Skeletal Muscle Relaxants

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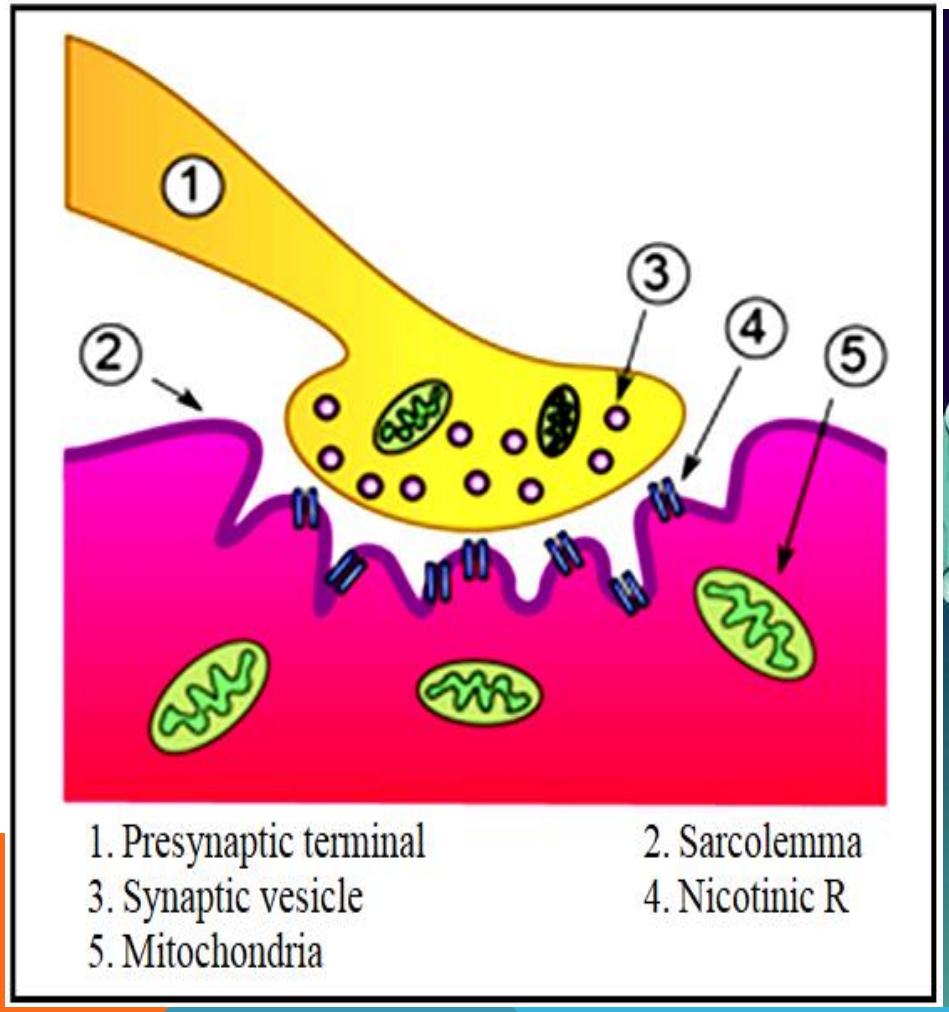
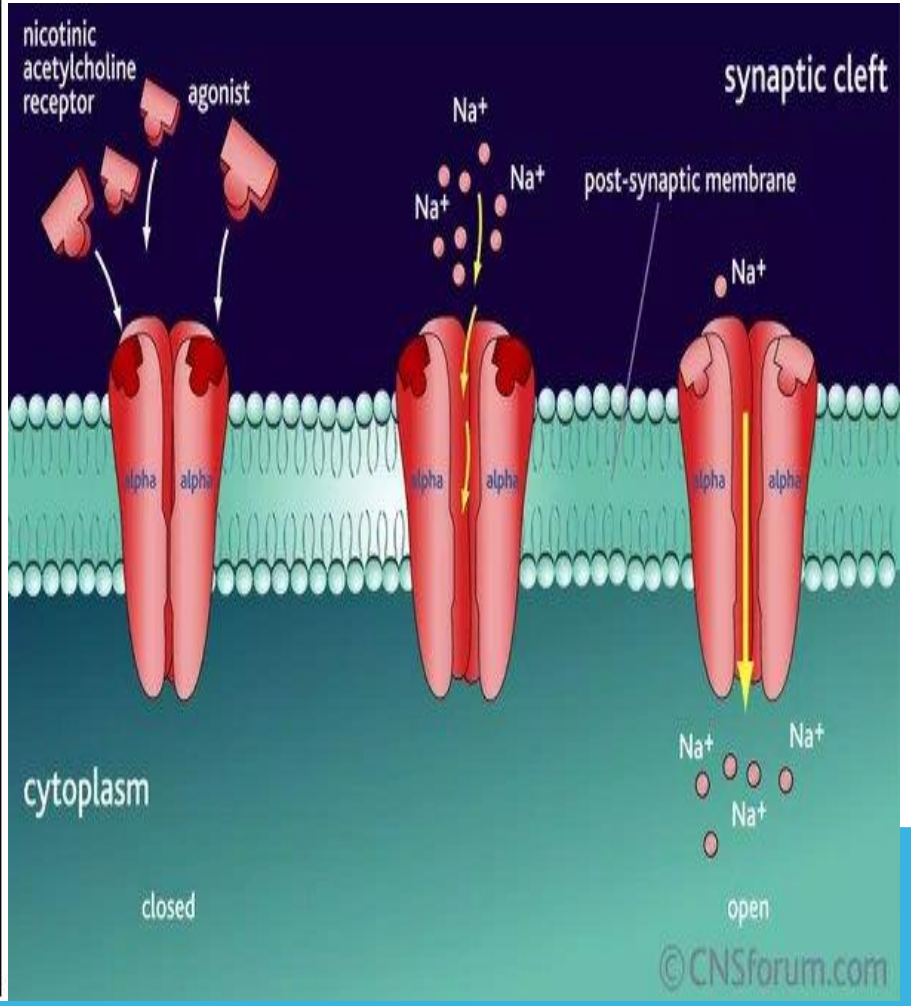
The Neuromuscular Junction (NMJ)



1. Presynaptic terminal
2. Sarcolemma
3. Synaptic vesicle
4. Nicotinic R
5. Mitochondria



Skeletal Muscle Relaxants

Classification Of Skeletal Muscle Relaxants:

Neuromuscular blockers (NMBs)

Spasmolytic drugs

NEUROMUSCULAR BLOCKERS (NMBS)

Competitive (non-depolarizing) NMBs

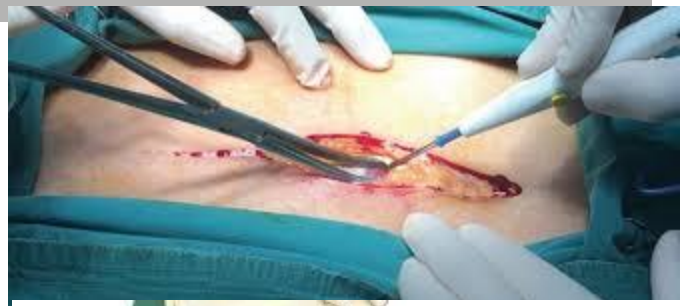
compete with Ach for nicotinic (N_m) receptors at motor end plate causing muscle paralysis

Non-competitive (depolarizing) NMBs:

- **They cause sustained depolarization of the motor end plate which leads to muscle paralysis.**
- **They produce initial stimulation of muscle (fasciculations) followed by paralysis.**

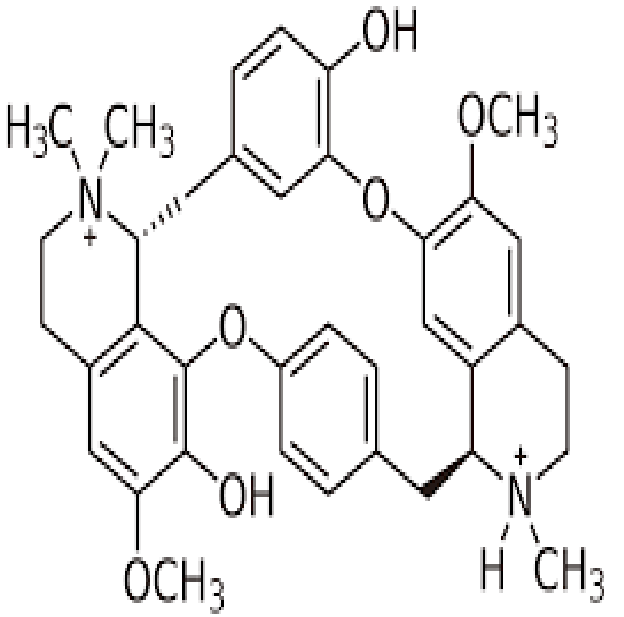
Therapeutic uses:

1) Skeletal muscle relaxation during surgery.
2) Facilitation of endotracheal intubation.
3) To facilitate mechanical ventilation.
4) To control severe convulsions during electroconvulsive therapy (ECT).

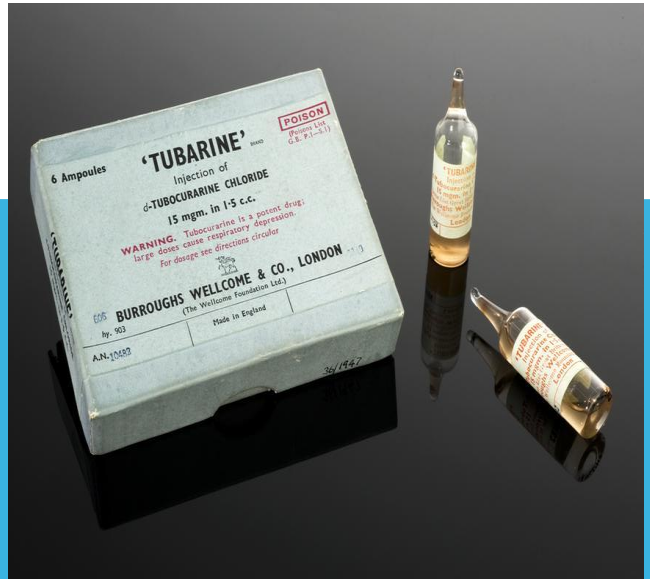


Competitive (Non-depolarizing) NMBs

(1) D-Tubocurarine (Curare)

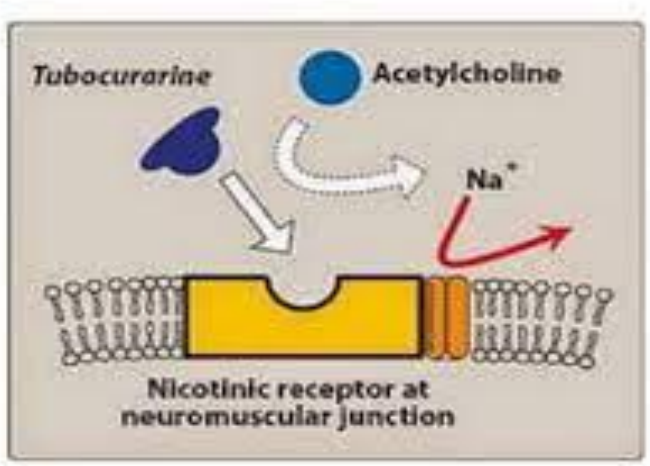


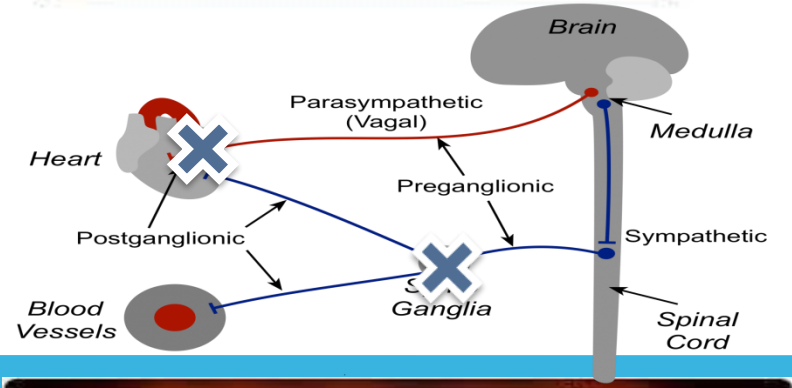
- It is quaternary ammonium compound ➔ given parentally & not absorbed orally.
- It has rapid onset.
- Recovery occurs within 30-60 min.
- It does not cross BBB ➔ No CNS actions.
- Excreted mainly in urine.

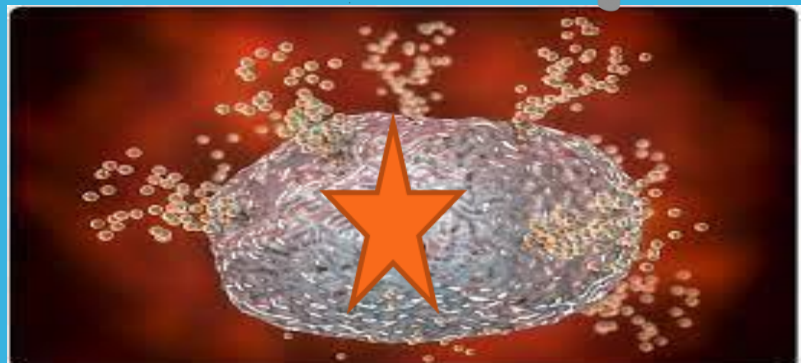


Mechanism of action:

1) Competes with acetylcholine for nicotinic receptors in the motor end plate (paralysis).
2) Curare is a weak ganglion blocker.
3) Histamine release (moderate).



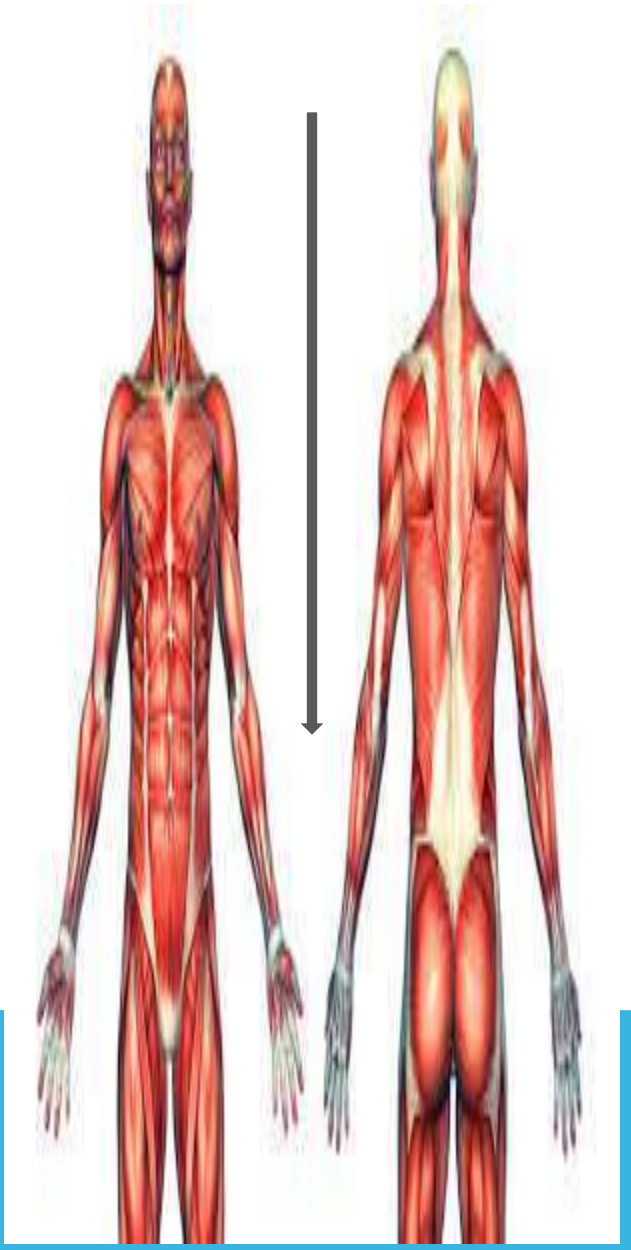




Pharmacological actions:

1)Skeletal muscle:

- skeletal muscle paralysis in the following order: Small rapidly contracting muscles of the eye, face, fingers & neck then the muscles of limbs & trunk are affected & the last muscles to be paralyzed are the intercostal muscles then the diaphragm.
- Recovery occurs in the reverse order.



2)CVS:

- **Hypotension due to:**

i. Weak ganglion blocking effect.

ii. Histamine release.

iii. Decreased venous return as a result of muscle paralysis → ↓↓ COP.

Adverse effects:

1. **Hypotension.**
2. **Bronchospasm.**
3. **Allergy.**
4. **Curare apnea: Death from overdose occurs due to paralysis of respiratory muscles.**

Treatment of toxicity:

1) **Artificial respiration with O_2 under pressure.**

2) **Neostigmine; preceded few minutes by atropine (to avoid marked bradycardia).**

Contraindications:

1) **Bronchial asthma.**

2) **Renal diseases.**

3) **Allergy.**

	Duration	Potency	Ganglion blocker	Histamine release	Special
Curare	30-60min	1			
Gallamine (Flaxidil)	15-35 min	(⅕ of curare).			tachycardia (M_2 blocker)
Pancuronium	60-90 min	6			tachycardia (↑NE release)
Atracurium	15-35 min			less	(Hofmann elimination)
Mivacurium	10-20 min	4		mild	(pseudocholine esterase enzyme).
Rocuronium	20-30 min	Used instead of succinylcholine for endotracheal intubation			Hepatic elimination
Vecuronium	30-40 min				Hepatic elimination

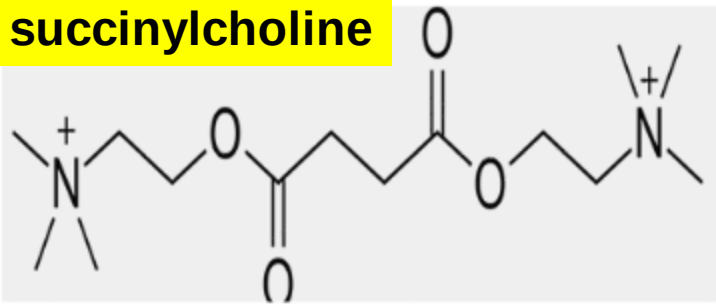
Depolarizing (Non-competitive) NMBs

Succinylcholine

- It is composed of two molecules of acetylcholine connected by an ether linkage.
- Not absorbed orally, not pass BBB.
- Short acting (5-10 min).
- Metabolized by pseudocholine esterase in two steps: rapid step into succinyl monocholine, then slow step into succinic acid + choline.

Ach

succinylcholine



Mechanism of action:

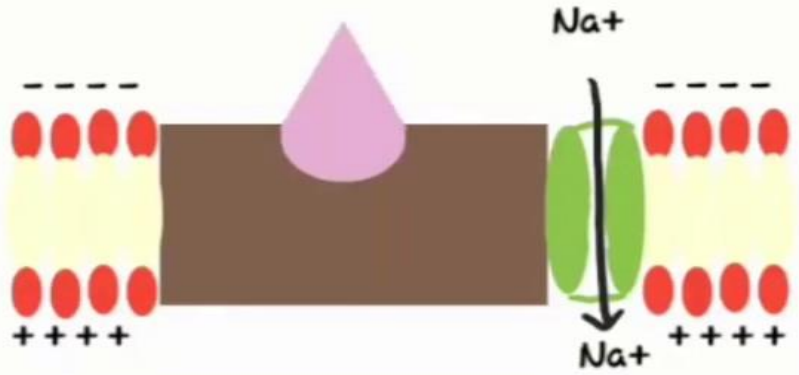
It has two phases of block:

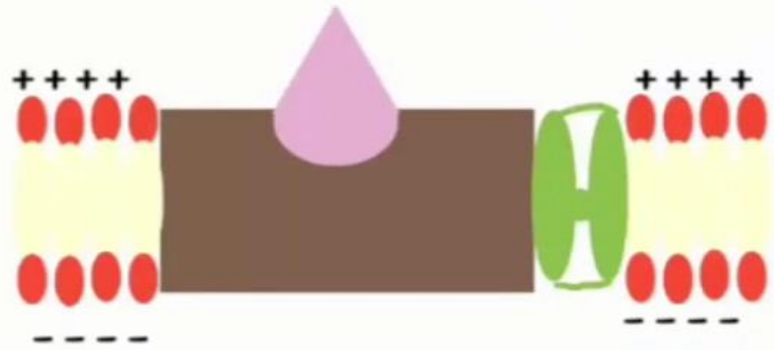
Phase I:

- **It binds to nicotinic receptors on the neuromuscular junctions & acts as agonist (depolarization of motor end plate & initially causing fasciculation).**
- **The slow dissociation and metabolism of succinylcholine at receptors lead to persistent depolarization, transmission failure & muscle paralysis.**

Phase II (desensitization):

- **Prolonged depolarization of receptors produces spontaneous closure of Na^+ channels which become partially reversible.**





Pharmacological actions:

1) Skeletal muscle paralysis preceded by fasciculations and this produces postoperative pain.
2) It stimulates both sympathetic and parasympathetic ganglia.
3) It is a mild histamine releaser.

Therapeutic uses:

It is very useful in endotracheal intubation because of its rapid onset and short duration of action.

Adverse effects

1) Succinylcholine apnea

Treatment of succinylcholine toxicity (apnea):

A. **Artificial respiration.**

B. **After diagnosis of the phase block:**

- **In phase I: give fresh frozen plasma or fresh blood transfusion to restore cholinesterase enzyme.**
- **In phase II: I.V. neostigmine or edrophonium preceded by atropine.**

2) Post-operative muscle pain.

3) Malignant hyperthermia (pharmacogenetic defect): treated by I.V. dantrolene.

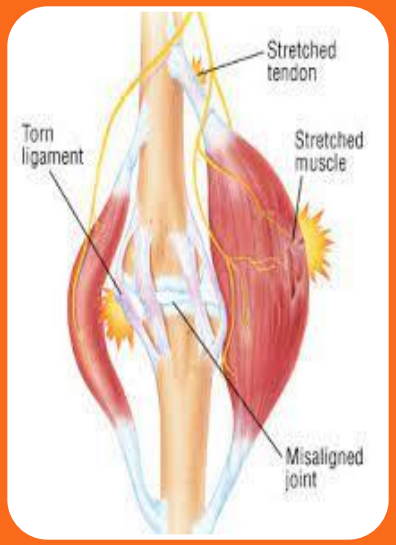
4) Hyperkalemia which can cause arrhythmias.

5) Increased intra-abdominal & intra-gastric pressures.

6) Increased IOP.

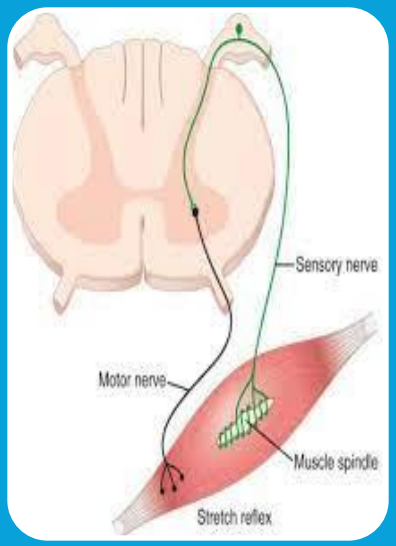
Contraindications:

1) Deficiency of pseudocholinesterase.
2) Glaucoma or eye injury.
3) Hypersensitivity to the drug.
4) Severe tissue damage.
5) History of malignant hyperthermia.



A-Skeletal muscle spasm :

due to local trauma or nerve root irritation e.g. prolapsed intervertebral disk



B. Spasticity :

due to excessive afferent stimulation of spinal alpha-motor neurons cells (located in anterior horn) whose axons innervate skeletal muscles leading to hypertonicity

It occurs in upper motor neuron lesion (UMNL) such as strokes , cerebral palsy , multiple sclerosis and spinal cord lesions

Spasmolytic Drugs

They are used to decrease skeletal muscle spasm

1- Centrally acting (on CNS): mephenesin & baclofen

2- Direct or peripherally acting (on skeletal muscles): dantrolene

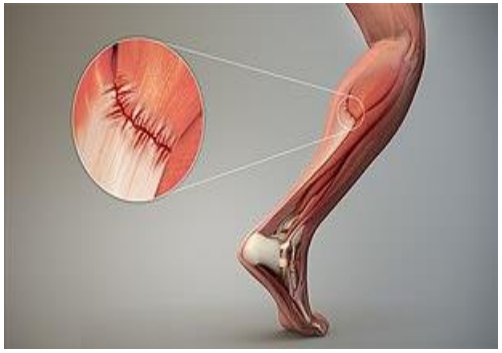
Therapeutic Uses

1) Spasticity of skeletal muscles due to local causes e.g. trauma, inflammation & rheumatism.

2) Low back pain syndrome.

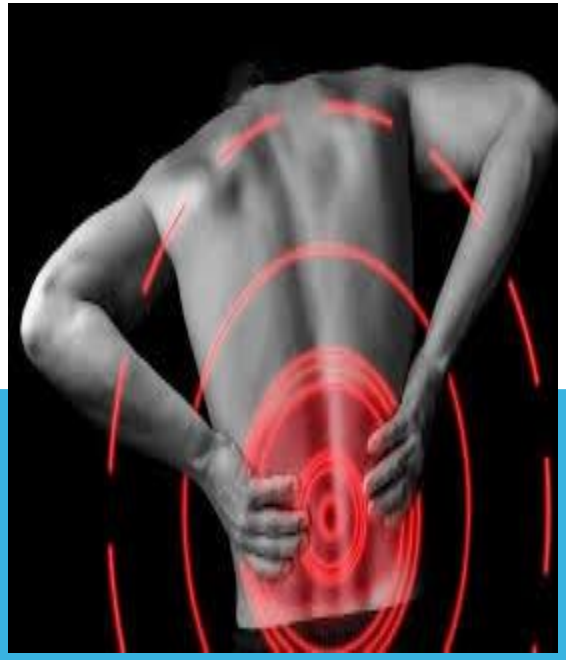
3) Cerebral causes of spasticity e.g. cerebral palsy & strokes.

4) Spinal causes of spasticity e.g. spinal cord injury or degenerative diseases.



Mephenesin

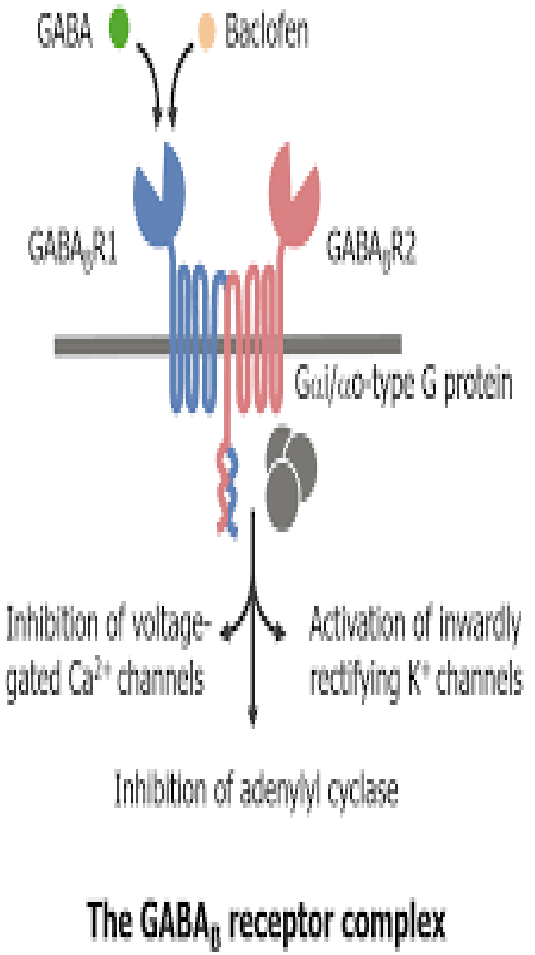
- Taken orally.
- Acts on subcortical (spinal) polysynaptic pathway ➔ muscle relaxation without hypnosis or anesthesia.
- It is used in:
  1. Strychnine poisoning (specific antidote).
  2. Painful muscle spasm and stiffness.



Baclofen

❖ **Mechanism of action:**

- **Selective $GABA_B$ agonist which produces inhibition of the release of excitatory transmitters in the brain and spinal cord.**
- It also decreases pain transmission in spinal cord by decrease release of substance P from nerve ending of primary afferent sensory neurons .



The $GABA_B$ receptor complex

Indications of Baclofen:

- **Used in muscle spasticity due to spinal cord lesions (e.g. spinal cord injury).**
- **Baclofen is not an appropriate treatment for muscle spasm associated with an acute injury.**

DIAZEPAM

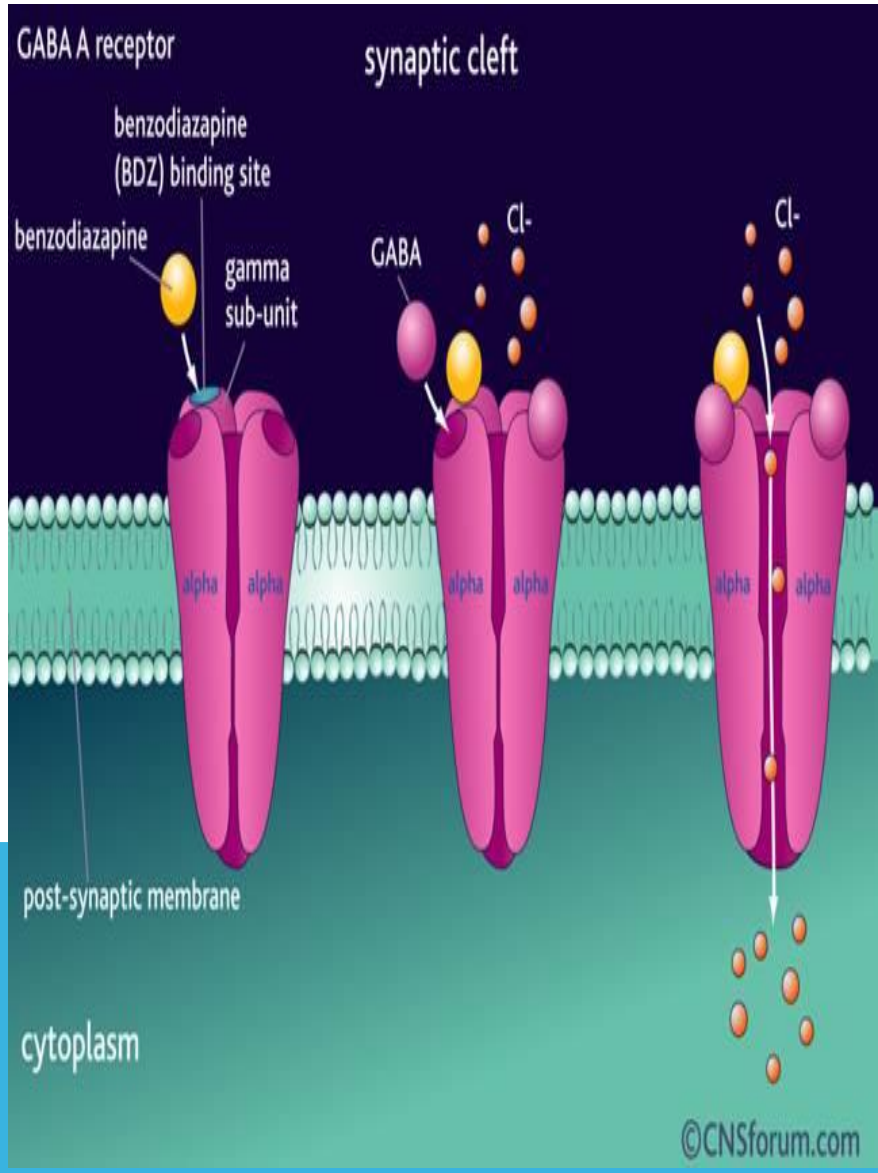
1-GABA A agonist

2-Enhancing polysynaptic and presynaptic inhibition on the spinal motoneurons.

USES:

A. Spasticity

B. Skeletal muscle spasm due to local trauma or disc prolapse:



Tizanidine

- It is a new α_2-adrenoceptor agonist.
- **Mechanism of action:** Stimulates α_2-adrenoceptors in CNS ➔ muscle relaxation.
- Taken orally.
- It has fewer CVS effects.

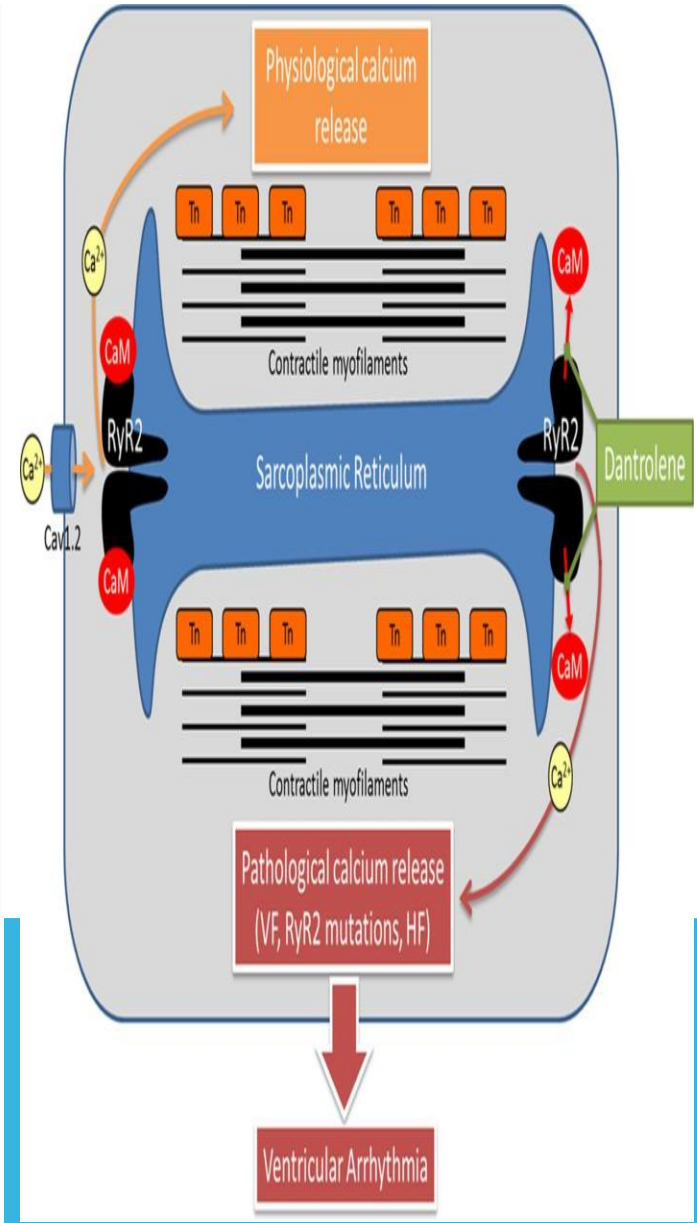
Dantrolene

❖ Mechanism of action:

- Acts directly on skeletal muscle and so has minimal CNS effects.
- It relaxes skeletal muscles directly by interfering with release of Ca^{+2} from sarcoplasmic reticulum.

Indications: (oral or IV)

1. Treatment of chronic muscle spasm caused by spinal cord (e.g. spinal cord injury) or cerebral (e.g. Cerebral palsy) causes.



Adverse effects:

1. Hypotension.
2. Muscle weakness.
3. Diarrhea.
4. Damage of liver (with long-term use).
5. Drowsiness, vertigo, and dizziness (with long-term use).


Thank you!