Autonomic Nervous System

Drugs affecting the autonomic nervous system are divided into two groups according to the type of neuron involved in their mechanism of action.
The first group **cholinergic drugs**, act on receptors that are activated by **acetylcholine.**
The second group the **adrenergic drugs**, act on receptors that are stimulated by **norepinephrine or epinephrine**.
Cholinergic and adrenergic drugs both act by either stimulating or blocking receptors of the autonomic nervous system.

Neurotransmission at cholinergic neurons:-

Neurotransmission in cholinergic neurons involves sequential six steps. The **synthesis**, **storage**, **release**, **binding**, **degradation and recycling of choline.**

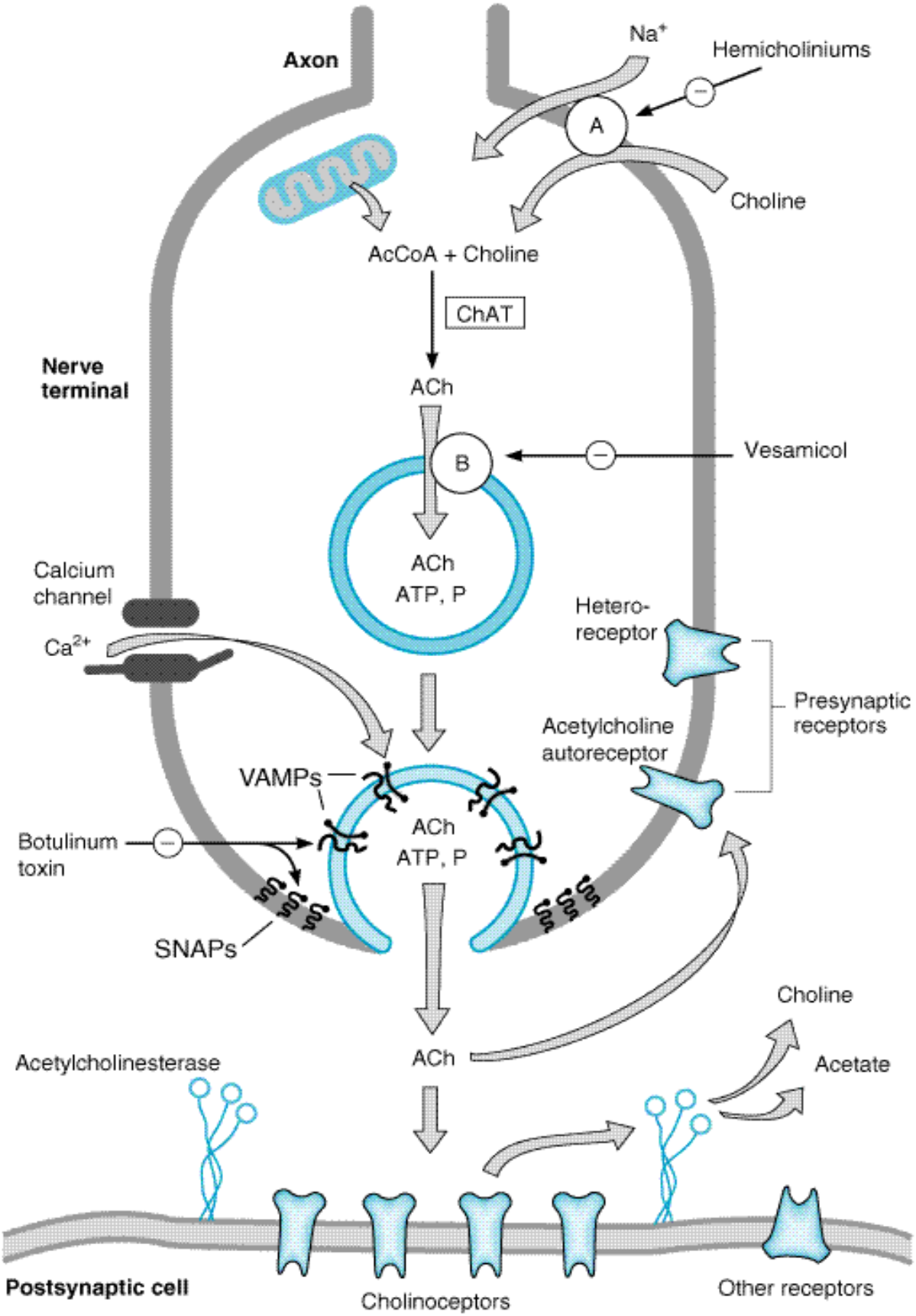
A-The Choline is transported into the presynaptic nerve terminal by a sodium-dependent carrier this transport can be inhibited by hemicholinium drugs.

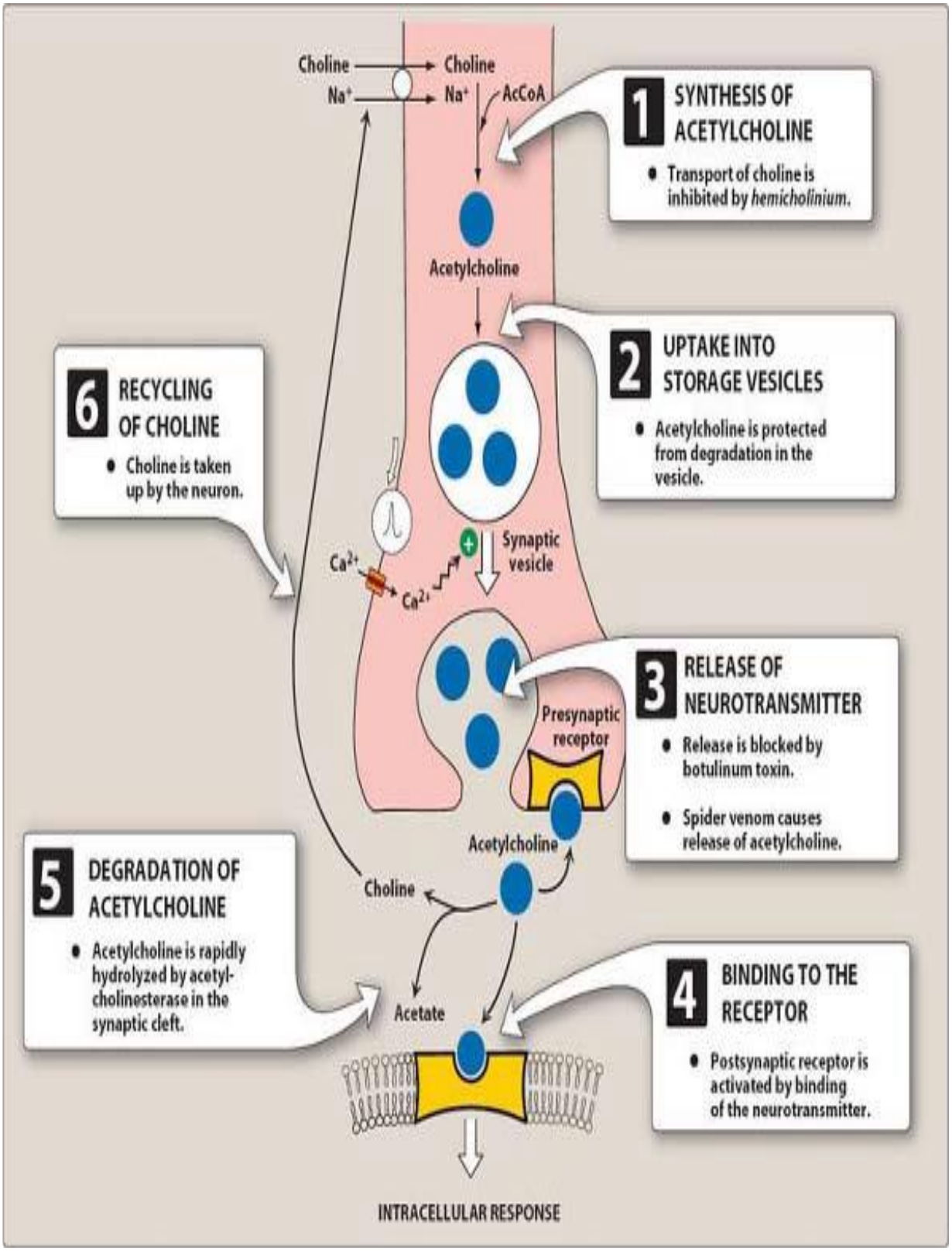
B-ACh is transported into the storage vesicle by a second carrier ,that can be inhibited by vesamicol. Peptide(P),ATP ,and proteoglycan are also stored in the vesicle.

C-Release of transmitter occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. the resulting increase in intracellular calcium causes fusion of vesicles with surface membrane and exocytotic expulsion of ACh and cotransmitters into the junctional cleft.
This step is blocked by botulinum toxin.

Receptors on the presynaptic nerve ending regulate transmitter release. (SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins).

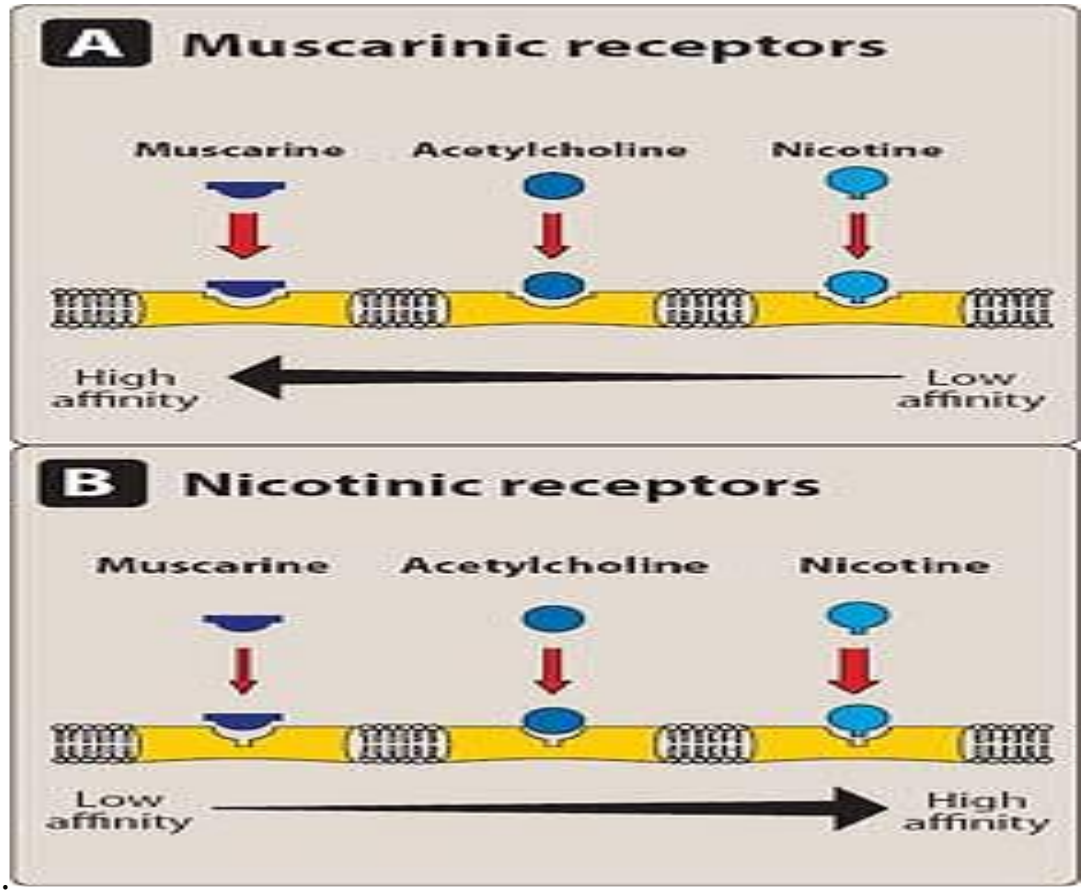
4- Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in postganglionic fiber or activation of specific enzymes in effector cells as mediated by second-messenger molecules.


Axon
Na+
Hemicholiniums
A
Choline
AcCoA + Choline
ChAT
Nerve terminal
ACh
B
Vesamicol
ACh
ATP, P
Calcium channel
Ca2+
Hetero-receptor
Presynaptic receptors
Acetylcholine autoreceptor
VAMPs
ACh
ATP, P
Botulinum toxin
SNAPs
Choline
ACh
Acetylcholinesterase
Acetate
Postsynaptic cell
Cholinoceptors
Other receptors


Choline
Choline
Na+
Na+
AcCoA
1 SYNTHESIS OF ACETYLCHOLINE
• Transport of choline is inhibited by hemicholinium.
Acetylcholine
2 UPTAKE INTO STORAGE VESICLES
• Acetylcholine is protected from degradation in the vesicle.
6 RECYCLING OF CHOLINE
• Choline is taken up by the neuron.
Synaptic vesicle
Ca2+
Ca2+
3 RELEASE OF NEUROTRANSMITTER
• Release is blocked by botulinum toxin.
• Spider venom causes release of acetylcholine.
Presynaptic receptor
Acetylcholine
Choline
5 DEGRADATION OF ACETYLCHOLINE
• Acetylcholine is rapidly hydrolyzed by acetyl-cholinesterase in the synaptic cleft.
Acetate
4 BINDING TO THE RECEPTOR
• Postsynaptic receptor is activated by binding of the neurotransmitter.
INTRACELLULAR RESPONSE

Cholinergic Receptors

Receptor Name	**Typical Locations**	**Result of ligand Binding**
Muscarinic M1	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP3 and DAG, increased intracellular calcium
Muscarinic M2	Myocardium, smooth muscle, some presynaptic sites	Opening of potassium channels, inhibition of adenylyl cyclase
Muscarinic M3	Exocrine glands, vessels (smooth muscle and endothelium)	Formation of IP3 and DAG, increased intracellular calcium
Nicotinic NN	Postganglionic neurons, some presynaptic cholinergic terminals	Opening of Na+, K+ channels, depolarization
Nicotinic NM	Skeletal muscle neuromuscular end plates	Opening of Na+, K+ channels, depolarization



Types of cholinergic receptors

Cholinergic Receptors (Cholinoceptors):-

Two families of cholinoceptors, designated Nicotinic and Muscarinic receptors.

Nicotinic receptors: These receptors, in addition to binding acetylcholine, also recognize nicotine but show only a weak affinity for muscarine .

The nicotinic receptor is composed of five subunits, and it functions as a ligand-gated ion channel.

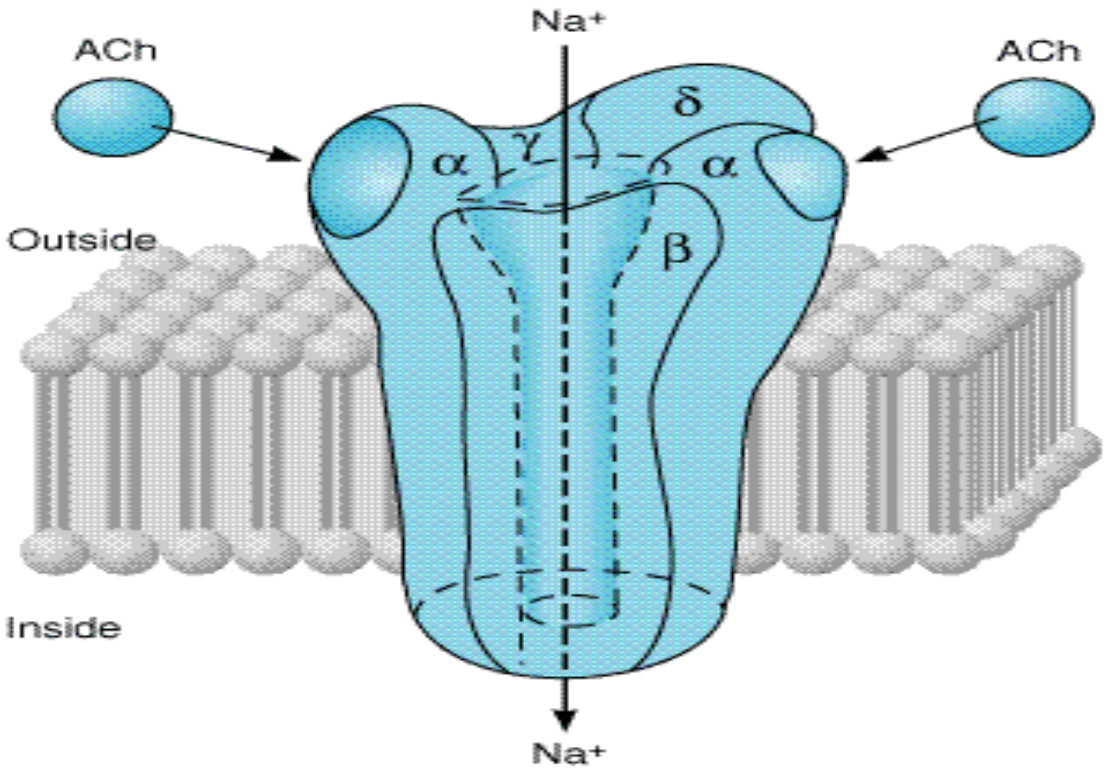
Binding of two acetylcholine molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell.

Nicotine (or acetylcholine) initially stimulates and then blocks the receptor.

Nicotinic receptors are located in the CNS, adrenal medulla, autonomic ganglia, and the neuromuscular junction.

Those at the neuromascular junction are sometimes

designated NM and the others NN. The nicotinic receptors of autonomic ganglia differ from those of the neuromuscular junction. For example, ganglionic receptor are selectively blocked by hexamethonium, where as neuromuscular junction receptors are specifically blocked by tubocuranine.



The nicotinic acetylcholine receptor, a ligand-gated ion channel. The receptor molecule is depicted as embedded in a rectangular piece of plasma membrane, with extracellular fluid above and cytoplasm below. Composed of five subunits (two , one , one , and one), the receptor opens a central transmembrane ion channel when acetylcholine (ACh) binds to sites on the extracellular domain of its subunits.

Muscarinic receptors:-

These receptors, in addition to binding acetylcholine, also recognize muscarine, an alkaloid that is present in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for nicotine . Binding studies and specific inhibitors, as well as cDNA characterization, have distinguished five subclasses of muscarinic receptors: M1, M2, M3, M4, and M5.

Although five muscarinic receptors have been identified by gene cloning, only M1, M2 and M3, receptors have been functionally characterized.

Locations of muscarinic receptors:
These receptors have been found on ganglia of the peripheral nervous system and on the autonomic effector organs, such as the heart, smooth muscle, brain, and exocrine glands
Specifically, although all five subtypes have been found on neurons, **M1** receptors are also found on **gastric parietal cells**,**M2** receptors on **cardiac** cells and **smooth muscle**, and M3 receptors on the **bladder** ,**exocrine glands**, and a **smooth muscle**.
[Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues but at high concentration they may show some activity at nicotinic receptors.

Cholinergic Agonists :-

Direct-Acting Cholinergic Agonists :-

1-Direct acting:-
A-Acetylcholine.
B-Bethanechol.
C-Carbachol.
D-Pilocarpine.

2-Indirect Acting (reversible):-
A-Neostigmine
B-Physostigmine.
C-Pyridostigmine .
D-Rivastigmine.
E-Edrophonium.
H-Galantamine .
G-Tacrine.

Cholinergic agonists (also known as parasympathomimetics) mimic the effects of acetylcholine by binding directly to cholinoceptors.
These agents may be broadly classified into two groups: choline esters, which include acetylcholine and synthetic esters of choline, such as **carbachol** and **bethanechol**. Naturally occurring alkaloids, such as **pilocarpine.**

Acetylcholine:-

Acetylcholine therapeutically no importance because of its **1-multiplicity** of actions and its **2-rapid inactivation** by the cholinesterases.

Acetylcholine has both muscarinic and nicotinic activity, Its actions include**:-**

1- Decrease in heart rate and cardiac output

2-Decrease in blood pressure:

Injection of acetylcholine causes vasodilation and lowering of blood pressure.

Acetylcholine activates M3 receptors found on endothelial cells lining the smooth muscles of blood vessels.

3-Other actions:

A-In the gastrointestinal tract, acetylcholine increases salivary secretion and stimulates intestinal secretions and motility.

B- Bronchiolar secretions are also enhanced

C- In the genitourinary tract, the tone of the detrusor urine muscle is increased, causing expulsion of urine.

D-In the eye, acetylcholine is involved in stimulating ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (Marked constriction of the pupil). Acetylcholine (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

Bethanechol:-

Bethanechol have strong muscarinic activity. Its major actions are on the smooth musculature of the bladder and gastrointestinal tract. It has a duration of action of about 1 hour.

Actions:

directly stimulates muscarinic receptors.

1- causing increased intestinal motility and tone.

2-It also stimulates the detrusor muscles of the bladder whereas the trigone and sphincter are relaxed, causing expulsion of urine.

Therapeutic applications:

In urologic treatment, Bethanechol is used to stimulate the atonic bladder.

Bethanechol may also be used to treat neurogenic atony.

Adverse effects: Bethanechol *:-*

causes the effects of generalized cholinergic stimulation .

These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

Carbachol (carbamylcholine):-

Carbachol has both muscarinic as well as nicotinic actions
A single administration can last as long as 1 hour.

Actions: Carbachol

Locally instilled into the eye, it mimics the effects of acetylcholine, causing miosis and a spasm of accommodation in which the ciliary muscle of the eye remains the eye remains in aconstant state of contraction .

Therapeutic uses: Because of its high potency, receptor non selectivity, and relatively long duration of action, carbachol is rarely used therapeutically except in the eye as a miotic agent to treat **glaucoma** by causing pupillary contraction and decrease in intraocular pressure.

Adverse effects: At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration .

Pilocarpine

The alkaloid pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology.
penetrate the CNS at therapeutic doses.

Actions:

1- Applied topically to the cornea, pilocarpine produces a rapid miosis and contraction of the ciliary muscle ,making it impossible to focus .
2-Pilocarpine is one of the most potent stimulators of secretions (secretagogue) such as sweat, tears, and saliva ,but its use for producing these effects has been limited due to its lack of selectivity.

Pilocarpine is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck.

Sjagrens syndrome, which is characterized by dry mouth and lack of tears, is treated with oral pilocarpine tablets and cevimeline.

Therapeutic:- use in glaucoma:

Pilocarpine is the drug of choice in the emergency lowering of intraocular pressure .
Pilocarpine is causing an immediate drop in intraocular pressure

as a result of the increased drainage of aqueous humor. This action lasts up to 8 hours and can be repeated.

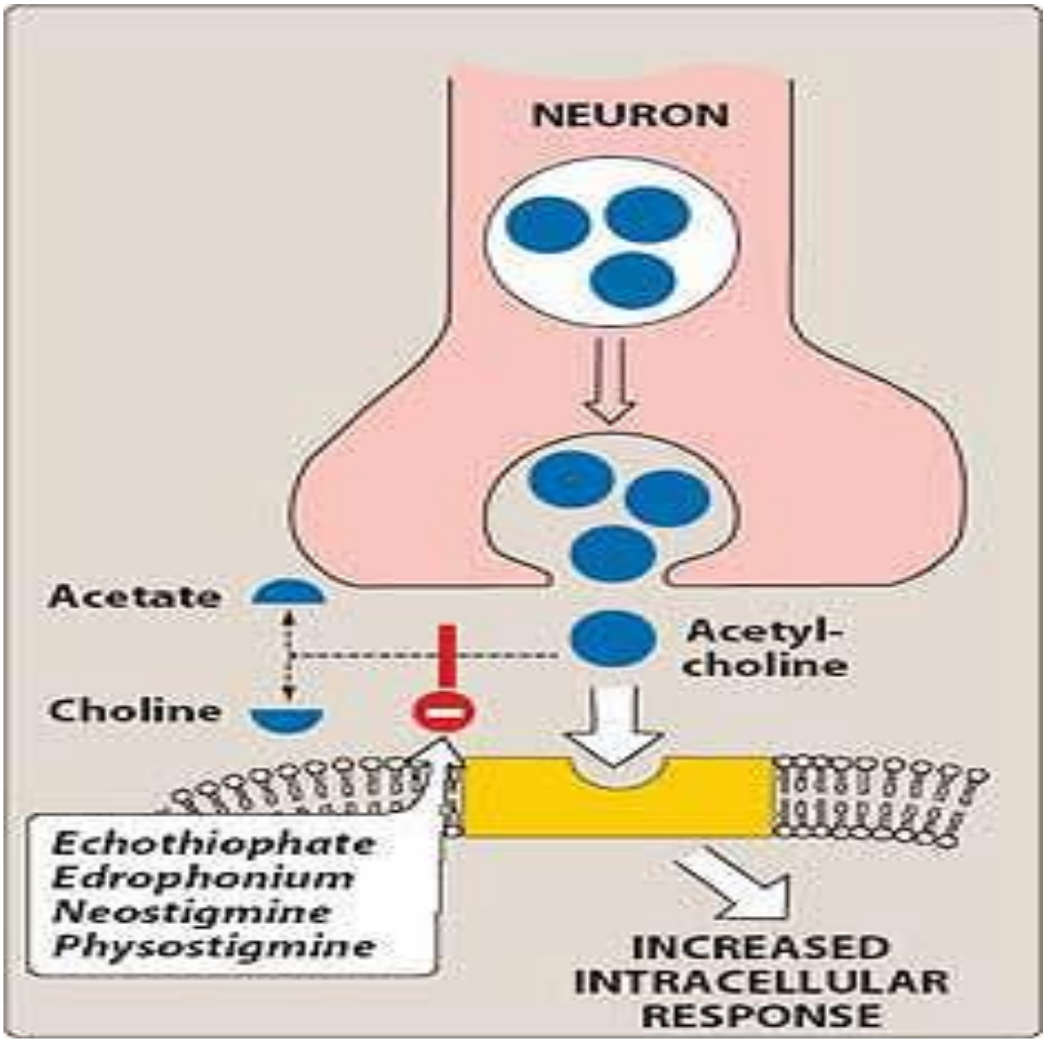
Adverse effects: Pilocarpine can enter the brain and cause CNS disturbances. It stimulates profuse sweating and salivation.

Indirect-Acting Cholinergic Agonsists: Anticholinesterases (Reversible)

Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal.

Inhibitors of acetylcholinesterase indirectly provide acholinergic action by prolonging the lifetime of acetylcholine produced endogenously at the cholinergic nerve endings. This results in the accumulation of acetylcholine in the synaptic space.

These drugs can response at all cholinoceptors in the body , including both muscarinic and nicotinic receptors of the autonomic nervous system, as well as at neuromuscular junction and in the brain.



Physostigmine:-

Actions:

Physostigmine has a wide range of effects as a result of its action, and not only the muscarinic and nicotinic site of the autonomic nervous system but also the nicotinic receptors of the neuromuscular junction are stimulated.

Its duration of action is about 2 to 4 hours, and it is considered to be an intermediate-acting agent.

Physostigmine can enter and stimulate the cholinergic sites in the CNS.

Therapeutic uses:

1-The drug increases intestinal and bladder motility, which serve as its therapeutic action in atony of their organ.

2-Placed topically in the eye, it produces miosis and lowering the intraocular pressure, It is used to treat glaucoma.

3-Physostigmine is also used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, phenothiazines, and tricyclic antidepressants.

Adverse effects: The effects of physostigmine on the CNS may lead to **convulsions** when high doses are used.
Bradycardia.
Inhibition of acetylcholinesterase at the skeletal neuromuscular junction causes the accumulation of acetylcholine and, ultimately, results in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses.

Neostigmine
Neostigmine does not enter the CNS. Its effect on skeletal muscle is greater than that of physostigmine, and it can stimulate contractility before it paralyzes.
Neostigmine has a moderate duration of action ,usually 30 minutes to 2 hours.
1- It is used to stimulate the bladder and GI tract.
2-used as an antidote for tubocurarine and other competitive neuromuscular blocking agents.
3-Neostigmine has found use in symptomatic treatment of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptor at neuromuscular junctions.

Adverse effects:- of neostigmine include those of **generalized cholinergic stimulation**, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.
Neostigmine does not cause CNS side effects and is not used to overcome toxicity of atropine.

Indirect-Acting Cholinergic Agonsists: Anticholinesterases (Irreversible)
Organophosphates, these agents also undergo initial binding and hydrolysis by the enzyme (Anticholinesterase)resulting in a phosphorylated active site. The covalent phosphorus-enzyme bond is extremely stable and hydrolyzed in water at a very slow rate (hundreds of hours). After the initial binding-hydrolysis step, the phosphorylated enzyme complex may undergo a process called **aging.**
If given before aging has occurred, strong nucleophiles like

pralidoxime are able to split the phosphorus-enzyme bond and can be used as "cholinesterase regenerator drugs for organophosphate insecticide poisoning .

Echothiophate

Mechanism of action: Echothiophate is an organophosphate that covalently binds via its phosphate group to the serine-OH group at the active site of acetylcholinesterase .
The enzyme is permanently inactivated, and restoration of acetylcholinesterase activity requires the synthesis of new enzyme molecules.
Following covalent modification of acetylcholinesterase, the phosphorylated enzyme slowly releases one of its ethyl groups The loss of an alkyl group, which is called aging, makes it impossible for chemical reactivators, such as pralidoxime to break the bond between the remaining drug and the enzyme.

Actions:

1-Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties),and convulsions.
2-Echothiophate produces intense miosis .
3-Atropine in high dose can reverse many of the muscarinic and some of the central effects of echothiophate.
Therapeutic uses: An ophthalmic solution of the drug is used directly in the eye for the chronic treatment of glaucoma .
Echothiofate is not a first-line agent in the treatment of glaucoma.

Reactivation of acetylcholinesterase:

Pralidoxime can reactivate inhibited acetylcholinesterase.
It is unable to penetrate into the CNS.
It essentially displaces the phosphate group of the organophosphate and regenerates the enzyme .
If given before aging of the alkylated enzyme occurs, it can reverse the effects of echothiophate.