Chapter ... 9

# PARASYMPATHOMIMETICS

### ♦ LEARNING OBJECTIVES ♦

After completing this unit, reader should be able to:

- ❖ Describe the pharmacodynamic properties of parasympathomimetics.
- ❖ Identify major adverse effects and clinical uses of parasympathomimetics drugs.

## 9.1 INTRODUCTION

The sympathetic and parasympathetic nervous systems usually do opposite things in the body. The sympathetic nervous system prepares body for physical and mental activity. It makes heart beat faster and stronger, opens airways for breathing more easily, and inhibits digestion. Whereas the parasympathetic nervous system is responsible for bodily functions at rest it stimulates digestion, activates various metabolic processes and helps us to relax. But the sympathetic and parasympathetic nervous systems do not always work in opposite directions; they sometimes complement each other too.

**Cholinergic Neurotransmitter:**

Acetylcholine is the major transmitter of the parasympathetic nervous system, but is also the transmitter at the ganglia of both the sympathetic and sympathetic nervous systems and the somatic nervous system. Cholinergic nerves are also present within the CNS. For this reason, drugs that modulate cholinergic neurotransmission can potentially produce a range of effects. Fewer responses are achieved by using drugs which act more selectively at muscarinic or nicotinic receptors.

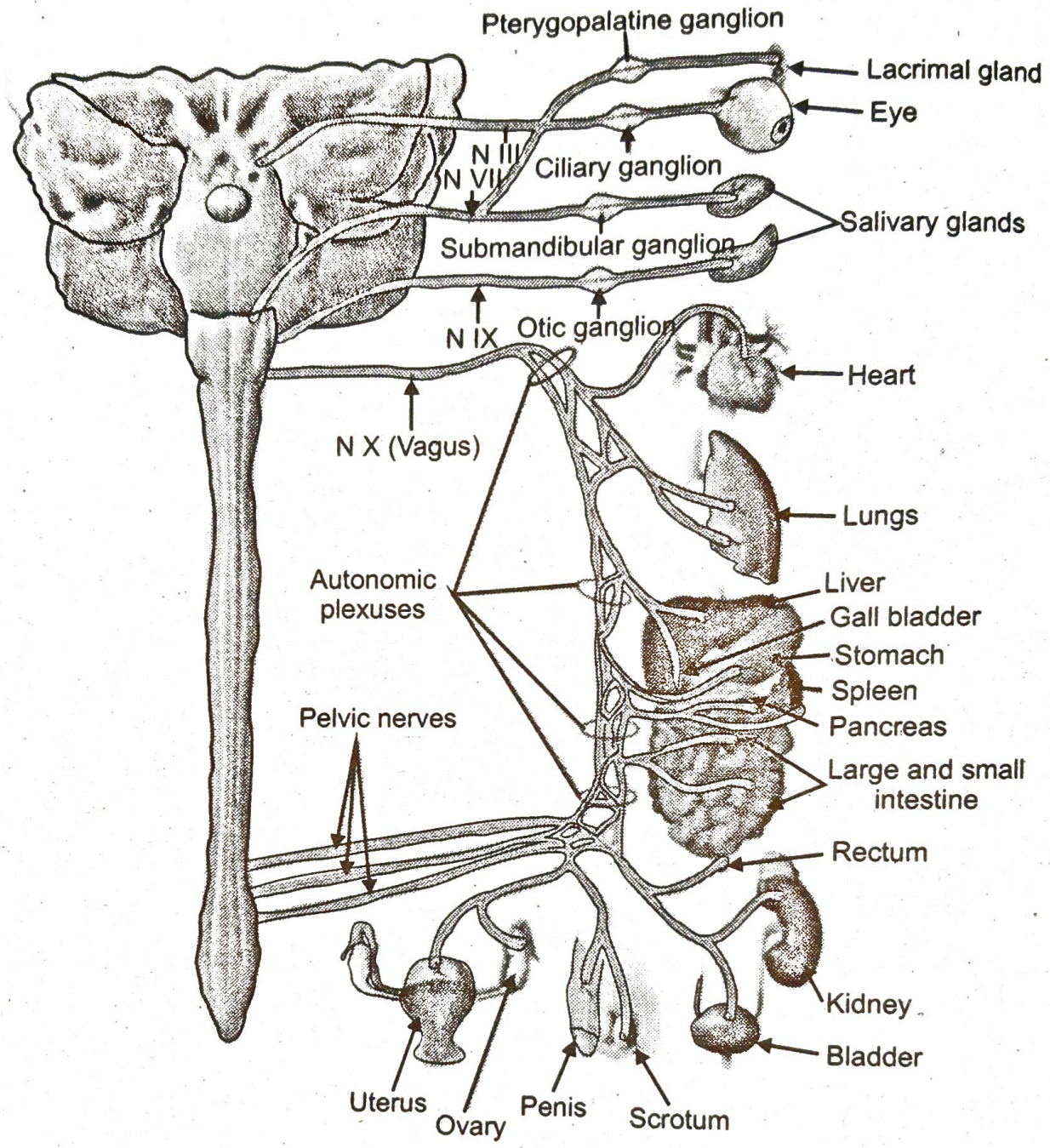



**Fig. 9.1: Parasympathetic Innervation**

## 9.2 ACETYLCHOLINE RECEPTORS

Acetylcholine Receptors are mainly of two types, and provide binding site for acetylcholine and transmit its signal: muscarinic AChRs and nicotinic AChRs, which are named after the agonists muscarine and nicotine, respectively. These receptors are functionally different, the muscarinic type being G-protein coupled receptors (GPCRs) that mediate a slow metabolic response via second messenger cascades, while the nicotinic type are ligand-gated ion channels that mediate a fast synaptic transmission of the neurotransmitter.

**Muscarinic acetylcholine receptor:** Muscarinic receptors, or mAChRs, are acetylcholine receptors that form G protein-receptor complexes in the cell membranes of certain neurons

and other cells. They play several roles, including acting as the main end-receptor stimulated by acetylcholine released from post-ganglionic fibers in the parasympathetic nervous system. Muscarinic receptors were named as such because they are more sensitive to muscarine than to nicotine. Muscarinic acetylcholine receptors use an intracellular secondary messenger system involving an increase of intracellular calcium to transmit signals inside cells. Binding of acetylcholine to a muscarinic AChR causes a conformational change in the receptor that is responsible for its association with and activation of an intracellular G protein, the latter converting GTP to GDP in order to become activated and dissociate from the receptor. The activated G protein can then act as an enzyme to catalyse downstream intracellular events. Muscarinic receptors are involved in a large number of physiological functions including heart rate and force, contraction of smooth muscles and the release of neurotransmitters.

There are five subtypes of muscarinic AChRs based on pharmacological activity: $M_1$-$M_5$. All five are found in the CNS, while $M_1$-$M_4$ are also found in various tissues: $M_1$ AChRs are common in secretory glands; $M_2$ AChRs are found in cardiac tissue; $M_3$ AChRs are found in smooth muscles and in secretion glands. M1, M3 and M5 receptors cause the activation of phospholipase C, generating two secondary messengers ($IP_3$ and DAG) eventually leading to an intracellular increase of calcium, while $M_2$ and $M_4$ inhibit adenylate cyclase, thereby decreasing the production of the second messenger cAMP. The activation of the $M_2$ receptor in the heart is important for closing calcium channels in order to reduce the force and rate of contraction.

**Table 9.1: Classification of Muscarinic acetylcholine receptor**

| Types of receptor | Location | Pathways | Role |
|---|---|---|---|
| $M_1$ | Autonomic ganglia, gastric gland, hippocampus from limbic system and at the corpous striatum. | **Gq** protein and activates phospholipase C (PLc) which generate DAG and IP3 as second messenger. | Increase Gastric and Histamine secretion. |
| $M_2$ | Located on the heart (SA node, AV node, atria, ventricle), on the cholinergic nerve ending and visceral smooth muscle. | They act through **Gi** protein which inhibits adenyl cyclase. | Resulting in hyperpolarisation of the neurons and decrease activity of SA node and conduction through AV node leads to bradycardia. As an inhibitory autoreceptor to acetylcholine release, albeit functioning actively primarily in the hippocampus and cerebral cortex. And inhibit all the functional activities. |

| Types of receptor | Location | Pathways | Role |
|---|---|---|---|
| $M_3$ | It is located on the visceral smooth muscle, iris, ciliary muscle and exocrine glands. | They are also GPCRs acts by Gq protein. | Increase exocrine secretion, smooth muscle contraction. |
| $M_4$ | CNS | Acts through Gi protein. | Inhibitory autoreceptors for acetylcholine. Activation of $M_4$ receptors inhibits acetylcholine release in the striatum. |
| $M_5$ | CNS | It acts by Gq protein. | Such as adenylate cyclase inhibition, phosphoinositide degradation and potassium channel modulation. |

**Nicotinic acetylcholine receptor:** Nicotinic receptors are characterised through their interaction with nicotine in tobacco. The nicotinic AChRs are ligand-gated ion channels that form pores in cell's plasma membranes, mediating fast signal transmission at synapses. Nicotinic AChRs are involved in a wide range of physiological processes, and can be either neuronal or muscle-type. Muscle-type nicotinic AChRs are localized at neuromuscular junctions, where an electrical impulse from a neuron to a muscle cell signals contraction and is responsible for muscle tone. Many types of neuronal nicotinic AChRs are located at synapses between neurons, such as in the CNS where they are involved in cognitive function, learning and memory, arousal, reward, motor control and analgesia. The binding of acetylcholine to nicotinic AChRs brings about their activation. When two molecules of acetylcholine bind a nicotinic AchR, a conformational change occurs in the receptor, resulting in the formation of an ion pore. At the neuromuscular junction, the opening of a pore produces a rapid increase in the cellular permeability of sodium and calcium ions, **resulting in** the depolarisation and excitation of the muscle cell, thereby producing a muscular contraction.

The activation of neuronal nicotinic AChRs also causes the movement of cations through the opening of an ion channel, with the influx of calcium ions affecting the release of neurotransmitters. Nicotinic AChRs on a postganglionic neuron are responsible for the initial fast depolarisation of that neuron. However, the subsequent hyperpolarisation and slow depolarisation, which represent the recovery of the postganglionic neuron from stimulation, are mediated by muscarinic AChR types $M_2$ and $M_1$, respectively. The binding of nicotine can activate nicotinic AChRs, modifying the neurons in two ways: the depolarisation of the membrane through the movement of cations results in an excitation of the neuron, while the influx of calcium acts through intracellular cascades affect the regulation of certain genes and the release of neurotransmitters.

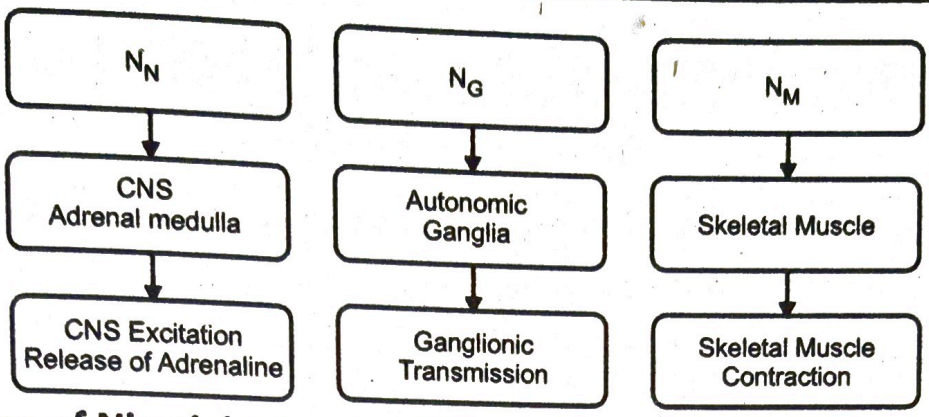
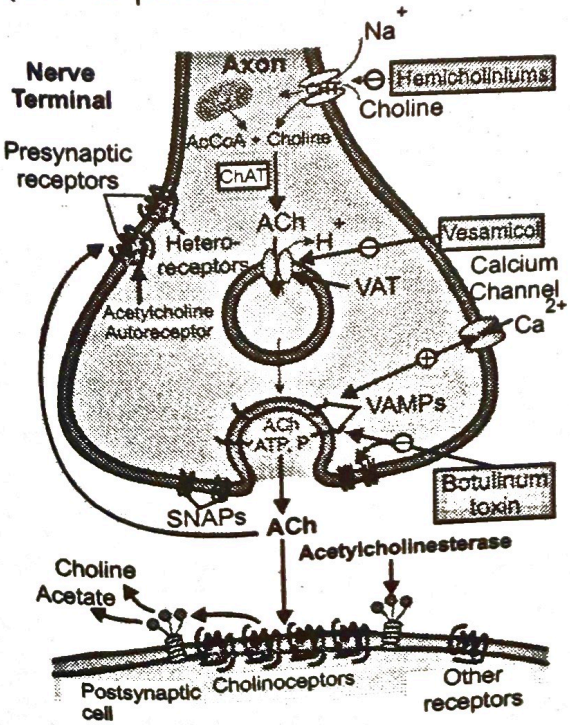



**Fig. 9.2: Location of Nicotinic receptor (N = Nicotinic receptor = Muscarinic receptor)**

**Cholinergic transmission:** Acetylcholine is a major neurotransmitter at autonomic as well as somatic sites. The two enzymes acetyltransferase (choline acetylase (ChAT) and acetyl cholinesterase (AChE) involved in the synthesis and degradation of acetylcholine.

**Synthesis, Storage and destruction of Acetylcholine (ACh):** Acetylcholine is synthesized locally in the cholinergic nerve endings by the following pathways:-

1. Choline is actively taken up by the axonal membrane acetylated with the help of ATP and coenzyme-A by the enzyme **cholineacetylase** present in the axoplasm. **Hemicholiniums** blocks choline uptake and inhibit the acetylcholine synthesis.
2. Synthesized acetylcholine is stored in ionic solution within small synaptic vesicles, but some free ACh is also present in the cytoplasm of cholinergic terminals. Transport of ACh into synaptic vesicles is blocked by **vesamicol**.
3. Release of ACh from nerve terminals occurs by exocytosis in response to a nerve action potential synchronous in synapse. Release is blocked by botulinus toxin and stimulate by black widow spider toxin.
4. Immediately after release, ACh is hydrolysed by the enzyme acetylcholine esterase (true or pseudocholinesterase) and choline is recycled.



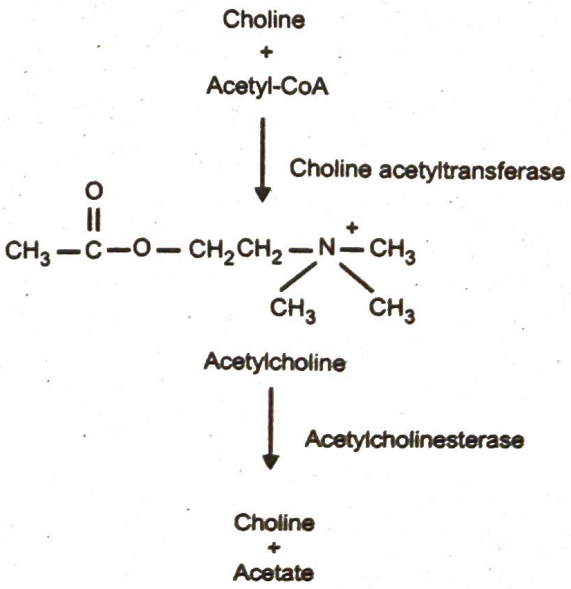




**Fig. 9.3: Cholinergic transmission**

## 9.3 PARASYMPATHOMIMETICS

Parasympathomimetic drugs activate the parasympathetic nervous system. As the neurotransmitter of the PSNS is acetylcholine, parasympathomimetics are also called cholinomimetic agents. These are drugs which produce action similar to that of ACh, either by directly interacting with cholinergic receptors or by increasing availability of ACh at these sites.

These are classified according to whether they act as direct agonists of acetylcholine receptors (ACh) or indirect agonists of ACh (also called anticholinesterase). While direct agonists act by binding directly to muscarinic or nicotinic ACh receptors, indirect agonists prolong the action of endogenous acetylcholine by inhibiting acetylcholinesterase. Direct agonists of ACh are used topically in ophthalmology to induce miosis, while indirect agonists are used to treat, e.g., postoperative ileus or urinary retention and myasthenia gravis.

**Classification of cholinergic agents:**

**A. Direct acting cholinergic agonists**
- **(a) Choline esters:** Acetylcholine, Methacholine, Carbachol, Bethanechol.
- **(b) Cholinomimetic alkaloids:** Muscarine, Pilocarpine, Arecoline, oxytremorine.

**B. Indirect acting cholinergic agents (Anticholinesterases)**
- **(a) Reversible Anticholinesterases**
  - **(i) Carbamates:** Physostigmine, Neostigmine, Pyridostigmine, Edrophonium, Rivastigmine, Donepezil.
  - **(ii) Acridine:** Tacrine.
- **(b) Irreversible Anticholinesterases**
  - **(i) Organophosphates:** Dyflos, Echothiophate, Parathion, Malathion, Diazinon, Tabun, Sarin Soman.
  - **(ii) Carbamates:** Carbaryl, Propoxur.

### 9.3.1 Choline Esters

Acetylcholine is an ester of choline with acetic acid, available in powder form as chloride or bromide; it is extremely hygroscopic. It rapidly undergoes hydrolysis in neutral or alkaline medium and the solution has to be preserved at an acidic pH. Given orally, it is rapidly destroyed in the gastrointestinal tract and hence, it has to be administered intravenously to elicit its pharmacological actions.

**Mechanism of Action:** The mechanisms of action of endogenous ACh at the postjunctional membranes of the effector cells and neurons that correspond to the four classes of cholinergic synapses.

1. Autonomic effector sites, innervated by postganglionic parasympathetic fibres.
2. Sympathetic and parasympathetic ganglion cells and the adrenal medulla innervated by preganglionic autonomic fibres.
3. Motor end plates on skeletal muscle, innervated by somatic motor nerves.
4. Certain synapse peripherally and within the central nervous system where the actions can be either pre or postsynaptic.

When ACh is administered systemically, it has the potential to act at all of these sites; however, as a quaternary ammonium compound, its penetration into the CNS is limited, and butyrylcholinesterase in the plasma reduces the concentrations of ACh that reach areas in the periphery with low blood flow.

All cholinergic drugs produce their effect through two types of receptors:

1. **Muscarinic receptors:** The actions are similar to those of muscarine at the postganglionic sites of the parasympathetic system. These actions are antagonized by atropine organs affected by muscarinic action are heart, arterioles, salivary glands, penis, eyes, stomach, intestine, bronchi, urinary bladder, uterus, spleen and skin vessels. Muscarinic receptors are metabotropic. That is they are associated with trimeric guanine nucleotide binding proteins (G proteins). When an agonist binds to muscarinic receptors, G proteins exchange GDP for GTP and as a consequence of this the α subunit of the protein, bound to GTP dissociates from the β and α-subunits, and α-GTP stimulates the effector of the cell to initiate the chain of events that lead to intracellular responses. Effectors with which G proteins interact include adenyl cyclase and phospholipase-C. $M_1$, $M_3$ and $M_5$ receptors activate a G protein that causes stimulation of phospholipase-C activity. $M_2$ and $M_4$ receptors interact with Gi protein which leads to the inhibition of adenyl cyclase, activation of $K^+$ channel (Heart), modulation of $Ca^{2+}$ channels in certain cell types.

2. **Nicotinic receptors:** Nicotinic receptors are found in autonomic ganglia and skeletal muscles. These effects are similar to those produced by the alkaloid nicotine, hence the name. The effect at the ganglionic level is antagonized by ganglionic blocking agents like hexamethonium and that at the skeletal muscles by neuromuscular blocking agents like d-tubocurarine. Nicotinic receptors are ionotropic receptors. They are ligand gated ion channels through which $Na^+$, $K^+$ and $Ca^{2+}$ flow. Neurotransmitters regulate the opening and closing of the channels.

(i) **$N_N$ Nicotinic Receptor:** It is present on the cell body of the autonomic ganglia. It is a trimeric protein molecule. It is responsible for the EPSP and action potential in the postsynaptic neuron and for neuronal transmission.

(ii) **$N_M$ Nicotinic Receptor:** They are present at the end plate of skeletal muscle fibres. It is a pentameric protein molecule. These receptors are responsible for the end plate potential and neuromuscular transmission.

**Table 9.2: Pharmacological effects of Choline Esters**

| Organ system | Response |
|---|---|
| **Muscarinic Responses** | |
| Cardiovascular system | • Vasodilation<br>• Negative ionotropic and chronotropic effect on heart.<br>• Decrease in cardiac output |
| Gastrointestinal system | • Increase in tone and motility<br>• Increase in secretion (gastric, pancreatic, intestinal)<br>• Relaxation of sphincters<br>• Contraction of gall bladder and ducts. |
| Respiratory system | • Bronchoconstriction<br>• Increase in tracheobronchial secretions. |

| Organ system | Response |
|---|---|
| Urinary tract | • Contraction of detrusor muscle of bladder<br>• Relaxation of trigone and external sphincter<br>• Increase in tone and motility of ureters |
| Uterus | • Contraction of uterine smooth muscle. |
| Skin and salivary gland | • Increases sweating and salivation. |
| Eye | • Contraction of circular muscle of iris → miosis.<br>• Contraction of ciliary muscle → spasm of accommodation, increased outflow facility, reduction in intraocular tension (especially in glaucoma).<br>• Increases lacrimal secretion. |
| Male sex organs | • Erection |
| **Nicotinic Responses** | |
| Skeletal muscle | • Muscular fasciculations<br>• If drug persists for a long time → persistant depolarization → paralysis |
| Autonomic ganglia | • Stimulation of both sympathetic and parasympathetic ganglia at higher doses. |
| Adrenal medulla | • Release of epinephrine → increase in B.P. |

**Therapeutic uses:** Owing to its extremely transient action. ACh cannot be employed for any therapeutic purpose. Hence, several acetylcholine substitutes have been synthesized which are effective orally and more selective in their action.

**Methacholine:** Methacholine is a quaternary ammonium parasympathomimetic agent with the muscarinic actions of ACh.It differs from acetylcholine in being effective orally though its absorption on oral administration is variable. It is hydrolyzed by acetylcholinesterase at a considerably slower rate than acetylcholine and is more resistant to hydrolysis by non-specific (pseudo) cholinesterases so that its actions are more prolonged. It is used as a parasympathomimetic bronchoconstrictor agent and as a diagnostic aid for bronchial asthma.

**Carbachol:** Carbachol is also known as carbamylcholine is a cholinomimetic drug that binds and activates acetylcholine receptors. Thus it is classified as a cholinergic agonist. It is more potent than methacholine and bethanechol. Carbachol is resistant to both true and pseudocholinesterase and better absorbed from the gastrointestinal tract than other choline esters. It is primarily used for various ophthalmic purposes, such as for treating glaucoma, or for use during ophthalmic surgery. It is generally administered as an ophthalmic solution (i.e. eye drops).

Carbachol, when administered parenterally in therapeutic doses in man, produces flushing of the face, sweating, salivation and lacrimation. The carbachol increases carbachol gastrointestinal and urinary tract activity may produce desire for defecation and micturition. Carbachol occasionally produces hypotension and syncope particularly in elderly subjects. The muscarinic effects of carbachol are not adequately antagonized by atropine.

**Preparations and dosage:** Carbachol tablet contains 1 mg of the drug.

**Dose:** 1 to 4 mg. Carbachol injection contains 0.25 mg by subcutaneous injections. For ophthalmic use 3% eye drop.

**Bethanechol:** Bethanechol chloride as a cholinergic agent is a synthetic ester which is structurally and pharmacologically related to acetylcholine. It is a white, hygroscopic crystalline powder having a slight amine-like odor, freely soluble in water, and has a molecular weight of 196.68. Like Carbachol, this choline ester, is resistant to hydrolysis by both true and pseudocholinesterase and has mainly muscarinic actions. It exerts effects mainly on the GI tract and the urinary bladder. Side effects are prominent bleching, colic, involuntary urination, defecation flushing, sweating, fall in BP, bronchospasm.

**Indications:** Bethanechol chloride is indicated for the treatment of acute postoperative and post-partum non-obstructive (functional) urinary retention and for neurogenic atony of the urinary bladder with retention.

**Dosage and Administration:** Dosage must be individualized, depending on the type and severity of the condition to be treated. Preferably give the drug when the stomach is empty. If taken soon after eating, nausea and vomiting may occur.

The usual adult oral dose ranges from 10 to 50 mg three or four times a day. The minimum effective dose is determined by giving 5 to 10 mg initially and repeating the same amount at hourly intervals until satisfactory response occurs, or until a maximum of 50 mg has been given. The effects of the drug sometimes appear within 30 minutes and are usually maximal within 60 to 90 minutes. The drug's effects persist for about one hour.

**Contraindication for the use of choline esters:**

- **Hyperthyroidism:** as these agents may precipitate cardiac arrhythmias.
- **Bronchial asthma:** because of the danger of aggravating or precipitating bronchospasm.
- **Peptic ulcer:** as these agents increase the gastric secretion.
- **Myocardial infarction:** because of the danger of hypotension and development of conduction blocks.

**Cholinomimetic alkaloids:** Pilocarpine is obtained from *Pilocarpus microphyllus* and *Pilocarpus jaborandi*. Muscarine is obtained from *Amanita muscaria*. Arecoline is obtained from *Areca catechu*.

It acts by direct stimulation of the effector organs getting cholinergic innervation and produces both muscarinic and nicotinic actions of acetylcholine. The former are antagonized by atropine. Pilocarpine usually produces hypertension and tachycardia by stimulation of the sympathetic ganglia, particularly in spinal animals. When applied topically to the eye, Pilocarpine produces miosis, a transient increase followed by a more sustained fall in the intraocular tension and a spasm of accommodation. Pilocarpine produces an initial stimulation of the central nervous systemic pilocarpine therapy.

**Pharmacological Properties:**

***Smooth muscle:***

- Contraction of GIT smooth muscle → increase in tone and motility.
- Bronchoconstriction.
- Increase in tone and motility of ureters, urinary bladder, gall bladder and ducts.
- Eye – Miosis, spasm of accommodation, fall in intraocular pressure.

**Exocrine glands:**

- Profuse sweating (diaphoresis) in man.
- Increase in salivary, lacrimal, gastric, pancreatic, intestinal and bronchial secretions.

**CVS:**

- Fall in blood pressure.
- Slowing of heart beat.

**Adverse reactions:** It has all the side effects of choline esters. Because of the prominent secretory response, pulmonary edema is major hazard of systemic pilocarpine therapy.

**Preparation and dosage:** 1-4% pilocarpine nitrate eye drops.

**Therapeutic uses:**

The drug is too toxic for systemic use. Pilocarpine alone (0.5-4% aqueous solution) or in combination with 1% eserine is used to reduce intraocular tension in acute congestive glaucoma. Pilocarpine is often used alternately with mydriatics like homatropine.

### 9.3.2 Anticholinesterase Agents

These are indirectly acting parasympathomimetic agents. They inhibit acetyl cholinesterase (AChE) enzyme resulting in accumulation of ACh at cholinergic effector sites. So, their effects are due to accumulation and function of ACh.

**These drugs may be classified into two groups:**

1. **Reversible Inhibitors:** They bind to the active sites of the enzyme reversibly to act as an alternate substrate for AChE. They do not allow the main substrate, ACh, to bind to the enzyme resulting in inhibition of hydrolysis of ACh. In compare to physostigmine or neostigmine (long acting), the binding with edrophonium is easily reversible (short acting).

**Physostigmine:** This is an alkaloid obtained from the calabar bean, the dried ripe seed of African woody climber Physostigma venenosum. A cholinesterase inhibitor that is rapidly absorbed through membranes. It can be applied topically to the conjunctiva. It also can cross the blood-brain barrier and is used when central nervous system effects are desired, as in the treatment of severe anticholinergic toxicity.

**Pharmacodynamics:** Physostigmine is a parasympathomimetic, specifically, a reversible cholinesterase inhibitor which effectively increases the concentration of acetylcholine at the sites of cholinergic transmission. Physostigmine is used to treat glaucoma. Because it crosses the blood-brain barrier, it is also used to treat the central nervous system effects of atropine overdose and other anticholinergic drug overdoses. Physostigmine can reverse both central and peripheral anticholinergic.

**Mechanism of action:** Physostigmine inhibits acetylcholinesterase, the enzyme responsible for the breakdown of acetylcholine. By interfering with the metabolism of acetylcholine, physostigmine indirectly stimulates both nicotinic and muscarinic receptors due to the consequential increase in available acetylcholine at the synapse.

**Therapeutic uses:** For the treatment of glaucoma, and in the treatment of severe anticholinergic toxicity.

**Preparations and dosage:** Physostigmine salicylate is used in eye as 0.25-0.50% aqueous solution. Physostigmine salicylate inj. contains 2 mg/2 ml ampoule.

**Side effect:** Side effects include increased sweating, loss of bladder control, muscle weakness, nausea, vomiting, diarrhoea, or stomach cramps or pain, shortness of breath, tightness in chest, or wheezing, slow or irregular heartbeat, unusual tiredness or weakness, watering of mouth, blurred vision or change in near or distant vision, and eye pain.

**Table 9.3: Pharmacodynamic Action of Anticholinesterase Agents**

| | |
|---|---|
| **Physostigmine (eserine)** | • It is an alkaloid obtained from *Physostigma venenosum.*<br>• It is well absorbed from GIT, mucous membrane and S.C. tissues.<br>• It induces miosis.<br>• Large doses may cause fasciculation, and then paralysis of skeletal muscles. |
| **Neostigmine** | • It is a synthetic compound, stable for longer time than physostigmine.<br>• It is well absorbed orally. It does not penetrate BBB.<br>• It stimulates the actions of ACh.<br>• In addition to the anticholinesterase activity, neostigmine also has a direct action on nicotinic receptors of skeletal muscle.<br>• It reverses the neuromuscular blockade produced by curare and its derivatives. The mechanism of this action involves cholinesterase inhibition, release of increased amount of ACh from nerve endings, and a direct action on skeletal muscle nicotinic receptors.<br>• It is the drug of choice in the treatment of myasthenia gravis. |
| **Edrophonium** | • It is more rapidly absorbed and has a shorter duration of action than neostigmine. It is administered parenterally.<br>• Its actions are similar to those of neostigmine, except that at high dose it stimulates neuromuscular junction without affecting muscarinic effector organ. |

**Therapeutic uses of reversible anticholinesterases:**

- Glaucoma (Glaucoma is a group of related eye disorders that cause damage to the optic nerve that carries information from the eye to the brain.)
- Acute congestive glaucoma
- Chronic (wide angle) simple glaucoma
- Myasthenia gravis
- Postoperative paralytic ileus and urinary retention
- Snake venom poisoning
- Curare poisoning

2. **Irreversible Inhibitors:** The organophosphorous compounds bind to esteretic site of the enzyme by a covalent bond resulting in the formation of an irreversible or very highly stable complex. Unless regenerated by drugs, the inhibited enzyme cannot hydrolyse ACh, which is accumulated at its effector sites and produces persistant cholinergic responses.

**Organophosphorous poisoning:** Organophosphorous compounds are of importance from the toxicology point of view. The poisoning may occur due to accidental consumption of agricultural products sprayed with insecticides, homicidal or suicidal tendencies, or in persons occupationally involved in spraying insecticides. The signs of acute poisoning are as follows.

***Muscarinic effects:*** Miosis of eye, conjuctival congestion, watery nasal discharge, bronchospasm, increased bronchial secretions, tightness in the chest, bradycardia, hypotension, involuntary defecation and urination.

***Nicotinic Effects:*** Fatigability and weakness or muscles, involuntary twitching, fasiculations and tachycardia.

***Central Nervous system effects:*** Ataxia, confusion, slurred speech, loss of reflexes, convulsion, coma and respiratory paralysis. Death may occur due to respiratory failure and cardiovascular failure.

**Antidotes:** Antidotes are atropine (2-4 mg I.V. total 50 mg) and cholinesterase reactivates. Besides antidotal therapy, one has to give artificial respiration or oxygen inhalation and anticonvulsant agents.

Chronic toxicity with Organophosphorous compounds causes demyelination of nerves leading to polyneuritis.

**Regeneration of Inhibited AChE:** The enzyme re-activators or oximes (2 PAM or pralidoxime, obidoxime, diacetyl monoxime, etc.) remove organophosphorous compounds (after binding with them) from the active sites of AChE. The free regenerated enzyme is now able to hydrolyse ACh.

## QUESTIONS

1. What is a parasympathomimetics agent?
2. Enlist the cholinergic receptor with their location.
3. Classify parasympathomimetics agents.
4. Write the biosynthetic pathways for synthesis of acetylcholine.
5. Classify cholinergic agent with suitable examples. Write pharmacology of reversible anticholinesterases.
6. Write the pharmacological account of acetylcholine.
7. Write the pharmacological account of neostigmine.

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