SKELETAL MUSCLE RELAXANTS

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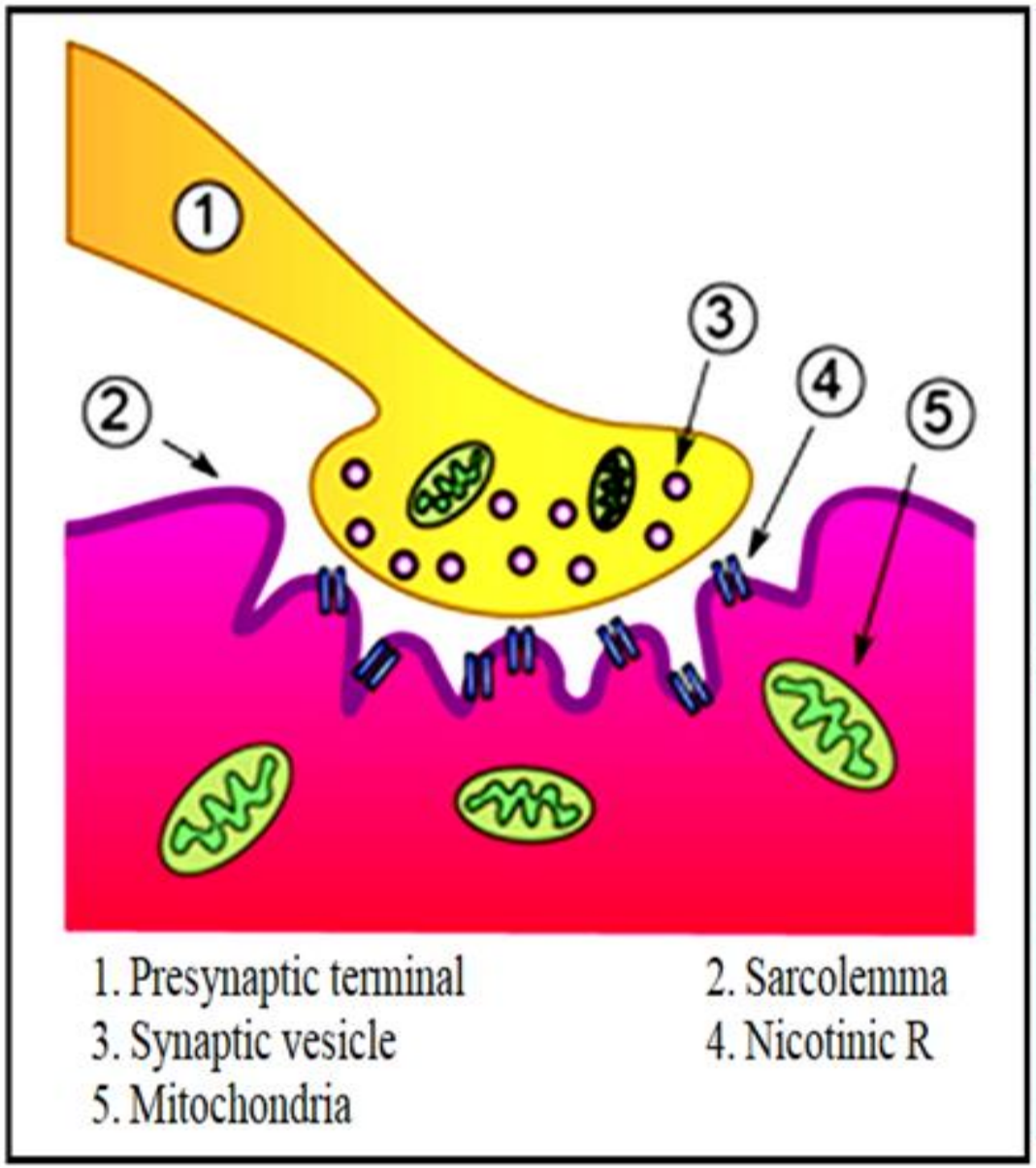
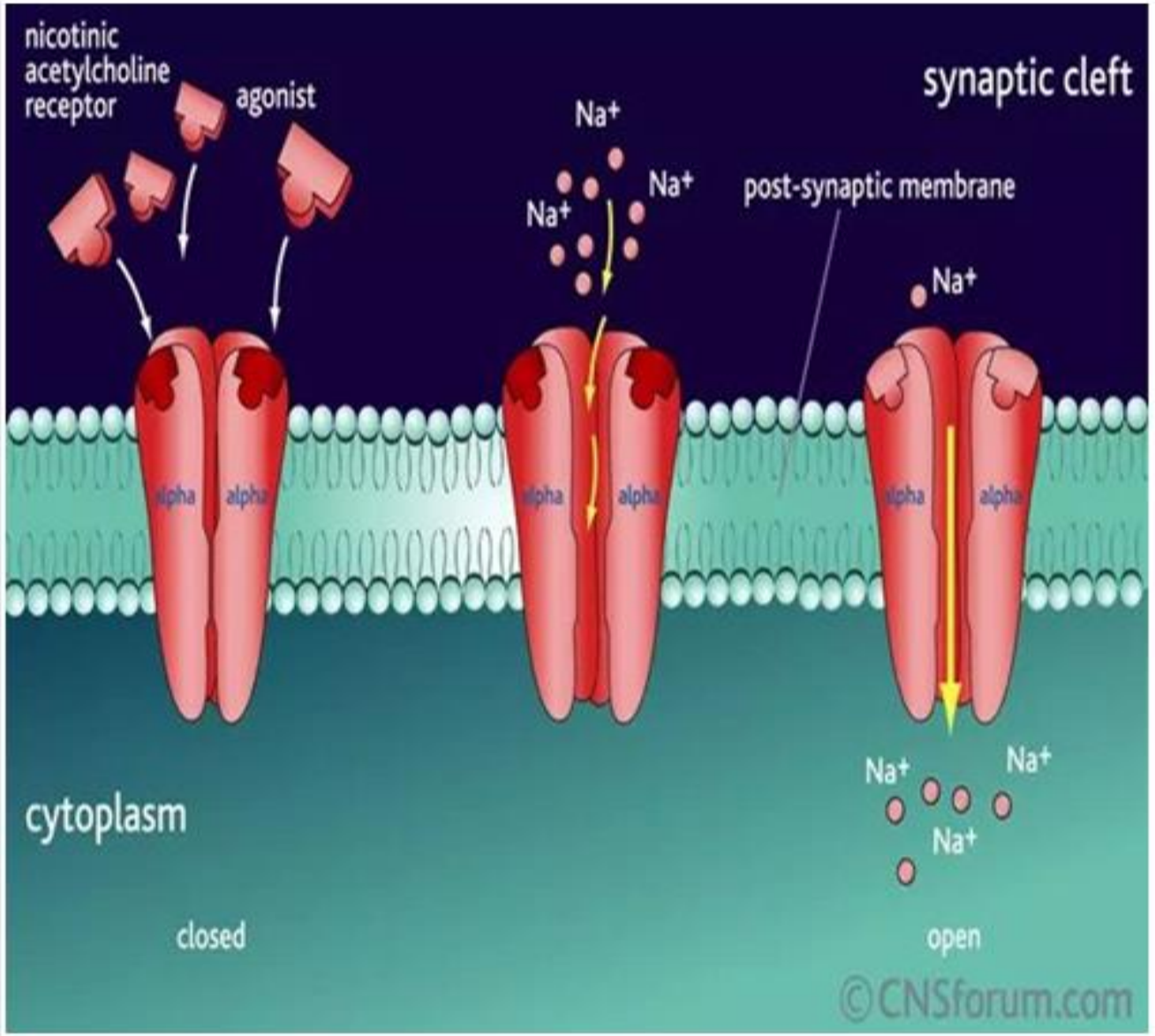
The Neuromuscular Junction (NMJ)





Classification Of Skeletal Muscle Relaxants:

- Neuromuscular blockers (NMBs)
- Spasmolytic drugs

Skeletal muscle relaxants

1- NMB: are drugs used to produce muscle paralysis or reduce muscle tone and alleviate muscle spasms or spasticity.

2-Spasmolytics: They act on the central nervous system (CNS) or directly on the skeletal muscles to relieve conditions such as muscle spasms, spasticity, and associated pain.

1-Neuromuscular blockers (NMBs)

Competitive (non-depolarizing) NMBs

competes with Ach for nicotinic (N_m) receptors at the motor end plate, causing muscle paralysis

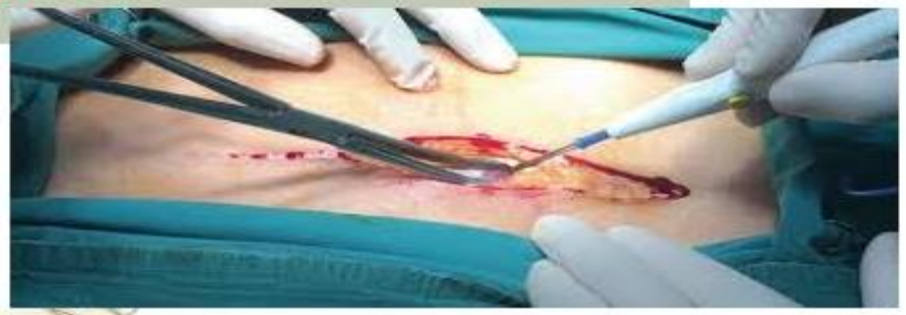
(small and large doses) ?

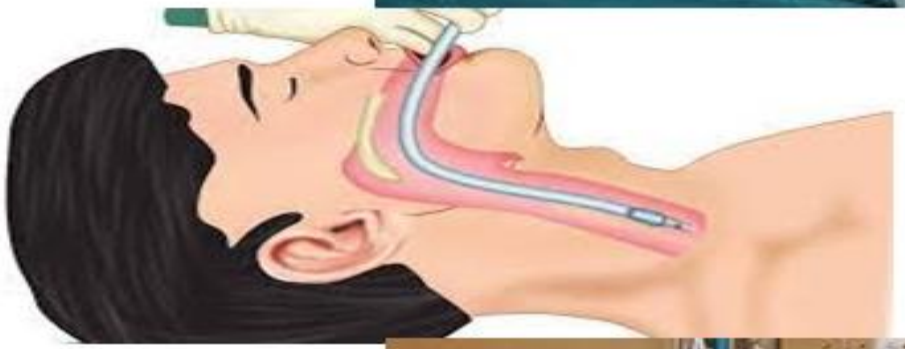
Non-competitive (depolarizing) NMBs:

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

Therapeutic uses:

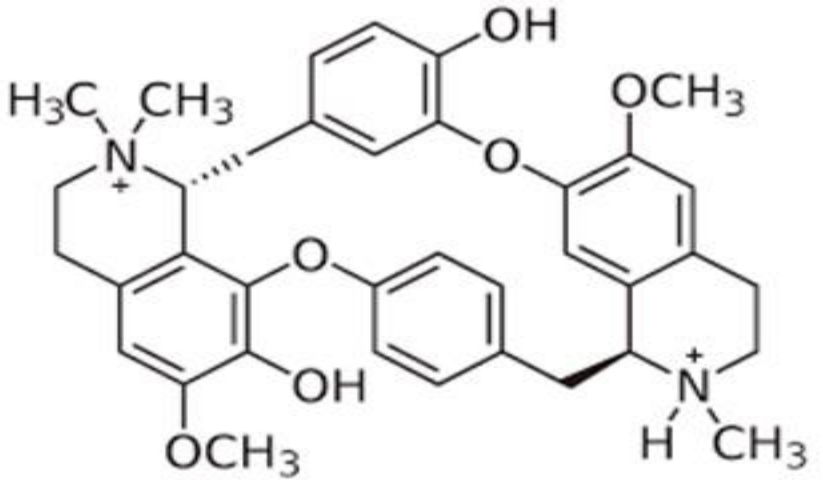
1) Skeletal muscle relaxation during surgery.
2) Facilitation of endotracheal intubation.
3) To facilitate mechanical ventilation.
4) To control severe convulsions during electroconvulsive therapy (ECT).





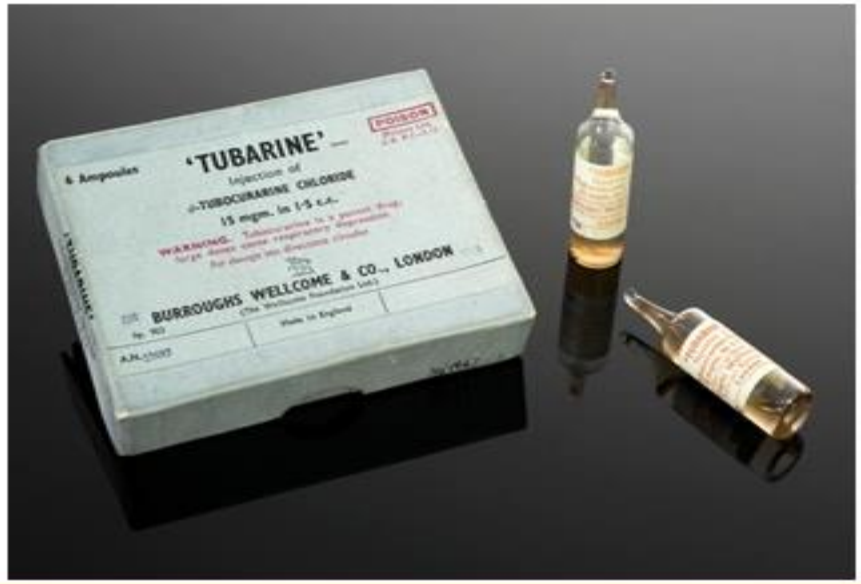
Competitive (Non-depolarizing) NMBs

(1) D-Tubocurarine (Curare)



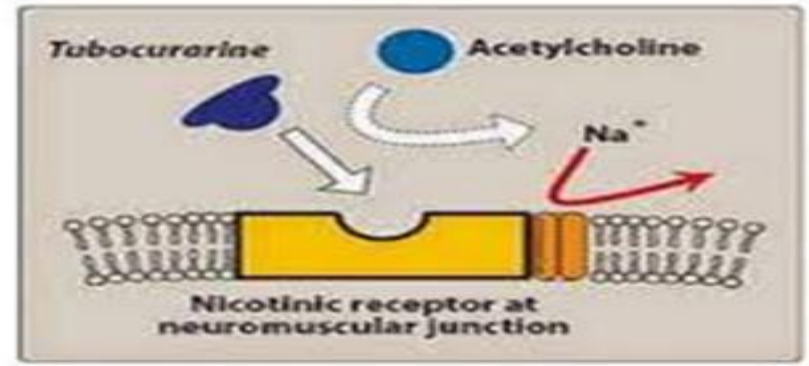
PK

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



Mechanism of action:

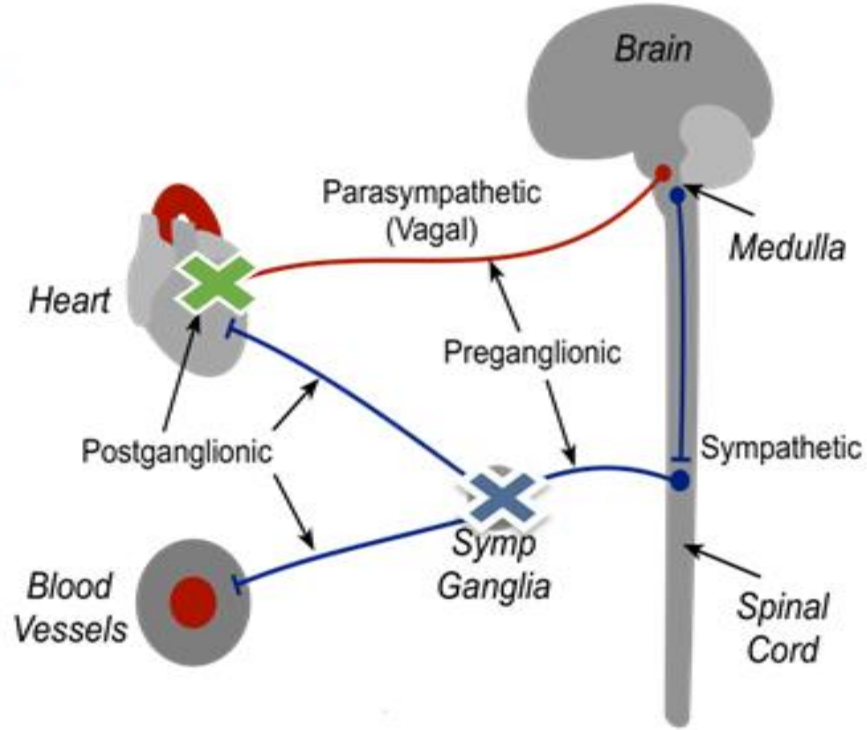
1) Competes with acetylcholine f nicotinic receptors in the moto plate (paralysis) (SD).



2) Close ion channel of receptor (LD)

3) Curare is a weak ganglion blocker.

4) Histamine release (moderate).



Pharmacological actions:

1)Skeletal muscle

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

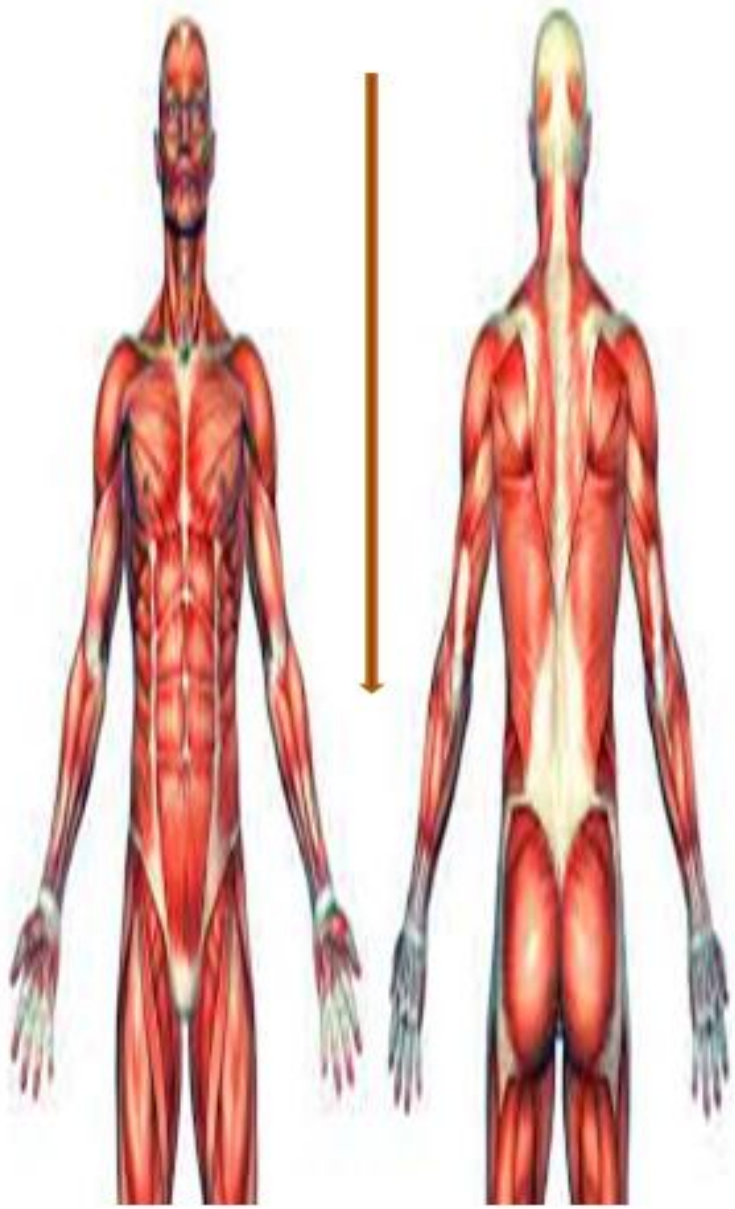
2)CVS

Hypotension due to:

i. Weak ganglion blocking effect.

ii. Histamine release.

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



Adverse effects

i. Hypotension.

ii. Bronchospasm.

iii. Allergy.

iv. 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/ min	Potency	Ganglion blocker	Histamine release	Special
Curare	30-60min/2 min	1			
Gallamine (Flaxidil)	15-35 min	(⅕ of curare).			tachycardia (M_2 blocker)
Pancuronium	60-90 min	6			tachycardia (↑NE release)
Atracurium Cisatracurium	15-35 min 90/3 min			less	(Hofmann elimination by ester hydrolysis) Seizure less with Cisatracurium
Mivacurium	10-20 min/2 min			mild	(pseudocholine esterase enzyme).
Rocuronium amiosteroids	20-30 min/1 min	Used instead of succinylcholine for endotracheal intubation			Hepatic elimination
Vecuronium amiosteroids	30-40 min				Hepatic elimination

Drug- drug interactions

1- Cholinesterase inhibitors increase acetylcholine levels at the neuromuscular junction by preventing its breakdown, directly counteracting d-tubocurarine's competitive blockade of nicotinic receptors, thereby reversing neuromuscular blockade. √

2-Botulinum toxin type A potentiates d-tubocurarine's neuromuscular blocking effects through additive inhibition of acetylcholine release, leading to major synergy and risks.

3-Aminoglycoside antibiotics enhance the effect of curare by inhibition of acetylcholine release.

4- Halogenated hydrocarbon anesthetics (halothane) enhance the effects of NMB. This synergy increases the risks of prolonged paralysis, especially during recovery.

5- Calcium channel blockers (e.g., verapamil, nifedipine, diltiazem) involve significant potentiation of neuromuscular blockade. they reduce calcium influx at the neuromuscular junction, impairing acetylcholine release.

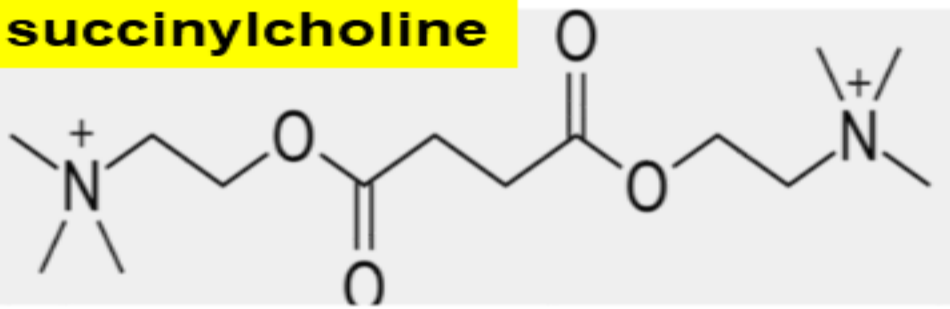
Depolarizing (Non-competitive) NMBs

Succinylcholine(suxamethonium)

- 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 (PLASMA) in two steps: a rapid step into succinyl monocholine, then a slow step into succinic acid + choline.

Ach

succinylcholine



•Mechanism of action

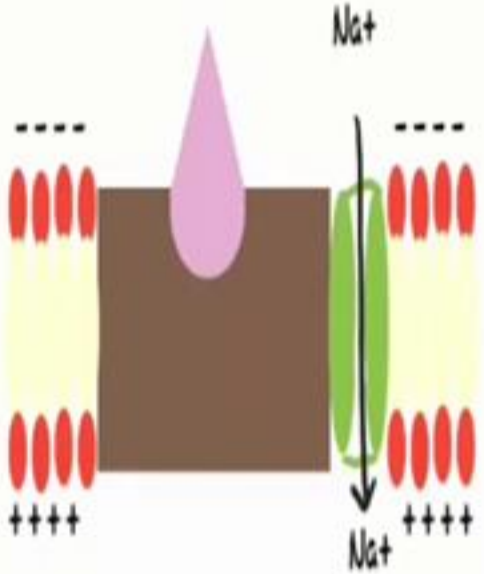
•It has two phases of block:

Phase I:

- It binds to nicotinic receptors on the neuromuscular junctions & acts as an agonist (depolarization of the motor end plate & initially causing fasciculation).

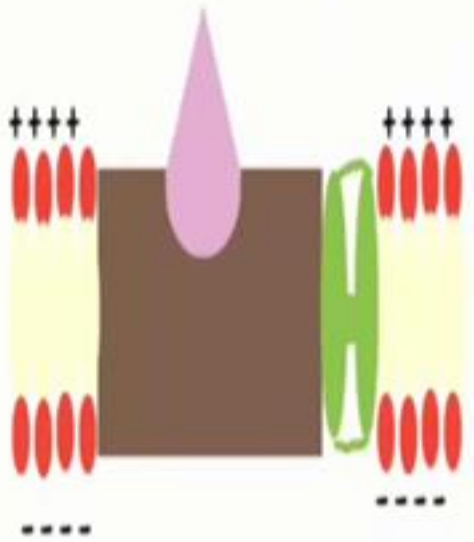
Phase II (desensitization):

- Prolonged depolarization of receptors produces spontaneous closure of Na+ channels, which become partially reversible.
- The slow dissociation and metabolism of succinylcholine at receptors lead to persistent depolarization, transmission failure & muscle paralysis.



Phase I

Depolarising phase



Phase II

Desensitising phase

Pharmacological actions:

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

Therapeutic uses

1) 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)

-Artificial respiration.

-After diagnosis of the phase block:

In phase I: give fresh frozen plasma or a fresh blood transfusion to restore the 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.

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

3. Botulinum Toxin (Botox): Blocks acetylcholine release at the neuromuscular junction, leading to muscle paralysis

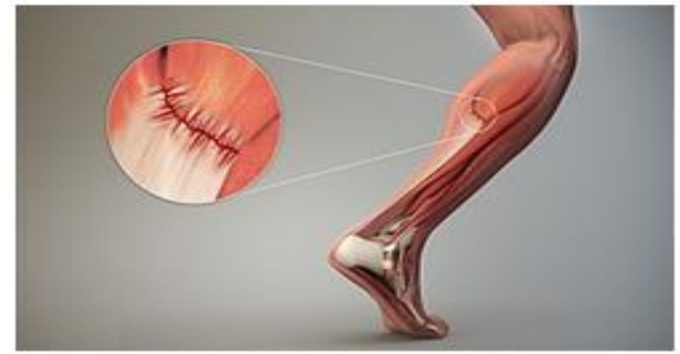
Therapeutic Uses

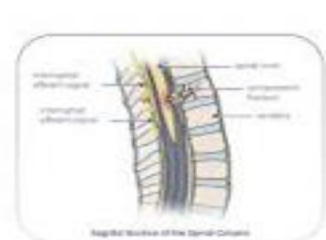
1)Spasticity of skeletal muscles due to local causes e.g. trauma, inflammation & rheumatism.

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 the 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

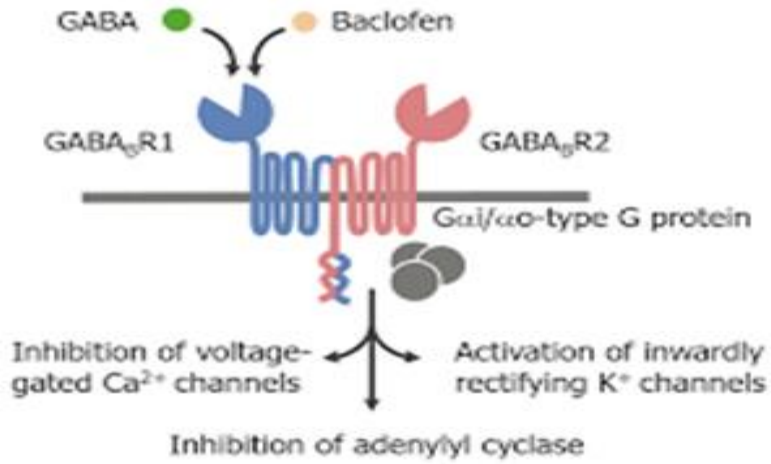
Mechanism of action:

- A 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 the spinal cord by decrease release of substance P from the nerve ending of primary afferent sensory neurons.

- **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.



The GABA$_B$ receptor complex

Diazepam

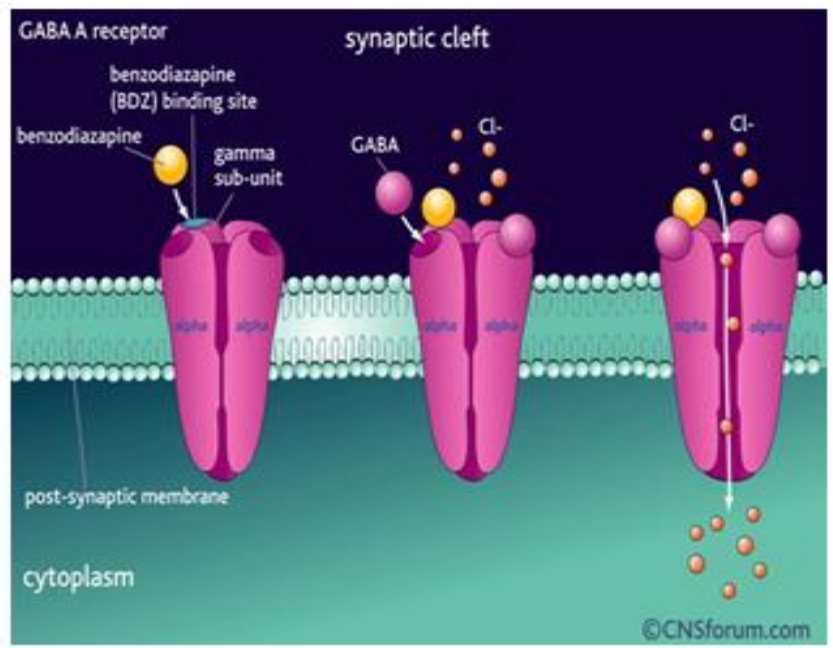
1-GABA A agonist

2-Enhancing polysynaptic and presynaptic inhibition on the spinal motor neurons.

uses:

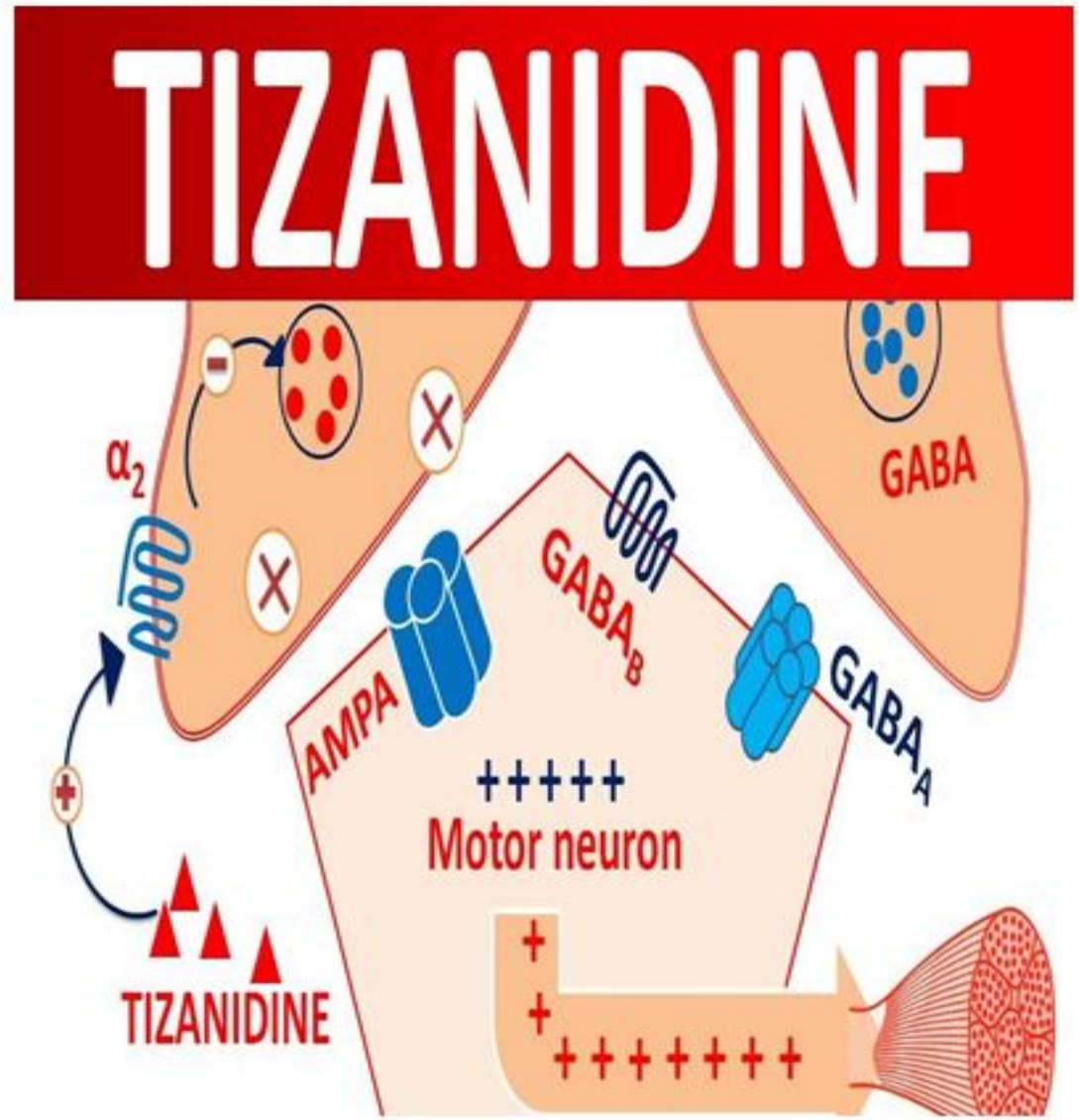
A. Spasticity

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 the CNS ➔ muscle relaxation.
- Taken orally.
- It has fewer CVS effects.



Dantrolene

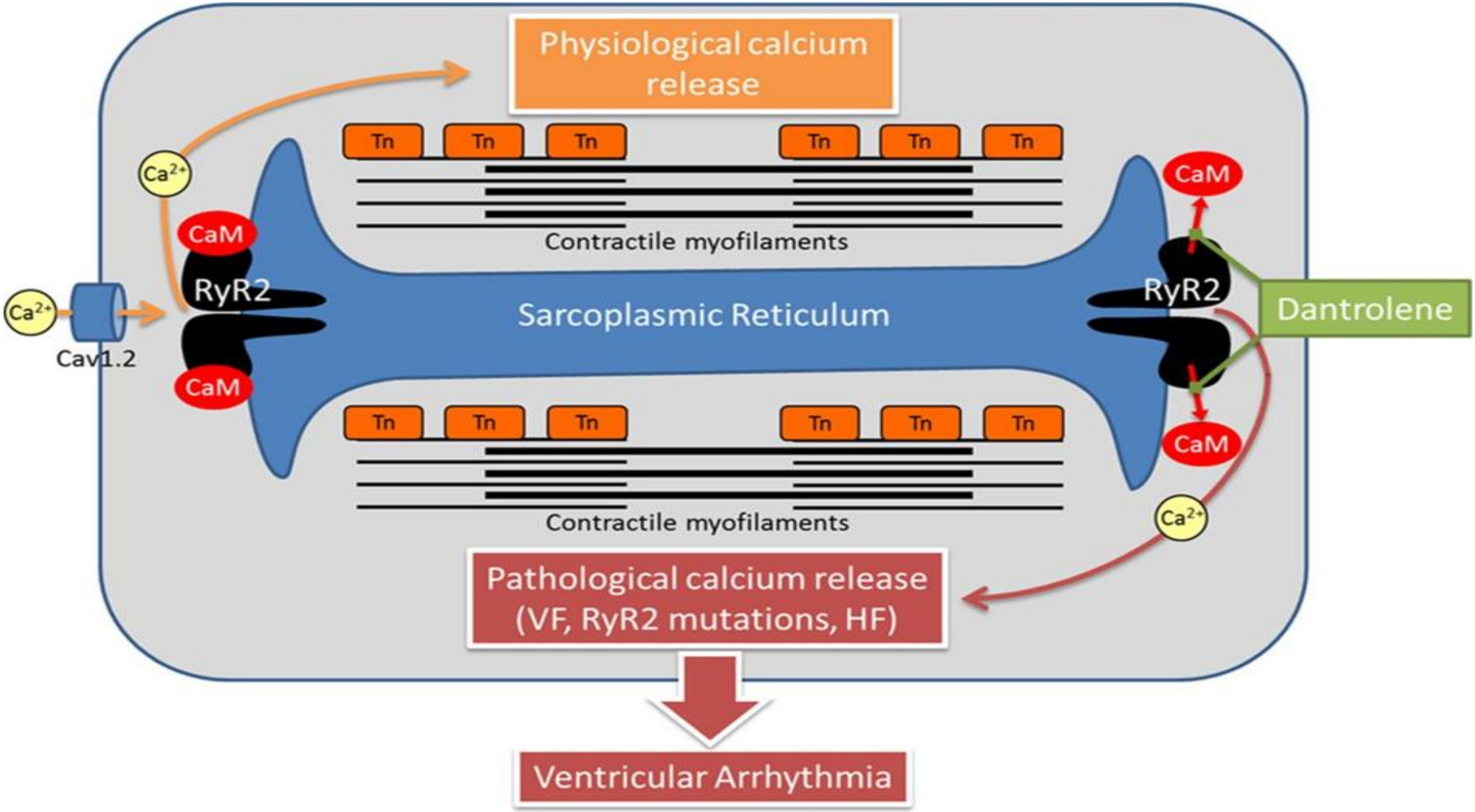
❖ **Mechanism of action:**

- Acts directly on skeletal muscle and so has minimal CNS effects.
- It relaxes skeletal muscles directly by interfering with the release of Ca^{+2} from the 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.
2. Treatment of malignant hyperpyrexia.
3. Treatment of the neuroleptic malignant syndrome.

Adverse effects

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


Physiological calcium release
Tn
Tn
Tn
Tn
Tn
Tn
Ca2+
CaM
RyR2
Contractile myofilaments
Ca2+
Cav1.2
Sarcoplasmic Reticulum
RyR2
CaM
Dantrolene
CaM
CaM
Tn
Tn
Tn
Tn
Tn
Tn
Contractile myofilaments
Ca2+
Pathological calcium release
(VF, RyR2 mutations, HF)
Ventricular Arrhythmia

Malignant hyperthermia VS NMS

Feature	NMS	Malignant Hyperthermia
Trigger	Antipsychotics	Anesthetics + succinylcholine
Onset	Days	Minutes
Cause	Dopamine blockade	Ca^{2+} release from SR
Treatment	Dantrolene, Bromocriptine	Dantrolene


Thank you!