Al-Mustaqbal University

Pharmacology I

3rd stage

Cholinergic Antagonists (60-70)

Dr. Hasanain Owadh

Cholinergic Antagonists

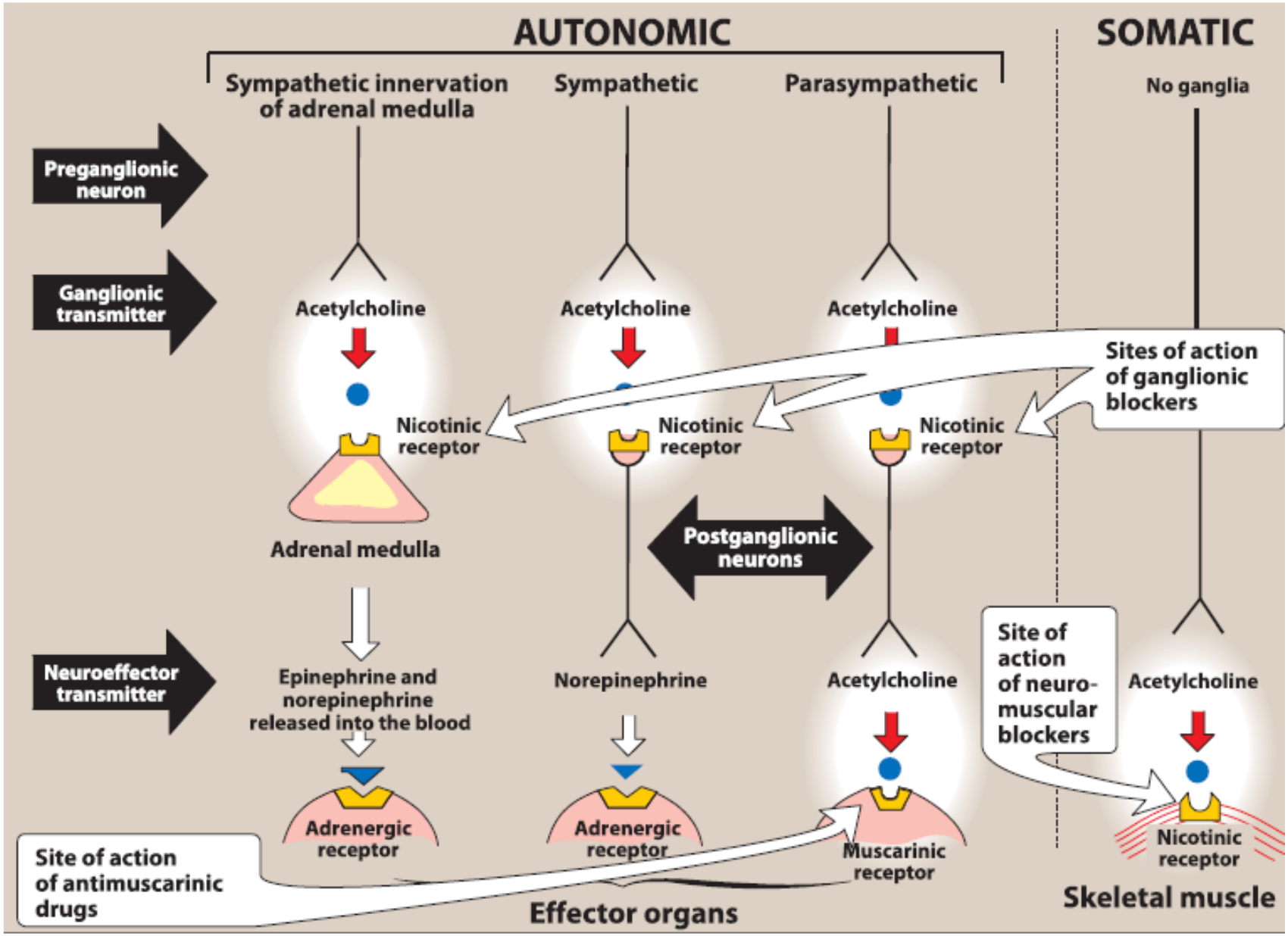
also called cholinergic blockers, or anticholinergic drugs.

• **Cholinergic antagonist is a general term for agents that bind to cho linoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.**

1- The most clinically useful of these agents are **selective blockers of muscarinic receptors (antimuscarinic drugs or** parasympatholytics).

2- A second group of drugs, the **ganglionic blockers**, shows a preference for the **nicotinic receptors** of the **sympathetic and parasympathetic ganglia**. Clinically, **they are the least important of the cholinergic antagonists.**

• 3- A third family of compounds, the **neuromuscular-blocking agents (mostly nicotinic antagonists)**, interfere with transmission of efferent impulses to skeletal muscles. **These agents are used as skeletal muscle relaxant adjuvants in anesthesia during surgery and ICU.**



Antimuscarinic Agents

Commonly known as **anticholinergic drugs**, these agents (for example, ***atropine and scopolamine***) **block muscarinic receptors ,causing inhibition of muscarinic functions. Because they do not block nicotinic receptors, these drugs have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia.**

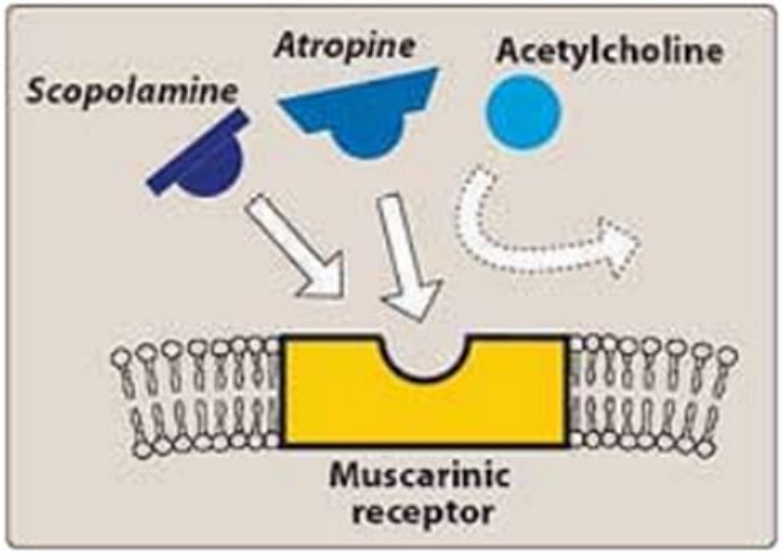
I- Atropine

Atropine is a **belladonna alkaloid**, has a high affinity for muscarinic receptors, where it binds competitively, preventing acetylcholine from binding to those sites.

Atropine acts both centrally and peripherally. Its general actions last about 4 hours except when placed topically in the eye, where the action may last for days.

Actions:

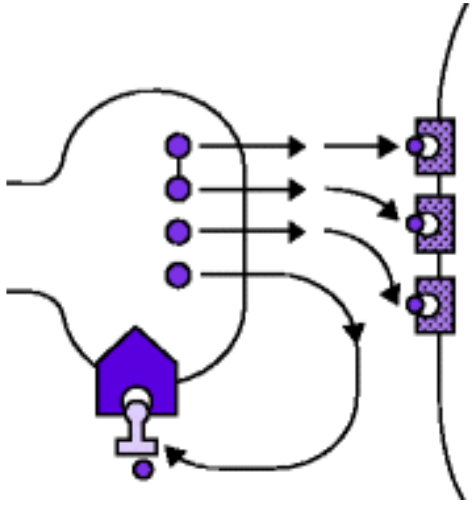
Eye: mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision). **It is contraindicated in patients with narrow-angle glaucoma**, intraocular pressure may rise dangerously.



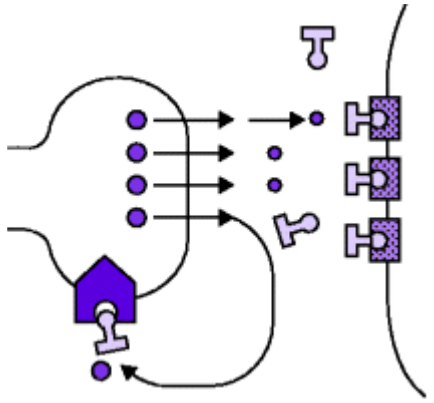
Gastrointestinal (GI): Atropine can be used as an antispasmodic to reduce activity of the GI tract. Atropine and scopolamine are probably the most potent drugs available that produce this effect. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, atropine is not effective for the treatment of peptic ulcer.

Cardiovascular: At low doses of atropine (0.5mg), the predominant effect is a decreased cardiac rate (bradycardia) results from blockade of the M1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased acetylcholine release.

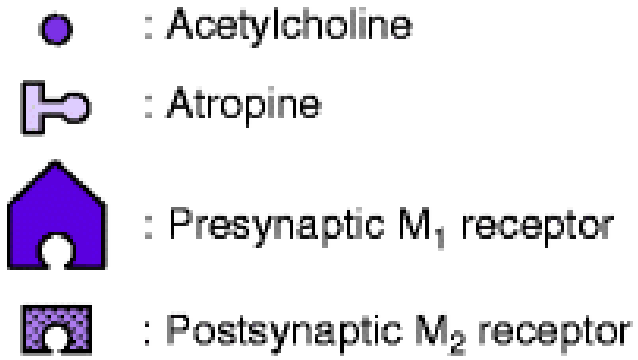
With higher doses of atropine (5mg), the M2 receptors on the sinoatrial node are blocked, and the cardiac rate increases modestly. Arterial blood pressure is unaffected.



Low dose



High dose

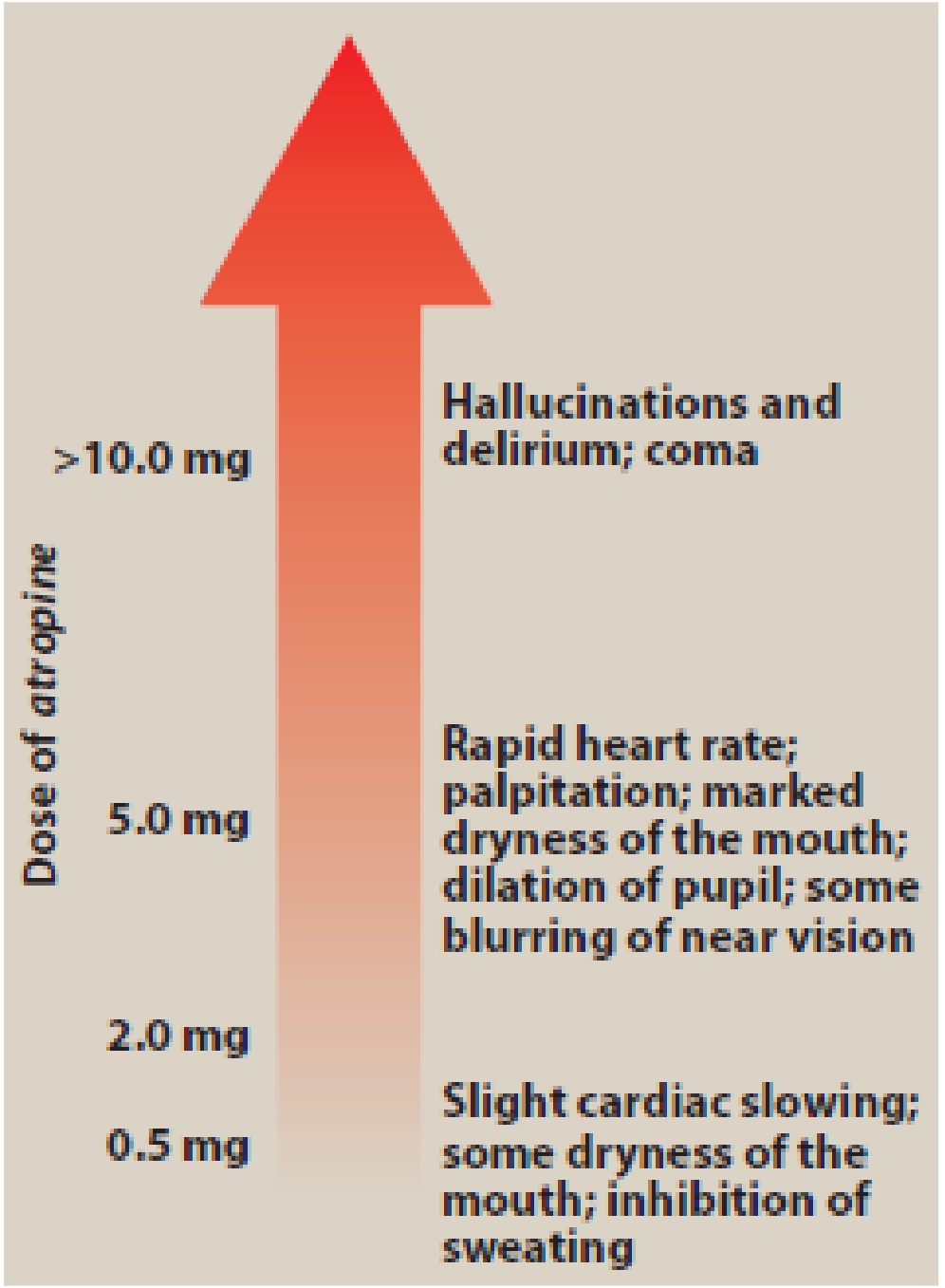


Urinary system: Atropine is also employed to reduce hypermotility states of the urinary bladder. It is still occasionally used in enuresis (involuntary voiding of urine) among children.

Secretions: Atropine blocks the **salivary glands**, producing a dry mouth (xerostomia). **Sweat** and **lacrimal** glands are also affected. [Note: Inhibition of secretions by sweat glands can cause elevated body temperature.]

Note: The greatest inhibitory effects are on bronchial tissue and the secretion of sweat and saliva and the heart

Dose-dependent effects of atropine.



Therapeutic uses:

1- Ophthalmic: In the eye, topical atropine exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors the eye. Shorter-acting antimuscarinics (cyclopentolate and tropicamide) have largely replaced atropine due to prolonged mydriasis observed with atropine (7-14 days versus 6-24 hours with other agents).

2- Antispasmodic: Atropine is used as an antispasmodic agent to relax the GI tract and bladder.

3- Antidote for cholinergic agonists: large dose of atropine is used for the treatment of overdoses of cholinesterase inhibitor (Physostigmine, organophosphate) peripheral and CNS toxicity.

4- Antisecretory: The drug is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

5- Cardiovascular: The drug is used to treat bradycardia of varying etiologies.

Pharmacokinetics: Atropine is readily absorbed, partially metabolized by the liver, and eliminated primarily in the urine.

Adverse effects: Depending on the dose, atropine may cause dry mouth, blurred vision, tachycardia, and constipation.

Effects on the CNS include restlessness, confusion, hallucinations, and delirium which may progress to depression, collapse of the circulatory and respiratory systems, and death.

II. Scopolamine

Scopolamine produces peripheral and central effects (unlike with atropine, CNS effects are observed at therapeutic doses) and a longer duration of action in comparison to those of atropine.

Actions:

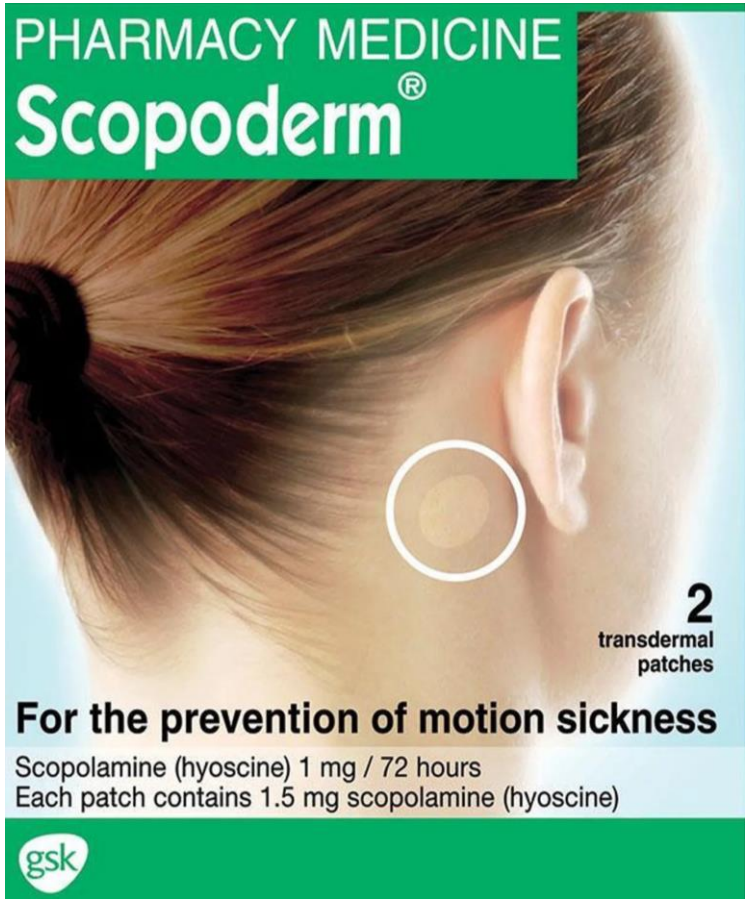
- Bblocking short-term memory makes it an important adjunct drug in anesthetic procedures.
- Scopolamine produces sedation, but at higher doses, it can produce excitement.
- Scopolamine may produce euphoria and is susceptible to abuse.

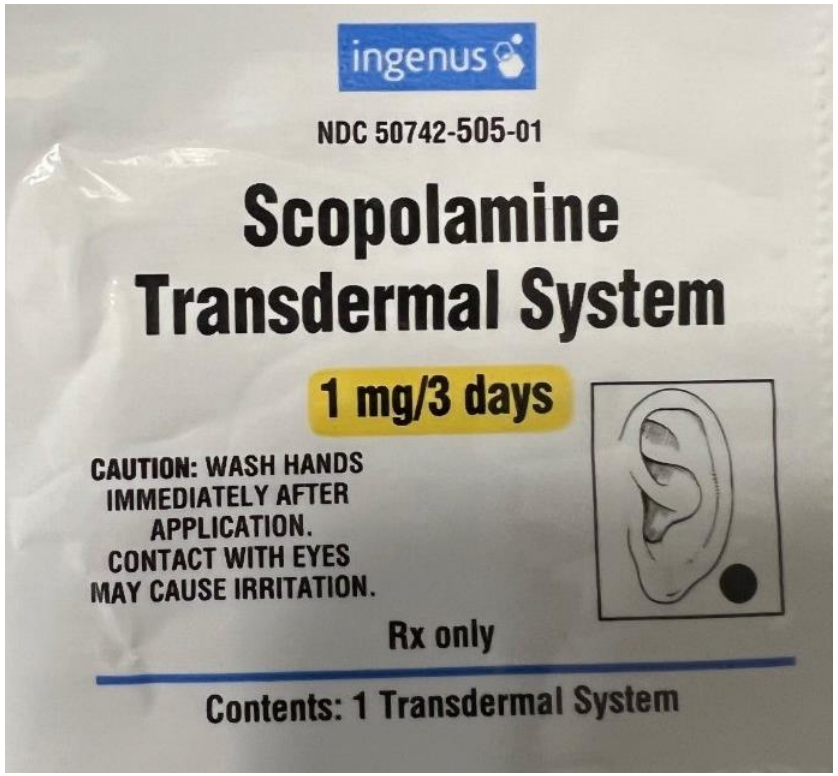
Pharmacokinetics and adverse effects: These aspects are similar to those of atropine.

Therapeutic uses:

- prevention of motion sickness and postoperative nausea and vomiting.

- For motion sickness, it is available as a topical patch that provides effects for up to 3 days.





III- Aclidinium, glycopyrrolate, Ipratropium and tiotropium

- Ipratropium (atropine derivative) is classified as a short-acting muscarinic antagonist (SAMA)

- Glycopyrrolate, tiotropium (atropine derivative) , and aclidinium are classified as long-acting muscarinic antagonists (LAMAs)

SAMA & LAMAs are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

Ipratropium is used in the acute management of bronchospasm in asthma.
Tiotropium is used in the chronic management of asthma.
Because of the positive charge, these drugs do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system.

All of these agents are delivered via inhalation.

IV. Tropicamide and cyclopentolate

These agents are used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of *atropine*.

Tropicamide produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.

V. Benztropine and trihexyphenidyl

Benztropine and trihexyphenidyl are useful as adjuncts with other antiparkinsonian agents to treat Parkinson's disease and other types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms.

VI. Oxybutynin and other antimuscarinic agents for overactive bladder:

Oxybutynin, darifenacin, fesoterodine, solifenacin, tolterodine, and trospium are synthetic atropine-like drugs with antimuscarinic actions.

1. Actions

By competitively blocking muscarinic (M3) receptors in the bladder, cause decreasing pressure and increasing capacity of bladder.

Antimuscarinic actions at M3 receptors in the GI tract, salivary glands, CNS, and eye may cause adverse effects.

Darifenacin and solifenacin are relatively more selective M3 antagonists
Oxybutynin, fesoterodine, tolterodine, and trospium have M3 and other muscarinic antagonists

VI. Oxybutynin and other antimuscarinic agents for overactive bladder:

2- Therapeutic uses

These agents are used for management of overactive bladder and urinary incontinence. *Oxybutynin* is also used in patients with neurogenic bladder.

3. Pharmacokinetics

- oral dosage forms.

"Oxybutynin is also available in a transdermal patch and topical gel formulation".

- long half-life,
- once-daily administration. [Note: Immediate-release *oxybutynin* and *tolterodine* must be dosed two or more times daily].

These drugs are hepatically metabolized by CYP 3A4 and 2D6,

with the exception of *trospium*, which is thought to undergo ester hydrolysis.

4. Adverse effects

- Dry mouth,
- Constipation, and
- Blurred vision, which limit tolerability of these agents.

Extended-release formulations and the transdermal patch have a lower incidence of adverse effects and may be better tolerated.

Trospium is a quaternary compound that minimally crosses the blood–brain barrier and has fewer CNS effects than do other agents, making it a preferred choice in treating overactive bladder in patients with dementia

Which of the following is preferred in treating overactive bladder in patients with dementia:

a- Tolterodine
b- Oxybutynin
c- Darifenacin
d- Trospium
e- Solifenacin

All the following are metabolized by CYP 3A4 and 2D6, except:

a- Tolterodine
b- Oxybutynin
c- Darifenacin
d- Trospium
e- Solifenacin

Q- A 50-year-old male who is noncompliant with medications was recently diagnosed with chronic obstructive pulmonary disease (COPD). His physician would like to prescribe an inhaled anticholinergic that is dosed once or twice daily. Which drug is most appropriate for this patient?

A. Atropine

B. Ipratropium

C. Tiotropium

D. Trospium

Ganglionic Blockers

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.

These drugs show no selectivity toward the parasympathetic or sympathetic ganglia, so responses observed are complex and unpredictable, making it impossible to achieve selective actions. Therefore, ganglionic blockade is rarely used therapeutically.

but often serves as a tool in experimental pharmacology.

A.Nicotine

- A component of cigarette smoke, nicotine is a poison with many undesirable actions. Depending on the dose, nicotine depolarizes autonomic ganglia, **resulting first in stimulation and then in paralysis of all ganglia.**

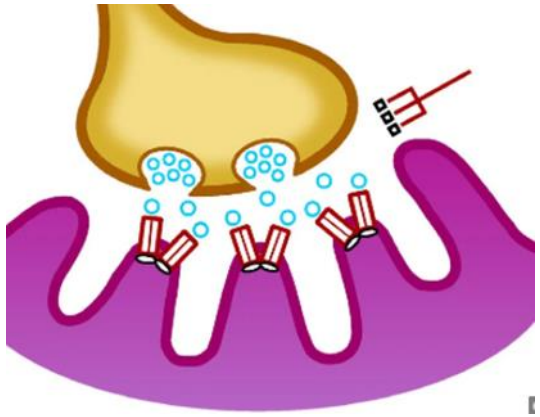
- The stimulatory effects are complex due to effects on both sympathetic and parasympathetic ganglia. **The effects include increased blood pressure and cardiac rate** (**due to release of transmitter from adrenergic terminals and from the adrenal medulla**) **and increased peristalsis and secretions.**
- At higher doses, the blood pressure falls because of ganglionic blockade, and activity both in the GI tract and bladder musculature ceases.

Neuromuscular Blocking Drugs

These drugs **block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular end plate of skeletal muscle**.

These neuromuscular blockers are structural analogs of acetylcholine, and they act either **as antagonists** (**nondepolarizing type**) or **agonists** (**depolarizing type**) at the receptors on the end plate of the neuromuscular junction.

Neuromuscular blockers are clinically useful during surgery for producing complete muscle relaxation, at lower anesthetic doses , also useful in facilitating intubation as well in the intensive care unit (ICU).



Cisatracurium, (via Hofmann elimination).
Mivacurium (by plasma AchE).
Pancuronium (unchanged in urimn).
Vecuronium (liver and excreted in bile).

A.Nondepolarizing (competitive) blockers

The first drug that was found to be capable of blocking the skeletal neuromuscular junction NMJ was **curare (Amazon hunters used to paralyze prey).**

The neuromuscular blocking agents have significantly increased the safety of anesthesia, because less anesthetic is required to produce muscle relaxation, allowing patients to recover quickly and completely after surgery.

Mechanism of action:

At low doses: Nondepolarizing neuromuscular blocking drugs competitively block ACh at the nicotinic receptors. These drugs thus prevent depolarization of the muscle cell membrane and inhibit muscular contraction. Their competitive action can be overcome by increasing the concentration of acetylcholine in the synaptic gap for example, by administration of cholinesterase inhibitors, such as neostigmine, or pyridostigmine.

At high doses: Nondepolarizing blockers can block the ion channels of the end plate. This leads to further weakening of neuromuscular transmission, and it reduces the ability of acetylcholinesterase inhibitors to reverse the actions of nondepolarizing muscle relaxants.

Therapeutic uses:

As adjuvant drugs in anesthesia during surgery to relax skeletal muscle.

2. Actions:

face and eye muscles are paralyzed first.
followed by the fingers, limbs, neck, and trunk muscles.
Next, the intercostal muscles are affected and,
lastly, the diaphragm.

The muscles recover in the reverse manner.

Note: Sugammadex is a selective relaxant binding agent that terminates the action of both rocuronium and vecuronium and can be used to speed recovery

Q- An ICU patient with severe lung injury requires a neuromuscular blocking agent to assist in his ventilator management. He has liver disease and is currently in renal failure. Which neuromuscular blocker is the best choice for this patient?

A. Cisatracurium

B. Pancuronium

C. Vecuronium

D. Rocuronium

Pharmacokinetics:

All NMBs are injected intravenously or occasionally intramuscularly. These agents penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier.

Pancuronium is excreted unchanged in urine.

Cisatracurium undergoes organ-independent metabolism (via Hofmann elimination) to laudanosine (which can provoke seizures.), which is further metabolized and renally excreted.

The amino steroid drugs vecuronium and rocuronium are deacetylated in the liver and excreted unchanged in bile.

Mivacurium is eliminated by plasma cholinesterase.

Drug interactions:

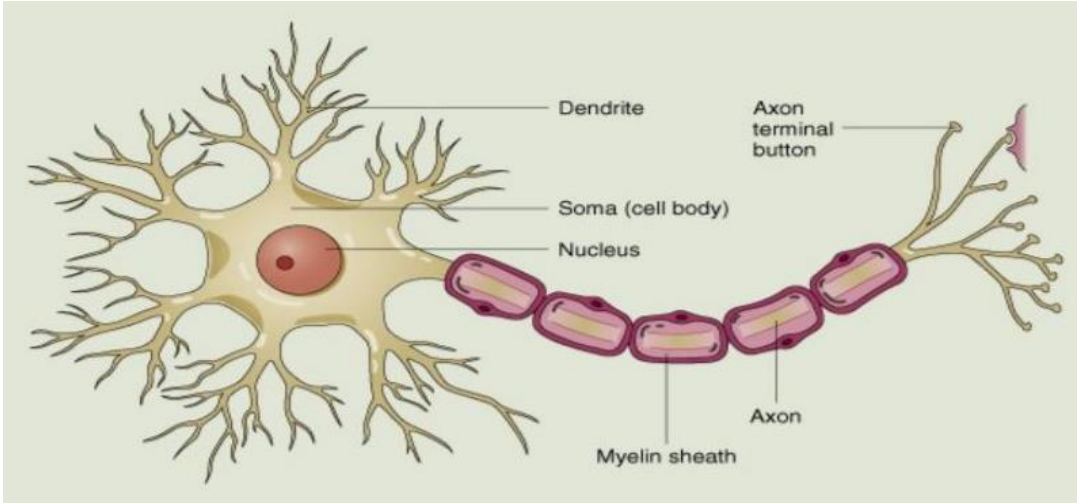
a. Cholinesterase inhibitors (e.g. *neostigmine)* **:** can overcome the action of nondepolarizing neuromuscular blockers.

However, with increased dosage, cholinesterase inhibitors can cause a depolarizing block as a result of elevated ACh concentrations at the endplate membrane. If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.

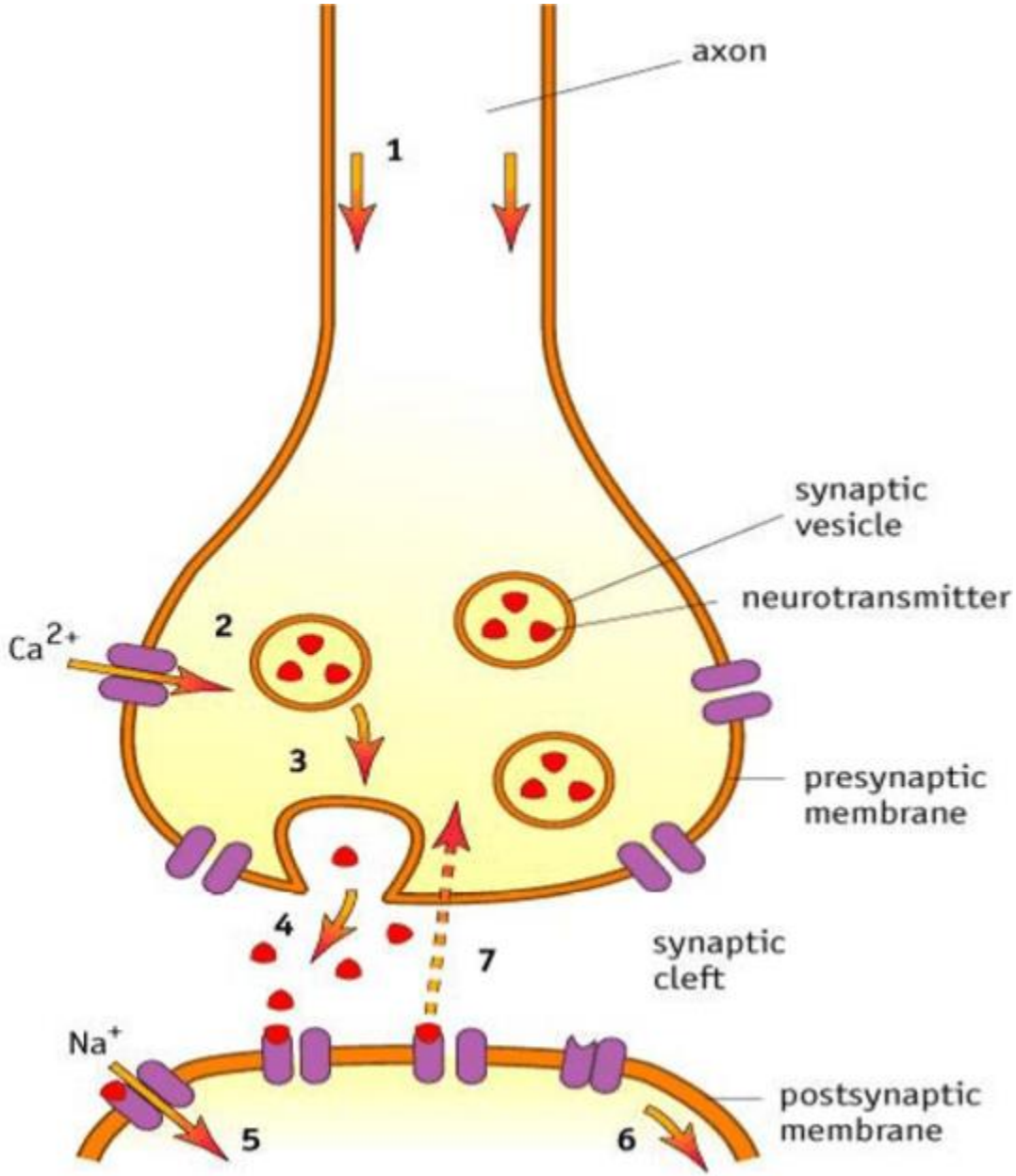
b. Halogenated hydrocarbon anesthetics (*desflurane)* **:** enhance neuromuscular blockade.

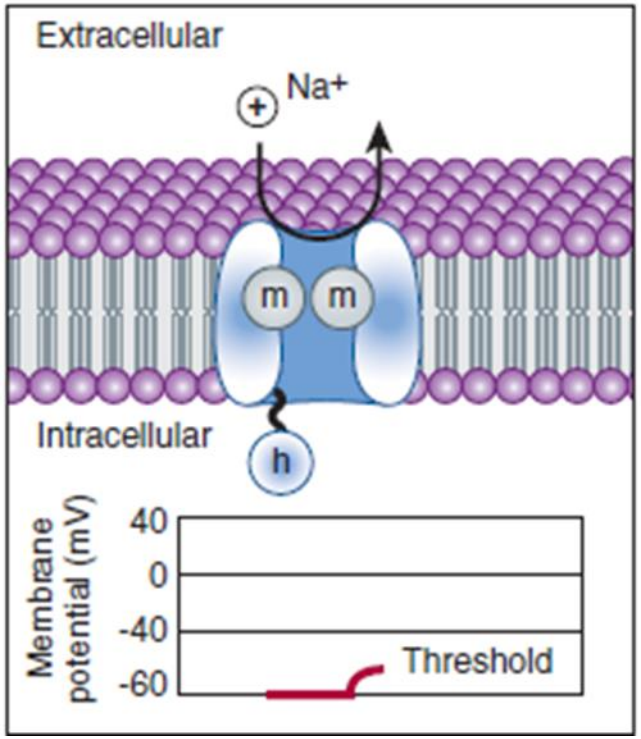
c. Aminoglycoside antibiotics: Drugs such as *gentamicin* and *tobramycin* inhibit Ach release from cholinergic nerves by competing with calcium ions. enhancing the blockade.

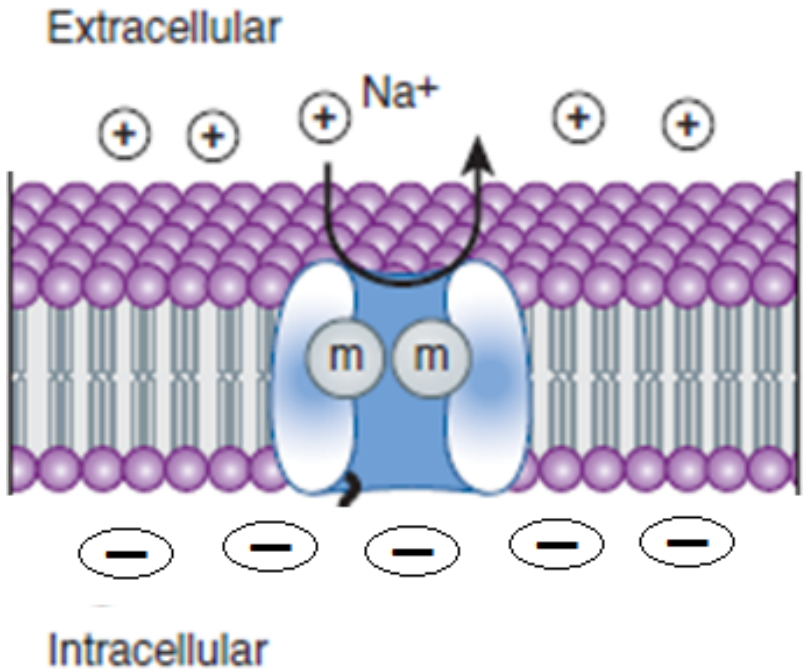
d. Calcium channel blockers: These agents may increase the neuromuscular blockade of competitive blockers.



SYNAPTIC CLEFT
AND
ACTION POTENTIAL

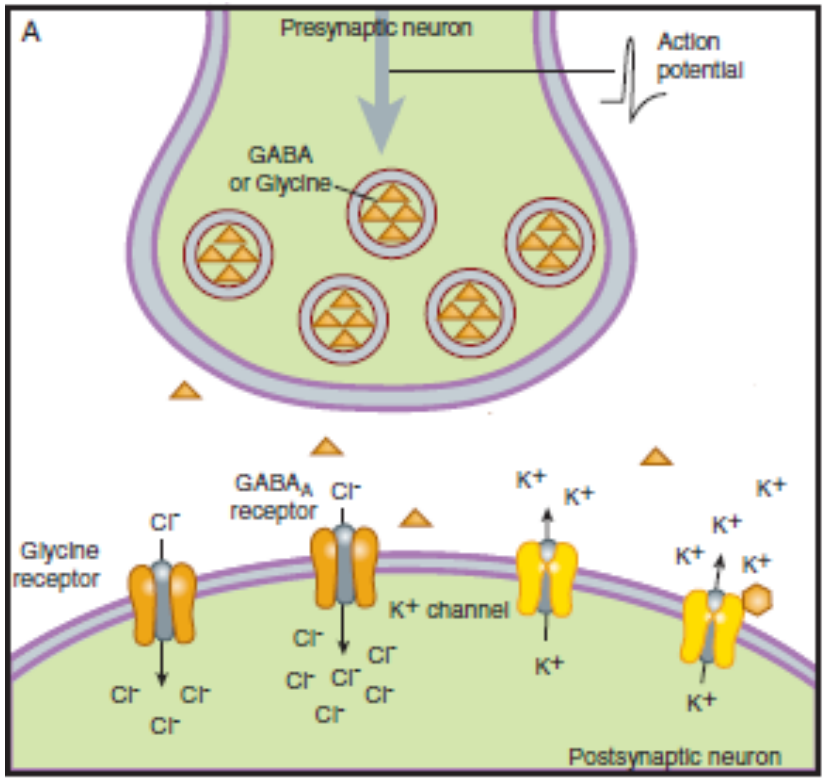




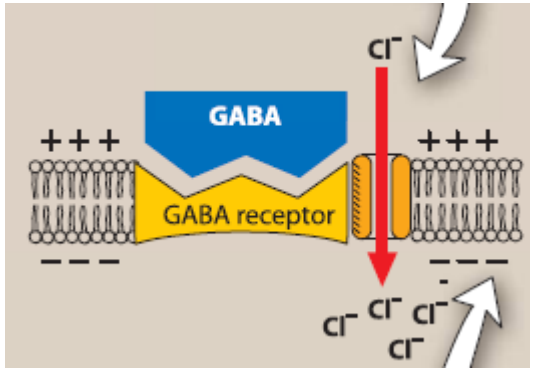


polarized cell membrane

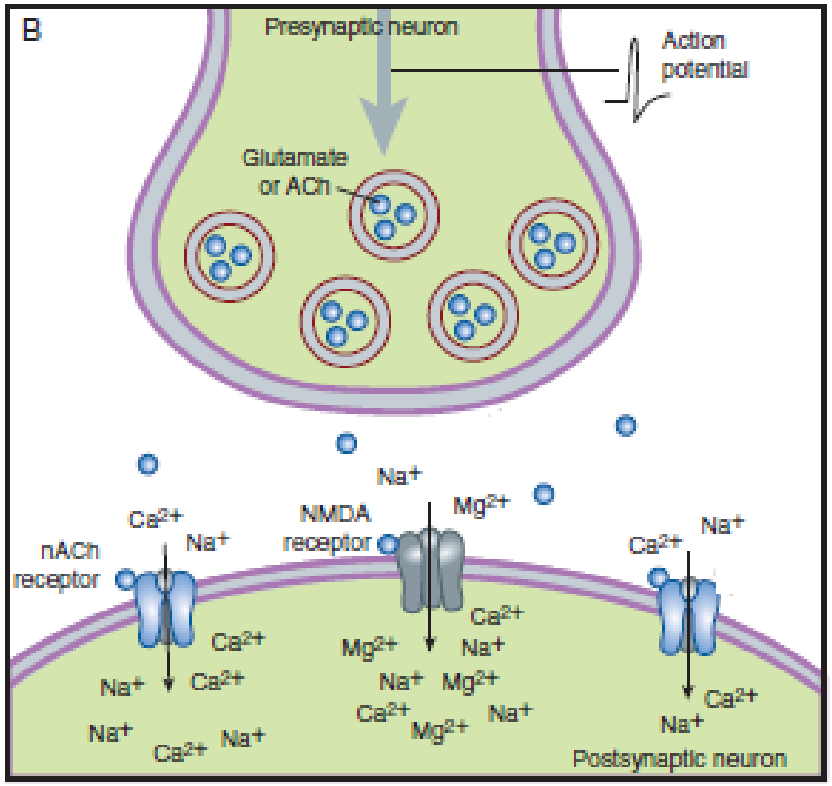
Resting membrane potential



Inhibitory postsynaptic potentials (IPSP)

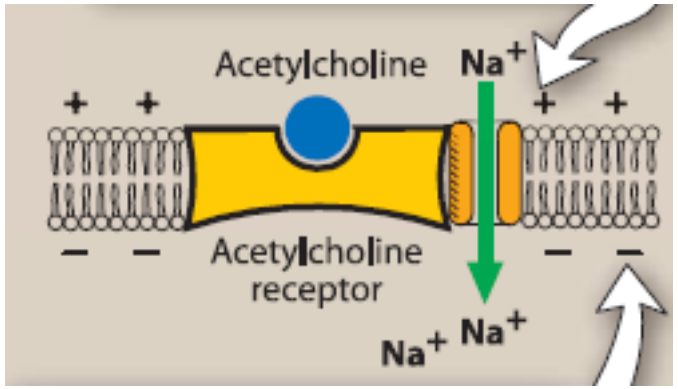


hyperpolarized cell membran



excitatory postsynaptic potentials (EPSP)

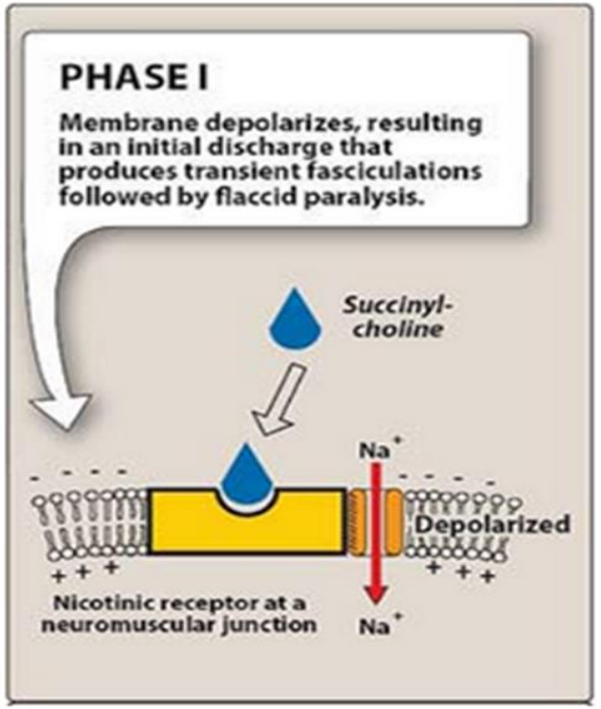
depolarized cell membrane



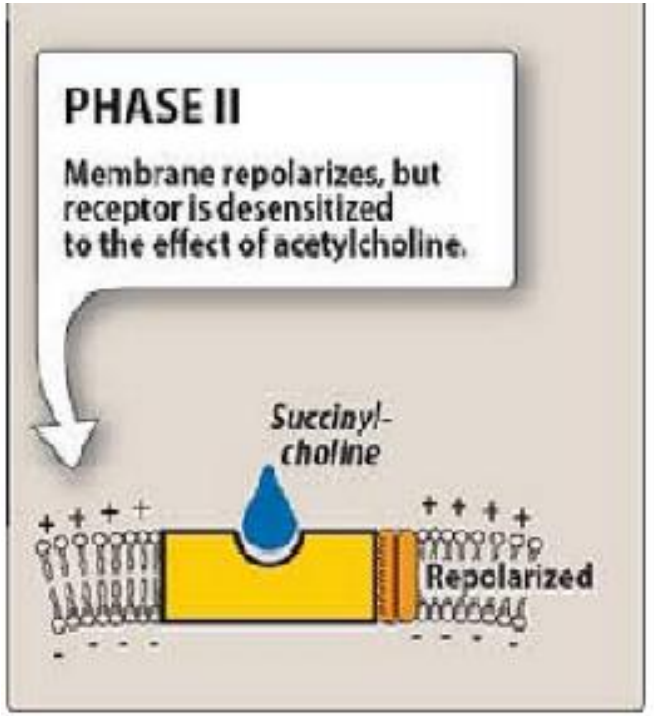
B- Depolarizing agents (Succinylcholine)

Mechanism of action: The depolarizing neuromuscular blocking drug **succinylcholine** attaches to the nicotinic receptor and acts like acetylcholine to depolarize the junction. Unlike acetylcholine, which is instantly destroyed by acetylcholinesterase, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing a constant stimulation of the receptor.

- The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations) .



•Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and paralysis.



Therapeutic uses: Because of its rapid onset and short duration of action, succinylcholine is useful when rapid endotracheal intubation is required during the induction of anesthesia.

Succinylcholine is injected intravenously. Its brief duration of action (several minutes) results from redistribution and rapid hydrolysis by plasma pseudocholinesterase.

Adverse effects:

1- Hyperthermia: administration of succinylcholine has occasionally caused malignant hyperthermia in genetically susceptible people.

2- Apnea: Administration of succinylcholine to a patient who is genetically deficient in plasma cholinesterase or has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm.

3- Hyperkalemia: Succinylcholine increases potassium release from intracellular stores. This may be particularly dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost or in patients with renal failure..

Which drug is useful in treating sinus bradycardia?

A. Atropine

B. Cisatracurium

C. Neostigmine

D. Succinylcholine

References

Lippincott Illustrated Reviews: Pharmacology. 7TH ed, Wolters Kluwer.

Thank you