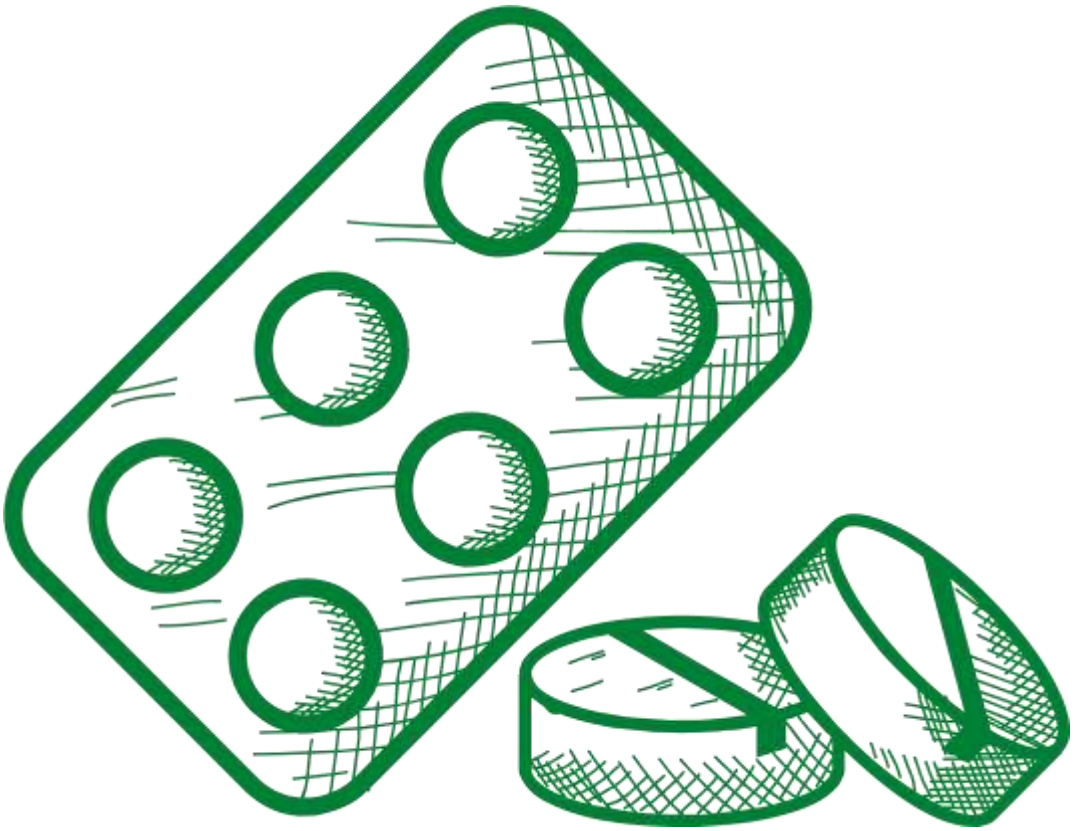
MSS

Sheet no. **4**

Pharmacology



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NEUROMASCULAR DRUGS:

Mechanism of action (depolarizing drugs)

Phase I block (depolarizing):

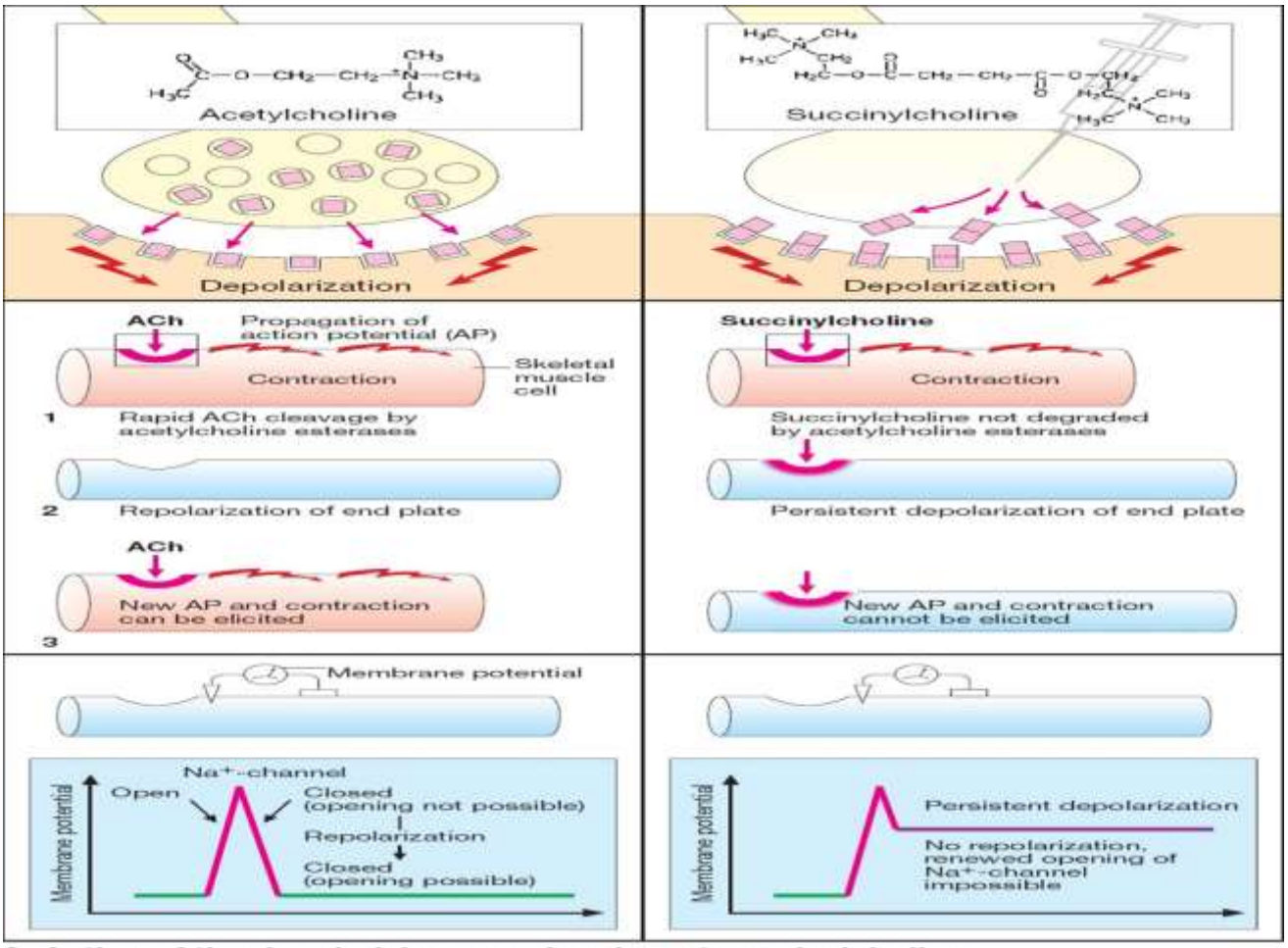
- Succinylcholine (Ach agonist) is the only depolarizing drug that is still used clinically.
- **-Mechanism of Action**: succinylcholine interacts with nicotinic receptors to open sodium channels and cause depolarization of the motor endplate which will spread to adjacent membranes, causing continuous contractions of muscle motor units so the depolarized membranes remain depolarized and unresponsive to subsequent impulses causing flaccid paralysis.
  -Can enter the channel to produce a prolonged "flickering" of the ion conductance.
  The concept of **"flickering"** means that ion channels in the motor endplates are opening and closing randomly (زي الضو الخربان لما بيطفي يفتح ورا بعضه) causing the continuous depolarization of the muscle because the membrane potential is always above the threshold.
- in phase I block, AchE inhibitors increase (augment) the effect of succinylcholine. Accordingly, neostigmine has augmented effect on this phase.
- Succinylcholine has a short duration of action (10 minutes) so it is not used a lot because of the other alternatives of nondepolarizing drugs which have short duration of action. But if it is used, it is used in procedures that require a short time to be completed eg: used in children who need intensive monitoring.
- -Succinylcholine is metabolized and destructed by **plasma choline esterase**, which explains the short duration of this drug (only **20%** of drug reaches the skeletal muscle endplate).
  -in the skeletal muscle endplate, the activity of plasma choline esterase is low, so the proper way to increase the activity of succinylcholine is the direct IV infusion to skeletal endplate.
- Burn victims and patients with spinal cord injuries are prohibited from using these types of drugs because they have increased numbers of functional Ach receptors, so they won't respond very well to these drugs.

Phase II block (desensitizing):

- **-Mechanism of action:** the exact mechanism of this phase is not precisely known but one of the expected mechanisms is that with continuous exposure of these drugs depolarization decreases, and the membrane becomes repolarized and cannot be depolarized again because it is desensitized.
  -Desensitization of these receptors is explained by the **tow state model theory of drug-receptor interaction** which indicates that receptors keep changing from the active state to inactive state. Another explanation of that theory is that ion channels keep changing between 4 phases: depolarized, repolarized, sensitized, and

desensitized. So, it is possible that these drugs cause the receptors to remain desensitized thus unresponsive.

- ❖ Getting rid of succinylcholine is done by diffusion from the skeletal end plate.
- ❖ This phase is reversed by acetylcholinesterase inhibitors. Accordingly, neostigmine has antagonistic effect on phase.



A. Action of the depolarizing muscle relaxant succinylcholine

This picture compares between the effect of Ach and succinylcholine, notice that the membrane potential caused by succinylcholine is persisted in the depolarization phase and no repolarization occur (phase I). later, there is occurrence of repolarization, but ion channels are desensitized thus unresponsive to further action potentials.

Actions of Neuromuscular Blockers:

Effect/action:	Details:
Skeletal Muscle Paralysis	**Depolarizing drugs:** *Action stars by transient muscle fasciculations over the chest and abdomen within 30 seconds. *Paralysis develops rapidly (within 90 seconds), the arm, neck, and leg muscles followed by the respiratory muscles. *Blockade lasts less than 10 minutes.
	Nondepolarizing drugs: *Onset of effect is very rapid. *Motor weakness followed by flaccidity. *Starts with small muscles, large muscles are more resistant to blockade and *recover more rapidly. *Diaphragm is last to be paralyzed. *Effects lasts for 45-60 minutes.
Cardiovascular Effects	*Mediated by autonomic nervous system or histamine receptors (recall that histamine cause vasodilation →hypotension) Both sympathetic and parasympathetic ganglia and muscarinic receptors in the heart can be stimulated. *Usually cause hypotension, which can be attenuated by antihistamines (antihistamines are used during surgeries, because halogenated carbons used in general anesthesia stimulate respiratory secretions so anti histamines reduce these secretions. Also, antihistamine used to maintain blood pressure during surgeries).
Hyperkalemia	Can result in cardiac arrest in patients with burns, nerve damage, or neuromuscular disease, head injury, and other trauma.
Increased Intraocular Pressure	Due to tonic contraction of myofibrils or transient dilation of ocular choroidal blood vessels.
Increased Intragastric Pressure	In obese, heavily muscled, diabetics, traumatic patients, fasiculations of succinylcholine can cause regurgitation and aspiration of gastric contents.
Muscle Pain	Due to unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis.

Drug interaction of Neuromuscular blockers:

Anesthetics:

– Mostly with isoflurane, and least with nitrous oxide.
– May be due to a central action, increased muscle blood flow.
– Can cause **Malignant Hyperthermia (genetic variation in one of the receptors)** -discussed at the end of this sheet-**.**

Antibiotics:

– Depress release of acetylcholine due to blockade of specific P-type of calcium channels.

Local anesthetics and antiarrhythmic Drugs.

Other Neuromuscular Blockers.

Spasmolytic Drugs:

- Most of these drugs work centrally, but they are used to treat certain spastic conditions occurring in musculoskeletal system.
- Nondepolarizing neuroblocking drugs can be used to treat spasm but these drugs are not suitable for patients since they are given by injection.

Diazepam (Benzodiazepines):

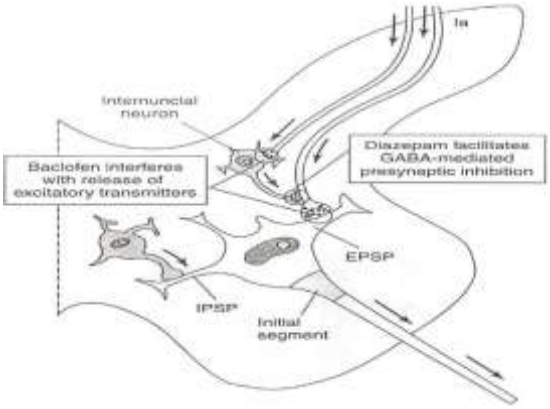
- **Mechanism of action**: Acts at $GABA_A$ (inhibitory neurotransmitter) receptors in the CNS which decreases muscle tonicity thus muscle contraction.
- Used to treat **muscle spasms** of almost any origin (local muscle trauma) also it causes **sedation.**

  Sedation: is the reduction of irritability or agitation by administration of sedative drugs, generally to facilitate a medical and diagnostic procedures or dental procedures (muscle relaxation and pain relief) بالعربي لا تخدير عام ولا تخدير موضعي يعني هيك و هيك
- Side effect: Excessive use of it leads to addiction.

Baclofen:

- **Mechanism of action**: Acts at GABAB receptors, resulting in hyperpolarization and presynaptic inhibition through reducing calcium influx.
- Can also reduce spasticity by inhibiting release of substance P in the spinal cord.
- Less sedative but can cause drowsiness.

- Can be injected intrathecally (theca mater).
- Can reduce craving in alcoholics and in migraine.



Tizanidine:

- Related to clonidine (**Alpha 2 agonist**) -clonidine used for ADHD-
- **Mechanism of action**: binds to alpha2 presynaptic receptors (auto receptors). When Epinephrine and NE levels increase, they bind to these receptors thus stopping their own release which causes **hypotension**. In addition to that it works in reducing muscle tonicity.
- Used to treat **hypertension and muscle spasticity** due to spinal cord injury or multiple sclerosis.
- **Side effects**: dizziness, weakness, depression, hallucinations, and dry mouth (It should not be given to patients with persistent hypotension).

Gabapentin:

- An antiepileptic glycine مضاد للصرع (given only in severe cases of muscle spasms).

Directly Acting Drugs:

Dantrolene:

- Related to **phenytoin(close in structure)**, an antiepileptic agent.
- **Mechanism of action:** Interferes with excitation-contraction coupling in the muscle fibers by interfering with the release of activator calcium by binding with the ryanodine receptor (RyR) channel of the sarcoplasmic reticulum → muscle relaxation.
- **Side effects**: weakness, sedation, hepatitis (inflammation in liver).
- **Used to treat malignant hyperthermia**.

Malignant Hyperthermia:

- Rare life-threatening heritable disorder triggered by a variety of stimuli including **general anesthetics and neuromuscular blockers**
  (some individuals are more susceptible to malignant hyperthermia than others due to genetic variation among those individuals).

- Patients have a hereditary impairment of the sarcoplasmic reticulum to sequester calcium.
- The trigger can cause sudden and prolonged release of calcium, with massive contraction, lactic acidosis, and increased body temperature.
- Treatment is by cooling, correcting acidosis, and **dantrolene** to reduce calcium release.

Botulinum Toxin:

- Produced by clostridium Botulinum bacteria (Botox).
- Inhibits acetylcholine release.
- Food poisoning caused by this bacterium can result in diplopia, dysphagia, dysarthria, and dyspnea, within 12-36 hours.
- Toxin is use for ophthalmic purposes, local muscle spasms, and in the cosmetic treatment of facial wrinkles around the eyes and mouth, as well as for generalized spastic disorders like cerebral palsy.

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