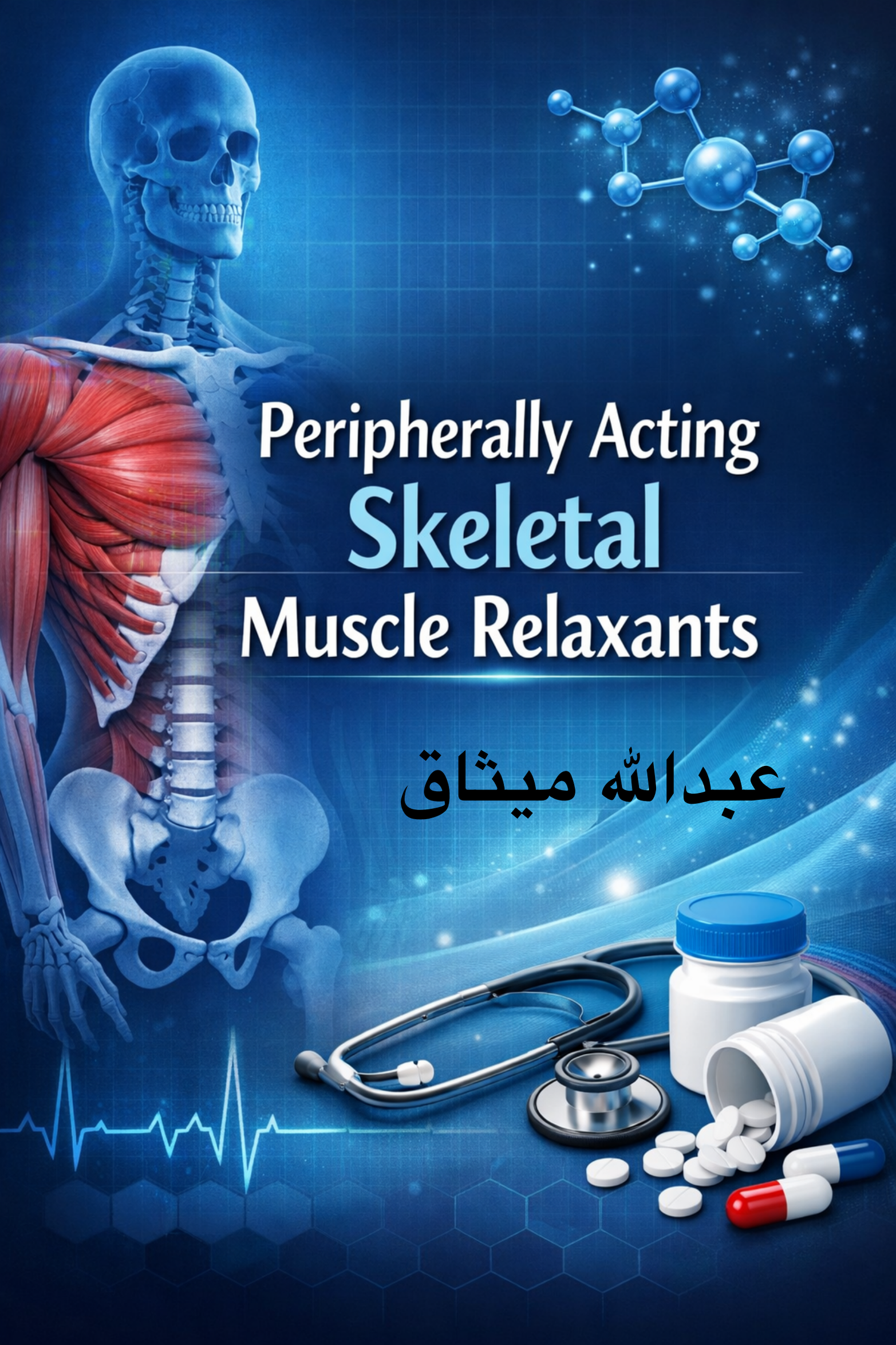

Peripherally Acting
Skeletal
Muscle Relaxants
عبدالله میثاق

Skeletal Muscle Relaxants

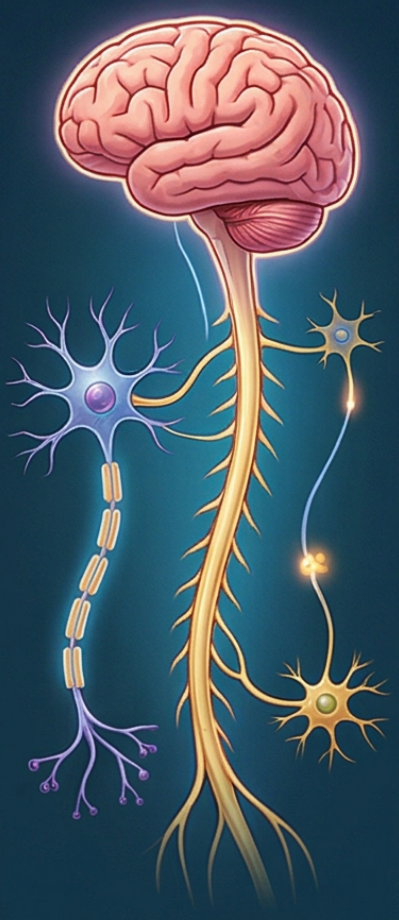
Overview & Clinical Importance

- Easier tracheal intubation
- Assist with mechanical ventilation
- Optimal surgical working conditions

Historical Origin

Classification of Skeletal Muscle Relaxants

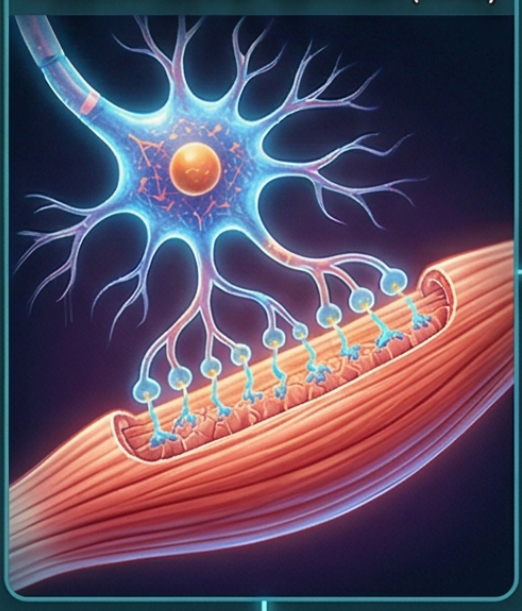
Centrally Acting



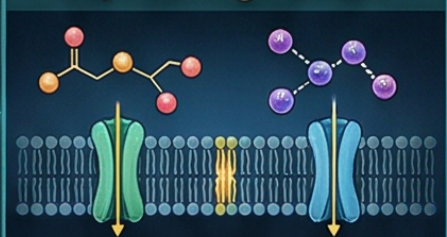
Diazepam
Methocarbamol
Baclofen
Gabapentin

Peripherally Acting

Drugs acting at the Neuromuscular Junction (NMJ)



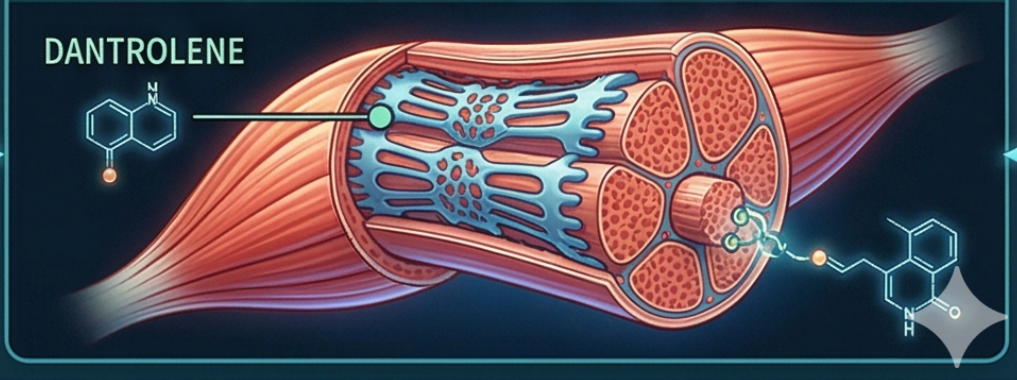
Depolarizing blockers



Non-depolarizing (Competitive) blockers

d-TUBOCURARINE	long-acting
PANCURONIUM	long-acting
VECURONIUM	intermediate-acting
ATRACURIUM	short-acting
MIVACURIUM	short-acting

Drugs acting directly on skeletal muscle



Overview & Clinical Importance

- **Purpose:** Skeletal muscle relaxants are mainly used alongside general anesthetics.

- **Clinical Benefits:** They make tracheal intubation easier, assist with mechanical ventilation, and provide optimal surgical working conditions.

- **Historical Origin:** The history goes back to "Curare," a plant extract alkaloid (from *Chondrodendrone tomentosum* and *Strychnos toxifera*) originally used as arrow poison in Central and South America.

Classification of Skeletal Muscle Relaxants

Skeletal muscle relaxants are divided into two main categories:

1. **Centrally Acting:** Examples include Diazepam, Methocarbamol, Baclofen, and Gabapentin.

2. **Peripherally Acting:**
    - **Drugs acting at the Neuromuscular Junction (NMJ):**
        - *Depolarizing blockers:* Succinylcholine, Decamethonium.

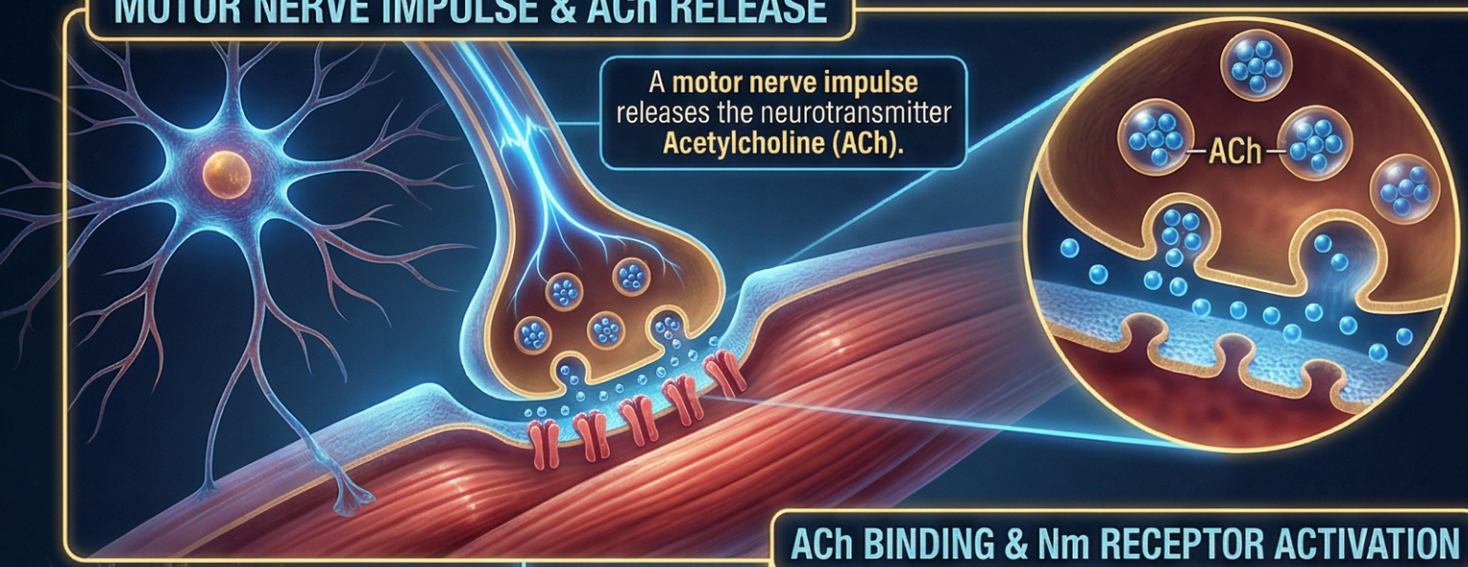
        - *Non-depolarizing (Competitive) blockers:* Divided into long-acting (e.g., d-Tubocurarine, Pancuronium), intermediate-acting (e.g., Vecuronium, Atracurium), and short-acting (e.g., Mivacurium).

    - **Drugs acting directly on skeletal muscle:** Dantrolene.

NORMAL MUSCLE CONTRACTION PHYSIOLOGY

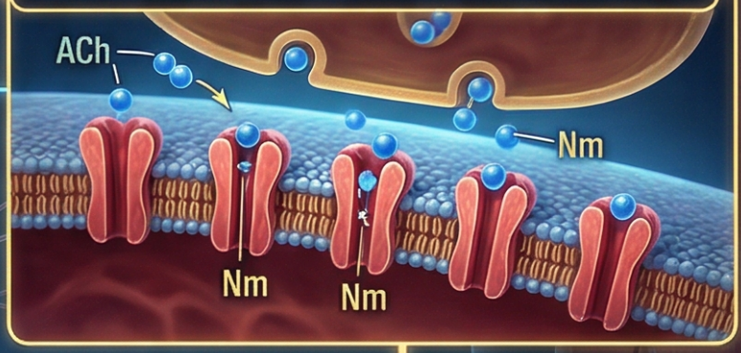
MOTOR NERVE IMPULSE & ACh RELEASE

A **motor nerve impulse** releases the neurotransmitter **Acetylcholine (ACh).**



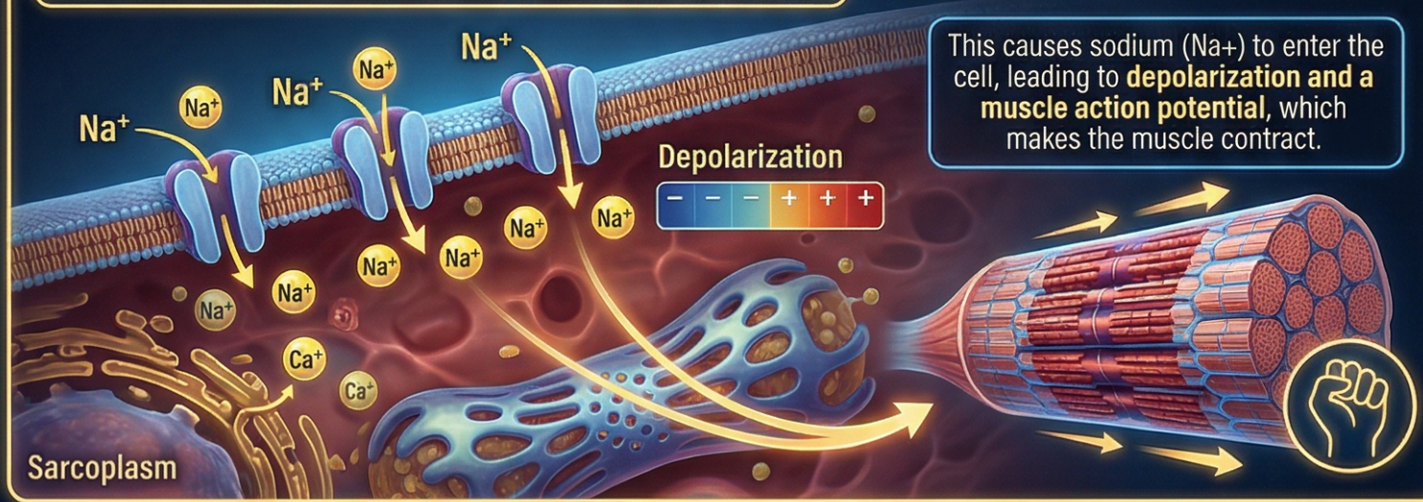
ACh BINDING & Nm RECEPTOR ACTIVATION

ACh binds to **Nicotinic receptors (Nm)** at the Neuromuscular Junction (NMJ).



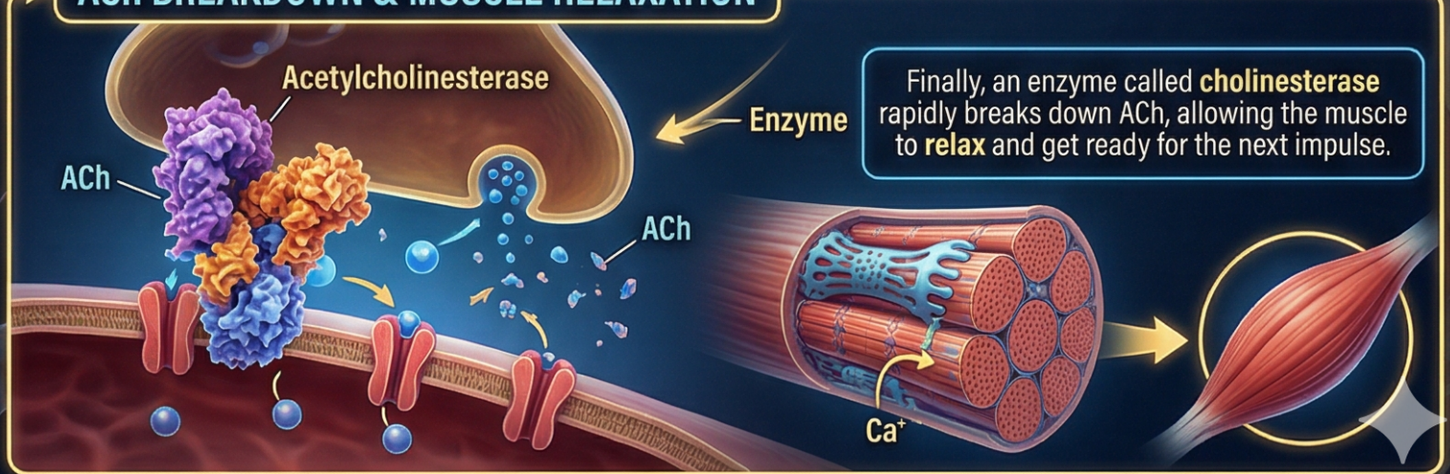
DEPOLARIZATION & MUSCLE ACTION POTENTIAL

This causes sodium (Na+) to enter the cell, leading to **depolarization and a muscle action potential**, which makes the muscle contract.



ACh BREAKDOWN & MUSCLE RELAXATION

Finally, an enzyme called **cholinesterase** rapidly breaks down ACh, allowing the muscle to **relax** and get ready for the next impulse.

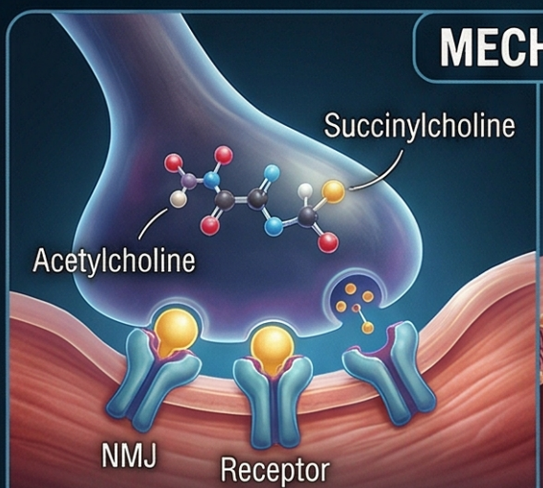


Normal Muscle Contraction Physiology

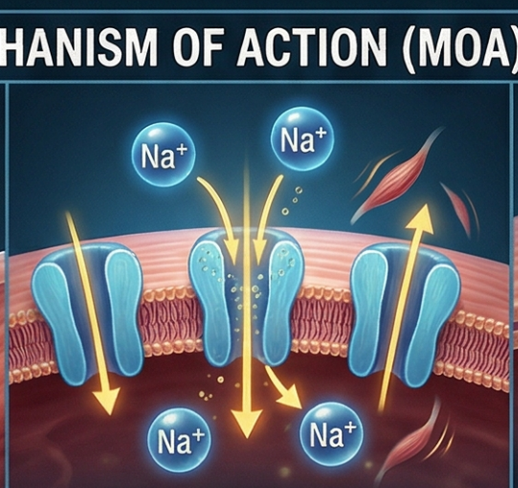
- A motor nerve impulse releases the neurotransmitter **Acetylcholine (ACh)**.
- ACh binds to Nicotinic receptors (Nm) at the Neuromuscular Junction (NMJ).
- This causes sodium (Na+) to enter the cell, leading to depolarization and a muscle action potential, which makes the muscle contract.
- Finally, an enzyme called cholinesterase rapidly breaks down ACh, allowing the muscle to relax and get ready for the next impulse.

DEPOLARIZING BLOCKERS: SUCCINYLCHOLINE

MECHANISM OF ACTION (MOA)



Neuromuscular junction (NMJ) mimicis Acetylcholine (agonist)

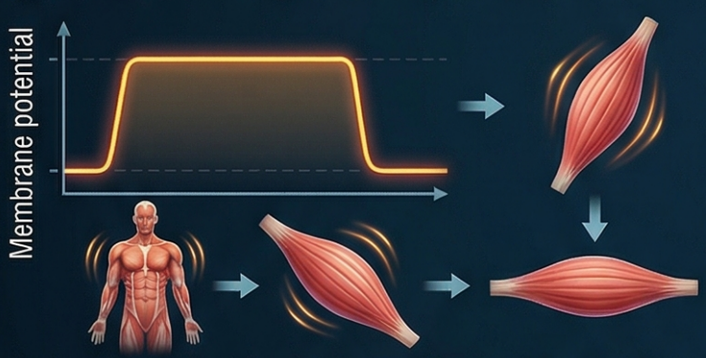


Sodium (Na^+) channels open into small muscle twitches.

Does not leave receptor quickly, causes prolonged depolarization, locking sodium channels in an inactive state

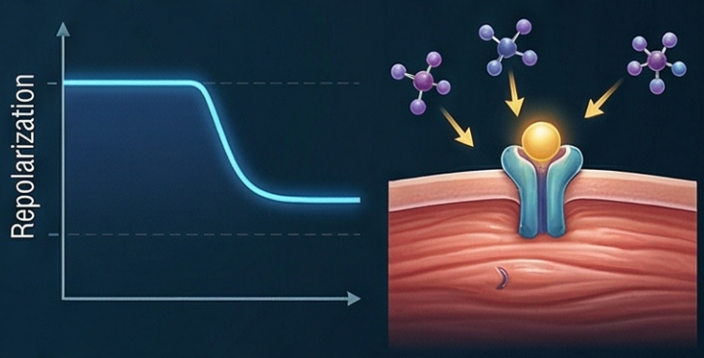
PHASES OF BLOCKADE

1 Phase I: Depolarization Block



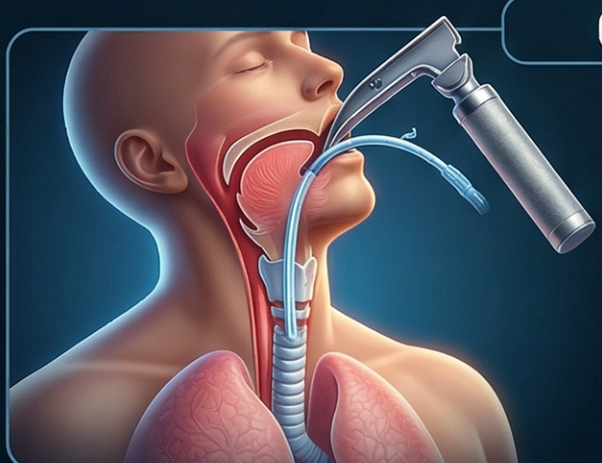
The membrane depolarizes, causing transient muscle twitches (fasciculations) followed by flaccid paralysis.

2 Phase II: Desensitization Block



The membrane repolarizes, but the receptor becomes desensitized and ignores any new Acetylcholine.

CLINICAL USES



Works very fast

Tinmuninum (1-2 min)

Lasts for a short time

Timtonnirum (5-10 min)

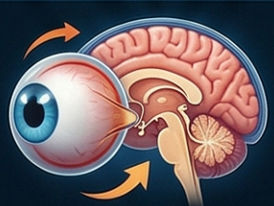
It is the only drug in this class used clinically, most commonly for **tracheal intubation**

The standard dose is **1-1.5 mg/kg**

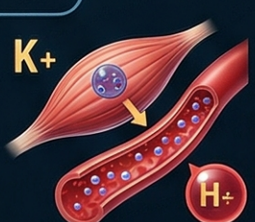
SIDE EFFECTS

Muscle pain

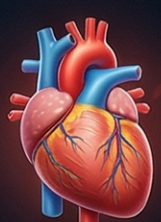
Unpredictable blood pressure and heart rate



Increased pressure in the eyes and brain



Dangerous increases in potassium levels (Hyperkalemia)



Which is life-threatening for patients with Cardiac Heart Failure

1. Depolarizing Blockers: Succinylcholine

- **Mechanism of Action:** It mimics Acetylcholine (acts as an agonist). It opens sodium channels, causing initial muscle twitching (fasciculations). Because it does not leave the receptor quickly, it causes prolonged depolarization, locking the sodium channels in an inactive state.

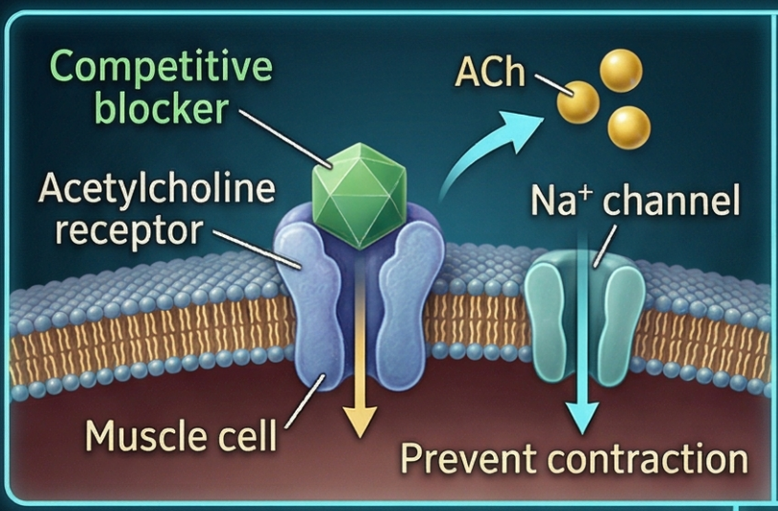
- **Phases of Blockade:**
    - **Phase I:** The membrane depolarizes, causing transient muscle twitches (fasciculations) followed by flaccid paralysis.

    - **Phase II:** The membrane repolarizes, but the receptor becomes desensitized and ignores any new Acetylcholine.

- **Clinical Uses:** It is the only drug in this class used clinically, most commonly for tracheal intubation because it works very fast (1-2 minutes) and lasts for a short time (5-10 minutes). The standard dose is 1-1.5 mg/kg.

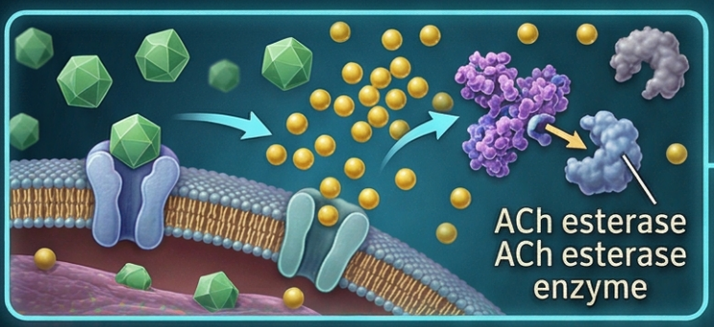
- **Side Effects:** Muscle pain, unpredictable blood pressure and heart rate, increased pressure in the eyes and brain, and dangerous increases in potassium levels (Hyperkalemia), which is life-threatening for patients with Cardiac Heart Failure.

NON-DEPOLARIZING BLOCKERS (COMPETITIVE BLOCKERS)



MECHANISM OF ACTION

- Act as antagonists
- Bind to ACh receptors but do not activate them (no intrinsic activity)
- Physically block Na+ channels, preventing muscle contraction



REVERSAL

- Effect overcome by increasing ACh levels or giving ACh esterase inhibitors.

KEY DRUGS & CHARACTERISTICS

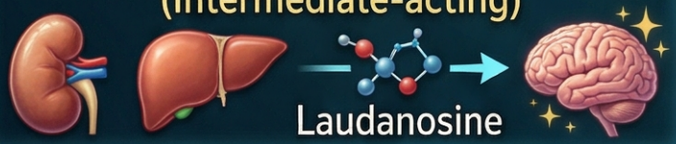
d-TUBOCURARINE
(Long-acting)

- First investigated clinically
- Long duration (60-120 mins)
- Low blood pressure (hypotension)
- Histamine release (skin flushing, bronchospasm)

PANCURONIUM
(Long-acting)

- Increased heart rate (tachycardia)

ATRACURIUM
(Intermediate-acting)



ATRACURIUM
(Intermediate-acting)

- Highly safe for kidney/liver impairment
- Spontaneously breaks down into laudanosine (can cause seizures)

VECURONIUM
(Intermediate-acting)

- Fewer side effects
- No histamine release
- No ganglion blockade
- No antimuscarinic action

MIVACURIUM
(Short-acting)

- Fast onset and short duration
- Metabolized by pseudocholinesterase

2. Non-Depolarizing Blockers (Competitive Blockers)

- **Mechanism of Action:** These act as antagonists. They bind to the Acetylcholine receptors but do not activate them (no intrinsic activity). They physically block the sodium channels from opening, which prevents muscle contraction.

- **Reversal:** Their effect can be overcome by increasing Acetylcholine levels or by giving ACh esterase inhibitors.

- **Key Drugs & Characteristics:**
    - **d-Tubocurarine (Long-acting):** The first agent investigated clinically. It has a long duration (60-120 mins). Side effects include low blood pressure (hypotension) and histamine release (which causes skin flushing and bronchospasm).

    - **Pancuronium (Long-acting):** Known to cause an increased heart rate (tachycardia).

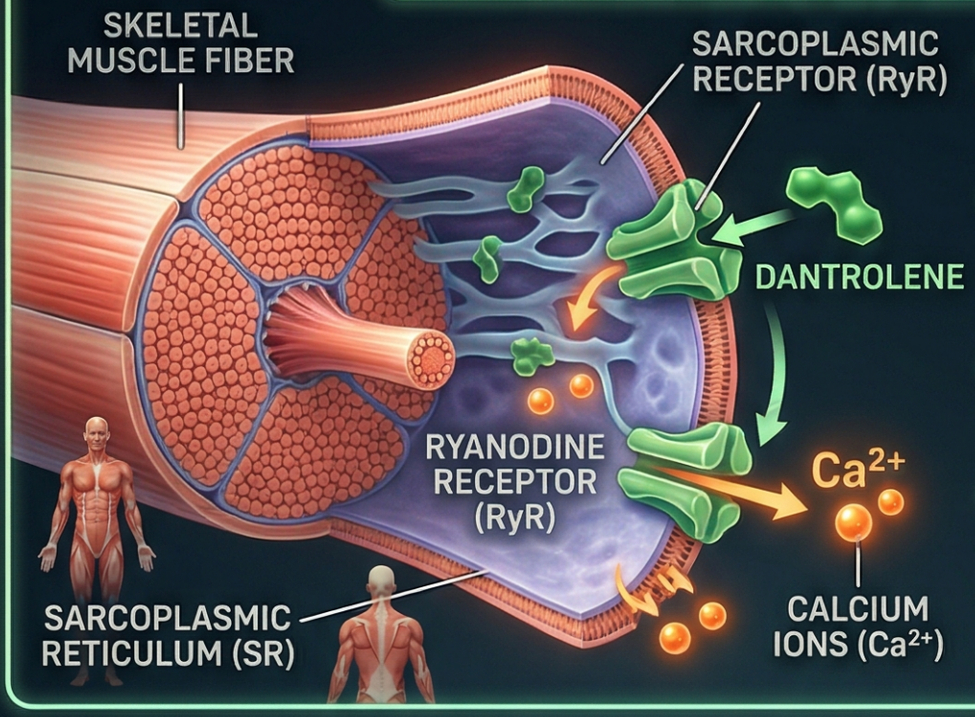
    - **Atracurium (Intermediate-acting):** Highly safe for patients with kidney or liver impairment. However, it spontaneously breaks down into "laudanosine," which can cause seizures.

    - **Vecuronium (Intermediate-acting):** Has fewer side effects (no histamine release, no ganglion blockade, no antimuscarinic action).

    - **Mivacurium (Short-acting):** Fast onset and short duration, metabolized by pseudocholinesterase.

DANTROLENE: DIRECTLY ACTING MUSCLE RELAXANT

MECHANISM OF ACTION



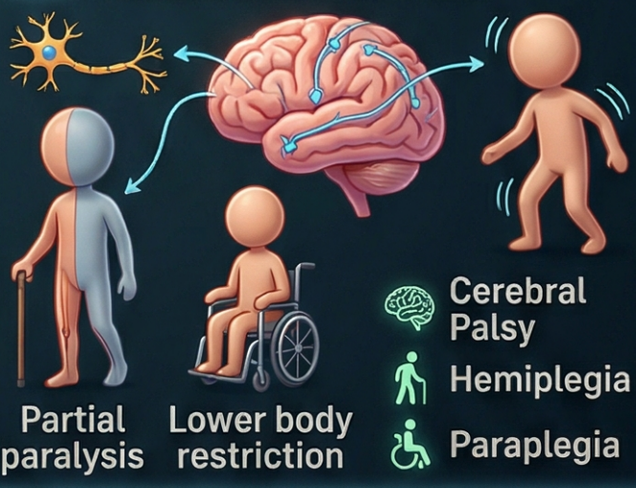
- WORKS DIRECTLY INSIDE MUSCLE
- NO ACTION ON NEUROMUSCULAR TRANSMISSION
- BLOCKS RYANODINE RECEPTORS (RyR)
- PREVENTS INTRACELLULAR CALCIUM RELEASE

CLINICAL USES

DRUG OF CHOICE FOR MALIGNANT HYPERTHERMIA

Emergency Treatment

USED FOR UPPER MOTOR NEURON DISORDERS

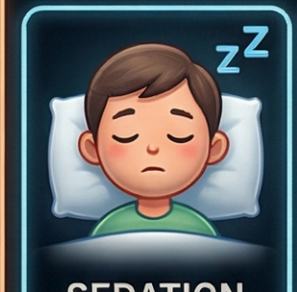


Partial paralysis

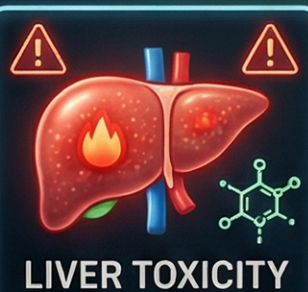
Lower body restriction

- Cerebral Palsy
- Hemiplegia
- Paraplegia

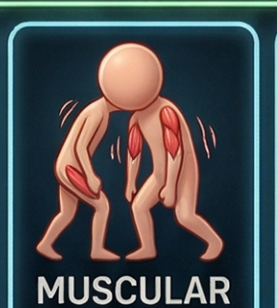
ADVERSE EFFECTS



SEDATION



LIVER TOXICITY (HEPATOTOXICITY)



MUSCULAR WEAKNESS

MALAISE

DIARRHEA

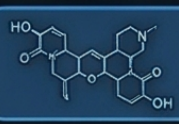
3. Directly Acting Relaxants: Dantrolene

- **Mechanism of Action:** Unlike the other drugs, Dantrolene works directly inside the muscle and has no action on neuromuscular transmission. It blocks Ryanodine receptors (RyR) calcium channels, preventing the release of intracellular calcium.

- **Clinical Uses:** It is the drug of choice for **Malignant Hyperthermia**. It is also used for Upper Motor Neuron disorders like cerebral palsy, hemiplegia, and paraplegia.

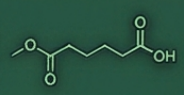
- **Adverse Effects:** Sedation, liver toxicity (hepatotoxicity), muscular weakness, malaise, and diarrhea.

KEY COMPARISONS: d-TUBOCURARINE vs. SUCCINYLCHOLINE

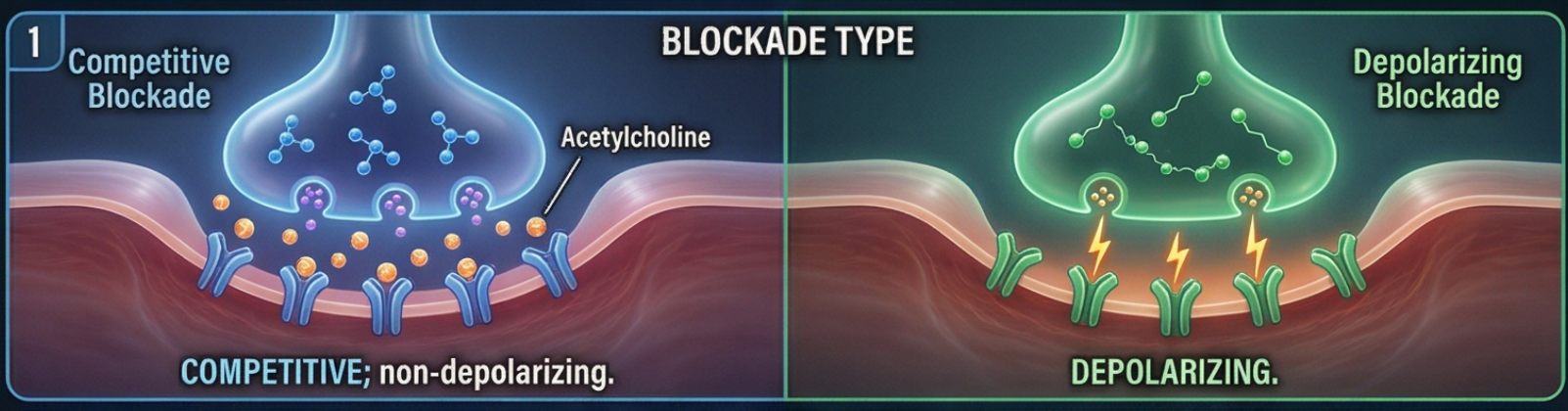


d-TUBOCURARINE

SUCCINYLCHOLINE



1 BLOCKADE TYPE



COMPETITIVE; non-depolarizing.

DEPOLARIZING.

2 RELAXATION STYLE

CAUSES FLACCID PARALYSIS.

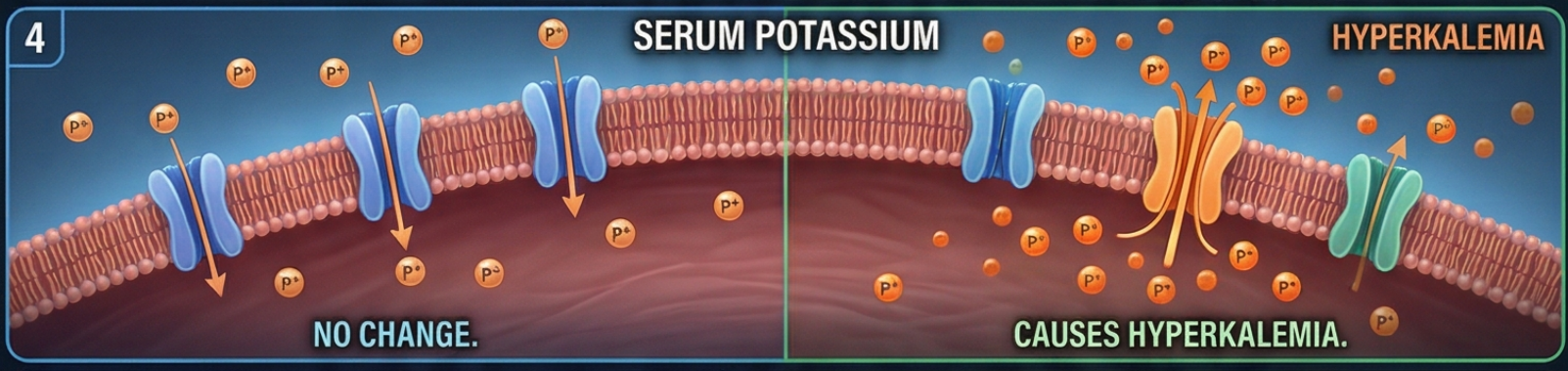
INITIAL TWITCHING (FASCICULATION) BEFORE PARALYSIS.

3 HISTAMINE RELEASE

HIGH (++).

NEGLIGIBLE.

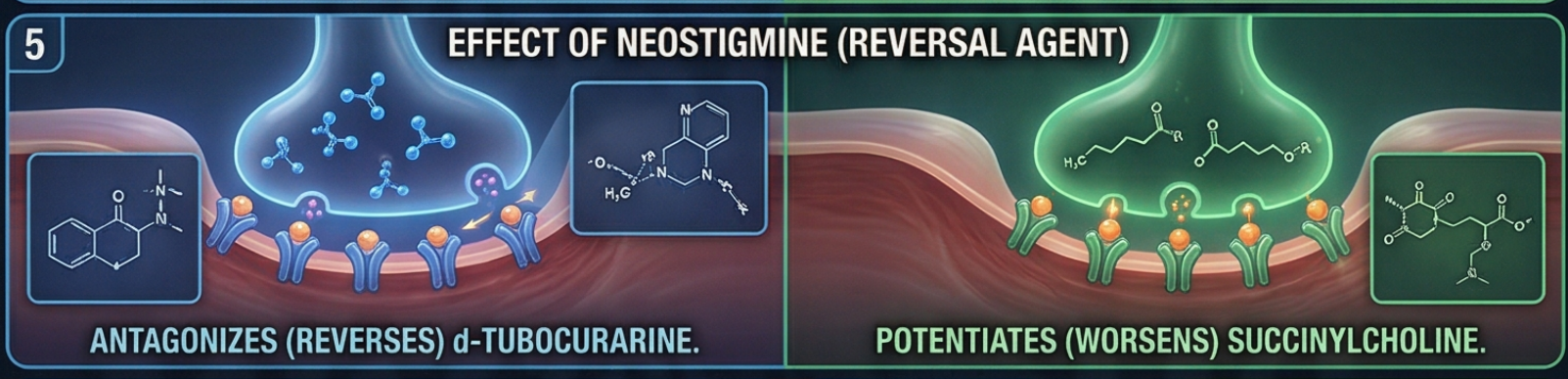
4 SERUM POTASSIUM



NO CHANGE.

CAUSES HYPERKALEMIA.

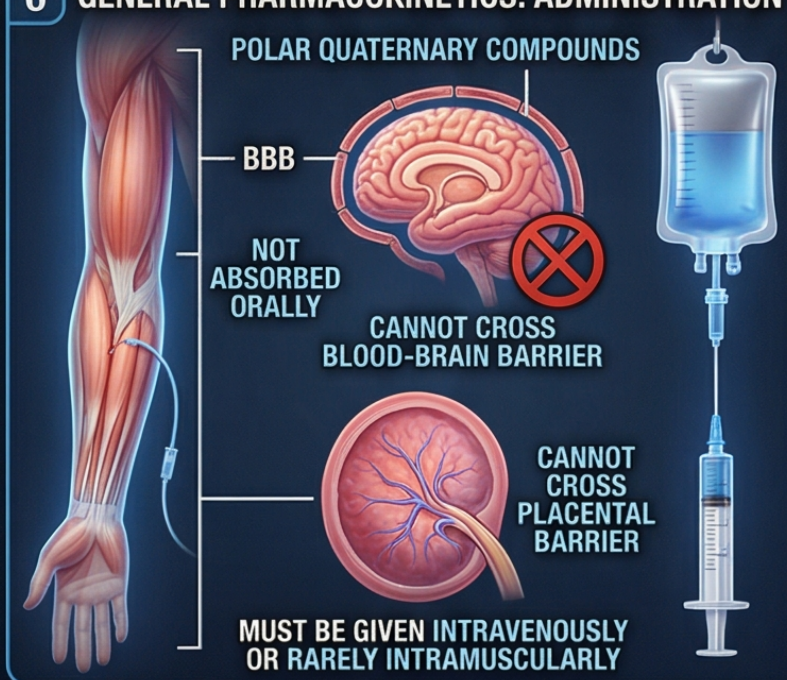
5 EFFECT OF NEOSTIGMINE (REVERSAL AGENT)



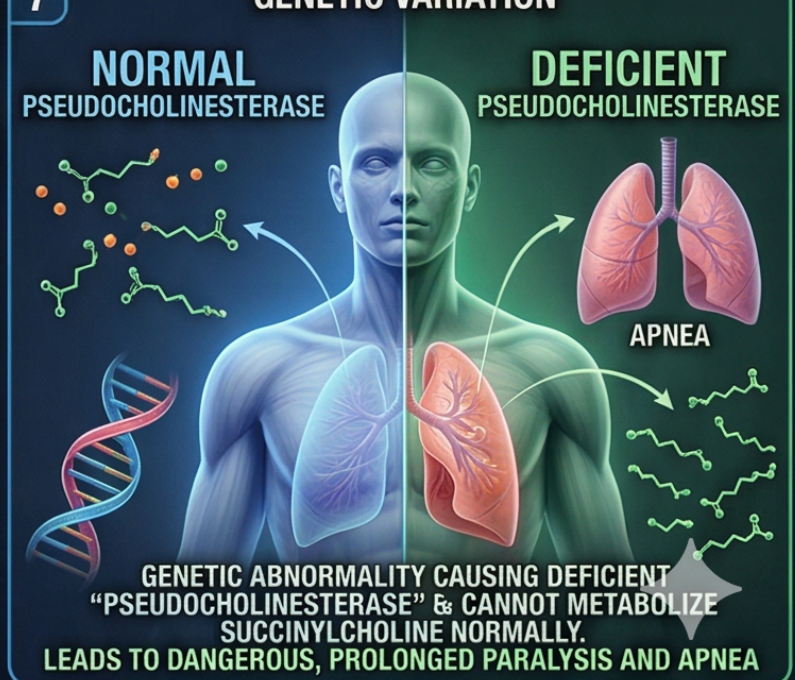
ANTAGONIZES (REVERSES) d-TUBOCURARINE.

POTENTIATES (WORSENS) SUCCINYLCHOLINE.

6 GENERAL PHARMACOKINETICS: ADMINISTRATION



7 GENETIC VARIATION



GENETIC ABNORMALITY CAUSING DEFICIENT "PSEUDOCHOLINESTERASE" & CANNOT METABOLIZE SUCCINYLCHOLINE NORMALLY.
LEADS TO DANGEROUS, PROLONGED PARALYSIS AND APNEA

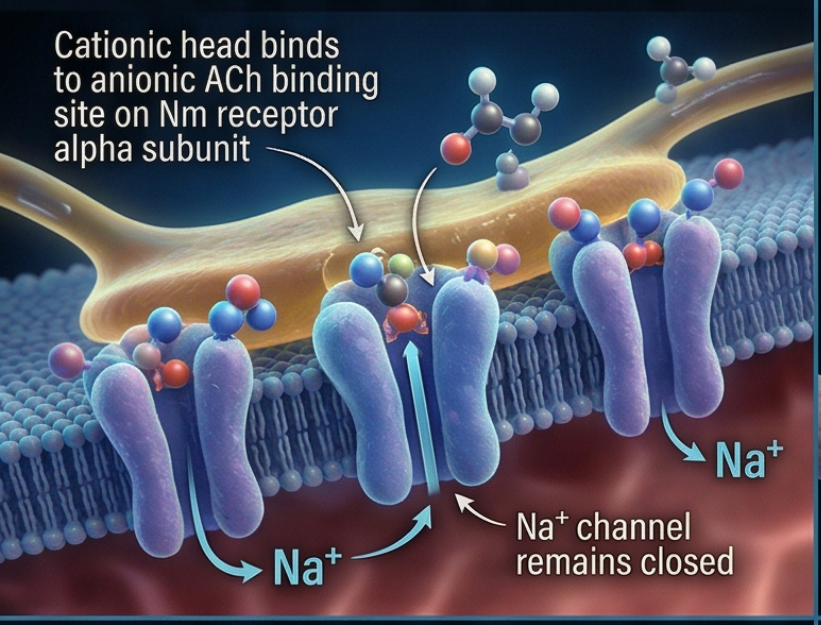
Key Comparisons: d-Tubocurarine vs. Succinylcholine

- **Blockade Type:** d-Tubocurarine is competitive; Succinylcholine is depolarizing.
- **Relaxation Style:** d-Tubocurarine causes flaccid paralysis; Succinylcholine causes initial twitching (fasciculation) before paralysis.
- **Histamine Release:** High (++) with d-Tubocurarine; negligible with Succinylcholine.
- **Serum Potassium:** No change with d-Tubocurarine; causes Hyperkalemia with Succinylcholine.
- **Effect of Neostigmine (Reversal agent):** Antagonizes (reverses) d-Tubocurarine; potentiates (worsens) Succinylcholine.

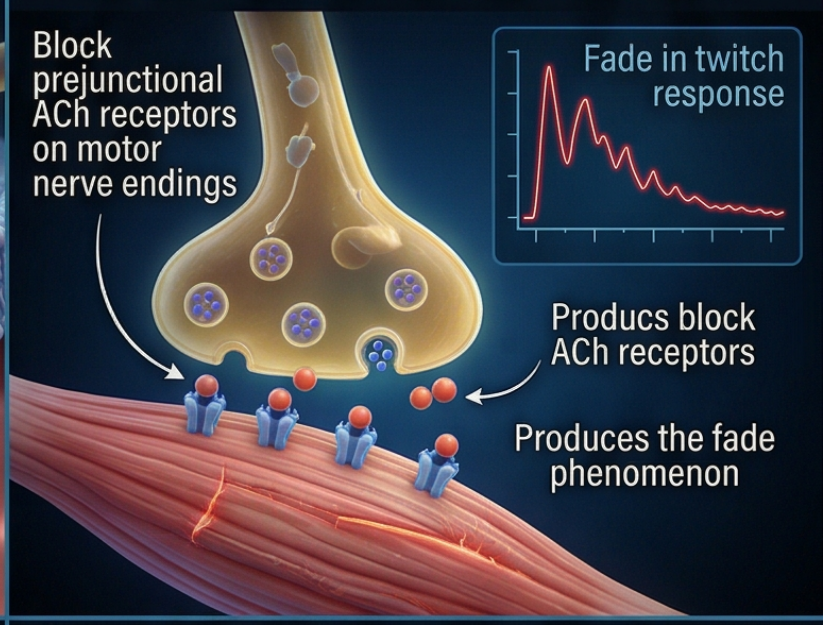
General Pharmacokinetics

- **Administration:** These drugs are polar quaternary compounds, meaning they are not absorbed orally and cannot cross the blood-brain barrier or the placental barrier. They must be given intravenously or rarely intramuscularly.
- **Genetic Variation:** Patients with a genetic abnormality causing deficient "pseudocholinesterase" cannot metabolize Succinylcholine normally, leading to dangerous, prolonged paralysis and apnea.

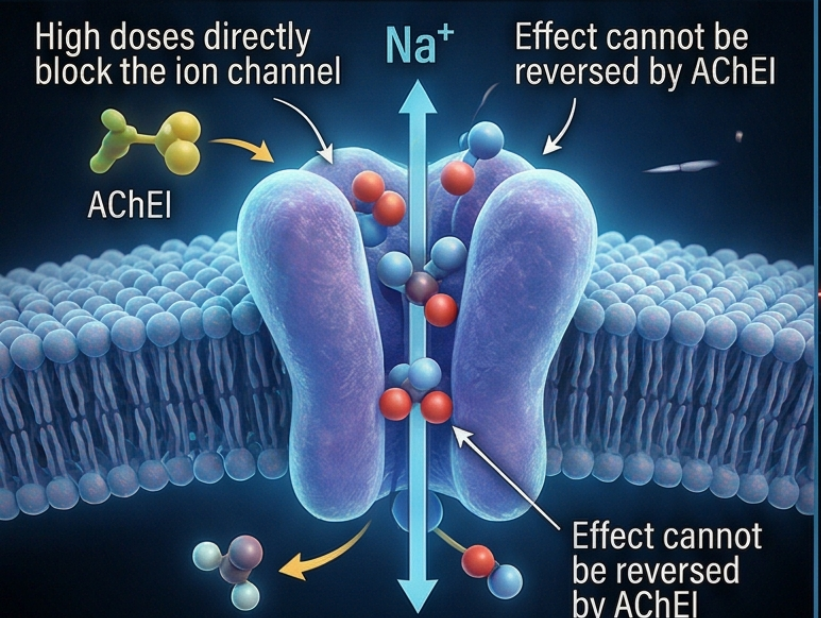
1 Nm RECEPTOR BLOCKADE: NON-DEPOLARIZING DRUGS



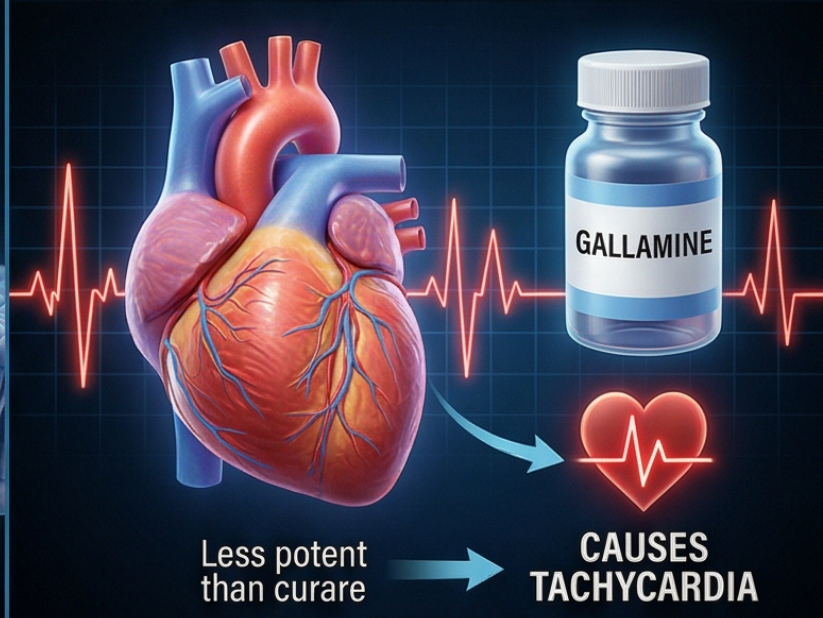
2 PREJUNCTIONAL ACh RECEPTOR BLOCKADE: FADE PHENOMENON



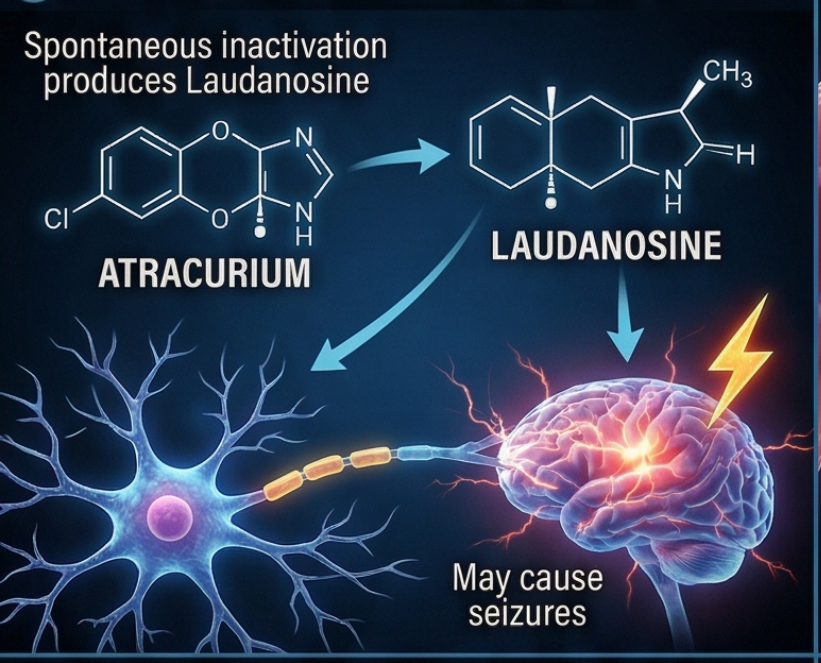
HIGH DOSES: ION CHANNEL BLOCKADE



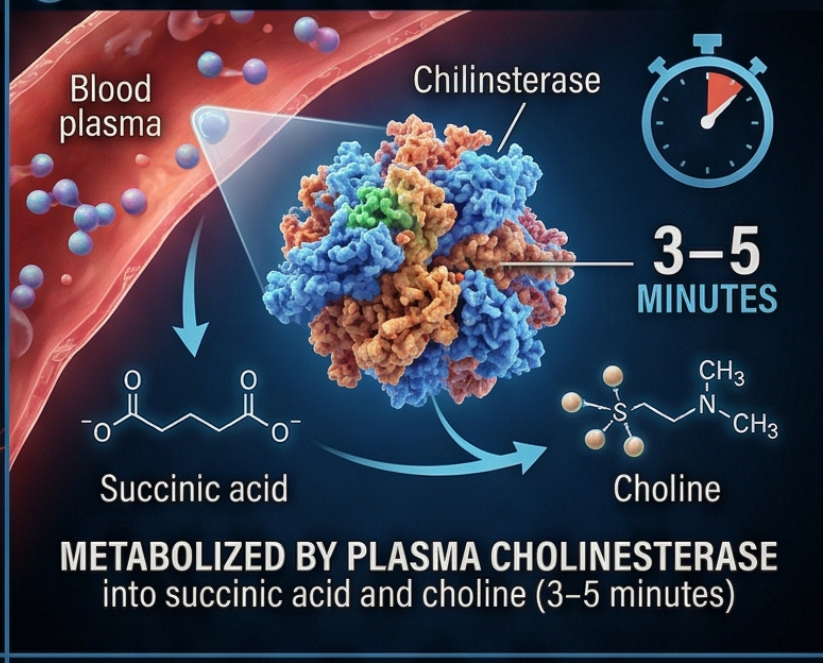
4 GALLAMINE & TACHYCARDIA



5 ATRACURIUM METABOLISM

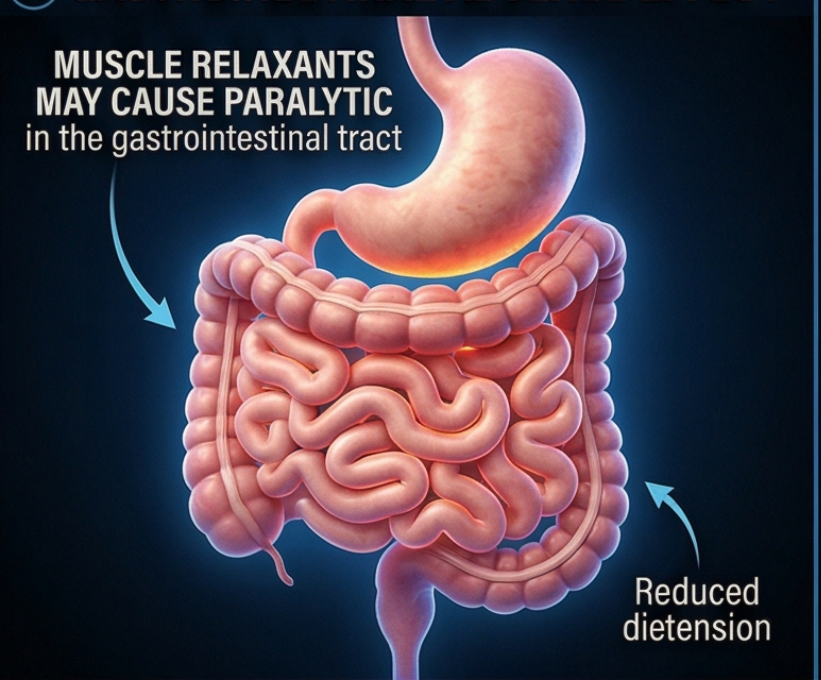


6 SUCCINYLCHOLINE METABOLISM

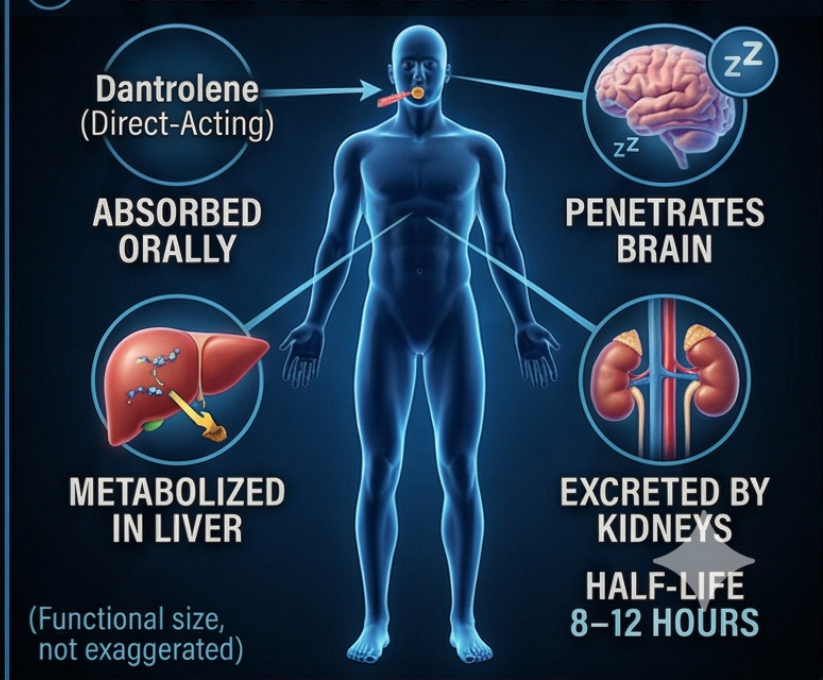


METABOLIZED BY PLASMA CHOLINESTERASE into succinic acid and choline (3–5 minutes)

7 GASTROINESTINAL ADVERSE EFFECT



8 DIRECT-ACTING: DANTROLENE



- The cationic head of non-depolarizing drugs binds to the anionic acetylcholine (ACh) binding site on the alpha subunit of the Nm receptor, and the Na^+ channel remains closed.
- Non-depolarizing drugs can also block prejunctional ACh receptors on motor nerve endings, producing the fade phenomenon.
- At high doses of non-depolarizing drugs, the ion channel becomes blocked and the effect cannot be reversed by acetylcholinesterase inhibitors.
- Gallamine is less potent than curare and causes tachycardia.
- Spontaneous inactivation of atracurium produces laudanosine, which may cause seizures.
- Succinylcholine is metabolized by plasma cholinesterase into succinic acid and choline within 3–5 minutes.
- Muscle relaxants may cause paralytic ileus in the gastrointestinal tract.
- Direct-acting muscle relaxants such as dantrolene are absorbed orally, penetrate the brain producing sedation, are metabolized in the liver, and are excreted by the kidneys with a half-life of 8–12 hours.