Pharmacology Team 4

Our notes are in orange

Maha Al-Balharith **Nasser Al-Wehaibi**

Nourhan Al-Shamma’ ♥

NEUROMUSCULAR BLOCKERS and CENTRAL MUSCLE RELAXANTS

Classification:

- Peripheral acting drugs
- Central acting drugs
- Direct acting drugs

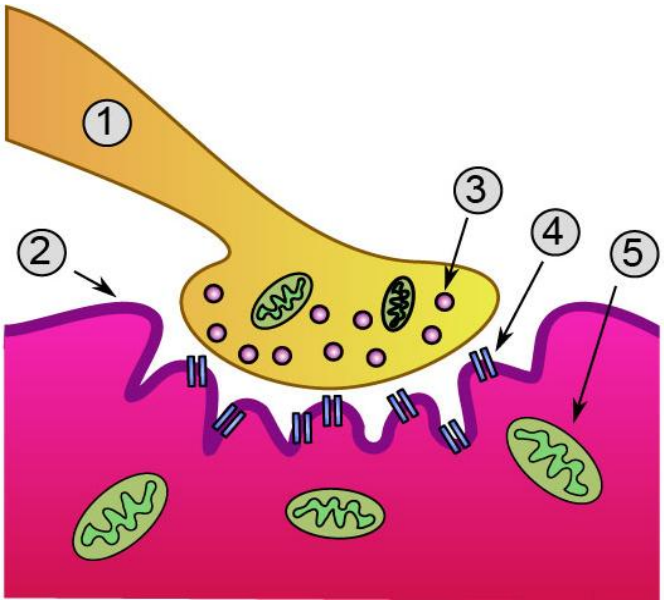
1. **Peripherally acting** (Neuromuscular blockers)

a) non-depolarizing blockers:Cholinergic antagonists (Tubocurarine, Atracurium, Mivacurium , Pencuronium..others)

b) Depolarizing blockers :cholinergic agonists (succinylcholine)

2. **Centrally acting** skeletal muscle relaxants (Diazepam , Baclofen)

3. **Direct acting** skeletal muscle relaxants (Dantroline)



1: Cholinergic motor neurone,

2: motor end-plate,

3: vesicles,

4: N_MR (neuromuscular receptor)

5: mitochondrion

- Skeletal muscle contraction is evoked by nicotinic cholinergic transmission.
- Blockade of this transmission is clinically useful in producing muscle relaxation.
- This is required for surgical relaxation and control of ventilation.

- **Neuromuscular transmission**

Initiation of impulse → release of acetylcholine → activation of nicotinic receptors at motor end plate → opening of ion channel, passage of Na+ → depolarization of end plate → Muscle contraction.

Neuromuscular blocking agents used in clinical practice interfere with this process.

1. Peripherally Acting Drugs

A) Presyneptic NMB

- **a)Inhibit acetylcholine synthesis**
  e.g Triethylcholine , Hemicholinium

- **b)Inhibit acetylcholine release**
  e.g. Botulinum toxin

B) Postsynaptic NMB (important)

- **Competetive (non depolarizing blockers) doesn't allow Ach to reach its receptors & prevents its binding, leading to (relaxant) paralysis of the muscle.**
- **Depolarizing blockers – it works like Ach, it allows Na influx & contraction (depolarization), then relaxation of muscle occurs after it gets tired from too much depolarization.**

A. Competeive (Non-Depolarizing):

- **Tubocurarine (important)**
- **is the prototype of this group. It is a quaternary alkaloid.**

MOA:

- **At low doses (therapeutic Dose) these drugs combine with nicotinic receptors and prevent acetylecholine binding, thus prevents depolarization at nicotinic end-plate. In this way prevents contraction, and relaxation of skeletal muscle occurs.**
- **NOTE: their action can be overcome by increasing concentration of acetylcholine in the synaptic gap by e.g. Neostigmine (this inhibits a choline esterase - enzyme that breaks down the Ach)**
- **At High dose :these drugs block ion channel of the end plate and leads to further weakening of the transmission ,and difficult to overcome by acetylcholinestrase inhibitors**

Pharmacokinetics:

- **Administered intravenouly (i.v and i.m)**
- **Cross blood brain barrier poorly (highly ionized)**
- **Tubocurarine, mivacurine and metocurine are not metabolized in liver ,their action is terminated by redistribution (spontaneous breakdown)**
- **يتم تكسيرهم تلقائياً.**
- **Excreted in urine unchanged**
- **Mivacurium is degraded by plasma cholinestrase rapidly ,it has *shortest* duration of action than others. (important)**

They differ in onset , duration and recovery

USES:

- As adjuncvant مساعده to general anesthetics during surgery especially intrabdominal ,and intrathorasic.

Adverse effects

(أهـــم شيء: *HISTAMINE RELEASE* which is responsible for bronchospasm & hypotension)

- **Bronchospam due to release of Histamine**
- **Hypotension due to ganglion block may also br due to histmaine release**
- **Tachycardia (by *pancuronium* *the only drug in this group causing tachycardia*) due to blockade of muscarinic receptors in heart**

  NB: stimulation of the muscarinic receptors leads to bradycardia

  Blockade of muscurinic receptors = Tachycardia

B. DEPOLARIZING NEUROMUSCULAR BLOCKERS

SUCCINYLECHOLINE: (important)

ياخذ مكان الاسيتايل كولين و يشتغل مثله و يفرق عنه انو ما يتكسر بسهوله زي الاستايل كولين

يتكسر بواسطة

Plasmacholineesterase while Ach breakdown by acetylcholinestrase

- **These drugs act like acetylcholine but persist at the synapse at higher concentration and for longer duration and constantly stimulate the receptor.**
- **first opening of the Na+ channel occurs resulting in depolarization,muscle twitching occurs , continued binding of drug make the receptor incapable of trasmitting the impulses.PARALYSIS OCCURS.**

Therapeutic uses:

يستخدم في العمليات البسيطه (القصيره) ، أماالعمليات الطويلة نستخدم لها المجموعة السابقة

- endotracheal intubation

Electroconvulsive shock therapy >> (used to prevent sever muscular contraction during electroconvulsive shock therapy .this procedure is used for depression treatment)

Pharmacokinetics

- Administered intravenously It can also be used in continuous infusions (due to rapid inactivation)
- its duration of action is 5-10 minutes (Short)
- In low doses it causes negative ionotropic and chronontropic effect and (bradycardia)
- In high doses positive ionotropic and chronotropic effect. (paradoxical effect: blocks muscurinic receptors = tachycardia)

-The last two points (doses) are considered adverse effects-

Adverse effects:

The adverse effect in high dose is opposite

- Bradycardia (common)preventable by (يعالج بـ) atropine
- Hyperkalemia in patients with trauma or burns this may cause dysrhythmia or even cardiac arrest. (contraindication)
- Increased intraocular pressure (important) due to contracture of of extra ocular muscles applying pressure to the eye ball.
- Increased intragastric pressure (important)
  which may lead to emesis (vomiting) and aspiration of gastric content
  يدخل في مجرى التنفس

- **Malignant hyperthermia (VERY important) due to a rare inherited condition probably caused by Ca++ release channel of sarcoplamic reticulum implicated by succinylecholine and treated by DANTROLENE**

2. Centrally Acting Drugs (Spasmolytic drugs)

- **Diazepam (act through GABA $_A$) receptors**
- **Baclofen (GABA $_B$) receptors**
- **NB: GABA are inhibitory neurotransmitters –in the CNS-**
- **These spasmolytic drugs do not resemble A.Choline in structure or effect.**
- **They act in CNS or in skeletal muscle cell**
- **spasticity is characterized by increase in tonic stretch reflexes and flexor muscle spasm, muscle tone is increase, it is often associated with cerebral palsy ,muscle sclerosis and stroke.**
- **DIAZEPAM:**

  In small dose :مهدئ sedative

  In high dose : منوم hypnotic

- **Fasilitates (potentiates)the GABA (Gap Amino Butirc Acid)receptors (transmitter) in CNS .It can be used in the patients with muscle spasm of almost any origin, including local muscle trauma.**
- **(important) It is a drug of choice to overcome and abolish if the convulsion are continuous and persistent such as in epilepsy (if there are continuous and persistent convulsions) called: status epilepticus تشنجات متتابعه وهي نوع من أنواع الصرع.**
- **BACLOFEN:**
- **It is structurally related to GABA and possess GABA agonist activity.**

- It causes hyperpolarization by increasing potassium conductance reducing calcium influx
- It reduces pain in patients with spasticity
- It is administered orally
- It has a half life of 3-4 hours

How to memorize in easier way :

Baclofen :

- - GABA agonist
- -inhibit release of excitatory transmitter
- Hyperpolarization (increase K^+ outflux) = muscle relaxation
- Reducing Ca influx

3. Directly Acting Drugs

- Dantroline (act directly by interfering release of calcium from sarcoplasmic reticulum)

DANTROLENE ⟺ treatment of Malignant Hyperthermia (VERY imp.)

- It acts directly on muscle by interfering with excitation – contraction coupling in the muscle fiber and prevents the release of calcium from sarcoplasmic reticulum .It is not useful in surgery
- Used in malignant hyperthermia (a rare heritable disorder triggered by volatile anesthetics and depolarizing neuromuscular blocker Succinylcholine.There is rise in temprature and massive muscle contraction due to impairment in ability of SR to sequester (to store back ،تحجز) calcium
- It can be administerd orally and parentrally
- Has a half life of 8-9 hours