Shree H.N.Shukla institute of Pharmaceutical Education & Research Rajkot

B.Pharm

Semester IV

Subject Name: Pharmacology I
Subject code:BP404TP

TOPIC:

Pharmacology of drugs acting on peripheral nervous system

a. Organization and function of ANS.

b.Neurohumoral transmission,co-transmission and classification of neurotransmitters.

c. Parasympathomimetics, Parasympatholytics, Sympathomimetics, sympatholytics.

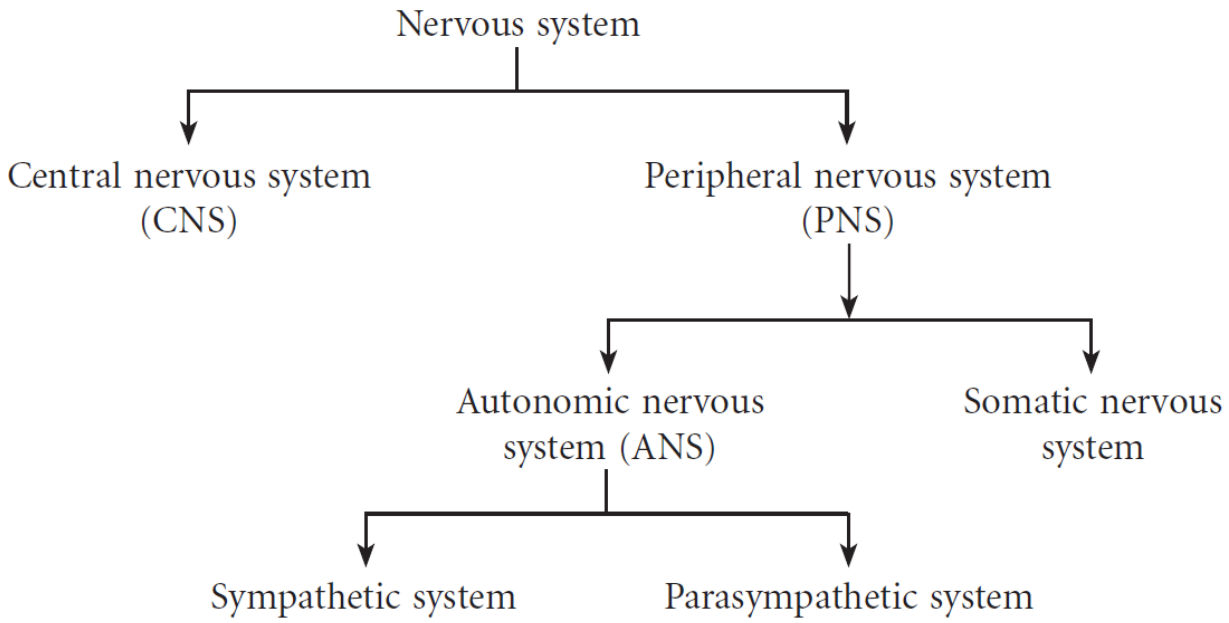
d. Neuromuscular blocking agents and skeletal muscle relaxants (peripheral).

e. Local anesthetic agents.

f. Drugs used in myasthenia gravis and glaucoma

INTRODUCTION TO AUTONOMIC NERVOUS SYSTEM

The nervous system is divided into central nervous system (CNS: brain and spinal cord) and peripheral nervous system (PNS). PNS can be further divided into somatic nervous system and autonomic nervous system (ANS). The differences between these two systems are given in Table



The ANS has two divisions – sympathetic and parasympathetic. The sympathetic division arises from thoracolumbar region (T1–L3, thoracolumbar outflow) and the parasympathetic division arises from two separate regions in the CNS. The cranial outflow arises from cranial nerves (III, VII, IX and X) and sacral outflow from S2, S3 and S4 spinal roots. In sympathetic system, the preganglionic fibres are short and postganglionic fibres are long. On the contrary, the parasympathetic preganglionic fibres are long and postganglionic fibres are short. Most of the visceral organs have dual nerve supply, i.e. they are supplied by both divisions of the ANS, but effects of one system predominate. The ciliary muscle, pancreatic and gastric glands receive only parasympathetic supply; sweat glands, hair follicles, spleen and most of the blood vessels have only sympathetic

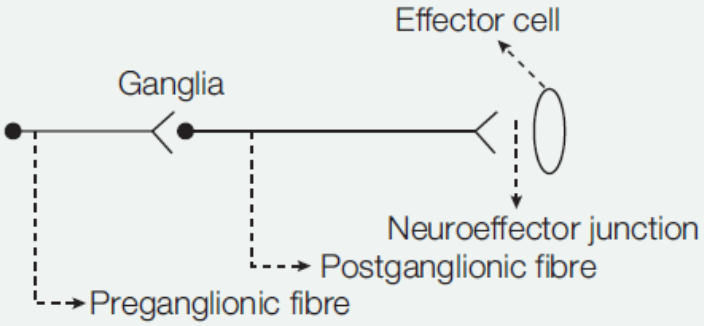
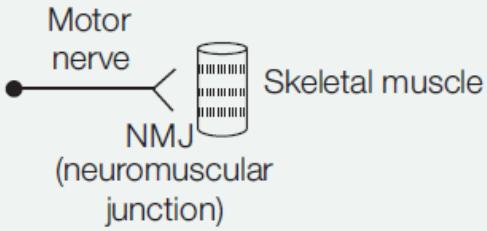
supply. Their stimulation usually produces opposite effect on the innervating organ

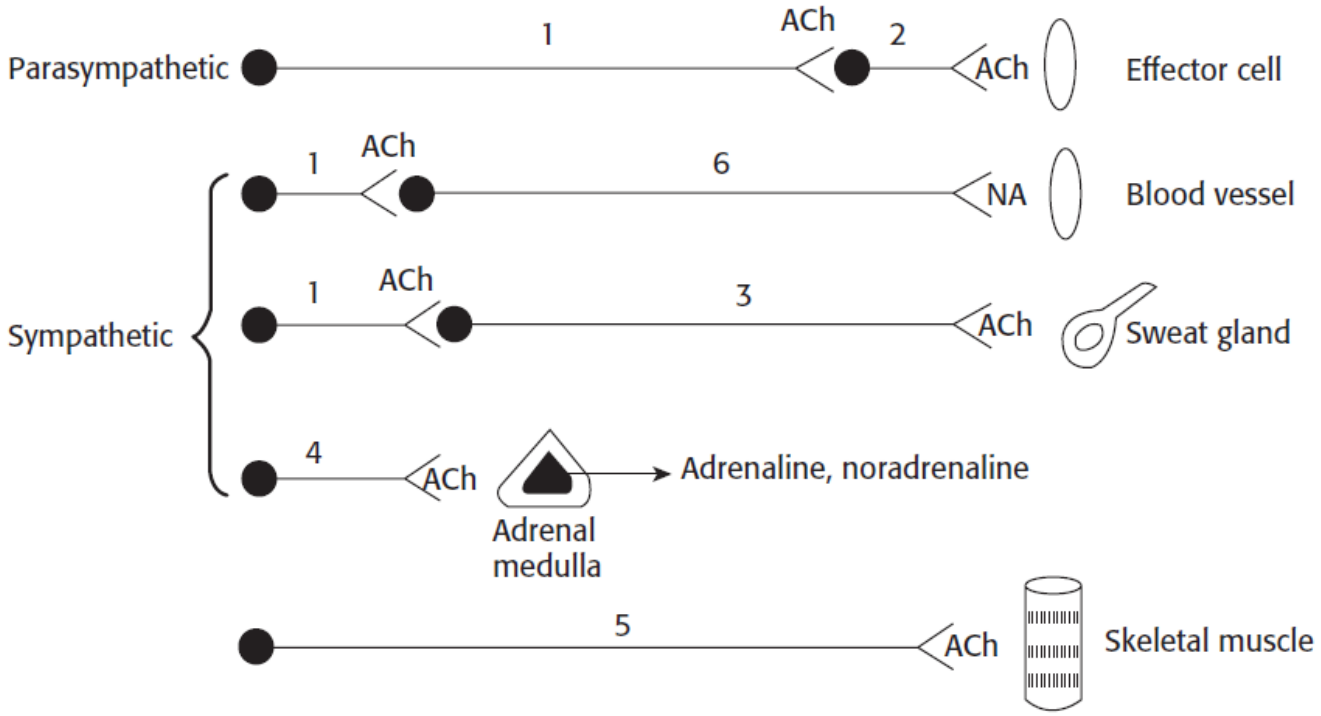
CHOLINERGIC SYSTEM

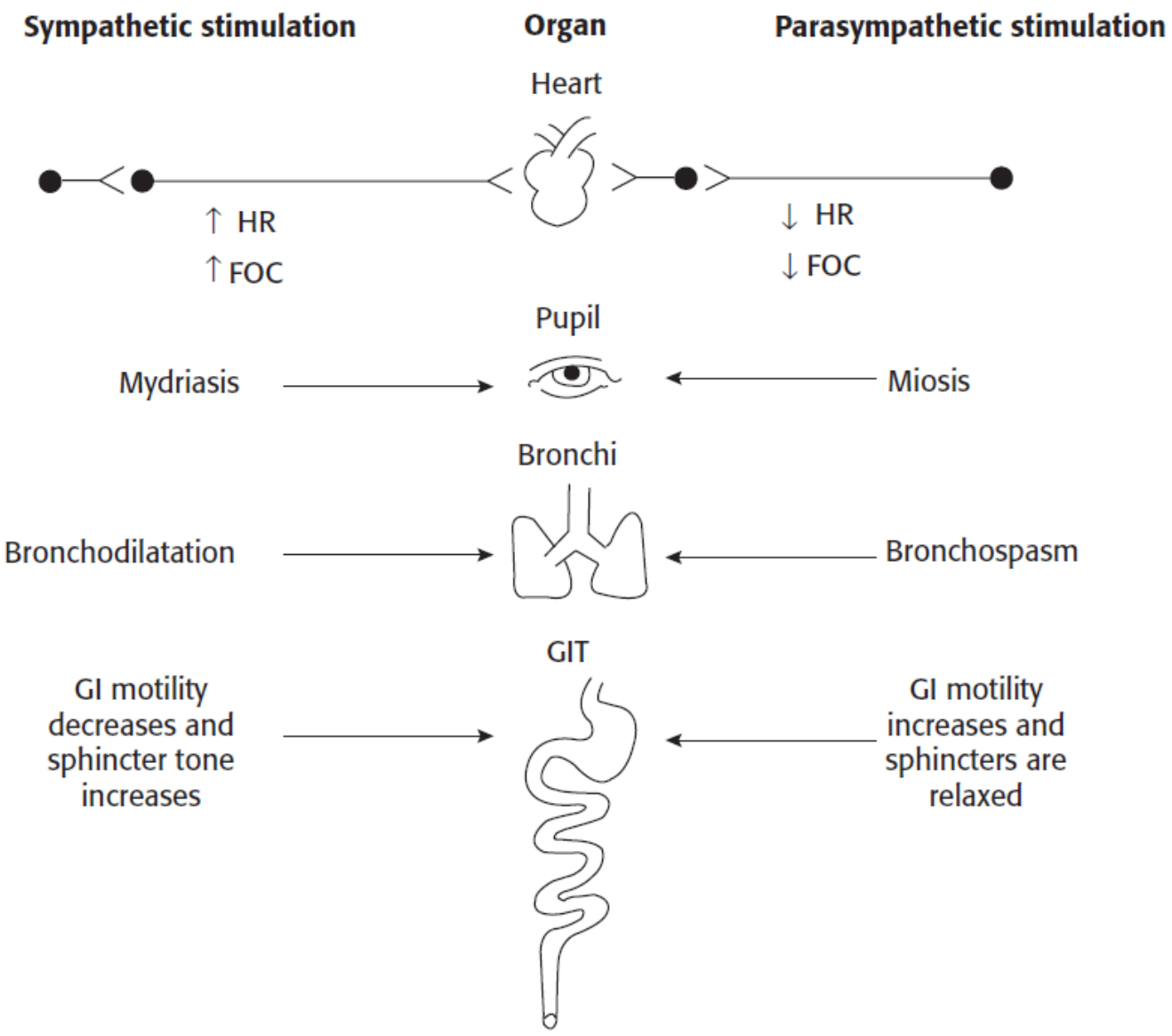
CHOLINERGIC TRANSMISSION

Acetylcholine (ACh) is the neurotransmitter in the cholinergic system. The sites of cholinergic transmission are shown in Fig. The neurons that synthesize, store and release ACh are called cholinergic neurons.

Table 2.1 ■ **Differences between ANS and somatic nervous system**

Autonomic nervous system	Somatic nervous system
Auto: self; *nomos:* governing; this system is involuntary and maintains homeostasis	Somatic nervous system is under voluntary control
Each autonomic fibre is made up of two neurons arranged in series	Each somatic fibre is made up of single motor neuron, which connects CNS to skeletal muscles
	
It innervates the heart, smooth muscles and exocrine glands	It innervates skeletal muscle
It controls visceral functions such as circulation, digestion and excretion	It controls skeletal muscle tone


Parasympathetic
1
ACh
2
ACh
Effector cell
Sympathetic
1
ACh
6
NA
Blood vessel
1
ACh
3
ACh
Sweat gland
4
ACh
Adrenaline, noradrenaline
Adrenal medulla
5
ACh
Skeletal muscle



Synthesis of Acetylcholine

Choline enters the cholinergic neuron by carrier-mediated transport, where it reacts with acetyl-CoA with the help of choline acetyltransferase (ChAT) to form ACh. The ACh is then stored in storage vesicles. It is released into synaptic cleft when an action potential reaches the nerve terminals. The released ACh interacts with cholinergic receptors on effector cell and activates them. In the synaptic cleft, ACh is rapidly hydrolysed by acetylcholinesterase (AChE) enzyme.

Cholinesterases

ACh is rapidly hydrolysed to choline and acetic acid by enzyme cholinesterases. There

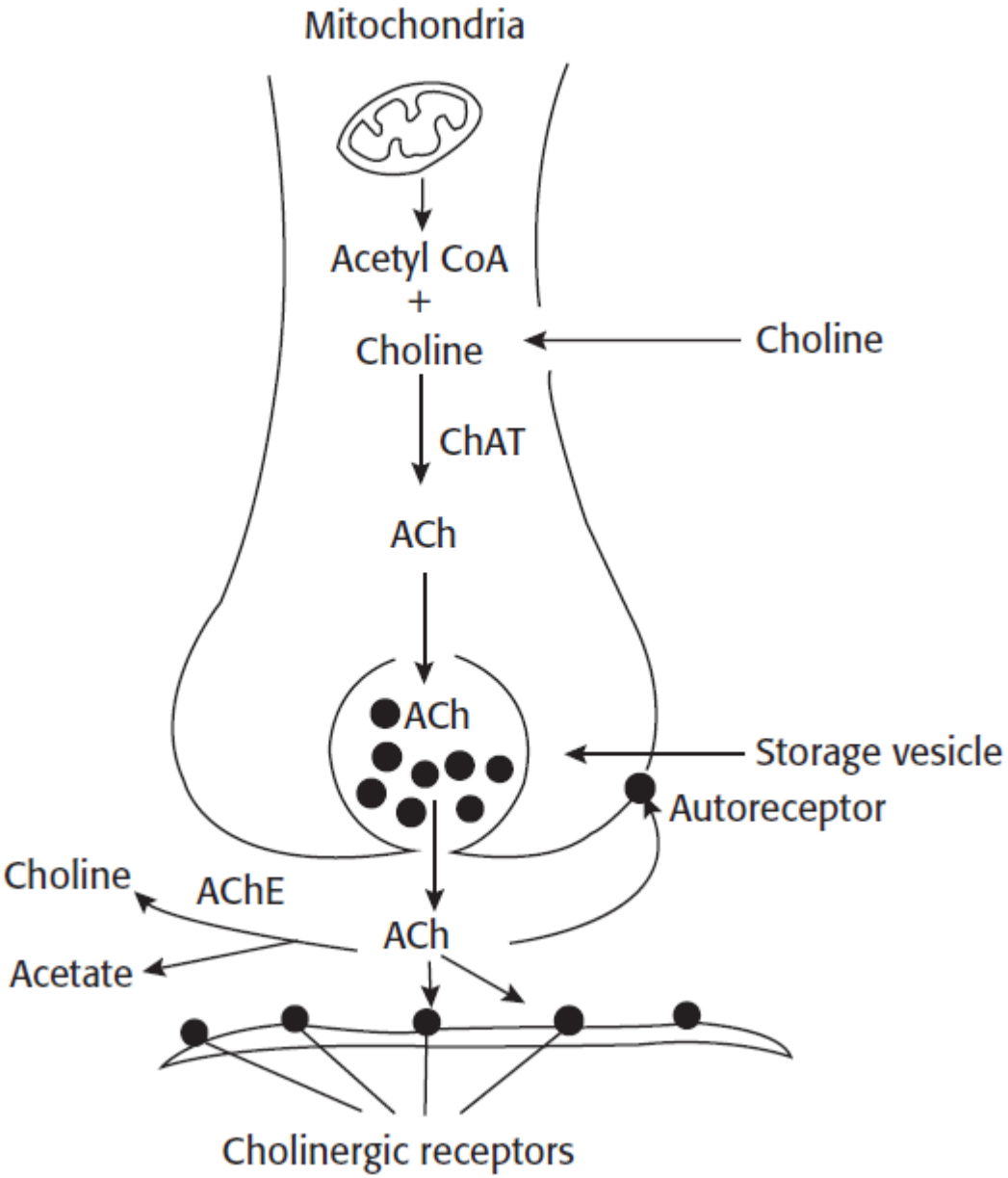
are two types of cholinesterase:

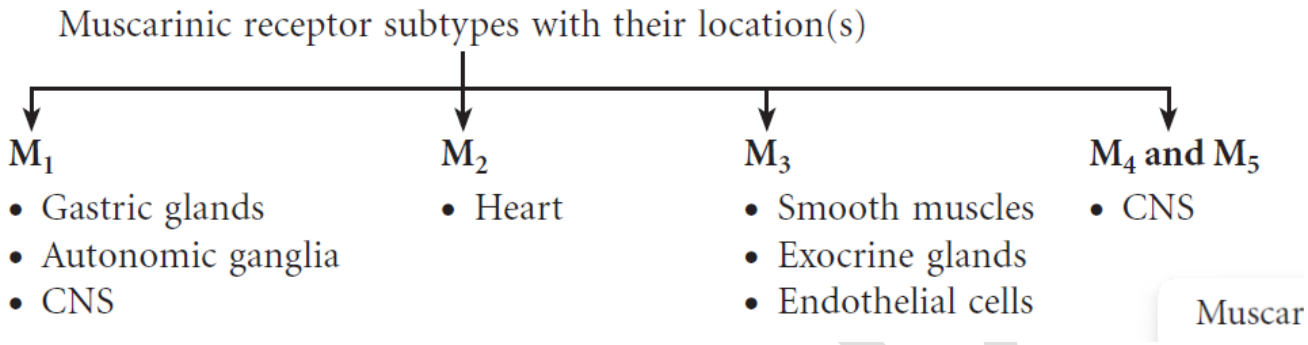
1. **True cholinesterase or AChE**: It is found in cholinergic neurons, ganglia, RBCs and neuromuscular junction (NMJ). It rapidly hydrolyses ACh and methacholine.

2. **Pseudocholinesterase or butyrylcholinesterase**: It is found in plasma, liver and glial cells. Pseudocholinesterase can act on a wide variety of esters including Ach (hydrolysis is slow) but does not hydrolyse methacholine.

Cholinergic Receptors

They are divided broadly into two types – muscarinic and nicotinic. Muscarinic receptors are further divided into five different subtypes: M1–M5. Only M1, M2 and M3 are functionally recognized. M4 and M5 subtypes are found in CNS. All muscarinic receptors are G-protein–coupled receptors and regulate the production of intracellular second messengers.


Mitochondria
Acetyl CoA
+
Choline
Choline
ChAT
ACh
ACh
Storage vesicle
Autoreceptor
Choline
AChE
ACh
Acetate
Cholinergic receptors



Muscar

Nicotinic receptors are divided into two subtypes – NN and NM. Activation of these receptors directly opens ion channels and causes depolarization of the membrane. The characteristics of muscarinic and nicotinic receptors are shown in Table.

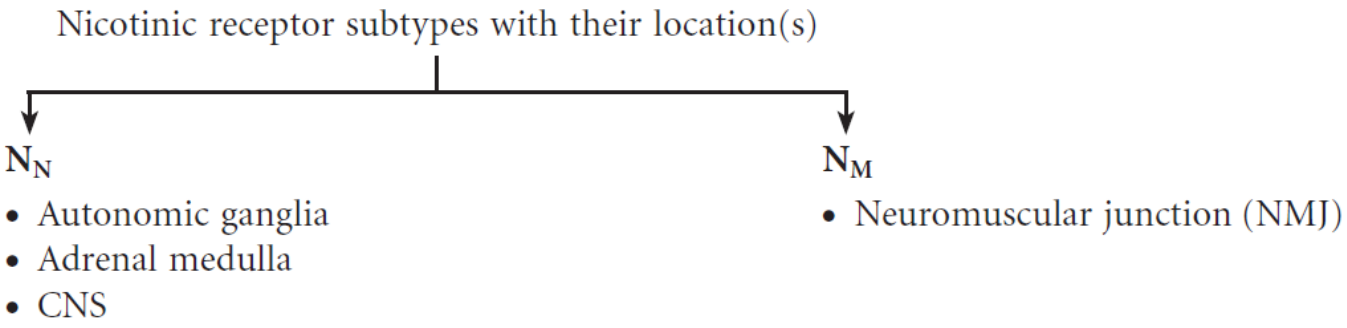


Table 2.2 ■ **Characteristics of muscarinic and nicotinic receptor subtypes**

Receptor type(s)	Intracellular effects	Response
M_1 and M_3	↑ Inositol triphosphate (IP_3) and ↑ diacylglycerol (DAG)	• Increases learning and memory • Promotes glandular secretion and smooth muscle contraction
M_2	↓ Cyclic adenosine monophosphate (cAMP), opening of K^+ channels	Hyperpolarization • Depresses SA node • Depresses AV node • Decreases atrial and ventricular contraction
N_N	Opening of ion channels (Na^+, K^+)	Depolarization • Release of adrenaline and nor-adrenaline from adrenal medulla
N_M	Opening of ion channels (Na^+, K^+)	• Depolarization • Skeletal muscle contraction

Cholinergic Agents (Cholinomimetics,Parasympathomimetics)

ACh is a quaternary ammonium compound and is rapidly hydrolysed by cholinesterases. Hence, it has no therapeutic application. It has to be given intravenously to study its pharmacological actions. Even when given intravenously, a large amount of the drug is destroyed by pseudocholinesterase in blood.

Classification

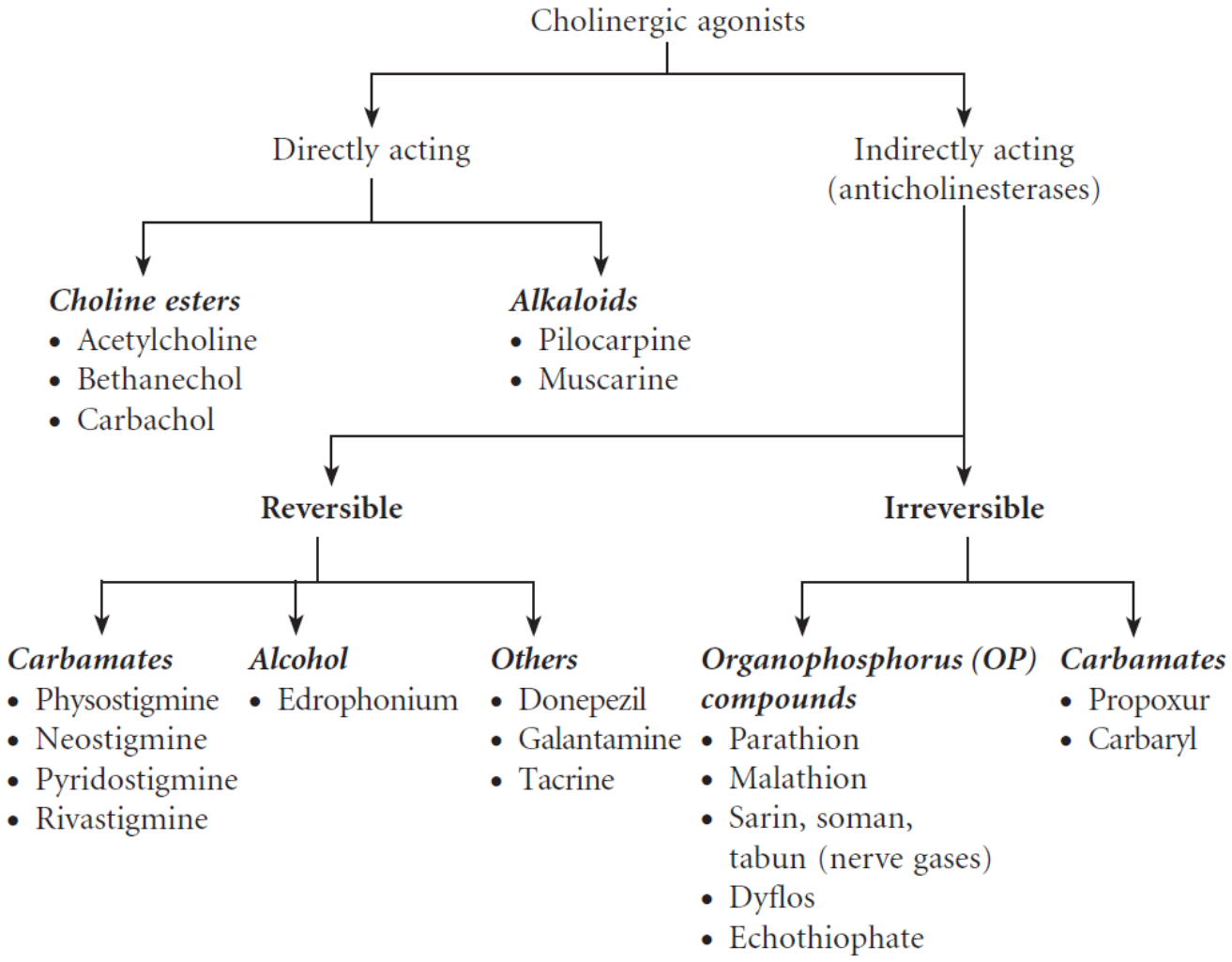


Table 2.3 ■ **Pharmacological properties and uses of choline esters**

	Acetylcholine	Carbachol	Bethanechol
Metabolized by	True and pseudo-cholinesterase enzymes	Resistant to both enzymes	Resistant to both enzymes
Muscarinic actions	+	+	+
Nicotinic actions	+	+	–
Effect of atropine	Muscarinic actions are completely blocked by atropine	Muscarinic actions are not completely blocked by atropine	Muscarinic actions are completely blocked by atropine
Uses	Not useful in therapy because of very short duration of action	Glaucoma	More selective for bladder and GIT – useful in postoperative urinary retention and paralytic ileus

+, present; –, absent.

Choline Esters

Choline esters include ACh, carbachol and bethanechol. Acetylcholine. ACh produces muscarinic and nicotinic effects by interacting with respective receptors on the effector cells.

Muscarinic Actions

1. Cardiovascular system

(a) Heart: The effects of ACh are similar to those following vagal stimulation. ACh, by stimulating M2 receptors of the heart, opens K! channels resulting in hyperpolarization. Therefore, SA and AV nodal activity is reduced.

(b) Blood vessels: ACh stimulates M3 receptors of vascular endothelial cells, which release endothelium-dependent relaxing factor (EDRF; NO) leading to vasodilatation and a fall in blood pressure (BP).

2. Smooth muscles

(a) Gastrointestinal tract

(b) Urinary bladder

(c) Bronchi

3. Exocrine glands: Increase in salivary, lacrimal, sweat, bronchial, gastric and other gastrointestinal (GI) secretions.

4. Eye: ACh does not produce any effect on topical administration because of its poor penetration through tissues.

Nicotinic Actions. To elicit nicotinic actions, larger doses of ACh are required.

1. Autonomic ganglia: Higher doses of ACh produce dangerous muscarinic effects especially on the heart. Hence, prior administration of atropine is necessary to elicit nicotinic actions. Higher doses of ACh stimulate both sympathetic and parasympathetic ganglia causing tachycardia and rise in BP.

2. Skeletal muscles: At high concentration, ACh initially produces twitching, fasciculations followed by prolonged depolarization of NMJ and paralysis.

3. Actions on CNS: Intravenously administered ACh does not cause any central effects because of its poor penetration through the blood–brain barrier (BBB). Bethanechol . It has selective muscarinic actions on GIT and urinary bladder. It is preferred in postoperative urinary retention and paralytic ileus.

Cholinomimetic Alkaloids

They mimic the actions of ACh; examples are pilocarpine, muscarine and arecoline.

Fig. 2.10 Stimulation of parasympathetic and sympathetic ganglia.

Pilocarpine. Pilocarpine is a cholinomimetic alkaloid obtained from Pilocarpus plant. It is a tertiary amine. It produces muscarinic and nicotinic effects by directly interacting

with the receptors. It has predominant muscarinic actions especially on secretory activity.

Uses

1. Pilocarpine 0.5%–4% solution is used topically in the treatment of open-angle glaucoma and acute congestive glaucoma. It increases the tone of the ciliary muscle and causes miosis by contracting sphincter pupillae, opens the trabecular meshwork around the canal of Schlemm, facilitates drainage of aqueous humour and reduces intraocular pressure (IOP). It acts rapidly but has short duration of action. Pilocarpine ocusert that releases the drug slowly over 7 days is available.

2. It is used alternatively with mydriatics to break adhesions between the iris and lens.

3. It is used to reverse the pupillary dilatation after refraction testing.

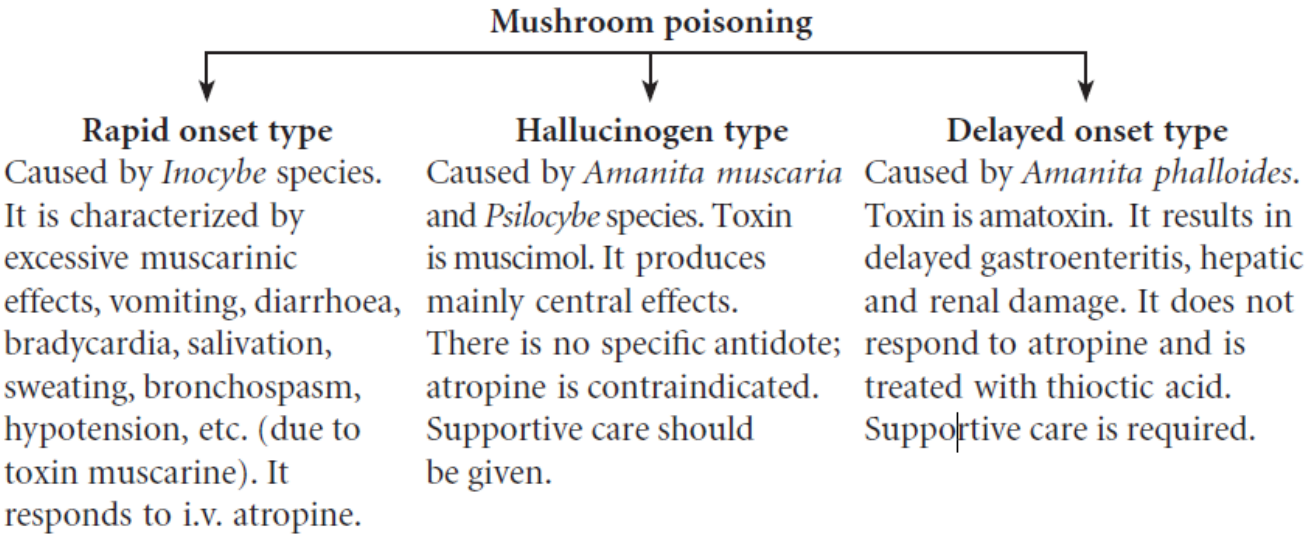
4. Pilocarpine is used as a sialagogue (drug used to augment salivary secretion).

Adverse Effects. They are salivation, sweating, bradycardia, diarrhoea and bronchospasm;

pulmonary oedema can occur following systemic therapy.

Muscarine. It is an active ingredient of poisonous mushroom, Amanita muscaria and

Inocybe species. Some types of mushroom poisoning are explained as follows:



Treatment of mushroom poisoning is mainly supportive.

Arecoline. It is an alkaloid obtained from areca nut. It has muscarinic and nicotinic

actions similar to choline esters.

Anticholinesterases

They inhibit the enzyme cholinesterase that is responsible for hydrolysis of ACh. Thus, ACh is not metabolized, gets accumulated at muscarinic and nicotinic sites and produces cholinergic effects. Hence, anticholinesterases are called indirectly acting cholinergic drugs.

Mechanism of action: ACh is rapidly hydrolysed by both true and pseudocholinesterases.

ACh binds to anionic and esteratic sites of cholinesterase n acetylated enzyme n undergoes rapid hydrolysis n acetate and free enzyme.

Carbamates bind to both the sites (i.e. anionic and esteratic) of cholinesterase (so ACh cannot bind the enzyme) n carbamoylated enzyme n undergoes slow hydrolysis to release the enzyme.

Edrophonium binds only to anionic site of ChE. It forms weak hydrogen bond with the enzyme. It diffuses away from the enzyme. Duration of action is 8–10 minutes.

Organophosphates bind covalently to esteratic site of cholinesterases and inhibit them irreversibly as hydrolysis of phosphorylated enzyme is extremely slow.

Echothiophate binds to both anionic and esteratic sites of the enzyme.

Reversible Anticholinesterases

Physostigmine

Neostigmine

Pyridostigmine

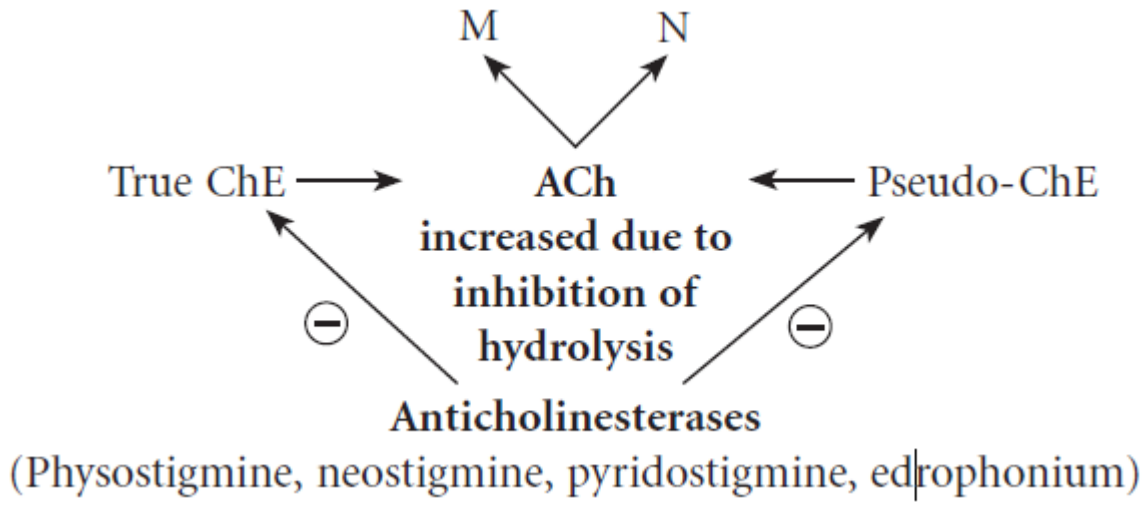
Edrophonium

Galantamine

Rivastigmine

Donepezil

Reversible anticholinesterases inhibit both true and pseudocholinesterases reversibly.



Physostigmine (Eserine). It is an alkaloid obtained from Physostigma venenosum. It is a tertiary amine and has good penetration through tissues. Its actions are similar to those of other cholinergic agents.

Table 2.4 ■ **Comparative features of physostigmine and neostigmine**

Physostigmine	Neostigmine
Natural alkaloid obtained from *Physostigma venenosum*	Synthetic agent
Tertiary amine, has good penetration through tissues, hence topically effective	Quaternary ammonium compound, has poor penetration, hence topically not effective
Crosses BBB – produces both central and peripheral effects	Does not cross BBB, hence no central effects
Uses • Atropine poisoning • Glaucoma	Uses • Postoperative urinary retention and paralytic ileus • Myasthenia gravis • Curare poisoning

Uses

1. Glaucoma: Physostigmine reduces IOP by producing miosis, thus facilitates the drainage of aqueous humour. On chronic use, it accelerates cataract formation; hence, it is rarely used in glaucoma.

2. Atropine poisoning: Intravenous physostigmine is used for severe atropine and other antimuscarinic drug poisoning because it has both central and peripheral actions. It competitively reverses the effects of atropine poisoning, but it should be used cautiously by slow i.v. injection as it may cause bradycardia.

Neostigmine. Neostigmine is a synthetic anticholinesterase agent. Its actions are pronounced on NMJ, gastrointestinal tract (GIT) and urinary bladder than on

cardiovascular system (CVS) or eye. On skeletal muscle, it has both direct and indirect actions.

Indirect Actions. By inhibiting cholinesterases, neostigmine increases ACh concentration at NMJ.

Direct Actions. Because of structural similarity with ACh (i.e. quaternary ammonium compound), neostigmine also directly stimulates NM receptors at NMJ. Thus, it improves muscle power in patients with myasthenia gravis. Neostigmine does not cross BBB and has no central side effects. Therefore, neostigmine is preferred to physostigmine in myasthenia gravis. It is available for oral, s.c., i.v. and i.m. administration.

Pyridostigmine. All features are same as neostigmine. Pyridostigmine has a longer duration of action and can be given twice daily in sustained release form; hence, it is preferred to neostigmine in myasthenia gravis. Even though pyridostigmine is less potent than neostigmine, it is better tolerated by myasthenic patients.

Edrophonium. It is a quaternary ammonium compound. On i.v. administration, it has a rapid onset but short duration of action (8–10 minutes).

Uses

1. Edrophonium is used in the diagnosis of myasthenia gravis.

2. It is used to differentiate myasthenic crisis from cholinergic crisis.

3. In curare poisoning, edrophonium is preferred because of its rapid onset of action.

Adverse Effects of Anticholinesterases. They are due to overstimulation of both muscarinic and nicotinic receptors – increased sweating, salivation, nausea, vomiting, abdominal cramps, bradycardia, diarrhoea, tremors and hypotension.

Therapeutic Uses of Reversible Anticholinesterases

1. **Eye**

(a) Glaucoma

(b) To reverse pupillary dilatation after refraction testing

(c) Miotics are used alternatively with mydriatics to break adhesions between iris and lens

2. **Myasthenia gravis**

3. Postoperative urinary retention and paralytic ileus

4. Curare poisoning and reversal of nondepolarizing neuromuscular blockade

5. Belladonna poisoning

6. Alzheimer's disease

1. **Glaucoma**. The aqueous humour formed by ciliary process is drained mainly through trabecular meshwork. Glaucoma is optic nerve damage with loss of visual function that is frequently associated with raised IOP. Normal IOP varies between 10 and 20 mm Hg. Management of this disorder is almost always directed at lowering the existing IOP either by improving drainage or decreasing the formation of aqueous humour. Acute congestive glaucoma: It is usually precipitated by mydriatics in people with narrow iridocorneal angle and shallow anterior chamber. Acute congestive glaucoma is a medical emergency. Once the attack is controlled, treatment is surgical or laser iridotomy.

Chronic simple glaucoma: It is a genetically predisposed condition affecting the patency of trabecular meshwork. The IOP rises gradually. Pharmacotherapy is the definitive treatment in a majority of cases.

Drugs for glaucoma

1. Osmotic agents: Mannitol (20%) i.v. infusion (1.5 g/kg body weight) and 50% glycerol oral (1.5 g/kg) are used. They draw fluid from the eye into the circulation by osmotic effect and reduce IOP in acute congestive glaucoma.

2. Carbonic anhydrase inhibitors: Acetazolamide (oral, i.v.), dorzolamide (topical) and brinzolamide (topical) are carbonic anhydrase inhibitors. They inhibit carbonic anhydrase enzyme, decrease bicarbonate formation in ciliary epithelium and decrease the

formation of aqueous humour. Topical carbonic anhydrase inhibitors, which have a much lower risk of systemic side effects, are preferred to systemic carbonic anhydrase inhibitors in chronic simple glaucoma. In acute congestive glaucoma, acetazolamide is administered intravenously and orally.

3. beta-Adrenergic blockers: Topical nonselective #-blockers are timolol, betaxolol, levobunolol and carteolol. They decrease aqueous humour formation by blocking Beta 2-receptors on ciliary epithelium. #-Blockers also decrease ocular blood flow. Timolol is widely used in glaucoma because (i) it lacks local anaesthetic or partial agonistic properties; (ii) it does not affect pupil size or accommodation; (iii) it has longer duration of action; (iv) it is well tolerated; (v) it is less expensive. Topical timolol is safer and highly effective. Betaxolol is a selective beta 1-blocker used in glaucoma, but it is less effective than nonselective agents. Betaxolol is protective to retinal neurons. Levobunolol is long acting. #-Blockers should be cautiously used in patients with bronchial asthma and heart failure.

4. Prostaglandins (PGs): They reduce IOP probably by facilitating uveoscleral outflow. Topical PGs such as latanoprost, travoprost and bimatoprost (PGF2 $-analogues) are the drug of choice in open-angle glaucoma because of their longer duration of action (once a day dosing), high efficacy and low incidence of systemic toxicity. They are also useful in acute congestive glaucoma. Latanoprost is also available in combination with timolol. They usually do not cause systemic side effects but may cause ocular irritation and iris pigmentation.

5. Miotics: Pilocarpine is a tertiary amine and is well absorbed through cornea. It is used topically in the treatment of open-angle and acute congestive glaucoma. It facilitates drainage of aqueous humour and reduces IOP.

6. alpha -Adrenergic agonists

(a) Apraclonidine is used topically as an adjunct in glaucoma. It does not cross the BBB, hence has no hypotensive effect like clonidine. They act on $2-receptors on ciliary epithelium.

• Apraclonidine

• Brimonidine !2-Agonists

Reduce formation of aqueous humour Decrease IOP

(b) Dipivefrin is a prodrug of adrenaline. It penetrates the cornea and with the

help of esterases, gets converted into adrenaline.

2. **Myasthenia Gravis**. Myasthenia gravis is an autoimmune disorder where antibodies are produced against NM receptors of NMJ resulting in a decrease in the number of NM receptors. There is an increased incidence of myasthenia gravis in patients with thymoma. Thymectomy can induce remission in most of the cases. In myasthenia, there is marked muscular weakness varying in degree at different times. Myasthenia gravis is diagnosed by:

1. Typical signs and symptoms – weakness and easy fatigability.

2. Edrophonium test – edrophonium (2–10 mg) given slow intravenously shows dramatic improvement of symptoms in patients with myasthenia gravis but not in other muscular dystrophies; it is also useful to differentiate myasthenic crisis from cholinergic crisis.

3. Demonstration of circulating antibodies to NM receptors.

Treatment. Anticholinesterases (neostigmine, pyridostigmine and ambenonium) are effective in providing symptomatic relief. They inhibit metabolism of ACh, thus prolonging its action at the receptors. Neostigmine also directly activates the NM receptors. Pyridostigmine is commonly used.

Long-term use or overdose of anticholinesterases leads to cholinergic crisis (severe muscular weakness and neuromuscular paralysis due to prolonged depolarization). This may be differentiated from myasthenic crisis (severe weakness due to exacerbation of myasthenia) by injecting a small dose of edrophonium (2 mg, i.v.). If the patient shows improvement in muscle power n myasthenic crisis. If the muscular weakness deteriorates n cholinergic crisis. Ventilator should be kept ready before injecting edrophonium as it

may aggravate cholinergic crisis, which is dangerous. Corticosteroids and other immunosuppressants like azathioprine or cyclophosphamide are useful in the induction and maintenance of remission. Plasmapheresis and immune therapy may be useful in resistant cases.

Note: Drugs that aggravate myasthenia (drugs that are contraindicated in myasthenia) are aminoglycoside antibiotics, d-tubocurarine (d-TC) and other neuromuscular blockers,

#-blockers, ether, phenytoin, etc.

3. Postoperative Urinary Retention and Paralytic Ileus (Fig. 2.13). Neostigmine is used because it increases the tone of the smooth muscle and relaxes the sphincters.

4. Curare Poisoning and Reversal of Nondepolarizing Neuromuscular Blockade. Edrophonium or neostigmine is used. They antagonize neuromuscular blockade by increasing the concentration of ACh at the NMJ. Prior administration of atropine is a must to block the muscarinic side effects.

5. **Belladonna Poisoning**. Physostigmine is preferred because it reverses both central and peripheral effects of atropine poisoning.

6. Alzheimer's Disease. It is a degenerative disease of the cerebral cortex. Donepezil, galantamine and rivastigmine are cerebroselective anticholinesterases. They increase cerebral levels of ACh and have shown to produce some benefit in these patients.

Irreversible Anticholinesterases

Organophosphorus Insecticides. All organophosphorus (OP) compounds except echothiophate have no therapeutic applications. Echothiophate is rarely used in resistant cases of glaucoma. OP compounds have only toxicological importance. OP poisoning is one of the most common poisoning all over the world. Common OP compounds are parathion, malathion, dyflos, etc. They irreversibly inhibit cholinesterases and cause accumulation of ACh at muscarinic and nicotinic sites.

Signs and Symptoms

1. Muscarinic effects: Profuse sweating, salivation, lacrimation, increased tracheobronchial secretions, bronchospasm, vomiting, abdominal cramps, miosis, bradycardia, hypotension, involuntary urination and defecation.

2. Nicotinic effects: Twitchings, fasciculations, muscle weakness and paralysis are due to prolonged depolarization.

3. Central effects: Headache, restlessness, confusion, convulsions, coma and death are usually due to respiratory failure.

Diagnosis. OP poisoning can be diagnosed by:

History of exposure

Characteristic signs and symptoms

Estimating the cholinesterase activity in blood, which is decreased

Treatment. General measures

1. Remove the contaminated clothes; wash skin with soap and water.

2. Gastric lavage should be continued till the returning fluid is clear.

3. Airway should be maintained.

4. Artificial respiration is given, if necessary.

5. Diazepam should be used cautiously by slow i.v. injection to control convulsions.

Specific Measures

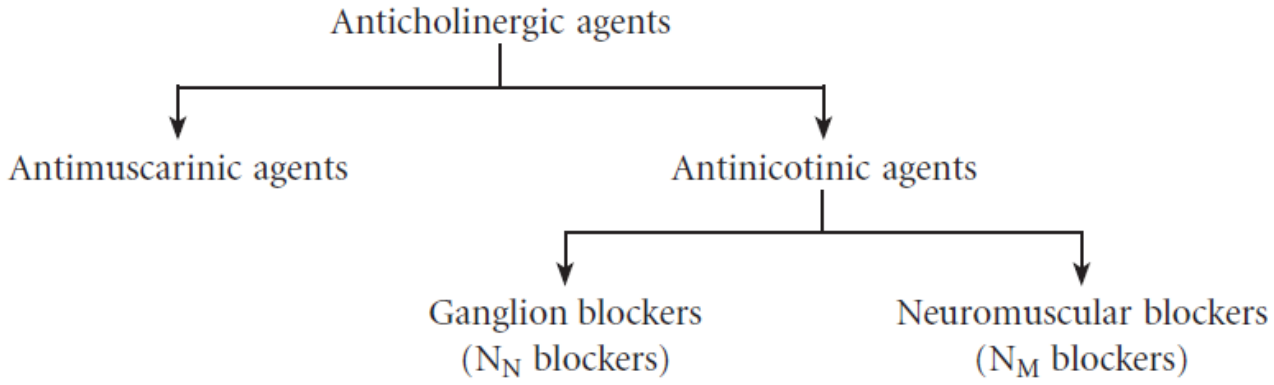
1. Atropine: Atropine is the first drug to be given in OP poisoning. Inject atropine 2 mg i.v. stat and it should be repeated every 5–10 minutes doubling the dose, if required, till the patient is fully atropinized (fully dilated, nonreactive pupils, tachycardia, etc.). Atropine should be continued for 7–10 days.

2. Oximes: Atropine is not effective for reversal of neuromuscular paralysis. Neuromuscular transmission can be improved by giving cholinesterase reactivators such as pralidoxime and obidoxime. Pralidoxime is administered intravenously slowly in a dose of 1–2 g.

Oximes are not effective in carbamate poisoning; they also have mild anti-ChE activity

Delayed toxicity of organophosphates: Prolonged exposure to OP compounds can cause neurotoxicity.

ANTICHOLINERGIC AGENTS



Generally, anticholinergics refer to antimuscarinic drugs.

Antimuscarinic Agents (Muscarinic Receptor Antagonists)

These drugs block muscarinic receptor mediated actions of ACh on heart, CNS, smooth muscles and exocrine glands. Atropine and scopolamine are belladonna alkaloids. Atropine is obtained from Atropa belladonna and scopolamine from Hyoscyamus niger.

Mechanism of Action. Both natural and synthetic drugs competitively block the muscarinic effects of ACh (competitive antagonism).

Classification of Antimuscarinic Agents

1. Natural alkaloids (Belladonna alkaloids): Atropine, scopolamine (hyoscine).

2. Semisynthetic derivatives:

Hyoscine butyl bromide

Homatropine (mydriatic)

Ipratropium bromide, tiotropium bromide (bronchial asthma)

3. Synthetic antimuscarinic agents:

(a) Used as mydriatic – cyclopentolate, tropicamide

(b) Used in peptic ulcer – pirenzepine, telenzepine, clidinium, propantheline

(c) Used as antispasmodic – dicyclomine, valethamate, flavoxate, oxybutynin, tolterodine, darifenacin

(d) Used as preanaesthetic agent – glycopyrrolate

(e) Used in parkinsonism – benzhexol (trihexyphenidyl), benztropine, biperiden,

procyclidine

Atropine. Atropine is the prototype drug and the chief alkaloid of belladonna. It is a tertiary amine. It blocks actions of ACh on all the muscarinic receptors. Atropine is administered by topical (eye), oral and parenteral routes.

Pharmacological Actions of Atropine

1. CNS: In therapeutic doses, atropine has mild CNS stimulant effect. It produces antiparkinsonian effect by reducing cholinergic overactivity in basal ganglia. It suppresses vestibular disturbances and produces antimotion sickness effect. Large doses can produce excitement, restlessness, agitation, hallucinations, medullary paralysis, coma and death.

2. CVS: At low doses, atropine causes initial bradycardia due to blockade of presynaptic

muscarinic autoreceptors (M1) on vagal nerve endings. In therapeutic doses, tachycardia is seen due to blockade of M2 receptors of the heart; it also improves A–V conduction. In high doses, flushing of the face and hypotension may occur due to cutaneous vasodilatation.

3. Glands: All secretions under cholinergic influence are reduced due to blockade of M3 receptors, i.e. sweat, salivary, nasal, throat, bronchial, gastric, lacrimal, etc. Milk and bile secretions are not affected. The skin and mucous membranes become dry.

4. Eye: Effects of atropine on eye are depicted as follows:

5. Smooth muscles:

(a) GIT: Atropine decreases tone and motility of the gut, but increases sphincter tone and may cause constipation. It also relaxes smooth muscle of the gall bladder.

(b) Urinary bladder: Atropine relaxes detrusor muscle of the bladder, but increases the tone of trigone and sphincter – may cause urinary retention, especially in elderly men with enlarged prostate.

(c) Bronchi: Atropine relaxes the bronchial smooth muscle. It also reduces secretion and mucociliary clearance resulting in mucus plug that may block the airway.

Pharmacokinetics. Atropine, scopolamine and most of the synthetic tertiary amines are well absorbed from the conjunctiva and GI tract; are widely distributed all over the body; cross BBB; partly metabolized in liver and partly excreted unchanged in urine.

Atropine Substitutes: Atropine acts on all subtypes of muscarinic receptors. Atropine substitutes have selective or relatively selective action on a particular organ, hence produce less adverse effects than atropine.

Table 2.6 ■ **Effects of atropine and phenylephrine/ephedrine on eye**

Atropine	Phenylephrine/ephedrine
1. It is an anticholinergic agent – causes passive mydriasis	1. It is a sympathomimetic agent – causes active mydriasis due to contraction of radial muscle fibres of the iris
2. There is loss of accommodation (it is cycloplegic), photophobia and blurring of vision; cycloplegia is due to paralysis of ciliary muscle; the lens becomes flat and vision is fixed for distant objects.	2. It does not cause cycloplegia
3. There is loss of light reflex	3. There is no loss of light reflex
4. IOP may rise and acute congestive glaucoma may be precipitated in person with shallow anterior chamber; it causes mydriasis and relaxation of ciliary muscle which occlude the canal of Schlemm, resulting in obstruction to the flow of aqueous humour	4. IOP is reduced due to a decrease in the formation of aqueous humour

1. Atropine substitutes used in the eye

(a) Homatropine

Semisynthetic atropine derivative

Less potent than atropine

Duration of action (mydriasis and cycloplegia) is 1–3 days

(b) Cyclopentolate and tropicamide

Synthetic atropine derivatives with rapid onset (tropicamide is the fastest acting) and shorter duration of action than atropine.

Action of cyclopentolate lasts for 24 hours; tropicamide is the shortest acting and action lasts for 6 hours.

2. Antispasmodics

(a) Dicyclomine

Tertiary amine

Has antispasmodic and antiemetic properties

Useful in dysmenorrhoea and abdominal colic

(b) Valethamate

Tertiary amine

Has antispasmodic effect

Useful in intestinal and urinary colic

(c) Oxybutynin

Has selective action at M1 and M3 receptors in urinary bladder and salivary gland.

Has vasicoselective action – useful for relief of spasm after urologic surgeries, for increasing bladder capacity in paraplegics and in nocturnal enuresis.

(d) Tolterodine

More selective for urinary bladder than salivary glands, hence dryness of mouth is less.

Used to decrease frequency and urgency in detrusor overactivity.

(e) Flavoxate

Similar to oxybutynin

Used to relieve urgency and frequency due to cystitis, prostatitis or urethritis

(f) Darifenacin, Solifenacin

Have selective action on urinary bladder (M3) – useful for relief of spasm after urologic surgeries and urinary incontinence.

Are longer acting than oxybutynin.

Oxybutynin, flavoxate, tolterodine, darifenacin and solifenacin are vasicoselective anticholinergics.

Drotaverine

Not an anticholinergic agent

Inhibits phosphodiesterase enzyme

Used as antispasmodic for relief of uterine spasm, intestinal and renal colic

3. Ipratropium bromide and tiotropium bromide

Quaternary compounds administered by inhalation route.

Have a selective action on bronchial smooth muscle – bronchodilatation (mainly in the larger airways).

Do not affect mucociliary clearance.

Tiotropium (24 hours) is longer acting than ipratropium (6 hours).

Dryness of mouth is the main side effect of these agents.

4. Pirenzepine

Has selective action on gastric acid secretion (M1) – useful in peptic ulcer.

Anticholinergic side effects – dryness of mouth, constipation, tachycardia and urinary retention are rare.

5. Benzhexol and benztropine

They are centrally acting anticholinergic agents used in parkinsonism.

6. Glycopyrrolate

Quaternary compound – central side effects are rare.

Used for preanaesthetic medication.

7. Propantheline

Useful in peptic ulcer and as an antispasmodic.

Rarely used at present.

8. Clidinium

Quaternary compound

Has antisecretory and antispasmodic properties

Useful in peptic ulcer and irritable bowel syndrome

9. Hyoscine butylbromide

Quaternary compound; available for oral and parenteral administration.

Used as antispasmodic for relief of oesophageal and GI colics.

Therapeutic Uses of Atropine and Its Substitutes

1. Ophthalmic uses:

As mydriatic and cycloplegic – for refraction testing. Atropine, homatropine, cyclopentolate or tropicamide are used topically. The action of atropine lasts for 7–10 days. Tropicamide is the preferred mydriatic as it has a short duration of action. In children, atropine is preferred because of its greater efficacy.

As mydriatic – for funduscopic examination, short-acting agent is used.

In iridocyclitis – atropinic mydriatics are used alternatively with miotics to break or prevent adhesions between iris and lens.

2. As preanaesthetic medication: Atropine or glycopyrrolate is used. They are used prior to the administration of general anaesthetics:

To prevent vagal bradycardia during anaesthesia.

To prevent laryngospasm by decreasing respiratory secretions.

Glycopyrrolate is a quaternary ammonium compound and has only peripheral anticholinergic effects.

3. Sialorrhoea: Synthetic derivatives (glycopyrrolate) are used to decrease excessive salivary secretion, e.g. in heavy metal poisoning and parkinsonism.

4. Chronic obstructive pulmonary disease (COPD) and bronchial asthma: Ipratropium bromide and tiotropium bromide are used in COPD and bronchial asthma. They are administered by metered dose inhaler or nebulizer. They produce bronchodilatation without affecting mucociliary clearance, hence are preferred to atropine.

5. Anticholinergics are useful as antispasmodic in dysmenorrhoea, intestinal and renal colic. They are less effective in biliary colic.

6. Urinary disorders: Oxybutynin and flavoxate have more prominent effect on bladder smooth muscle, hence are used to relieve spasm after urologic surgery.

Tolterodine has selective action on bladder smooth muscle (M3), hence is used to relieve urinary incontinence.

7. Poisoning:

In OP poisoning, atropine is the life-saving drug.

In some types of mushroom poisoning (Inocybe species), atropine is the drug of choice.

Atropine is used in curare poisoning with neostigmine to counteract the muscarinic effects of neostigmine.

8. As vagolytic: Atropine is used to treat sinus bradycardia and partial heart block due to increased vagal activity. It improves A–V conduction by vagolytic effect.

9. Parkinsonism: Centrally acting anticholinergic drugs such as benzhexol (trihexyphenidyl), benztropine, biperiden, procyclidine, etc. are the preferred agents for prevention and treatment of drug-induced parkinsonism. They are also useful in idiopathic parkinsonism, but less effective than levodopa. They control tremor and rigidity of parkinsonism.

Adverse Effects and Contraindications. The adverse effects of atropine are due to the

extension of its pharmacological actions.

1. GIT: Dryness of mouth and throat, difficulty in swallowing, constipation, etc.

2. Eye: Photophobia, headache, blurring of vision; in elderly persons with shallow anterior chamber, they may precipitate acute congestive glaucoma. Hence, anticholinergics are contraindicated in glaucoma.

3. Urinary tract: Difficulty in micturition and urinary retention especially in elderly men with enlarged prostate. So, they are contraindicated in these patients.

4. CNS: Large doses produce restlessness, excitement, delirium and hallucinations.

5. CVS: Tachycardia, palpitation and hypotension.

6. Acute belladonna poisoning: It is more common in children. The presenting features include fever, dry and flushed skin, photophobia, blurring of vision, difficulty in micturition, restlessness, excitement, confusion, disorientation and hallucinations.

Severe poisoning may cause respiratory depression, cardiovascular collapse, convulsions, coma and death.

Treatment of belladonna poisoning (Atropine poisoning):

It is mainly symptomatic.

1. Hospitalization.

2. Gastric lavage with tannic acid in case poison was ingested.

3. Tepid sponging to control hyperpyrexia.

4. Diazepam to control convulsions.

5. The antidote for severe atropine poisoning is physostigmine (1–4 mg). It is injected intravenously slowly. It is a tertiary amine – counteracts both peripheral and central effects of atropine poisoning. Hence, physostigmine is preferred to neostigmine.

Scopolamine. Scopolamine (hyoscine), another belladonna alkaloid, produces all the actions of atropine. In therapeutic doses, it produces prominent CNS depression with sedation and amnesia. Scopolamine has shorter duration of action than atropine. It has more prominent actions on eye and secretory glands. By blocking cholinergic activity, scopolamine suppresses vestibular disturbances and prevents motion sickness. It is the drug of choice for motion sickness – can be administered orally or as a transdermal patch. It is more effective for prevention of motion sickness, hence should be given (0.2 mg oral) at least half an hour before journey. The patch is placed behind the ear over the mastoid process. The patch should be applied at least 4–5 hours before the journey, and its effect lasts 72 hours. Scopolamine causes sedation and dryness of mouth. It can be administered parenterally as a preanaesthetic agent.

Drug Interactions of Anticholinergics. H1-blockers, tricyclic antidepressants (TCAs), phenothiazines, etc. have atropine-like action, hence may potentiate anticholinergic side effects.

Atropine alters absorption of some drugs by delaying gastric emptying – the bioavailability of levodopa is reduced, whereas the absorption of tetracyclines and digoxin is enhanced due to increased GI transit time.

Ganglion Blockers

They act at NN receptors of the autonomic ganglia (block both parasympathetic and sympathetic ganglia) and produce widespread complex effects. The ganglion blockers have ‘atropine-like’ action on heart (palpitation and tachycardia), eyes (mydriasis and cycloplegia), GIT (dryness of mouth and constipation), bladder (urinary retention). They

decrease sweat secretion and cause impotence in males. Blockade of sympathetic ganglia results in marked postural hypotension.

No selective ganglion blockers are available till now. Hence, they are rarely used in therapy.

Trimethaphan is a short-acting ganglion blocker that must be given by i.v. infusion. At present, the only use of trimethaphan is to produce controlled hypotension during neurosurgery.

Nicotine is obtained from tobacco leaves. It has initial stimulating, later a prolonged blocking effect on the autonomic ganglia. Tobacco smoking and chewing is a serious risk factor for oral, lung, heart and other diseases.

Treatment of nicotine addiction

Nicotine chewing gum and transdermal patch: They are useful as nicotine replacement

therapy.

Bupropion: It inhibits NA and DA reuptake and is used for smoking cessation.

Varenicline: It is a partial agonist at nicotinic receptors. It decreases craving and withdrawal symptoms during smoking cessation.

Skeletal Muscle Relaxants

Skeletal muscle relaxants decrease skeletal muscle tone by peripheral or central action.

Physiology of Skeletal Muscle Contraction

Motor nerve impulse
↓
Release of acetylcholine
↓
Binds with N_M receptors at NMJ
↓
Depolarization and development of end-plate potential (EPP) at motor end plate (mainly due to influx of Na^+)
↓
Muscle- action potential (MAP) – contraction of skeletal muscle
↓
ACh is rapidly inactivated by cholinesterase leading to repolarization
↓
Muscle is ready for a fresh nerve impulse

Classification

Skeletal muscle relaxants

Centrally acting
- Diazepam and other benzodiazepines
- Methocarbamol
- Chlorzoxazone
- Tizanidine
- Baclofen
- Carisoprodol
- Thiocolchicoside

Peripherally acting

Drugs acting at NMJ

Directly acting on skeletal muscle
- Dantrolene

Depolarizing blockers
- Succinylcholine
- Decamethonium

Nondepolarising blockers (competitive blockers)
- d-TC
- Pancuronium
- Doxacurium
- Pipecuronium

} Long acting

- Vecuronium
- Rocuronium
- Rapacuronium
- Atracurium
- Cisatracurium

} Intermediate acting

- Mivacurium — Short acting

Others
- Botulinum toxin A

Centrally Acting Skeletal Muscle Relaxants

Most of the centrally acting skeletal muscle relaxants are available in combination with one or other nonsteroidal anti-inflammatory drugs (NSAIDs). All of them cause certain degree of sedation. They act by depressing polysynaptic pathways in spinal and supraspinal sites. They are used to reduce spasm associated with cerebral palsy, trauma, sprain, tetanus, multiple sclerosis, etc.

Neuromuscular Blockers

Unlike centrally acting skeletal muscle relaxants, these drugs interfere with neuromuscular transmission, do not affect CNS and are administered intravenously. Neuromuscular blockers include nondepolarizing (competitive) and depolarizing blockers.

Depolarizing Blockers: Succinylcholine (Suxamethonium). Succinylcholine (SCh) is a quaternary ammonium compound. The structure resembles two molecules of Ach linked together. It acts as a partial agonist at NM receptors, hence causes initial fasciculations and later flaccid paralysis due to prolonged depolarization (phase I block). With continued exposure to the drug, the membrane becomes desensitized that leads to phase II block, which resembles the nondepolarizing block and is partially reversed by anticholinesterases.

Phase II block can occur in patients with atypical pseudocholinesterase. SCh is rapidly hydrolysed by pseudocholinesterase, hence has a very short duration of action (3–8 minutes). Transient apnoea is usually seen at the peak of its action. In people with liver disease or atypical pseudocholinesterase due to genetic defect, the metabolism of SCh becomes slow which results in severe neuromuscular blockade leading to respiratory paralysis with prolonged apnoea. This is referred to as ‘prolonged succinylcholine apnoea’. There is no antidote available, therefore:

Fresh frozen plasma should be infused.

Patient should be ventilated artificially until full recovery.

Adverse Effects

1. Muscle pain is due to initial fasciculations (muscle soreness).

2. Increased IOP due to contraction of external ocular muscles and it lasts for few minutes.

3. Aspiration of gastric contents may occur due to increased intragastric pressure.

4. Hyperkalaemia – fasciculations release K! into the blood.

5. Sinus bradycardia is due to vagal stimulation.

6. SCh apnoea (prolonged apnoea).

7. Malignant hyperthermia especially when used with halothane in genetically susceptible individuals. This is treated with intravenous dantrolene, rapid cooling, inhalation of 100% oxygen and control of acidosis.

Competitive Blockers. Claude Bernard showed experimentally the site of action of curare. Curare is a mixture of alkaloids and was used as an arrow poison. Among them, d-TC is the most important alkaloid which has NM blocking activity. d-TC is the prototype drug of competitive blockers.

Mechanism of Action. ACh is the agonist, whereas d-TC is the antagonist at NM receptors. Curariform drugs competitively antagonize the actions of ACh at the NM receptors of the NMJ. Anticholinesterases (neostigmine or edrophonium) are used to reverse the effects of competitive blockers by increasing the concentration of ACh. Actions. Competitive blockers produce flaccid paralysis. The order of muscles affected is extrinsic eye muscles–neck (muscles of phonation and swallowing)–face–hands–feet–limbs–trunk and finally, the respiratory muscles (intercostal muscles and diaphragm). But recovery occurs in reverse order – the respiratory muscles are the first to recover. Consciousness and appreciation of pain are not affected.

d-TC, mivacurium and atracurium cause histamine release which can manifest as hypotension, bronchospasm, etc.

Pancuronium, vecuronium, doxacurium and rocuronium have minimal/no tendency to cause histamine release.

Vecuronium, doxacurium and rocuronium have minimal tendency to cause cardiovascular effects like hypotension, cardiovascular collapse, etc. These effects are also less marked with pancuronium and pipecuronium. Cardiovascular side effects are prominent with d-TC and mivacurium.

Among competitive neuromuscular blockers, rocuronium has a rapid onset of action; hence, it can be used for endotracheal intubation.

Pharmacokinetics. Neuromuscular blockers are quaternary ammonium compounds. They are highly ionized, hence poorly absorbed from GI tract. They are administered intravenously. They are mainly confined to ECF space; do not cross placental and blood–brain barrier. They are metabolized in liver and some are excreted unchanged in urine. Adverse Effects. The adverse effects of nondepolarizing drugs are hypotension, respiratory paralysis, bronchospasm and aspiration of gastric contents.

Drug Interactions of Skeletal Muscle Relaxants

1. Nondepolarizing blockers % antibiotics Aminoglycosides inhibit the release of ACh from motor nerve and potentiate the effect of nondepolarizing blockers, hence require dose reduction in patients treated with aminoglycosides. Tetracyclines and clindamycin also potentiate the effect of nondepolarizing blockers.

2. Thiazides/loop diuretics % nondepolarizing blockers Hypokalaemia caused by thiazides/loop diuretics may potentiate the effect of nondepolarizing blockers.

3. SCh % thiopentone These drugs are chemically incompatible (in vitro; pharmaceutical interaction) hence result in precipitation when mixed in the same syringe.

4. General anaesthetics % nondepolarizing blockers Ether has curarimimetic effect on skeletal muscle, hence enhances the effect of nondepolarizing blockers. Fluorinated anaesthetics (isoflurane, desflurane and sevoflurane) also produce similar effect but to a lesser extent.

Factors Affecting Action of Neuromuscular Blockers

1. pH changes: Metabolic acidosis and respiratory acidosis increase the duration of block.

2. Hypothermia: It potentiates neuromuscular block by delaying the metabolism and elimination of these drugs.

3. Myasthenia gravis: Myasthenic patients are highly sensitive to competitive neuromuscular blockers.

4. Aminoglycoside antibiotics: They potentiate the effect of both competitive and nondepolarizing blockers by inhibiting presynaptic release of ACh.

5. Inhalational anaesthetics: Anaesthetics like halothane, isoflurane and ketamine increase the effects of neuromuscular blocking agents.

Uses

1. The main use of neuromuscular blockers is as adjuvant to general anaesthetics for producing satisfactory skeletal muscle relaxation during surgical procedures in abdomen and thorax, orthopaedics, etc. SCh is preferred for short procedures, e.g. diagnostic endoscopies, endotracheal intubation and orthopaedic manipulations. Vecuronium is commonly used in routine surgeries. Pancuronium and pipecuronium are used in surgeries of long duration.

2. SCh /mivacurium is used during electroconvulsive therapy (ECT) to prevent trauma due to convulsions.

3. For tetanus and status epilepticus when not controlled by other drugs, competitive neuromuscular blockers can be used.

4. Competitive neuromuscular blockers, e.g. vecuronium, can be used for ventilatory support in critically ill patients. Reversal of Neuromuscular Blockade. Edrophonium or neostigmine by increasing the concentration of ACh reverses the effect of d-TC and other competitive blockers at NMJ. Use of prior atropine administration is necessary to block the muscarinic effects of anticholinesterases.

Mivacurium (short acting), atracurium (intermediate acting), etc. do not require reversal.

Sugammadex. It is administered intravenously for rapid reversal of neuromuscular blocking action of rocuronium and vecuronium. It encapsulates the drugs, thus preventing their action.

Directly Acting Skeletal Muscle Relaxant: Dantrolene. Dantrolene is a directly acting skeletal muscle relaxant. It inhibits depolarization-induced Ca2! release (by blocking ryanodine receptors) from sarcoplasmic reticulum and produces skeletal muscle relaxation.

Intravenous dantrolene is the life-saving drug in malignant hyperthermia. It is used orally to reduce spasm in multiple sclerosis, cerebral palsy, spinal injuries, etc. The side effects are drowsiness, diarrhoea, dizziness, headache, fatigue and rarely hepatotoxicity.

Adrenergic Agonists (Sympathomimetic Agents)

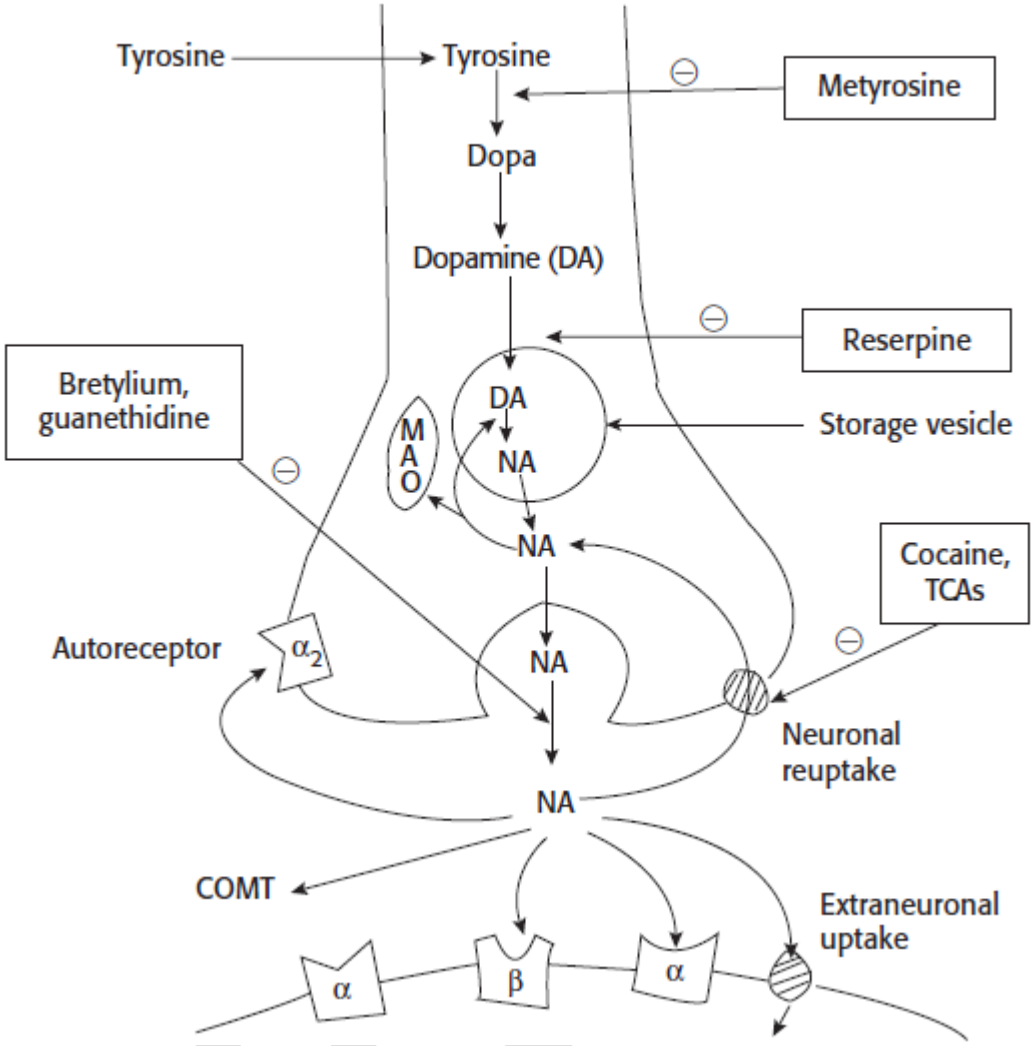
Adrenergic agonists mimic the actions of sympathetic stimulation.

Adrenergic Transmission

The transmitter in the sympathetic system is noradrenaline (NA; norepinephrine). Nerves that synthesize, store and release NA are called adrenergic (sympathetic) nerves.

Synthesis of catecholamines begins with the amino acid tyrosine, which is transported into the adrenergic neuron by active transport. In the neuronal cytosol, tyrosine is converted to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase and DOPA to dopamine (DA) by dopa decarboxylase. DA enters storage vesicles of the nerve terminal by active transport, where it is converted to NA by the enzyme dopamine

alpha-hydroxylase (this enzyme is present only in the storage vesicles); NA formed gets stored in the vesicles. In the adrenal medulla, NA is further converted to adrenaline by N-methyltransferase. Small quantities of NA are released continuously into the synaptic cleft and large quantities during nerve stimulation



Three processes are involved in termination of action of released NA in the synaptic cleft (fate of released NA in the synaptic cleft):

1. Most of the released NA is taken back into adrenergic nerve terminals (neuronal reuptake), which is either stored in vesicles or inactivated by mitochondrial monoamine oxidase (MAO) in the cytosol. Neuronal reuptake is the most important mechanism through which termination of action of NA takes place in the synaptic cleft.

2. Small amount of NA from the synaptic cleft diffuses into circulation and gets inactivated in liver by catechol-O-methyltransferase (COMT) and MAO.

3. Small quantity of NA is transported into other tissues (extraneuronal uptake).

Metabolism of Catecholamines

Vanillylmandelic acid (VMA) is the main metabolite of catecholamines excreted in urine. Normal value of VMA is 4–8 mg per 24 hours urine. Its levels are raised in pheochromocytoma, a tumour of adrenal medulla and sympathetic ganglia. Estimation of the levels of catecholamines and their metabolites in blood and urine is of great value in the diagnosis of pheochromocytoma. CT (computed tomography) and MRI (magnetic resonance imaging) scan are the important diagnostic aids.

Types, Distribution and Functions of Adrenergic Receptors

Ahlquist divided adrenergic receptors into $ and # types, which are located on the cell membrane. All adrenergic receptors are G-protein coupled receptors and regulate the production of intracellular second messengers; increase in IP3/DAG ($1), gcAMP ($2) and hcAMP.

1. Effect of activation of "1-receptors Blood vessels: Constriction

GI sphincter (anal): Increase in tone

Urinary sphincter: Increase in tone

Radial muscle (iris): Contraction (mydriasis)

2. Effect of activation of presynaptic "2-receptors Mediate negative feedback control on NA secretion (i.e. stimulation of $2-receptors decreases release of NA from sympathetic nerve endings)

3. Effect of activation of postsynaptic vascular "2-receptors

Mediate stimulatory effects: Vasoconstriction and venoconstriction

4. Effect of activation of "2-receptors on various secretions

Beta cells of islets of Langerhans in pancreas: Decrease in insulin secretion

Ciliary epithelium: Reduction of aqueous humour secretion

Sympathetic nerve endings: Decrease in NA release

5. Effect of activation of !1-receptors

Heart: Cardiac stimulation

Kidney: Promote renin release

6. Stimulatory effects due to activation of !2-receptors

Liver: Stimulation of glycogenolysis

Skeletal muscle: Contraction

Ciliary epithelium: Increase in secretion of aqueous humour

Uptake of K! into cells

7. Inhibitory effects due to activation of !2-receptors

Bronchial, uterine (pregnant), vascular and bladder smooth muscles: Relaxation

In GI smooth muscle, activation of both $- and #-receptors causes relaxation

8. Effect of activation of !3-receptors

Adipose tissue: Lipolysis

Adrenergic Drugs (Sympathomimetics)

The sympathomimetic drugs mimic effects of sympathetic stimulation. They are also referred to as adrenergic agonists.

Classification of Adrenergic Drugs (sympathomimetics)

1. On the basis of their chemical structure

(a) Catecholamines: Sympathomimetics with catechol nucleus (3,4-dihydroxy benzene) are called catecholamines, e.g. adrenaline, noradrenaline, DA, isoprenaline and dobutamine.

(b) Noncatecholamines: Sympathomimetics that lack catechol nucleus are called noncatecholamines, e.g. tyramine, ephedrine, amphetamine, phenylephrine and salbutamol.

2. On the basis of their mechanism of action:

(a) Direct acting: They act directly by stimulating adrenergic receptors.

(b) Indirect acting: They act by releasing noradrenaline from adrenergic nerve endings.

(c) Mixed acting: These drugs act both directly and indirectly.

3. On the basis of their therapeutic use:

(a) To raise BP in shock: DA, noradrenaline, ephedrine, phenylephrine, methoxamine, mephentermine.

(b) As bronchodilator: Salbutamol, levalbuterol, pirbuterol, terbutaline, bambuterol, salmeterol, formoterol.

(c) As cardiac stimulant: Adrenaline, isoprenaline, dobutamine.

(d) As CNS stimulant: Amphetamine, dextroamphetamine, methamphetamine.

(e) As nasal decongestant: Phenylephrine, xylometazoline, pseudoephedrine, oxymetazoline, naphazoline.

(f) As anorexiant: Dextroamphetamine, mazindol, phentermine, sibutramine.

(g) As uterine relaxant: Isoxsuprine, terbutaline, salbutamol, ritodrine.

Direct-Acting Sympathomimetics

Adrenaline (Epinephrine): "1-, "2-, !1-, !2- and !3-Agonist. It is a catecholamine, which is secreted mainly by adrenal medulla. Adrenaline is a direct-acting, nonselective adrenergic agonist.

Pharmacological Actions. Adrenaline acts on $1-, $2-, #1-, #2- and #3-receptors.

1. Cardiovascular system

(a) Heart: Adrenaline is a powerful cardiac stimulant. It acts mainly by interacting with #1-receptors and produces various effects. They are as follows:

Increase in heart rate – h rate of spontaneous depolarization in SA node

(positive chronotropic effect)

Increase in myocardial contractility (positive inotropic effect)

Increase in conduction velocity (positive dromotropic effect)

Increase in cardiac output

Increase in automaticity

Cardiac work and its oxygen requirement is markedly increased

Increase in the excitability and tendency to cause cardiac arrhythmias

(b) Blood vessels and BP: Blood vessels of the skin and mucous membranes ($1-receptors) are constricted by adrenaline. It also constricts renal, mesenteric, pulmonary and splanchnic vessels, but dilates blood vessels of skeletal muscle and coronary vessels (#2). Intravenous administration of adrenaline in moderate doses produces biphasic effect. There is an initial rise in BP due to $1 (blood vessels) and #1 (heart) actions, followed by a fall in BP due to #2-mediated dilatation of blood vessels in skeletal muscle. Administration of adrenaline after $-blocker produces only a fall in BP (#2-action). This is

referred to as vasomotor reversal of Dale.

If adrenaline is rapidly injected intravenously, there is an increase in both systolic and diastolic BP.

2. Respiratory system: Adrenaline rapidly relaxes (#2) bronchial smooth muscle. It is a potent bronchodilator but has a short duration of action. It inhibits the release of inflammatory mediators from mast cells (#2). It also reduces secretions and relieves mucosal congestion by vasoconstrictor effect ($1).

3. GIT: It relaxes the smooth muscle of the gut ($ and #2). It reduces the intestinal tone and peristaltic movements but the effects are transient.

4. Bladder: It relaxes the detrusor muscle (#2) and contracts the sphincter ($1). As a result, it may cause difficulty in urination.

5. CNS: In therapeutic doses, adrenaline does not cross BBB; hence, CNS effects are minimal. But in high doses, it may cause headache, restlessness and tremor.

6. Eye: Adrenaline has poor penetration through cornea when applied topically into the eye. Hence, it is administered as a prodrug .

7. Metabolic effects:

! Adrenaline increases blood glucose level by:

(i) Stimulating hepatic glycogenolysis (!2), which is the predominant effect.

(ii) Reducing insulin secretion through "2-action.

(iii) Decreasing uptake of glucose by peripheral tissues.

! It increases blood lactic acid level by stimulating glycogenolysis in skeletal muscles.

8. Other effects

! Adrenaline facilitates neuromuscular transmission and postpones fatigue.

! It reduces plasma K# levels by promoting uptake of K# into cells, particularly into the skeletal muscle (!2).

Pharmacokinetics. Adrenaline is not suitable for oral administration because of its rapid inactivation in the GI mucosa and liver. Adrenaline can be given subcutaneously.

In anaphylactic shock, absorption of s.c. adrenaline is poor; hence, it is given intramuscularly.

In cardiac arrest, it is given intravenously. It does not cross BBB; is rapidly metabolized by COMT and MAO, and the metabolites are excreted in urine.

Adverse Effects and Contraindications. The adverse effects of adrenaline are an extension of its pharmacological actions. They are tachycardia, palpitation, headache, restlessness, tremors and rise in BP. The serious side effects are cerebral haemorrhage and cardiac arrhythmias. In high concentration, adrenaline may cause acute pulmonary oedema due to shift of blood from systemic to pulmonary circulation. Adrenaline is contraindicated in most of the cardiovascular diseases such as hypertension, angina, cardiac arrhythmias and congestive cardiac failure (CCF). In patients on !-blockers, it may cause hypertensive crisis and cerebral haemorrhage due to unopposed action on vascular "1-receptors.