PASSION ACADEMIC TEAM YU - MEDICINE

MUSCULOSKELETAL SYSTEM

Sheet#1 - Pharmacology

Lec. Title : Muscle Relaxants

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Muscle relaxants

- **neuromuscular blocking agents,** they possess some **chemical similarities to (ACh).**

1 An action potential in a motor neuron is propagated to the axon terminal (terminal button).

2 This local action potential triggers the opening of voltage-gated Ca^{2+} channels and the subsequent entry of Ca^{2+} into the terminal button.

3 Ca^{2+} triggers the release of acetylcholine (ACh) by exocytosis from a portion of the vesicles.

4 ACh diffuses across the space separating the nerve and muscle cells and binds with receptor-channels specific for it on the motor end plate of the muscle cell membrane.

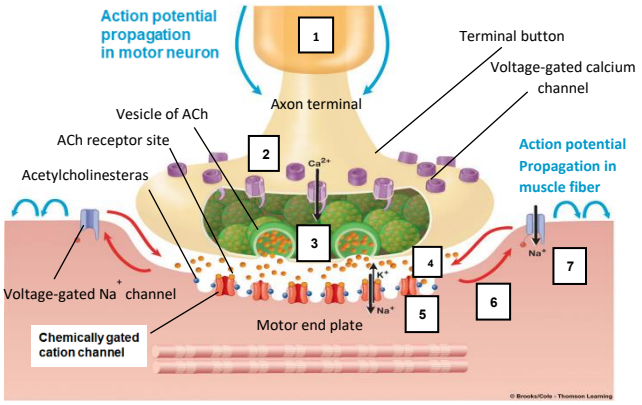
5 This binding brings about the opening of these nonspecific cation channels, leading to a relatively large movement of Na^+ into the muscle cell compared to a smaller movement of K^+ outward.

6 The result is an end-plate potential. Local current flow occurs between the depolarized end plate and the adjacent membrane.

7 This local current flow opens voltage-gated Na^+ channels in the adjacent membrane.

8 The resultant Na^+ entry reduces the potential to threshold, initiating an action potential, which is propagated throughout the muscle fiber.

9 ACh is subsequently destroyed by acetylcholinesterase, an enzyme located on the motor end-plate membrane, terminating the muscle cell's response.



- **Uses:** (adjacent to anesthesia)
  1- facilitate tracheal intubation (tube inside trachea to start mechanical ventilation in abdominal surgeries, respiratory failure? preferable to relax laryngeal and jaw muscles during process)
  2- provide complete muscle relaxation at lower anesthetic doses (the aim is to reduce side effects)
  a- allow for more rapid recovery from anesthesia (in ICU)
  b- reduce postoperative respiratory depression (respi. Dep. happened at high anesthetic doses)

- They are 2 classes:
  1- Nondepolarizing blockers (competitive with ACh receptors)**, remember _cur_**
  2- Depolarizing agents (one agent)**, Succinylcholine**

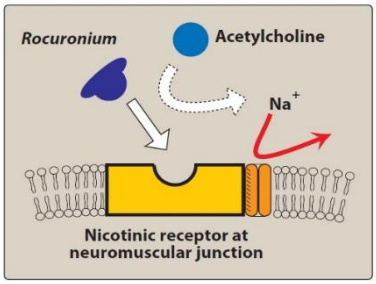
Neuromuscular blockers should not be used to substitute for inadequate depth of anesthesia.????

Neuromuscular blockers just cause muscle paralysis & have no effect as analgesic nor effect in consciousness (no sedation)>>> they aren't enough for surgeries (dr. mentioned an extremely interesting rare syndrome called Lockdin syndrome, you can google it), just know that **(for surgeries, patients have to be in a deep analgesia & anesthesia)**

I) Nondepolarizing (competitive) blockers:

- ***Curare*** was the first drug known to block the skeletal NMJ >>>> **Tubocurarine** was developed, but showed a **high incidence of side effects** >>> Replaced **by other agents with fewer adverse effects**, such as: **cisatracurium, pancuronium, rocuronium, vecuronium**

1) At low doses:



- ***MOA:***

a. they **compete with Ach** at the receptor **without stimulating it.**
b. **prevent the depolarization** of the muscle cell membrane and **inhibit muscular contraction**.

- ***Controlling:***

a. Neuromuscular blockers can be **overcome by administration of cholinesterase inhibitors**, such as ***neostigmine*** and ***edrophonium***.
b. Decrease the degradation of Ach & **increase the of ACh** in the neuromuscular junction. (In the competitive action the agent with higher dose will exert its effect)
c. At low doses, the muscle will respond to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, allowing for monitoring of the extent of neuromuscular blockade. To know how, check the note, page5

2) At high doses:

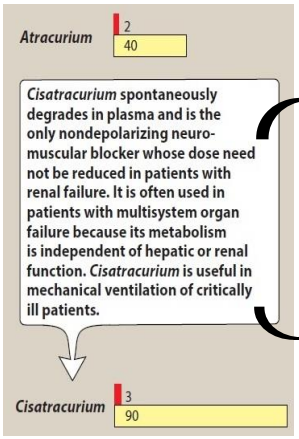
- ***MOA:***

a. **block the ion channels** of the motor endplate (no Na^+, K^+ movement)
b. **further weakening** of neuromuscular transmission
c. muscles have **different sensitivities** …order of muscles' response:
   1) small, rapidly contracting muscles of the face
   2) fingers, limbs, neck, and trunk muscles
   3) intercostal muscles
   4) diaphragm
d. The muscles recover in the reverse manner.

- ***Controlling:***

a. thereby **reducing the ability of cholinesterase inhibitors to reverse the actions** of the nondepolarizing blocker
b. With complete blockade, **the muscle does not respond to direct electrical stimulation.**
c. Many of the drugs **are not metabolized**, and their **actions are terminated by redistribution.**
d. The choice of an agent **depends on** the desired **onset and duration** of the muscle relaxation

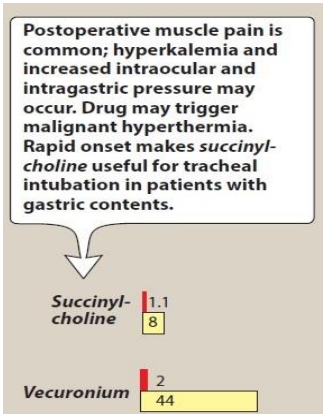
- ***Pharmacokinetics: (at high/low doses)***
    a. are not absorbed from the gut, **why?** They contain two or more quaternary amines (**polar**)
    b. Administered by **IV or occasionally IM**, not orally

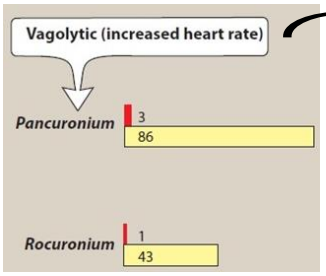


Cisatracurium is more potent & less side effect

-Used in ICU, for patient in mechanical ventilation.

- (not all patient), (used with analgesics)





It's a nicotinic receptor antagonist have some muscarinic activity

Very rapid effect(paralysis), used in tracheal intubation

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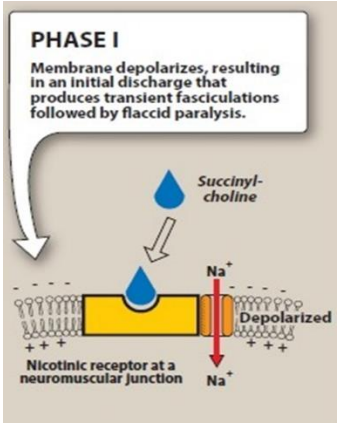
- ***Side effects:***
    a. **Atracurium releases histamine** (allergic reactions).
    b. and is **metabolized to laudanosine**, which can **provoke seizures** .
    c. Cisatracurium has the same pharmacokinetic properties as atracurium, but is less likely to have these effects.
- ***Drug interactions:***
    a. **Cholinesterase inhibitors**: (neo**stigmine**, physo**stigmine**, pyrido**stigmine**, and **edrophonium)**: overcome the action of nondepolarizing neuromuscular blockers (at low dose as we discussed).
    b. **Halogenated hydrocarbon anesthetics**: (*desflurane): they **sensitize the NMJ** to the effects of neuromuscular blockers* **by exerting a stabilizing their action**.
    c. **Aminoglycosides:** (Abs such as gentamicin & tobramycin): **inhibit ACh release** from cholinergic nerves **by competing with calcium ions**, enhancing the blockade (**Synergistic effect**).
    d. Calcium channel blockers: increase the neuromuscular blockade

II) Depolarizing agents

- **Succinylcholine, work as ACh** by depolarizing the plasma membrane of the muscle fiber, more persistently depolarize the muscle fibers
- It's **more resistant to** degradation by **acetylcholinesterase (AChE)**
- **MOA:**
    - **Phase I:**
        a. causes the **opening** of the **sodium channel** associated with the nicotinic receptors.

        (depolarization of the receptor)

        b. transient twitching of the muscle (**fasciculations**, very small contraction)
        c. Continued binding of the depolarizing agent **renders the receptor incapable of transmitting further impulses**



    - **Phase II:**
        a. **resistance to depolarization** and **flaccid paralysis** (العضلات غير مرتخية), as the sodium channel closes/blocked (**desensitized**, due to prolong depo in phase I).
        b. unlike Ach, it **persists at high concentrations** in the synaptic cleft, remaining **attached to the receptor** for **longer** & providing constant stimulation. (it's more resistant to Ach)
    - duration of action dependent on **diffusion from the motor endplate** and **hydrolysis by plasma pseudocholinesterase** (not AChE)
    - **Genetic variants** (in which plasma pseudocholinesterase levels are low or absent) lead to **prolonged neuromuscular paralysis**
    - the **respiratory muscles** are **paralyzed last**.
    - Muscle fasciculations may cause muscle soreness .Prevented by administering a **small dose of nondepolarizing neuromuscular blocker** prior to it.
    - Onset of action is rapid (less than 1 minute after IV administration), and with single administration lasts approximately 4 to 6 minutes (due to **pseudocholinesterase)**
- ***Uses:***
    a. **rapid endotracheal intubation** is required during the **induction of anesthesia**
    b. **Its rapid action** is essential **if aspiration of gastric contents is to be avoided** during intubation
    c. during **electroconvulsive shock** treatment.

- ***Pharmacokinetics:***

  As we said, it has a brief duration of action, therefore, sometimes given by **continuous infusion** to **maintain a longer duration of effect**. (Drug effects rapidly disappear upon discontinuation)

- ***Side effects:***
  a. **Hyperthermia**: and malignant hyperthermia in susceptible patients
  b. **Hyperkalemia:** increases potassium release from intracellular stores, dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost from within cells
  c. **Apnea:**
     1. patient who is **deficient in plasma cholinesterase or has an atypical form of the enzyme >due to paralysis of the diaphragm**
     2. patients with **electrolyte imbalances >rapid release of potassium may also contribute to prolonged apnea**
     3. In patients with electrolyte imbalances who **are also receiving digoxin or diuretics (such as heart failure patients) succinylcholine should be used cautiously or not at all.**

Note: Used to make sure how muscle respond in these stimuli ..(if it's partially or complete paralysis),we make 4 stimulation in a specific rhythm and then monitor how many time the cell is responding to the stimuli

if complete blocking of the muscle [zero out of four]

if no paralysis [four out of four]

use it to titrate neuromuscular agent doses, must be [1- 2 out of 4]

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