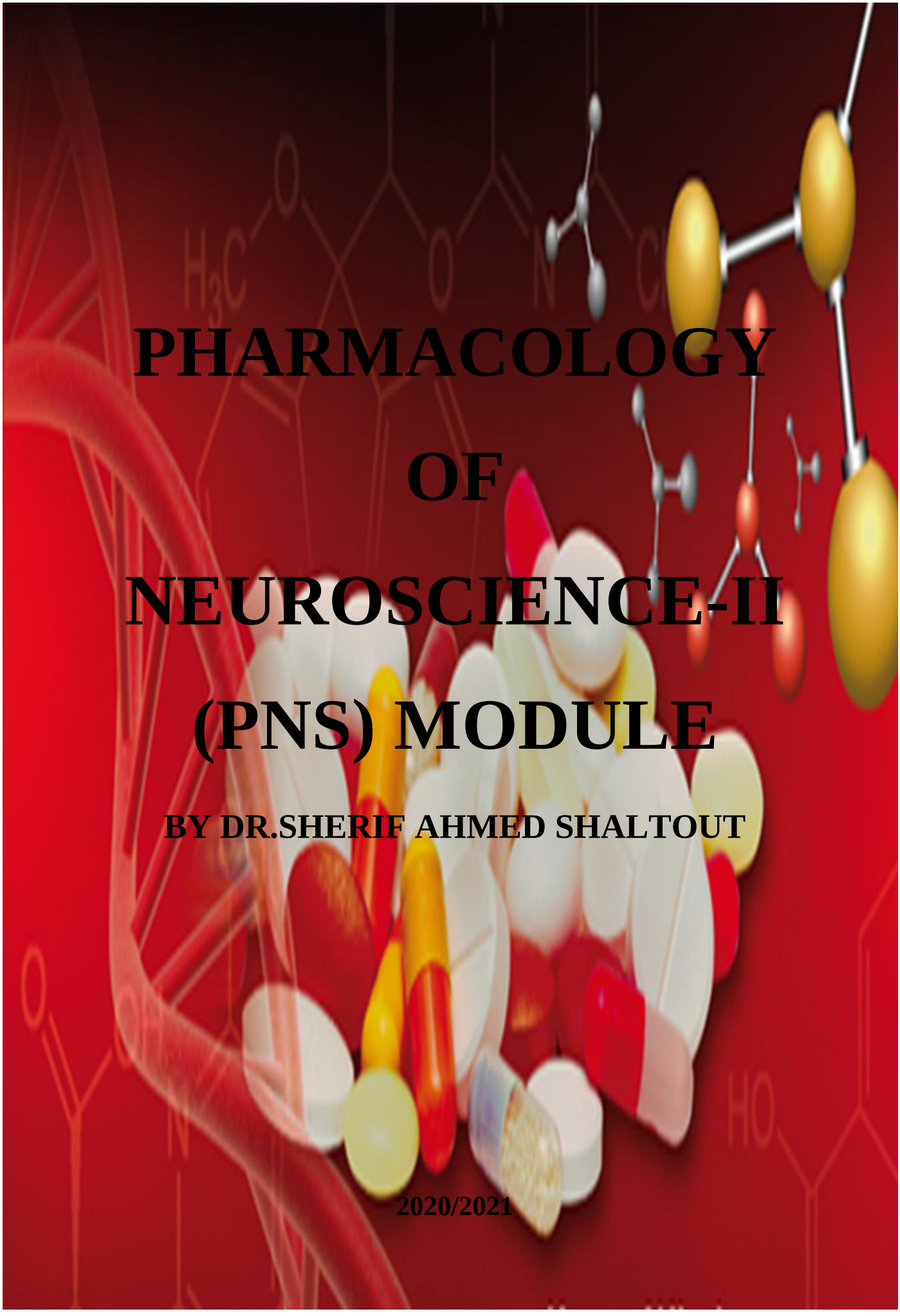


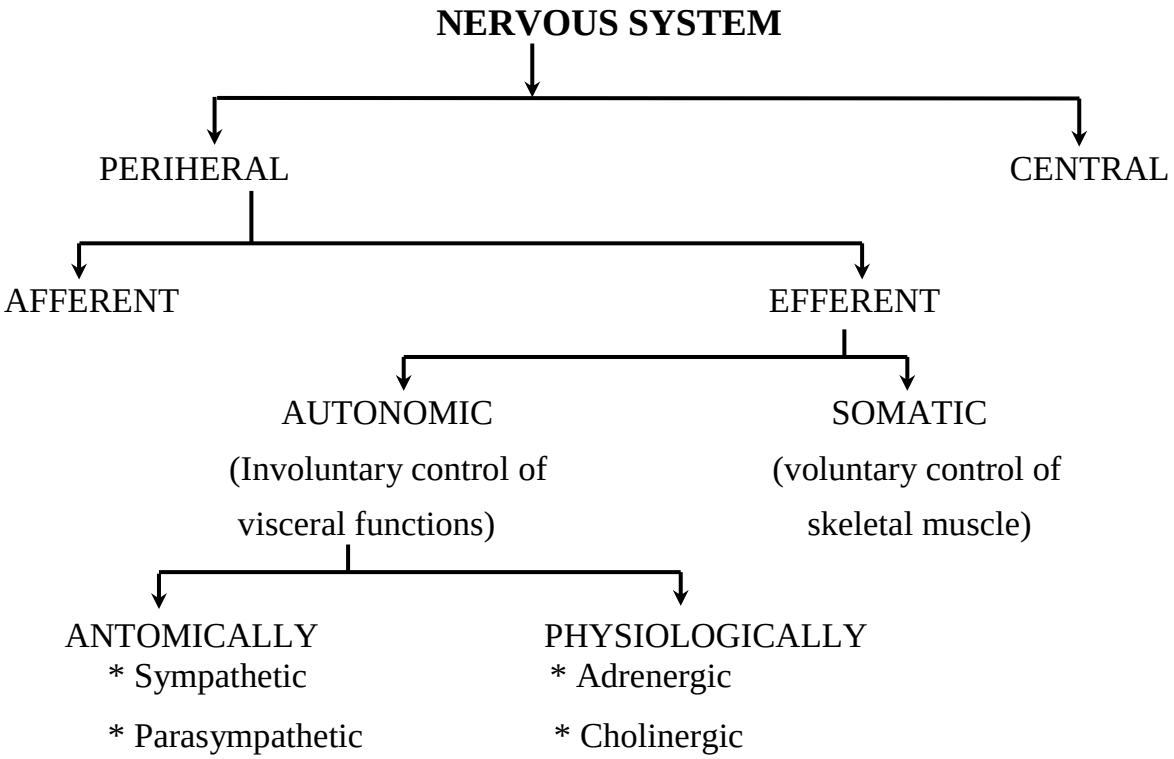
PHARMACOLOGY OF NEUROSCIENCE-II (PNS) MODULE

BY DR.SHERIF AHMED SHALTOUT

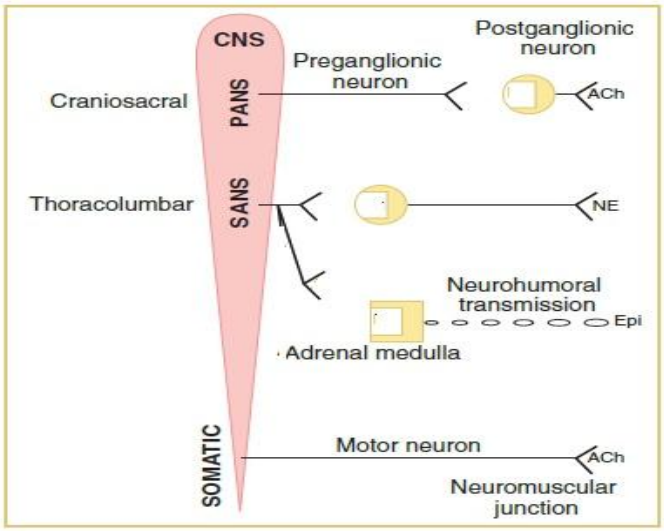
2020/2021

AUTONOMIC NERVOUS SYSTEM

PHARMACOLGY



Somatic Nervous System	Autonomic Nervous System
• Controls voluntary skeletal muscles. • Somatic nerves have no ganglia. • Somatic nerves originate from the anterior horn cells of the spinal cord.	• Controls involuntary organs. • Autonomic nerves relay in ganglia. • Most autonomic nerves originate from the lateral horn cells of the spinal cord.



The involuntary effector organs controlled by A.N.S. are:

a) Heart: Cardiac properties include:

1- Automaticity (the ability of pacemaker cells to initiate an impulse) and rhythmicity.

2- Conductivity (the impulse is conducted in atria, AV node & bundle, and ventricles).

3- Excitability (the ability of cardiac cells to respond to external stimuli).

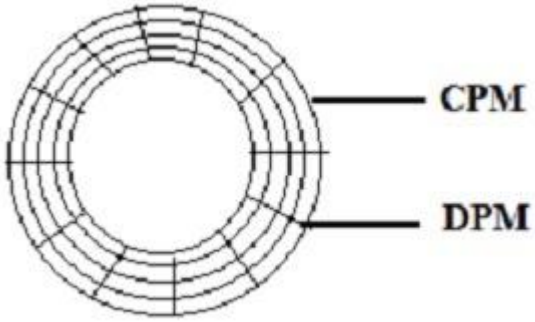
4- Contractility.

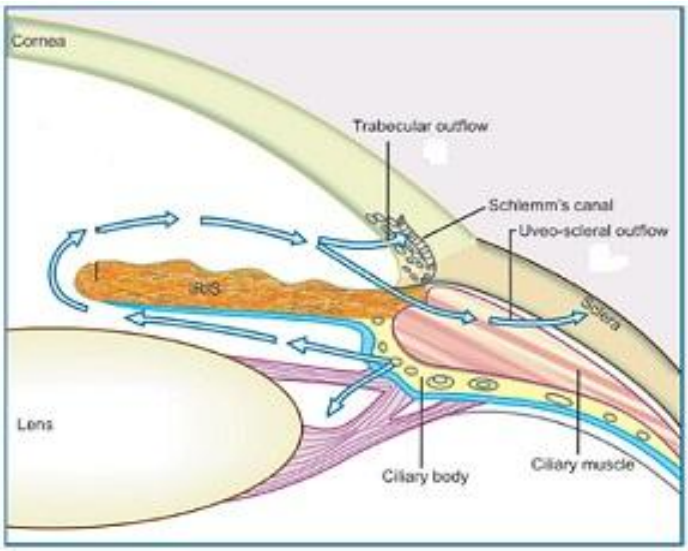
* The cardiac properties also determine the cardiac output (COP = SV X HR) and myocardial oxygen requirements.

b) Smooth muscle fibers (SMF):

1- Blood vessels: especially the arterioles, which determine the total peripheral resistance (TPR) and arterial blood pressure (ABP: SBP depends on COP & TPR while DBP depends on TPR).

2- Eye: dilator pupillae muscle (DPM), constrictor pupillae muscle (CPM), and ciliary muscle & ciliary body.





3- Bronchi

4- GIT & Urinary bladder: both in the wall and sphincters.

5- Sex organs: The uterus - the male sex organs.

c) Exocrine glands:

Including salivary, lacrimal, bronchial, gastric (secreting HCl), intestinal, and sweat glands.

❖ **Differences between sympathetic and parasympathetic divisions of ANS**

	Sympathetic	**Parasympathetic**
1- Origin	Thoraco-lumbar (T1 to L2 or L3)	Cranio-sacral (III, VII, IX, X and S2–S4)
2- Ganglia	Away from the organs (paravertebral)	On or close to the organ (terminal)
3- Preganglionic fiber	Short	Long
4- Postganglionic fiber	Long	Short
5- Neurotransmitter	Major: noradrenaline (NA) and adrenaline	Major: acetylcholine (ACh)
6- Stability of transmitter	NA: stable, diffuses for wider actions	ACh: rapidly destroyed locally
7- Function:		
• **CVS:**	* ↑ all cardiac properties, COP and myocardial O_2 consumption	* ↓ all cardiac properties (**except** atrial conduction↑), COP and myocardial O_2 consumption
• **SMF:**		
***Bl.vesseles**	* V.C. of blood vessels **except** skeletal & coronary → VD	No effect (most blood vessels are non-innervated by parasympathetic But contain muscarinic receptors → VD by release of NO)
	* ↑ blood pressure	* ↓ blood pressure
*** eye**	Mydriasis	Miosis, accommodation for near vision, ↓ IOP
***Bronchi**	Dilatation	Constriction
***GIT & urinary**	Relax wall and contract sphincters	Contract wall and relax sphincters
*** Sex organs**	Ejaculation in male	Erection in male
• **Exocrine gl.:**		
*** salivary**	↑ secretion (scanty, viscid)	↑secretion (profuse, watery)
*** sweat**	↑ sweat: - thermotegulatory glands present all over the body but cholinergic transmission	No effect

Important Notes:

1) Most of the involuntary organs receive "dual (double) innervation".

2) The predominant tone in these organs is usually parasympathetic; except in stress conditions (fear, fight, exercise) when the sympathetic tone becomes predominant.

3) Few organs have single innervation;

Sympathetic only: Ventricles of the heart, most blood vessels, dilator pupillae muscle, sweat glands, adrenal medulla (which is considered as a "modified sympathetic ganglion), and erector pili muscles,

Parasympathetic only: Constrictor pupillae muscle and ciliary muscle.

4) In most involuntary organs receiving dual innervation, sympathetic and parasympathetic actions are antagonistic except the action on:

a. Atrial conduction (both systems increase atrial conduction)
b. Salivary glands (both increase salivation)
c. Male sex organs is complementary to each other.

5) Both systems are controlled by higher centers in the hypothalamus and cerebral cortex.

6) The activity of A.N.S. is based on the presence of specific "neurotransmitters" acting on specific "receptors".

NEUROHUMORAL TRANSMISSION

- The nerves transmit their message across synapses and postsynaptic tissues by the release of humoral (chemical) messengers
- **Steps in neurohumoral transmission:**

  I. Impulse conduction:

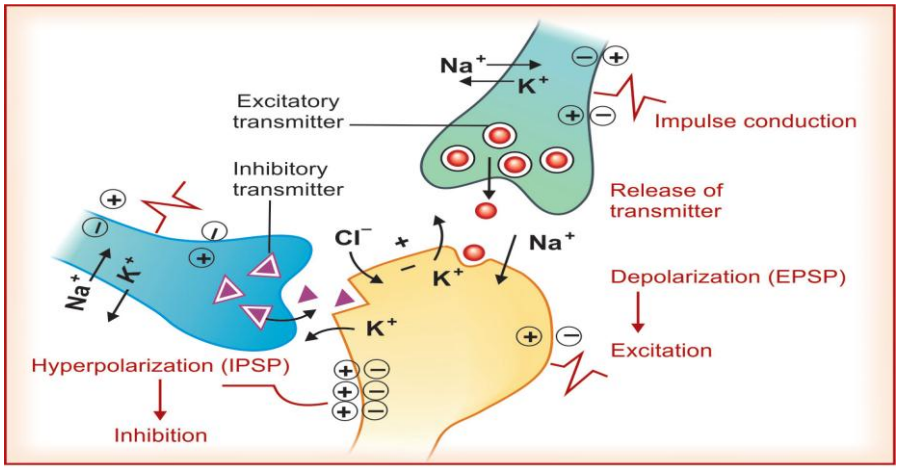
  - Stimulation or arrival of an electrical impulse → ↑ Na^+ influx → depolarization, then ↑ K^+outflux → repolarization
  - The action potential (AP) → activate ionic channels at the next excitable part of the membrane → propagation of the AP

II. Transmitter release

- The transmitter (excitatory or inhibitory) is stored in presynaptic nerve endings within 'synaptic vesicles'
- Nerve impulse → Ca^{2+}entry → fusion of vesicles with axonal membranes → exocytosis of all contents of the vesicle (transmitter, enzymes and other proteins) in the synaptic cleft
- The release process can be modulated by the transmitter itself and by other agents through activation of specific presynaptic receptors

III. Transmitter action on postsynaptic membrane

- The released transmitter combines with specific receptors on the postsynaptic membrane → an excitatory postsynaptic potential (**EPSP**; by ↑ Na^+ or Ca^{2+} influx→ depolarization) or an inhibitory postsynaptic potential (**IPSP**; by ↑ Cl^- influx or K^+ outflux→ hyperpola).



IV. Postsynaptic activity

- EPSP → a propagated postsynaptic AP → nerve impulse (in neuron), contraction (in muscle) or secretion (in gland).
- IPSP stabilizes the postsynaptic membrane and resists depolarizing stimuli

V. Termination of transmitter action:

1- Local degradation (e.g. ACh)

2- Active reuptake into the presynaptic neuron by specific carrier proteins (transporters)

3- Diffusion away (e.g.NA)

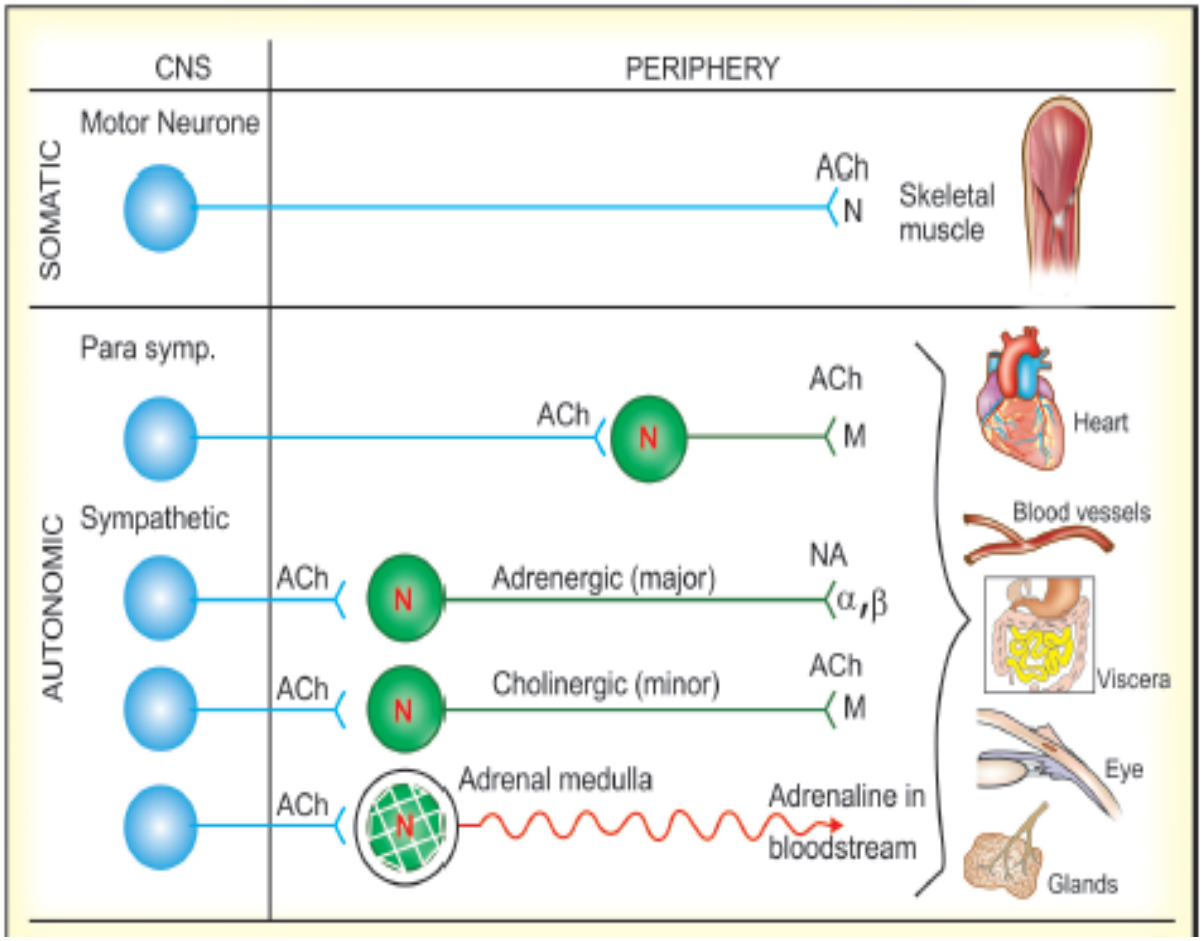
COTRANSMISSION:

- The classical‘ one neuron—one transmitter’ model is an over simplification.
- Most peripheral and central neurons on stimulation have been shown to release more than one active substance
- In the ANS, besides the primary transmitters ACh and NA, neurons have been found to release:
  - purines (ATP, adenosine),
  - peptides (vasoactive intestinal peptide or VIP, neuropeptide-Y or NPY, substance P, enkephalins, somatostatin, etc.),
  - nitric oxide (NO)
  - prostaglandins
- Function of contransmitters:
  1- Neuromodulator: Regulate the presynaptic release of the primary transmitter and/or postsynaptic sensitivity to it
  2- Act as an alternative transmitter having its own effects on postsynaptic structures

CHOLINERGIC PHARMACOLOGY

CHOLINERGIC TRANSMISSION

- Acetylcholine (ACh) is a major neurohumoral transmitter at autonomic, somatic as well as centralsites:
  1- All preganglionic fibers (parasymp. &symp.)
  2- All ganglia (parasymp. &symp.)
  3- All postganglionic parasympathetic fibers
  4- Postganglionic **sympathetic** fibers to **sweat** glands
  5- Adrenal medulla (modified sympathetic ganglion)
  6- Skeletal muscles (NMJ)
  7- CNS (cortex, basal ganglia, spinal cord and other sites)



Synthesis of Acetylcholine (ACh)

- Choline is transported by a membrane carrier **(Na^+: choline cotransporter)** from the extracellular fluid into the cholinergic neuron
- Then, it is acetylated in the cytoplasm:

Acetyl CoEn-A+ choline $\xrightarrow{\textbf{choline acetyl transferase (CAT)}}$ ACh

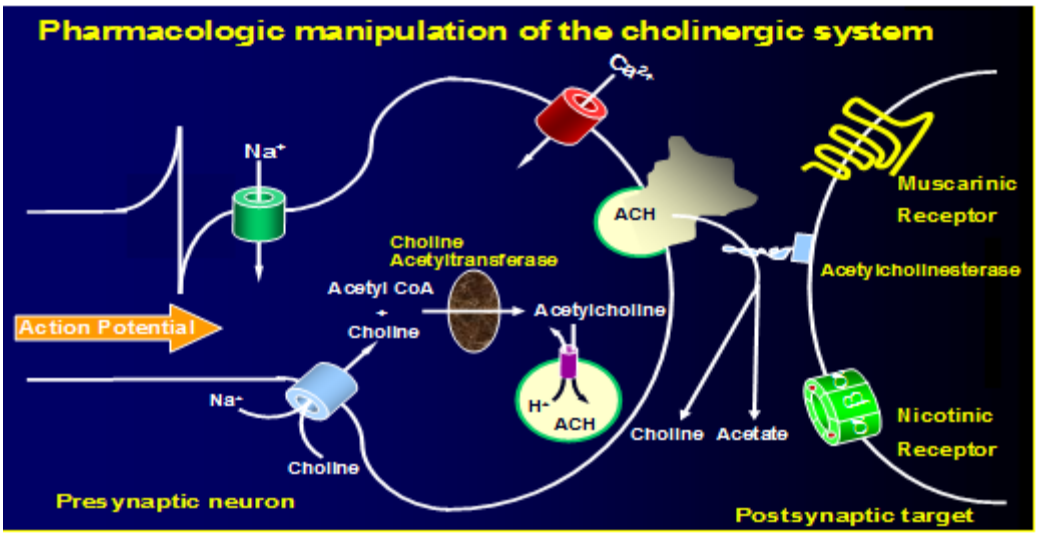
- ***Hemicholinium*** blocks choline uptake (the rate limiting step in ACh synthesis) and depletes ACh.

Storage of ACh

- ACh is stored in small membrane-bound vesicles, which are concentrated in the terminals of cholinergic neurons.
- ***Vesamicol*** blocks active transport of ACh into synaptic vesicles.

Release of ACh

- Arrival of an action potential triggers Ca^{2+}influx, which stimulates release of ACh by exocytosis.
- Control of ACh release by **presynaptic receptors:**
  - M_2→inhibitory (**dominant**).
  - α_2→ inhibitory.
  - N_n→ facilitatory.
- ***botulinum toxin*** inhibits ACh. release
  - It is exotoxin produced by Clostridium botulinum → 'botulism'(a type of food poisoning). →long-lasting loss of cholinergic transmission
  - Local injection of botulinum toxin-A (BOTOX) used in:
    1. ***Spastic conditions*** due to over activity of cholinergic nerves, e.g. spastic cerebral palsy, spasmodic torticollis
    2. ***Beauty treatment***: removal of age-related facial wrinkles.
  - its incorrect injection or overdose → ptosis, diplopia, facials welling, dry mouth, dysphagia, dysarthria, muscular weakness and even respiratory paralysis



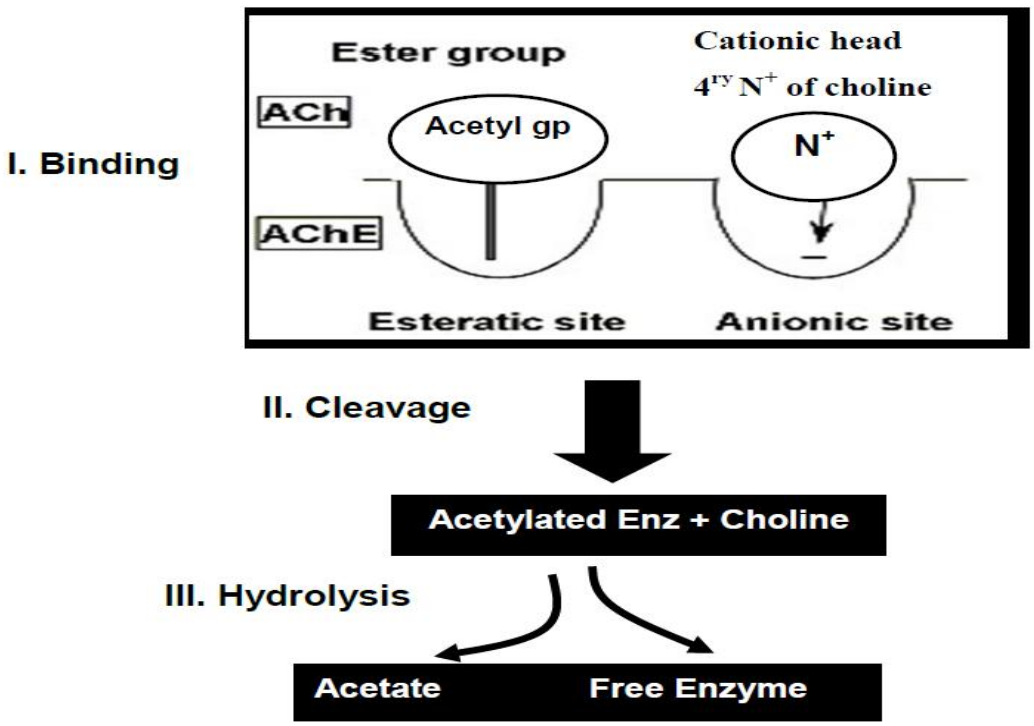
Termination of Acetylcholine

- Action of ACh is terminated by rapid hydrolysis by **choline esterase**.
- Hydrolysis by choline esterase enzyme through **3 steps**:

1. **Binding:** The acetyl (ester) group of ACh binds to the esteratic site of the enzyme by a covalent bond

   - The N^+ (cationic) head binds to the anionic site by a weaker ionic bond.

2. **Cleavage**: choline is cleaved leaving the acetylated enzyme.
3. **Hydrolysis:** hydration of acetylated enzyme releases acetate & the free enzyme.



- **Types of cholinesterase enzymes**

True Cholinesterase (acetylcholinesterase = AChE)	**Pseudo Cholinesterase (butyrylcholinesterase = ButyrylChE)**
- Present at terminals of cholinergic fibers & RBCs& gray matter. - Hydrolysis: (specific to ACh.) ACh: very fast Methacholine: slower than ACh - Inhibition: more sensitive to physostigmine	- Present in plasma, liver, Intestine, white matter. - Hydrolysis:(nonspecific to ACh.) - ACh: slow - Methacholine: Not + hydrolyzes other esters as succinylcholine. -Inhibition: more sensitive to organophosphorus compounds

CHOLINERGIC RECEPTORS &ACh ACTIONS

- **ACh** mediates its effects by activating **muscarinic & nicotinic** cholinergic receptors present centrally & peripherally:

I. Muscarinic receptors: $M_{1,2,3,}{}_{4,5}$

M_1 receptors (excitatory)	**M_2 receptors (inhibitory)**	**M_3 receptors (excitatory)**
coupled to G_q → ⊕ PLC → ↑ DAG & IP_3 →↑Ca^{++}	* coupled to G_i → ⊖ adenylate cyclase * opening of K^+ channels	coupled to G_q → ⊕ PLC → ↑ DAG& IP_3 →↑Ca^{++}
• CNS: a. Arousal, learning &short-term memory b. controls movement in basal ganglia, in balance withDA. • **Gastric:** **a. ↑ histamine release → ↑ HCL** b. **Relax lower esophageal sphincter (LES)**	• **Heart:** **a. ⊖ SAN & AVN → ↓ heart rate** b. Atria →↓contractility -(↑ atrial conductivity). • CNS→inhibitory • Presynaptic neurons → inhibit ACh & NA release.	• **SMF:** **- Vascular endothelium →NO release → VD → ↓ BP.** **- Bronchi → spasm** **- Eye → - (⊕ constrictor pupillae)→miosis** **- (⊕ ciliary muscle) → accommodation, ↓ IOP** **- GIT,Ur.→ ⊕ wall & relax sphincters & Contractlower esophageal sphincter (LES) (with M_2)** • **Exocrine glands → ↑ All secretions (except milk, bile)**

II. Nicotinic receptors (excitatory): ligand-gated Na^+ ion channels:

- **Neuronal (N_N):** in all autonomic ganglia, presynaptic & in adrenal medulla → ↑ catecholamines release.
- **Muscle (N_M):** at NMJ →skeletal muscle depolarization → contraction.
- **CNS :** ADH release.

Actions of ACh:

I. Muscarinic actions:

1. **CVS:**
   - **a. Heart:** - ↓ all HR→↓ COP & ↓AVN conduction
     - ↑ atrial conductivity (due to ↓ APD, ↓ RP)
   - **b. Blood vessels**: VD (NO release)
   - **c. Blood pressure:** hypotension
2. **Eye:**
   - a. Miosis → wide angle of filtration
   - b. Spasm of ciliary muscle → - Accommodation for NEAR vision
     - Open canal of Schlemm
   - c. ↓ IOP
   - d. ↑ lacrimation
3. **Respiration:**- Bronchospasm - ↑ bronchial secretions
4. **GIT & Ur.Bladder:** - Contract the wall - Relax the sphincters
5. **Exocrine glands:**↑ all secretions (watery secretions) [except milk, bile]

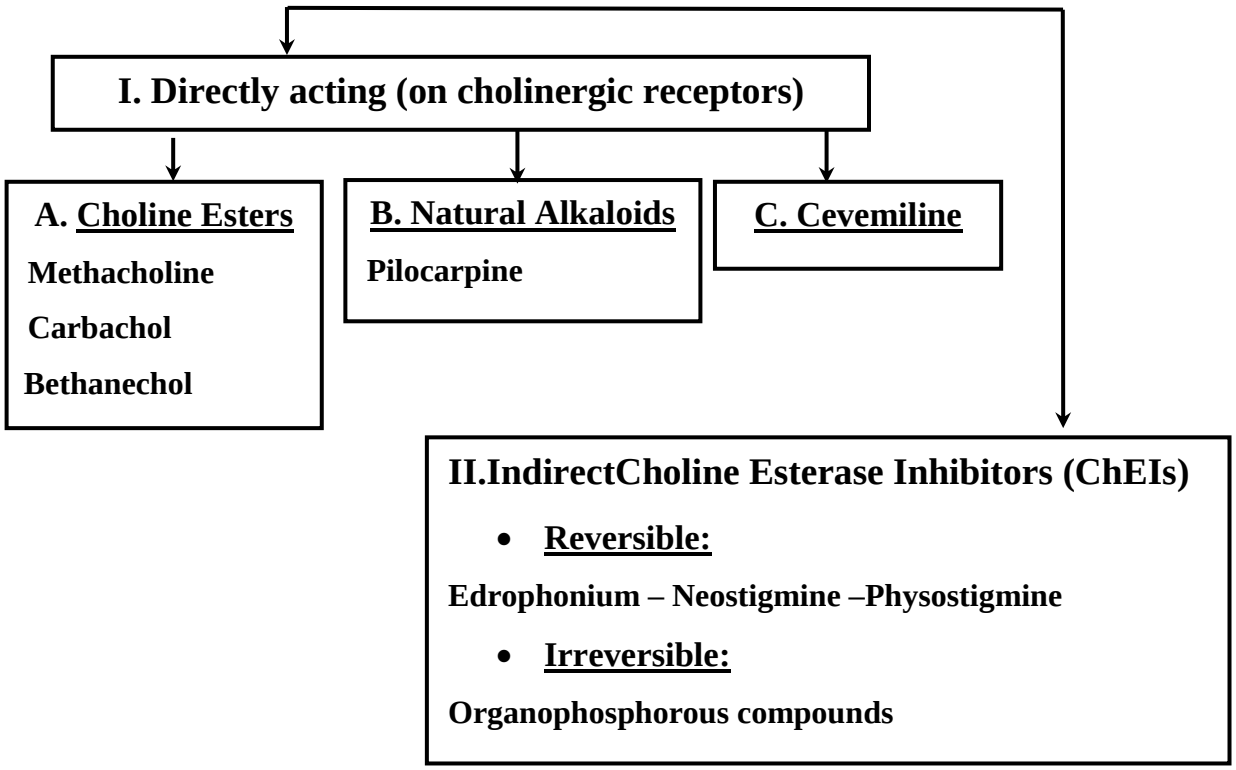
II. Nicotinic actions (ACh large dose):

1. **Hypertension** (Nn in autonomic ganglia & adrenal medulla)
2. **Skeletal muscle twitches** (Nm in neuromuscular junction)
   - The nicotinic actions of exogenous acetylcholine are "masked" by its muscarinic actions but can be demonstrated by an experiment performed on the blood pressure of an anaesthetized cat or dog → **"Atropine Reversal"** : atropine can reverse effect of all parasympathomimetics (with muscarinic & nicotinic actions) on A.B.P.

Uses of ACh: Not used clinically

** If Ach is given systemically: - Not absorbed orally → must be given by I.V.
-Rapidly hydrolysed→ very short duration
- Non specific → stimulates all **(M**) receptors

CLASSIFICATION OF CHOLINOMIMETICS



A.Choline Esters

- All are quaternary ammonium compounds
- More stable than Ach

	Methacholine (Methyl ACh. → weak nicotinic effect)	**Carbachol** (Carbamoyl choline → more lipid soluble)	**Bethanechol** (Methyl carbachol)
Oral absorption	Partial	Complete	Complete
Administration	Oral & SC	Oral & SC Eye drops	Oral & SC Eye drops
Metabolism by Ch.E enzyme	True only	Not hydrolyzed by ChE	
Muscarinic effect	Marked muscarinic effect		
Nicotinic effect	Weak	Marked	NO
Specificity	CVS	Eye, GIT, Ur.Bladder	

Uses of Choline esters:

Methacholine: it **was used** in:

1. **P**aroxysmal atrial tachycardia (PAT)
2. **P**eripheral vascular disease (PVD)
3. Diagnosis of **P**aroxysmal Pheochromocytoma,
   - used nowadays in diagnosis of bronchial asthma (provocative test)

Carbachol & Bethanechol:

1. **Glucoma** (eye drops)
2. Non-obstructive**Urine retention** e.g. postoperative
3. Non-obstructive**Paralytic ileus** e.g. postoperative
4. Neurogenic bladder
5. Congenital megacolon
6. Gastroesophageal reflux

Adverse effects and contraindications of choline esters:

Adverse effects	contraindications
1-Bradycardia. →	1-Bradycardia.
2-Slow AV conduction. →	2-AV block (heart block).
3-Hypotension. →	3-Hypotension.
4-Bronchospasm + ↑ secretions →	4-Bronchial asthma.
5-↑ HCl secretion. →	5-Peptic ulcer.
6- Choline esters passing B.B.B. worsen parkinsonism →	6-Carbachol and bethanechol are contraindicated in parkinsonism
7. ↑ Secretions: lacrimat., saliva....	7-Ischemic heart disease (hypotension → ↓ coronary blood flow).
8. ↑ Urination	8-Thyrotoxicosis (increased atrial conduction → atrial fibrillation).
9. Nausea,Vomiting, Diarrhea, Colic	9-IV and IM injection→ severe bradycardia & hypotension (treated by atropine).
7. Choline esters with nicotinic → - Lid twitches, frontal headache (with eye drops) - Skeletal muscle Fasciculations	

B.Natural alkaloid

- **Pilocarpine**: - 3ry ammonium → **well absorbed orally, pass BBB**
  - **Not** affected by Cholinesterase enzyme
  - More selective on **M_3**

a. Eye:Miotic (the preferred miotic due to M_3 selectivity, rapid action and short acting) used for:

Was used in

1. **Glaucoma**
2. After fundus examination→ counteracting mydriatics.
3. Iridocyclitis→ alternating with mydriaticsto prevent adhesions.

b. Exocrine glands: ↑ secretion → in dryness of eye & mouth (xerostomia).

c. Scalp blood vessels: VD→ used as hair tonic.

C.Cevemiline

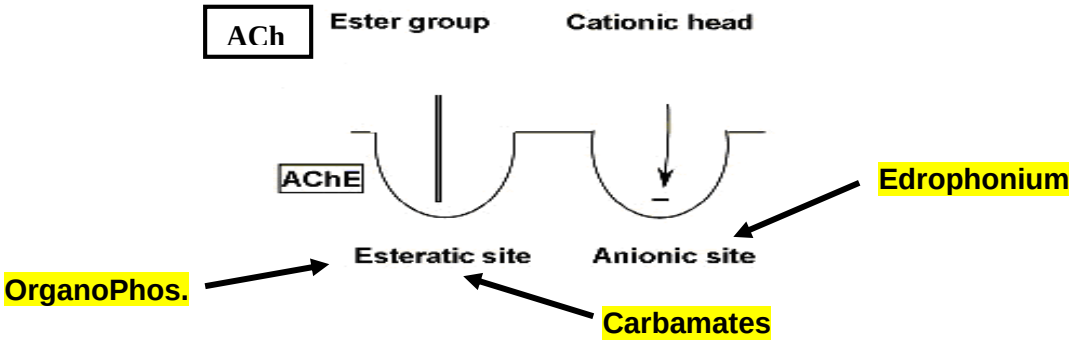
- More Selective on**M_3** → used in **dryness of eye & mouth**.

CHOLINE ESTERASE INHIBITORS (ChEIs)

ANTI-CHOLINESTRASES

Mechanism of Action

• ChEIs act indirectly by inhibiting choline esterase → accumulation of ACh.



Reversible Ch.EIs

1. Simple Alcohols: Edrophonium

- Weak, **short-acting** (2-10 min) 4ry compound
- Binds electrostatically to the **anionic site** of enzyme
- **Uses:IV, short acting** used in

1. **Diagnosis of myasthenia gravis** → muscle improvement
2. **Differentiation between myasthenic & cholinergic crisis**

2. Carbamate esters Physostigmine – Neostigmine & its substitutes

- medium-duration (3-4 hours)
- The carbamyl group binds covalently to **esteratic site** of enzyme (active site) → carbamylated enzyme

	Physostigmine (Eserine)	Neostigmine(Prostigmine)
Nature:	Natural – 3ry amine	Synthetic – 4ry ammonium
Kinetics:	- Well absorbed **orally** - Pass **BBB & conjunctiva**	- **Poor oral** absorption - **NOT** Pass BBB & conjunctiva
Dynamics:	- **Mainly muscarinic**& weak nicotinic effects - **CNS stimulation**	- **Muscarinic & Nicotinic**effects - **Direct skeletal ms. stimulation**
Uses:	1. **Miotic**: eye dropsAs pilocarpine **but with lid twitches** 2. **Atropine toxicity** (correct central & peripheral effects)	**1. Non-obstructive paralytic ileus &urine retention** **2. Myasthenia gravis**(preceded by **atropine** to ⊖ muscarinic side effects): **diagnosis and treatment** **3. Antidote to neuromuscular blockers** (Nicotinic + Direct) (preceded by **atropine**)
Toxicity:	1. **Exaggerated ACh. Like actions** → treated by **Atropine**	
	2. **Convulsions** → treated by **Anticonvulsants**	NO convulsions → NO need for anticonvulsants

Neostigmine substitutes:

- **Pyridostigmine & Ambenonium :** in **myasthenia gravis** (long acting - ↑ selectivity on skeletal muscles - fewer visceral side effects).
- **Donepezil:**in **Alzheimer disease** (3^{ry} → crosses BBB -long acting).
- **Demecarium:** eye drops in **Glucoma**

Myathenia gravis

- Autoimmune disease of skeletal muscles → antibodies → ↓ number of Nm → weakness of extraocular, neck, followed by other muscles)
- **Diagnosis:**

  1. IV Edrophonium

  2. IM Neostigmine 0.5 mg (preceded by 0.5 mg atropine)

  3. Antibody titre
- **Treatment:**

  1. Neostigmine, Pyridostigmine, Ambenonium

  2. Ephedrine & Caffeine are adjuvants

  3. Immunosuppressants: Corticosteroids &Antimetabolits e.g. Azathioprine

  4. Thymectomy (thymus gland→ antibodies)

  5. Plasmaphoresis (purify plasma from antibodies)
- **Drugs contraindicated in Myasthenia gravis:**

  1. Skeletal muscle relaxants

  2. Aminoglycosides: curare-like effect

  3. Beta-blockers (↓ blood flow to skeletal ms.)

  4. Quinidine (sk.ms. relaxant effect)

Myasthenic crisis	Cholinergic crisis
- due to **ineffective or insufficient treatment**→ ↓ ACh→ sever muscle weakness - Edrophonium→**mucleimprovement**	- due to **excessive treatment**→ ↑ ACh→ maintained depolarization → muscle exhaustion and weakness - Edrophonium→**more mucle weakness**

Irreversible Ch.EIs

Organophosphorous compounds

- Very long duration
- The phosphate group binds covalently **to the esteratic site** of the enzyme.
- The **covalent phosphorous enzyme bond** is extremely stable and hydrolyzes in water at a very slow rate (hundreds of hours)→ reactivation time of phosphorylated enzyme > the regeneration time of the enzyme→ **irreversible inhibition**
- **Ageing** occurs in the phosphorylated enzyme bond within 2 min-12hrs → strengthening of covalent bond →recovery of enzyme cannot occur. Thus, choline esterase regenerators in organophosphate toxicity should be given early before ageing occurs.

Members & uses:

1-Malathion& parathion: Insecticides.

2- Sarin: Nerve gas

3- Echothiophate: **Eye** drops

a. Antagonizes atropine after fundus exam. b. Glaucoma

4- Pyrantel pamoate: Paralysis of round worms

Toxicity of Organophosphorus Compounds

- Organophosphorus compounds are highly lipid-soluble &are well absorbed from all sites & cross BBB **(except Echothiophate has 4^{ry} N^{+}→ ↓systemic toxicity).**
- Poisoning occurs due to suicide or accidental exposure to drugs during spraying insecticides or Nerve gases during war.

I- Acute toxicity

- **Excessive muscarinic effects:**
  - Miosis, Bronchospasm, Colic
  - Lacrimation, Sweating, Salivation
  - Vomiting, diarrhea, Urination
  - Bradycardia, Hypotension

- **Nicotinic effects:** Skeletal muscle twitches followed by paralysis.
- **CNS effects**: (stimulation): Excitation, Anxiety, convulsions followed by(depression): coma & respiratory depression.

Death is due to respiratory failure:

- Respiratory center depression.
- Paralysis of respiratory muscles due to persistent depolarization block.
- Excessive bronchial secretions with **acute pulmonary oedema**.

Treatment of acute Organophosphorus Toxicity

1. Maintain vital signs:

Aspirate bronchial secretions, endotracheal intubation & artificial respiration.

2. Decontamination (to prevent further absorption):

Remove contaminated clothes - wash skin (Na hypochlorite) - gastric lavage.

3. Atropine (large doses) for CNS & muscarinic effects:

2 -5 mg/ 5 min→ **Full Atropinization**

Mydriasis, Dry mouth, Tachycardia >80/min, Systolic pr.>80 mmHg, ***bronchial secretions & wheezes stop***.

4. Choline esterase reactivators (oximes): PAM (pralidoxime)

React with phosphorous → Harmless compounds = Chelation → Regenerates choline esterase (IV infusion 1-2 g over 15-30 minas soon as possible before enzyme ageing).

5. Diazepam: for convulsions.

II- Chronic Toxicity: → **delayed neuropathy**.

ANTIMUSCARINIC AGENTS

Atropine & Atropine Substitutes

Atropine

- It is a 3^{ry} ammonium ester of tropic acid → well absorbed from **GIT** if given orally or from **conjunctiva** after ocular instillation & can **cross BBB**.

Mechanism of Action

- Atropine causes **reversible competitive blockade** of the actions of ACh at **muscarinic receptors** (nonselective for muscarinic receptors).

Pharmacological Actions

1. CNS

- Stimulates cardioinhibitory center (vagal nucleus) → initial bradycardia
- Respiratory center stimulation (blocks M_2 receptors) .
- Antiemetic (blocks M_1 receptors in vestibular pathway).
- Antiparkinsonian (blocks M_1 receptors in basal ganglia).
- Stimulation of vasomotor center
- High doses → cortical excitation followed by depression

2. Eye (effects persist for > 72 hrs)

- **Passive Mydriasis** (paralysis of constrictor pupillae).
- **Cycloplegia** (ciliary muscle paralysis & loss of accommodation for near vision).

} ↓ Aquous out flow → ↑IOP → acute glaucoma in narrow anterior chamber

3. Secretions

- ↓ Salivation (→ dry mouth), ↓ lacrimation (→ dry sandy eyes).
- ↓ Sweating (→↑ body temperature) & ↓ bronchial secretions.
- Gastric secretion is least affected.(so, atropine is less efficacious than H2 blockers in reducing HCL)

4. Smooth Muscle

- GIT& Urinary: relaxes wall & contracts sphincters → constipation, urine retention & antispasmodic.
- Bronchi: Bronchodilation.

5. CVS

- **Tachycardia (mainly)** & ↑AVN conduction (blocks M_2 receptors)**.**
- **Initial bradycardia on IM/Sc injection**: initial central vagal stimulation & presynaptic M_2 block → ↑ ACh release.
- **Tachycardia+ VMC stimulation** → ↑ BP
- **Vasodilation** (histamine release). → ↓ BP

Clinical Uses Atropine

1. **Preanesthetic medication** → inhibits secretions - dilates bronchi - antiemetic - inhibits bradycardia - stimulates respiration.
2. **Hyperactive carotid sinus - heart block - bradycardia** (in infarction or digitalis toxicity).
3. **Antiemetic** in motion sickness
4. **Organophosphate poisoning**.
5. **Cycloplegic in children** (atropine is preferred to atropine substitutes in children as their ciliary muscle is strong & atropine substitutes are weaker cycloplegics than atropine)**.**
6. **Travelers diarrhea** (+ **Diphenoxylate**) to ↑ constipating effect &↓ abuse.

Adverse effects of atropine & contraindications (CI)

1.Confusion, restlessness → hallucinations, delirium & mania
2. Dry mouth and skin
3. Hyperthermia (complete skin dryness)
4. Vasodilation & flushing 5. Tachycardia.
6. Blurred vision - photophobia
7. Acute glaucoma in patients with narrow anterior chamber **(CI: glaucoma)**.
8. Urine retention in old patients with enlarged prostate **(CI: enlarged prostate)**.
9. Constipation.

Acute atropine toxicity:

1. Dry as bone	**2. Red as beet root**
3. Hot as hare	**4. Blind as bat**
5. Mad as wet hen	
6. Bladder loses its tone	**7. Heart runs alone**

Peripheral actions:

1) ↓ Sweat → ↑ temperature → **Dry & Hot skin**

2) V.D. → **Flushed skin**

4) Eye: **Dilated & Fixed** Pupil, **blurring** of vision and **diplopia**.

5) Constipation & Urine retention

6) ↑ Pulse, ↑ B.P. & ↑ Resp.

CNS:

Cortical excitation (restlessness, convulsions, hallucinations and delirium) followed by depression (respiratory depression and coma)

Treatment of atropine poisoning

1- Symptomatic: VERY IMPORTANT

- **Cold foment**→ for atropine fever
- **Catheter**→ for urine retention
- **Sedative & tranquillizers** e.g. diazepam → in stimulation stage
- **Stimulants** e.g. caffeine → in depression stage

2- Gastric lavage

3- Dialysis →↑ excretion

4-Physiological Antidote

A-**P**ilocarpine (**p**eripheral action only)

B-**P**hysostigmine→ peripheral action + cross BBB → central action.

Atropine Substitutes

I. Natural atropine substitutes

Scopolamine (Hyoscine)

	Atropine	Scopolamine (Hyoscine)
CNS effect	**Excitatory**	**Depressants** → amnesia, fatigue, drowsiness, twilight sleep High dose → excitation
Antimuscrinic effect	More on **heart, bronchi and intestine**	More on **eye and secretions**
Antimotion sickness	++	+++
Duration	**Longer**	**Shorter**

Uses

- **Mydriatic** (briefer than atropine).
- **Antiemetic** in motion sickness & Minieres disease (more effective > atropine).
- **Preanesthesia medication** (no initial bradycardia).

II. Synthetic atropine substitutes (more selective → fewer side effects)

1. Mydriatic cycloplegics (cyclopentolate -tropicamide - homatropine):

Used in

- **Iridocyclitis**; alternating with miotics to prevent synechia**.**
- To **measure refractive errors**
- For **fundus examination**.

Advantages : **shorter acting** than atropine → action is easier to reverse

→ preferred to atropine (except in children).

2. Antisecretory& antispasmodics:

- **Hyoscine butyl-bromide: antispasmodic in** renal, biliary & intestinal colic & in irritable bowel syndrome**.**
- **Dicyclomine, Pirenzepine**; selective M_1 blocker → **antispasmodic, Peptic ulcer**.

3. Urinary atropine substitutes:

- **Oxybutynin**: used in **nocturnal enuresis** & in **urine incontinence**.

4. Anti-parkinsonian (**benztropine - benzhexol**): Used in

- Drug induced parkinsonism
- Adjuvants in Parkinsonism presenting with tremors & to control sialorrhea.

5. Bronchial atropine substitutes

Ipratropium (non selective M_2 / M_3 blocker)

- **Inhaled** bronchodilator (M_3 blocker)
- **Advantages over atropine:**
  1- Poor CNS penetration
  2- No systemic atropine side effects
  3- No ↓ in mucociliary clearance of bronchial epithelium.
- **Differences between ipratropium & inhaled β_2 agonist**
  1- Gradual onset & late peak (40-60 min)
  2- Suitable for regular prophylactic use > rapid symptomatic relief
- Used in **asthma & COPD (more effective in COPD > asthma** because the parasympathetic tone is the major factor in COPD).
- **Tolerance** develops due to block of presynaptic M_2 receptor →↑ ACh.
- **A/E (transient):** dryness of mouth, tracheal irritation, cough, bad taste

Tiotropium (selective M_3 blocker)

- **Longer acting** than ipratropium → used once/d;
- For maintenance in **COPD**.
- Does not block M_2 receptors → **no tolerance**.

Drugs with Atropine-Like Action

- Antiarrhythmics: quinidine - procainamide.
- Antihistamines (1^{st} generation).
- Tricyclic antidepressants – antipsychotics– pethidine.
- Atropine substitutes.

GANGLIONIC STIMULANTS

Nicotine (small dose)

Mechanism of action:

1. Small dose →ganglionic stimulants (large dose→ blocker)
2. ↑Release of catecholamine from adrenal medulla
3. Act on Nn in CNS

Actions: depend on predominant tone

- **CVS:** Tachycardia – hypertension – VC of all vessels (except skeletal muscle and coronary)
- **Blood:** ↑ Fatty acid concentration & platelet aggregation
- **GIT:** ↑ motility
- **CNS:** ↑ CTZ, ADH, CNS stimulation
- **Enzyme inducer**

Effects of chronic tobacco smoking:

- **GIT:** Salivation, inhibition of hunger pain
- **CVS:** Extrasystole, Atherosclerosis, Angina pectoris
- **Respiratory:** Cancer lung and larynx – nasopharyngeal and bronchial irritation
- **Eye:** Spasm of retinal vessels
- **Pregnancy:** ↑ incidence of abortion and neonatal mortality

Drugs used in smoking cessation:

1. **Nicotine replacement therapy**: gum, inhaler, patch
2. **Bupropion**
3. **Vareniciline:** - direct Nn partial agonist
   - reduce craving for tobacco

GANGLIONIC BLOCKERS

Only used is **Trimetaphan**→ ultrashort acting ganglion blocker & direct VD

Uses: **IV in - Hypertensive emergency - controlled hypotension in surgery**

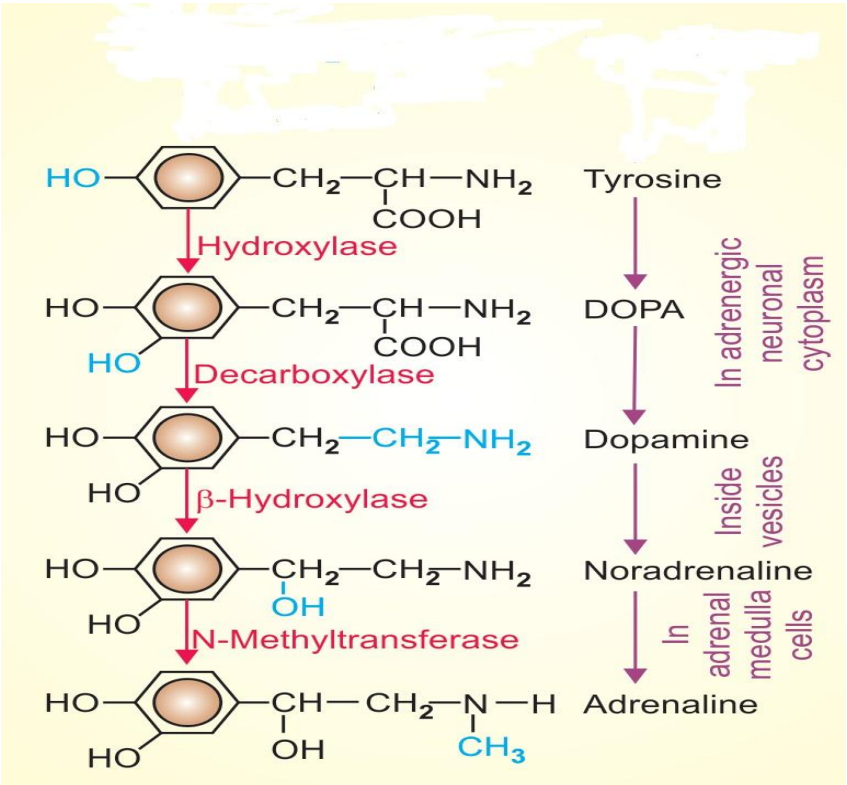
ADRENERGIC PHARMACOLOGY

- The sympathetic system is an important regulator of activities of the heart & peripheral vasculature especially in response to stress.
- Adrenergic neurotransmitters are responsible for transmission at all postganglionic sympathetic neurons, except those of sweat glands.

Adrenergic Neurotransmitters (endogenous catecholamines)

1. **Norepinephrine (NE)**: The transmitter of postganglionic sympathetic fibers & of certain tracts in the CNS.
2. **Epinephrine**: major hormone of adrenal medulla. The adrenal medulla receives preganglionic cholinergic neurons & releases epinephrine**.**
3. **Dopamine (DA)**: Central transmitter in the extrapyramidal, mesolimbic & tuberoinfundibular pathways & in the CTZ. It is also a peripheral transmitter.

Synthesis of CAs (Catecholamines):



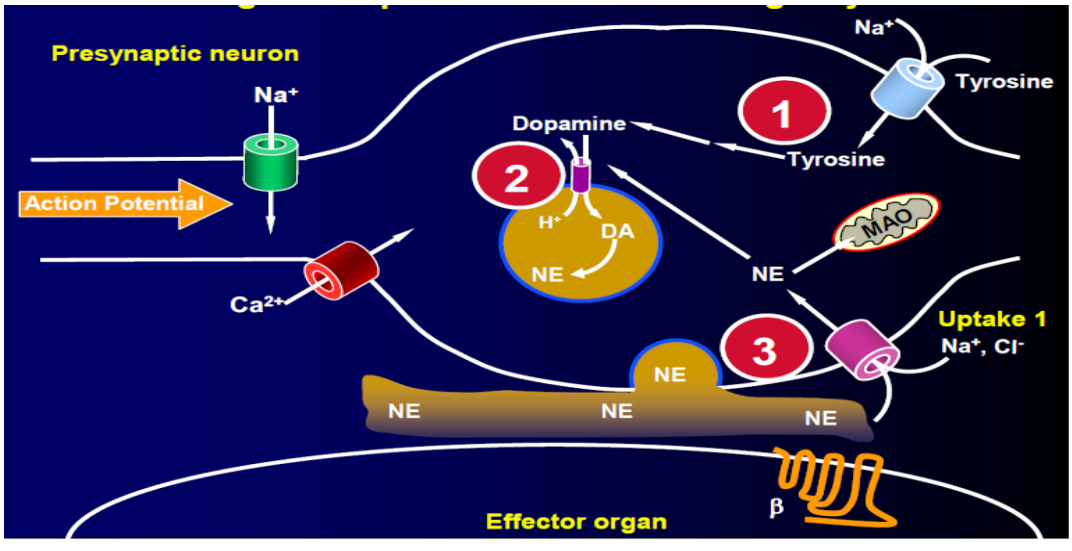
- **Tyrosine hydroxylase is a specific and the rate limiting enzyme**.
  - Its inhibition by ***α-methyl-p-tyrosine*** → depletion of CAs → can be used in pheochromocytoma before surgery & in inoperable cases.
- NE is synthesized in the nerve cell & is stored in synaptic vesicles at the terminal end of the adrenergic neurons
- Synthesis of Adrenaline occurs only in the adrenal medullary cells. It requires high concentration of glucocorticoids 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 & a protein chromogranin

Release of CAs

- The nerve impulse → release of CA by exocytosis
- All the vesicular contents (NA or Adr, ATP, dopamine β hydroxylase, chromogranin) are released



Drugs Affecting NE Release

NE release is controlled centrally by nucleus tractus solitarus (NTS)

& peripheral by presynaptic neurones

Drugs ↑ release

- Low conc. of NE → activates presynaptic β_2 receptors.
- Tyramine
- Amphetamine
- Ephedrine.
- Nicotine (presynaptic Nn)

Drugs ↓ release

- High conc. of NE → activates presynaptic α_2 receptors→ -ve feedback.
- ACh (presynaptic M_2).
- Clonidine.
- Methyldopa

} Central α_2 agonists

Fate of catecholamines

I. Uptake

A. Uptake 1 (amine pump): actively transports NE from synaptic cleft **into neuronal cytoplasm** to be stored in granules or metabolized by MAO enzyme (the main fate of released NE).

- **Blocked by:** tricyclic antidepressants (TCA) - cocaine.

B. Vesicular: from neuronal cytoplasm to **storage vesicles** for re-use.

- **Blocked by:** Reserpine (depletes stores).

C. Uptake II: to **target organs** for metabolism.

- **Blocked by:** glucocorticoids.

II. Enzymatic Degradation of catecholamines

- The monoamines, epinephrine, NE & DA are catecholamines (contain catechol nucleus (a benzene ring with 2 OH groups)).
- They are degraded **mainly** by oxidative deamination by monoamine oxidase **(MAO)** & to a lesser extent by methylation by catechol-o-methyl transferase (COMT).
- The end product; vanilylmandelic acid (**VMA**) is excreted in urine → ↑ in pheochromocytoma (used in diagnosis).

Classification of Adrenergic Receptors:

I-ALPHA (α):

α_1	α_2
Coupled to Gq → ⊕ PLC → ↑IP3& DAG →↑Ca2+ & ⊕ PKC	Coupled to Gi → ⊖ adenylate cyclase →↓ cAMP → ⊖PKA
1. Vasoconstriction 2. Relaxation of walls & Contraction of sphincters of GIT & urinary tracts. 3. Contraction of prostate & vas deferens. 4. Active mydriasis. 5. Liver glycogenolysis & K+ release.	1. ↓ Central sympathetic outflow → ↓BP. 2. ↓ Lipolysis. 3. ↓ **Insulin secretion (predominant).** 4. ↓ Renin release. 5. ↑ Platelet aggregation.

II- BETA (β):

β_1	β_2
Coupled to Gs protein→⊕ adenylate cyclase →↑cAMP → ⊕PKA	
1. Cardiac stimulation. 2. Lipolysis → ↑ plasma FFA (β1 **and β3**). 3. ↑Renin secretion.	1. Bronchodilation & mast cell stabilization. 2. Vasodilation of skeletal & coronary blood vessels. 3. Uterine and intestinal relaxation. 4. Liver & muscle glycogenolysis & k+ uptake. 5. Stimulate insulin release (weak effect). 6. Skeletal muscle tremors

Presynaptic α_2: 1. Inhibit NE release from sympathetic nerves.

2. ↓ Ach release in the heart & intestine.

Postsynaptic β_3: ↑ Lipolysis → ↑ plasma FFA

III. DOPAMINE RECEPTORS

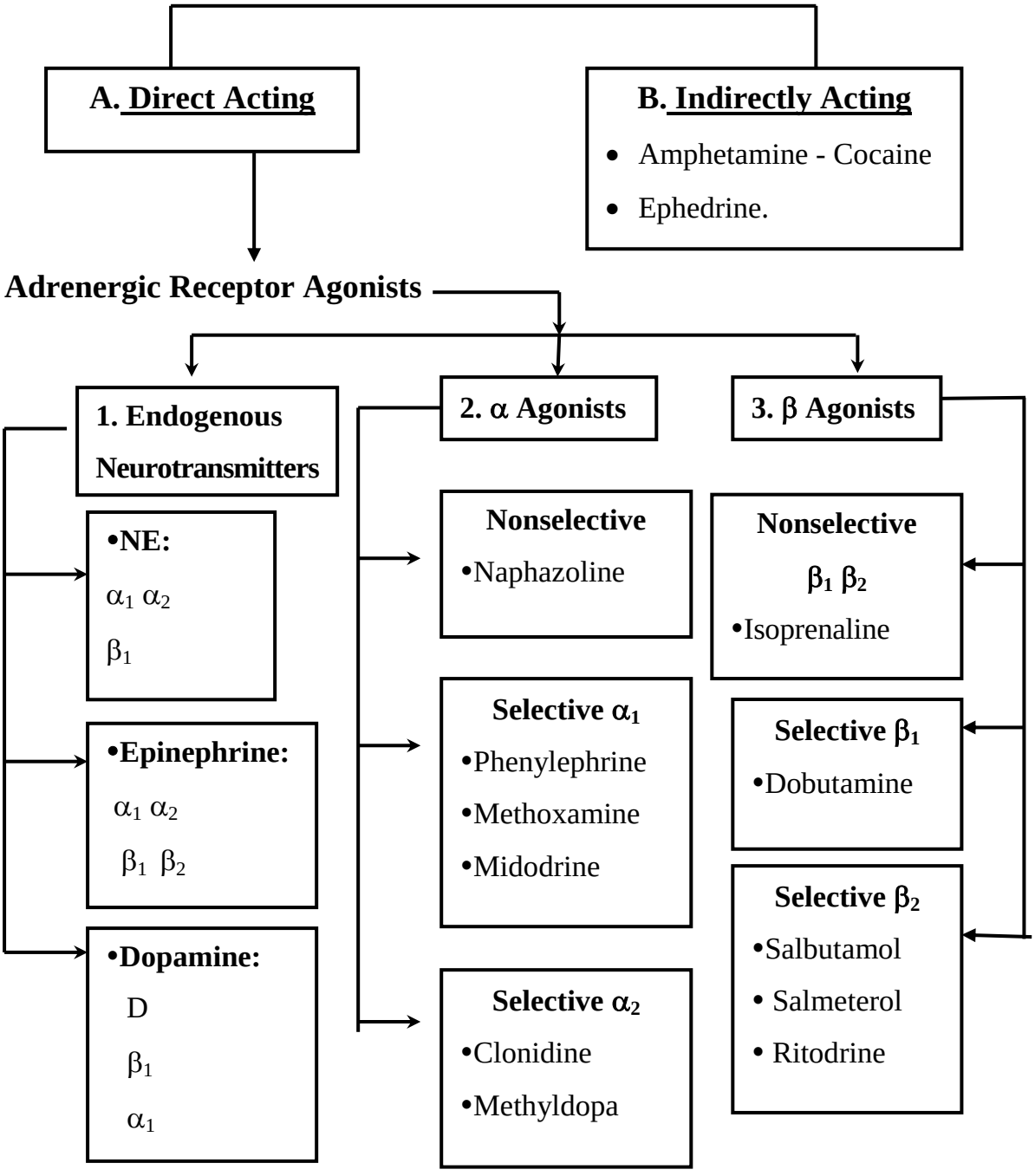
D_1: vasodilation of renal, coronary, cerebral & mesenteric blood vessels.

D_2: **Postsynaptic**: central in the extrapyramidal, tuberoinfundibular, & mesolimbic pathways & in the CTZ.

Presynaptic: ↓ DA & NE release from nerve endings.

Sympathomimetic Drugs

Classification According to Mechanism of Action



4. DA agonists: Dopexamine (**D_1 D_2 B_2**) – fenoldopam (**D_1**) – bromocriptine (**D_2**).

N.B.:

- Selective α_2- agonists are sympatholytics as they ↓ NE release.

1. Epinephrine

Pharmacological actions

I. Cardiovascular System

A. Heart (β_1)

- ↑Force of contraction (positive inotropic).
- ↑ Heart rate (positive chronotropic).
- ↑ Conduction velocity (positive dromotropic) in atria, A-V node, conductive tissues & ventricles.
- ↑ Automaticity → Arrhythmias.

B. Blood vessels

- VC of arterioles of skin, mucosa, splanchnic & renal vessels (α_1).
- VC of veins (α_1).
- Vasodilatation of skeletal & coronary vessels (β_2 effect).

C. Effects on Blood Pressure

Large dose: ↑ systolic & diastolic BP →↑mean BP through**:**

- Vasoconstriction of arterioles and veins (α_1).
- Positive chronotropic & inotropic actions (β_1) (overcome reflex bradycardia).

Small dose: ↑ systolic BP but ↓ diastolic BP due to VD of skeletal blood vessels (β_2) with no change in mean BP → no reflex bradycardia.

Epinephrine Reversal

- The hypotensive effect of epinephrine (β_2-mediated VD of skeletal blood vessels) is masked by its hypertensive effect (α_1). **After α-blockade, the β_2-mediated hypotensive effect is unmasked.**

II. Respiratory System:

- Bronchodilatation (β_2 action).
- Decongestion of BV of mucous membrane of upper respiratory tract (α_1).

III. Eye

- Contraction of dilator pupillae (α_1) → Active mydriasis **without cycloplegia.**
- ↓ IOP by decreasing aqueous humor formation.

IV. Effect on other smooth muscles

- Relaxation of GIT wall (β, α, α_2).
- Contraction of sphincters of GIT & urinary tracts (α_1).
- Inhibition of uterine tone & contractions in last months of pregnancy (β_2).

V. Metabolic actions

- Hepatic & skeletal muscle glycogenolysis → β_2 (mainly) & α_1.
- Insulin release → inhibited by α_2 (dominant).
- Lipolysis (β_1 & β_3).
- Renin release (β_1)
- ↓ serum K^+ (by renin release; β_1 & ↑ hepatic uptake; β_2)

VI. CNS: mild stimulation → Anxiety.

VII. Skeletal muscle: tremors → β_2 & central.

Therapeutic Uses

1. **A**naphylactic shock (reverses bronchospasm & hypotension → life saving).
2. **A**sthma (β_2 - agonists are preferred).
3. Cardiac **A**rrest.
4. **A**rrests bleeding (topical hemostatic →VC, e.g. in epistaxis).
5. **A**dded to local **A**nesthetics to prolong their action.
6. Open **A**ngle glaucoma (↓ IOP).

Adverse effects:

1. CNS: Anxiety, restlessness
2. CVS: Hypertension → cerebral hemorrhage
   Tachycardia, Arrhythmia & Angina
3. Eye: irritation, blurred vision
4. Skeletal muscle tremors
5. Gangrene if injected around finger or toe

Contraindications:

1. Around finger, toe & circumcision
2. Hypertension, cerebral hemorrhage
3. Patients on beta-blocker therapy (unopposed alpha → sever HTN)
4. Ischemic heart disease
5. Arrhythmia, with Digitalis & General anesthesia
6. Thyrotoxicosis

Preparations and Dosage

- **SC or IM** injection of **1:1,000** in **mild anaphylactic shock**.
- **IV** in **severe anaphylactic shock** or **cardiac arrest**; **1:10,000**.
- **Intracardiac in cardiac arrest**.
- Epinephrine inhalation 1:100 in asthma.
- Topical: 1:100 in bleeding states - 1% solution for ophthalmic use.

2. Norepinephrine (Noradrenaline)

- Acts on **α & β_1** receptors (minimal effect on β2 receptors).
- α effect → **marked vasoconstriction** →↑↑ BP.
- β_1 effect → positive inotropic & chronotropic effect.
- **Marked ↑↑ BP → reflex bradycardia** which overcomes its direct positive chronotropic effect
- **Used in shock:**

  Septic - cardiogenic (if BP < 70mmHg) - **after resection of pheochromocytoma.**

3. Dopamine (immediate precursor of NE)

- At **low** doses → activates **D_1** receptors in several vascular beds; renal **vasodilation →↑ renal blood flow**.
- At **moderate** doses → activates cardiac **β_1** receptors → positive inotropic & chronotropic effects→ arrhythmia.
- At **high** doses → activates **α_1** receptors → **vasoconstriction**, including the renal vascular bed & ↑ BP.

Used in:

- **Acute HF & cardiogenic shock** after myocardial infarction or surgery especially if there is renal impairment
- **Chronic refractory heart failure**.

B. α- agonists

Selective α_1- agonists

1. Phenylephrine

- Not a CA→ **Not inactivated by COMT → Longer acting** than CA.

Uses: ***Local***: **a. Mydriatic** for fundus examination.

b. Eye & nasal **decongestant**.

Systemic: **a. Hypotension**.

b. Paroxysmal supraventricular tachycardia (**PSVT**) associated **with marked hypotension** (↑ BP→ reflex vagal stimulation).

2. Methoxamine

- **Uses**: hypotensive states (parenteral).

3. Midodrine

- A **prodrug** that is hydrolyzed to **desglymidodrine** (α_1 agonist).
- **Uses**: postural hypotension (mainly).

Adverse effects of α_1- agonists

1. Hypertension & bradycardia.
2. Rebound nasal congestion & atrophic rhinitis (with **local** application)

C. β- agonists

I-Non-selective β- agonists:

Isoprenaline:

- β_1 effect → +ve chronotropic (↑HR) & inotropic (↑contractility) → marked ↑ in cardiac output.
- β_2 effect → vasodilation →↓ diastolic BP → reflex tachycardia.
- **Marked ↑↑ in HR → anginal attack & sudden death**.
- **Used in**: **Bradycardia** 2^{ry} to heart block.

II-Selective β1- agonist

Dobutamine

Used in:

- **Acute HF & cardiogenic shock** especially in normotensives (no α effect) with preserved renal function (no renal VD effect).
- **Chronic refractory heart failure**.

Adverse effects

- Palpitation.
- Anginal pain.
- Arrhythmia.

Comparison between Dopamine and Dobutamine

Dopamine	Dobutamine
• Natural catecholamine.	• Synthetic catecholamine.
• D_1-agonist (at low dose)→ - VD of renal blood vessels. - Headache, nausea, vomiting.	• **No D_1** agonist effect.
• β_1-agonist (at moderate dose): - Cardiac stimulation (+ve inotropic & chronotropic) - Anginal pain and arrhythmia.	• β_1-agonist: - Cardiac stimulation: **inotropic > chronotropic.** - **Less arrhythmogenic**.
• α_1-agonist (At high dose): - Vasoconstriction - Hypertension, gangrene	• **No α_1-agonist** effect.
Used in • Acute HF & cardiogenic shock especially if there is hypotension or renal impairment . • Chronic refractory heart failure.	**Used in** • Acute HF & cardiogenic shock especially in normotensives with preserved renal function . • Chronic refractory heart failure.

III-Selective β_2 agonists

Advantages over nonselective β agonists

1. No cardiac complications **in regular doses**.
2. Longer acting (not metabolized by MAO or COMT).
3. May be given by many routes (oral, inhalation, parenteral).

Therapeutic uses

1. Bronchial asthma (**salbutamol - salmeterol**).
2. Prevent premature labor & threatened abortion (**terbutaline & ritodrine**).

Adverse effects (less with inhalation therapy):

1. Anxiety, restlessness and headache.
2. **T**remors of skeletal muscle.
3. **T**achycardia (**at high concentration** they stimulate β_1 receptors).
4. **T**olerance **on long term systemic** use (β receptor downregulation).
5. **H**ypokalemia and muscle cramps.
6. **H**ypoxemia: (β_2 effect→ VD > bronchodilation → ↓ blood oxygenation).
7. **H**yperglycemia & increased free fatty acids.

D. D-agonists

1. Dopamine (see before)

2. Dopexamine

- A **dopamine analogue** → activates **D_1 & D_2 + β_2** receptors.
- **Powerful splanchnic vasodilator** → ↓ afterload & improves blood flow to vital organs, including the kidney.
- **Use**: in **Shock** following myocardial infarction, trauma, open heart surgery in those **with low cardiac output & peripheral vasoconstriction**.

3. Fenoldopam

- **D_1** receptor agonist → peripheral V.D. in some vascular beds.
- **Used**: mainly **IV** for the treatment of **severe hypertension**.

II. INDIRECTLY ACTING SYMPATHOMIMETICS

1. Amphetamine

Mechanism of actions: release NE centrally & peripherally →

A. CNS:

- CNS stimulation - alertness - ↓ fatigue - marked mood elevation
- Appetite Suppression

B. CVS: ↑ arterial blood pressure → **reflex bradycardia**.

Therapeutic uses (CNS):

1-Attention deficit hyperactivity disorder (**ADHD**) in children

2- **Narcolepsy**.

3. **Obesity** (largely replaced by newer agents e.g. **phenteramine** **sibutramine**)

Adverse effects:

1. CNS:

- **Psychological dependence** - schizophrenia-like syndrome.
- Anorexia & weight loss
- Insomnia & tremors → depression & fatigue (depletion of CA store).
- Convulsion → coma & cerebral hemorrhage (severe toxicity)

2. CVS: palpitation, arrhythmia, anginal pain and hypertension

2. Ephedrine & pseudoephedrine

- Ephedrine acts **directly** (as epinephrine) & **indirectly** (↑ CA release).
- **Less potent & less CNS** effect than amphetamine.

Uses

1. **Nasal decongestant** (ephedrine **&** pseudoephedrine).
2. Topical hemostatic in **epistaxis** (ephedrine)
3. **Spinal shock** (IV) (ephedrine)
4. **Bronchial asthma** (ephedrine)

Adverse effects

1. Minimal CNS stimulation → insomnia & anxiety.
2. Minimal CVS stimulation → palpitation, arrhythmia.
3. Urinary retention.

3. Cocaine (local anesthetic):

- **Inhibits CA reuptake → peripheral sympathomimetic** action.
- Readily enters **CNS → amphetamine-like** effect (more intense, more addictive, shorter acting).

Contraindications of sympathomimetic drugs

1. Patients on β blockers (unopposed α-actions → severe hypertension).
2. Hypertensive patients or those with ischemic heart disease (specially decongestants in OTC cold remedies).
3. Adding epinephrine to local anesthetics in cardiac patients & around finger and toes.
4. Diabetes.
5. Thyrotoxicosis.

Sympatholytic Drugs

I-Centrally-Acting Sympatholytics

1. Methyl dopa

Mechanism:

- Prodrug → metabolized in the brain to α-methyl NE which stimulates **central α_2** receptors in brain stem (NTS) → ↓ central sympathetic outflow.

Uses: Antihypertensive especially in **pregnancy**.

Adverse effects: (limit its use)

1.Sympatholytic: **S**edation - **S**exual dysfunction - Dry mouth - Diarrhea
Peptic ulcer aggravation – Bradycardia.

2. Salt and water retention → Tolerance & Weight gain.

3. Hepatitis, hemolytic anemia, systemic lupus (immune based).

4. Depression (↓ DA, ↓ 5HT synthesis).

5. Parkinsonism & Hyperprolactinemia (↓ DA).

2. Clonidine

Mechanism of Action

1. Activates **central α_2** and **Imidazoline** receptors → ↓central sympathetic outflow → ↓ BP.
2. Acts on **peripheral presynaptic α_2** receptors → ↓ NE release.
3. Stimulates **peripheral postsynaptic α_2** receptors → ↓ renin & aldosterone.

Uses

1. Preanesthetic medication (sedative & analgesic).
2. **M**orphine withdrawal
3. **M**enopausal hot flushes.
4. **M**igraine prophylaxis

} ↓ Sympathetic discharge

5. Hypertensive urgencies.

Adverse effects

1.Sympatholytic: **S**edation - **S**exual dysfunction - Dry mouth - Diarrhea

Peptic ulcer aggravation – Bradycardia.

2. Salt and water retention → Tolerance & Weight gain.

3. **Rebound hypertension**: treated by α & β blockers e.g. labetalol.

II- Alpha Adrenoceptor Antagonists

Classification

Non-selective		**Selective**	
Irreversible Long acting	**Reversible Short acting**	**Alpha$_1$ Selective**	**Alpha$_2$ Selective**
Phenoxybenzamine ($\alpha_1 > \alpha_2$)	Phentolamine ($\alpha_1 = \alpha_2$) + **Direct VD**	Prazosin Doxazosin Terazosin Tamsulosin	Yohimbine

Other α Blockers: labetalol- carvedilol.

Selective α_1 blockers

I. Cardiovascular actions

1. Mixed vasodilators:

a. Arteriodilators→↓ peripheral resistance→ ↓blood pressure.

b. Venodilators→↓ venous return→ postural hypotension.

2. Tachycardia: more with nonselective agents (they block presynaptic α_2 receptors, → ↑ NE release → stimulate cardiac β_1 receptors).

3. Fluid retention on chronic use (compensatory ↑ in blood volume).

II. Other actions

- Block α receptor at base of **bladder & prostate** →↓ resistance to urine flow→ useful in benign prostatic hyperplasia (BPH).
- Relaxation of **vas deferens**→ inhibition of ejaculation.
- **Miosis - Nasal congestion (stuffiness).**

Therapeutic uses of α blockers

1. **BPH**.
2. **Essential hypertension**. (***with hyperlipidemia***)
3. **Hypertensive emergencies**
   - **In most** hypertensive emergencies (labetalol)
   - **Clonidine rebound & pheochromocytoma** (**phentolamine+βB /or/ labetalol**).
4. **Extravasation of α-agonists** (prevent VC & dermal necrosis).
5. **Raynaud's disease**: Ca^{2+} channel blockers are preferred.
6. **Pheochromocytoma**: medical treatment: **before surgery or if inoperable** (phenoxybenzamine is preferred; irreversible blocker).

Adverse Effects of αblockers

1. **1st dose postural hypotension**: ↓ by giving small dose (1 mg) at bed time.
2. **Tachycardia** (marked with non-selective agents).
3. **Impaired ejaculation and sexual dysfunction**.
4. **Nasal congestion**, **flushing**, **headache**.

Tamsulosin

- High affinity for **α_{1A}** receptors (responsible for prostate smooth muscle contraction) than α_{1B} receptors (responsible for VC) →↑efficacy in benign prostatic hyperplasia with less effect on blood vessels than other selective $\alpha_1$blockers→ **minimal change in BP**.

Selective α2 blockers

- **Yohimbine**: used as an **aphrodisiac** →↑NE release→ stimulates ejaculation

III-Beta Adrenoceptor Blockers (βBs)

- βBs antagonize the effects of catecholamines at β-adrenoceptors.
- Different βBs are distinguished by:
  1. Relative **selectivity** for β_1 & β_2 receptors
  2. Differences in **lipid solubility**
  3. Intrinsic sympathomimetic activity (**ISA**),
  4. Membrane-stabilizing activity (**MSA**)
  5. **Vasodilator** effects.

Members of Different Generations of βBs

	Lipophilic	Balanced	Hydrophilic	Advantages
Non-selective βBs	• **P**ropranolol (MSA)	• **P**indolol (ISA)	• **N**adolol	
Selective β_1Bs	• **M**etoprolol	• **B**isoprolol	• **A**tenolol • **E**smolol	• Less bronchospasm. • Less delay in recovery from hypoglycemia. • Less risk of Raynaud's phenomenon.
Vasodilator βBs	• Carvedilol (β_1 β_2 Blocker plus α-blockade)	• Celiprolol ($\beta_1$blocker plus β_2 agonist)		• Preferred as antihypertensives. • Carvedilol decreases mortality in HF.

* **Other Vasodilator βBs**: labetalol & nebivolol (see below).

- βBs with **MSA** (local anesthetic effect due to Na^+ channel blockade) → corneal anesthesia → In glaucoma, βBs without MSA e.g. timolol & betaxolol are used instead.
- βBs with **ISA** (initial stimulation then blocking of β-receptors i.e. partial agonist) induce less bradycardia, bronchospasm & vasospasm.

Pharmacokinetics of β-blockers

- βBs are classified according to their pharmacokinetics into 3 main groups: **lipophilic, hydrophilic & balanced** (properties in between those of lipophilic & hydrophilic)**.**
- Esmolol is hydrophilic, yet it has a very short duration of action ($t_{1/2}$ 8 min) due to hydrolysis by plasma esterases.

	Lipophilic	Hydrophilic
Absorption	• Well absorbed	• Irregularly absorbed
First pass effect	• Extensive	• Less
Bioavailability	• Less	• More
Distribution	• More CNS penetration → more CNS side effects	• Less CNS penetration → less CNS side effects
Elimination	• Mainly hepatic → suitable in renal impairment.	• Mainly renal → suitable in hepatic impairment.
t½	• Short t½ → frequent administration.	• Long t½ (except esmolol) → once/ day administration.

Pharmacological Actions of βBs

A. Cardiovascular Actions

1. Antianginal effect: improve imbalance between O_2 supply & demand

A. ↓ O_2 demand:

- ↓ HR & myocardial contractility.
- ↓ BP.

B. ↑ O_2 supply:

- ↑ coronary filling during diastole (by ↓ HR → ↑ diastolic period).
- Redistribution of coronary flow to subendocardial area.

2. Antiarrhythmic effect

- Block intrinsic sympathetic activity in slow fibres:
  - ↓ SAN rate & AVN conduction.
  - ↓ Phase 4 slope → slow automaticity of sympathetically – induced ectopic focus.

3. Antihypertensive effect

- β_1-blockade (mainly)
  - Suppress **renin** release (mainly)
  - **Negative inotropic & chronotropic** effects.
- β_2 – blockade
  - Central **sympatholytic** effect (block presynaptic β_2 receptors in NTS)
  - Peripheral sympatholytic effect (block presynaptic β_2 receptors)
- **Resetting of baroreceptors**.
- Some β-blockers are **vasodilators**.

4. Vasoconstriction (unopposed α actions)

- In ciliary vessels→↓ aqueous humor production → ↓ IOP.
  (+ blockade of β_2 in ciliary epithelium→↓cAMP →↓ aqueous humor production)
- In mesenteric vessels →↓ hepatic blood flow.
- In skeletal muscles → ↓ blood flow during exercise→ ↓work capacity.

B. Non-cardiovascular Actions

1. Respiratory: bronchoconstriction - inhibit CA induced mast cell stabilization.

2. Metabolic

- Inhibit CA-induced glycogenolysis→ delay recovery from hypoglycemia.
- Inhibit CA-induced lipolysis.
- ↑ Plasma TG (↑ VLDL) - ↓ HDL (↓ HDL/LDL ratio).
- ↓ Insulin release.
- ↑ Plasma K^+ during exercise (inhibit uptake by liver).
- Inhibit conversion of T4 → T3.

3. CNS: CNS depression (**lipophilic βB**) - anxiolytics.

Therapeutic Uses

1. 2^{ry} to β_1 blockade

a. Hypertension

b. Angina pectoris: except vasospastic angina → ↑vasospasm.

c. M. infarction **(**prophylactic & in acute phase→ ↓ infarct size & mortality).

d. Arrhythmias.

e. Heart failure**:** low doses of carvedilol, bisoprolol, nebivolol & metoprolol.

f. Hyperthyroidism & thyrotoxic crisis (**propranolol**): cardio-protective, inhibit T4-T3 conversion & improve anxiety & tremors.

g. Hypertrophic obstructive cardiomyopathy:↓ outflow resistance by relaxing hypertrophied septum.

2. 2^{ry} to β_2 blockade

a. Open-angle glaucoma (timolol & betaxolol)

b. Prophylactic in oesophageal varices: **non-selective ßBs** reduce portal blood flow by: splanchnic vasoconstriction (β_2 block) - ↓COP (β_1 block).

c. Prophylaxis of migraine

i. ↓ NE release which triggers attack.

ii. Vasoconstriction of extracranial blood vessels.

d. Essential tremors.

3. 2ry to α blockade (labetalol; of choice)

a. Acute dissecting aortic aneurysm

- Powerful antihypertensive due to combined α & β blocking effects →↓dissection while awaiting surgery.

b. Pheochromocytoma

- If propranolol is used it should be preceded by an α- blocker to avoid marked ↑ BP due to unopposed α-action after β-blockade.

4. 2ry to CNS effects:

- **Social anxiety disorder**

Adverse effects, contraindications & precautions

1. Due to β1 blockade

- **B**radycardia - heart **B**lock.
- **H**eart failure (may be precipitated with high dose).
- **H**ypotension (more severe with vasodilator βBs).
- **H**ypertriglyceridaemia.
- **Mask** warning symptoms of hypoglycemic coma (tachycardia)

2. Due to β2 blockade

- **C**old extremities, fatigue & **C**laudications (**CI in peripheral vascular disease & vasospastic angina**).
- **B**ronchospasm **(CI in asthma)**.
- **P**rolongation of insulin-induced hypoglycemia.
- Hyperkalemia in susceptible patients (e.g. renal impairment & diabetes).

3. <u>CNS effects</u>: nightmares & depression.

4. <u>Other adverse effects</u>

i. **Abrupt cessation → rebound angina & arrhythmias** in ischemic heart disease **(**due to up regulation of ß receptors; less severe with ßBs with ISA) → **gradual withdrawal.**

ii. **Sexual dysfunction** (impotence may be due to VC and ↓ blood pressure in erectile tissue of penis).

Specific beta adrenoceptor antagonists

Esmolol

- It is an **ultra-short–acting β_1-selective** adrenoceptor antagonist.
- **Hydrophilic** but has a **short $t_{1/2}$** (8 minutes) due to **hydrolysis** by plasma esterases.
- Useful in **Arrhythmias** (supraventricular & due to thyrotoxicosis), **perioperative hypertension**, **myocardial ischemia in acutely ill patients**.

Labetalol

- Selective α_1 & **Nonselective βB**.
- Used in **most hyperetensive emergencies.**
- Used in hypertension during pregnancy & labor (**pre-eclampsia**).

Carvedilol

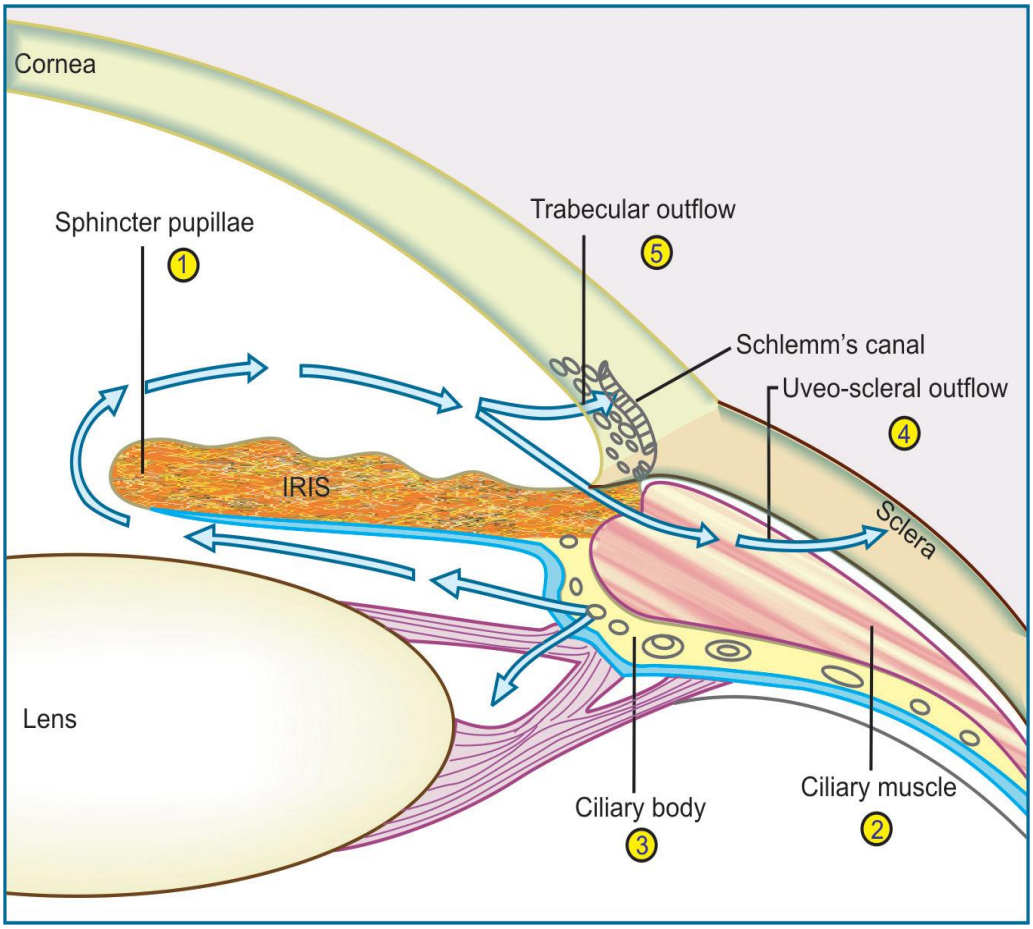
- α_1-selective blocker & **Nonselective βB → vasodilator** βB.
- Beneficial in **chronic heart failure** →

  i. ↓ Oxygen free radical→ antioxidant.

  ii. Inhibits vascular smooth muscle mitogenesis

DRUGS FOR GLAUCOMA

- Glaucoma is characterized generally by raised intraocular pressure (IOP) with progressive form of optic nerve damage.
- Etiology: is unknown and there are many risk factors.
- The chief therapeutic measure is to lower IOP:
  1. ↓ secretion of aqueous humor or
  2. ↑ its drainage.



- Glaucoma is seen in two principal clinical forms:
  1. Open angle glaucoma
  2. Closed angle glaucoma

A. Open angle (wide angle, chronic simple) glaucoma

- It is probably a genetically predisposed degenerative disease affecting patency of the trabecular meshwork
- Ocular hypotensive drugs are used on a long term basis and constitute the definitive treatment in majority of cases:

1. β-adrenergic blockers

- **Topical β blockers were first line drugs but recently, PG-F2α analogues are the preferred drugs.**

Advantages of topical β blockers over miotics

- No change in pupil size: no diminution of vision in dim light and in patients with cataract
- No induced myopia which is especially troublesome in young patients
- No headache/brow pain due to persistent spasm of iris and ciliary muscles

- Ocular β blockers are lipophilic with no/weak local anesthetic activity (to avoid corneal hypoesthesia and damage).
- Ocular side effects: mild and infrequent → stinging, redness and dryness of eye, corneal hypoesthesia, allergic blepharoconjunctivitis and blurred vision
- Systemic adverse effects **These are the major limitations** in the use of ocular β blockers, and occur **due to absorption through nasolacrimal duct.**

- **Timolol** It is the prototype of ocular β blockers; is nonselective (β1 + β2) and has no local anaesthetic or intrinsic sympathomimetic activity.
- **Levobunolol:** very similar to timolol except for **longer duration** of action.

2. Prostaglandin analogues

- It acts by increasing uveoscleral outflow
- **Latanoprost:** PGF2α derivative has shown efficacy similar to timolol

- No systemic side effects
- Blurring of vision, increased iris pigmentation, thickening and darkening of eyelashes have occurred in some cases.

3. α-adrenergic agonists

- **Dipivefrine** It is a prodrug of Adrenaline → penetrates cornea → hydrolysis by the esterases enzymes→Adrenaline

- **A/E:** ocular burning .

- **Apraclonidine** It is a clonidine congener

- It decreases aqueous production by:
  1. α_2 (main) → ↓cAMP in the ciliary epithelium
  2. additional α_1 action → VC of ciliary blood vessels.
- -A/E: Itching, lid dermatitis, follicular conjunctivitis, mydriasis, dryness of mouth and nose are
- Its use is restricted to short term control IOP after laser intervention

4. Carbonic anhydrase inhibitors

- **Acetazolamide** : orally
- **Dorzolamide:** topically

5. Miotics:

- Because of several drawbacks they are now used only as the **last option**.
- Pilocarpine, physostigmine, echothiophate

B. Angle closure (narrow angle, acute congestive) glaucoma

- It occurs in individuals with a narrow iridocorneal angle and shallow anterior chamber.
- The IOP remains normal until an attack is precipitated usually by mydriasis
- Failure to lower IOP quickly may result in loss of sight →Vigorous therapeutic measures to reduce IOP. is needed:
    1. **Hypertonic mannitol (20%)** IV infusion
    2. **Acetazolamide:** IV followed by oral is started concurrently.
    3. **Miotic:e.g. pilocarpine**
    4. **Topical β blocker: Timolol**
    5. **Apraclonidine/latanoprost** may be added.
- Drugs are used only to terminate the attack of angle closure glaucoma.
- Definitive treatment is surgical or laser iridotomy.
- Few cases, who have chronic narrow angle glaucoma, may be treated with a miotic/other ocular hypotensive drug for long periods