Autonomic Nervous System: General Considerations

The autonomic nervous system (ANS) is autonomic (auto = self, nomic = law) or involuntary part of nervous system that controls the body activities automatically. The ANS usually operates without conscious control. The centers present in hypothalamus and brain stem regulate ANS activities. The effects produced by ANS are rapid and the major effector organs are **smooth muscles** (e.g. change in airway or blood vessel diameter), **cardiac muscles** (change in rate and force of heart beat) and **secretory glands** (increase or decrease in glandular secretions).

- **Autonomic sensory neurons** provide input to ANS. These neurons are associated with interoceptors (sensory receptors) located in blood vessels, visceral organs, muscles and the nervous system that monitor conditions in the internal environment. *E.g.* Chemoreceptors that monitor blood CO_2 level and mechanoreceptors that detect the degree of stretch in the walls of organs or blood vessels.

- **Autonomic motor neurons** regulate body activities by either increasing (exciting) or decreasing (inhibiting) activities in effector tissues (cardiac muscle, smooth muscle and glands). Changes in the diameter of the pupils, dilation and constriction of blood vessels and adjustment of the rate and force of the heartbeat are examples of autonomic motor responses.

The output (motor) part of the ANS has two divisions: **the sympathetic division** and **the parasympathetic division**.

In general, nerve impulses from sympathetic division of the ANS stimulate the organ to increase its activity (excitation) and impulses from parasympathetic division decrease the organ's activity (inhibition). *E.g.* Increase in nerve impulses from the sympathetic division increases heart rate and an increase in nerve impulses from the parasympathetic division decreases heart rate.

The sympathetic division is often called the **fight-or-flight** division because its activation results in increased alertness and metabolic activities in order to prepare the body for an emergency situation. Responses to such situations, which may occur during physical activity or emotional stress, include a rapid heart rate, faster breathing rate, dilation of the pupils, dry mouth, sweaty but cool skin, dilation of blood vessels to organs involved in combating stress (such as the heart and skeletal muscles), constriction of blood vessels to organs not involved in

combating stress (such as the gastrointestinal tract and kidneys), and the release of glucose from the liver.

The parasympathetic division is also called as **rest-and-digest** division because its activities conserve and restore body energy during times of rest or digesting a meal. The parasympathetic division conserves energy and replenishes nutrient stores. The responses produced by parasympathetic division are opposite to that of sympathetic division.

Most organs have dual innervation; that is, they receive impulses from both sympathetic and parasympathetic neurons.

Anatomy of Autonomic Motor Pathway

Autonomic motor pathway consists of 3 anatomical components: **Preganglionic neuron**, **Autonomic ganglion** and **Postganglionic neuron**.

1. **Preganglionic Neuron:** It is the first of two motor neurons present in autonomic motor pathway. Its cell body is in the brain or spinal cord and its axon exits the CNS as part of a cranial or spinal nerve. The axon of a preganglionic neuron is a small-diameter, myelinated and extends to an autonomic ganglion where it synapses with a postganglionic neuron.

- In the sympathetic division, the preganglionic neurons arise from 12 thoracic segments and the first two lumbar segments of the spinal cord. For this reason, the sympathetic division is also called the **thoracolumbar division**.

- In parasympathetic division, preganglionic neurons of the parasympathetic division arise from 4 cranial nerves in the brain stem (III, VII, IX, and X) and in the 2nd – 4th sacral segments of the spinal cord. Hence, the parasympathetic division is also known as the **craniosacral** division.

2. **Autonomic Ganglia:** These are the sites of synapse between preganglionic and postganglionic neurons.There are two major groups of autonomic ganglia: (1) sympathetic ganglia (2) parasympathetic ganglia

- **Sympathetic ganglia:** The sympathetic ganglia are the sites of synapses between sympathetic preganglionic and postganglionic neurons. There are two major types of sympathetic ganglia: **sympathetic trunk ganglia** and **prevertebral ganglia**.

o **Sympathetic trunk ganglia:** (also called vertebral chain ganglia or paravertebral ganglia) These lie in a vertical row on either side of the vertebral column. These ganglia extend from the base of the skull to the coccyx. Postganglionic axons from sympathetic trunk ganglia primarily innervate organs above the diaphragm. Because the sympathetic trunk ganglia

are near the spinal cord, most sympathetic preganglionic axons are short and most sympathetic postganglionic axons are long.

Once axons of sympathetic preganglionic neurons pass to sympathetic trunk ganglia, they may connect with postganglionic neurons in one of the following ways:

●1 An axon may synapse with postganglionic neurons in the ganglion it first reaches.

●2 An axon may ascend or descend to a higher or lower ganglion before synapsing with postganglionic neurons. The axons of incoming sympathetic preganglionic neurons that pass up or down the sympathetic trunk collectively form the sympathetic chains.

●3 An axon may continue, without synapsing, through the sympathetic trunk ganglion to end at a prevertebral ganglion and synapse with postganglionic neurons there. Beyond the sympathetic trunk ganglia, these axons form nerves known as **splanchnic nerves**.

●4 An axon may also pass without synapsing, through the sympathetic trunk ganglion and a prevertebral ganglion and then extend to chromaffin cells of the adrenal medullae.

o **Prevertebral (collateral) ganglia**: These are the second group of sympathetic ganglia which lies anterior to the vertebral column. In general, postganglionic axons from prevertebral ganglia innervate organs below the diaphragm.

- **Parasympathetic ganglia:** Preganglionic axons of the parasympathetic division synapse with postganglionic neurons in terminal ganglia. Most of these ganglia are located close to or actually within the wall of a visceral organ. Because terminal ganglia are located either close to or in the wall of the visceral organ, parasympathetic preganglionic axons are long and parasympathetic postganglionic axons are short in length.

3. **Postganglionic Neuron:** This is second neuron present in autonomic motor pathway and it lies entirely outside the CNS. Its cell body and dendrites are located in an autonomic ganglion, where it forms synapses with one or more preganglionic axons. The axon of a postganglionic neuron is a small-diameter, unmyelinated and terminates in a visceral effector. Thus, preganglionic neurons convey nerve impulses from the CNS to autonomic ganglia and postganglionic neurons relay the impulses from autonomic ganglia to visceral effectors.

Sympathetic Division of ANS:
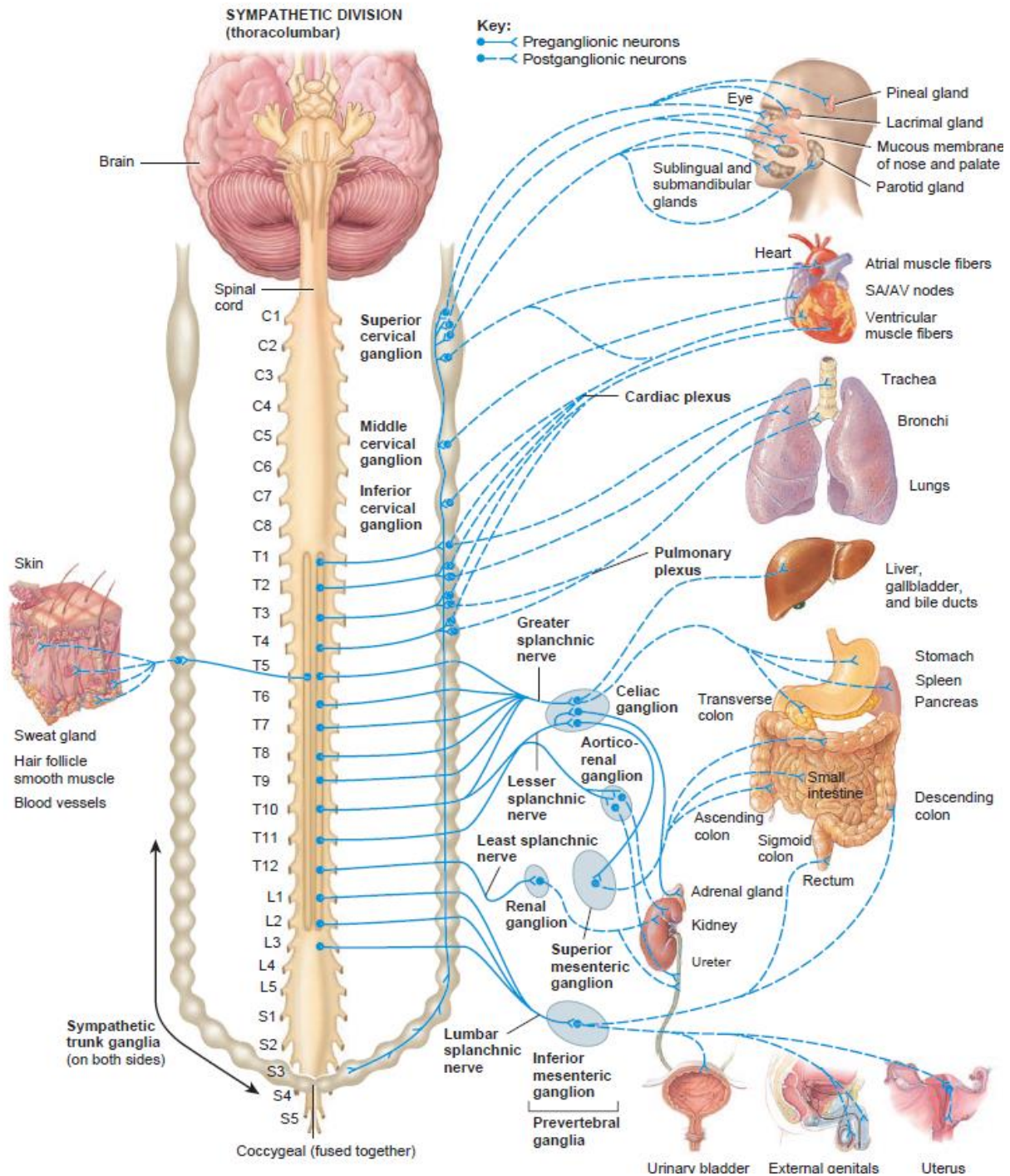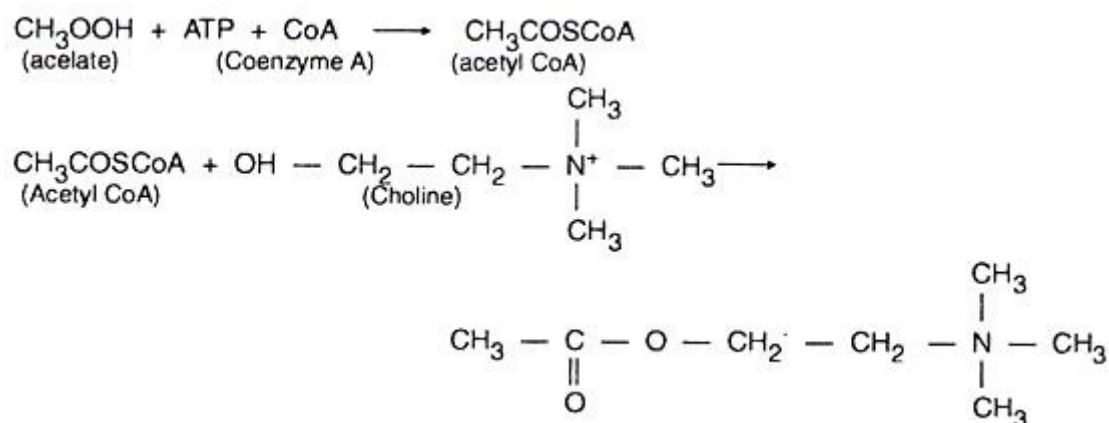
Parasympathetic Division of ANS
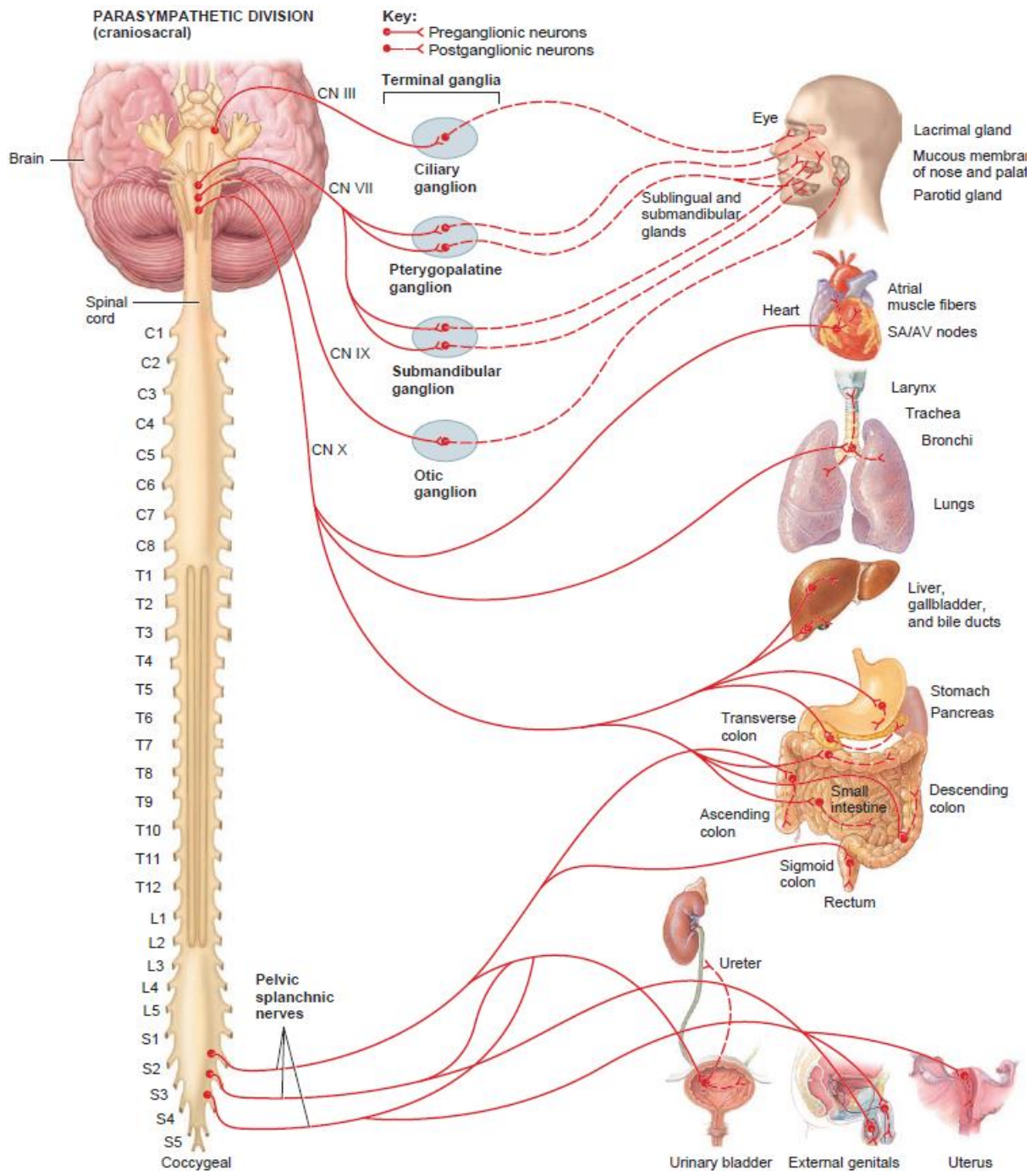
Cholinergic System and Drugs

CHOLINERGIC TRANSMISSION
Acetylcholine (ACh) is a major neurohumoral transmitter at autonomic, somatic as well as central sites.

Synthesis, storage and destruction of ACh
Acetylcholine is synthesized locally in the cholinergic nerve endings by the following pathway—

$$CH_3OOH + ATP + CoA \longrightarrow CH_3COSCoA$$
(acelate)   (Coenzyme A)   (acetyl CoA)

$$CH_3COSCoA + OH - CH_2 - CH_2 - \overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{N^+}} - CH_3 \longrightarrow$$
(Acetyl CoA)   (Choline)

$$CH_3 - \overset{}{\underset{\underset{O}{\|}}{C}} - O - CH_2 - CH_2 - \overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{N}} - CH_3$$

Choline is actively taken up by the axonal membrane by a Na+: choline cotransporter and acetylated with the help of ATP and coenzyme- A by the enzyme *choline acetyl transferase* present in the axoplasm. *Hemicholinium* (HC3) blocks choline uptake (the rate limiting step in Ach synthesis) and depletes ACh. Most of the Ach is stored in ionic solution within small synaptic vesicles, but some free ACh is also present in the cytoplasm of cholinergic terminals. Active transport of ACh into synaptic vesicles is effected by another carrier which is blocked by *vesamicol*.

Release of ACh from nerve terminals occurs in small quanta—amount contained in individual vesicles is extruded by exocytosis. In response to a nerve AP synchronous release of multiple quanta triggers postjunctional events.

Two toxins interfere with cholinergic transmission by affecting release: *botulinum toxin* inhibits release, while *black widow spider toxin* induces massive release and depletion.

Cholinesterase Immediately after release, Ach is hydrolyzed by the enzyme cholinesterase and choline is recycled. A specific (*Acetylcholinesterase*— AChE or true cholinesterase) and a nonspecific (*Butyrylcholinesterase*—BuChE or pseudocholinesterase) type of enzyme occurs in the body. While
AChE is strategically located at all cholinergic sites and serves to inactivate ACh instantaneously, BuChE present in plasma and elsewhere probably serves to metabolize ingested esters.
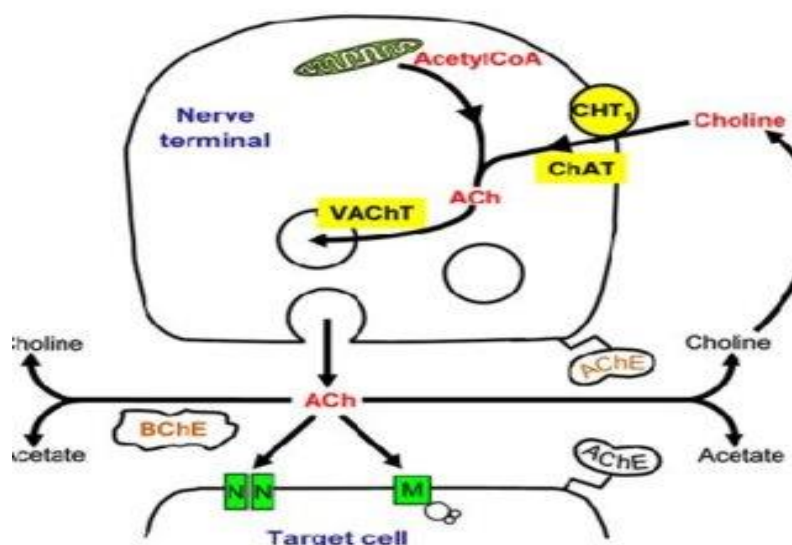
Cholinoceptors
Two classes of receptors for ACh are recognised —muscarinic and nicotinic; the former is a G protein coupled receptor, while the latter is a ligand gated cation channel.

Muscarinic These receptors are selectively stimulated by muscarine and blocked by atropine. They are located primarily on autonomic effector cells in heart, blood vessels, eye, smooth muscles and glands of gastrointestinal, respiratory and urinary tracts, sweat glands, etc. and in the CNS. Subsidiary muscarinic receptors are also present in autonomic ganglia where they appear to play a modulatory role by inducing a long-lasting late EPSP.

Types:

M1: The M1 is primarily a neuronal receptor located on ganglion cells and central neurones, especially in cortex, hippocampus and corpus striatum. It plays a major role in mediating gastric secretion, relaxation of lower esophageal sphincter (LES) caused by vagal stimulation, and in learning, memory, motor functions, etc.

M2: Cardiac muscarinic receptors are predominantly M2 and mediate vagal bradycardia. Autoreceptors on cholinergic nerve endings are also of M2 subtype. Smooth muscles express some M2 receptors as well which, like M3, mediate contraction.

M3: Visceral smooth muscle contraction and glandular secretions are elicited through M3 receptors, which also mediate vasodilatation through EDRF release. Together the M2 and M3 receptors mediate most of the well-recognized muscarinic actions including contraction of LES.

Nicotinic These receptors are selectively activated by nicotine and blocked by tubocurarine or hexamethonium. They are rosette-like pentameric structures (*see* Fig. 4.4) which enclose a ligand gated cation channel: their activation causes opening of the channel and rapid flow of cations resulting in depolarization and an action potential. On the basis of location and selective

agonists and antagonists two subtypes NM and NN (previously labelled N1 and N2) are recognized

NM: These are present at skeletal muscle endplate: are selectively stimulated by phenyl trimethyl ammonium (PTMA) and blocked by tubocurarine. They mediate skeletal muscle contraction.

NN: These are present on ganglionic cells (sympathetic as well as parasympathetic), adrenal medullary cells (embryologically derived from the same site as ganglionic cells) and in spinal cord and certain areas of brain. They are selectively stimulated by dimethyl phenyl piperazinium (DMPP), blocked by hexamethonium, and constitute the primary pathway of transmission in ganglia.

CHOLINERGIC DRUGS

These are drugs which produce actions similar to that of ACh, either by directly interacting with cholinergic receptors (cholinergic agonists) or by increasing availability of ACh at these sites *(anticholinesterases).*

Cholinergic Agonists:

Choline esters: Acetylcholine, Methacholine, Carbachol, Bethanechol.

Alkaloids: Muscarinic, Pilocarpine, Arecholine**.**

Pharmacological Actions

Muscarinic effects:

<u>**CVS:**</u>
    Heart, The cardiac muscarinic receptors are of the M2 subtype.
- ACh hyperpolarizes the SA nodal cells and decreases their rate of diastolic depolarization. As a result, rate of impulse generation is reduced—*bradycardia* or even cardiac arrest may occur.
- Ventricular contractility is also decreased but the effect is not marked.

Blood vessels, Muscarinic (M3) receptors are present on vascular endothelial cells:
- All blood vessels are dilated, though only few (skin of face, neck, salivary glands) receive cholinergic innervation.
- vasodilatation is primarily mediated through the release of an *endothelium dependent relaxing factor* (EDRF) which is nitric oxide (NO).

<u>**Smooth muscle**</u>
 Smooth muscle in most organs is contracted (mainly through M3 receptors).
- Tone and peristalsis in the gastrointestinal tract is increased and sphincters relax □□abdominal cramps and evacuation of bowel.
- Peristalsis in ureter is increased.

- The detrusor muscle contracts while the bladder trigone and sphincter relaxes, voiding of bladder.
- Bronchial muscles constrict, asthmatics are highly sensitive, bronchospasm, dyspnoea, precipitation of an attack of bronchial asthma.

Glands

Secretion from all parasympathetically innervated glands is increased *via* M3 and some M2 receptors: sweating, salivation, lacrimation, increased tracheobronchial and gastric secretion. The effect on pancreatic and intestinal glands is not marked. Secretion of milk and bile is not affected.

Nicotinic Effects:

Autonomic ganglia Both sympathetic and parasympathetic ganglia are stimulated. This effect is manifested at higher doses. High dose of Ach given after atropine causes tachycardia and rise in BP due to stimulation of sympathetic ganglia and release of catecholamines.

Skeletal muscles Iontophoretic application of ACh to muscle endplate causes contraction of the fibre. Intraarterial injection of high dose can cause twitching and fasciculations, but i.v. injection is generally without any effect (due to rapid hydrolysis of ACh).

CNS actions
ACh injected i.v. does not penetrate blood-brain barrier and no central effects are seen. However, direct injection into the brain produces arousal response followed by depression. Cholinergic drugs which enter brain produce complex behavioral and neurological effects.

ALKALOIDS
Pilocarpine It is obtained from the leaves of *Pilocarpus microphyllus* and other species.
It has prominent muscarinic actions and also stimulates ganglia—mainly through ganglionic muscarinic receptors.
Pilocarpine cause marked increase in secretion of various glands.
It gives a complex action CVS. Small dose can cause fall in BP, but hagher dose can cause rise in BP and can even cause Tachycardia.
In eye it can cross cornea and can induce miotic effect. It can be a beneficial drug in glaucoma

ANTICHOLINESTERASES

Anticholinesterases (anti-ChEs) are agents which inhibit ChE, protect ACh from hydrolysis, thus increase the amount of ACh at synapses, which will further increase the cholinergic effect.

Classification:

1. **Reversible:**
   a) **Carbamates:** Physostigmine, Neostigmine, Pyridostigmine, Donepezil, Galantamine.
   b) **Acridine:** Tacrine.

2. **Irreversible:**

   a) **Organophosphates**: Dyflos, Echothiopate, Malathion, Diazinon.
   b) **Carbamate:** Carbaryl.

Mechanism of Action:

They act by increasing the concentration of Ach at cholinoceptors by inhibiting AchE. Thus they prevent the degradation of Ach into choline and acetate.

- The anti-ChEs react with the enzyme essentially in the same way as ACh.
- The carbamates and phosphates respectively carbamylate and phosphorylate the esteratic site of the enzyme.
- The acetylated enzyme reacts with water extremely rapidly and the esteratic site is freed in a fraction of a millisecond, whereas the carbamylated enzyme (reversible inhibitors) reacts slowly and the phosphorylated enzyme (irreversible inhibitors) reacts extremely slowly.
- It is noteworthy that edrophonium and tacrine attach only to the anionic site and do not form covalent bonds with the enzyme(REVERSIBLE INHIBITION), while organophosphates attach only to the esteratic site forming covalent bonds (IREVERSIBLE INHIBITION).

PHARMACOLOGICAL ACTIONS

- **Ganglia** Local hydrolysis of ACh is less important in ganglia: inactivation occurs partly by diffusion and hydrolysis in plasma. Anti-ChEs stimulate ganglia primarily through muscarinic receptors present there. High doses cause persistent depolarization of the ganglionic nicotinic receptors and blockade of transmission.
- **CVS** Cardiovascular effects are complex. Whereas muscarinic action would produce bradycardia and hypotension, ganglionic stimulation would tend to increase heart rate and BP. Action on medullary centres (stimulation followed by depression) further complicates the picture, so does ganglionic blockade with high doses.
- **Skeletal muscles:** After treatment with anti- ChEs, the ACh released by a single nerve impulse is not immediately destroyed. It re-binds to the receptor and produce its effect.
- **Other effects** These result from stimulation of smooth muscles and glands of the gastrointestinal respiratory, urinary tracts and in the eye as described for ACh.

THERAPEUTIC USES

I. EYES

1. Glaucoma
Acute congestive glaucoma: Pilocarpine is the preferred cholinergic drug (pilocarpine eye drops 0.5-4% every 4-6 hourly), the main action is that they improve the aqueous outflow. Physostigmine (0.1%) is used to supplement action of pilocarpine in closed angle glaucoma.

2. Pilocarpine or Physostigmine is used alternate with a mydriatic in iritis, uveitis or corneal ulcer.

II. ALZHEIMER'S DISEASE
Treatment: Cholinergic replacement using cholinesterase inhibitors such as: Donepezil 5-10 mg/day (drug of choice), Rivastigmine 1.5 mg BID (max: 12 mg/day).

Iii Myasthenia gravis

Myasthenia gravis is an autoimmune disorder, due to development of antibodies directed to the nicotinic receptors (NR) at the muscle endplate ▯▯reduction in number of free NM cholinoceptors to 1/3 of normal or less and structural damage to neuromuscular junction. This results in weakness and easy fatigability on repeated activity, with recovery after rest.

Treatment:

1.Pyridostigmine 60-120 mg 3-4 times/day orally [less frequent dosing compared to Neostigmine]

2. or Pyridostigmine 2 mg IM

3. Or Neostigmine 15 mg q 6hourly.

Iv Cobra bite Cobra venom has a curare like neurotoxin. Though specific antivenom serum is the primary treatment, neostigmine + atropine prevent respiratory paralysis.

Anticholinergic Drugs

Conventionally, the term 'anticholinergic drugs' is restricted to those which block actions of Ach on autonomic effectors and in the CNS exerted through muscarinic receptors. Though nicotinic receptor antagonists also block certain actions of ACh, they are generally referred to as 'ganglion blockers' and 'neuromuscular blockers'.

Atropine, the prototype drug of this class, is highly selective for muscarinic receptors, but some of its synthetic substitutes do possess significant nicotinic blocking property in addition.

CLASSIFICATION
1. *Natural alkaloids* Atropine, Hyoscine (Scopolamine).

2. *Semisynthetic derivatives* Homatropine, Atropine methonitrate, Hyoscine butyl bromide, Ipratropium bromide, Tiotropium bromide.

3. *Synthetic compounds*
(a) *Mydriatics:* Cyclopentolate, Tropicamide□

(b) *Antisecretory-antispasmodics*:

      (i) *Quaternary compounds:* Propantheline, Oxyphenonium, Clidinium, Pipenzolate methyl bromide, Isopropamide, Glycopyrrolate.

      (ii) *Tertiary amines:* Dicyclomine, Valethamate, Pirenzepine.

(c)*Vasicoselective:* Oxybutynin, Flavoxate

(d)*Antiparkinsonian:* Benzhexol, Procyclidine.

PHARMACOLOGICAL ACTIONS

1. **CNS:** Atropine has a CNS stimulant action. It has poor ability to cross the blood brain barrier so it produce such stimulant effect only at high doses.
- Atropine stimulates many medullary centres—vagal, respiratory, vasomotor.
- It depresses vestibular excitation and has anti-motion sickness property.
- It supress the tremors and rigidity in Parkinsonism, by blocking over excitation of cholinergic system in basal ganglia.
- High doses cause cortical excitation, restlessness, disorientation, hallucinations and delirium followed by respiratory depression and coma.
2. **CVS**
   Heart The most prominent effect of atropine is tachycardia. It is due to blockade of M2 receptors on the SA node. With the help of this M_2 receptor vagal tone decreases Heart rate.
   BP Since cholinergic impulses are not involved in the maintenance of vascular tone, atropine does not have any consistent or marked effect on BP. Tachycardia and

vasomotor centre stimulation tend to raise BP, while histamine release and direct vasodilator action (at high doses) tend to lower BP.

3. **EYE**
   Topical application of atropine causes mydriasis, which leads to abolition of light reflex and cycloplegia, which may last up to 7–10 days. This results in photophobia and blurring of near vision.

4. **Smooth muscles**
   All visceral smooth muscles that receive parasympathetic motor innervation are relaxed by atropine by M3 blockade.

5. **Glands** Atropine markedly decreases sweat, salivary, tracheobronchial and lacrimal secretion (M3 blockade). Skin and eyes become dry, talking and swallowing may be difficult. Atropine decreases secretion of acid, pepsin and mucus in the stomach.

6. **Body temperature** Rise in body temperature occurs at higher doses. It is due to both inhibition of sweating as well as stimulation of temperature regulating centre in the hypothalamus.

PHARMACOKINETICS
Atropine and hyoscine are rapidly absorbed from g.i.t. Applied to eyes they freely penetrate cornea. Passage across blood-brain barrier is somewhat restricted. About 50% of atropine is metabolized in liver and rest is excreted unchanged in urine. It has a t½ of 3–4 hours. Hyoscine is more completely metabolized and has better blood-brain barrier penetration.

ATROPINE SUBSTITUTES

Quaternary compounds
These have certain common features—
• Incomplete oral absorption.
• Poor penetration in brain and eye; central and ocular effects are not seen after parenteral/ oral administration.
• Elimination is generally slower; majority are longer acting than atropine.
• Have higher nicotinic blocking property. Some ganglionic blockade may occur at clinical dose ☐postural hypotension, impotence are additional side effects.
• At high doses some degree of neuromuscular blockade may also occur.

Hyoscine butyl bromide 20–40 mg oral, i.m., s.c., i.v.; less potent and longer acting than atropine; used for esophageal and gastrointestinal spastic conditions.

Propantheline 15–30 mg oral; it was a popular anticholinergic drug used for peptic ulcer and gastritis. It has some ganglion blocking activity as well and is claimed to reduce gastric secretion at doses which produce only mild side effects. Gastric emptying is delayed and action lasts for 6–8 hours. Use has declined due to availability of H2 blockers and proton pump inhibitors

Tertiary amines
Dicyclomine 20 mg oral/i.m., children 5–10 mg; has direct smooth muscle relaxant action in addition to weak anticholinergic. It exerts antispasmodic action at doses which produce few

atropinic side effects. However, infants have exhibited atropinic toxicity symptoms and it is not recommended below 6 months of age. It also has antiemetic property: has been used in morning sickness and motion sickness. Dysmenorrhoea and irritable bowel are other indications.

Vasicoselective drugs

1. *Oxybutynin* This newer anti-muscarinic has high affinity for receptors in urinary bladder and salivary glands along with additional smooth muscle relaxant and local anaesthetic properties. It is relatively selective for M1/M3 subtypes with less action on the M2 subtype. Because of vasicoselective action, it is used for detrusor instability resulting in urinary frequency and urge incontinence. Beneficial effects have been demonstrated in post-prostatectomy vasical spasm, neurogenic bladder, spina bifida and nocturnal enuresis

Mydriatics

Atropine is a potent mydriatic but its slow and long-lasting action is undesirable for refraction testing. Though the pupil dilates in 30–40 min, cycloplegia takes 1–3 hours, and the subject is visually handicapped for about a week. The substitutes attempt to overcome these difficulties.

Homatropine It is 10 times less potent than atropine. Instilled in the eye, it acts in 45–60 min, mydriasis lasts 1–3 days while accommodation recovers in 1–2 days. It often produces unsatisfactory cycloplegia in children who have high ciliary muscle tone.

USES

I. As antisecretory:

Preanaesthetic medication When irritant general anaesthetics (ether) were used, prior administration of anticholinergics (atropine, hyoscine, glycopyrrolate) was imperative to check increased salivary and tracheobronchial secretions.
Peptic ulcer Atropinic drugs decrease gastric secretion and afford symptomatic relief in peptic ulcer.
Pulmonary embolism These drugs benefit by reducing pulmonary secretions evoked reflexly by embolism.

II. As antispasmodic

1. Intestinal and renal colic, abdominal cramps: symptomatic relief is afforded if there is no mechanical obstruction.
2. Nervous, functional and drug induced diarrhoea may be controlled to some extent, but anticholinergics are not useful in infective diarrhoea.
3. Spastic constipation, irritable bowel syndrome: modest symptomatic relief may be afforded.
4. To relieve urinary frequency and urgency, enuresis in children. Oxybutynin, tolterodine and flavoxate have demonstrated good efficacy.

III. Bronchial asthma, asthmatic bronchitis, COPD

Reflex vagal activity is an important factor in causing bronchoconstriction and increased secretion in chronic bronchitis and COPD, but to a lesser extent in bronchial asthma. Orally administered atropinic drugs are bronchodilators. But they dry up the secretions of respiratory tract so is not clinically given orally. Given by aerosol, it neither decreases respiratory secretions nor impairs mucociliary clearance, and there are few systemic side effects. Thus, it has a place in the management of COPD. Tiotropium bromide is an equally effective and longer acting alternative to ipratropium bromide.

IV. As mydriatic and cycloplegic

For testing error of refraction, both mydriasis and cycloplegia are needed. Tropicamide having briefer action has now largely replaced homatropine for this purpose.
Because of its long lasting mydriatic-cycloplegic and local anodyne (pain relieving) action on cornea, atropine is very valuable in the treatment of iritis, iridocyclitis, choroiditis, keratitis and corneal ulcer.

V. As cardiac vagolytic

Atropine is useful in counteracting sinus bradycardia and partial heart block in selected patients where increased vagal tone is responsible, e.g. in some cases of myocardial infarction and in digitalis toxicity. However, cardiac arrhythmias or ischaemia may be precipitated in some cases.

VI. For central action

Parkinsonism Central anticholinergics are less effective than levodopa; They are used in mild cases, in drug induced extrapyramidal syndromes and as adjuvant to levodopa.
Motion sickness Hyoscine is the most effective drug for motion sickness. It is particularly valuable in highly susceptible individuals and for vigorous motions.

VII. Poisoning
Atropine is the specific antidote for anti ChE and early mushroom poisoning. Atropine or glycopyrrolate is also given to block muscarinic actions of neostigmine used for myasthenia gravis, decurarization or cobra envenomation.

Adrenergic System and Drugs

Adrenergic (more precisely transmission is restricted to the sympathetic division of the ANS. There are three closely related endogenous catecholamines (CAs).

1. Adrenaline
2. Noradrenaline
3. Dopamine

Synthesis of CAs

Catecholamines are synthesized from the amino acid phenylalanine. Tyrosine hydroxylase is a specific and the rate limiting enzyme. Its inhibition by □-methyl-p-tyrosine results in depletion of CAs. All other enzymes of CA synthesis are rather nonspecific and can act on closely related substrates, e.g. dopa decarboxylase can form 5-HT from 5-hydroxytryptophan and □□methyl DA from □□methyl dopa. Synthesis of NA occurs in all adrenergic neurones, while that of Adr occurs only in the adrenal medullary cells. It requires high concentration of glucocorticoids reaching through the intra-adrenal portal circulation for induction of the methylating enzyme.
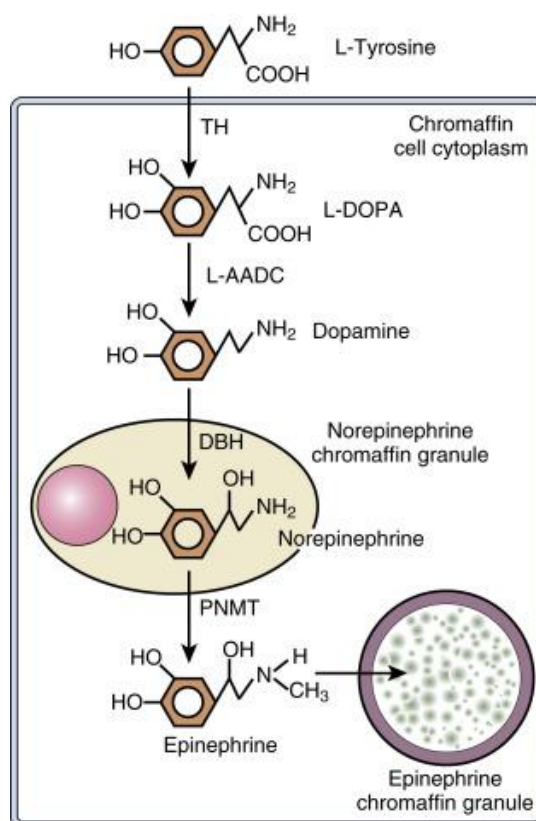
Storage of CAs NA is stored in synaptic vesicles or 'granules' within the adrenergic nerve terminal. The vesicular membrane actively takes up DA from the cytoplasm and the final step of synthesis of NA takes place inside the vesicle which contains dopamine β- hydroxylase. NA is then stored as a complex with ATP which is adsorbed on a protein *chromogranin*. In

the adrenal medulla the NA thus formed within the chromaffin granules diffuses out into the cytoplasm, is methylated and Adr so formed is again taken up by a separate set of granules. The cytoplasmic pool of CAs is kept low by the enzyme monoamine oxidase (MAO) present on the outer surface of mitochondria.

Release of CAs

The nerve impulse coupled release of CA takes place by *exocytosis* and all the vesicular contents (NA or Adr, ATP, dopamine β□hydroxylase, chromogranin) are poured out. In case of vesicles which in addition contain peptides like enkephalin or neuropeptide Y (NPY), these co-transmitters are simultaneously released. The release is modulated by presynaptic receptors, of which □2 inhibitory control is dominant.

Uptake of CAs

There is a very efficient mechanism by which NA released from the nerve terminal is recaptured. This occurs in 2 steps—

Axonal uptake An active amine pump (NET) is present at the neuronal membrane which transports NA by a Na+ coupled mechanism. It takes up NA at a higher rate than Adr and had been labelled *uptake-1*. The indirectly acting sympathomimetic amines like tyramine, but not isoprenaline, also utilize this pump for entering the neurone. This uptake is the most important mechanism for terminating the post-junctional action of NA. From 75% to 90% of released NA is retaken back into the neurone. This pump is inhibited by cocaine, desipramine and few other drugs.

Vesicular uptake The membrane of intracellular vesicles has another amine pump the 'vesicular monoamine transporter' (VMAT-2), which transports CA from the cytoplasm to the interior of the storage vesicle. The VMAT-2 transports monoamines by exchanging with H+ ions. The vesicular NA is constantly leaking out into the axoplasm and is recaptured by this mechanism. This carrier also takes up DA formed in the axoplasm for further synthesis to NA. Thus, it is very important in maintaining the NA content of the neurone. This uptake is inhibited by reserpine, resulting in depletion of CAs.

Extraneuronal uptake of CAs (uptake-2) is carried out by extraneuronal amine transporter (ENT or OCT3) and other organic cation transporters OCT1 and OCT2 into cells of other tissues. In contrast to NET this uptake transports Adr at a higher rate than NA, is not Na+ dependent and is not inhibited by cocaine, but inhibited by corticosterone. It may capture circulating Adr, but is quantitatively minor and not of physiological or pharmacological importance.

Metabolism of CAs

The pathways of metabolism of CAs. Part of the NA leaking out from vesicles into cytoplasm as well as that taken up by axonal transport is first attacked by MAO, while that which diffuses into circulation is first acted upon by catecholo- methyl transferase (COMT) in liver and other tissues. In both cases, the alternative enzyme can subsequently act to produce vanillylmandelic acid (VMA).
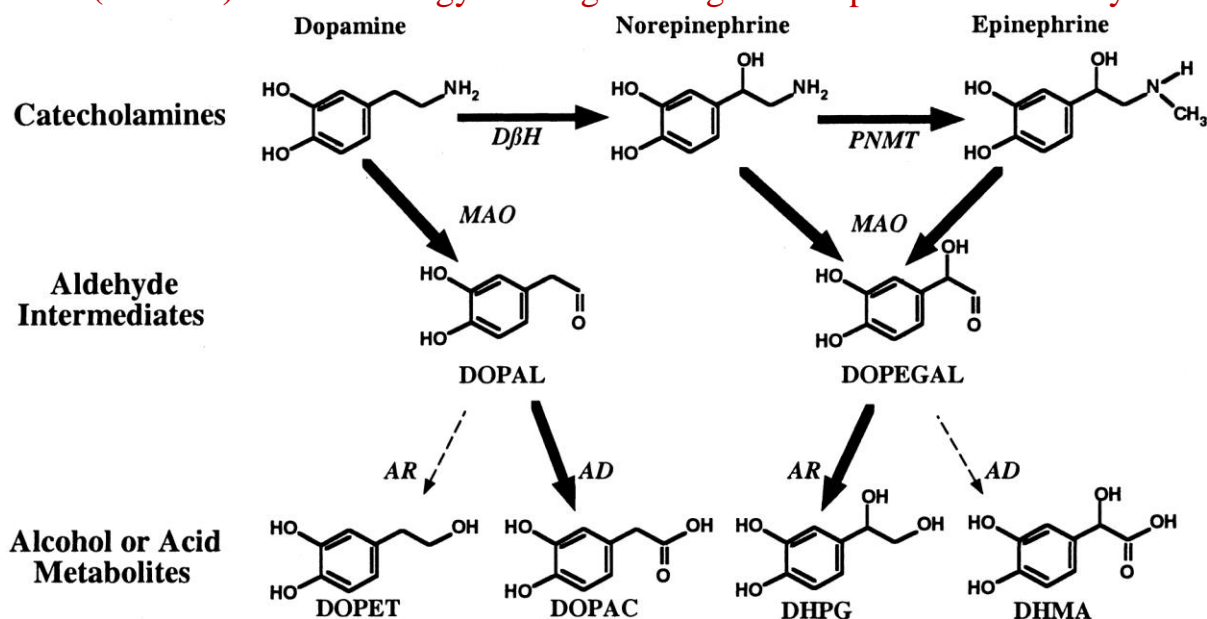
Adrenergic receptors

Adrenergic receptors are membrane bound G-protein coupled receptors which function primarily by increasing or decreasing the intracellular production of second messengers cAMP or IP3/DAG. In some cases the activated G-protein itself operates K+ or Ca2+ channels, or increases prostaglandin production.

Adrenergic receptors are classified into two types: α and β. On the basis of relative organ specificity of selective agonists and antagonists the βreceptors were further subdivided intoβ1 and β2 subtypes. Later, β3 (atypical β) receptors were described which are more sensitive to NA than to Adr, and have very low affinity for the standard β blockers. These are located on adipocytes, mediate lipolysis and induce thermogenesis. Selective β3 agonists have the potential to be used as antiobesity drugs.

ADRENERGIC DRUGS

These are drugs with actions similar to that of Adr or of sympathetic stimulation.

Direct sympathomimetics

They act directly as agonists on α and/or β adrenoceptors—Adr, NA, isoprenaline (Iso), phenylephrine, methoxamine, xylometazoline, salbutamol and many others.

Indirect sympathomimetics

They act on adrenergic neurone to release NA, which then acts on the adrenoceptors—tyramine, amphetamine.

Mixed action sympathomimetics

They act directly as well as indirectly—ephedrine, dopamine, mephentermine.

ACTIONS

Heart
1. Adr increases heart rate by increasing the slope of slow diastolic depolarization of cells in the SA node.
2. Force of cardiac contraction is increased. Cardiac output and oxygen consumption of the heart are markedly enhanced.
3. Conduction velocity through A-V node, bundle of His, atrial and ventricular fibres is increased; refractory period (RP) of all types of cardiac cells is reduced. All cardiac actions are predominantly β1 receptor mediated.

Blood vessels
Both vasoconstriction (α) and vasodilatation (β2) can occur depending on the drug, its dose and vascular bed. Constriction predominates in cutaneous, mucous membrane and renal beds. Vasoconstriction occurs through both α1 and α2 receptors. Dilatation predominates in skeletal muscles, liver and coronaries.

BP The effect depends on the amine, its dose and rate of administration.
• NA causes rise in systolic, diastolic and mean BP; it does not cause vasodilatation (no β2 action), peripheral resistance increases consistently due to ☐☐action.
• Isoprenaline causes rise in systolic but marked fall in diastolic BP (β1—cardiac stimulation, β2— vasodilatation). The mean BP generally falls.
Adr given by slow i.v. infusion or s.c. injection causes rise in systolic but fall in diastolic BP; peripheral resistance decreases because vascular β2 receptors are more sensitive than αreceptors. Mean BP generally rises. Pulse pressure is increased.
Rapid i.v. injection of Adr (in animals) produces a marked increase in both systolic as well as diastolic BP (at high concentration α☐response predominates and vasoconstriction occurs even in skeletal muscles). The BP returns to normal within a few minutes and a secondary fall in mean BP follows. The mechanism is—rapid uptake and dissipation of Adr →☐concentration around the receptor is reduced →low concentrations are not able to act on α☐receptors but continue to act on β2 receptors.
        When an α☐blocker has been given, only fall in BP is seen—*vasomotor reversal of Dale.*

Respiration Adr and isoprenaline, but not NA are potent bronchodilators (β2). This action is more marked when the bronchi are constricted.

Eye Mydriasis occurs due to contraction of radial muscles of iris (α1), but this is minimal after topical application, because Adr penetrates cornea poorly.

GIT In isolated preparations of gut, relaxation occurs through activation of both α☐and βreceptors. In intact animals and man peristalsis is reduced and sphincters are constricted, but the effects are brief and of no clinical import.

Uterus Adr can both contract and relax uterine muscle, respectively through α and β☐receptors. The overall effect varies with species, hormonal and gestational status. Human uterus is relaxed by Adr at term of pregnancy, but at other times, its concentrations are enhanced.

Skeletal muscle Neuromuscular transmission is facilitated. In contrast to action on autonomic nerve endings, α☐receptor activation on motor nerve endings augments ACh release, probably because it is of the α1 subtype. The direct effect on muscle fibres is exerted through β2 receptors and differs according to the type of fibre.

CNS Adr, in clinically used doses, does not produce any marked CNS effects because of poor penetration in brain, but restlessness, apprehension and tremor may occur. Activation of α2 receptors in the brainstem (by selective α2 agonists) results in decreased sympathetic outflow →☐fall in BP and bradycardia.

Administration and preparations
CAs are absorbed from the intestine but are rapidly degraded by MAO and COMT present in the intestinal wall and liver. They are thus orally inactive.

1. *Adrenaline (Epinephrine)* For systemic action, 0.2–0.5 mg s.c., i.m., action lasts ½ to 2 hrs.
2. *Noradrenaline (Norepinephrine, levarterenol)* 2–4 μg/min i.v. infusion; local tissue necrosis occurs if the solution extravasates; do not mix with NaHCO3 in the same bottle (rapid oxidation occurs); action starts declining within 5 min of discontinuing infusion. It is rarely used now as a pressor agent.
3. *Isoprenaline (Isoproterenol)* 20 mg sublingual, 1–2 mg i.m., 5–10 μg/min i.v. infusion; action lasts 1–3 hrs. It is occasionally used to maintain idioventricular rate till pacemaker is implanted. For bronchial asthma, it has been superseded by selective β2 agonists.

Adverse effects and contraindications
• Transient restlessness, headache, palpitation, anxiety, tremor and pallor may occur after s.c./ i.m. injection of Adr.
• Marked rise in BP leading to cerebral haemorrhage, ventricular tachycardia/fibrillation, angina, myocardial infarction are the hazards of large doses or inadvertant i.v. injection of Adr.
• Adr is contraindicated in hypertensive, hyperthyroid and angina patients.
• Adr should not be given during anaesthesia with halothane (risk of arrhythmias) and to patients receiving β☐blockers (marked rise in BP can occur due to unopposed α☐action).

THERAPEUTIC CLASSIFICATION OF ADRENERGIC DRUGS

I. *Pressor agents*
Noradrenaline, Phenylephrine, Ephedrine, Methoxamine, Dopamine, Mephentermine

II. *Cardiac stimulants*
Adrenaline, Dobutamine, Isoprenaline

III. *Bronchodilators*
Isoprenaline, Salmeterol, Salbutamol, Formoterol(Albuterol), Bambuterol, Terbutaline

IV. *Nasal decongestants*

Phenylephrine, Naphazoline, Xylometazoline, Pseudoephedrine, Oxymetazoline, Phenyl propanolamine

V. *CNS stimulants*
Amphetamine, Methamphetamine, Dexamphetamine

VI. *Anorectics*
Fenfluramine, Sibutramine, Dexfenfluramine

VII. *Uterine relaxant and vasodilators*
Ritodrine, Salbutamol, Isoxsuprine, Terbutaline

Anti-Adrenergic Drugs

These are drugs which antagonize the receptor action of adrenaline and related drugs. They are competitive antagonists at α or β or both α and β adrenergic receptors and differ in important ways from the "adrenergic neurone blocking agents", which act by interfering with the release of adrenergic transmitter on nerve stimulation.

α ADRENERGIC BLOCKING DRUGS
These drugs inhibit adrenergic responses mediated through the α☐adrenergic receptors without affecting those mediated through β☐receptors.

CLASSIFICATION

I. *Nonequilibrium type*
(i) β-*Haloalkylamines*—Phenoxybenzamine.

II. *Equilibrium type (competitive)*

A. Nonselective
(i) *Ergot alkaloids*—Ergotamine, Ergotoxine
(ii) *Hydrogenated ergot alkaloids*—Dihydroergotamine (DHE), Dihydroergotoxine
(iii) *Imidazoline*—Phentolamine
(iv) *Miscellaneous*– Chlorpromazine

B. α1 selective—Prazosin, Terazosin,
Doxazosin, Alfuzosin,
Tamsulosin

C. α2 selective—Yohimbine

GENERAL EFFECTS OF α BLOCKERS

1. Blockade of vasoconstrictor α1 (also α2) receptors reduces peripheral resistance and causes pooling of blood in capacitance vessels →venous return and cardiac output are reduced →fall in BP. Postural reflex is interfered with →marked *hypotension* occurs on standing →dizziness and syncope. Hypovolemia accentuates the hypotension. The α blockers abolish the pressor action of Adr (injected i.v. in animals), which then produces only fall in BP due to β mediated vasodilatation.
2. Reflex *tachycardia* occurs due to fall in mean arterial pressure and increased release of NA due to blockade of presynaptic α2 receptors.
3. *Nasal stuffiness* and *miosis* result from blockade of α☐receptors in nasal blood vessels and in radial muscles of iris respectively.
4. Intestinal motility is increased due to partial inhibition of relaxant sympathetic influences—loose motion may occur.
5. Hypotension produced by α blockers can reduce renal blood flow →g.f.r. is reduced and more complete reabsorption of Na+ and water occurs in the tubules →*Na+ retention* and

expansion of blood volume. This is accentuated by reflex increase in renin release mediated through β1 receptors.

6. Tone of smooth muscle in bladder trigone, sphincter and prostate is reduced by blockade of α1 receptors (mostly of the α1A subtype) →□*urine flow in patients with* benign hypertrophy of prostate *(BHP) is improved*.

7. Contractions of vas deferens and related organs which result in ejaculation are coordinated through α□receptors—α□blockers can *inhibit ejaculation*; this may manifest as *impotence*.

USES OF α BLOCKERS

Pheochromocytoma It is a tumour of adrenal medullary cells. Excess CAs are secreted which can cause intermittent or persistent hypertension. Estimation of urinary CA metabolites (VMA, normetanephrine) is diagnostic. In addition, pharmacological tests can be performed.

Hypertension: α blockers other than those selective for α1 (prazosin-like) have been a failure in the management of essential hypertension, because vasodilatation is compensated by cardiac stimulation. Moreover, postural hypotension, impotence, nasal blockage and other side effects produced by nonselective α blockers are unacceptable. However, phentolamine/phenoxybenzamine are of great value in controlling episodes of rise in BP during clonidine withdrawal and cheese reaction in patients on MAO inhibitors.

Benign hypertrophy of prostate (BHP) The urinary obstruction caused by BHP has a static component due to increased size of prostate and a dynamic component due to increased tone of bladder neck/prostate smooth muscle. Two classes of drugs are available:
• α1 adrenergic blockers (prazosin like): decrease tone of prostatic/bladder neck muscles.
• 5-α reductase inhibitor (finasteride): arrest growth/reduce size of prostate.

Congestive heart failure (CHF) The vasodilator action of prazosin can afford symptomatic relief in selected patients of CHF in the short-term, but long-term prognosis is not improved.

Papaverine/Phentolamine Induced Penile Erection (PIPE) therapy for impotence In patients unable to achieve erection, injection of papaverine (3–20 mg) with or without phentolamine (0.5–1 mg) in the corpus cavernosum has been found to produce penile tumescence to permit intercourse.

β ADRENERGIC BLOCKING DRUGS
These drugs inhibit adrenergic responses mediated through the β□receptors.

*Nonselective (*β1 *and* β2*)*

a. *Without intrinsic sympathomimetic activity*
Propranolol, Sotalol, Timolol.

b. *With intrinsic sympathomimetic activity*
Pindolol

c. *With additional* α *blocking property*
Labetalol, Carvedilol

Cardioselective (β1)
Metoprolol, Atenolol, Acebutolol, Bisoprolol,
Esmolol, Betaxolol, Celiprolol, Nebivolol

PHARMACOLOGICAL ACTIONS

1. CVS

(a) Heart Propranolol decreases heart rate, force of contraction (at relatively higher doses) and cardiac output (c.o.). Cardiac work and oxygen consumption are reduced as the product of heart rate and aortic pressure decreases. Total coronary flow is reduced (blockade of dilator β□receptors). Propranolol abbreviates refractory period of myocardial fibres and decreases automaticity. Propranolol blocks cardiac stimulant action of adrenergic drugs but not that of digoxin, methylxanthines or glucagon.

(b) Blood vessels Propranolol blocks vaso-dilatation and fall in BP evoked by isoprenaline and enhances the rise in BP caused by Adr. Propranolol has no direct effect on blood vessels and there is little acute change in BP. On prolonged administration BP gradually falls in hypertensive subjects but not in normotensives. Total peripheral resistance (t.p.r.) is increased initially (due to blockade of βmediated vasodilatation) and c.o. is reduced. With continued treatment, resistance vessels gradually adapt to chronically reduced c.o. and t.p.r. decreases—both systolic and diastolic BP fall. This is considered to be the most likely explanation of the antihypertensive action. Other mechanisms that may contribute are:
(i) Reduced NA release from sympathetic terminals due to blockade of βreceptor mediated facilitation of the release process.
(ii) Decreased renin release from kidney (β1 mediated).
(iii) Central action reducing sympathetic outflow.
However, βblockers which penetrate brain poorly are also effective anti-hypertensives.

Respiratory tract Propranolol increases bronchial resistance by blocking dilator β2 receptors. The effect is hardly discernible in normal individuals because sympathetic bronchodilator tone is minimal.

CNS No overt central effects are produced by propranolol. However, subtle behavioural changes, forgetfulness, increased dreaming and nightmares have been reported with long-term use of relatively high doses.
Propranolol suppresses anxiety in short-term stressful situations, but this is due to peripheral rather than a specific central action.

Local anaesthetic Propranolol is as potent a local anaesthetic as lidocaine, but is not clinically used for this purpose because it causes irritation at the injected site.

Skeletal muscle Propranolol inhibits adrenergically provoked tremor. This is a peripheral action exerted directly on the muscle fibres (through β2 receptors). It tends to reduce exercise capacity by attenuating β2 mediated increase in blood flow to the exercising muscles, as well as by limiting glycogenolysis and lipolysis which provide fuel to working muscles.

Eye Instillation of propranolol and some other β blockers reduces secretion of aqueous humor, i.o.t. is lowered. There is no consistent effect on pupil size or accommodation.

Uterus Relaxation of uterus in response to isoprenaline and selective β2 agonists is blocked by propranolol. However, normal uterine activity is not significantly affected.

USES

1. *Hypertension:* β blockers are relatively mild anti-hypertensives. All agents, irrespective of associated properties, are nearly equally effective. They are one of the first choice drugs because of good patient acceptability and cardio-protective potential.

2. *Angina pectoris:* All β blockers benefit angina of effort. Taken on a regular schedule they decrease frequency of attacks and increase exercise tolerance. High doses, however, may worsen angina in some patients by increasing ventricular size and reducing coronary flow. β blockers are not suitable for variant (vasospastic) angina.

3.*Cardiac arrhythmias:* β blockers (mainly propranolol) suppress extrasystoles and tachycardias, especially those mediated adrenergically (during anaesthesia, digitalis induced)—may be used i.v. for this purpose. Propranolol controls ventricular rate in atrial fibrillation and flutter, but only occasionally restores sinus rhythm. Esmolol is an alternative drug for paroxysmal supraventricular tachycardia.

4. *Congestive heart failure:* Although β blockers can acutely worsen heart failure, several studies have reported beneficial haemodynamic effects of certain β blockers including *metoprolol, bisoprolol, nebivolol, carvedilol* over long-term in selected patients with dilated cardiomyopathy.

5.*Migraine* Propranolol is the most effective drug for chronic prophylaxis of migraine.

6. *Anxiety* Propranolol exerts an apparent antianxiety effect, especially under conditions which provoke nervousness and panic, e.g. examination, unaccustomed public appearance, etc. This is probably due to blockade of peripheral manifestations of anxiety (palpitation, tremor) which have a reinforcing effect. Propranolol is largely ineffective in anxiety neurosis, but may benefit the somatic symptoms.

7.*Glaucoma* Ocular β blockers are widely used for chronic simple (wide angle) glaucoma; also used as adjuvant in angle closure glaucoma