بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

SKELETAL MUSCLE RELAXANTS

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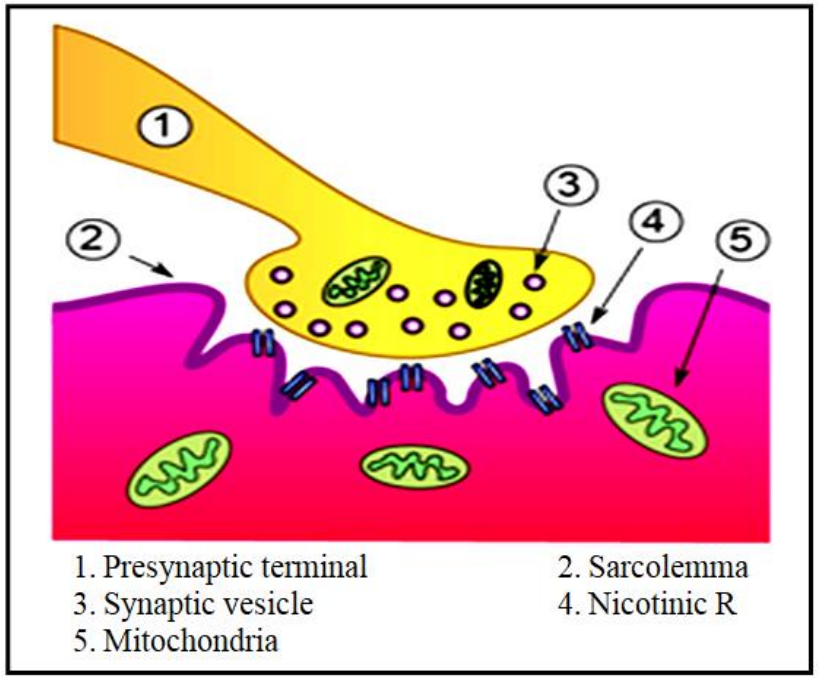
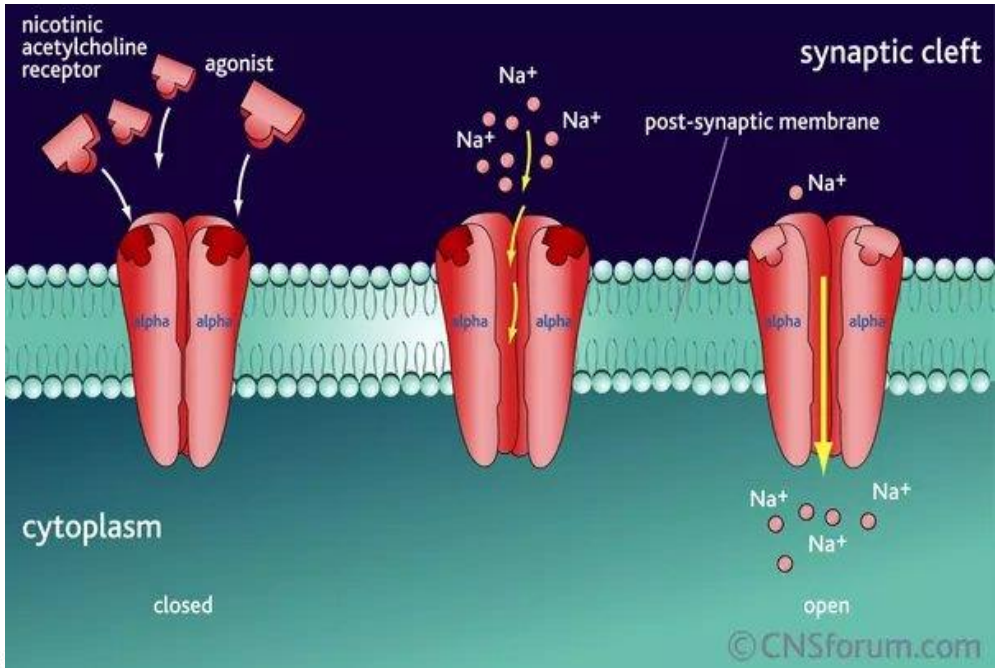
The Neuromuscular Junction (NMJ)





- **Skeletal muscle relaxants** are drugs used to produce muscle paralysis or reduce muscle tone and alleviate muscle spasms or spasticity.
- 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.

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:

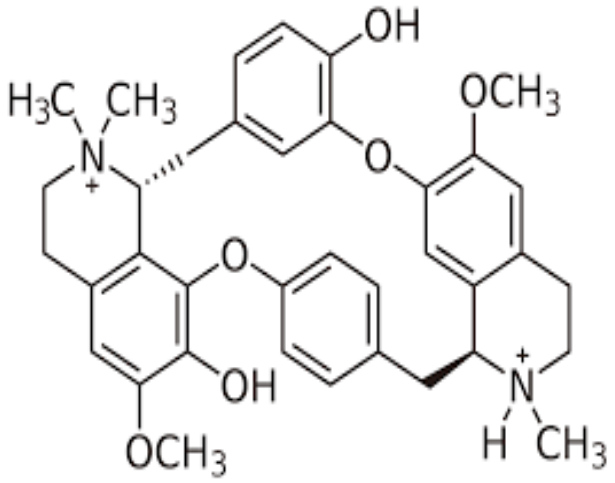
- They cause sustained depolarization of the motor end plate ,leading to muscle paralysis.
- They produce initial stimulation of muscle (fasciculations) followed by paralysis.

Therapeutic uses:

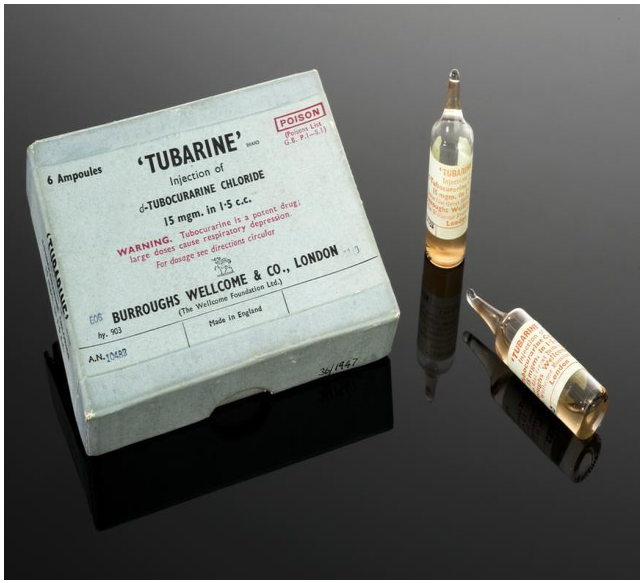
1) Skeletal muscle relaxation during surgery.
2) Facilitation of endotracheal intubation.
3) To facilitate mechanical ventilation.
4) To control severe convulsions during electroconvulsive therapy (ECT).

Competitive (Non-depolarizing) NMBs

(1) D-Tubocurarine (Curare)

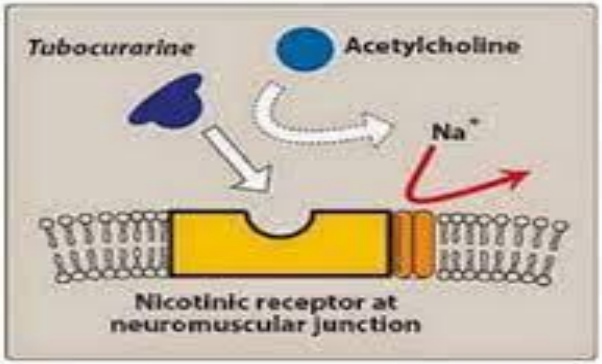


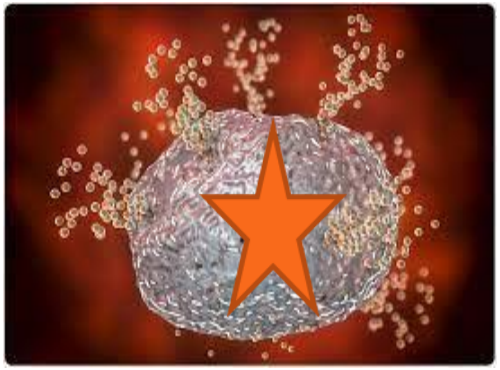
- It is a quaternary ammonium compound ➔ given parentally & not absorbed orally.
- It has a rapid onset.
- Recovery occurs within 30-60 min.
- It does not cross BBB ➔ No CNS actions.
- Excreted mainly in urine.

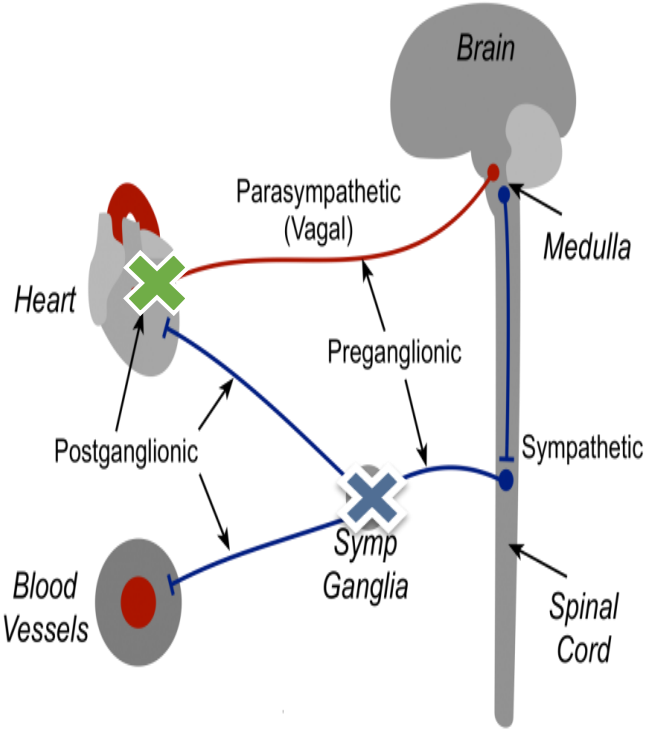


Mechanism of action:

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



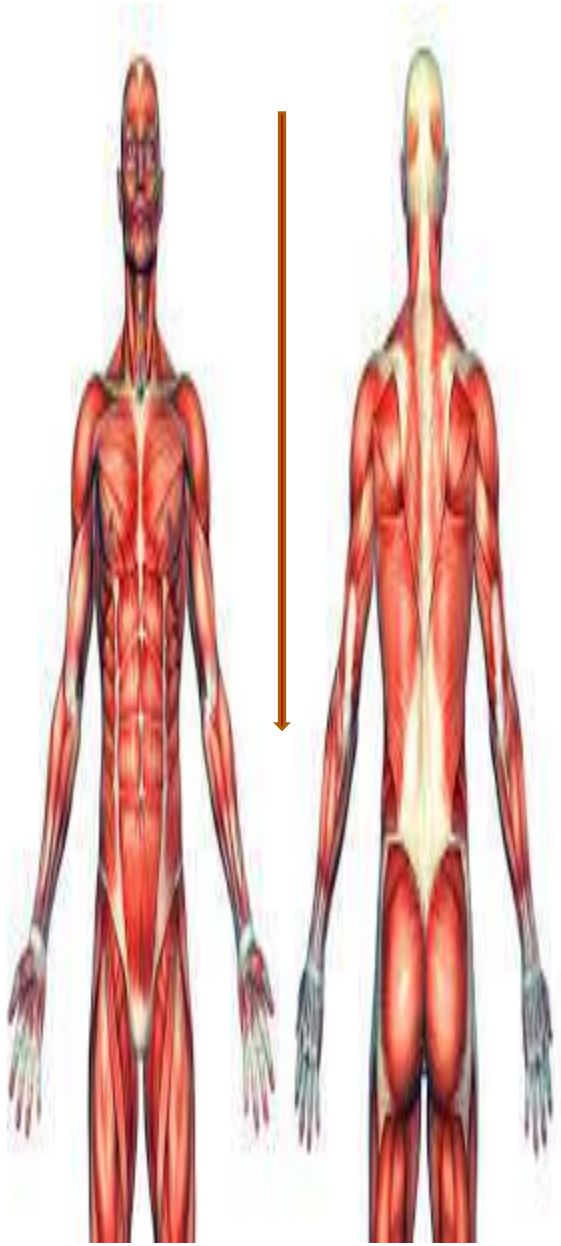




Pharmacological actions:

1)Skeletal muscle

- skeletal muscle paralysis in the following 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:** The sympathatic is Dominant in B.V.

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	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	أترع هوف	✕	less	(Hofmann elimination) بتكسر لوحدها Specefic
Mivacurium	10-20 min	4 ميفا الروسيه مميزة	✕	mild	(pseudocholine esterase enzyme).
Rocuronium	20-30 min	Used instead of succinylcholine for endotracheal intubation			Hepatic elimination
Vecuronium	30-40 min		✕	✕	Hepatic elimination

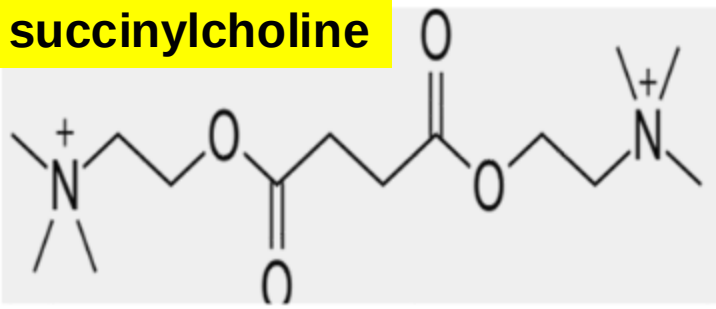
Depolarizing (Non-competitive) NMBs

Succinylcholine(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 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:

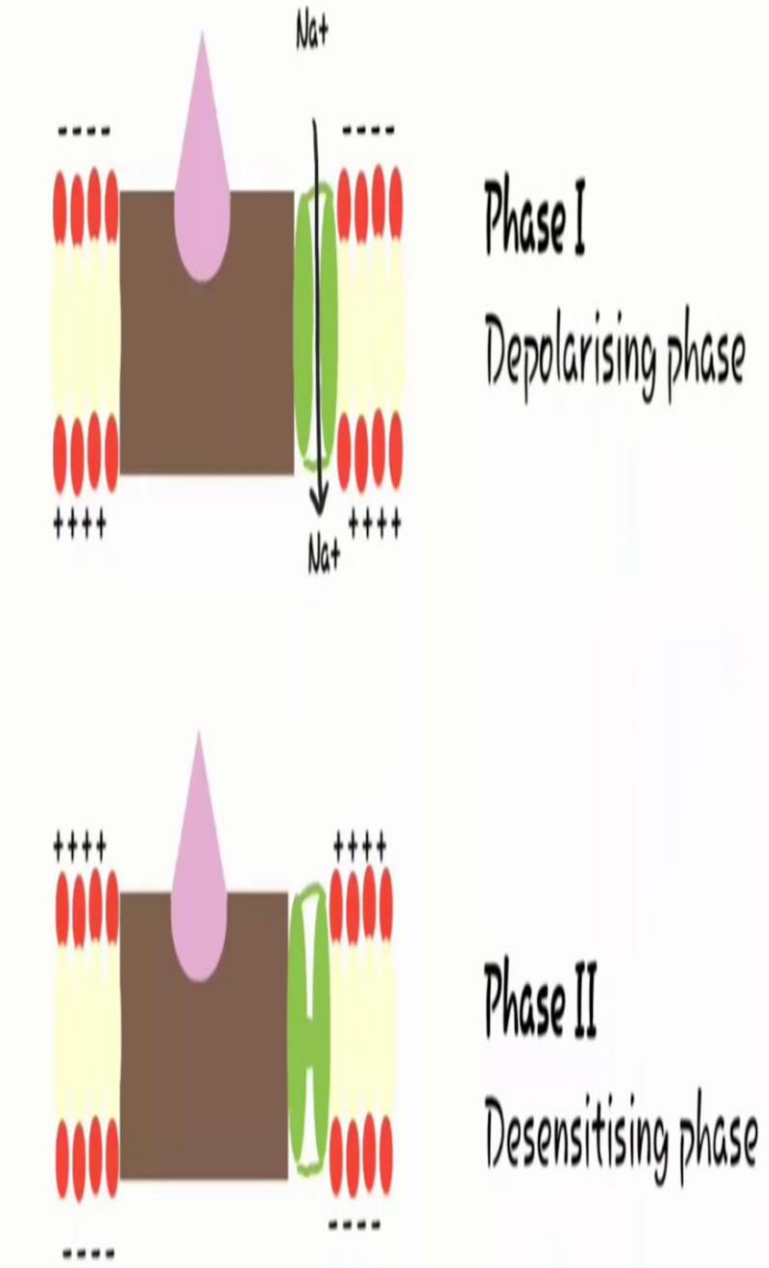
Phase I:

❖It binds to nicotinic receptors on the neuromuscular junctions & acts as an 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 is 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

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

Adverse effects

1- Succinylcholine apnea low level of pseudocholine esterase or upnormality in pseudocholine esterase enzyme.

Treatment of succinylcholine toxicity (apnea)

-Artificial respiration.

-After diagnosis of the phase block:

In phase I: give fresh frozen plasma or fresh blood transfusion to restore cholinesterase enzyme. in phase 1 worsen the effect "More Depolarization".

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

Relase Tone
Relase stretch

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

6 month

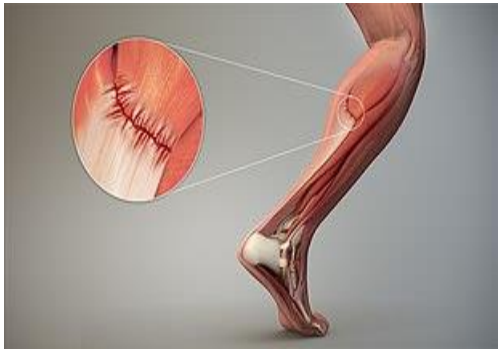
Therapeutic Uses

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

2) Low back pain syndrome. "Disc" ↳ Diazepam

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

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



Mephenesin

استخدم قديمًا

- 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.

أهم شيء هو الـ orally
والـ Antidote للزرنيخ

Baclofen

الأكثر استخدامًا

Mechanism of action:

Inhibitory receptor

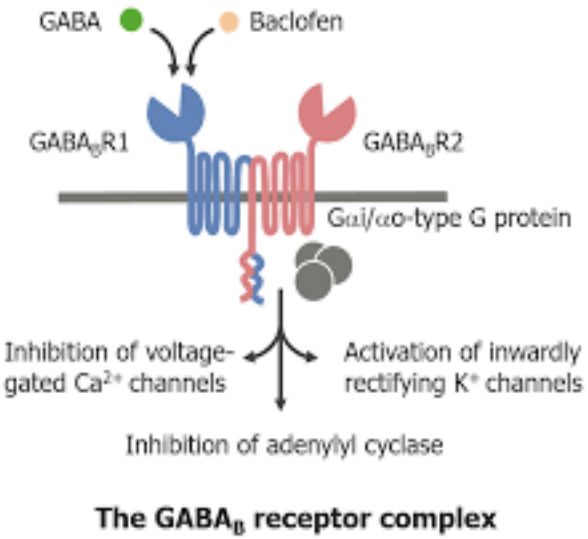
- A selective $GABA_B$ agonist, which produces inhibition of the release of excitatory transmitters in the brain and spinal cord.
- It also decreases pain transmission in spinal cord by decrease release of substance P from nerve ending of primary afferent sensory neurons .

قبل النوم

- **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. ⇐ لأنه بتأثر لذلك ما بعطيه في الـ



The GABA$_B$ receptor complex

Diazepam

Disc + GABA A

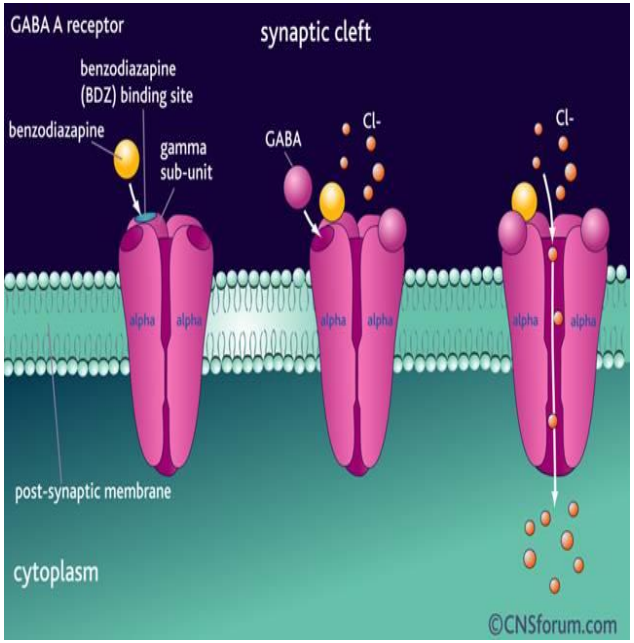
1-GABA A agonist

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

uses:

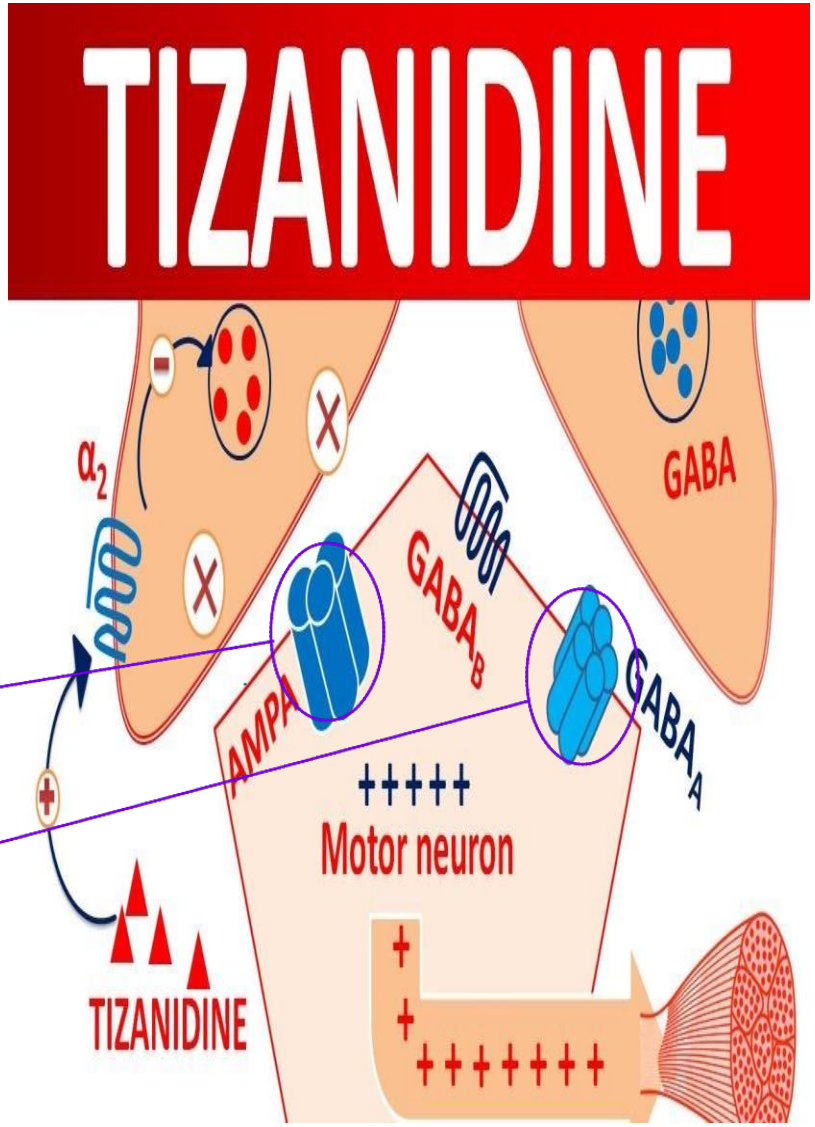
A. Spasticity

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

Liver Toxicity

❖ **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)

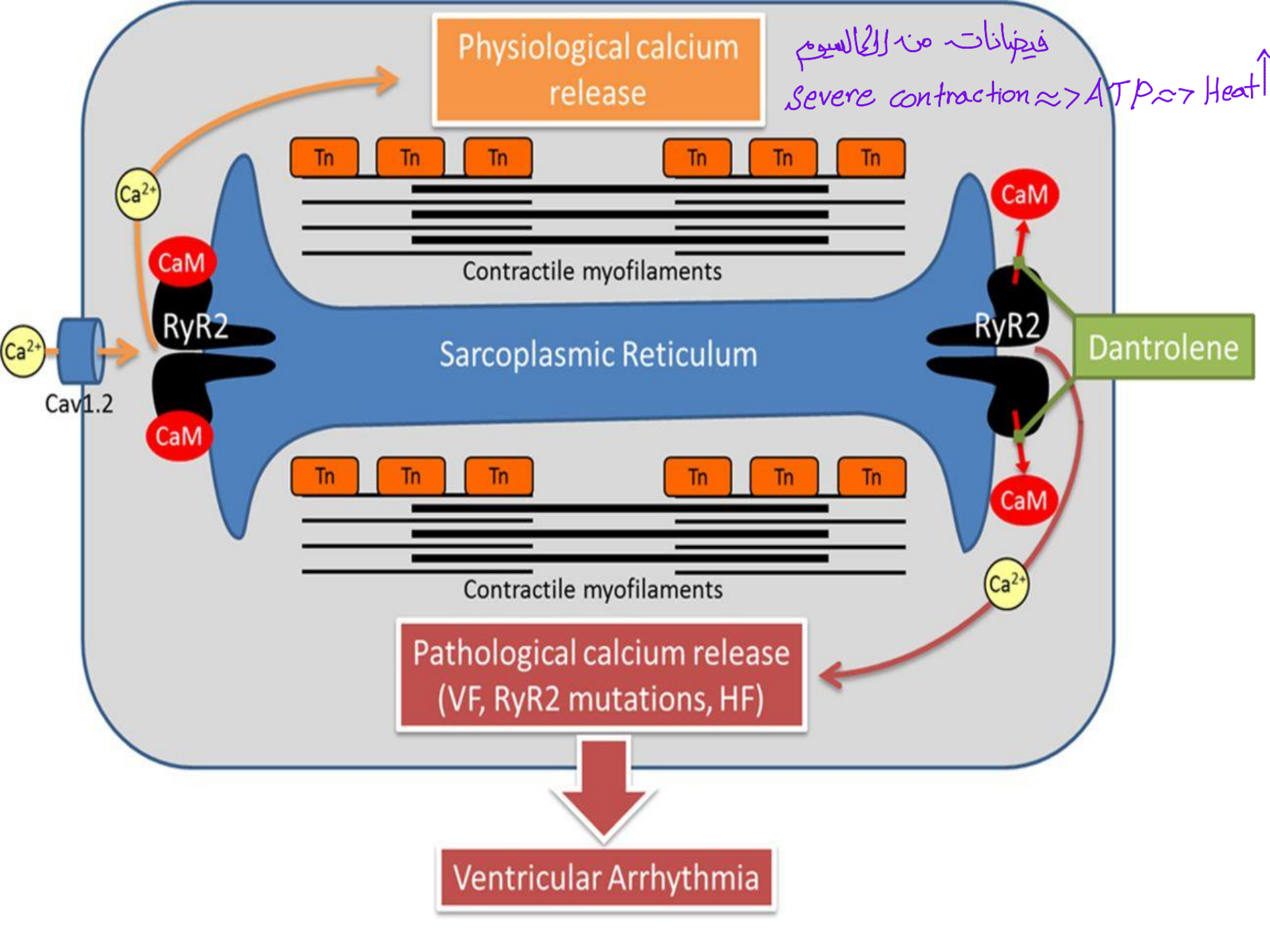
Ryanodine Receptor

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. + Ice.
3. Treatment of the neuroleptic malignant syndrome.

psychotic

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
فيضانات من الكالسيوم
Severe contraction => ATP => Heat
Tn
Tn
Tn
Tn
Tn
Tn
Contractile myofilaments
CaM
RyR2
Sarcoplasmic Reticulum
RyR2
Dantrolene
CaM
Ca2+
Cav1.2
CaM
CaM
Ca2+
Tn
Tn
Tn
Tn
Tn
Tn
Contractile myofilaments
Pathological calcium release
(VF, RyR2 mutations, HF)
Ventricular Arrhythmia


Thank you!