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Pharmacology *for* Nurses

As per Revised INC Syllabus for BSc Nursing

Semester III & IV

Padmaja Udaykumar



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SECTION 5

Drugs Acting on Autonomic Nervous System

SECTION OUTLINE

9. Cholinergic, Anticholinergic, Adrenergic and Antiadrenergic Drugs

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CHAPTER 9

Cholinergic, Anticholinergic, Adrenergic and Antiadrenergic Drugs

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INTRODUCTION TO AUTONOMIC PHARMACOLOGY

The nervous system is divided into central and peripheral nervous systems **(Flowchart 9.1)**. The peripheral nervous system consists of autonomic and somatic nervous systems. The autonomic nervous system (ANS) is *not under voluntary control* and therefore was so named by Langley (*Autos* = self, *nomos* = governing—in Greek). The ANS innervates the heart, the smooth muscles, the glands and the viscera and controls the functions of these organs **(Fig. 9.1)**.

The centers for autonomic reflexes are present in the hypothalamus, medulla and spinal cord. Hypothalamus coordinates the autonomic activity.

The ANS consists of two major divisions—the *sympathetic* and the *parasympathetic*

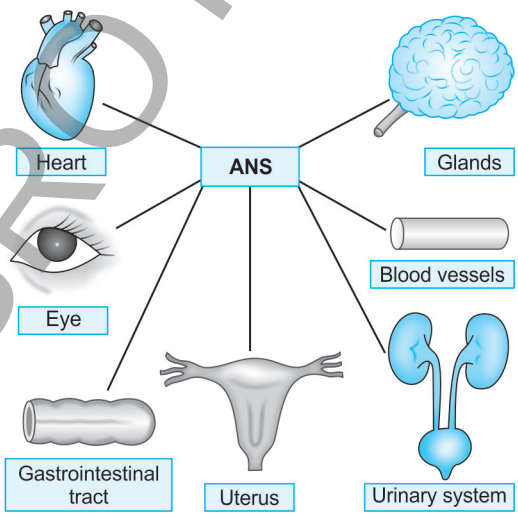
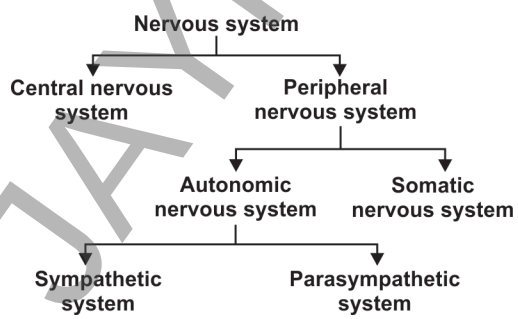


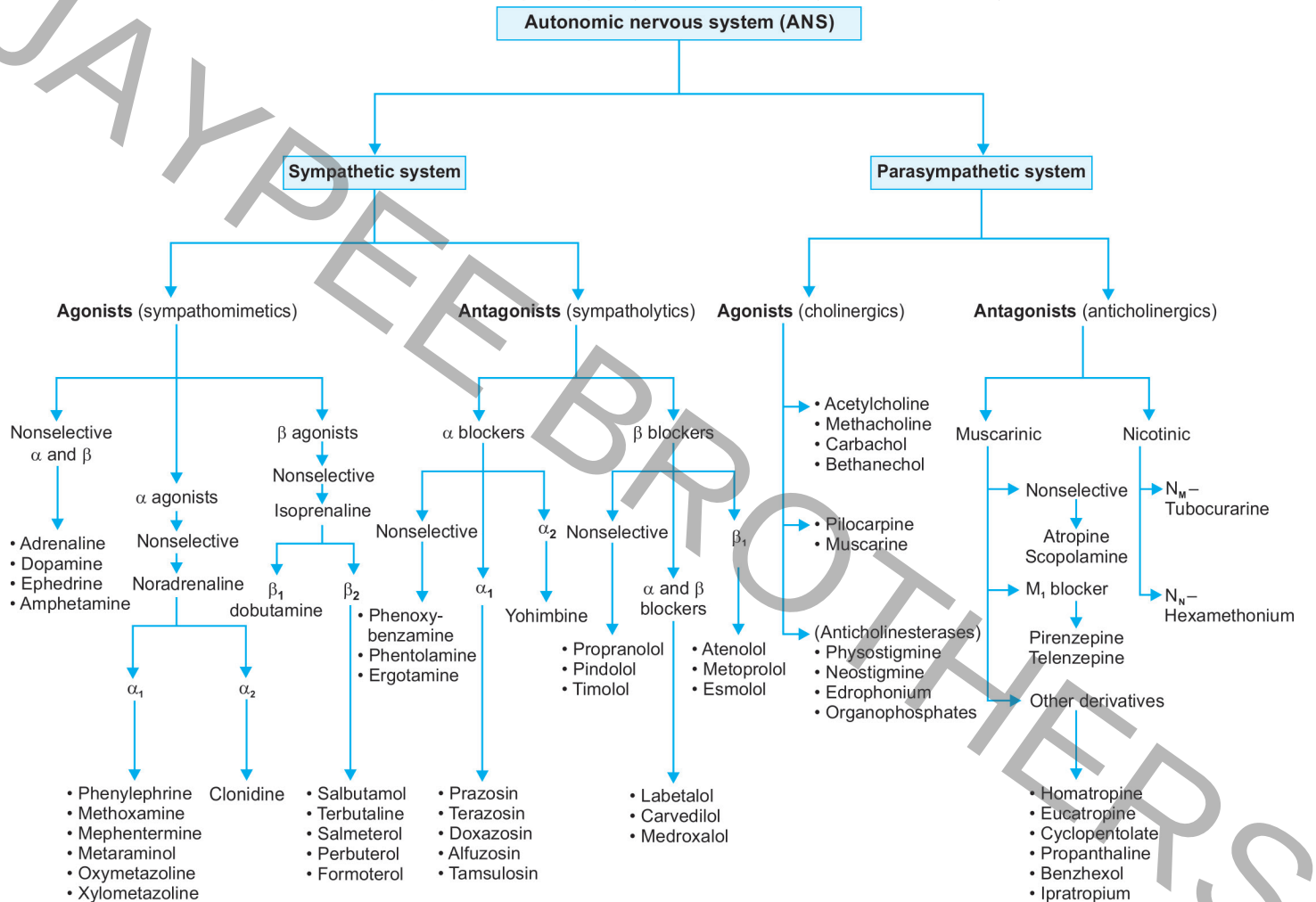
Fig. 9.1: Structures under the control of autonomic nervous system (ANS).

Flowchart 9.1: Nervous system.



(Flowchart 9.2). Most of the viscera have both sympathetic and parasympathetic innervation. The two divisions have opposing effects and normally their effects are in a state of equilibrium. The prime function of the sympathetic system is to help a person to adjust to stress and prepare the body for fight or flight reactions, while the parasympathetic mainly participates in tissue building reactions. Man can still survive without sympathetic system (if maintained stress-free) but not without parasympathetic.

Flowchart 9.2: Examples of drugs acting on sympathetic and parasympathetic nervous system.



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Neurotransmitters: For the transmission of an impulse across a synapse, a neurohumoural transmitter substance is released into the synaptic cleft. In the ANS, the neurotransmitters released are acetylcholine, noradrenaline, dopamine and in adrenal medulla, they are adrenaline and noradrenaline.

CHOLINERGIC SYSTEM

Acetylcholine (ACh) an ester of choline, is the neurotransmitter of the parasympathetic system. The nerves that synthesize, store and release ACh are called *'cholinergic.'*

The *sites* of release of acetylcholine are **(Fig. 9.2)**:

1. Ganglia—all the preganglionic fibers of ANS, i.e. at both the sympathetic and parasympathetic ganglia.
2. The postganglionic parasympathetic nerve endings.
3. Sweat glands—the sympathetic postganglionic nerve endings supplying the sweat glands.
4. Skeletal muscles—somatic nerve endings supplying skeletal muscles.
5. Adrenal medulla.
6. Central nervous system (CNS)—brain and spinal cord.

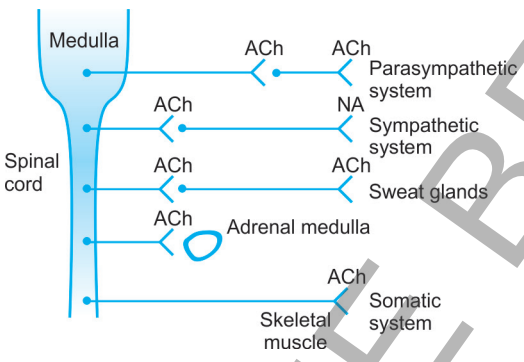


Fig. 9.2: Sites of release of neurotransmitters—acetylcholine and noradrenaline in the peripheral nervous system.

Synthesis of acetylcholine: Acetylcholine is synthesized from acetyl-CoA and choline, catalyzed by the enzyme choline acetyltransferase. This ACh is stored in small oval vesicles in the cholinergic nerve terminals.

Transmission of an impulse: When an action potential reaches the presynaptic membrane, ACh is released into the synaptic cleft **(Fig. 9.3)**. This ACh binds to and activates the cholinergic receptor on the postsynaptic membrane leading to the depolarization of this membrane. Thus the impulse is transmitted across the synapse.

ACh released into the synaptic cleft is rapidly destroyed by the enzyme acetylcholinesterase (AChE). Then the postsynaptic membrane is repolarized.

Cholinesterases: Acetylcholine is hydrolyzed to choline and acetic acid by the enzymes cholinesterases. Two types of AChE are present:

1. True cholinesterase—at neurons, ganglia and neuromuscular junction (NMJ).

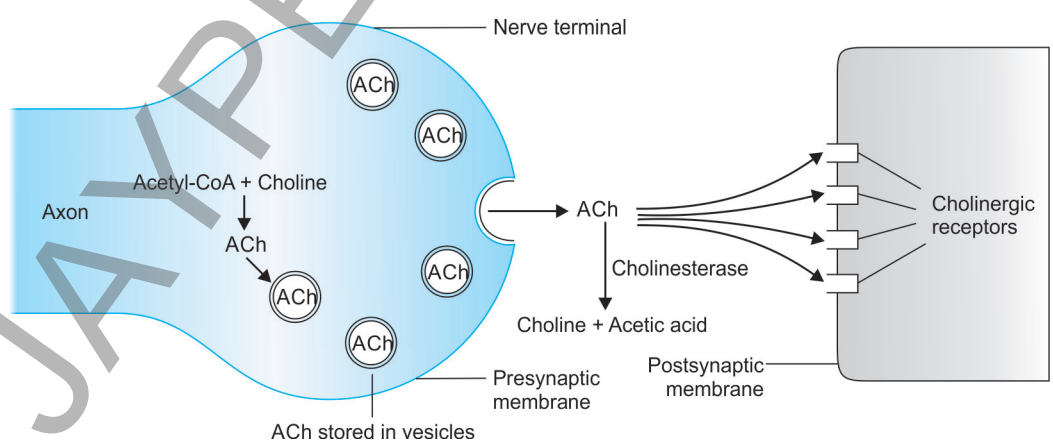
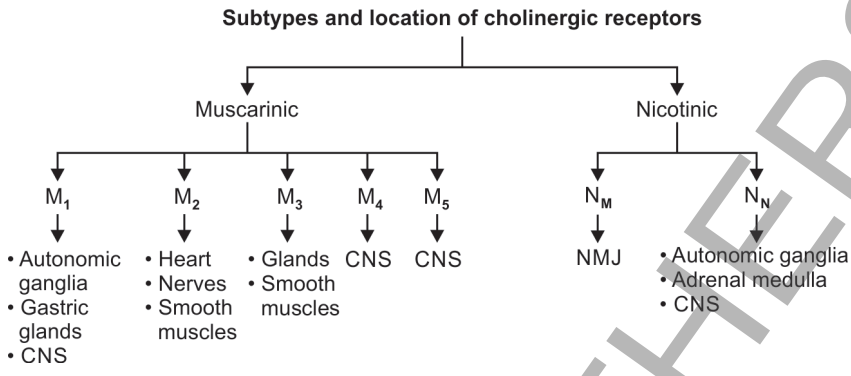


Fig. 9.3: Cholinergic transmission—schematic representation.

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Flowchart 9.3: Subtypes and location of cholinergic receptors.



(CNS: central nervous system; NMJ: neuromuscular junction)

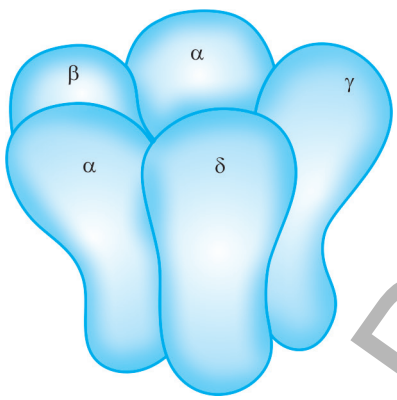


Fig. 9.4: Nicotinic receptor: Nicotinic receptor contains 5 subunits—2α + β + γ + δ. Acetylcholine binds to the sites on α subunits resulting in opening of the channel.

2. Pseudocholinesterase (butyrylcholinesterase)—in plasma, liver and other organs.

Cholinergic receptors: There are two classes of cholinergic receptors—**muscarinic** and **nicotinic**. Muscarinic receptors are present in the heart, smooth muscles, glands, eyes and central nervous system (CNS). Five subtypes of muscarinic receptors, M_1–M_5 are recognized **(Flowchart 9.3)**.

Nicotinic receptors are present in the neuromuscular junction, autonomic ganglia and adrenal medulla. Nicotinic receptors are ion channels **(Fig. 9.4)** made of five subunits (2α + 1β + 1γ + 1δ). Binding of acetylcholine to the receptor opens the channel allowing the entry of Na^+ into the cell. Two subtypes of nicotinic receptors are identified **(Flowchart 9.3)**–N_M receptors are present at the skeletal muscle end plate and N_N receptors at the autonomic ganglia and adrenal medulla.

CHOLINERGIC DRUGS

Cholinergic drugs are chemicals that act at the same sites as acetylcholine and thereby mimic its actions. They are therefore called parasympathomimetics or cholinomimetics.

Cholinergic drugs may be classified as:

1. **Directly acting**
   Esters of choline
   Acetylcholine
   Methacholine
   Carbachol
   Bethanechol
   Cholinomimetic alkaloids
   - Pilocarpine
   - Muscarine.
2. **Indirectly acting**
   (Anticholinesterases)

Reversible	*Irreversible*
• Neostigmine	**Organophosphorus compounds**
• Physostigmine	
• Pyridostigmine	• Malathion
• Ambenonium	• Parathion
• Edrophonium	• Sumithion

DIRECTLY ACTING CHOLINERGIC DRUGS

Acetylcholine

Actions of Acetylcholine

Acetylcholine is taken as the prototype of parasympathomimetic drugs.

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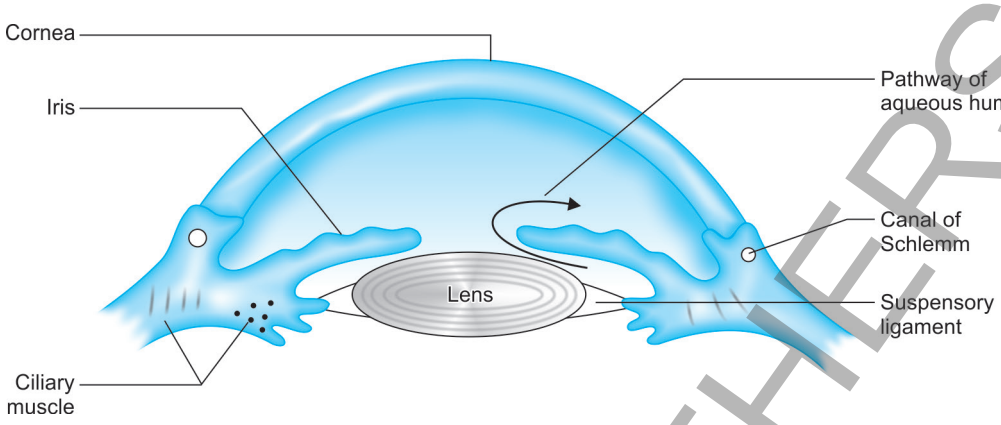
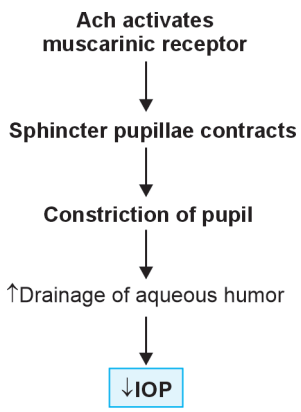


Fig. 9.5: Schematic diagram showing pathway for the drainage of aqueous humor.

Muscarinic Actions

Muscarinic actions resemble the actions of the alkaloid muscarine found in some mushrooms. These actions result from the stimulation of the muscarinic receptors by acetylcholine.

1. **Heart:** The action of ACh is similar to that of vagal stimulation. It reduces the heart rate and force of contraction. In larger doses, AV conduction is depressed.
2. **Blood vessels:** ACh relaxes the vascular smooth muscles and dilates the blood vessels of the skin and mucous membrane. The BP falls due to a fall in total peripheral resistance.
3. **Smooth muscle:** ACh increases the tone of all other (nonvascular) smooth muscles.
   Gastrointestinal tract—tone and peristalsis is enhanced, sphincters are relaxed, resulting in rapid forward propulsion of intestinal contents.
   Urinary bladder—detrusor contracts and trigonal sphincter relaxes—promotes voiding of urine.
   Bronchial smooth muscle—contracts resulting in bronchospasm.
4. **Secretory glands:** Acetylcholine increases the secretions of all glands; salivary, lacrimal, nasopharyngeal, tracheobronchial, gastric and intestinal secretions are increased. Sweating is also increased. Enhanced bronchial secretions and bronchospasm result in severe dyspnea.
5. **Eye:** Acetylcholine brings about constriction of pupil (miosis) by contracting the circular muscles of the iris **(Fig. 9.5)**. Stimulation of muscarinic receptors present in the sphincter pupillae results in miosis. Drainage of aqueous humor is increased and intraocular pressure falls. Ciliary muscle contracts resulting in spasm of accommodation.



Nicotinic Actions

These effects resemble the actions of the alkaloid nicotine and are brought about by stimulation of the nicotinic receptors by acetylcholine.

1. **NMJ:** Acetylcholine brings about contraction of skeletal muscles by stimulating N_M receptors present in the neuromuscular junction. Large doses cause persistent depolarization of skeletal muscles resulting in paralysis.
2. **Autonomic ganglia:** Acetylcholine stimulates the sympathetic and

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Table 9.1: Actions of acetylcholine.	
CVS	Vasodilation, ↓HR, ↓BP
Smooth muscle (Nonvascular)	Contraction→, ↑ gut peristalsis, promotes urine voiding, bronchospasm
Glands	↑ secretion
Eye	Miosis, spasm of accommodation, ↓IOP
NMJ	Muscle contraction
Ganglia	Stimulation

(CVS: cardiovascular system; HR: heart rate; BP: blood pressure; NMJ: neuromuscular junction; IOP: intraocular pressure)

parasympathetic ganglia and the adrenal medulla.

3. **CNS:** Acetylcholine is a neurotransmitter at several sites in the CNS.

The important actions of acetylcholine are summarized in **Table 9.1**.

Uses: Acetylcholine is destroyed in the gut when given orally. On intravenous administration, it is rapidly metabolized by pseudocholinesterases in the plasma and by true cholinesterase at the site of action. Therefore, it is **not used therapeutically** except occasionally as 1% eyedrops to produce miosis during some eye surgeries.

Esters of choline are effective orally; carbachol and bethanechol are resistant to both cholinesterases and have a longer duration of action. Their muscarinic actions are prominent with a sustained effect on GI smooth muscles and urinary bladder. Methacholine is rarely used. Carbachol is used in glaucoma. Bethanechol may be used in:

- Hypotonia of bladder and GI smooth muscles
- Some cases of postoperative paralytic ileus
- Urinary retention
- Xerostomia as an alternative to pilocarpine.

Adverse effects include diarrhea, flushing, salivation, sweating, bradycardia, hypotension, syncope and bronchospasm.

CHOLINOMIMETIC ALKALOIDS

Pilocarpine is an alkaloid obtained from the leaves of *Pilocarpus microphyllus*. Like ACh it stimulates cholinergic receptors, but its muscarinic actions are prominent. Pilocarpine causes hypotension.

Its actions on the eye are important—when applied to the eye it causes miosis, spasm of accommodation and a fall in intraocular tension. It also increases sweat (diaphoretic) and salivary secretions (sialogogue).

Adverse effects: When used as eyedrops, burning sensation, painful spasm of accommodation, browache and corneal edema can occur. Long-term use can cause retinal detachment.

Uses

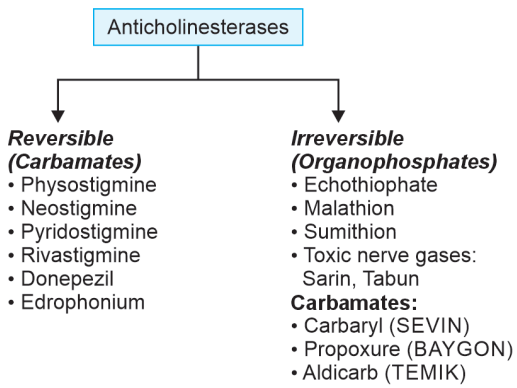
1. Pilocarpine is used in glaucoma as it causes miosis and reduces IOP (*see* page 126). Pilocarpine ocusert is available and can deliver pilocarpine constantly for 7 days.
2. Pilocarpine is also used alternately with mydriatics, such as homatropine to break the adhesions between the iris and the lens.
3. It is used to counter dryness of mouth that is seen following radiation of head and neck.

Cevimeline a derivative of acetylcholine directly stimulates the muscarinic receptors and can be used to increase salivary secretions in Sjogren's syndrome and radiation-induced xerostomia.

INDIRECTLY ACTING ANTICHOLINESTERASES

Anticholinesterases (antiChEs) or cholinesterase inhibitors are drugs which inhibit the enzyme cholinesterase **(Flowchart 9.4)**.

Flowchart 9.4: Anticholinesterases.



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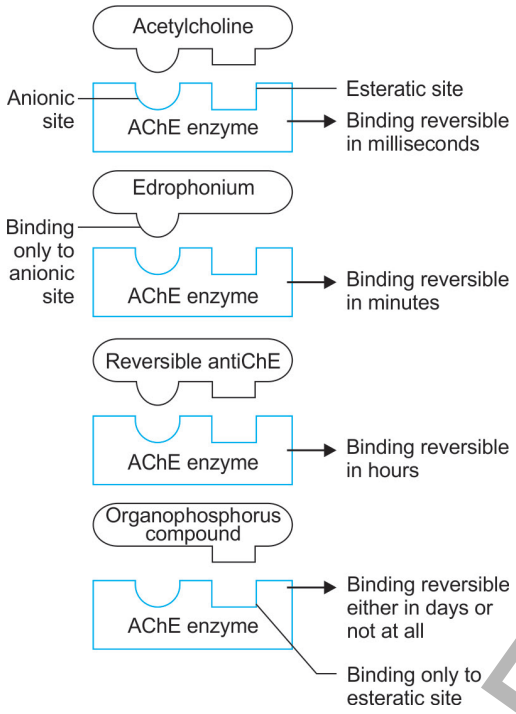


Fig. 9.6: Acetylcholine and reversible anticholinesterases bind to both anionic and esteratic sites of the acetylcholinesterase (AChE) enzyme. Edrophonium binds only the anionic site and is short acting as the binding is rapidly reversible. OP compounds bind only esteratic site but exception is echothiophate which binds both anionic and esteratic sites.

Mechanism of Action

As the structure of anticholinesterases resemble that of ACh, they bind to acetylcholinesterases and inactivate them.

Acetylcholine
↓ Cholinesterase ←✕— AntiChE
Choline + Acetic acid

Thus, ACh is not hydrolyzed and it accumulates. The actions of all these drugs are due to the accumulated ACh. Hence the actions are similar to cholinergic agonists. The structure of AChE contains an anionic site and an esteratic site **(Fig. 9.6)**. Reversible anticholinesterases except edrophonium bind to both anionic and esteratic sites. Edrophonium binds only to anionic site and the binding is quickly reversible—hence it is very short acting. Organophosphates (OP) bind only to the esteratic site but the enzyme is phosphorylated (by covalent bonds) and the binding is stable. With some OPs the binding takes many days to be reversed while with others it is not fully reversible at all.

Physostigmine is an alkaloid obtained from the plant *Physostigma venenosum* **(Table 9.2)**. It is a tertiary ammonium compound—hence has better penetration into tissues and also crosses the BBB. It is available as IV injection, as 0.1–1% eyedrops and in combination with pilocarpine nitrate 2%.

Uses

- **Glaucoma:** Physostigmine used as eyedrops but can cause browache and on long-term use, retinal detachment and cataract.
- **Poisoning:** In atropine and tricyclic antidepressant poisoning.

Neostigmine is a synthetic quaternary ammonium compound—poorly absorbed from the gut; it does not cross the BBB. It is used in myasthenia gravis, postoperative paralytic ileus and atony of the urinary bladder. **Pyridostigmine** and **ambenonium** are similar to neostigmine but longer acting.

Edrophonium is rapid and short-acting. It is used in myasthenia gravis, and intravenously in snake bite and in curare poisoning.

Rivastigmine is a longer acting carbamate that somewhat selectively binds to the AchE in the brain. Being highly lipid soluble, rivastigmine is rapidly absorbed and reaches the brain and augments cholinergic transmission in the brain. It is used in the treatment of mild to moderate Alzheimer's disease. Started with 1.5 mg BD the dose may be gradually increased at 2 week intervals to a maximum of 6 mg BD.

Donepezil is another reversible anticholinesterase with longer duration of action—



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Table 9.2: Compare and contrast physostigmine and neostigmine.

Features	*Physostigmine*	*Neostigmine*
Source	Natural *(Physostigma venenosum)*	Synthetic
Chemistry	Tertiary ammonium compound	Quaternary ammonium compound
Absorption	Absorbed orally	Not absorbed
Tissue penetration	Good	Poor
BBB	Crosses BBB—has CNS effect	Does not cross BBB—no CNS effects
Primary use	In glaucoma	In myasthenia gravis
Use in poisoning	Used in atropine poisoning	Used in curare poisoning
Similarities—mode of action	Cholinesterase inhibitor	Cholinesterase inhibitor

(BBB: blood brain barrier; CNS: central nervous system)

given once daily. It was shown to produce improvement in the symptoms in Alzheimer's disease. Dose: 5–10 mg OD.

Uses of Reversible Anticholinesterases

1. **Myasthenia gravis** is a chronic autoimmune disease characterized by progressive weakness with rapid and easy fatiguability of skeletal muscles. Antibodies to nicotinic receptors are formed, resulting in a decrease in the number of these receptors at NMJ.

   Treatment: Neostigmine (15 mg tab 6 hourly) or pyridostigmine or a combination of these may be given. In addition to its antiChE activity, neostigmine directly stimulates the nicotinic receptors and increases the amount of ACh released during each nerve impulse. AntiChEs enhance ACh levels at NMJ by preventing its destruction. They thus increase the force of contraction and improve muscle power by more frequent activation of the existing nicotinic receptors. Edrophonium is used IV for the diagnosis.

   Factors, such as infection, surgery and stress can result in severe muscle weakness called—*myasthenic crisis*. Severe weakness may also result from an excess dose of an anticholinesterase drug (flaccid paralysis due to more of acetylcholine) called *cholinergic crisis*. These two crises can be differentiated by administering edrophonium 2 mg intravenously. The patient immediately improves if it is myasthenic crisis but the weakness worsens if it is cholinergic crisis. Treatment of cholinergic crisis is with atropine while myasthenic crisis requires a higher dose of or an alternative anticholinergic drug.

   Other drugs used in myasthenia gravis are:
   - **Glucocorticoids:** Inhibit the production of antibodies to the nicotinic receptors. These are used when anticholinesterases alone are not adequate.
   - **Immunosuppressants:** Azathioprine and cyclosporine can be used as alternatives to prednisolone in advanced myasthenia gravis. They inhibit the production of antinicotinic receptor antibodies.
2. **As a miotic:** Physostigmine causes miosis, spasm of accommodation and a ↓IOP. It is used in:
   - Glaucoma—can be used with pilocarpine for better effect.
   - Alternately with a mydriatic to break adhesions between the iris and the lens.
   - To reverse the effects of mydriatics.
3. **Poisoning due to anticholinergic drugs:** Physostigmine is used in atropine poisoning, belladonna poisoning and in toxicity due to other drugs with anticholinergic activity, such as phenothiazines, tricyclic antidepressants and antihistamines. Because physostigmine crosses the BBB, it reverses all the symptoms of atropine poisoning including CNS effects.
4. **Curare poisoning:** Skeletal muscle paralysis caused by curare can be antagonized by

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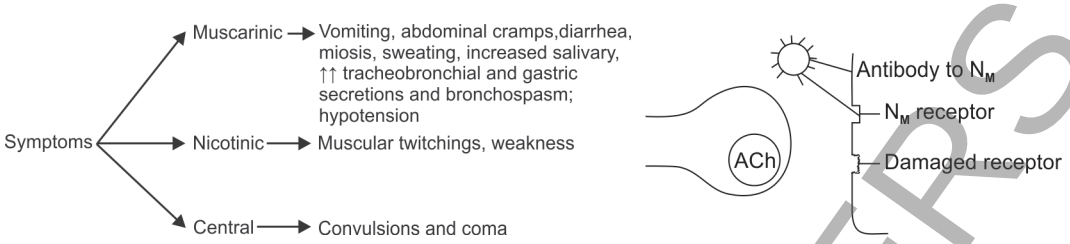


Fig. 9.7: Clinical features of OP poisoning.

AntiChEs. Though edrophonium has fast action, it is less effective than neostigmine.

5. **Postoperative paralytic ileus and urinary retention:** Neostigmine (subcutaneous) may be useful.
6. **Cobra bite:** Cobra venom, a neurotoxin causes skeletal muscle paralysis. Specific treatment is antivenom. Intravenous edrophonium prevents respiratory paralysis.
7. **Reversal of muscle relaxants:** Neuromuscular paralysis due to NMBs used with anesthesia may be reversed with neostigmine or pyridostigmine.
8. **Alzheimer's disease:** To overcome the deficient cholinergic neurotransmission, rivastigmine and donepezil are tried in Alzheimer's disease.

Mnemonic–uses of anticholinesterases

MAAM C CUP
M—myasthenia gravis
A—atropine poisoning
A—Alzheimers
M—miotic
C—curare poisoning
C—Cobra bite
U—urinary retension
P—Post Op Paralytic ileus

Irreversible Anticholinesterases

Organophosphorus (OP) compounds are powerful inhibitors of AChE enzyme; binding with the enzyme is stable—by covalent bonds. They bind only the esteratic site and the enzyme is phosphorylated. Effects are similar to that of cholinergic stimulation as ACh accumulates in the tissues. Organophosphates are highly lipid soluble and hence are **absorbed from all routes including intact skin.** This makes OP poisoning possible even while insecticides are used for spraying the plants.

Uses

Glaucoma—echothiophate eyedrops are sometimes used in glaucoma.

Organophosphorus Poisoning

Acute Toxicity

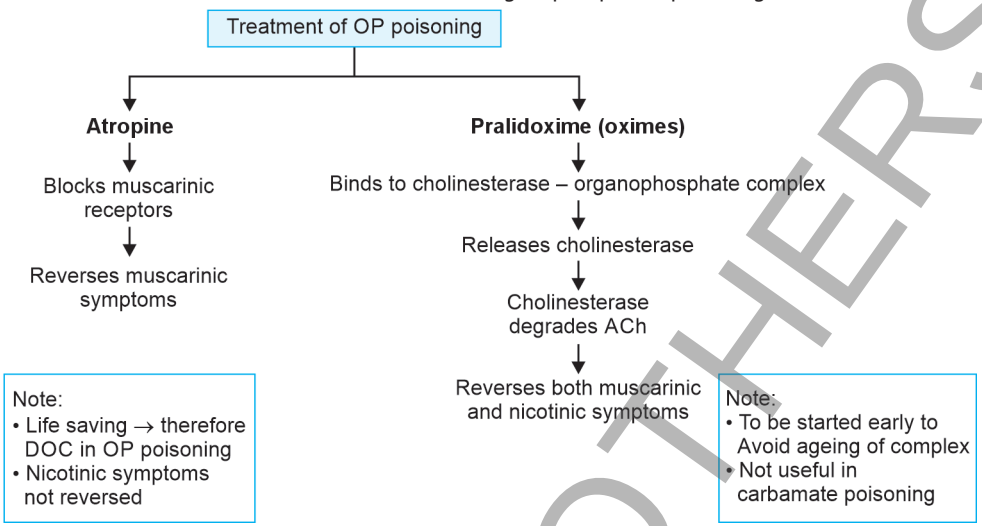
As organophosphates are used as agricultural and domestic insecticides, poisoning by them is quite common. Poisoning may be occupational—as while spraying insecticides, accidental or suicidal. Symptoms **(Fig. 9.7)** result from muscarinic, nicotinic and central effects; vomiting, abdominal cramps, diarrhea, miosis, sweating, increased salivary, tracheobronchial and gastric secretions and bronchospasm; hypotension, muscular twitchings, weakness, convulsions and coma. Death is due to respiratory paralysis.

Treatment (Flowchart 9.5)

1. If poisoning is through skin—remove clothing and wash the skin with soap and water; if consumed by oral route—gastric lavage is given.
2. Patient should be put-in prone position to avoid aspiration of secretions.
3. Maintain BP and patent airway.
4. Drug of choice is *atropine* IV 2 mg every 10 minutes till pupil dilates. Maximum dose can be anything from 50 to 100 mg or more depending on the severity of the poisoning. Treatment should be carefully monitored because of the risk of reappearance of symptoms due to delayed absorption of the OP compounds.

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Flowchart 9.5: Treatment of organophosphorus poisoning.



5. Cholinesterase reactivators: *Pralidoxime, obidoxime* and *diacetylmonoxime* are oximes which combine with cholinesterase organophosphate complex, release the binding and set free AChE enzyme. Thus they reactivate the cholinesterase enzyme. They should be given within minutes after poisoning preferably immediately, because the complex undergoes *'ageing'* and the enzyme cannot be released. The complex becomes more stable by loss of a chemical group and this is responsible for 'ageing'. Cholinesterase reactivators are not useful in poisoning due to carbamate compounds because these compounds do not have a free site for the binding of oximes. Moreover, pralidoxime itself has weak anticholinesterase activity particularly at higher doses. In severe poisoning 1–2 g of IV pralidoxime given within five minutes of poisoning gives best results. In practice, it is rather uncommon for a patient to get such quick treatment within minutes particularly in the rural setup and cholinesterase reactivators are tried up to a few hours (maximum 6 hours) after poisoning.

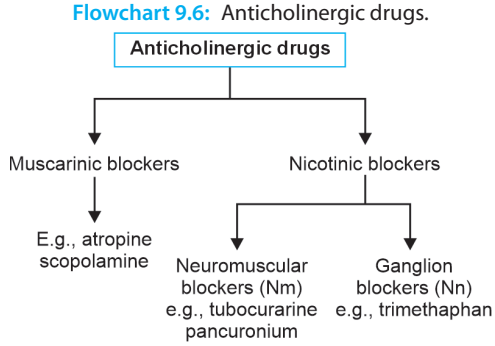
Chronic Organophosphate Toxicity

Some OP compounds can produce neurotoxicity (polyneuropathy) several days after exposure to the compound. This toxicity came to light when thousands of people developed paralysis in America after consuming 'Jamaica ginger' which contained small amounts of an OP compound (triorthocresylphosphate). The symptoms include weakness, fatigue, ataxia, sensory disturbances, muscle twitching and in severe cases flaccid paralysis—which may last for several years.

ANTICHOLINERGIC DRUGS

Anticholinergic drugs are agents which block the effects of acetylcholine on cholinergic receptors but conventionally antimuscarinic drugs are referred to as anticholinergic drugs. They are also called cholinergic blocking (or parasympatholytic drugs). Drugs that block the nicotinic receptors are ganglion blockers and neuromuscular blockers **(Flowchart 9.6)**.

Flowchart 9.6: Anticholinergic drugs.



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Anticholinergic drugs include atropine and related drugs—atropine is the prototype.

Atropine is obtained from the plant *Atropa belladonna*. Atropine and scopolamine (hyoscine) are the belladonna alkaloids.

Mechanism of Action

Atropine and scopolamine bind to muscarinic receptors, compete with Ach and block the effects of acetylcholine (and other cholinergic agonists) on these receptors. These are competitive antagonists and the antagonism is reversible by increasing the concentration of the agonist. Atropine and scopolamine are nonselective antagonists and block all the subtypes (M_1 to M_5) of muscarinic receptors.

Classification

1. **Natural alkaloids:** Atropine, hyoscine (scopolamine).
2. **Semisynthetic agents:** Homatropine, ipratropium bromide, tiotroprium bromide.
3. **Synthetic agents:**
   - **Mydriatics:** *Eucatropine, cyclopentolate, tropicamide.*
   - **Antispasmodic—antisecretory agents:** *Propantheline, dicyclomine, oxyphenonium, glycopyrrolate, telenzepine, tolterodine, propiverine.*
   - **Antiparkinsonian agents:** *Benzhexol, benztropine, trihexyphenidyl.*
   - **Used in urinary disorders:** *Tolterodine, oxybutynin.*

Actions

The actions of atropine and scopolamine are similar except that atropine is a CNS stimulant while scopolamine is a CNS depressant and causes sedation **(Table 9.3)**.

1. **Cardiovascular system (CVS)**—atropine increases heart rate. In large doses, vasodilation and hypotension occurs.
2. **Secretions**—atropine reduces all secretions except milk. Lacrimal, salivary, nasopharyngeal, tracheobronchial and gastric secretions are decreased. Decreased salivation (antisialogogue) results in dry mouth and difficulty in swallowing. Sweating is also reduced.
3. **Smooth muscle**
   - **GIT:** ↓ tone and motility and relieves spasm → may result in constipation.
   - **Biliary tract:** Smooth muscles are relaxed; biliary spasm is relieved.
   - **Bronchi:** Atropine causes bronchodilatation.
   - **Urinary bladder:** Relaxes ureter and urinary bladder and may cause urinary retention particularly in the elderly men because they may be having prostatic hypertrophy.
4. **Eye**—on local instillation, atropine produces mydriasis (dilatation of the pupil) by blocking the muscarinic receptors in the sphincter pupillae. The ciliary muscle is paralyzed resulting in cycloplegia or paralysis of accommodation. Because of mydriasis, the iris may block the drainage

Table 9.3: Differences between atropine and scopolamine.

Features	*Atropine*	*Scopolamine*
1. Source	*Atropa belladonna*	*Hyoscyamus nigra*
2. BBB	Does not readily cross Higher doses are needed to reach CNS	Readily crosses—even low doses produce CNS effects
3. Principle effect on CNS	CNS stimulation	CNS depression
4. Prominent actions on CNS	Confusion, excitement, hallucinations	Sedation, drowsiness, ataxia, amnesia
5. Use in motion sickness	Not used	Used
6. Duration of action	Longer	Shorter
7. Used to increase heart rate (vagolytic)	Yes	Not used

(BBB: blood brain barrier; CNS: central nervous system)

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of aqueous humor—intraocular pressure increases and may precipitate glaucoma in some patients.

5. **CNS**—in higher doses atropine stimulates the CNS resulting in restlessness, disorientation, hallucinations and delirium. In contrast, scopolamine produces sedation and drowsiness.

Pharmacokinetics: Atropine and hyoscine are well-absorbed, cross the BBB and are metabolized in the liver.

Adverse effects are common but not serious and include blurring of vision (**d**iplopia), **d**ry mouth, difficulty in swallowing (**d**ysphagia), **d**ry skin, fever, constipation and urinary retention (**d**ifficulty in defecation and urination). Skin rashes may appear.

Atropine/Belladonna poisoning: Atropine/Belladonna poisoning: High doses of atropine cause palpitation, flushing, restlessness, **d**elirium, hallucinations, psychosis, convulsions and coma. Treatment is symptomatic. Antidote is physostigmine - given IV. Diazepam/lorazepam is used to treat seizures.

(Note '**D**' in atropine ADR)

ATROPINE SUBSTITUTES

Atropine and scopolamine can produce a wide range of effects, but these can also result in various side effects since they lack selectivity. Hence several semisynthetic and synthetic derivatives have been introduced and some of them have selective actions **(Table 9.4)**.

Uses of Atropine and Atropine Substitutes (Belladonna Alkaloids)

1. **As antispasmodics**
   - In diarrhea and dysentery, atropine dicyclomine, propiverine relieve colic and abdominal pain.
   - In renal and biliary colic, atropine is used with morphine because atropine partly overcomes spasm of the sphincter of Oddi.
   - Bed wetting (Nocturnal enuresis) in children and in paraplegia, atropine reduces urinary frequency.
2. **As mydriatic and cycloplegic**—mydriasis and cycloplegia produced by atropine last for 7–10 days. The derivatives **homatropine, eucatropine, cyclopentolate** have shorter action (6–24 hours), and **tropicamide** is shortest acting (4–6 hours). Some can selectively produce mydriasis or cycloplegia.
   a. **Diagnostic:** For testing errors of refraction and fundoscopic examination of the eye, dilatation of pupil helps to see the fundus better and because of cycloplegia, accommodation correction is also prevented (tropicamide preferred in adults and cyclopentolate/atropine in children).
   b. **Therapeutic:** To provide rest to the iris in iritis, iridocyclitis and keratitis and after iridectomy.
   c. Mydriatics are used alternately with miotics to **break the adhesions**

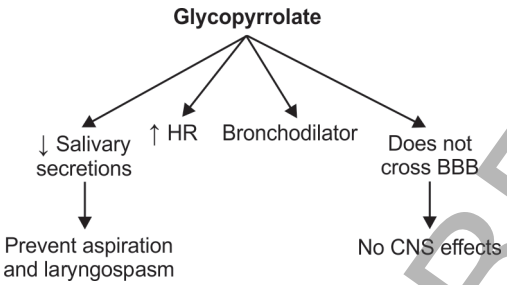
Table 9.4: Atropine substitutes.

Indications	*Derivatives*
On the eye—mydriatics and cycloplegics	Homatropine, eucatropine, cyclopentolate, tropicamide
As antispasmodics	Propantheline, methantheline, dicyclomine, flavoxate, oxybutynin, oxyphenonium, glycopyrrolate, clidinium
Peptic ulcer	Pirenzepine, telenzepine
Bronchial asthma	Ipratropium, tiotropium
Preanesthetic medication	Glycopyrrolate
Urinary disorders	Darifenacin, oxybutynin, tolterodine, propiverine, trospium
Antiparkinsonian drugs	Benzhexol (trihexyphenidyl), benztropine

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(synechiae) between iris and lens in uveitis and iritis.

3. **As preanesthetic medication:** Given 30 minutes IM before anesthesia, atropine reduces salivary and respiratory secretions but **glycopyrrolate** is **preferred** for this use because glycopyrrolate:
   - Reduces the salivary secretions (antisialogogue) and this will prevent the development of laryngospasm and aspiration pneumonia.
   - Prevents bradycardia during surgery.
   - Has bronchodilator action which is of additional value.
   - Does not cross the BBB and no effects on CNS.



4. **In poisoning:**
   a. ***Organophosphorus poisoning:*** Atropine is lifesaving in OP poisoning.
   b. ***Mushroom poisoning:*** Atropine is used (Inocybaceae family mushrooms).
   c. ***Curare poisoning:*** Atropine is used with neostigmine (to block muscarinic effects).
5. **Bronchial asthma and COPD:** Atropine thickens the bronchial secretions and interferes with the movement of cilia, thus leading to formation of mucus plugs in bronchial asthma and COPD. However, the derivatives are useful.
   - Ipratropium, tiotropium and revefenacin are bronchodilators (block M3 receptors).
   - Do not affect mucociliary activity.
   - Given as inhalation, act only on the airways and have no significant systemic effects because they are poorly absorbed.
   - Tiotropium is longer-acting (OD).
   - Revefenacin is a long-acting M3 blocker used once daily as nebulization for long-term control of COPD.
6. **Peptic ulcer:** Pirenzepine and telenzepine are selective M1 blockers—selectively inhibit gastric secretions. Pirenzepine also does not cross the BBB, hence has no CNS effects.
7. **Parkinsonism:** Benztropine, benzhexol, and biperiden are used in drug-induced parkinsonism due to their anticholinergic effects. They control tremors and rigidity.
8. **In cardiovascular disorders:** Atropine produces tachycardia—hence useful in patients with bradycardia or partial heart block due to excessive vagal tone.
9. **Motion sickness:** Hyoscine or scopolamine is similar to atropine but produces CNS depression. Given 30 minutes before the journey, it prevents traveling sickness. The exact mode of action is not known but scopolamine acts as a **vestibular sedative** by blocking the muscarinic receptors in the vestibular apparatus. Transdermal hyoscine patches are applied behind the ear for a prolonged action.
10. **Urinary disorders:** As muscarinic receptors are present in the epithelial cells lining the urinary tract, atropine and its vasicoselective derivatives are used in urinary disorders like in **overactive bladder and urinary incontinence**.
    - Darifenacin, solifenacin, tolterodine, fesoterodine, oxybutynin and trospium are more M3 selective in the bladder and therefore anticholinergic side effects are negligible.
    - They reduce urinary urgency and frequency, relieve bladder spasm and improve bladder capacity and reduce involuntary voiding in urinary disorders and following urologic surgeries.
    - Also tried in bed wetting (nocturnal enuresis) in children.

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Oxybutynin can be given orally or instilled into the bladder cavity or applied **transdermally**.

11. **Labor:** Hyoscine can also be used during labor to produce sedation and amnesia.
12. **Truth serum:** Hyoscine is used in truth serum to obtain information from suspects and criminals and as a lie detector.

Drug Interactions and Contraindications

- When anticholinergics are given with other drugs that also have anticholinergic property, such as antihistaminics, phenothiazines, tricyclic antidepressants-side effects get added up.
- **Glaucoma:** Anticholinergics are contra-indicated in glaucoma
- **BPH:** Anticholinergics should be avoided in elderly men as they can cause difficulty in micturition.

ADRENERGIC DRUGS

SYMPATHETIC NERVOUS SYSTEM

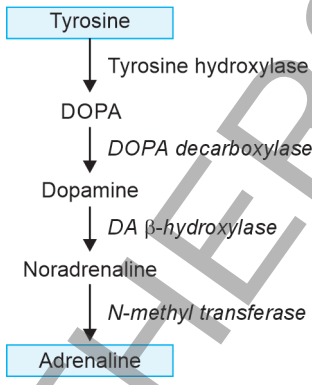
The prime function of the adrenergic or sympathetic nervous system is to help the human being to adjust to stress and prepare the body for fight or flight reactions. When exposed to stress:

- The heart rate and stroke volume increase with the resultant increase in cardiac output.
- The blood is shifted from the skin, gut, kidney and glands to the heart, skeletal muscles, brain and lungs, as these organs need more blood during stress.
- Pupils are dilated to see better
- Bronchi are dilated for more oxygen
- Sweating is increased to cool the body.
- Blood glucose increases by glycogenolysis.

Neurotransmitters of the sympathetic system are noradrenaline (NA, norepinephrine) and dopamine (DA). Adrenaline (epinephrine) is the major hormone secreted by the adrenal medulla.

Synthesis, storage and release of catecholamines: The three catecholamines—noradrenaline, adrenaline and dopamine are synthesized from the amino acid tyrosine **(Flowchart 9.7)**.

Flowchart 9.7: Biosynthesis of catecholamines.



The sympathetic postganglionic nerve fibers that synthesize, store and release NA are called adrenergic. Noradrenaline is stored in small vesicles in the *adrenergic* nerve terminals **(Fig. 9.8)** In response to nerve impulse, NA is released into the synaptic cleft by a process called *exocytosis.* This NA binds to adrenergic receptors located on the postsynaptic membrane to produce the response. A small portion of NA is metabolized by the enzyme COMT but a large portion (nearly 80%) is taken back into the nerve terminals by an active transport process termed *uptake 1*, which thus terminates action of NA. Of this portion which is taken up, a fraction is metabolized by MAO and the remaining NA is then transferred to the storage vesicles. Some part of NA released into the synaptic cleft penetrates into the effector cells and is known as *uptake 2.*

Adrenergic receptors: Adrenergic receptors are classified into two types—α and β and these are further subdivided into α_1, α_2, β_1, β_2 and β_3 adrenergic receptors.

Dopamine acts on dopamine (DA) receptors. There are five subtypes of DA receptors.

The stimulation of α receptors mainly produces excitatory effects (exception—GIT); β stimulation causes mainly inhibitory effects (exception-heart). The characteristics of these

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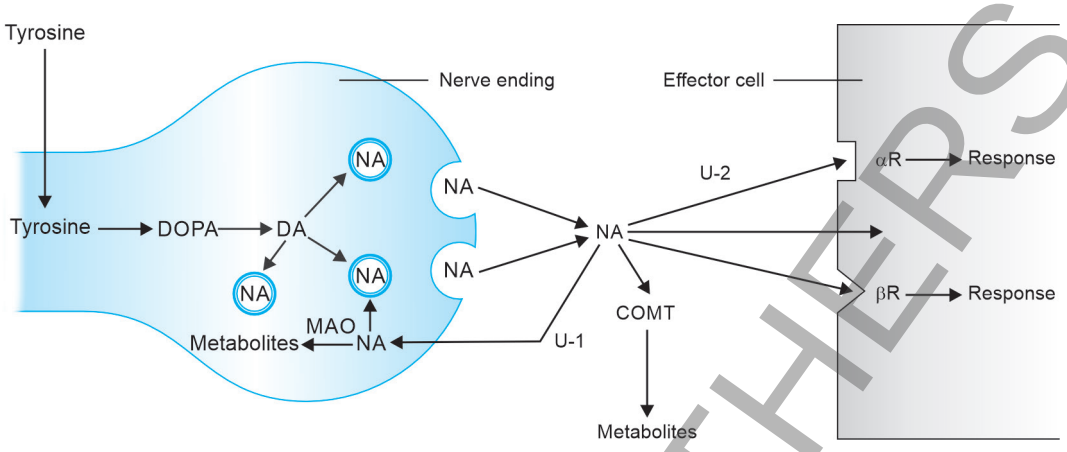


Fig. 9.8: Synthesis, storage, release and metabolism of noradrenaline.

(DA: dopamine, NA: noradrenaline, U-1: Uptake 1, U-2: Uptake 2, MAO: monoamine oxidase, COMT: catechol-O-methyltransferase)

Table 9.5: Characteristics of adrenergic receptors.

Receptor type	*Location*	*Response*	*Selective agonist*	*Selective antagonist*
α_1	Vascular smooth muscle Gut Genitourinary smooth muscle	Contraction Relaxation Contraction	Phenylephrine Mephentermine Methoxamine	Prazosin Terozosin
α_2	Pancreatic β cells Platelets Nerve terminals	↓ Insulin release Aggregation ↓ NE release	Clonidine	Yohimbine
β_1	Heart	↑ Force of contraction, ↑ heart rate, ↓AV conduction velocity	Dobutamine	Metoprolol Atenolol
β_2	Smooth muscle–vascular, bronchial, gut and genitourinary Liver	Relaxation Glycogenolysis	Salbutamol	Butoxamine
β_3	Adipose tissue	Lipolysis	Mirabegron	Cyanopindolol

receptors are given in **Table 9.5** . α_2 receptors are present on the presynaptic membrane **(Fig. 9.9)**. Stimulation of presynaptic α_2 receptors inhibits the further release of NA. Thus α_2 receptors have a negative feedback on NA release. α_2 receptors are also present postsynaptically in pancreatic islets, platelets and brain.

Mechanism of action: Both α and β adrenergic receptors are G-protein coupled receptors. Stimulation of alpha receptors activates phospholipase C in the cell membrane which acts through generation of second messengers inositol triphosphate and diacylglycerol and increase intracellular calcium.

Stimulation of beta receptors activates an enzyme adenylyl cyclase resulting in increased intracellular cyclic AMP levels. This second messenger acts through various intracellular proteins to bring about the response.

Adrenergic Drugs (Sympathomimetics)

Sympathomimetics are drugs, whose actions mimic that of sympathetic stimulation. Catecholamines and sympathomimetics or

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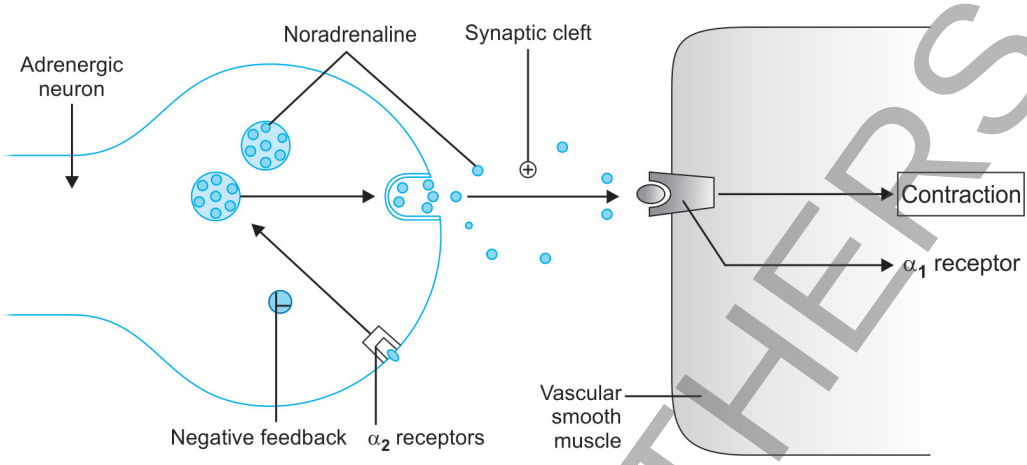


Fig. 9.9: α_1 and α_2 receptor stimulation: NA binds to α_1 receptors and stimulates it to produce response like vasoconstriction. Presynaptic α_2 receptor stimulation inhibits the further release of NA from the storage vesicles.

adrenergic drugs may be classified in various ways depending on the presence/absence of catechol nucleus, mode of action and therapeutic indications as follows:

Classification

i. Therapeutic or clinical classification

1. **Vasopressors:** *Noradrenaline, phenylephrine, dopamine, methoxamine, metaraminol.*
2. **Cardiac stimulants:** *Adrenaline, dopamine, dobutamine, isoprenaline, ephedrine.*
3. **CNS stimulants:** *Amphetamine, ephedrine.*
4. **Bronchodilators:** *Adrenaline, isoprenaline, salbutamol, terbutaline, salmeterol, perbuterol, fenoterol, formoterol.*
5. **Nasal decongestants:** *Ephedrine, pseudoephedrine, phenylephrine, oxymetazoline, xylometazoline.*
6. **Uterine relaxants:** *Salbutamol, terbutaline, isoxsuprine, ritodrine.*
7. **Appetite suppressants (anorectics):** *Fenfluramine, dexfenfluramine (banned).*

ii. Depending on the mode of action

1. **Directly acting sympathomimetics (by stimulating adrenergic receptors):**
   A. *Catecholamines*
      Natural: *Noradrenaline, adrenaline, dopamine*
      Synthetic: *Isoprenaline, dobutamine, dopexamine, dipivefrine*
   B. ***Noncatecholamines:*** *Phenylephrine, salbutamol, xylometazoline.*
2. **Indirectly acting sympathomimetics (by releasing NA from nerve terminals):** *Amphetamine, tyramine.*
3. **Mixed action amines (both direct and indirect actions):** *Ephedrine, methoxamine.*
4. **Catecholamine reuptake inhibitors:** *Atomoxetine, reboxetine, duloxetine.*

Actions

1. Cardiovascular System

Heart: Adrenaline is a powerful cardiac stimulant. Acting through β_1 receptors, it increases the heart rate, force of contraction, cardiac output and conduction velocity. The work done by the heart and the resultant oxygen consumption are increased.

Blood vessels and BP: Blood vessels of the skin and mucous membrane are constricted (α_1) and that of the skeletal muscles are dilated (β_2) by adrenaline. Since injection of adrenaline causes local vasoconstriction, it is used to prolong the duration of action of local anesthetics.

Moderate doses given intravenously produce a rapid increase in BP followed by a fall—a biphasic response. The pressor effect is due

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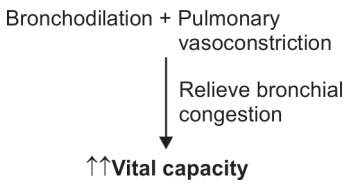
to α_1 mediated vasoconstriction. Action on β receptors is more persistent and as the action on alpha receptors wears off, the action on β receptors gets unmasked resulting in a fall in BP.

Noradrenaline is mainly an alpha agonist and brings about a rise in BP.

Other vascular beds: Adrenaline causes renal vasoconstriction resulting in a fall in renal blood flow; it also causes pulmonary and mesenteric vasoconstriction. Cerebral and coronary blood flow is enhanced.

2. Smooth Muscles

- **Bronchi:** Adrenaline is a powerful bronchodilator and a weak respiratory stimulant. Pulmonary vasoconstriction relieves bronchial congestion. All these result in an increase in vital capacity.



- **Uterus**
  - Nonpregnant uterus—contracts
  - Last month of pregnancy—relaxes
- **Gut:** Smooth muscle is relaxed—but weak and transient action.
- **Splenic capsule** contracts resulting in the release of RBCs into the circulation.
- **Pilomotor** muscles of the hair follicle contract.
- **Bladder:** Detrusor is relaxed (β receptors) while trigone is contracted thereby increasing the urine holding capacity of the bladder.

3. Eye

Adrenaline causes mydriasis due to contraction of the radial muscles of the iris (α_1); it also reduces intraocular pressure.

4. Metabolic Effects

Adrenaline increases the blood sugar level by enhancing hepatic glycogenolysis. It also inhibits insulin release. By enhancing breakdown of triglycerides in the adipose tissue, more free fatty acids are made available in the plasma by action on β_3 receptors in adipocytes.

5. Skeletal Muscles

Catecholamines facilitate neuromuscular transmission by action on both α and β receptors—they increase the amount of ACh released.

Pharmacokinetics: Because catecholamines are rapidly inactivated in the gut and the liver, they are not given orally. Adrenaline and NA are metabolized by catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAO).

Adverse reactions: Anxiety, palpitation, weakness, tremors, pallor, dizziness, restlessness and throbbing headache may follow adrenaline/NA administration. In patients with ischemic heart disease, both adrenaline and NA can precipitate anginal pain. Rapid IV injection can cause sudden sharp rise in BP which may precipitate arrhythmias, subarachnoid hemorrhage or hemiplegia.

Preparations: Adrenaline 1:1000, 1:10,000 and 1:1,00,000 solutions are available for injection. Adrenaline is given SC/IM; intracardiac in emergencies. Adrenaline aerosol for inhalation and 2% ophthalmic solution are also available.

Uses of Adrenaline

1. **Anaphylactic shock:** Adrenaline is the drug of choice (0.3–0.5 mL of 1:1000 solution). Adrenaline is life saving in anaphylactic shock because:
   In anaphylactic shock, large amounts of histamine released is responsible for the signs and symptoms as well as death. Adrenaline is the physiological antagonist of histamine. It promptly reverses hypotension, laryngeal edema and bronchospasm **(Fig. 9. 10)**. IM route is preferred as absorption by SC route is not reliable in shock.
   Adrenaline is also life-saving in angioneurotic edema of the larynx.
2. **Cardiac arrest:** Sudden cardiac arrest due to drowning, electrocution, etc., are treated

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