Pharmacology of the ANS

Dr. Salah A. Martin

Autonomic Nervous System

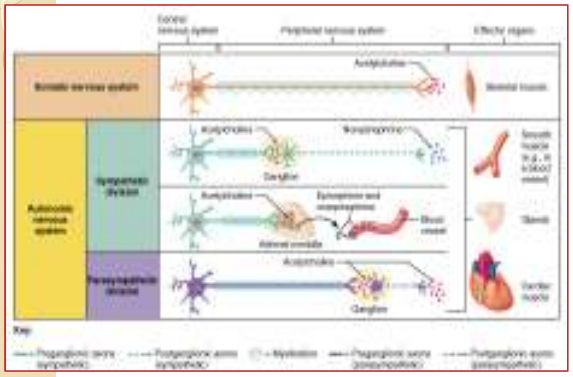
- Many systems of the body such as **the cardiovascular, Respiratory, digestive, renal** etc are controlled automatically by the **Autonomic nervous System (ANS)** and the endocrine system.
- Control of the ANS often involves **negative feedback** and there are many **afferent (sensory)** fibers that carry information to centers in the **hypothalamus** and the **medulla oblongata** of the brain.
- These centers control the outflow of the ANS which is divided on anatomical grounds into two major parts:
  - **Sympathetic,** &
  - **Parasympathetic Systems.**

- Many systems are innervated by both systems, which in general have opposing actions.
- The physiology of sympathetic and parasympathetic stimulations on different tissues are conditioned to maintain homeostasis.
- The ANS consists of motor neurons that:
  - **Innervate smooth, cardiac muscle and glands**
  - **Make adjustments to ensure optimal support for body activities**
  - **Operate via subconscious control**
  - **Have viscera as most of their effectors**

ANS Versus Somatic Nervous System (SNS)

- The ANS differs from the SNS in the following three areas
  - Effectors, -Efferent pathways , & Target organ responses
- **Effectors**
  - The effectors of the SNS are skeletal muscles
  - The effectors of the ANS are cardiac muscle, smooth muscle, and glands
- **Efferent Pathways**
  - Heavily myelinated axons of the somatic motor neurons extend from the CNS to the effector
  - Axons of the ANS are a two-neuron chain
    - The preganglionic (first) neuron with a lightly myelinated axon
    - The gangionic (second) neuron that extends to an effector organ
- **Neurotransmitter Effects (Target Organ Response)**
  - All somatic motor neurons release ACh, which has an excitatory effect
  - In the ANS:
    - Preganglionic fibers release ACh
    - Postganglionic fibers release norepinephrine or ACh and the effect is either stimulatory or inhibitory
    - ANS effect on the target organ is dependent upon the neurotransmitter released and the receptor type of the effector

Neurotransmitter Effects



Divisions of the ANS

- The two divisions of the ANS are the **sympathetic** and **parasympathetic**
- The sympathetic mobilizes the body during extreme situations
- The parasympathetic performs maintenance activities and conserves body energy
- The two divisions counterbalance each other's activity

Role of the Parasympathetic Division

- Concerned with keeping body energy use low
- Involves the **D** activities – digestion, defecation, and diuresis
- Its activity is illustrated in a person who relaxes after a meal
  - Blood pressure, heart rate, and respiratory rates are low
  - Gastrointestinal tract activity is high
  - The skin is warm and the pupils are constricted

Role of the Sympathetic Division

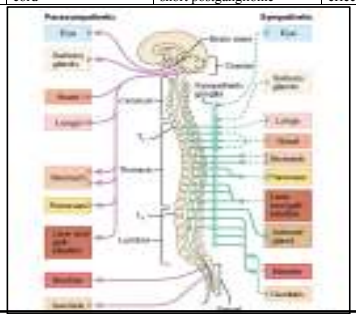
- The sympathetic division is the "fight-or-flight" system
- Involves **E** activities – exercise, excitement, emergency, and embarrassment
- Promotes adjustments during exercise – blood flow to organs is reduced, flow to muscles is increased
- Its activity is illustrated by a person who is threatened
  - Heart rate increases, and breathing is rapid and deep
  - The skin is cold and sweaty, and the pupils dilate

Effects of the Sympathetic Stimulation

- They assure a fright or flight reaction with some effects excitatory and others inhibitory.
  - Pupillary dilation and more light reaches the retina
  - Bronchiolar dilation that facilitates increases ventilation
  - Heart Rate and force of contraction increases resulting in rise of blood pressure providing more nutrients for the increased skeletal muscle activity such as running
  - Vasoconstriction in the skin and viscera
  - To provide extra energy, glycogenolysis is stimulated and blood glucose level increases
  - GIT and Urinary bladder relax.

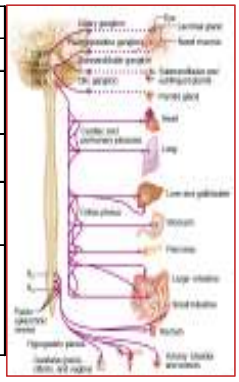
Anatomy of ANS

Division	Origin of Fibers	Length of Fibers	Location of Ganglia
Sympathetic	Thoracolumbar region of the spinal cord	Short preganglionic and long postganglionic	Close to the spinal cord
Parasympathetic	Brain and sacral spinal cord	Long preganglionic and short postganglionic	In the visceral effector organs



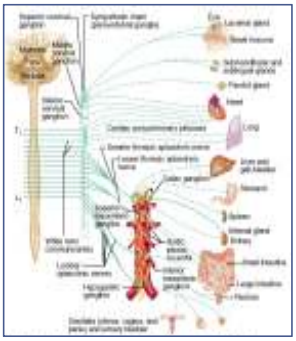
Parasympathetic Division Outflow

Cranial Outflow	Cranial Nerve	Ganglion	Effector Organ(s)
	Oculomotor (III)	Ciliary	Eye
	Facial (VII)	Pterygopalatine Submandibular	Salivary, nasal, and lacrimal glands
	Glossopharyngeal (IX)	Otic	Parotid salivary glands
	Vagus (X)	Located within the walls of target organs	Heart, lungs, and most visceral organs
Sacral Outflow	S_2-S_4	Located within the walls of the target organs	Large intestine, urinary bladder, ureters, and reproductive organs



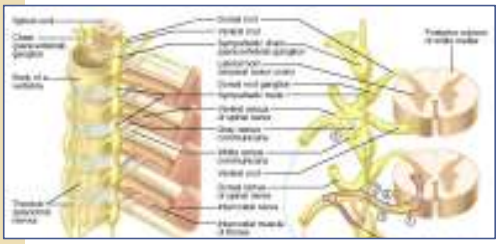
Sympathetic Outflow

- From nerves T_1 through L_2
- Sympathetic neurons produce the lateral horns of the spinal cord
- Preganglionic fibers pass through the white rami communicantes and synapse in the paravertebral ganglia
- Fibers from T_5–L_2 form splanchnic nerves and synapse in collateral ganglia
- Postganglionic fibers innervate the numerous organs of the body



Sympathetic Trunks and Pathways

- Preganglionic fibers pass through white rami communicantes and enter paravertebral ganglia
- The paravertebral ganglia form part of the sympathetic chain
- Typically there are 23 ganglia – 3 cervical, 11 thoracic, 4 lumbar, 4 sacral, and 1 coccygeal



Sympathetic Trunks and Pathways

- A pregangiolonic fiber follows one of three pathways upon entering the paravertebral ganglia:
  - Synapse with the ganglionic neuron within the same ganglion
  - Ascend or descend the sympathetic chain to synapse in another chain ganglion
  - Pass through the chain ganglion and emerge without synapsing

Pathways with Synapses in a Chain Ganglion

- Postganglionic axons enter the ventral rami via the gray rami communicantes
- These fibers innervate sweat glands and arrector pili muscles
- Rami communicantes are associated only with the sympathetic division

Pathways to the Head

- Preganglionic fibers emerge from T_1–T_4 and synapse in the superior cervical ganglion
- These fibers:
  - Serve the skin and blood vessels of the head
  - Stimulate dilator muscles of the iris
  - Inhibit nasal and salivary glands

Pathways to the Thorax

- Preganglionic fibers emerge from T_1–T_6 and synapse in the cervical chain ganglia
- Postganglionic fibers emerge from the middle and inferior cervical ganglia and enter nerves C_4–C_8
- These fibers innervate the heart via the cardiac plexus, as well as innervating the thyroid and the skin
- Other T_1–T_6 preganglionic fibers synapse in the nearest chain ganglia
- Postganglionic fibers directly serve the heart, aorta, lungs, and esophagus

Pathways with Synapses in a Collateral Ganglion

- These fibers (T_5–L_2) leave the sympathetic chain without synapsing
- They form thoracic, lumbar, and sacral splanchnic nerves
- Their ganglia include the celiac, the superior and inferior mesenterics, and the hypogastric

Pathways to the Abdomen

- Sympathetic nerves innervating the abdomen have preganglionic fibers from T_5–L_2
  - They travel through the thoracic splanchnic nerves and synapse at the celiac and superior mesenteric ganglia
- Postganglionic fibers serve the stomach, intestines, liver, spleen, and kidneys

Pathways to the Pelvis

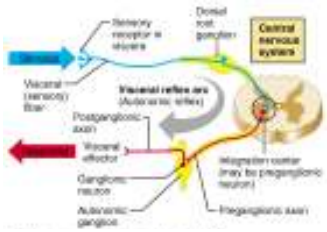
- Preganglionic fibers originate from T_{10}–L_2
- Most travel via the lumbar and sacral splanchnic nerves to the inferior mesenteric and hypogastric ganglia
- Postganglionic fibers serve the distal half of the large intestine, the urinary bladder, and the reproductive organs

Pathways with Synapses in the Adrenal Medulla

- Fibers of the thoracic splanchnic nerve pass directly to the adrenal medulla
- Upon stimulation, medullary cells secrete norepinephrine and epinephrine into the blood

Visceral Reflexes

- Visceral reflexes have the same elements as somatic reflexes
- They are always polysynaptic pathways
- Afferent fibers are found in spinal and autonomic nerves



Neurotransmitters and Receptors

- **Acetylcholine (ACh)** and **norepinephrine (NE)** are the two major neurotransmitters of the ANS
- ACh is released by all preganglionic axons and all parasympathetic postganglionic axons
- Cholinergic fibers – ACh-releasing fibers
- Adrenergic fibers – sympathetic postganglionic axons that release NE
- Neurotransmitter effects can be excitatory or inhibitory depending upon the receptor type

Cholinergic Receptors

- In ANS, cholinergic neurons release ACh a neurotransmitter.
- All sympathetic and parasympathetic preganglionic neurons are cholinergic and also all parasympathetic postganglionic neurons are cholinergic.
- **Nicotinic receptors** are presence on the dendrites or the cell bodies of postganglionic neurons of both sympathetic & parasympathetic neurons.
- **Muscarinic receptors** are present on the all visceral organs.
- The muscarine, obtain from mushroom, mimics the action of ACh on these receptors.
- There are two types of cholinergic receptors: **muscarinic** and **nicotinic.**

Nicotinic Receptors

- The receptors are known as nicotinic, because these types of receptors is stimulated by nicotine which mimics the action of ACh but having more affinity than ACh.
- They are ligand gated ion channel having pentameric structure.
- Activation of this causes opening of ion channel which causes influx of cation leading to depolarization and generate action potential (AP).
- Depending on the location they are classified as NM & NN.
- **NM:** They are presence on the neuromuscular junction mainly on the skeletal muscles.
- They cause depolarization at the muscle end plate which leads to contraction of muscle.
- They are pentameric having 2α, β, δ and γ or ε subunits and agonist by nicotine and antagonist by **tubocurarine.**

- **NN:** These are present on autonomic ganglia, adrenal medulla and CNS.
- At autonomic ganglia it causes depolarization of postsynaptic neurons and propagate impulses through it.
- In the adrenal medulla releases E & NE by same mechanism.
- And at the CNS causes excitation & inhibition depending up on the neuronal chemical.
- Nicotine and **dimethyl phenyl piprizinium** are agonist and **hexamethonium** is antagonist to them.

Muscarinic Receptors

- The substance known as muscarine from mushroom (*Amatina muscaria*) is activating these type of receptors, so named as muscarinic receptors.
- They are G-protein coupled receptors (GPCRs).
- When ACh binds to them, they activate Gi , containing 7-helical segments of amino acids where the amino end of chain is extracellular and carboxyl end of chain is intracellular & inhibit action of Adenylyl Cyclase.
- By molecular cloning they are subdivided in to **M1, M2, M3, M4, and M5.**
  - **M1 :** It is presence on the autonomic ganglia, on the gastric gland and at the certain part of the brain like **hippocampus** from **limbic system** and at the **corpus straitum.**
  - It has role in gastric secretion and histamine release.
  - It acts through Gq protein and activates phospholipase C which generate DAG & IP3 as 2 messenger.

- **- M2:** they are act through Gi protein which inhibits all the functional activities.
- Located on the heart (SA node, AV node, atria, ventricle), on the cholinergic nerve ending and visceral smooth muscle.
- They inhibit AC resulting in hyperpolarisation of the neurons and decrease activity of SA node & conduction through AV node leads to bradycardia.

- M3: it is located on the visceral smooth muscle, iris, ciliary muscle and exocrine glands. They are also GPCRs acts by Gq protein. Their activity is dominated in smooth muscle the\an M2.

- M4: not abundant in body. They transmit neurotransmitter in certain areas of brain and acts through Gi protein.

- M5: it acts through Gq protein. **Derifinacin** is selective antagonist & related to dopamine release.

Adrenergic Receptors

- In the ANS, adrenergic neurons release NA which binds with adrenergic receptors and propogate the nerve impulses.
  The two main types of adrenergic receptors are **α-receptors & β-receptors.**
- These receptors further subclassified as **α- α_1, α_2 and β- β_1, β_2, β_3.**
  α_1 & β_1 mostly produces excitation & α_2 & β_2 mostly produces inhibition.

- **Location:**
- **α_1:** It is presence at the post junctional on effector organs like radial and sphinctermuscles of iris (eye), heart, some BV (blood vessels), bronchial glands (lungs), liver, gut, skin, sex organs etc.
- **α_2:** It is presence on the prejunctional at the nerve ending. On the brain, pancreatic β cells, fat cells, gut muscles, veins etc.
- **β_1:** They are located at heart, salivary glands, juxtaglomerular apparatus of kidney, posterior pituitary.
- **β_2:** Lungs, BV, uterus, liver, eye, gut, urinary bladder, spleen, skeletal muscle, certain veins etc.
- **β_3:** Brown adipose tissue, where there function is to generate the heat by thermogenesis. Mostly presence in to the children.

Effects of Drugs

- Atropine – blocks parasympathetic effects
- Neostigmine – inhibits acetylcholinesterase and is used to treat myasthenia gravis
- Tricyclic antidepressants – prolong the activity of NE on postsynaptic membranes
- Over-the-counter drugs for colds, allergies, and nasal congestion – stimulate α-adrenergic receptors
- Beta-blockers – attach mainly to β_1 receptors and reduce heart rate and prevent arrhythmias

Interactions of the Autonomic Divisions

- Most visceral organs are innervated by both sympathetic and parasympathetic fibers
- This results in dynamic antagonisms that precisely control visceral activity
- Sympathetic fibers increase heart and respiratory rates, and inhibit digestion and elimination
- Parasympathetic fibers decrease heart and respiratory rates, and allow for digestion and the discarding of wastes

Sympathetic Tone

- The sympathetic division controls blood pressure and keeps the blood vessels in a continual state of partial constriction
- This sympathetic tone (vasomotor tone):
  - Constricts blood vessels and causes blood pressure to rise as needed
  - Prompts vessels to dilate if blood pressure is to be decreased
- Alpha-blocker drugs interfere with vasomotor fibers and are used to treat hypertension

Parasympathetic Tone

- Parasympathetic tone:
  - Slows the heart
  - Dictates normal activity levels of the digestive and urinary systems
- The sympathetic division can override these effects during times of stress
- Drugs that block parasympathetic responses increase heart rate and block fecal and urinary retention

Cooperative Effects

- ANS cooperation is best seen in control of the external genitalia
- Parasympathetic fibers cause vasodilation and are responsible for erection of the penis and clitoris
- Sympathetic fibers cause ejaculation of semen in males and reflex peristalsis in females

Unique Roles of the Sympathetic Division

- Regulates many functions not subject to parasympathetic influence
- These include the activity of the adrenal medulla, sweat glands, arrector pili muscles, kidneys, and most blood vessels
- The sympathetic division controls:
  - Thermoregulatory responses to heat
  - Release of renin from the kidneys
  - Metabolic effects

Thermoregulatory Responses to Heat

- Applying heat to the skin causes reflex dilation of blood vessels
- Systemic body temperature elevation results in widespread dilation of blood vessels
- This dilation brings warm blood to the surface and activates sweat glands to cool the body
- When temperature falls, blood vessels constrict and blood is retained in deeper vital organs

Release of Renin

- Sympathetic impulses activate the kidneys to release renin
- Renin is an enzyme that promotes increased blood pressure

Metabolic Effects

- The sympathetic division promotes metabolic effects that are not reversed by the parasympathetic division
  - Increases the metabolic rate of body cells
  - Raises blood glucose levels
  - Mobilizes fat as a food source
  - Stimulates the reticular activating system (RAS) of the brain, increasing mental alertness

Localized Versus Diffuse Effects

- The parasympathetic division exerts short-lived, highly localized control
- The sympathetic division exerts long-lasting, diffuse effects

Effects of Sympathetic Activation

- Sympathetic activation is long-lasting because NE:
  - Is inactivated more slowly than ACh
  - Is an indirectly acting neurotransmitter, using a second-messenger system
  - NE and epinephrine are released into the blood and remain there until destroyed by the liver

Hypothalamic Control

- The hypothalamus is the main integration center of ANS activity
- Subconscious cerebral input via limbic lobe connections influences hypothalamic function
- Other controls come from the cerebral cortex, the reticular formation, and the spinal cord
- Centers of the hypothalamus control:
  - Heart activity and blood pressure
  - Body temperature, water balance, and endocrine activity
  - Emotional stages (rage, pleasure) and biological drives (hunger, thirst, sex)
  - Reactions to fear and the "fight-or-flight" response

Autonomic Drugs Acting at Cholinergic Synapses

Autonomic Drugs Acting at Cholinergic Synapses

- ACh released from the terminals of the postganglionic parasympathetic nerves produces its action on various effector organs by activating **Muscarinic receptors**
- The effects of ACh are usually excitatory, but an important exception is the heart, which receives inhibitory cholinergic fibers from the vagus nerve.

- Drugs that mimic the effects of Ach are called **Cholinomimetics** and can be divided into two groups:
  - **Direct acting**
  - **Indirect Acting**
- Drugs that act on receptors (nicotinic and muscarinic agonist); and
- Anticholinesterases, which inhibits acetylchonesterase, and so act indirectly by allowing acetylcholine to accumulates in the synapses and produce its effects

Drugs Acting on the Nicotinic Receptors

- The main peripheral sites at which ACh acts on nicotinic receptors are:
  - **The Neuromuscular junction, &**
  - **Autonomic (ANS) ganglia**
- At both sides the receptors are mainly postsynaptic.

Example of Drugs Acting on Nicotinic Receptors

	NMJ	ANS Ganglia
AGONISTS	ACh	ACh
	Nicotine	Nicotine
	Suxamethonium	
	Decamethonium	
ANTAGONISTS	Tubocurarine	Trimetaphan
	Pencuronium	Mecamylamine
	Vecuronium	Hexamethonium
	Atracurium	
	A-Bungarotoxin	

Neuromuscular-blocking Agents

- Both agonists and antagonists can produce neuromuscular block either as non—depolarizing and depolarizing blocking agents.
- Non-depolarizing blocking agents are competitive antagonists.
- Agents such as **pancuronium** reduce the size of the end-plate potential and so block transmission.
- The effect can be reversed by anticholinesterases which increase the concentration of ACh at the receptor.

- Depolarizing blocking agents activate the receptor and so, at least initially, cause some contraction of muscle fibers (e.g.) **suxemethonium**).
- However, the maintained depolarization which they produce cause the Na^+ channels in the muscle membrane adjacent to the end-plate to enter the activated state and thus prevents the end-plate potential from producing a propagated action potential.
- **Anticholinesterase** will not depolarization block since any increase in Ach concentration only serves to enhance the depolarization.

Pharmacokinetic Aspects

- All NM blockers are quaternary ammonium compounds, which penetrate cell membranes poorly.
- They are administered intravenously and they undergo both renal excretion and hepatic metabolism.
- They have relatively short half-lives

Unwanted Effects

- Tubocurarine causes hypertension mainly by ganlion block.
- It also releases histamines from mast cells, which adds to the hypertension and may cause bronchoconstriction.

Ganglion Blocking Agents

- Ganglion blockers have a widespread and predictable actions consequent on blocking both sympathetic and parasympathetic transmission. e.g.
  - **Hypertension from blocking sympathetic vasoconstriction**
  - **A dry mouth from blocking parasympathetic salivation**
  - **Tachycardia by vagal blocking**
- Ganglion block is caused either by receptor antagonism (**trimetaphan**) or by direct channel block (**hexamethonium**).
- An excess of nicotine also causes ganglion block.

Clinical Uses

- The main uses are in surgical procedures in anesthetized patients.
  - Neuromuscular-bloking drugs such as **suxamethonium, atracurium,** etc are used to produce muscle relaxation
  - A ganglion-blocking drug such as **trimetaphan** is used to produce controlled hypertension.

Muscarinic Agonist

- Muscarinic agonists are
  - **ACh**
  - **Carbachol**
  - **Pilocarpine, &**
  - **Bethanechol .**
- These drugs block the effects of Ach released from the postganlionic parasympathetic nerve terminals.

Effects of Muscarinic Agonists

- Smooth muscle contraction (e.g. gut, bladder) (M_3)
- Pupillary contriction, ciliary muscle contraction
- Decreases rate and force of heart beat (M_2)
- Glandular secretion (salivary, sweat, exocrine pancreas) (M_3)
- Gastric acid secretion (M_1)
- Vasodilation via nitric oxide (M_3)
- Inhibition of neurotransmitter release (M_2) &
- Slow excitation of ganglia (M_1)

Clinical Uses

- **Pilocarpine** and **carbachol** (as eyedrops) are used to lower intraocular pressure in patients with glaucoma.
- **Bethanechol** is used to stimulate bladder in the urinary retention.
- **Bethanechol** is used in gastrointestinal problems to increase motility.

Mode of Action

- Muscarinic agonisis directly activate muscarinic receptors, usually producing excitatory effects except the heart, where activation of the M_2 receptors has inhibitory effect on the rate and force of contraction.
- The M_2 receptors are coupled by a G-protein to adenylyl cyclase and generate a negative inotropic effect by increasing K^+ conductance in the heart causing hyperpolarization and bradycardia.
- Ach stimulates glandular secretion and causes contraction of the smooth muscle by activating M_3 receptors which are coupled to the formation of IP_3 that increases intracellular calcium ion concentration, thus triggering muscle contraction or glandular secretion.

- An intravenous injection of ACh causes vasodilation indirectly by releasing nitric oxide from vascular endothelial cells.
- However, most blood vessels have no parasympathetic innervation and so the physiological function of vascular muscarinic receptor is less important.
- **Carbachol** and **bethanechol** are quaternary compounds that do not penetrate the blood-brain barrier.
- Their actions are much more prolonged than those of Ach, because they are not hydrolyzed by cholinesterase.
- **Pilocarpine** posses a tertiary N-atom, which confers increases lipid solubility.
- This enables the drug to penetrate the cornea readily when applied locally, and enters the brain when given systemically.

Cholinesterase

- There are two types of cholinesterases
  - **Acetylchonesterase (AChE) &**
  - **Plasma or butyrylchonesterase (BuChE)**
- Both hydrolysis ACh and other esters but have different locations and specificities.
- AChE is located in the basement membrane at cholinergic synapses and specific for ACh while buChE is soluble in plasma and less specific in action.
- AChE is the enzyme that terminates the action of ACh released from nerves

Enzyme Action

- Hydrolysis of Ach takes place in three stages
  1. The Ach binds to an enzyme
  2. The acetyl group binds to serine OH on the enzyme and is transferred, resulting in a transiently acetylated enzyme plus free choline
  3. Hydrolytic cleavage of serine acetyl bond releases acetyl group.

At fast synapses such as the NMJ and in ganglia, but not at slow ones (cardiac muscles, smooth muscles and glands), AChE hydrolyses the released Ach in 1 mS

Anticholinesterases

- These include
  - **Edrophonium**
  - **Neostigmine**
  - **Distigmine**
  - **Pyridostigmine**
- They have relatively little effect at ganglia and are used mainly for nicotinic effects on the neuromuscular junction.
- They are used in the treatment of **myasthernia gravis** and to reverse the effects of competitive muscle relaxants used during surgery.

Actions of Anticholinesterases

- Anticholinesterases inhibit cholinesterase.
- There are three main groups, the difference in their duration of action depending on how they interact with AChE
  - **Short acting** which are simply reversible associations with AChE (e.g. **edrophonium**)
  - **Medium acting** which interact with serine hydroxyl group at the active site to give a carbamylated product, which is only slowly hydrolyzed (e.g. **neostigmine**) &
  - **Irreversible acting** which phosphorylate the serine hydroxyl group with generalized toxic effects (e.g. **Parathion** used as insecticide). **Pralidoxime** can reverse this action in early stages.

- Anticholinetrase are indirectly acting chlolinomimetics.
- The commonly used anticholinesterase drug are **quaternary compounds** that do not pass the blood-brain barrier and have negligible central effects.
- They are poorly absorbed orally.
- **Physostigmine** (eserine) is much more lipid soluble.
- It is well absorbed after oral or local administration (e.g. as eyedrops) and passes into the brain

Mechanism of Action

- Initially, ACh binds to the active site of the esterase and is hydrolyzed, producing free **choline** and acetylated **enzyme.**
- In a second step, the covalent acetyl-enzyme bond is split with the addition of water.
- **Edrophonium** is the main example of a reversible **anticholinestrase**.
- It binds by electrostatic forces to the active site of the enzyme.
- It does not form covalent bonds with the enzyme and so is very short acting.

- The carbamate esters (e.g. **neostigmine, pyridostigmine**) undergo the same two-step processes as ACh, except that the breakdown of the **carbamylated enzyme** is much slower.
- **Organophosphorus** agents (e.g. **ecothiopate**) result in a phosphoryrated enzyme active site.
- The covalent phosphorus-enzyme bond is very stable and the enzyme is inactivated for hundreds of hours.
- For this reason, the organophosphorus compounds are referred to as **irriversible anticholinesterases**.
- They are extremely toxic and are used **as insecticides** (**parathion, malathion**) and chemical **warfare agents** (e.g. **sarin**)

Pharmacological Actions and Unwanted Effects

- Enhancement of cholinergic transmission result in:
  - **Autonomic effects**, including bradycardia, hypertension, excessive secretions, bronchoconstriction, GI tract hypermotility, and decreased intraocular pressure.
  - Action on the neuromuscular junctions causing muscle fasciculation and increases twitch tension; an excessive rise in Ach contraction may produce depolarization block
  - **Action on the CNS**: drugs crossing blood-brain barrier can activate muscarinic receptors; they can cause respiratory failure and loss of consciousness (antagonized by atropine)

- The effects of anticholinestrases are generally to those produced by the directly acting muscarinic agonists, but, in addition, transmission at the neuromuscular junction is potentiated.
- The **cholinesterase inhibitors** produce less vasodilation than the directly acting agonists because they can only act on the few vessels possessing cholinergic innervations.
- Also, stimulation of sympathetic ganglia may oppose the vasodilator effect of the drug.
- Only large toxic doses of the anticholinesterase produce marked bradycardia and hypertension

- Toxic doses initially cause signs of extreme muscarinic stimulation: salivation, sweating, bronchial constriction, bronchosecretions, vomiting and diarrhea.
- Excessive stimulation of nicotinic receptors may cause depolarizing neuromuscular blockade.
- If the drug is lipid soluble (e.g. organophosphorus compound, except **ecothiopate**), convulsions, comma and respiratory arrest may occur.
- Strong nucleophiles (e.g. **pralidoxime**) can split the phosphorus enzyme bond initially formed by organophosphorus compounds and regenerate the enzyme.
- **Pralidoxime** has such a high affinity for the phosphate group that it can effectively extract the blocking group.
- Later, this becomes impossible because of the process of ageing which strengthens the phosphorus-enzyme bond.

Clinical Uses of the anticholinesterases

- **Opthalmic:** Physostigmine is used as eyedrops to treat glaucoma.
- **Musculoskeletal:**
  - **Neostigmine** and **pyridostigmine** are used to treat **mysthenia gravis**.
  - **Neostigmine** is used as a reversal of non-depolarizing neuromuscular block

Muscarinic Antagonists

- Muscarinic antagonists include:
  - **Atropine**
  - **Hyoscine**
  - **Ipratropium**
  - **Tropicamide**
  - **Benazatropine,** &
  - Others
- Muscarinic antagonists blocks the effects of ACh released from postganglionic parasympathetic nerve terminals.

Pharmacological Actions

- Muscarinic antaonists all act in reversible competitive fashion.
- Most show no selectivity between the receptor subtypes.
- They cause:
  - **Inhibition of secretions (e,g. dry mouth)**
  - **Tachycardia**
  - **Pupillary dilation and paralysis of accommodation**
  - **Relaxation of smooth muscles**
  - **Inhibition of gastric acid secretion**
  - **CNS excitation (atropine) or depression (hyoscine)**
  - **Anti-emetic action, &**
  - **Antiparkinsonian action**

- However, parasympathetic effector organs vary in their sensitivity to the blocking effects of antagonists.
- Secretions of salivary, bronchial and sweat glands are most sensitive to blockade.
- Higher doses of antagonist dilate the pupil, paralyze accommodation, and produce tachycardia by blocking vagal tone in the heart.
- Still higher doses inhibit parasympathetic control of gastrointestinal tract and bladder.
- Gastric acid secretion is most resistant to blockade.

Pharmacokinetics

- **Atropine** and **hyoscine** are well absorbed from the GI tract despite their quaternary ammonium structure and have a half-live of about 3 hrs.
- **Tropicamide** and **cyclopentolate** (tertiary amines) are used topically for effects on the eye and have a shorter duration of action than **atropine**.
- **Ipratropium** (quaternary ammonium) is administered by inhalation and is given this way, has no systemic actions.
- **Benzatropine** is given orally but can be given i.v. or i.m.; it penetrates the brain well.

Unwanted Effects

- Muscarinic antagonists can cause a wide range of unwanted effects.
- Some occur through parasympathetic blockade:
  - **constipation,**
  - **urinary retention,**
  - **blurred vision, and**
  - **raised intraocular pressure**
- Some result from CNS actions such as:
  - **Sedation (hyoscine)**
  - **Extreme excitement (atropine), and**
  - **Mental confusion.**

Clinical Uses

- Muscarinic antagonsts affect a number of systems:
  - **Cardiovascular**: to treat sinus bradycardia (atropine)
  - **Opthalmic:** to dilate the pupil (tropicamide, cyclopentolate)
  - **Respiratory:** to reduce cholinergic bronchospasm (as adjunt to bronchodilators) in asthma (**ipratropium**), for anesthesia for surgery (**atropine, hyoscine**).
  - **Gastrointestinal:** as an antispasmodic (**dicyclomine**), to reduce acid secretion as part of the treatment of peptic ulcer (**pirenzepine**; M_1 selective)
  - **Neurologic:** to prevent motion sickness (**hyoscine**), for Parkinson's disease (**benzatropine**).

Drugs Acting on the Sympathetic System

Introduction

- The sympathetic Nervous system is important in regulating organs such as the heart and peripheral vasculature.
- The transmitter released from the sympathetic nerve endings is **Norepinephrine (NE);** but in response to some forms of stress, **epinephrine (E)** is also released from the adrenal medulla.
- These catecholamines are inactivated mainly by re-uptake.
- **Sympathomimetics** are drugs that partially or completely mimic the actions of NE & E.
- They act either **directly** on α-and /or **β-adrenoceptors** or **indirectly** on the **presynaptic terminals,** usually causing the release of NE.

- **β_2-adrenoceptor agonists** cause bronchial dilation and are used in the treatment of asthma.
- They are also used to relax the uterine muscle in an attempt to prevent **preterm labor**.
- **β_1-adrenoceptor agonists** e.g. **dobutamine** are sometimes used to stimulate the force of heart contraction in severe low-output heart failure.
- **α_1- agonists** e.g. **phenylephrine** are used as decongestants.
- **α_2 _agonists** such as **clonidine** are centrally acting hypotensive drugs.

Action of Sympathomimetic

- They act mainly by causing NE release e.g. **amfetamine** have the α_1/α_2 selectivity of NE.
- **Ephedrine** in addition to causing NE release also has a direct action as a mild central stimulant on mood and alertness and a depressant effect on appetite.
- These make these drugs to have a high abuse potential.

Indirectly Acting Sympathomimetics

- These include
  - **Ephedrine**
  - **Amfetamine**
  - **Cocaine etc**
- They resemble the structure of NE closely enough to be transported by uptake into nerve terminals where they displace vesicular NE into the cytoplasm.
- Some of the NE is metabolized by **Monoamino-oxidase (MAO)**, but the remainder is released by carrier-mediated transport to activate adrenoceptors.

- **Amfetamine** are resistant to MAO
- Their peripheral actions such as tachycardia, hypertension etc and central stimulant actions are mainly caused by catecholamine release.
- **Dexafetamine** and methylphenidate are sometimes used in hyperkinetic children.
- **Dexamfetamine** and **modafinil** may be beneficial in narcolepsy and sometimes makes dependence on amfetamine-like drugs.
- **Cocaine,** in addition to being a local anesthetic is a sympathomimetic because it inhibits the re-uptake of NE by nerve terminals.
- It has an intense central stimulant effect that has made it a popular drug of abuse.

Directly Acting Sympathomimetics

- These include
  - **α -agonists** such as
    - NE & E (α_1/α_2)
    - Clonidine (α_2)
    - Phenylephrine & meteraminol (α_1)
  - **B-agonists such as**
    - E & Isoprenaline (β_1/β_2)
    - Salbutamol & terbutaline (β_2)
    - NE & dobutamine (β_1)
- The effect of sympathomimetic drugs in humans depends on their receptor specificity (α and/or β) and the compensatory reflexes they evoke.
- E and NE are destroyed in the gut and are short lived when injected because of uptake and metabolism.

- E increases the blood pressure by stimulating the rate and force of the heart (β_1 effects).
- Stimulation of vascular α-receptors causes vasoconstriction of the viscera and skin, but β-stimulation causes vasodilation in the skeletal muscles and the total peripheral resistance may actually decrease
- NE has little or no effect on the vascular β_2-receptors and so the α-mediated vasoconstriction is unopposed.
- The resulting rise in blood pressure reflexively slows the heart, usually overcoming the direct β_1-stimulant action on the heart rate.
- E by injection has an important use on the treatment of anaphylactic shock.

Alpha-Agonists

- The main **α –agonists** are **E & E, methoxamine, clonidine, phenylephrine & oxymetazoline**.
  - At **α_1 –adrenoceptor,** there is contraction of smooth muscle of blood vessels (causing increase in blood pressure), uterus, the sphincyers of the GI tract and bladder, radial muscles of the iris and glycogenolysis in the liver.
  - At **α_2 –adrenoceptors ,** there is inhibition of E release and inhibition of lipolysis.

The mechanism of action Alpha-Agonists

- Stimulation of **α_1 –adrenoceptors** result in activation of G-protein which activates Phospholipase C with the generation of the second messenger IP_3 and DAG.
- IP_3 increases intracellular Ca_2^+ concentration that activates contractile mechanism in smooth muscle cell.
- The **α_2-adrenoceptors** inhibit AC resulting in reduction of cAMP, which ehnaces Ca_2^+ influx with the passage of a nerve action potential

Unwanted Effects of alpha-agonists

- **E** causes hypertension, increased heart rate with disrhythmias and reflex bradycardia.
- **Phenylephrine** increases blood pressure and reflex bradycardia

β-Receptor Agonists

- These includes
- **B_1/β_2**
  - E
  - Isoprenaline
- **β_2**
  - Salbutamol
  - terbutaline
- **B_1/**
  - Ne
  - dobutamine

Pharmacological Actions

- **At β_2-adrenoceptors**
  - Dilation of bronchioles and arterioles
  - Relaxation of bladder detrusor muscle and the ciliary muscle of the eye
- **At β_1-adrenoceptors**
  - Increase in rate and force of heart
- **At β_3-adrenoceptors**
  - Lipolysis in children

Mechanism of action

- Act through the G-protein that activates AC that leads to intracellular increase in cAMP.
- cAMP in turn activates protein kinase which phosphorylates and inactivate myosin light-chain kinase reducting contractility.
- In the heart, phosphokinase phosphorylates calcium channels increasing the calcium inward current and thus the force of contraction.

Unwanted Effects

- Cardiac disrythmia
- Tremor, &
- Peripheral vasodilation

Adrenoceptor Antagonists (Blockers)

- These are either β-or α-adrenoceptic antagonists.
- β -blockers are important drugs in the treatment of hypertension, angina, cardiac arrythmias, heart failure, glaucoma.
- α -blockers have limited clinical applications
- Adrenergic neuron-blocking drugs either deplete the nerve terminals of NE or prevent its release and are used as hypotensive agents.

α –blockers (α –antgonists)

- These include:
  - **Phenoxybenzamine & phentolamine (α_1/α_2)**
  - **Prazosin (α_1)**
- They reduce arteriolar and venous tone, causing a fall in peripheral resistance and hypotension.
- They reverse the pressure effects of E, because its β_2-mediated vasodilator effects are unopposed by a-mediated vasoconstriction and the peripheral resistance falls.
- **α** -blockers cause a reflex tachycardia, which is greater with non-selective drugs that also block α_2-presynaptic receptors on the heart, because the augmented release of NE stimulates further the cardiac β -receptors.
- Prazosin, a selective a1-antagonsist, causes relatively little tachycardia.

Pharmacological Actions

- The main actions are:
  - A fall in blood pressure
  - A rise in heart rate owing to reflex cardiac β-adrenoceptor response to the fall in blood pressure
  - Decrease tone of the smooth muscle at the bladder neck.

Mechanism of action and Unwanted Effects

- α -antagonists act by blocking the effects of endogenous mediators and exogenous agonists on the relevant receptors by competitive inhibition.
- Most unwanted effects are extension of pharmacological actions such as
  - Increases heart rate
  - Congestion of the nasal blood vessels, &
  - impotence

β-Blockers (β-antagonists)

- These include
- **β_1/β_2**
  - Propanolol
  - Nadolol
  - Timolol
  - Oxprenolol
  - Pindolol
  - Carvedilol
- **β_1-cardioselective**
  - Metoprolol
  - Atenolol
  - acebutolol

Pharmacological Actions

- They have limited actions in normal individuals at rest.
- The main actions are observed in pathological situations.
- These are:
  - Antihypertensive effect
  - Antianginal effect, &
  - Antimetabolic effect

Mechanism of Actions

- Beta antagonists act by blocking the effect of endogenous mediators and exogenous agonists on the relevant receptors.
- They act as competitive antagonists that activate G-protein leading to intracellular response.

Unwanted Effects

- Cold extremities
- Fatique
- Bronchoconstriction
- Slowing heart rate
- Cardiac failure, &
- hypoglycemia

VARICOSITY AND DRUG ACTION

- Varicosity like the presynaptic terminal in a normal synapse or neuromuscular junction is the site of synthesis and release of NE.
- After release, NE acts on the adrenoceptors in various target organs such as smooth muscles, glands and cardiac muscle.
- The events of varicosity are similar as in normal synaptic transmission.
- Drugs can act directly by inhibiting the re-uptake of NE or indirectly by NE exchange.

- NE uptake inhibitors cause an increase in the effects of NE because making it more available and long acting at the receptor site.
- **Cocaine** is used as a local anesthetics, while **phenoxybenzamine** is an α-antagonsist.
- Indirect acting sympathometic amines such as **ephedrine** have similar but weaker action to NE on receptors.
- They are taken up into the vesicle by exchange with NE, which in turn is released from the varicosity.
- Action in the CNS include increased alertness, and decreased appetite.

Peripheral mediators of the ANS

- These include
  - 5-Hyroxytrptamine (5-HT; Serotonin)
  - Purines
  - Peptides, &
  - Nitric Oxide
- Most of these mediators act both in the PNS and CNS to mediate transmission.

5-Hyroxytryptamine (5-HT; Serotonin)

- 5-HT is found in the GIT, Blood vessels and platelets, and in the CNS.
- In the CNS, it is found in the midbrain raphe and responsible for the regulation of appetite, sleep, vomitting and mood.
- In the PNS, it is responsible for the regulation of the microvascular control and influences pain sensation.
- In platelets, it plays a role in platelet aggregation and as inflammatory mediators.
- In the GIT, it influences gut motility

- 5-HT is synthesized from tryptophan and stored in granules like other neurotransmitters.
- 5-HT neurons have special re-uptake transporters which terminate its action.
- 5-HT neurotransmission is enhance by MAO inhibitors and this contributes to their antidepressant effects.
- 5-HT has seven types of receptors ($5\text{-}HT_{1\text{-}7}$) with activation that leads to various effects depending on the target organ and the mechanism of action either as ligand-gated ion channels of G-Protein coupling.
- 5-HT is responsible for the pathogenesis of Migraine.
- **Methysergide,** used to prevent migraine headaches, is a 5HT antagonist

Purines

- These include
  - Adenosine
  - ATP, &
  - ADP
- They interact with a wide range of tissues such as smooth muscles, cardiac muscles, and many cells such as mast cells, neurons, endothelial cells and platelets.
- ATP is stored in synaptic vesicles and either released as a neurotransmitter or a cotransmitter but ATP is not stored in the nerve endings.
- Adenosine is a neuromodulator rather than a neurotransmitter and plays a role as local hormone.

- Adenosine receptors are P_1 and ATP receptors are P_2.
- P_1 receptors act through G-Protein-coupled protein complex which either opens K^+ of Ca_2^+ channels depending on the subclass.
- **Methylxanthines** are adenosine receptor antagonists and the CNS stimulant action of caffeine is due to P_1 receptor activation.
- P2 recptors are ligand-gated ion channels and the ADP receptors are G-Protein couple activated by Protein kinase C and found mainly in platelets and plays a role in thrombosis.

Peptides

- These include
  - Angiotensin II
  - Bradykinin
  - Neuropeptide Y
  - Somatostatin
  - Cholecystokinin
  - Vasoactive Intestinal Peptide
  - Endothelins
  - Oxytocin
  - Vasopressin
  - Glucagon, &
  - Insulin

- They act as cotransmitters and interact with G-protein coupled receptors and via tyrosine kinase.
- They are poorly absorbed by oral administration and are quickly degraded by peptidases.
- Clinically peptides are used as replacement therapy where natural production is impaired, e.g. insulin, clotting factors, Growth hormone etc.
- Clinically, peptides antagonists are used against Hypertension, gut disorders, preterm labour, type II diabetes etc.

Nitric Oxide (NO)

- NO is produced in the body and has important roles as a mediator in the cardiovascular and nervous system and in the host defence again pathogens.
- NO is a transmitter in both the PNS and CNS, playing a role in appetide control and gastric emptying and in control of regional blood floor.
- NO protects against the proinflammatory mediators by inhibiting white blood cell activation and platelet aggregation, and by inducing vasodilation.
- It is synthesized by the oxidation of arginine resulting in three isoforms – endothelial, neuronal, & Inducible NO

- NO inhibits platelets adhesion and aggregation, monocyte adhesion and migration, and smooth muscle and fibroblast proliferation.
- NO binds to the hem moiety of the guanolyl cyclase and activates and enhances the synthesis of cGMP and inhibit cytochrome C and therefore regulate cellular respiration.
- NO is clinically used against lung disease
- Sildenafil (Viagra) is used to treat erectile dysfunction because it antagonized the effects of NO by breaking down cGMP.