Pharmacology

Anticholinergic drugs

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Ph.D Pharmacology

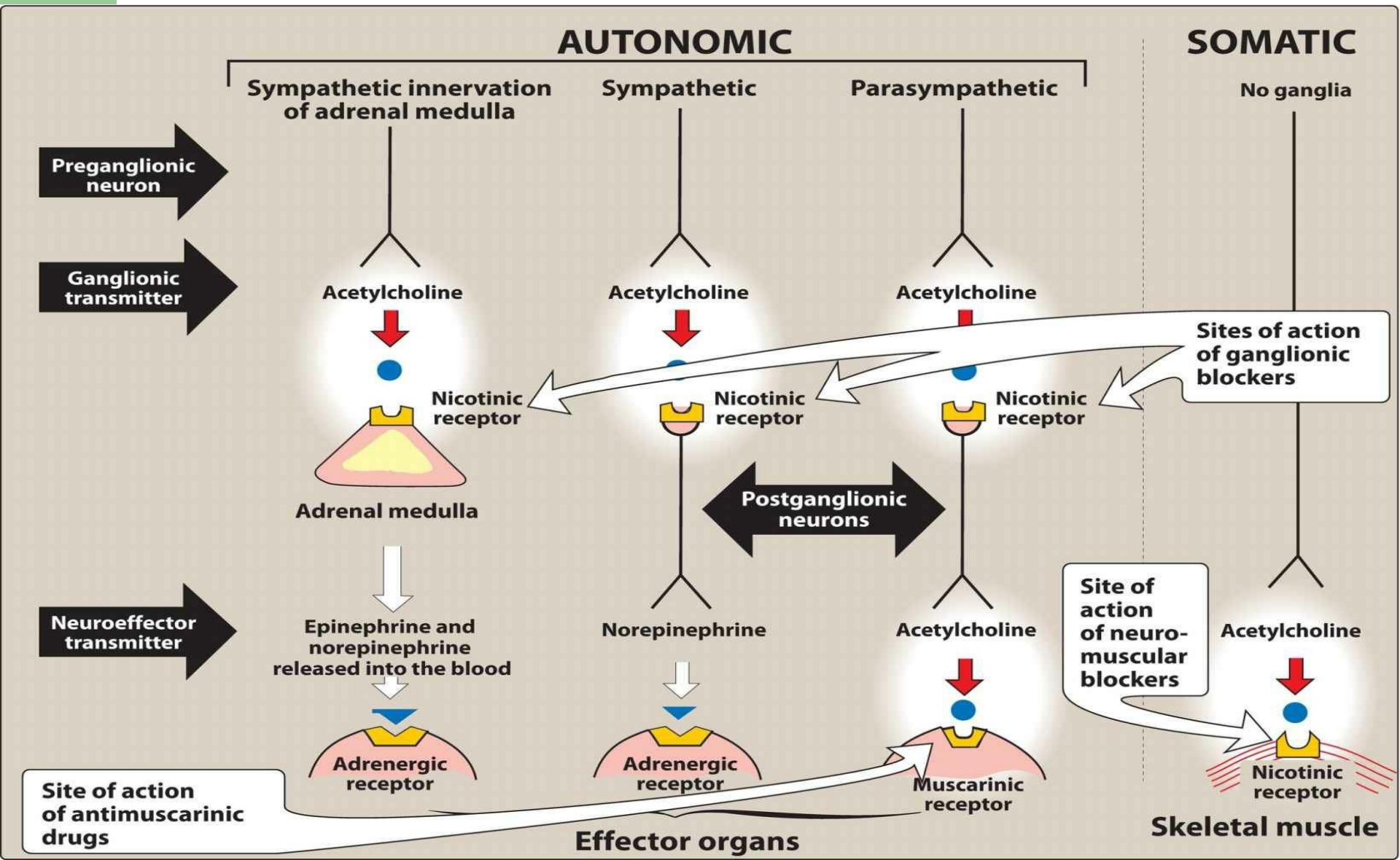
Lecture 5

Anticholinergic drugs

- Cholinergic antagonist binds to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.
- Classified into:

1. Antimuscarinic agents these agents are selective blockers of muscarinic receptors. Also known as parasympatholoytics agent.
2. A second group of drugs, the ganglionic blockers, that block nicotinic receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the least important 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 drugs are used as skeletal muscle relaxants in surgical anesthesia and as agents to facilitate intubation in surgical and critical care patients.

Sites of action of anticholinergic drugs



Anitmuscarnics drugs

- Commonly known as anticholinergic drugs, these agents (for example, *atropine* and *scopolamine*).
- Block muscarinic receptors, causing inhibition of muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating the salivary and sweat glands.
- Have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia
- A number of antihistamines and antidepressants (mainly tricyclic antidepressants) also have antimuscarinic activity.

Atropine

- Atropine, a tertiary amine 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, its action last for days.
- The greatest inhibitory effects are seen in bronchial tissue, salivary and sweat glands, and the heart.
- Its absorbed, partially metabolized by the liver, and eliminated primarily in urine. It has a half-life of about 4 hours.

Effect of Atropine on the body

Eye: Atropine block the M receptor in the eye causing persistent myderiasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision). It increase the intraocular pressure that is why it is contraindicate in glaucoma. Because of long duration of action of atropine eye drop it replace by another Shorter-acting antimuscarnic agents (Tropicamide) to produce mydriasis in ophthalmic examination.

Gastrointestinal: 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. Atropine is not effective for the treatment of ulcers because HCl acid is not significantly affected. It also reduce saliva secretion, ocular accommodation, and urination (side effect)

Urinary system: Atropine is also employed to reduce hypermotility states of the urinary bladder and cause relaxation of the urinary bladder.

- Cardiovascular: low doses, the predominant effect is a decreased cardiac rate (bradycardia) due to central activation of vagal efferent outflow, result from blockade of the M_1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased acetylcholine release.
- While With higher doses of atropine, the M_2 receptors on the sinoatrial node are blocked, and the cardiac rate increases(tachycardia) .

- Secretions: Atropine blocks the salivary glands, producing a drying effect on the oral mucous membranes (xerostomia). Sweat and lacrimal glands are also affected. [Note: Inhibition of secretions by sweat glands can cause elevated body temperature.]
- CNS stimulation followed by depression, can result in coma and death

Uses of Atropine

1. In Ophthalmic examination as mydriatic agent which allow the physician to measure the refractive errors .
2. Antispasmodic: Atropine is used as an antispasmodic agent to relax smoth muscle in the GI tract and bladder in treatment of ulcerative colitis and urinary incontinence and renal colic.
3. Antidote for cholinergic agonists: Atropine is used for the treatment of overdoses of cholinesterase inhibitor (Physostigmine): insecticides and some types of mushroom poisoning.
4. Antisecretory to block secretions in the upper and lower respiratory tracts prior to surgery.
5. Treatment the bradycardia.

Adverse effects

1. Depending on the dose, *atropine* may cause dry mouth, blurred vision, "sandy eyes," tachycardia, urinary retention, and constipation.
2. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death.
3. Low doses of cholinesterase inhibitors, such as *physostigmine*, may be used to overcome *atropine* toxicity.
4. *Atropine* may also induce troublesome urinary retention.
5. The drug may be dangerous in children, because they are sensitive to its effects, particularly to rapid increases in body temperature.

Scopolamine

- Non selective anti muscarinic tertiary alkaloid
- Produce peripheral and more CNS effects.
- Actions: blocking short-term memory; produces sedation, but at higher doses, it can produce excitement and may produce euphoria and is susceptible to abuse.
- used for the prevention of motion sickness and postoperative nausea and vomiting.
- Has long half life.

Oxybutynin and other antimuscarinic agents for overactive bladder

- Selective M3 blocking agent.
- Blocking M3 in bladder caused lowering in the intravesical pressure, increase in bladder capacity and reduce in frequency of bladder contractions.
- Darifenacin and solifenacin are relatively more selective M3 muscarinic receptor antagonists.
- Management of overactive bladder and urinary incontinence.
- Available as oral tablet and capsule, transdermal patch and gel.
- Hepatically metabolized by the cytochrome P450 system with the exception of trospium, undergo ester hydrolysis.
- Side effects include dry mouth, constipation, and blurred vision, which limit tolerability of these agents. 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.

Aclidinium, *glycopyrrolate*, *ipratropium*, and *tiotropium*

- *Ipratropium* and *tiotropium* are quaternary derivatives of *atropine*, and *glycopyrrolate*] and *aclidinium* are synthetic quaternary compounds.
- *Ipratropium* is classified as a short-acting muscarinic antagonist, while *glycopyrrolate*, *tiotropium*, and *aclidinium* are classified as long-acting muscarinic antagonists based on the duration of action.
- Used as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).
- *Ipratropium used in acute asthma* and *tiotropium* used in management of chronic management of asthma, respectively.
- All of them used as inhalers and do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system.

Other anticholinergic drugs

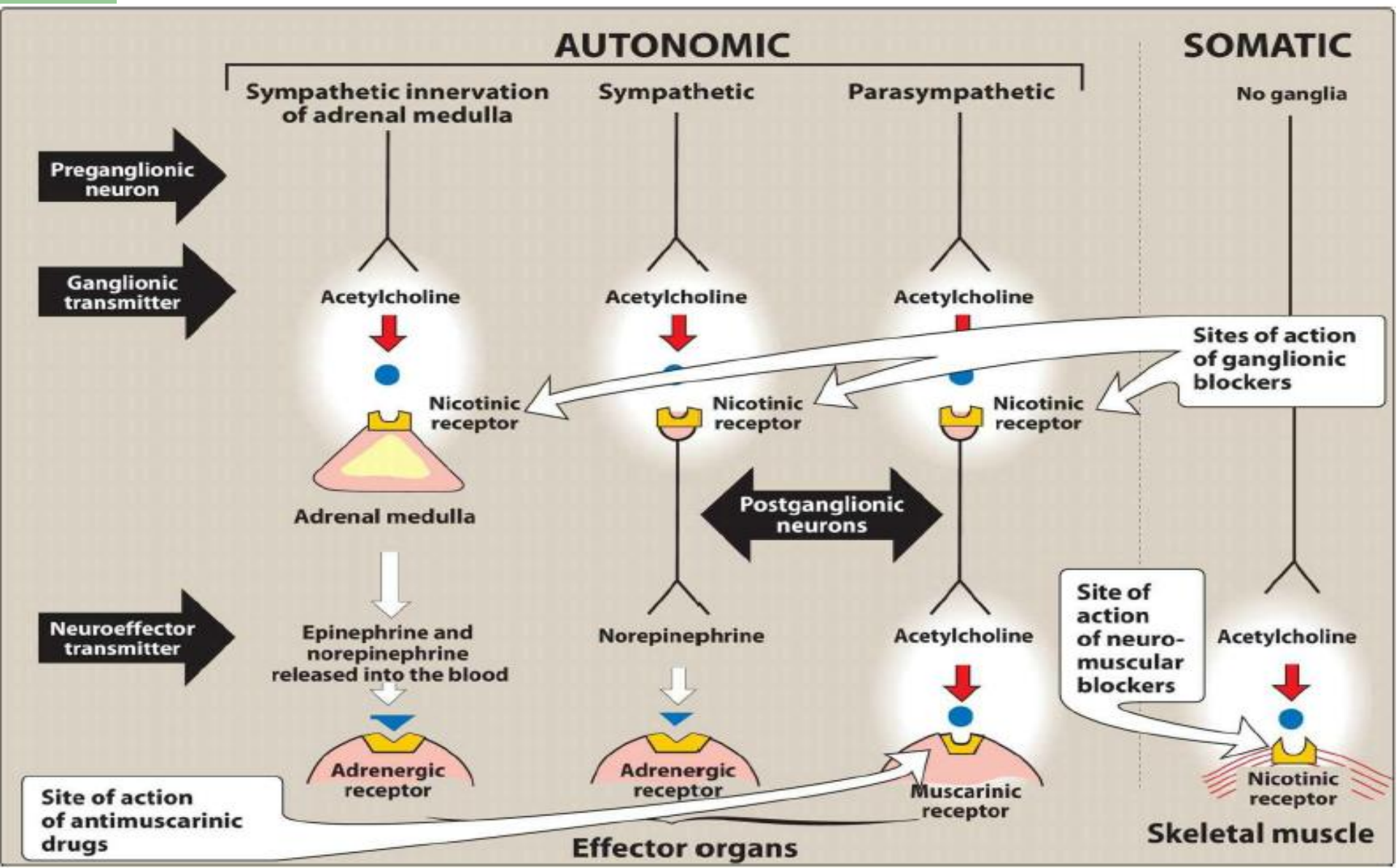
- ***Tropicamide* and *cyclopentolate***

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.

- ***Benztropine* and *trihexyphenidyl***

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

Ganglionic blockers



Ganglionic blockers

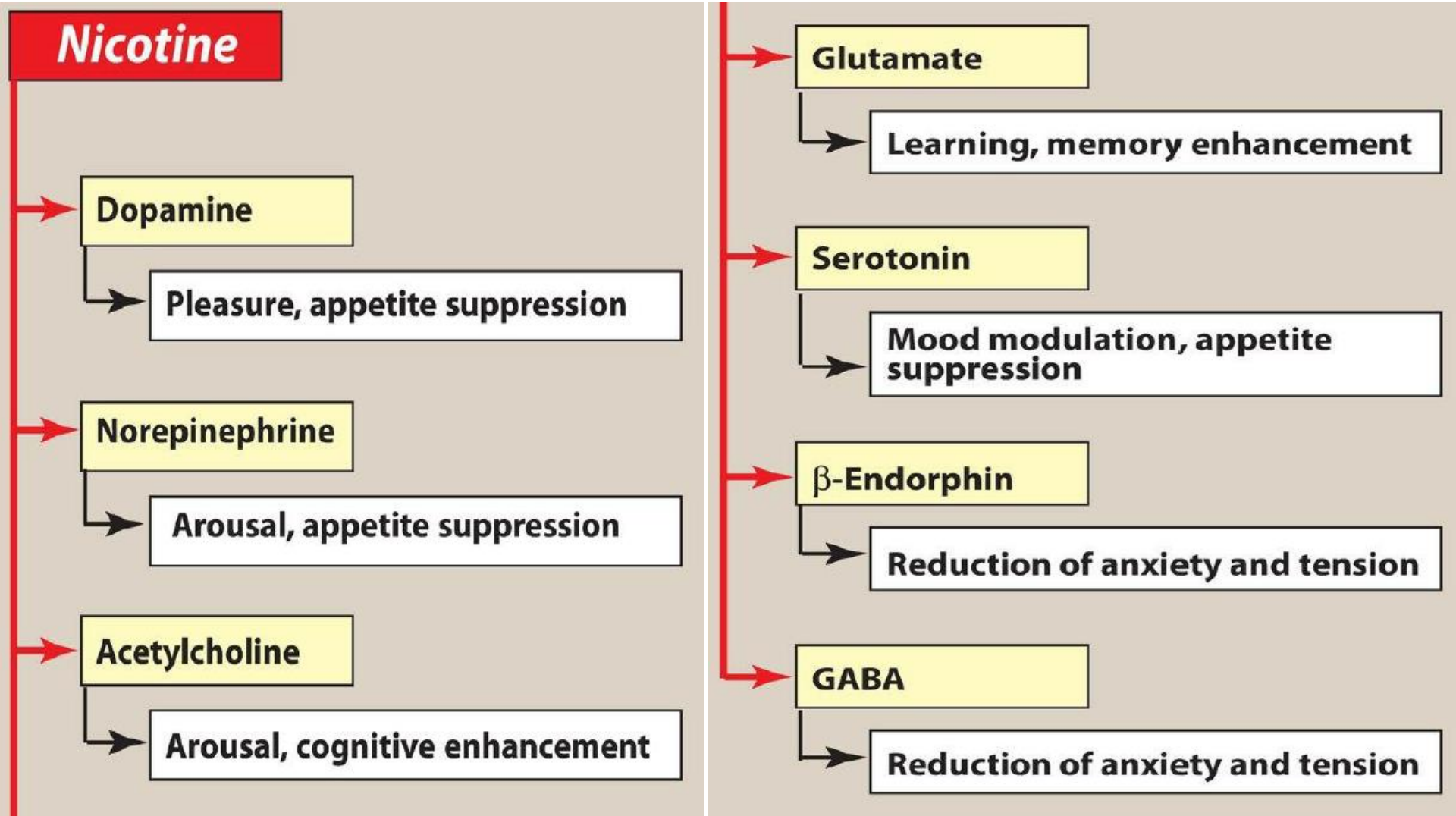
Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor.

Except for ***nicotine***, the other drugs mentioned in this category are nondepolarizing, competitive antagonists. The responses of the nondepolarizing blockers are complex and mostly unpredictable. Therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.

Nicotine

- **Mechanism of action:**
- In low doses, *nicotine* causes ganglionic stimulation by depolarization.
- At high doses, *nicotine* causes ganglionic blockade.
- *Nicotine* receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug.
- CNS Actions (by effect on many types of receptors): It crosses the blood–brain barrier. **low doses** of nicotine produces some degree of euphoria and arousal, as well as relaxation. It improves attention, learning, problem solving, and reaction time. **High doses** of nicotine result in central respiratory paralysis and severe hypotension caused by medullary paralysis. Nicotine is also an appetite suppressant.
- Peripheral actions: **Low dose** caused stimulation of sympathetic ganglia as well as of the adrenal medulla increases blood pressure, heart rate and vasoconstriction that decrease coronary blood flow. Thus, use of tobacco is harmful in hypertensive and anginal patients. Also nicotine stimulates parasympathetic ganglia increases motor activity of the bowel. **At higher doses**, Bp falls and activity ceases in both the gastrointestinal (GI) tract and bladder musculature as a result of a nicotinei-nduced block of parasympathetic ganglia.

Notes: The stimulatory effects are complex and result from increased release of neurotransmitters (as shown in the following figure) and due to effects on both sympathetic and parasympathetic ganglia



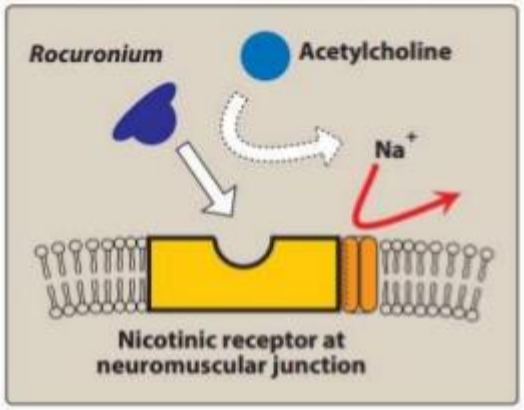
Neuromuscular blocking agent

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 act either as:

A) Nicotnic antagonists (nondepolarizing competitive NM blocking type) or

B) Nicotnic agonists (depolarizing-non-competitive type)

Uses: Neuromuscular blockers are clinically useful during surgery for producing complete muscle relaxation, without having to employ higher anesthetic doses to achieve comparable muscular relaxation. Agents are also useful in facilitating intubation as well.



A) Nondepolarizing NMB Drugs

- Mechanism of action:

At low doses: They interact with the nicotinic receptors to prevent the binding of acetylcholine and prevent depolarization of the muscle cell membrane and inhibit muscular contraction (Competitive blockers). Their action can be overcome by increasing the concentration of acetylcholine by administration of cholinesterase inhibitors, such as neostigmine..ect.

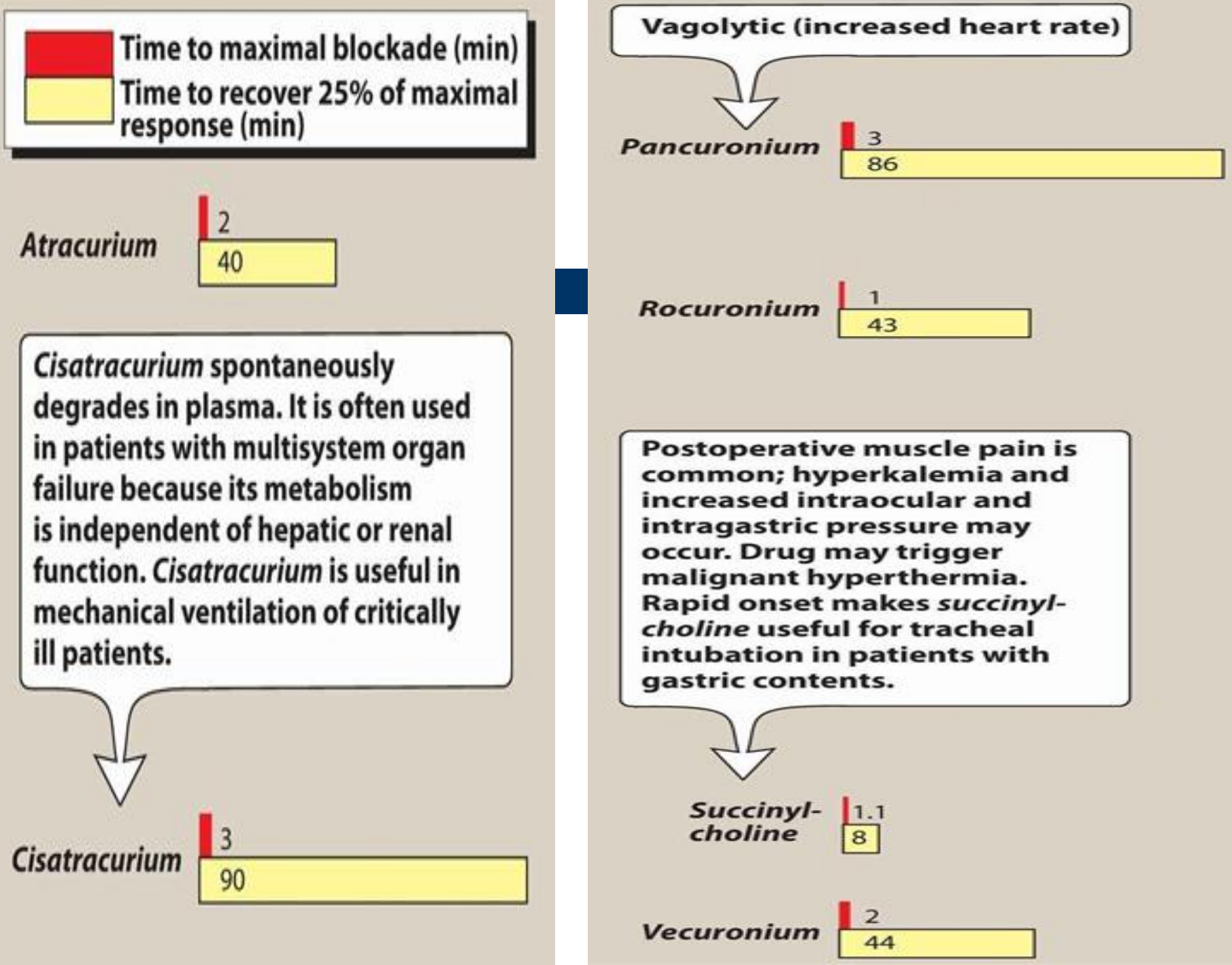
At high doses :Nondepolarizing blockers can block the ion channels of the end plate. This leads to further weakening of neuromuscular transmission, and it reduces the ability of acetylcholinesterase inhibitors to reverse the actions of nondepolarizing muscle relaxants.

Examples on Non-depolarizing NMB agents

- The first known NMB was curare, which Amazon hunters used to paralyze prey. but it has been replaced by agents with fewer adverse effects

1. Cisatracurium: metabolized in the liver and renal and has long duration of action.
2. Pancuronium: execreted unchanged in the urine and increase the heart rate.
3. Rocuronium ,and vecuronium: metabolized in the liver and some of them excreted unchanged in bile.
4. Mivacurium is eliminated by plasma cholinesterase.

- Note: The choice of agent depends on the desired onset and duration of muscle relaxation


Time to maximal blockade (min)
Time to recover 25% of maximal response (min)
Atracurium
2
40
Cisatracurium spontaneously degrades in plasma. It is often used in patients with multisystem organ failure because its metabolism is independent of hepatic or renal function. Cisatracurium is useful in mechanical ventilation of critically ill patients.
Cisatracurium
3
90
Vagolytic (increased heart rate)
Pancuronium
3
86
Rocuronium
1
43
Postoperative muscle pain is common; hyperkalemia and increased intraocular and intragastric pressure may occur. Drug may trigger malignant hyperthermia. Rapid onset makes succinylcholine useful for tracheal intubation in patients with gastric contents.
Succinylcholine
1.1
8
Vecuronium
2
44

Drug interactions

a. Cholinesterase inhibitors

Drugs such as *neostigmine*, *physostigmine* and *pyridostigmine*, can overcome the action of nondepolarizing NMBs. However, with increased dosage, cholinesterase inhibitors can cause a depolarizing block due to elevated ACh concentrations at the end plate membrane. If the NMB has entered the ion channel (is bound to the receptor), cholinesterase inhibitors are not as effective in overcoming blockade.

b. Halogenated hydrocarbon anesthetics

Drugs such as *desflurane* act to enhance neuromuscular blockade by exerting a stabilizing action at the NMJ. These agents sensitize the NMJ to the effects of NMBs.

c. Aminoglycoside antibiotics

Drugs such as *gentamicin* and *tobramycin* inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with competitive blockers, enhancing neuromuscular blockade.

d. Calcium channel blockers

These agents may increase the neuromuscular blockade of competitive blockers.

B) Depolarizing non-competitive NMB agents

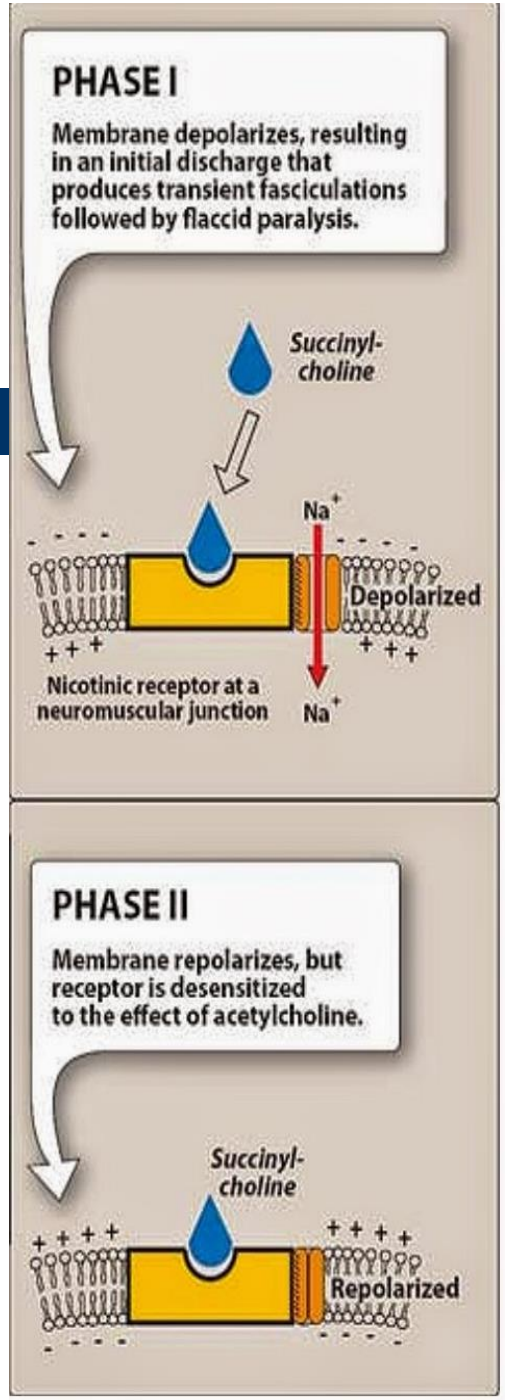
Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can more persistently depolarize the muscle fibers. Succinylcholine [suk-sin-il-KOE-leen] is the only depolarizing muscle relaxant in use today.

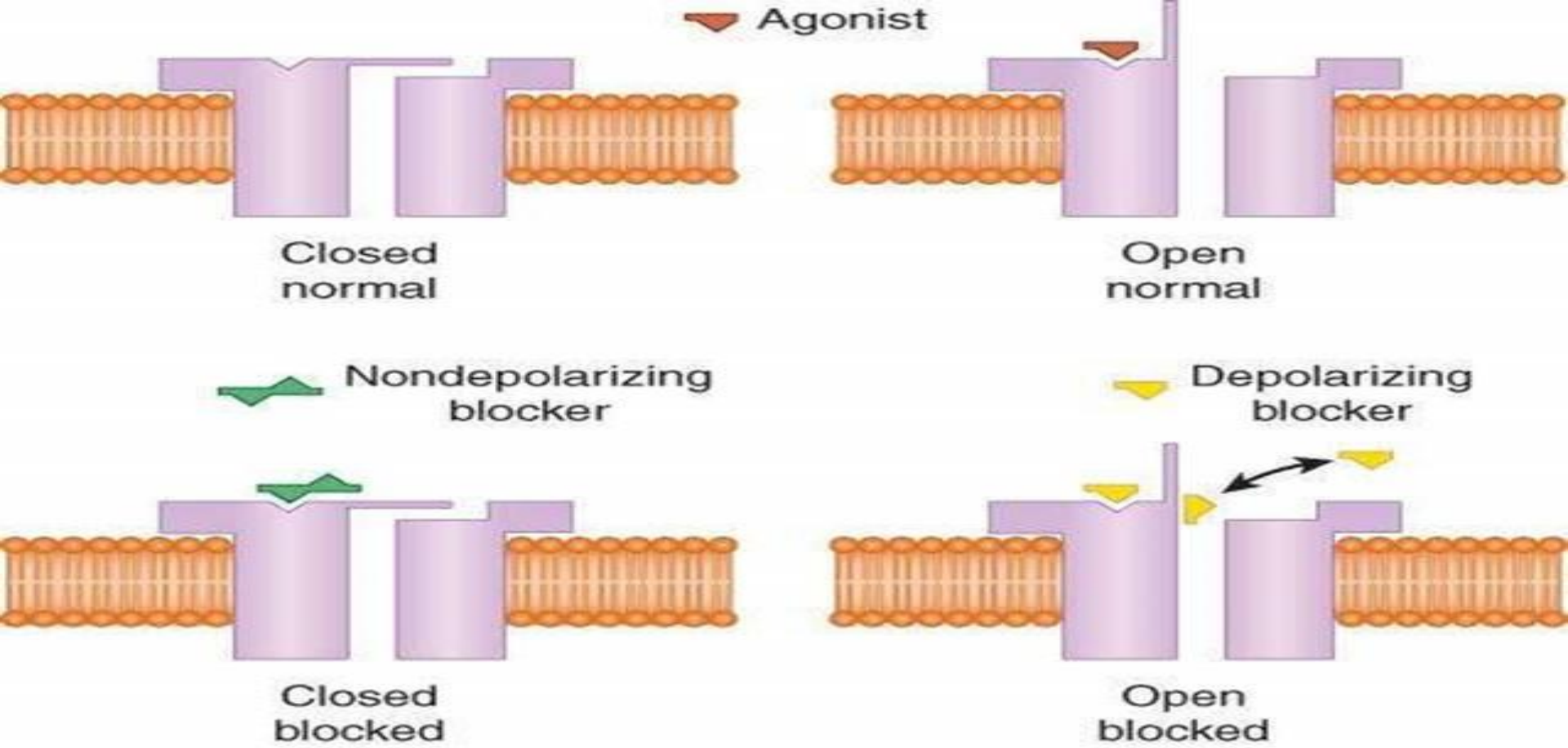
Mechanism of action of succinylcholine

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. It metabolized by plasma cholinesterase enzyme.

Note: Genetic variants in which plasma cholinesterase levels are low or absent lead to prolonged neuromuscular paralysis.

The depolarizing agent first causes opening of the sodium channel associated with 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 flaccid paralysis.





Therapeutic uses

Because of its rapid onset of action, *succinylcholine* is useful when rapid endotracheal intubation is required. It is also used during electroconvulsive shock treatment.

Side effects of succinylcholine

1. Hyperthermia can be overcome by dantroline
2. Apnea: due to paralysis of diaphragm occur in patient with atypical cholineesterase enzyme
3. Hyperkalemia: because succinylcholine stimulate the release of K from intracellular store so it CI in burn patient or in patient with renal failure.

Notes:

- Succinylcholine given by I.V route and has rapid and short duration of action. It useful when rapid endotracheal intubation.


THANKYOU