بسم الله الرحمن الرحيم

MSS module
Pharmacology Lecture
Skeletal muscle relaxants

By
Dr. Mohamad Salem

2024

ILOs:

1-Identify centrally and peripherally acting skeletal muscle relaxants and their therapeutic merits.

2- Classify neuromuscular (NM) blocker according to the mechanism of action.

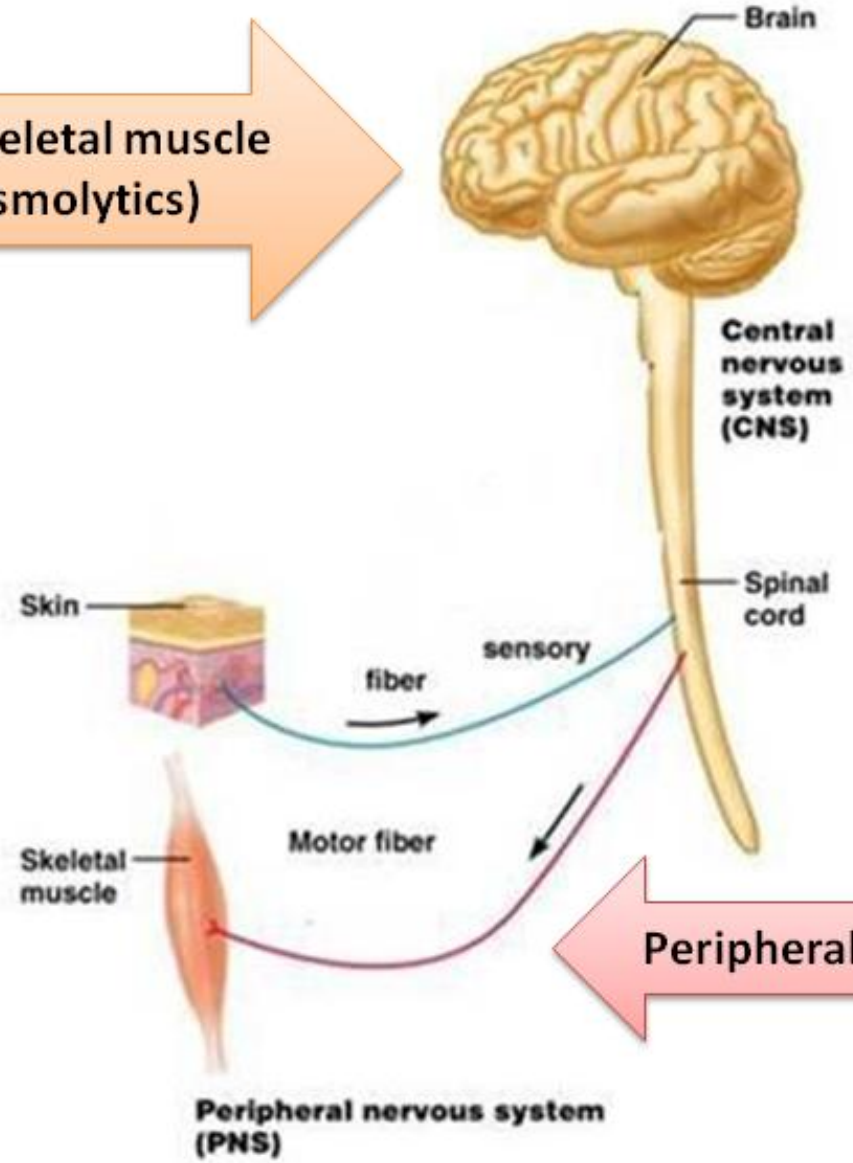
3- List the uses, and Adverse effects of NM blockers and identify the antidote of their toxicity.

Skeletal muscle relaxants

Skeletal muscle relaxants are drugs that are used to relax and reduce tension in muscles.

These drugs can act either on the CNS (**central muscle relaxants or spasmolytics**) or peripherally at the NM junction (**neuromuscular blockers**).

Centrally acting skeletal muscle relaxants (spasmolytics)



Peripherally acting NM blockers

1- Central skeletal muscle relaxants (spasmolytics)

- These drugs include general anesthetics (especially in high dose) and tranquilizers. These drugs decrease the muscle tone and spasticity.

- **Baclofen** is a central muscle relaxant which **activate GABA type B** receptors. **Diazepam** is one of the benzodiazepines (act by enhancing GABA A receptors).

- Central muscle relaxant drugs are useful in treatment of **spastic disorders** like multiple sclerosis, dystonia and cerebral palsy. These drugs decrease spasticity after stroke and spinal cord injury.

- They may be given to patients suffering from neuralgias and frequent skeletal muscle spasm.

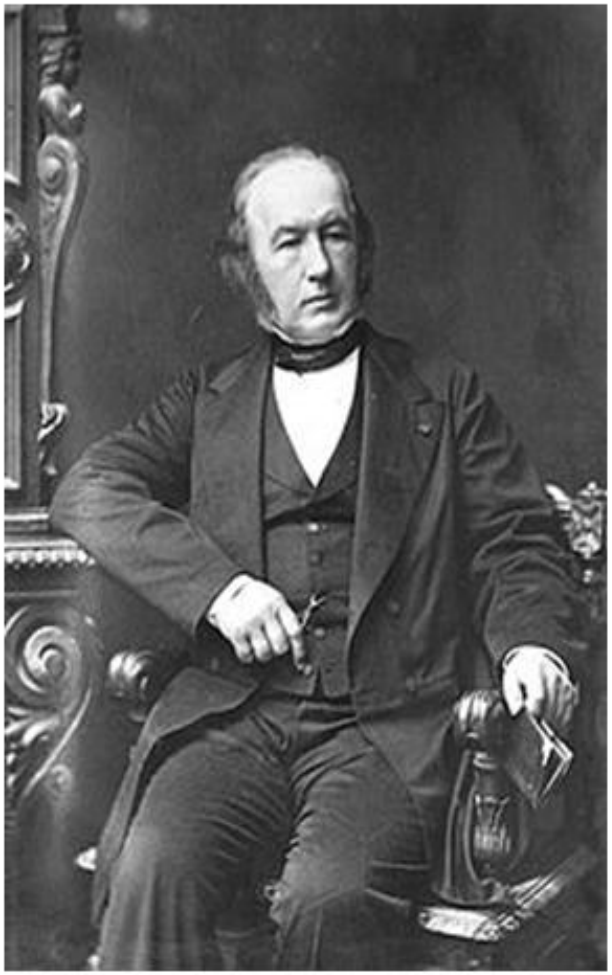
2- Peripherally acting neuromuscular (NM) blockers

Many surgical procedures require that voluntary muscle tone and reflex contraction are to be inhibited.

This can be attained by deep general anesthesia (central muscle relaxation) which carries the hazard of cardiovascular and respiratory complications and slow recovery.

Muscle relaxation brought about by **NM blockers** allows surgery under **light general anesthesia** and also **facilitates tracheal intubation**.

History of Skeletal Muscle Relaxants



- Curare is a common name for various plant extract alkaloid arrow poisons originating from Central and South America.

- Tubocurarine name because of packing in "hollow bamboo tubes"

Claude Bernard

Pharmacological properties of NM blockers

- These drugs affect the **impulse transmission** from motor nerves (like botulinum toxin), or **Block NM receptor** (e.g. curare), **Stabilize muscle membrane** in depolarized state (e.g. Acetylcholine or nicotine in high doses and succinylcholine) or **prevent calcium release** in the sarcoplasm (e.g. dantrolene).

- Neuromuscular (NM) blockers should be given only after induction of anesthesia. All NM blockers currently available for use are **quaternary nitrogenous compounds** and are virtually devoid of central effects because they cannot pass the blood-brain barrier.

Classification and mechanism of action of NM blockers

Two types of NM blockers are commonly uesd clinically :

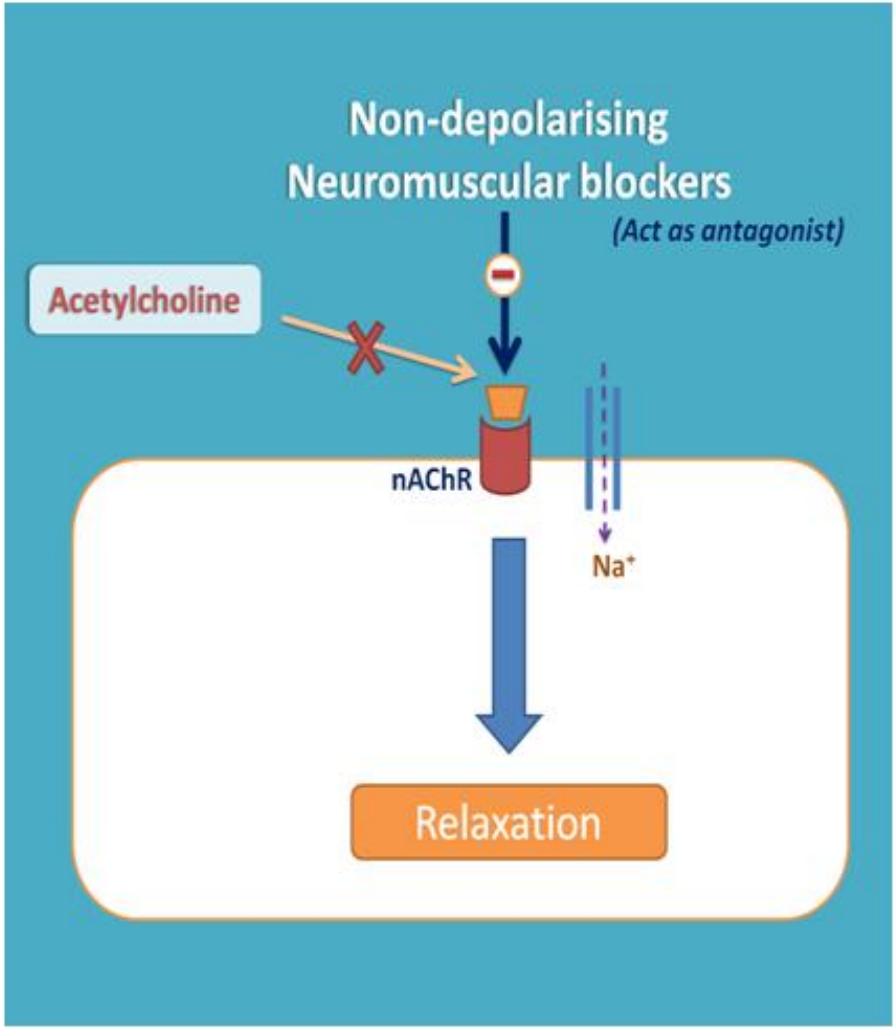
1- **Competitive** (non-depolarizing) blockers as d-tubocurarine.

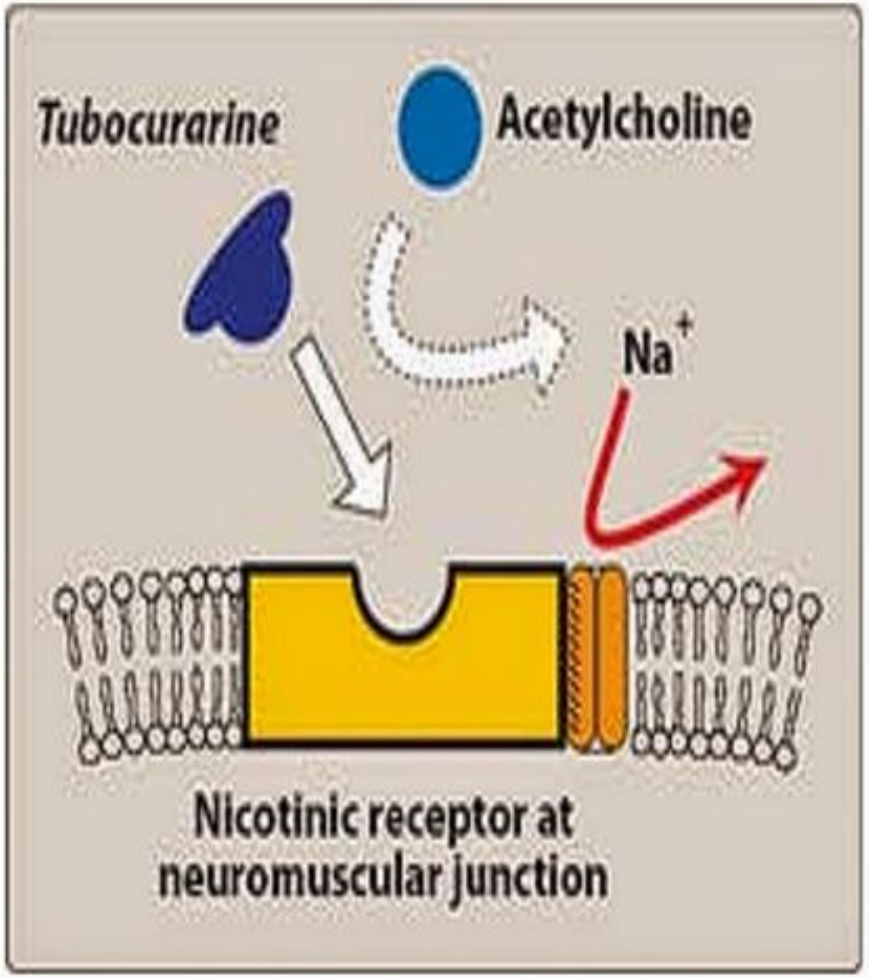
2-Depolarizing (non-competitive) blockers as succinylcholine

Depolarizing	Non-depolarizing
Short-acting Succinylcholine	Short-acting Mivacurium
	Intermediate-acting
	Atracurium; Cisatracurium
	Rocuronium; Vecuronium
	Long-Acting
	Doxacurium
	Pancuronium; Pipecuronium

1- Competitive (non-depolarizing) NM blockers

- They act by competing with ACh at the motor end plate to block NM receptors. These drugs causes muscle relaxation and paralysis starting with small muscles, then large muscle and finally respiratory muscles (diaphragm and intercostal m.). The recovery occurs in a reverse order.
- **Gallamine** (Flaxedil) is a competitive NM blocker with vagolytic action (antimuscarinic) which may cause tachycardia.
- **tubocurarine blocks autonomic ganglia** (sympathetic more than parasympathetic) and **causes histamine release**; both these effects may cause a transient drop in blood pressure. Histamine release, in addition, may cause bronchospasm.


Non-depolarising
Neuromuscular blockers
(Act as antagonist)
Acetylcholine
nAChR
Na+
Relaxation


Tubocurarine
Acetylcholine
Na+
Nicotinic receptor at
neuromuscular junction

Side effects (toxicity) of competitive NM blockers:

1-**Hypotension** due histamine release and ganglion blocking action.
2-**Bronchospasm**.
3-Respiratory failure due to paralysis of respiratory muscles.
4- **Tachycardia** and occasionally hypertension with gallamine only.
5- **Anaphylaxis** if massive histamine release occurs.

Treatment of competitive NM toxicity

1 The traditional pharmacological antidote

1-Neostigmine (which increases acetylcholine and has a direct NM agonistic activity.
2-Atropine or glycopyrollate (to counteract the muscarinic side effects of neostigmine).
3-Antihistaminic drugs.
4-Epinephrine in cases of anaphylaxis.

2- The new chemical antagonist Sugammadex

Sugammadex is a chemical antagonists (antidote) that selectively binds to rocuronium, vecuronium and pancuronium. It acts by encapsulating the rocuronium molecule.

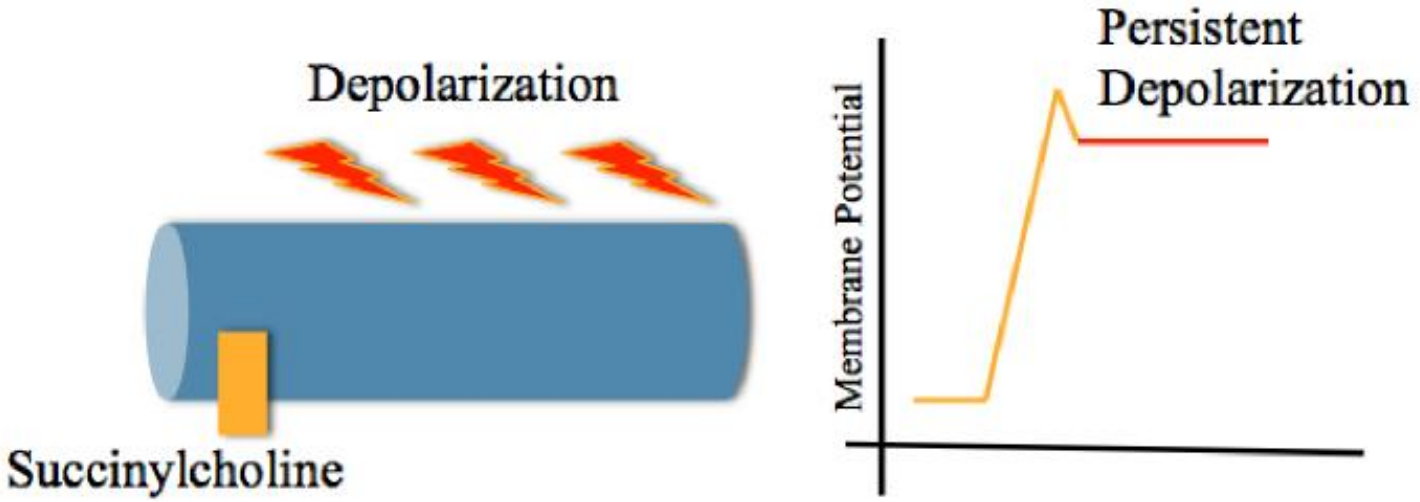
- Sugammadex, unlike neostigmine, does not inhibit acetylcholinesterase so cholinergic effects are not produced and co-administration of an antimuscarinic agent (e.g. atropine) is not needed.

- Sugammadex might therefore be expected to have fewer adverse effects than the traditional reversal agents.

2- Depolarizing (non-competitive) NM blockers

They **activate NM receptors** and cause **persistent depolarization** and this reduces the excitability of muscle membrane.

Acetylcholine and nicotine (in high doses) and suucinylcholine (also called ***suxamethonium***) are examples



Order of muscles affected :

(1) Small rapidly moving muscles as those of eyes, fingers, jaws, toes are involved first.

(2) Muscles of limbs, neck and trunk.

(3) Intercostal muscles.

(4) Diaphragm.

Recovery takes place in the reverse order of paralysis and is complete.

Other actions: Succinylcholine can cause cardiac arrhythmias when administered during halothane anesthesia. it also stimulates nicotinic receptors at both sympathetic and parasympathetic ganglia.

Side effects of depolarizing NM blockers:

1- **Hyperkalemia**.

2- Increase intraocular pressure and increased gastric pressure.

3- Malignant hyperthermia: occur in genetically susceptible individuals receiving halothane (general anesthetic) and succinylcholine. Abrupt onset of fever and muscle stiffness occurs due to over-release of calcium from sarcoplasmic reticulum of skeletal muscles and over heat production by muscle rigidity. Treatment includes cooling by **ice**, a centrally acting muscle relaxant like **diazepam** (GABA A agonist) and by a direct skeletal muscle relaxant **dantrolene** (inhibits release of calcium from sarcoplasmic reticulum). Diazepam is CNS depressant while Dantrolene is hepatotoxic.

4- **Myalgia** (pain in skeletal muscles) is a common postoperative complain.

5- **Succinylcholine apnea:** is a genetic defect in the amount or kind of **butyrylcholinesterase** (the enzyme responsible for the metabolism of succinylcholine in the plasma). This defect leads to paralysis that lasts for hours and produces apnea "**succinylcholine apnea**" after succinylcholine administration.

It is a dangerous idiosyncratic reaction to succinylcholine. It is treated by fresh blood transfusion and mechanical ventilation.

Therapeutic uses of NM blockers

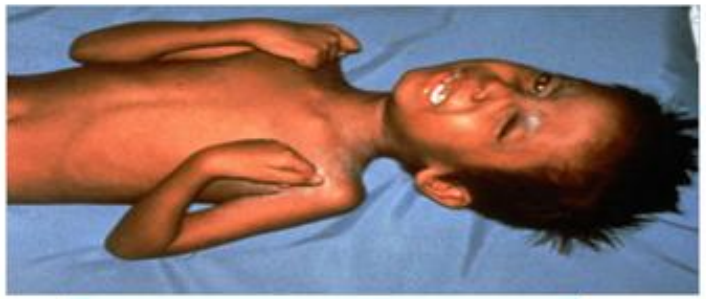
1-As **adjuvant to general anesthesia** to obtain muscle relaxation during surgery and **facilitates tracheal intubation**

- Competitive blockers have long duration of action, so used in major surgical procedures .
- Depolarizing blockers have short duration of action, so used in short procedures as to facilitate tracheal intubation and in endoscopy.

2-In electroconvulsive therapy (ECT), they are used to avoid injury caused by the fits.

3-They can be used in controlled ventilation and in tetanus.

electroconvulsive therapy



tetanus

Botulinum toxin

Clostridium **botulinum** and related species can secrete this toxin. **It prevents the release of the neurotransmitter acetylcholine** from axon endings at the neuromuscular junction and thus causes flaccid paralysis and respiratory arrest.

Uses of Botulinum toxin:

1- Botulinum toxin causes relaxation of skeletal muscles (spasmolytic effects); so it can be used to treat spastic conditions like multiple sclerosis, stroke, eyelid twitches and spinal cord injury.

2- It is commonly used **locally** for cosmetic purposes (Botox injection) to relax certain muscles and obtain anti-wrinkling effects

Other uses include:

1. Treatment of migraine and neuralgias (topical injection)
2. Treatment of hyperhidrosis (inhibits acetylcholine release at sweat glands).
3. Treatment of overactive bladder.(inhibits acetylcholine release urinary bladder).
4. Treatment of teeth grinding (bruxism) as it relaxes mastication muscles.


Thank
you