Pharmacology Team

Lecture - 1
Muscles relaxation

Objectives :

- A brief review of NM junction and its function.
- Mechanism and purpose of its block.
- Drugs used for this block.
- Indications for these drugs.
- Their adverse effects.
- How to overcome the overdose effects.

Neuromuscular junction:

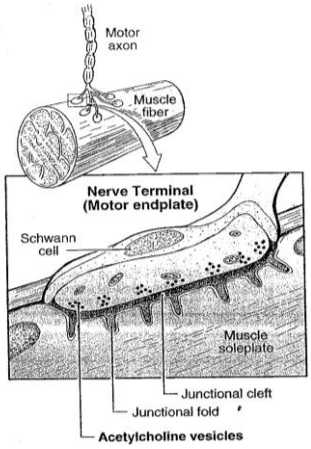
1: Cholinergic motor neuron,

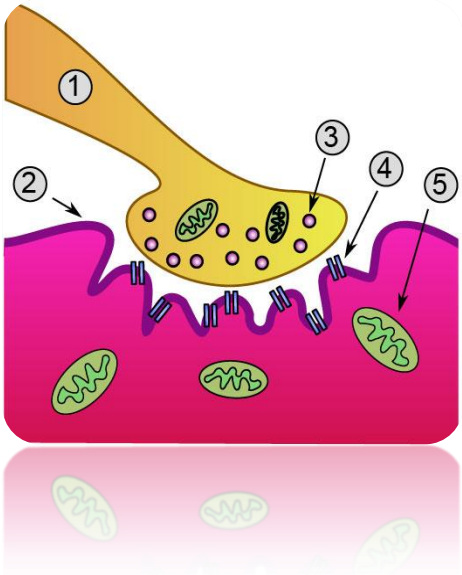
2: motor end-plate,

3: vesicles,

4: NMR (neuromuscular receptor)

5: mitochondrion





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

There are two types of Acetylcholine receptors (cholinergic receptors) :

1-Nicotinic acetylcholine receptors (nAChR) : present in skeletal muscles & ganglia

2-Muscarinic acetylcholine receptors (mAChR) : present in smooth & cardiac muscles

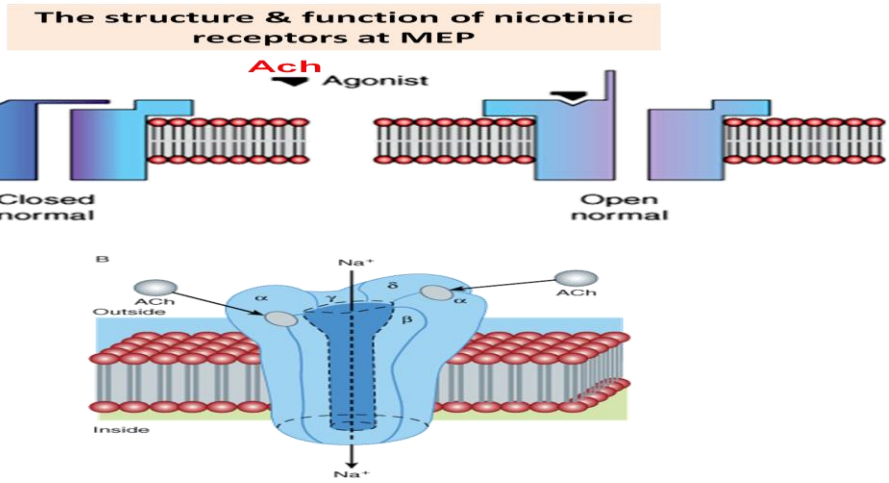
Neuromuscular transmission (in brief) :

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.

Normally , in a normal person there is a release of Acetylcholine , activity of contraction then acetylcholine is immediately inactivated by Acetylcholinesterase , muscle goes bac to resting state .

- Acetylcholinesterase : is an enzyme that degrades (breakdown) Acetylcholine , producing choline & acetate. Choline is reuptake again by nerve terminal to synthesize new acetylcholine.



Classification

Peripherally acting drugs	Centrally acting drugs	Direct acting drugs
inhibit neuron transmission to muscle by blocking the nicotinic Ach Rs.	acting Sk M relaxants (Baclofen – Diazepam); used in spasticity	acting Sk M relaxants (Dantrolene).

Drugs that inhibit ! neuromuscular transmission= neuromuscular blockers (NMBs):
interfere with transmission at ! NM end plate & lack CNS activity.
Because ! appropriate dose of NMB drug may paralyze muscles required for breathing (diaphragm), mechanical ventilation should be available to maintain adequate respiration.

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

- **Pre-synaptic:**

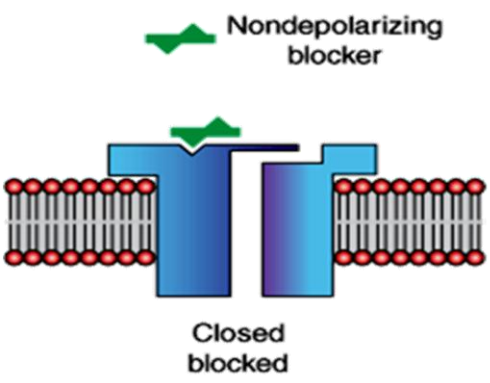
a) Inhibit acetylcholine synthesis : e.g Triethylcholine , Hemicholinium
b) Inhibit acetylcholine release : e.g.Aminoglycosides ,Botulinum toxin(BOTX)
tetrodotoxin are neurotoxins. (not clinically used as muscle relaxants)

- **Post-synaptic:**

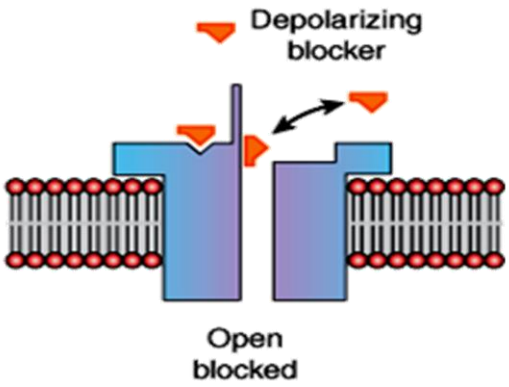
a) (competitive) Non-depolarizing blockers : Cholinergic antagonists (D-Tubocurarine, Gallamine, Atracurium, Mivacurium , Pencuronium, vecuronium, alcuronium)
b) Depolarizing blockers: Cholinergic agonists (Succinylcholine)

A) Competitive (non-depolarizing blockers) : they are Ach antagonist (competitive inhibitors) , they antagonize the Ach by blocking its receptors leading to muscle relaxation

B) Depolarizing blockers: they are Ach agonist , they bind to the Ach receptors and cause depolarization just like acetylcholine does . First , there will be severe contraction followed by paralysis because the muscle gets tired from too much depolarization



A nondepolarizing blocker, competes with Ach for the binding sites & prevents the opening of the channel



A depolarizing blocker occupies the receptor & blocks the channel. They even can desensitize the end plate by causing persistent depolarization.

A. Competitive (Non-Depolarizing) based on chemical nature :

ISOQUINOLINE DERIVATIEVES

1-Tubocurarine : the prototype of this group. It is a quaternary alkaloid.

2- Mivacurium (shortest duration immediately inactivated by plasma cholinesterase)

3- cisatracurium

4- Atracurium

5- Doxacurium

STEROID DERIVATIVES

1. Pancuronium
2. Vecuronium
3. Pipecuronium
4. Rocuronium

d-tubocurarine (extract) is isolated from Curare (Flexidil curare). have paralysing effect. D-tubocurarine can cause hypotension bec it blocks autonomic ganglia & causes histamine release.

A. Competitive (Non-Depolarizing) neuromuscular blockers :

- Mechanism of action :

- **At low doses (therapeutic dose)** : these drugs (non-depolarizing drugs) combine with nicotinic receptors and prevent acetylcholine binding, thus prevents depolarization at nicotinic end-plat .In this way contraction of skeletal muscles is inhibited.

Note that **:** their action at low doses can be overcome by increasing conc. of acetylcholine in the synaptic gap by e.g. Neostigmine cholinesterase inhibitors (No Cholinesterase)

- **At high doses** : these drugs block ion channel of the end plate and leads to further weakening of the transmission, and difficult to overcome by acetylcholinesterase inhibitors

-Pharmacokinetics :

1. Administered intravenously IV
2. Cross blood brain barrier poorly (Ionized) "have no effect on the brain" and doesn't cross palcenta.
3. Tubocurarine, mivacurine and metocurine are not metabolized in liver ,their action is terminated by redistribution.
4. Excreted in urine unchanged
5. Mivacurium is degraded by plasma cholinesterase rapidly ,it has shortest duration of action than others.
6. They differ in onset , duration and recovery. (the main difference)

- Uses of these drugs :

1. As adjuvant (كـ مساعد) to general anesthetics during surgery especially intrabdominal ,and intrathorasic.
2. Tracheal intubation (tube into the trachea) .
3. Control of ventilation (to reduce chest wall resistance)
4. Relieve of tetanus (prolonged contraction of skeletal muscle fibers) & epileptic convulsion.
5. Facilitate endoscopy.

- Adverse Effects :

1. Bronchospam due to release of Histamine
2. Hypotension due to ganglion block may also be due to histmaine release
3. Tachycardia (by pancuronium) due to blockade of muscarinic receptors in heart

Note that **:** The only drug in this group causing tachycardia is pancuronium

-Tachy : rapid , so tachycardia is heart is beating above normal due to blockade of muscarinic receptors
-brady : slow , so bradycardia is heart slowness due to stimulation of muscarinic receptors in the heart.

B. Depolarizing neuromuscular blockers :

- Succinylecholine
- These drugs act like acetylcholine but persist at the synapse at higher concentration and for longer duration and constantly stimulate the receptor.
- (there is inhibition of repolarization) and the receptor become insensitive

1-Plasma cholinesterase: degrades succinylecholine
2-acetylcholinestrase: degrades Acetylcholine

But 1 is much slower than 2 , so succinylecholine persist longer duration

- First opening of the Na+ channel occurs resulting in depolarization, muscle twitching occurs , continued binding of drug make the receptor incapable of transmitting the impulses. PARALYSIS OCCURS.

A good example of these drugs **:** is a friend comes to your home for the first time , you'll welcome him very warmly , next day he comes again , you'll welcome him again but not like the first time , and if he comes every day , you'll do nothing! **So drugs acts like acetylcholine there will be warm welcome " severe contraction " followed by " insensitive of the receptors "**

- Uses of these drugs :

1- When rapid endotracheal intubation (tube in trachea) is required.
2- Electroconvulsive shock therapy (used to prevent bone fracture)

- Pharmacokinetics :

1- Administered intravenously It can also be used in continuous infusions (due to rapid inactivation)
2- its duration of action is 5-10 minutes (Short)
3- In low doses it causes negative ionotropic and chronontropic effect and (bradycardia)
4- In high doses positive ionotropic and chronotropic effect may occur

- Adverse Effects :

1- **Bradycardia** : preventable (يعالج بـ) by atropine
2- **Hyperkalemia (release of K+) :** in patients with trauma or burns this may cause dysrhythmia or even cardiac arrest
3- **Increased intraocular pressure (in the eye) :** due to contracture of extra ocular muscles applying pressure to the eye ball.
4- **Increased intragastric pressure** which may lead to emesis and aspiration of gastric content.
5- **Muscle pain**
6- **Malignant hyperthemia:** due to a rare inherited condition probably caused by Ca++ release channel of sarcoplamic reticulum implicated by succinylcholine and treated by DANTROLENE (a direct acting muscle relaxant , as in the last page)

Drug	Speed of onset	Duration of action	Main side-effects	Notes
Tubocurarine	Slow (>5 min)	Long (1–2 h)	Hypotension (ganglion block plus histamine release) Bronchoconstriction (histamine release)	Plant alkaloid, now rarely used **Alcuronium** is a semisynthetic derivative with similar properties but fewer side-effects
Gallamine	Slow	Long	Tachycardia (muscarinic antagonist)	100% renal excretion; therefore, to be avoided in patients with poor renal function The first synthetic alternative to tubocurarine, now rarely used
Pancuronium	Intermediate (2–3 min)	Long	Slight tachycardia. No hypotension	The first steroid-based compound. Better side-effect profile than tubocurarine. Widely used **Pipecuronium** is similar
Vecuronium	Intermediate	Intermediate (30–40 min)	Few side-effects	Widely used. Occasionally causes prolonged paralysis, probably owing to active metaboli **Rocuronium** is similar, with faster onset
Atracurium	Intermediate	Intermediate (<30 min)	Transient hypotension (histamine release)	Unusual mechanism of elimination (spontaneous non-enzymic chemical degradation in plasma). Degradation slowed by acidosis Widely used **Doxacurium** is chemically similar but stable in plasma, giving it long duration of action **Cisatracurium** is the pure isomeric constituent of atracurium, similar but with
Mivacurium	Fast (~2 min)	Short (~15 min)	Transient hypotension (histamine release)	New drug, chemically similar to atracurium but rapidly inactivated by plasma cholinesterase (therefore, longer acting in patients with liver disease or with genetic cholinesterase deficiency (see p. 153)
Suxamethonium	Fast	Short (~10 min)	Bradycardia (muscarinic agonist effect) Cardiac dysrhythmias (increased plasma K^+ concentration—avoid in patients with burns or severe trauma) Raised intraocular pressure (nicotinic agonist effect on extraocular muscles) Postoperative muscle pain	Acts by depolarisation of endplate (nicotinic agonist effect)—the only drug of this type still in use Paralysis is preceded by transient muscle fasciculations Short duration of action owing to hydrolysis by plasma cholinesterase (prolonged action in patients with liver disease or genetic deficiency of plasma cholinesterase) Used for brief procedures (e.g. tracheal intubation, electroconvulsive shock therapy). Rocuronium has similar speed of onset and recovery with fewer unwanted effects

Drug drug interaction (**DDI**):

- Anesthetics: Inhaled anesthetics (isoflurane, sevoflurane) potentiate NM blockade produced by nondepolarizing muscle relaxants.
- Enhancement of NM blockade by antibiotics (aminoglycosides).

2. **Centrally acting drugs (Splasmolytic drugs):**

- These spasmolytic drugs do not resemble Acetylcholine in structure or effect
- Usually for diseases.
- Decrease the depolarization -> decrease the spasticity.
- They act in CNS or in skeletal muscle cell and used to overcome the spasticity.
- 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 :-

1- Facilitates the GABA (Gap Amino Butirc Acid) receptors in CNS .It can be used in the patients with muscle spasm of almost any origin, including local muscle trauma.
2- 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 في حالة الصرع).

- **Baclofen** :-

1- It is structurally related to GABA and possess $GABA_b$ agonist activity
2- It causes hyperpolarization by increasing potassium conductance reducing calcium influx (k^+ outflux = muscle relax)
3- It reduces pain in patients with spasticity
4- It is administered orally
5- It has a half life of 3-4 hours

3. **Direct acting drugs :**

- **Dantrolene :-**

- 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 temperature and massive muscle contraction due to impairment in ability of SR to sequester calcium.
- It can be administered orally and parentrally.
- Has a half life of 8-9 hours.