PHARMACOLOGY

Lecture 1: Skeletal muscle relaxants

OBJECTIVE:

-Identify classification of skeletal muscle relaxants
- Describe the pharmacokinetics and dynamics of neuromuscular relaxants
-Recognize the clinical applications for neuromuscular blockers
-Know the different types of spasmolytics
-Describe the pharmacokinetics and dynamics of spasmolytic drugs
-Recognize the clinical applications for spasmolytic drugs

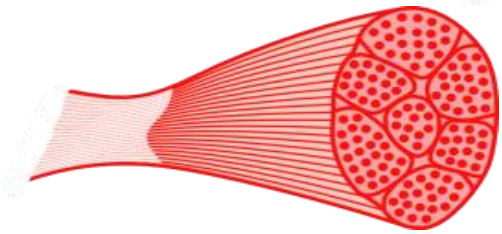
Before studying this lecture, we advise you to study lecture 6 in physiology: neuromuscular junction

- Important.
- Extra notes.

Skeletal muscle relaxants

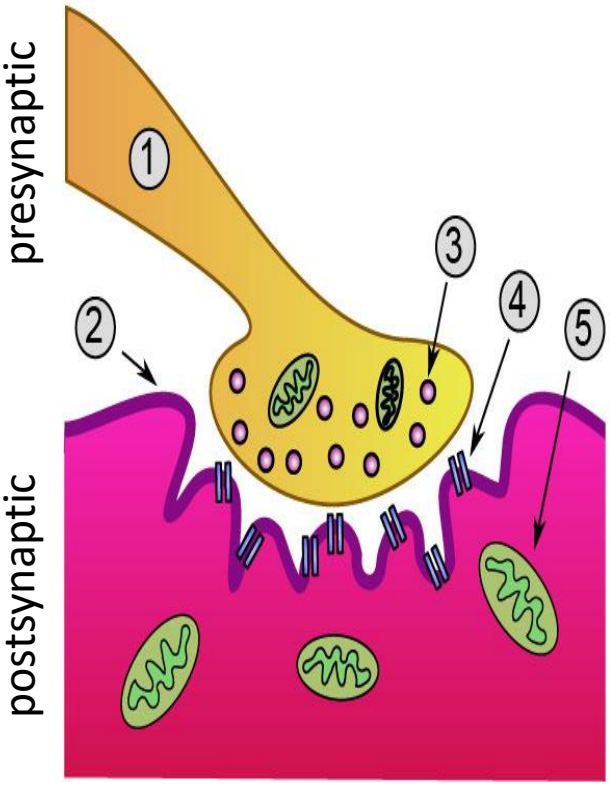
i.e. drugs used to induce skeletal muscle relaxation.

- **Skeletal muscle relaxants**
  - **Peripherally acting**
    - **Neuromuscular blockers**
      - **Non Depolarizing Blockers (Competitive)**
        - Atracurium
        - Mivacurium
        - Pancuronium
        - Vecuronium
        - **d-Tubocurarine (prototype)**
      - **Depolarizing Blockers**
        - **Succinylcholine**
  - **Spasmolytics**
    - **Centrally acting**
      - **Baclofen (act on Spinal cord)**
      - **Diazepam (act on CNS)**
    - **Direct acting**
      - **Dantrolene (act on skeletal muscles)**



FOR UNDERSTANDING!

Before studying how peripherally-acting muscle relaxants work (by cholinergic antagonism), we first need to understand how do muscles contract.



1) **Presynaptic Junction:** There are voltage-dependent calcium (VDC) channels on the presynaptic neuron's cell membrane
2) **Sarcolemma**
3) **Synaptic Vesicle** at presynaptic neuron's Cytosol, containing neuro-transmitter (ACH)
4) **Nicotinic Ach Receptor in sarcolemma.**
5) **Mitochondria**

- **(The dark brown outline) is presynaptic neuron cell membrane.**
- **Between the** presynaptic neuron **and the postsynaptic** muscle is a part of ECF called "synaptic cleft" where calcium normally exists.

Mechanism of muscles contraction:

After (VDC) channels open, Calcium ions flow from the ECF into the presynaptic neuron's cytosol. This influx of Ca2+ causes neurotransmitter-containing vesicles to fuse with the presynaptic neuron's cell membrane, resulting in the release of Ach into the synaptic cleft, a process known as exocytosis. Then, Ach diffuses into the synaptic cleft and binds to the nicotinic acetylcholine receptors on the motor endplate. The binding of two Ach molecules results in a conformational change in the receptor that opens the sodium-potassium channel of the nicotinic receptor. This allows Na+ and Ca2+ ions to enter the cell and K+ ions to leave the cell, causing a Depolarization of the end plate, resulting in Muscle Contraction.

YouTube Muscle Contraction Part 1: Events at the Neuromuscular Junction

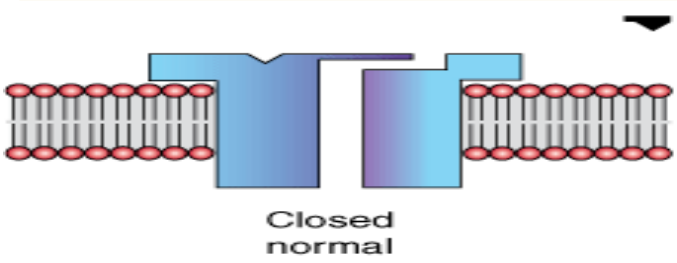
Peripherally acting Neuromuscular Blockers :

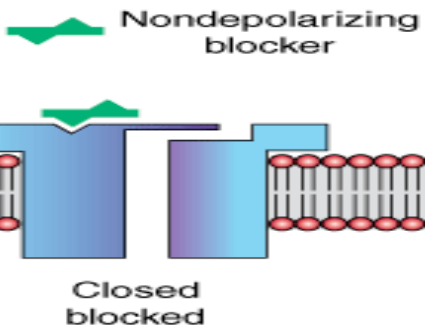
How to prevent the DEPOLARIZATION (Making The Muscle Relax)?

By Blocking The **Nicotinic** Ach Receptors at motor end plate.

This can be done by 2 mechanisms:

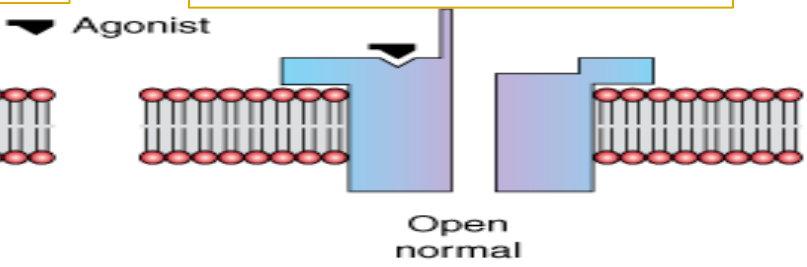
1. Non-depolarizing agents:

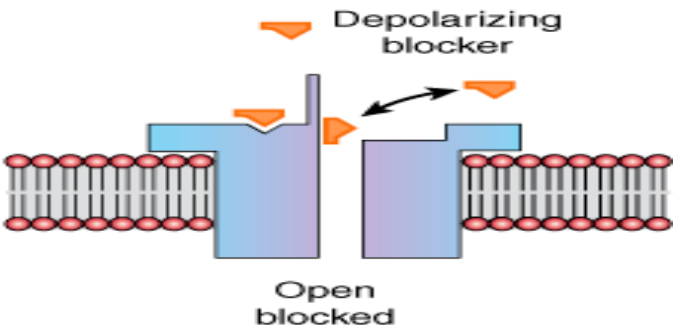




Non-depolarizing Blockers (Competitive) such as **Tubocurarine, act as** competitive antagonists with Ach. **They block the agonist (acetylcholine)** from binding to **Nicotinic Receptors** & activating them, thereby **Preventing Depolarization**.

2. Depolarizing agents:





Depolarizing Blockers such as **Succinylcholine**, act as Ach receptor agonists. They mimic Ach and block muscle contraction by depolarizing to such an extent that it **desensitizes the receptor** and it can no longer initiate an action potential.

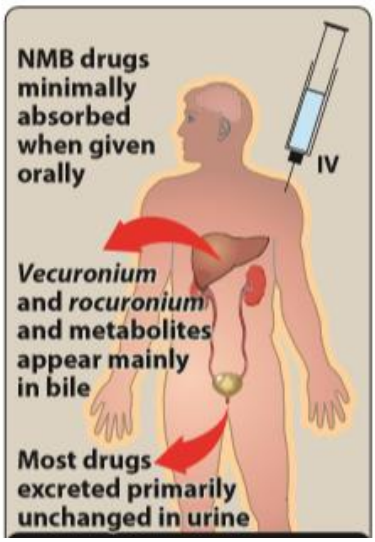
Muscle Relaxants [UndergroundMed]

1. Competitive (non-depolarizing) NM blockers :

Mechanism of Action:

- Are competitive antagonists for Ach at the nicotinic receptors present in post-junctional membrane of motor end plate.
- No depolarization of post-junctional membrane.
- Cholinesterase inhibitors can reverse blockade (**Neostigmine**).

Pharmacokinetics:



They are polar compounds, therefore

- inactive orally & taken parenterally
- Do not cross placenta & CNS, since they are not lipid soluble.

Metabolism depends upon kidney or liver **Except**:

- **Mivacurium** is degraded by pseudo-cholinesterase enzyme (made in the liver)
- **Atracurium** is metabolized by spontaneous degradation in plasma, thus it is the **drug of choice for patients with liver & kidney failure.**

Note that:

- Drugs excreted mainly by kidney have long duration of action (d-tubocurarine & pancuronium)
- Drugs excreted mainly by liver have intermediate duration of action (atracurium & vecuronium)
- Drugs excreted by enzymes e.g. Pseudo cholinesterase have Short duration of action (mivacurium & succinylcholine)

Pharmacological actions:

All are skeletal muscles relaxants, and produce different effects on the CVS mentioned in the table next slide.

D-Tubocurarine (a prototype drug) is the first muscle relaxant used clinically. Not used anymore due to its adverse effects, however, more safer derivatives are now available. (e.g. pancuronium)

Drug	D-Tubocurarine	Atracurium	Mivacurium	Pan-curonium	Ve-curonium
		Chemically related			
Duration	**1-2 h (Long)**	**30 min (intermediate)**	**15min (short)**	**1-2 h (Long)**	**40 min. (Intermediate)**
Metabolism & excretion	**Eliminated by kidney** 60% **& liver** 40%.	**Spontaneous hydrolysis, it is** not stable at body pH, thus goes through non enzymatic chemical degradation in plasma.	It has Fast onset, and fast metabolism by **Pseudo cholinesterase.**	Metabolized by **liver** Excreted **mainly by the kidney** (80 %) Its metabolic products also have some NM blocking activities	Metabolized by **liver**. Excretion in **bile**.
Side effects	• Strong release of histamine • Hypotension • Tachycardia • Bronchospasm	• Slight release of histamine • Transient hypotension • Bronchospasm	• Slight release of histamine • Transient hypotension	• **Hyper**tension • Tachycardia (↑ Heart Rate) • ↑ NE release from adrenergic nerve endings.	Widely used due to few side effects. No histamine release.
Contra-indications Should be avoided for patients with	Renal failure, since it is excreted mainly by the kidney.	Asthmatic patients, since it causes **Bronchospasm.** (prevented by using Anti-histamine)	Has longer duration of action in patients with liver disease, since it is metabolized by pseudo cholinesterase. (synthesized in the liver)	• Renal failure • coronary diseases. Since it causes tachycardia , a diseased heat can't tolerate the increase d load .	Liver failure, since it is excreted mainly by the liver.
Target of blockade	• autonomic ganglia	• No effect on muscarinic receptor nor ganglia		• muscarinic receptor in SA node of the heart (anti-parasympathetic action-atropine like effects)	• No effect on muscarinic receptor nor ganglia
Potency	A type of curare drugs.	As potent as curare.		6 times more potent than curare.	

2. Depolarizing NM Blockers:

E.g.: Succinylcholine (Suxamethonium):

Mechanism of action:

Phase I

- Combines with nicotinic receptors and activates depolarization of motor end plate (by opening Na channels → influx of Na → initial stimulation) → initial muscle twitching (weak brief contraction).

Phase II

- Persistent depolarization leading to paralysis.
- It will not repolarize, therefore the cell is not ready to bind with Ach and contract again.
- Phase II clinically resembles non-depolarizing muscle relaxants.

Pharmacokinetics:

Succinylcholine has short onset (1 min) and also short duration of action (5-10 min) . Onset = the time between drug administration and appearance of action

Contraindications :

1. Patients with **cardiovascular diseases.**
2. Patients with **glaucoma** (a group of eye diseases which result in damage to the optic nerve and vision loss).

Prolonged Half life (T 1/2) in:

3. Extremities (**Neonates & Elderly**)
4. Patients with **pseudo-cholinesterase deficiency**. Why?

Because it is metabolized by pseudo-cholinesterase (different from true-cholinesterase that it doesn't work in NMJ, but in blood circulation).

pseudo-cholinesterase deficiency is caused by:

- liver disease (liver is where most enzymes are synthesized)
- Malnutrition (no proteins = no pseudo-cholinesterase enzyme)
- Organophosphorus poisoning (cholinesterase inhibition: lecture 4).
- Genetic pseudo-cholinesterase deficiency

2. Depolarizing NM Blockers (cont.)

Pharmacological Actions (due to depolarization):	
Desirable:	**Undesirable (side effects):**
SK. muscle: fasciculation which leads to spastic paralysis. (fasciculation: A brief spontaneous contraction affecting a small number of muscle fibers, often causing a flicker of movement)	• **CVS**: arrhythmia (Any disturbance in the rhythm of heartbeat). • **Hyperkalemia** (elevated amount of K in blood, this reduces the electrical potential and leads to cardiac arrest. • **Eye:** increased intraocular pressure IOP (depolarization and contraction of extraocular muscle). Thus avoided in patients with glaucoma. • **GIT**: increased intra-gastric pressure leads to regurgitation of gastric content to esophagus and difficulty in opening mouth. regurgitate: bring swallowed food up again to the mouth. • May cause **succinylcholine apnea** (prolonged duration of action caused by pseudo-cholinesterase deficiency leads to paralysis of diaphragm and temporary cessation of breathing) • Can cause **Malignant Hyperthermia.**

❖ **Malignant Hyperthermia:** the rare bizarre inherited condition of having a body temperature greatly above normal.

It occurs upon administration of drugs as:

- general anesthesia e.g. halothane
- neuromuscular blockers e.g. succinylcholine

❖ **Disease mechanism:**

1. Inability to bind calcium by sarcoplasmic reticulum in some patients due to genetic defect, which is mutation of the ryanodine receptor (RYR1).
2. Opened RYR1 leads to increased intracellular **Ca** release which causes intense **muscle spasm.**
3. Severe rise in body temperature **(hyperthermia)**

❖ **Treatment:** Dantrolene (mentioned later in details)

Peripherally acting Neuromuscular Blockers :

Uses of neuromuscular blockers :

1. Relieve of tetanus and epileptic convulsion « تشنّجات الكزاز والصرع » .
2. Since it controls **convulsion** , it is used for **electroshock therapy** in psychotic patient
3. Facilitate **endoscopy and endotracheal intubation**
4. As adjuvant in **general anesthesia**, especially in abdominal and orthopedic surgery, because less anesthetic is required to produce muscle relaxation, allowing patients to recover quickly and completely after surgery.

Drugs and diseases that modify NM blockers effects:

- Disease states such as **myasthenia gravis** and **Parkinson** increase the response to muscle relaxants.
- Drugs, as Aminoglycosides (e.g.**streptomycin**), **General anesthetics,** and **Magnesium sulphate** enhance the effects of NM blockers.
- **Cholinesterase inhibitors** * may enhance the effect of depolarizing relaxants but decrease the effect of non-depolarizing relaxants. For example, prolonged muscle paralysis induced by Mivacuriuam (non-depolarizing) can be reversed by acetylcholinesterase inhibitors such as endrophonium or neostigmine, by increasing Ach level in NMJ and displacing Mivacuriam from nicotinic receptors.
  * (will be discussed further in lecture 4)

Myasthenia gravis: a condition causing abnormal weakness of certain muscles.

Parkinson's disease:

a degenerative disorder of the central nervous system mainly affecting the motor system.

Spasmolytics:

SPASMOLYTICS			
Muscle Relaxants	**Action**	**Act On**	**Clinical Uses**
Baclofen	Centrally	GABA* Agonist Act On Spinal Cord	They reduce muscle spasm in spastic states in neurological disorders as: - Spinal cord injury - Cerebral stroke - Cerebral palsy
Diazepam (Benzodiazepines)	Centrally	Facilitate GABA* Act on CNS	
Dantrolene	Direct		all the above + Malignant Hyperthermia

* GABA: γ-Aminobutyric acid is the chief inhibitory neurotransmitter in the mammalian CNS. It plays the principal role in reducing neuronal excitability throughout the nervous system, thus reducing contraction.

Dantrolene mechanism of Action :

- It acts directly by interfering with the release of calcium from the **sarcoplasmic reticulum** of skeletal muscles, where it is stored.
- It inhibits **excitation-contraction coupling** in the muscle fiber.
- Calcium is released from the sarcoplasmic reticulum via a calcium channel, called the Ryanodine Receptor (RyR) channel and Dantrolene blocks the opening of these channels.
- Given orally or intravenously (IV).
- t ½ = 8 - 9 h

Clinical Uses:

- Malignant Hyperthermia.
- Spastic states.

Dantrolene - Clinical Use (Malignant Hyperthermia)

Drugs (summary)

		Drug	Duration	Mechanism	Metabolism	Uses
Spasmolytics	Centrally	Diazepam		Act Centrally on CNS & facilitate GABA		**Reduce muscle spasm in :** • Spinal cord injury • Cerebral stroke • Cerebral palsy
		Baclofen		Act Centrally on spinal Cord & is GABA Agonist		
	Direct	Dantrolene	t ½ = 8 - 9 h	Interferes with the release of Ca from the sarcoplasmic reticulum. & inhibits excitation-contraction coupling in the muscle fibres.		Malignant Hyperthermia. & Spastic states. **Side effects**
Peripherally acting (Neuromuscular blockers)	Depolarizing	Succinylcholine	5-10min (short) • onset :1 min	**Phase I** Combines with nicotinic receptors → contraction Open Na channels → initial stimulation **Phase II** Persistent depolarization leading to paralysis. It will not repolarize, therefore the cell is not ready to bind with Ach.	by pseudo-cholinesterase in plasma.	1. Arrhythmia 2. cardiac arrest 3. intraocular pressure 4. intra-gastric pressure **5. succinylcholine apnea** **6. Malignant Hyperthermia**
	Non Depolarizing (Competitive)	Vecuronium	40 min. Intermediate	competitive antagonists for **Ach** at the **nicotinic receptors** present in post-junctional membrane of motor end plate.	by **liver**. Excretion in **bile**	• **No** histamine release • **No** tachycardia
		Pancuronium	1-2 h (Long)		by **liver**. Excretion **by the kidney**	• Hypertension • Tachycardia • Antimuscarinic action ↑ NE release
		Mivacurium	15min (Shortest)		pseudo cholinesterase	• Transient hypotension
		Atracurium	30 min Intermediate		spontaneous hydrolysis	• Transient hypotension • Bronchospasm
		D-Tubocurarine	1-2 h (Long)		**kidney** 60% **liver** 40%.	• Hypotension • Tachycardia • Bronchospasm

QUIZ

THANK YOU FOR CHECKING OUR WORK

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