Al-Mustaqbal University College

Pharmacology I 3rd stage

Cholinergic Antagonists

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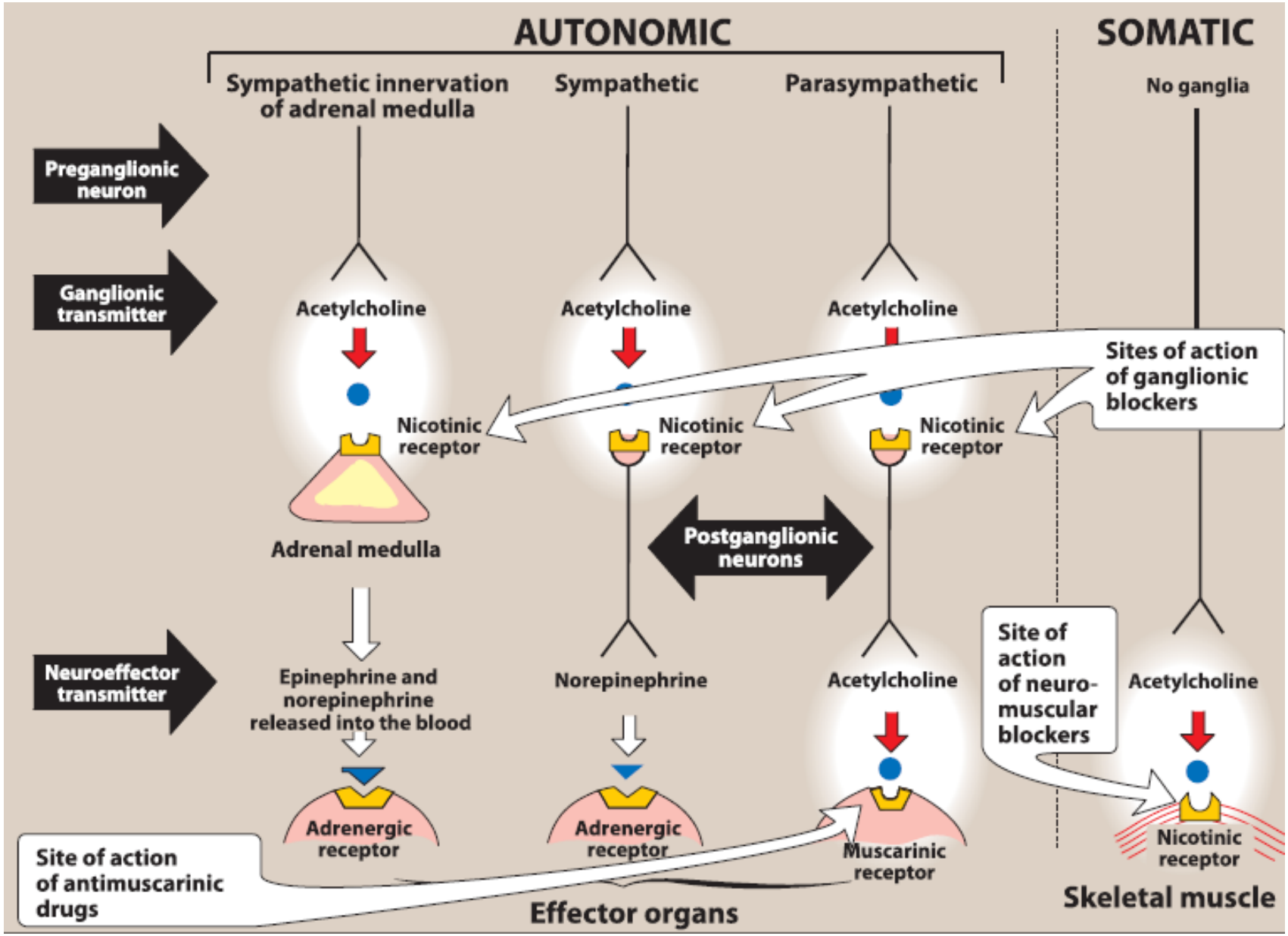
Cholinergic Antagonists

also called cholinergic blockers, parasympatholytics 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.** The most clinically useful of these agents are **selective blockers of muscarinic receptors (antimuscarinic drugs)**.

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.**

• 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**



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.**

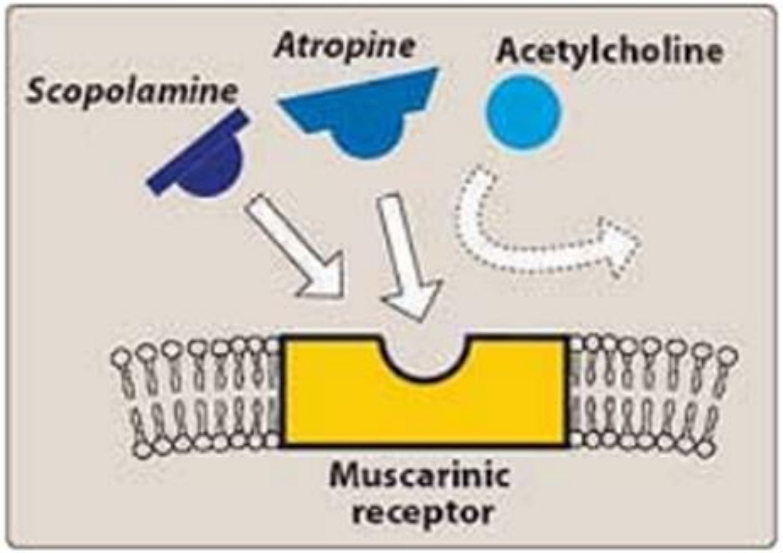
A)Atropine

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.

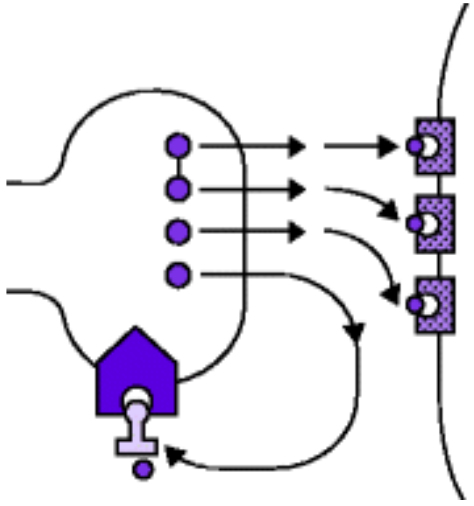


Gastrointestinal (GI): Atropine can be used as an antispasmodic to reduce activity of the GI tract. Atropine and scopolamine are probably the most potent drugs available that produce this effect.

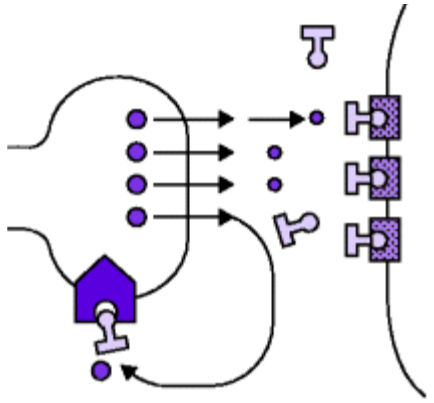
Urinary system: Atropine is also employed to reduce hypermotility states of the urinary bladder. It is still occasionally used in enuresis (involuntary voiding of urine) among children.

Cardiovascular: At low doses, 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.

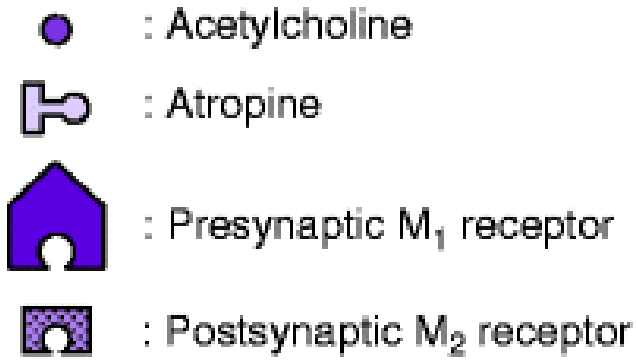
With higher doses of atropine, the M2 receptors on the sinoatrial node are blocked, and the cardiac rate increases modestly. Arterial blood pressure is unaffected.



Low dose



High dose



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.]

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 (cyclopentolante 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: Atropine is used for the treatment of overdoses of cholinesterase inhibitor.

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

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.

B. 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 and therapeutic uses:

- prevention of motion sickness
- blocking short-term memory makes it an important adjunct drug in anesthetic procedures.

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

C. Ipratropium Inhaled ipratropium is useful in

- treating asthma in patients who are unable to take adrenergic agonists.
- the management of chronic obstructive pulmonary disease.

Because of its positive charge, it does not enter the systemic circulation or the CNS.

Ganglionic Blockers

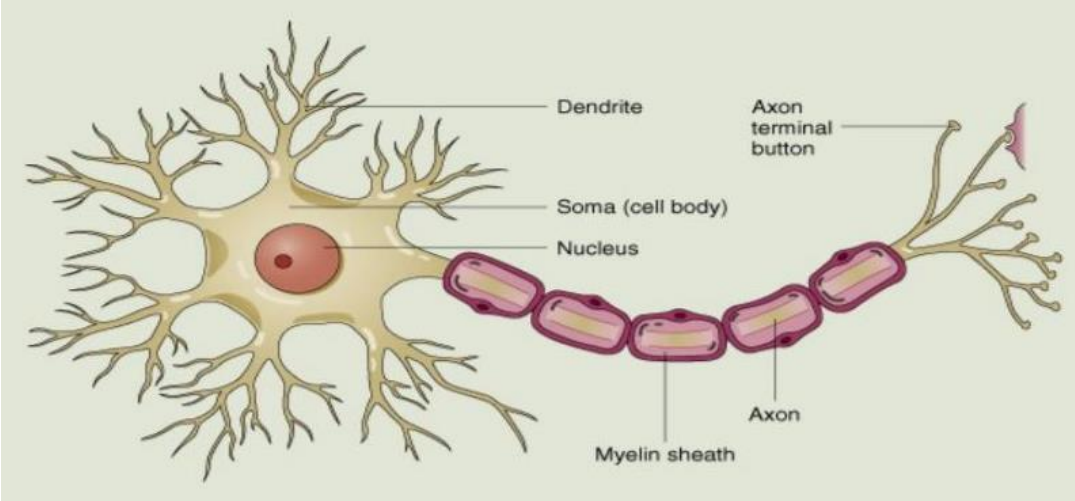
Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.

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.

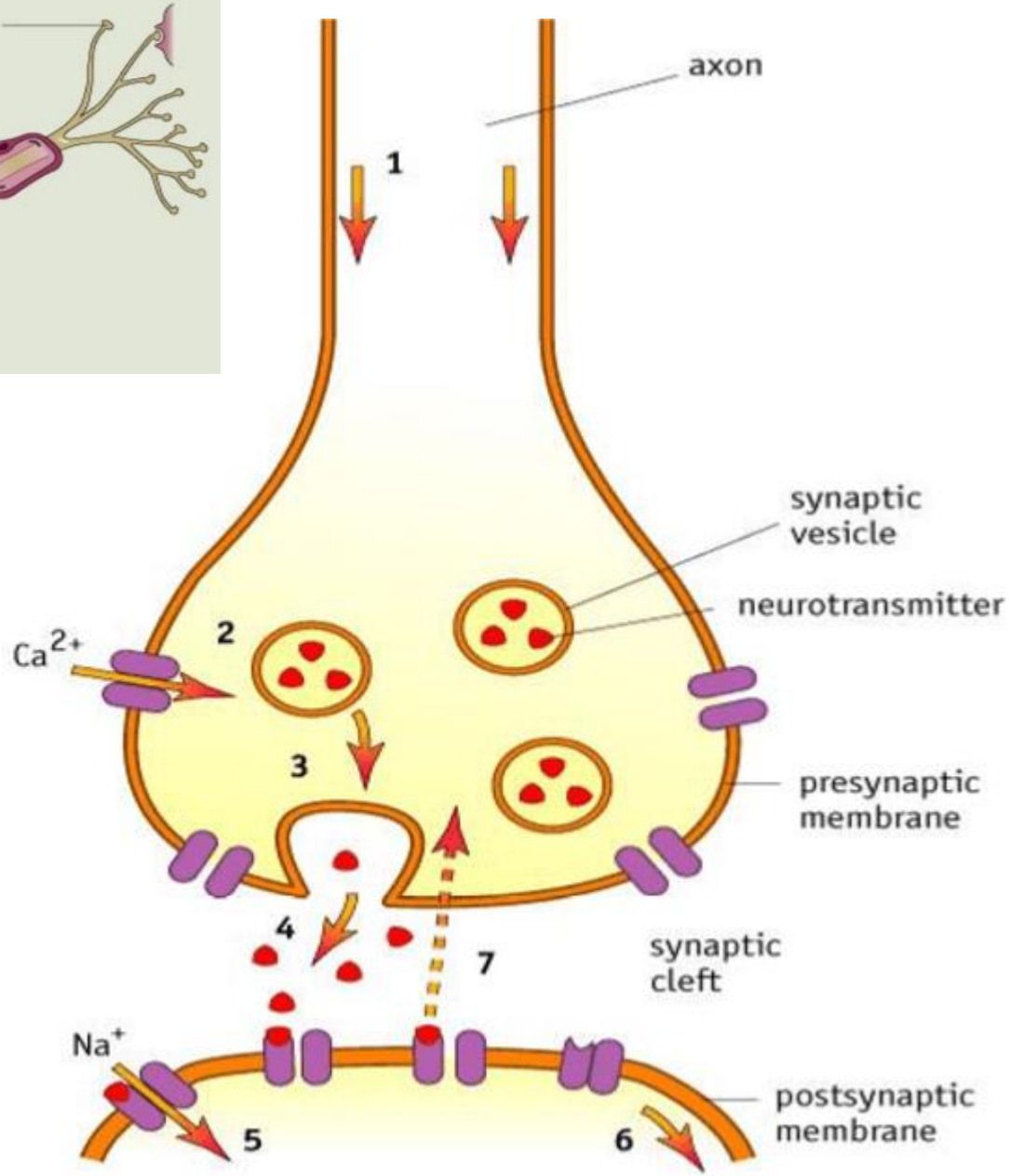
A.Nicotine

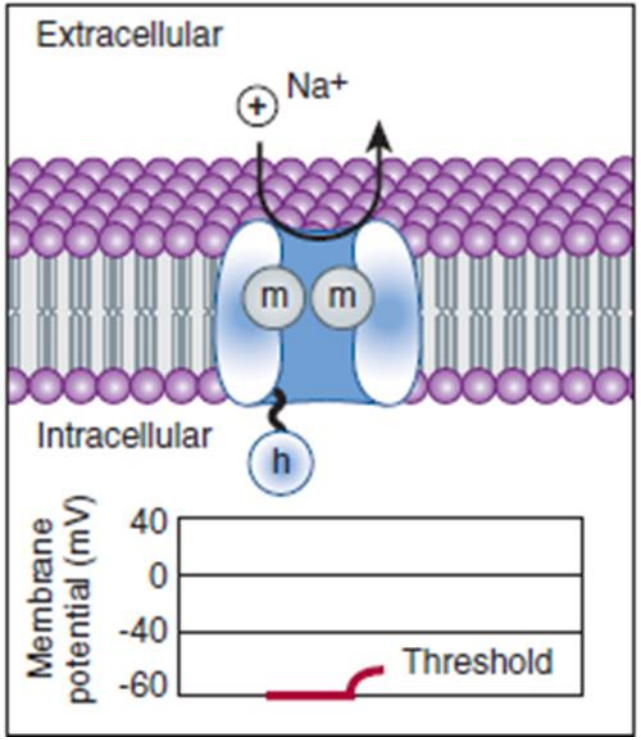
- A component of cigarette smoke, nicotine is a poison with many undesirable actions. Depending on the dose, nicotine depolarizes autonomic ganglia, **resulting first in stimulation and then in paralysis of all ganglia.**

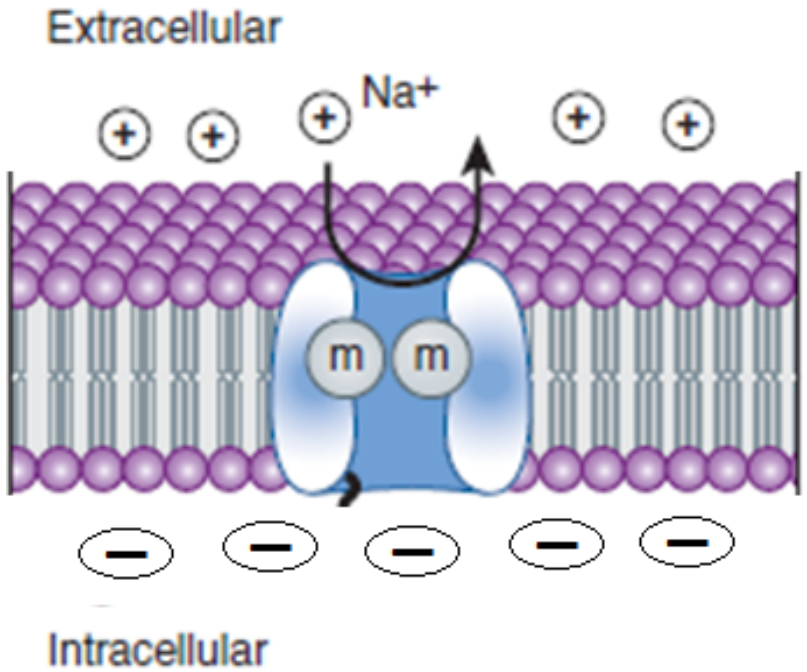
- The stimulatory effects are complex due to effects on both sympathetic and parasympathetic ganglia. **The effects include increased blood pressure and cardiac rate** (**due to release of transmitter from adrenergic terminals and from the adrenal medulla**) **and increased peristalsis and secretions.**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



SYNAPTIC CLEFT
AND
ACTION POTENTIAL

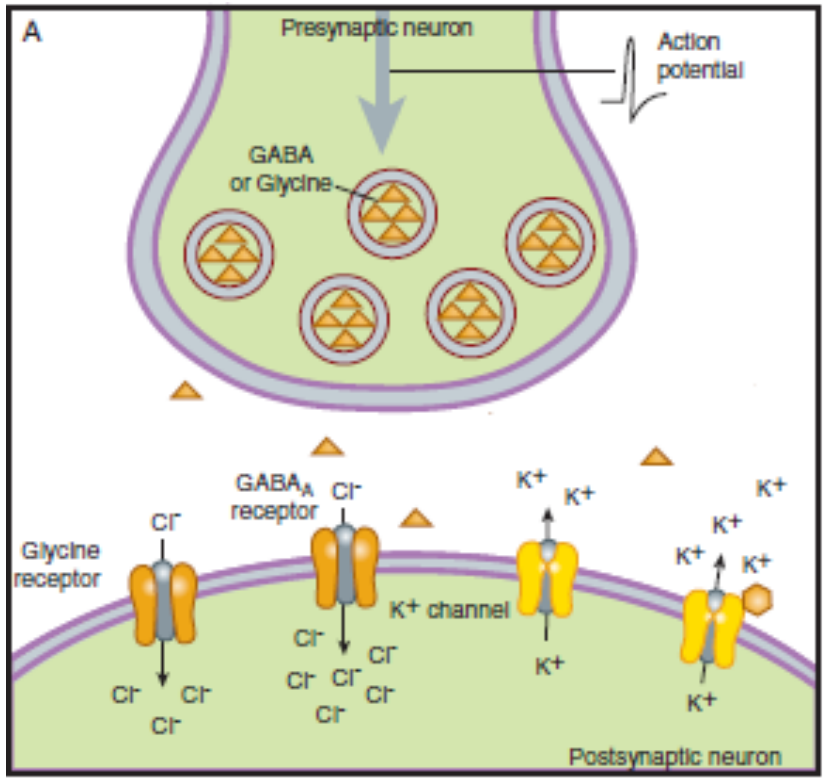






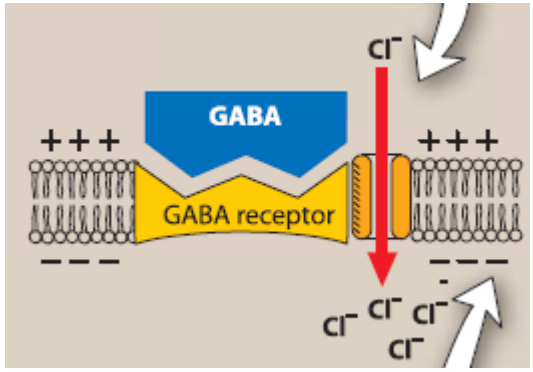
polarized cell membrane

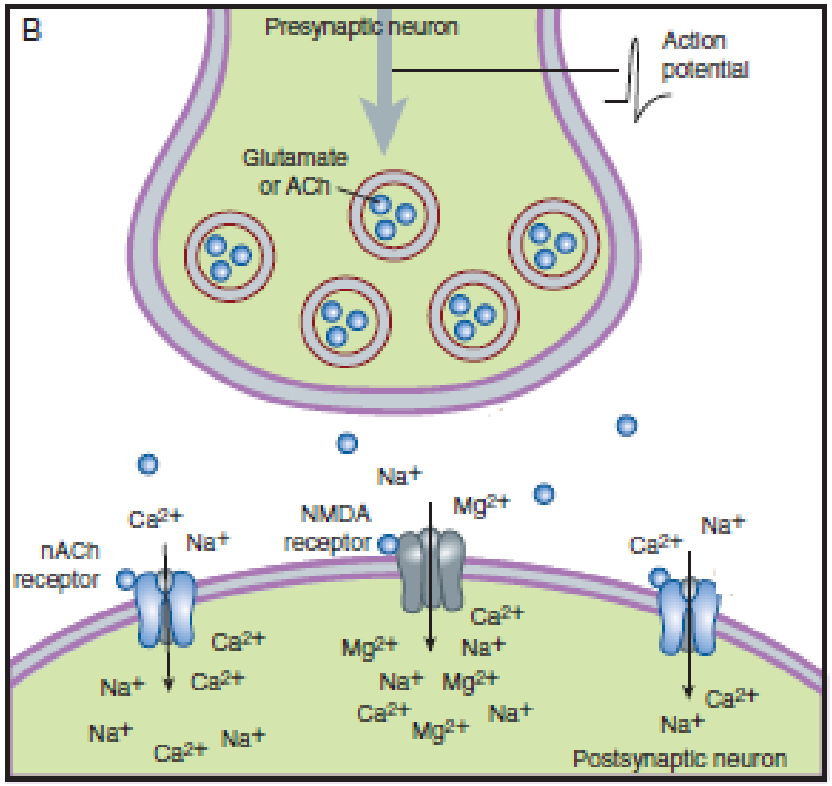
Resting membrane potential



Inhibitory postsynaptic potentials (IPSP)

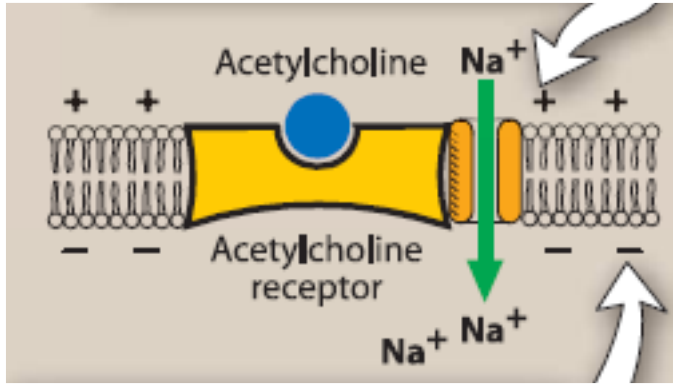
hyperpolarized cell membran





excitatory postsynaptic potentials (EPSP)

depolarized cell membrane

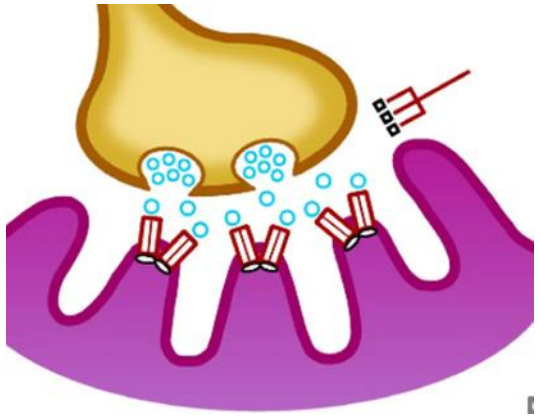


Neuromuscular Blocking Drugs

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.



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**

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:

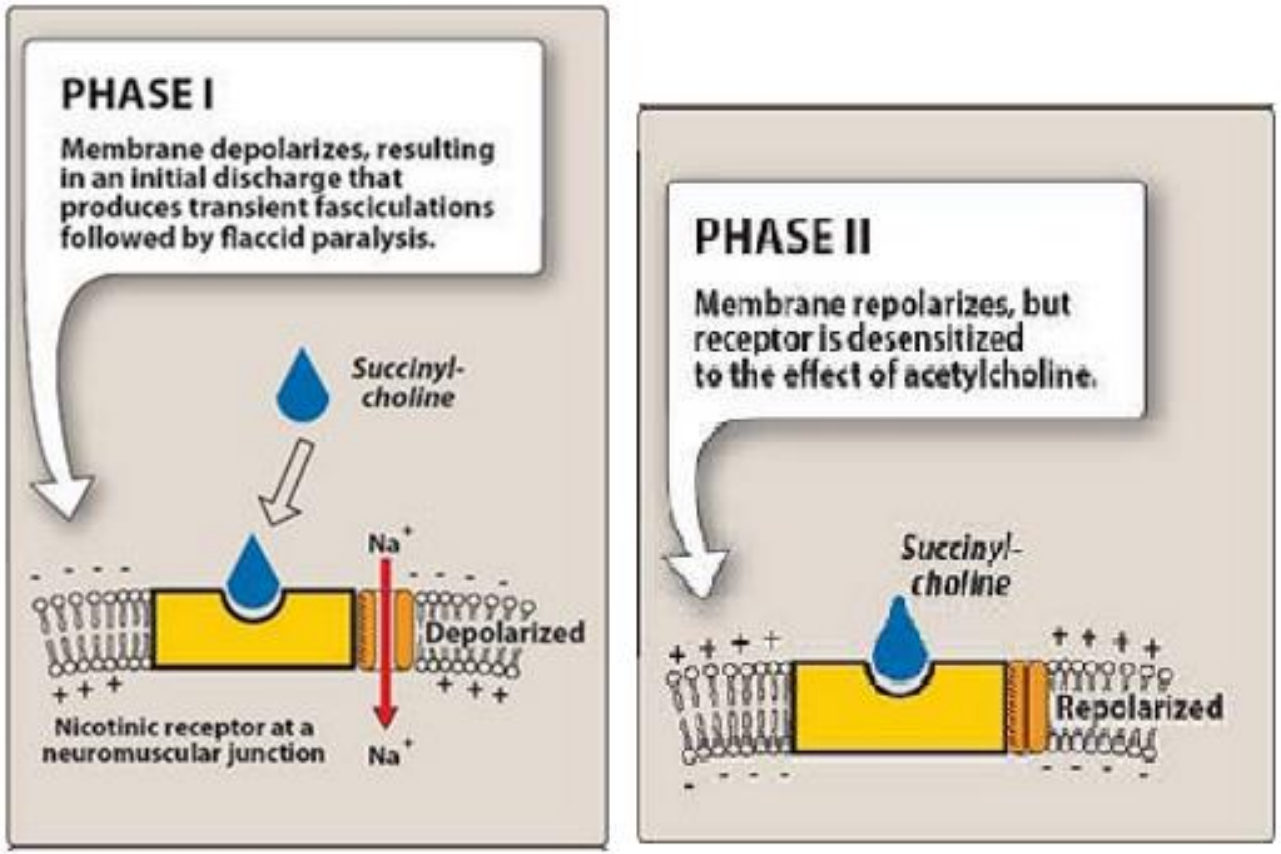
As adjuvant drugs in anesthesia during surgery to relax skeletal muscle.

B- Depolarizing agents

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 cholinesterase.

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.

References

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

Thank you