UNIT-III

Autonomic Nervous System (ANS)

Autonomic Nervous System

ANS along with the endocrine system coordinates the regulation and integration of bodily function. ANS is concerned with regulation of visceral function. So it is otherwise called involuntary nervous system.

Neuron

Neuron is defined as the basic structural and functional unit of the nervous system.
Neuron is like any other cell in the body having nucleus and all the organelles in the cytoplasm.

However it is different from other cells by two ways:

1. **Neuron has branches or processes called axon and dendrites.**
2. **Neuron does not have centrosome, so it cannot undergo division.**

Classification Of Nerve Cells

On the basis of functions the nerve cells are classified into two types

1. **Motor Neuron (Efferent)**
2. **Sensory Neuron (Afferent)**

Motor Neuron (Efferent)

Neurons, which carry the motor impulses from central nervous system to the peripheral effectors organ like muscles, gland, and blood vessels. Motor neurons are also known as efferent nerve cells; generally these neurons have long axons and short dendrites.

Sensory Neuron (Afferent)

These neurons carry the sensory impulses from periphery to the CNS generally these have short axons and long dendrites.

Receptor

Pharmacology defines a receptor as any biological molecule to which a drug binds and produces a measurable response. Thus, enzymes and structural protein can be considered to be pharmacological receptors.

Neurotransmitters

Neurotransmitter is a chemical substance that acts as the mediator for the transmission of nerve impulse from one neuron to another neuron through a synapse.
Communication between nerve cells and between nerve cells and effector organs occurs through the release of specific chemical signals called neurotransmitters.

Local Mediators

Most cells in the body secrete chemicals that act locally. These chemical signals are rapidly destroyed or removed; therefore, they do not enter the blood and are not distributed throughout the body etc Histamine.

Hormones

Specialized endocrine cells secrete hormones into the bloodstream where they travel throughout the body exerting effects on broadly distributed target cells in the body.

Anatomy of ANS

Efferent Neurons

Efferent neurons carry nerve impulse from CNS to the effector organs by way of two types of efferent neurons.

The first nerve cell is called preganglionic neuron, its cell body is located within the CNS, and it emerges from brainstem or spinal cord, and makes a synaptic connection in ganglia. These ganglia function as relay station between preganglionic neuron and a second nerve cell called postganglionic neuron. Cell body of second neuron is originates from ganglion and terminates on effector organs such as smooth muscles of the viscera, cardiac muscle and the exocrine glands.

Afferent Neurons

Afferent neurons of ANS bring nerve impulse back to CNS from periphery

Sympathetic Neurons

The efferent ANS is divided into the sympathetic and parasympathetic nervous system, as well as the enteric NS.

Anatomically they originate in the CNS and emerge from two different spinal cord regions. The preganglionic neurons of the sympathetic system come from thoracic and lumber regions of the spinal cord. Preganglionic neurons are short in comparison to the postganglionic neurons. Axons of the postganglionic neurons extend from ganglia to the tissues that they innervate and regulate.

Parasympathetic Neurons

The parasympathetic preganglionic fibers arise from cranium (cranial nerve 3, 7, 9 and 10) and from sacral region of the spinal cord and synapse in ganglia near or on the effector organs. In contrast to the sympathetic system the preganglionic fibers are long and postganglionic ones are short, with the ganglia close to or within the organ innervated.

Enteric Neurons

The enteric nervous system (ENS) is the third division of the autonomic NS. It is a collection of nerve fibers that innervate the gastrointestinal tract (GIT), pancreas and gallbladder. This system functions independently of the CNS and controls the motility, exocrine and endocrine secretions and microcirculation of GIT.

Action of Sympathetic and Parasympathetic Nervous System on Effecter Organs

Organ	Sympathetic Action	Parasympathetic Action
Eye	Contraction of iris redial muscle (Pupil dilate) Relaxation of ciliary muscles	Contraction of iris sphincter muscle (Pupil contracts) Contraction of ciliary muscle (lens accommodates for near vision)
Heart	Increase rate Increase contractility	Decrease rate Decreased contractility
Blood Vessels (skeletal muscle)	Dilate	…
Blood Vessels (skin, mucous membrane)	Constriction	…
Kidney	Rennin secretion (β1 increase, α1 decrease)	…
Trachea & Bronchioles	Dilate	Constrict Increase secretions
Gastrointestinal	Contraction of sphincters Decrease in muscle motility and tone	Increased muscle motility and tone
Genitalia (male)	Stimulation ejaculation	Stimulates erection
Genitalia (female)	Relaxation of uterus	…
Salivary Gland	Thick, viscous secretion	Large watery secretion
Adrenal Medulla	Epinephrine & Nor-epinephrine secreted	…
Lacrimal Gland	…	Stimulates tears

Prototype Drugs of ANS

Prototype Drug Definition

A first or preliminary form of drug from which other forms of drugs are developed or copied is called prototype drug.

Drugs affecting the autonomic nervous system are divided into two groups according to the type of neuron involved in their mechanism of action.

Group#1

Cholinergic Drugs Or Parasympathetic Drugs

Group#2

Adrenergic Drugs Or Sympathetic Drugs

Now we will discuss cholinergic drug/parasympathetic drugs, these drugs are classified into…

1. **Colinergic agonist or parasympathetomimetic**
2. **Colinergic antagonist or parasympathetolytic**

Cholinergic Agonists

(Parasympathomimetics)

Here Is The List Of Prototype Cholinergic Agonists

Direct Acting
➔Acetylcholine

Indirect Acting (reversible)
➔Physostigmine

Indirect Acting (irreversible)
➔Echothiophate

Reactivation of Acetylcholine esterase
➔Pralidoxime

Available Brands in the Market
Contrathion inj. (Pralidoxime)

Acetylcholine (Direct Acting)

Acetylcholine is a quaternary ammonium compound that cannot penetrate membrane. It is neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia. It is rapidly inactivate by acetylcholinesterase. Duration of action of acetylcholine is small (a few milliseconds) hence it is not used in therapeutics. Acetylcholine has both muscarinic and nicotinic activities.

Action of Acetylcholine

- It has following major actions
- Decrease in heart rate and cardiac output
- Decrease in blood pressure
- Other actions

Decrease In Heart Rate And Cardiac Output
Acetylcholine mimics the effect of vagal stimulation; as a result decrease in heart rate and cardiac output.

Decrease In Blood Pressure
Injection of acetylcholine causes vasodilation and lowering the blood pressure

Others Actions

- In GIT, acetylcholine increases salivary secretion intestinal secretions and motility
- It enhances the secretions in bronchioles
- It stimulates erection
- In eye, it causes contraction of iris sphincter muscle (pupil contraction), which is called miosis
- It causes contraction of ciliary muscle (lens accommodates for near vision)

Therapeutic Actions Of Acetylcholine

Acetylcholine (1% solution) is instilled into the eye to produce miosis during ophthalmic surgery.

Adverse Effects Of Cholinergic Drugs

Diarrhea, Miosis, Nausea, Urinary urgency, Bradycardia, Bronchoconstriction, AV block, Flushing, Salivation

Physostigmine (Indirect Acting, Reversible)

It is a natural alkaloid obtained from the plant physostigmine venenosum. It is a tertiary amine. It is absorbed from GIT. It can cross blood brain barrier. It stimulates CNS.

Mechanism Of Action

Physostigmine reversibly block acetylcholine esterase enzyme and prevent its breakdown. This action enhances the acetylcholine response by activating the postsynaptic receptors.

Action Of Physostigmine

Physostigmine has a wide range of effects. It acts on muscarinic and nicotinic receptors as well as on neuromuscular junction.
Its duration of action is about 2 to 4 hours. It can cross blood brain barrier and stimulate CNS.

Therapeutic Uses

- This drug increases intestinal and bladder motility
- It is used for treatment of glaucoma
- It produces miosis and spasm
- Physostigmine is also used in the treatment of overdose of drugs with anticholinergic actions

Adverse Effects Of Physostigmine

When high doses are used fall in cardiac output may occur. The cause of death in physostigmine poisoning is respiratory failure.

Echothiophate (Indirect Acting, irreversible)

A number of synthetic organophosphate compounds (organo-phosphorus compound) have the capacity to bind covalently to acetylcholinesterase. This result is a long lasting increase in acetylcholine at all sites where it is released.

Mechanism Of Action

Echothiophate is an organophosphate that covalently binds with acetylcholinesterase. After binding this enzyme permanently inactivated. Restoration of acetylcholinesterase activity requires the synthesis of new enzyme molecules.

Action Of Echothiophate

As acetylcholine released, it does not destroyed due to inactivation of acetylcholinesterase. Acetylcholine gets accumulated in the body to exert both muscarinic and nicotinic actions. Due to muscarinic action there will be miosis, salivation, sweating, bradycardia vasodilation and fall in blood pressure. Due to nicotinic actions there are muscle twitching in the whole body. Due to central effect there is restlessness confusion.

Therapeutic Uses

An ophthalmic solution of the drug is used directly in the eye for the chronic treatment of open angle glaucoma.

Cholinergic Antagonists

(Parasympatholytic Drugs)

Anti Muscarinic Agent
➔Atropine

Ganglionic Blockers
➔Mecamylamine

Neuromuscular Blockers
➔Succinylchoine
➔Tubocurarine

Available Brands in the Market

Atropa Drops (Atropine)
S-Cholin inj. (Succinylchoine)

Atropine (Anti Muscarinic Agent)

Mechanism Of Action

Atropine is a tertiary amine belladonna alkaloid. It has high affinity for muscarinic receptors, where it binds competitively, and preventing acetylcholine from binding to those sites. Atropine acts both centrally and peripherally. Its duration of action is about 4 hours except when placed topically in eye, where the action may last for days.

Action Of Atropine

Eye
Atropine dilate the pupil of eye (mydriasis) in patients with narrow angle glaucoma, intraocular pressure may rise dangerously.

GIT
Atropine can be used as an antispasmodic to reduce activity of the GIT.

Salivary Glands
Producing a dry effect, swallowing and talking become difficult.

Respiratory Tract
Atropine reduces secretions of the respiratory tract.

Cardiovascular System
At low doses it decrease cardiac rate (bradycardia). With high doses, cardiac rate increases.

Sweat Glands
Atropine inhibits activity of sweat glands. The skin becomes hot and dry.

Therapeutic Uses

Opthalmic: Atropine is used topically for examination of retina and optic disc for accurate measurement of refractive errors. It is used as mydriasis.

Antispasmodic
Atropine is used as an antispasmodic agent to relax the GIT and bladder.

Antisecretory
Atropine is used as an antisecretory agent to block secretions in the upper and lower respiratory tract and salivary secretions before the surgery.

Motion Sickness
Atropine is an effective prophylactic agent for motion sickness during short journey (4 to 6 hours).

Antidote For Cholinergic Agonists
Atropine is used for the treatment of overdoses of acetylcholinesterase inhibitors, insecticides and some types of mushroom poisoning.

Pharmacokinetics Of Atropine
Atropine is absorbed rapidly from the GIT. Partially metabolized by the liver and eliminated primarily in the urine, it has a half-life of about 4 hours.

Adverse Effects
Depending on the dose atropine may cause dry mouth, blurred vision, constipation, increase in temperature, effect on the CNS include restlessness, confusion.

Mecamylamine (Ganglionic Blockers)

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. These drugs block the entire output of the ANS at the nicotinic receptor. Ganglionic blockers rarely used therapeutically. However they often serve as tools in experimental pharmacology.

Mechanism Of Action
Mecamylamine produces a competitive nicotinic blockade of the ganglia.

Pharmacokinetics
The duration of action is about 10 hours after a single administration. It has good oral absorption.

Therapeutic Actions
It is primarily used to lower blood pressure in emergency situations.

Neuromuscular Blockers

These drugs blocks acetylcholine at neuromuscular junctions. These neuromuscular blockers are structural analogs of acetylcholine. These drugs are clinically useful during surgery for producing complete muscle relaxation.

Tubocurarine (Non-Depolarizing (Competitive) Blockers)

Mechanism Of Action
Non-depolarizing neuromuscular blocking drugs interact with the nicotinic receptors to prevent the binding of acetylcholine. These drugs thus prevent depolarizing of the muscles and inhibit muscular contraction. Because these agents compete with acetylcholine at the receptor that's why also called competitive blockers.

Therapeutic Uses
These blockers are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscle. These agents are also used to facilitate intubations as well as during orthopedic surgery.

Pharmacokinetics
All neuromuscular blocking agents are injected intravenously. They penetrate membrane very poorly and do not enter cells or cross the blood brain barrier, many drugs are not metabolized. They excreted in urine unchanged.

Succinylcholine (Depolarizing Agents)

Mechanism Of Action
The depolarizing neuromuscular blocking drug succinylcholine attaches to the nicotinic receptor and act like acetylcholine. This drug remains attached to the receptor for longer time and providing a constant stimulation of the receptor.

Action
Succinylcholine initially produces short lasting twitching of the muscle (fasciculation) followed within a few minutes by paralysis. The drug does not produce a ganglionic block except at high doses.

Therapeutic Uses
Because of its rapid onset and short duration of action, succinylcholine is useful when rapid endotracheal intubation is required during the anesthesia. For example if aspiration of gastric contents is to be avoided during intubations.

Pharmacokinetics
Succinylcholine is injected intravenously its duration of action is short therefore usually given by continuous infusion.

Adverse Effects
Hyperthermia, Hyperkalemia

Adrenergic Agonists
(Sympathomimetics)

The adrenergic drugs affect receptors that are stimulated by norepinephrine or epinephrine. Some adrenergic drugs act directly on the adrenergic receptors (adrenoceptor) by activating it and said to be sympathomimetics.

Sympathomimetic drugs stimulate postganglionic sympathetic adrenergic nerves. Adrenergic agonists may act directly on adrenergic receptors or indirectly through release of norepinephrine or may have mixed action (act directly and indirectly)

Direct Acting Agonists
➔Epinephrine

Indirect Acting Agonists
➔Amphetamine

Mixed Action Agonists
➔Ephedrine

Available Brands in the Market

Adrenaline Injection (Epinephrine)
Efedra Tab. (Ephedrine)

Epinephrine Or Adrenaline (Direct Acting Agonists)

Epinephrine or other direct acting agonists have direct action on tissues supplied by postganglionic sympathetic nerve ending. They interact with receptor sites on the cell

membranes. The drugs are effective even when the sympathetic nerves have been cut or inhibited by other drugs.

Adrenaline/epinephrine is produced in the body by the adrenal medulla and released along with small amount of norepinephrine into the blood stream.

Epinephrine interacts with both alpha and beta-receptors. At low doses, it act on beta-receptors (vasodilatation), and at high doses it act on alpha-receptors (vasoconstriction).

Pharmacological Actions

CVS
Epinephrine is a powerful cardiac stimulant (B1 receptor). Force of myocardial contraction increased, also increased in heart rate.

Respiratory Tract
Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (B2 receptor).

Blood Vessels
Epinephrine causes powerful vasodilatation in skeletal muscles and coronary vessels (B2 receptor).

GIT
Smooth muscles of GIT are generally relaxed by epinephrine and contract the sphincter muscle.

Therapeutic Uses

Bronchospasm (Bronchial Asthma)
Epinephrine is the primary drug used in the emergency treatment of any condition of the respiratory tract. Improved respiratory exchange observed within few minutes after subcutaneous administration of epinephrine.

Glaucoma
2% epinephrine solution may be used topically to reduce intraocular pressure in open angle glaucoma.

Cardiac Arrest
Epinephrine may be used in patient. Intra cardiac injection may be used in case of cardiac arrest due to anesthetic, electric shock.

Anesthetic
Local anesthetic solution usually contains 1:100000 part epinephrine. The effect of the drug is to greatly increase the duration of the local anesthesia. It does this by producing vasoconstriction at the site of injection.

Pharmacokinetics Of Epinephrine

Epinephrine is ineffective when given orally because it rapidly destroyed in GIT.
It is administered subcutaneously or intra muscularly.
It is not given intravenously as it is highly dangerous. It may be applied topically to produce vasoconstriction and stop oozing of blood.

Adverse Effects
CNS disturbance, Hemorrhage, Cardiac arrhythmias, pulmonary edema

Amphetamine (Indirect Acting)

Amphetamine is a non-catecholaminergic sympathetic amine that shows quite similar effects as cocaine.

Mechanism Of Action
Amphetamine has indirect action on the CNS and peripheral nervous system. Effects on CNS and peripheral nervous system depend upon the level of catecholamine neurotransmitters in synaptic space. Amphetamine shows their effect on CNS and peripheral nervous system by releasing intra cellular stores of catecholamine. Amphetamine also inhibits monoamine oxidase (MAO) that's why high levels of catecholamine are readily released into synaptic spaces and response increased.

Pharmacological Action Of Amphetamine
Amphetamine has more powerful effects on the CNS but less affects at all other sites. It has both alpha and beta effects and are largely indirectly.
Amphetamine increases both systolic and diastolic blood pressure. Large doses produce cardiac arrhythamias. It produces mydriasis.

Therapeutic Uses
Therapeutic uses of Amphetamine are limited due to psychological and physiological dependence and the development of tolerance.

Attention deficit hyperactivity disorder (ADHD)
Some young children are lack the ability to be involved in any one activity for longer than few minutes. Amphetamine and their derivatives are able to improve attention. The drug prolongs the patient's span of attention.

Narcolepsy
Narcolepsy is a rare sleep disorder. Patient is usually treated with drugs such as amphetamine.

Pharmacokinetics
Amphetamine is completely absorbed from the GIT, metabolized by the liver and excreted in the urine.

Adverse Effects
Undesirable side effects of amphetamine include insomnia, irritability, weakness, dizziness, and tremor. Amphetamine can also causes confusion suicidal tendencies especially in mentally ill patients.
Amphetamine causes cardiac arrhythmias, hypertension, angina pain, headache, excessive sweating, nausea, and diarrhea.

Adrenergic Antagonists

(Sympatholytic Agents/Drugs)

A large number of drugs inhibit the activity of the sympathetic nervous system. These drugs are called adrenergic antagonists or sympatholytics.
These adrenergic blocking drugs may be classified into groups based on their site of action.

Adrenergic Blockers Prototype Drugs

Alpha-Blocker
➔Prazosin

Beta-Blocker
➔Propranolol

Drugs Affecting Neurotransmitter Uptake Or Release
➔Reserpine

Available Brands in the Market

Minipress Tab. (Prazosin)
Inderal Tab. (Propranolol)
Betanol Tab. (Propranolol)
Reserpine Tab. (Reserpine)

Prazosin (Alpha-Blockers)

Prazosin is selective competitive blocker of α1 receptor. This drug is useful in the treatment of hypertension.

Pharmacological Actions

Prazosin decreases peripheral vascular resistance and lower arterial blood pressure by causing the relaxation of both arterial and venous smooth muscle. They prevent the response of effector organs to adrenaline, nor adrenaline. It also causes miosis in eye.

Therapeutic Uses

Hypertension
Usefulness of prazosin in hypertension is due to its lack of potency in inhibiting α 2 receptors. The first doses of these blockers may cause hypotensive response that can result fainting. This action termed a first-dose effect. It may be minimize by adjusting the first dose to one-third or one-fourth of the normal dose.

Adverse effect

α 1 blockers may cause dizziness, lack of energy, nasal congestion, headache, orthostatic, hypotension.

Propranolol (Non-Selective Beta Antagonists Or Beta-Blockers)

All the clinically available β-Blockers are competitive antagonists. Non-selective β-Blocker acts at both β 1 and β 2 receptors.
B-Blockers are useful in hypertension angina, cardiac arrhythmias, congestive heart failure and glaucoma. The names of all β -Blockers ends in 'olol' except for labetalol and carvedilol.

Propranolol is the prototype β -adrenergic antagonists block both β 1 and β 2 receptors. Sustained release preparation for once a day dosing is available.

Pharmacological Actions

Cardiovascular
Propranolol decreases the force of myocardial contraction. Cardiac output, work, and oxygen consumption are decreased. It is used in the treatment of angina and heart failure.

Respiratory Tract
Propranolol acts on B receptors and causes broncho-constriction.

Eye
Propranolol reduces intraocular pressure especially in glaucoma.

Increased Na+ Retention
Due to the decrease in blood pressure there is decrease in renal perfusion, resulting in an increase in Na+ retention and plasma volume.

Disturbance In Glucose Metabolism
B-Blocker leads to decreased glucose secretion. Therefore if type-I diabetic is to be given Propranolol very careful monitoring of blood glucose is essential.

Therapeutic Uses

Hypertension
Propranolol lowers blood pressure in hypertension. Decreased cardiac output is the primary mechanism.

Glaucoma
B-Blocker particularly topically applied and effective in diminishing intraocular pressure in glaucoma.

Migraine
Propranolol is also effective in reducing migraine episodes when used prophylactically.

Treatment Of Angina
Propranolol decreases the oxygen requirement of heart muscle and therefore is effective in reducing the pain.

Adverse Effects
Broncho-constriction, disturbance in metabolism, sexual impairment

Reserpine (Drugs Affecting Neurotransmitter Release Or Uptake)

Mechanism Of Action
Reserpine blocks the Mg^{2+} ATP-dependent transport of biogenic amine, norepinephrine, dopamine and serotonin from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissues.

Therapeutic Uses
Reserpine is used in the treatment of hypertension mild to moderate. Reserpine causes a slowly developing falling blood pressure.