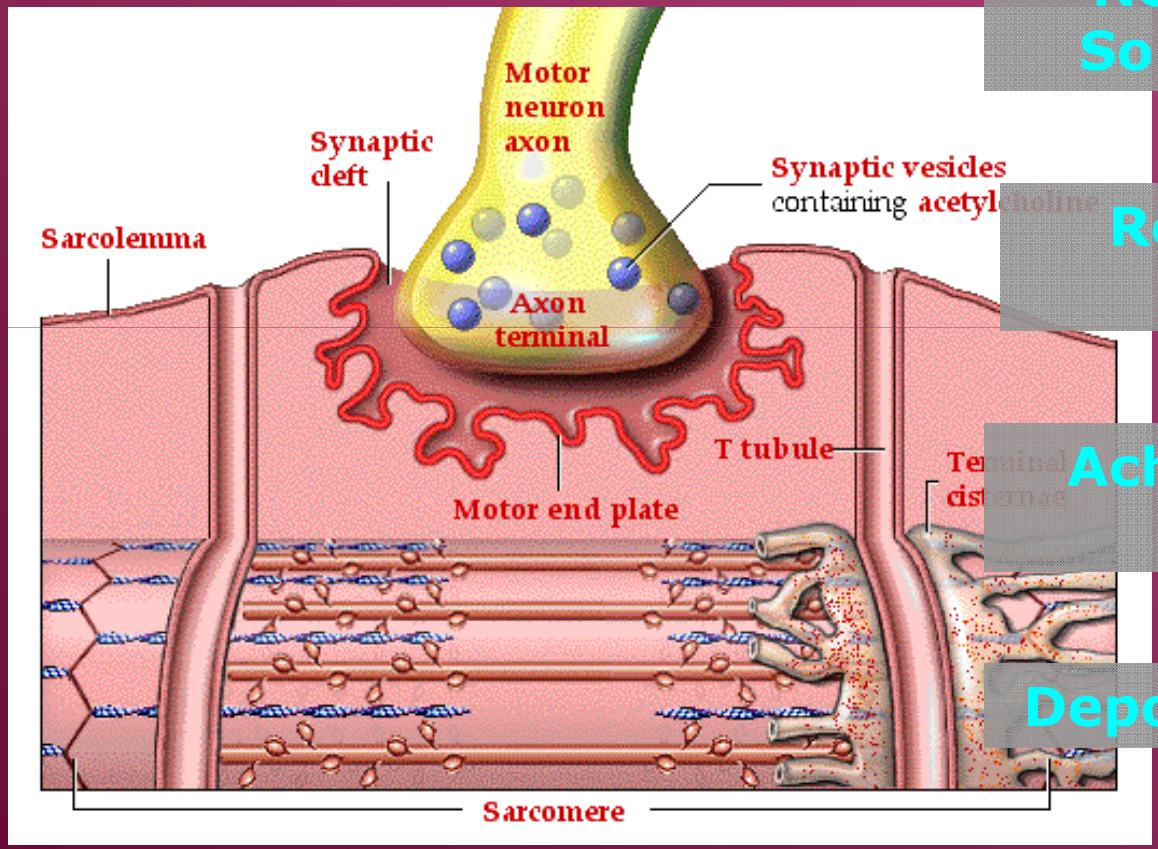
B. Nicotinic Receptors

C. Neuromuscular Blocking Agents

D. Botulinum Toxin

E. Acetylcholinesterase Inhibitors

NEUROMUSCULAR TRANSMISSION



Nerve Impulse from Somatic motor nerve

Release of Ach from nerve ending

Ach binds to Nicotinic receptors

Depolarize muscle fibres

Muscle Contraction

NICOTINIC RECEPTORS

- Large doses of 'Nicotine' acts as agonists to this group of cholinergic receptors.

- These are found at
  a) Sympathetic and Parasympathetic Ganglia.
  b) At Neuromuscular Junction
  c) At CNS
  d) At Adrenal Medulla

DRUGS ACTING AT NMJ

- Neuromuscular blocking drugs
  - Tubocurarine
  - Suxamethonium
- Acetylcholinesterase inhibitors
  - Edrophonium
  - Neostigmine

NEUROMUSCULAR BLOCKING DRUGS

1. Competitive Neuromuscular Blocking Drugs.

   e.g. Tubocurarine
   Atracurium
   Pancuronium
   Vecuronium

2. Depolarizing Neuromuscular Blocking Drugs

   e.g. Suxamethonium (Succinylcholine)

COMPETITIVE NEUROMUSCULAR BLOCKING DRUGS

- These are competitive antagonists of nicotinic acetylcholine receptors at NMJ

TUBOCURARINE

- **Paralysis in order of:**

muscles of eyelids

↓

muscles of swallowing and speech

↓

muscles of limbs and trunk

↓

respiratory muscles

(intercostal muscles & diaphragm)

TUBOCURARINE

- Does not cross the blood-brain barrier

No effect on level of consciousness

Has no analgesic properties

- Partial blockade at autonomic ganglia and at the adrenal medulla

Hypotension and tachycardia

TUBOCURARINE

- Stimulates Mast Cells and Release Histamine

Bronchospasm

Hypotension

excessive bronchial and salivary secretion

TUBOCURARINE

- Poorly absorbed from gut ⇒ administered i.v.
- Widely distributed in the body

  Doesn't cross placenta , blood brain barrier
- Onset in ~ 6 minutes and effects last from 40-80 minutes.
- It is not metabolised.
- It is excreted via the bile (30%) and urine (70%).

TUBOCURARINE

- **Adverse Effects:**

1. Hypotension – Due to blockage of autonomic ganglia and due to histamine release
2. Bronchospasm
3. Flushing
4. Skin Rash
5. Tachycardia

} Due to histamine release

DEPOLARISING NM BLOCKERS

- Clinical Use:
  - **For endotracheal intubation**
  - **In abdominal surgery (with GA)**
  - **In patients undergoing IPPV at ICUs**
  - **In the treatment of Tetanus**

PANCURONIUM

- Long acting competitive NM blocker(duration of effect 60-120 minutes)
- Elimination-Renal and hepatic
- Lacks Histamine releasing effect
- Blocks muscarinic receptors(Vagolytic Effect) $\rightarrow$ Hypertension

ATRACURIUM

- Intermediate acting competitive NM blocker (~ 45 min)
- Also cause histamine release to a lesser extent
- Metabolized by,
  a. Hofmann elimination (spontaneous degradation in plasma and tissue at normal body pH and temperature)
  b. ester hydrolysis (catalysis by nonspecific esterases)
- Can be used in patients with liver/kidney failure

REVERSAL OF COMPETITIVE NEUROMUSCULAR BLOCKAGE

- Achieved by Cholinesterase inhibitors

e.g. Neostigmine

Inhibition of Cholinesterase → **Accumulation of acetylcholine** → **Displace competitive blockers & occupy the nicotinic receptors**

REVERSAL OF COMPETITIVE NEUROMUSCULAR BLOCKAGE

Practical points:

- **An antimuscarinic drug is given prior to neostigmine.**
- **Action short lived(~ 30 min).Repeated doses may need to be given**

DEPOLARIZING NEUROMUSCULAR BLOCKERS

Suxamethoniom (Succinylcholine)

- Acts as an agonist for nicotinic receptors at NMJ

Depolarizing(Phase I) Block:

Initially Depolarization + Muscle contraction ⇒ **Persistent Depolarization** ⇒ **Motor endplate becomes non excitable** ⇓ **Muscle Relaxation**

DEPOLARIZING NEUROMUSCULAR BLOCKERS

Suxamethoniom (Succinylcholine)

With prolonged exposure to succinylcholine,

Phase II Block:

- **Similar in behaviour to competitive NM blockage**

SUXAMETHONIOM

- Has a rapid onset of action.(~1-1.5 minutes)
- But effect very short lived(~ 5 minutes)
- Effects wears off when suxamethonium degraded by,

    butyrylcholinesterase - in the liver

    pseudocholinesterase - in plasma

- Cholinesterase Inhibitors can not reverse the paralysis but worsens it.

SUXAMETHONIUM

- Clinical Use:
  a. To facilitate endotracheal intubation for artificial ventilation
  b. To paralyze skeletal muscles during electroconvulsive therapy for mental disorders
  c. In orthopaedic Surgery for short procedures like correction of dislocations

SUXAMETHONIUM

- **Adverse effects**
  - Muscle pain
  - Hyperkalaemia
  - Bronchospasm(Due to histamine release)
  - Transient Bradycardia(Due to stimulation of vagal ganglia)
  - Hypertension & Tachycardia (Due to stimulation of sympathetic ganglia)

SUCCINYLCHOLINE INDUCED HYPERKALAEMIA

Suxamethonium causes efflux of potassium ions via activating nicotinic receptors at NMJ

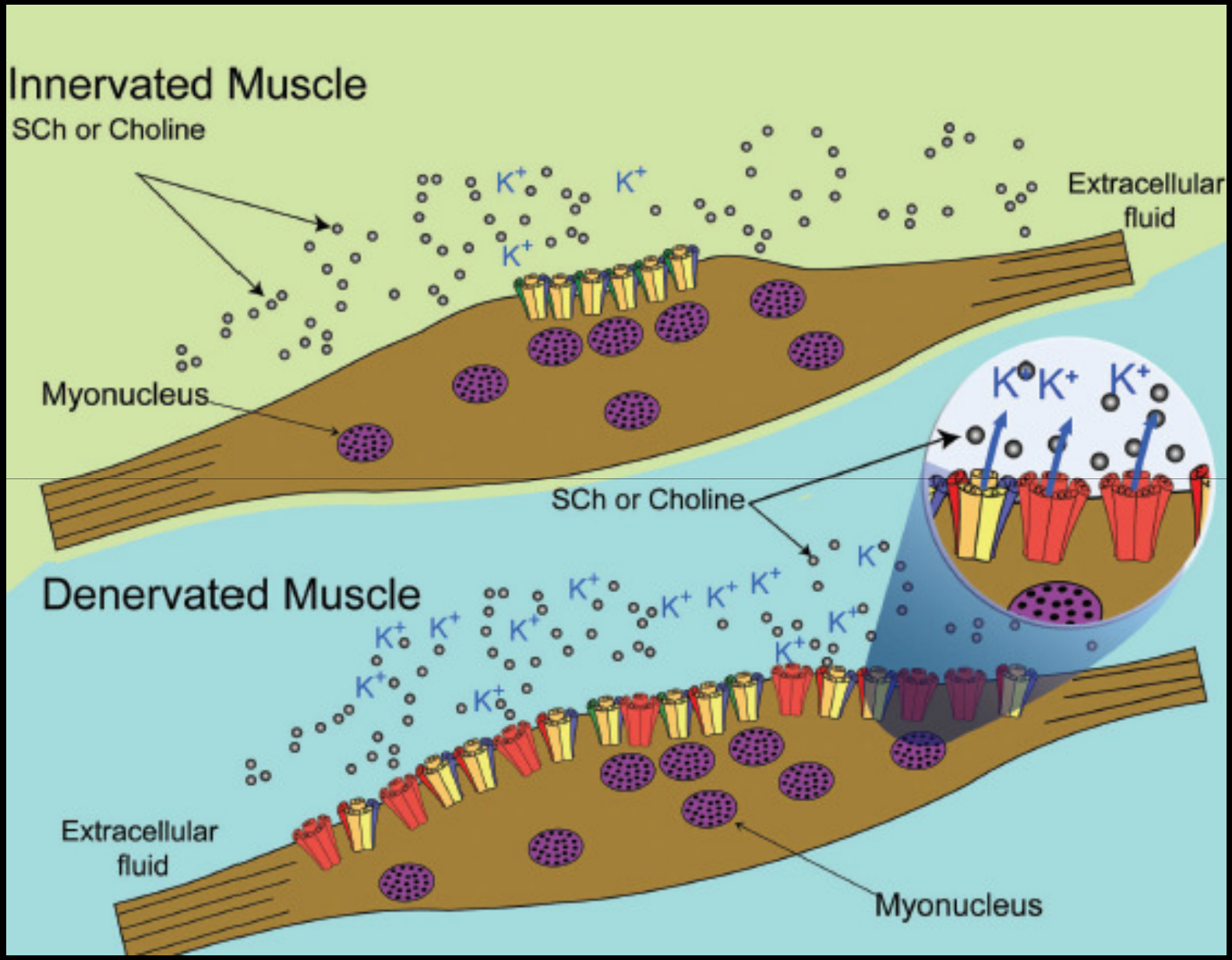
Loss of muscle excitation

e.g. Upper or lower motor neuron defect

Disuse atrophy

up regulation and spread of AChRs throughout the whole muscle membrane

Increased efflux of potassium


Innervated Muscle
SCh or Choline
Extracellular fluid
Myonucleus
SCh or Choline
Denervated Muscle
Extracellular fluid
Myonucleus

SUXAMETHONIUM

- **Adverse effects**
  - Malignant Hyperthermia (Potentially lethal)
  - ↑ Intraocular Pressure
  - Myoglobinaemia/myoglobinuria
  - Succinylcholine in susceptible individuals also induces trismus-masseter spasm(↑ jaw muscle tone)

MALIGNANT HYPERTHERMIA

- An uncommon pharmacogenetic disorder of muscle induced by exposure to suxamethonium and all the volatile anaesthetic agents
- Administration of triggering agents leads to an uncontrolled release of free calcium from the sarcoplasmic reticulum of skeletal muscle
- Susceptibility is inherited as an autosomal dominant condition

MALIGNANT HYPERTHERMIA

- **Clinical features:**

1. Hypermetabolism (increased CO2 production ,tachycardia,↑ body temperature)
2. Muscle rigidity
3. Rhabdomyolysis (raised plasma CK and myoglobinuria)

- **Treatment:**

Intravenous administration of dantrolene -blocks Ca^{2+} release from the sarcoplasmic reticulum of skeletal muscles

BOTULINUM TOXIN

- Irreversibly blocks acetylcholine release from cholinergic nerve endings
- Used in cosmetic surgery – facial enhancement
- Used as local injections in the Rx of involuntary muscle spasms
  - e.g. facial spasm ,blepharospasm
    dystonias

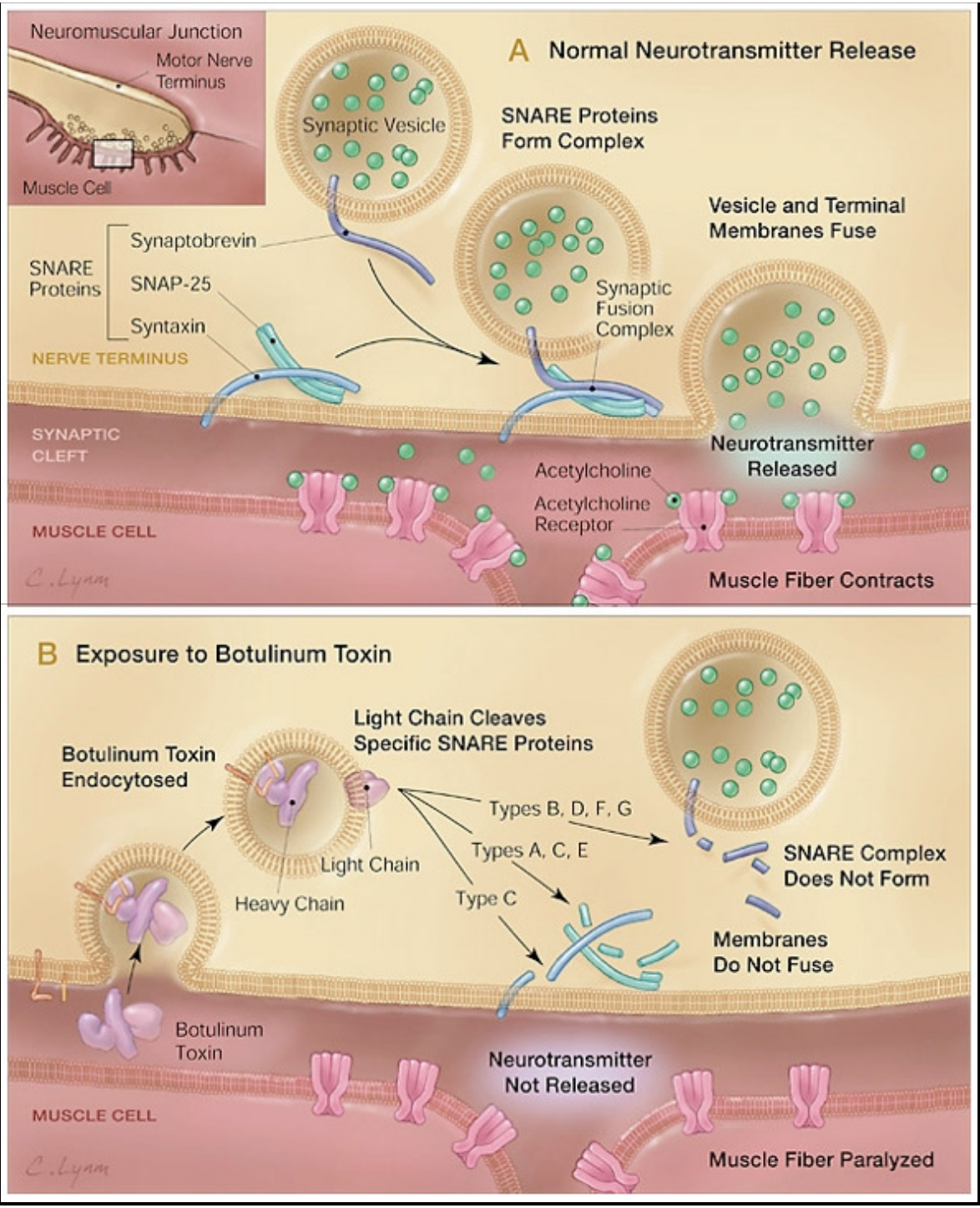
MODE OF ACTION BOTULINUM TOXIN A

Selective binding & internalization into Ach presynaptic neuron

Binds to the SNARE protein complex and causes proteolysis

Prevents docking of Ach vesicle on the inner surface of cell membrane

Prevents exocytosis of Ach vesicles


Neuromuscular Junction
Motor Nerve Terminus
Muscle Cell
A Normal Neurotransmitter Release
Synaptic Vesicle
SNARE Proteins Form Complex
Vesicle and Terminal Membranes Fuse
SNARE Proteins
Synaptobrevin
SNAP-25
Syntaxin
NERVE TERMINUS
Synaptic Fusion Complex
SYNAPTIC CLEFT
Neurotransmitter Released
Acetylcholine
Acetylcholine Receptor
MUSCLE CELL
Muscle Fiber Contracts
B Exposure to Botulinum Toxin
Light Chain Cleaves Specific SNARE Proteins
Botulinum Toxin Endocytosed
Types B, D, F, G
Types A, C, E
Type C
Light Chain
Heavy Chain
SNARE Complex Does Not Form
Membranes Do Not Fuse
Botulinum Toxin
Neurotransmitter Not Released
MUSCLE CELL
Muscle Fiber Paralyzed

BOTULINUM TOXIN

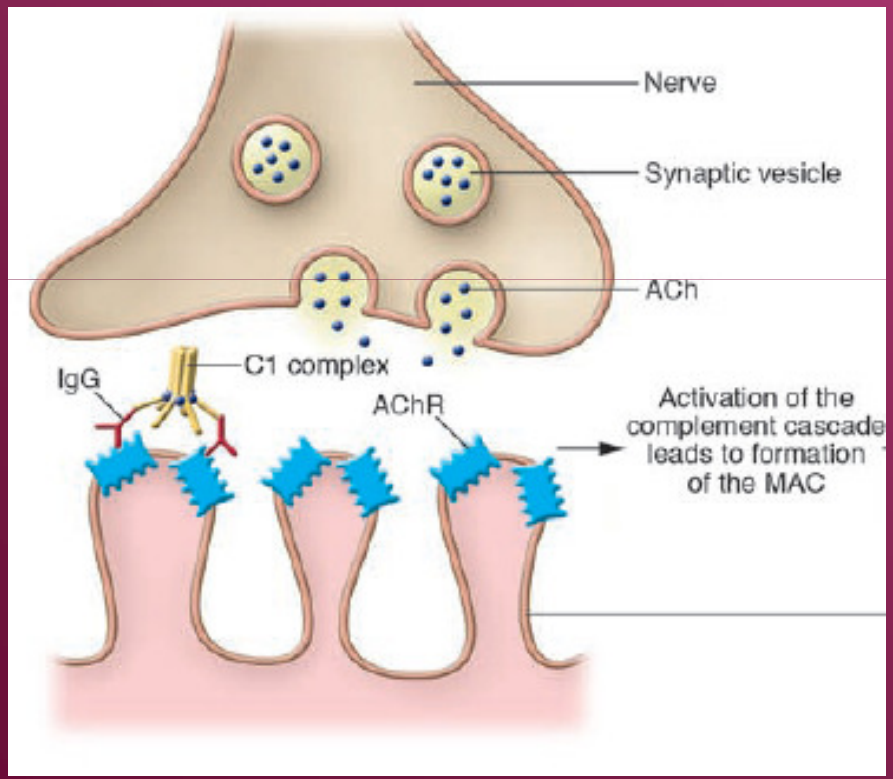
- When injected into a striate muscle, paresis occurs after 2 - 5 days
- Duration of effect 2-3months before it gradually starts to wear off
- When antibodies against BT are formed the duration of action and the extent of the maximal therapeutic effect are usually reduced

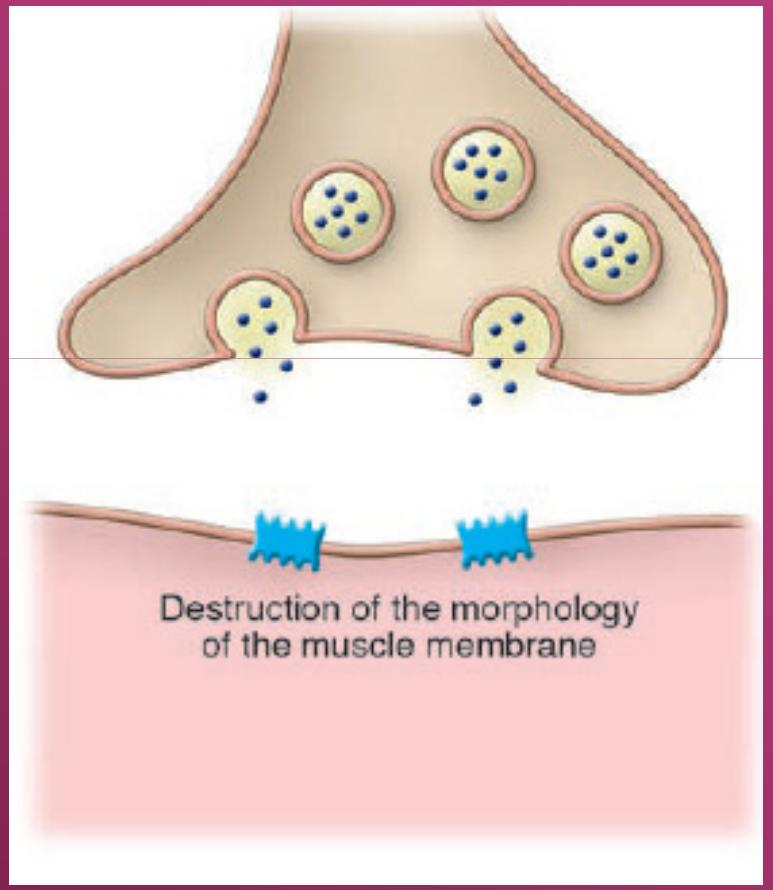
ACETYLCHOLINESTERASE INHIBITORS

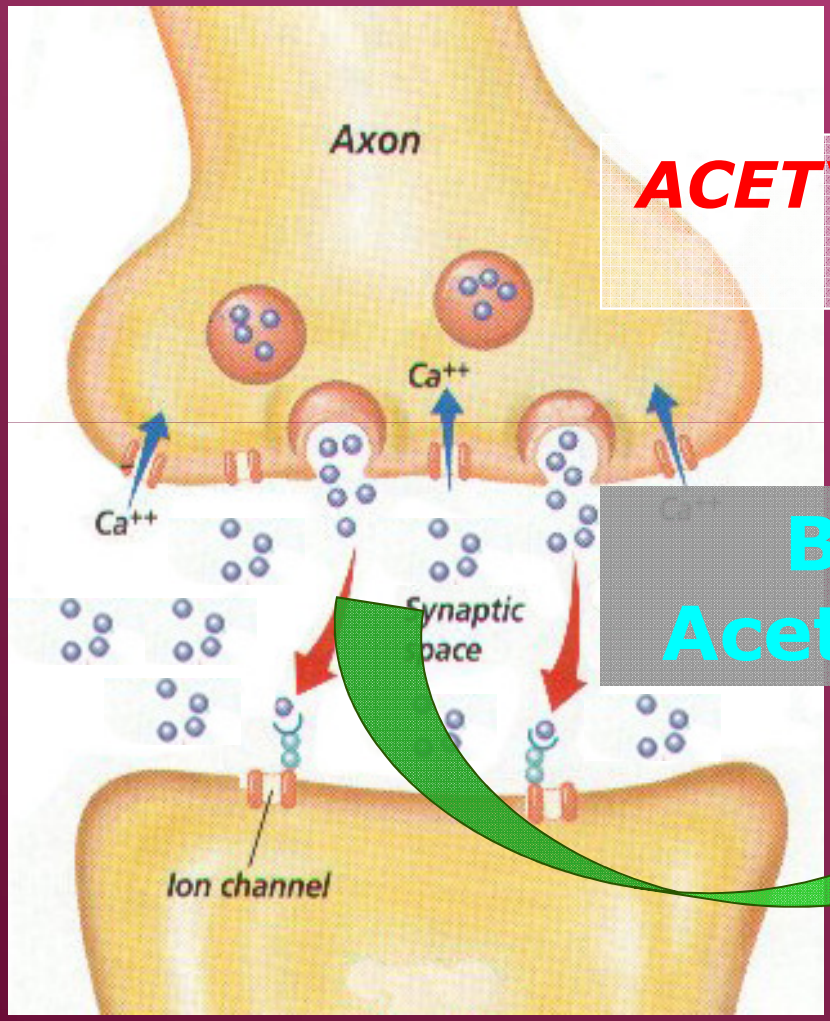
- Increase acetylcholine in NMJ
- Therapeutically used in the treatment of myasthenia gravis

  e.g. Neostigmine, edrophonium, pyridostigmine

MYASTHENIA GRAVIS







ACETYLCHOLINESTERASE INHIBITOR

Break down by Acetylcholinesterase

ACETYLCHOLINESTERASE INHIBITORS

- Adverse Effects:
  - Abdominal cramps
  - Diarrhoea
  - Excessive salivation
  - Lacrimation
  - Sweating

- These are muscarinic side effects and can be treated by anticholinergic drugs like propantheline without loss of nicotinic effect