INTRODUCTION TO CENTRAL NERVOUS SYSTEM PHARMACOLOGY

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INTRODUCTION

- The nervous system consists of the central nervous system (CNS) and the peripheral nervous system (PNS)

- The CNS consists of the brain and the spinal cord

- The PNS consists of;

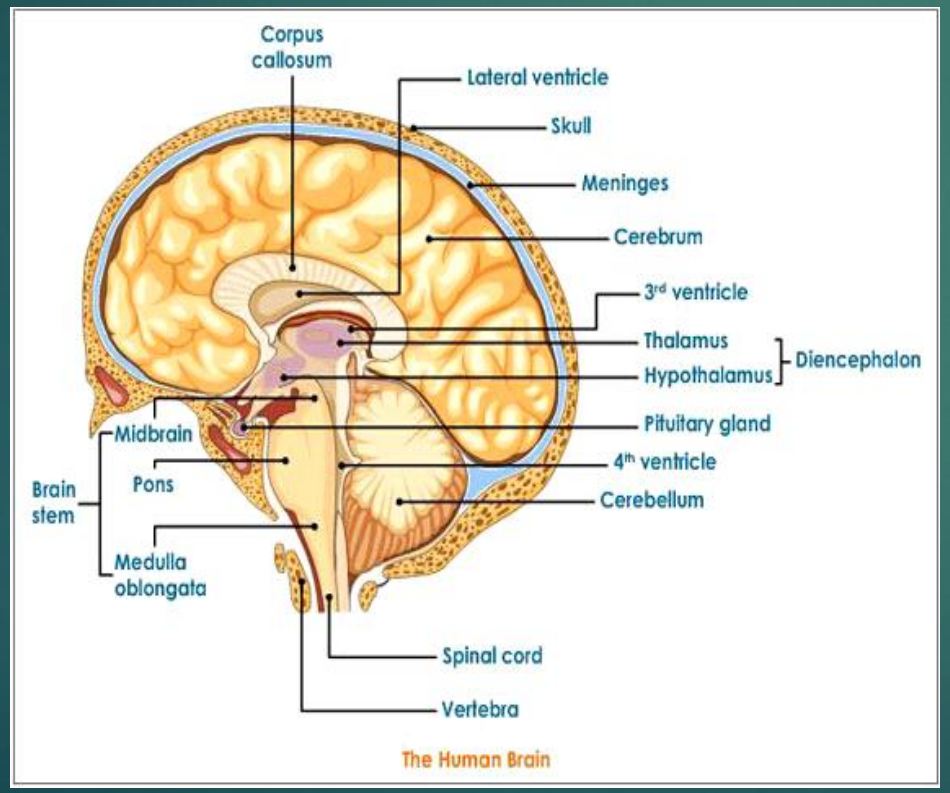
i. Autonomic nervous system
ii. Somatic nervous system

NB: The activities of the PNS are controlled by the CNS

The CNS

Consists:

- ***Brain***
- ***Spinal Cord***



Regulation or control of the PNS by the CNS

- The autonomic nervous system is regulated by the brain stem centers responsible for cardiovascular, respiratory and other visceral functions

- The somatic nervous system is activated by the corticospinal tracts originating from the cerebral motor cortex and the spinal reflexes

Effects of drugs on the CNS and PNS

- Drugs alter nervous system function by primarily affecting neurotransmitters and or their receptors
- In other instances, drugs alter the synthesis, storage, release, inactivation or neuronal reuptake of neurotransmitters
- Some drugs activate or block neurotransmitters
- Most drugs are relatively selective for a particular neurotransmitter or receptor
- The effects produced by the drug partly depend on the distribution of neurotransmitter in the central and peripheral nervous system

Location of the effect of drugs

- The effects of some drugs are localized to either the CNS or to the PNS

- Some drugs however affect both the CNS and PNS e.g. cocaine, amphetamine

THE PERIPHERAL NERVOUS SYSTEM

- The autonomic nervous system involuntarily modifies the activity of smooth muscles, exocrine glands, cardiac tissues and certain metabolic activities

- The somatic nervous system activates the skeletal muscle contraction and thereby, enabling voluntary body movements

AUTONOMIC NERVOUS SYSTEM

- This consists of the **sympathetic** and the **parasympathetic** divisions
- The sympathetic nervous system involves the nerves which arise from the thoracic and lumbar spinal cord
- The nerves in the sympathetic have a short preganglionic fibres and a long post ganglionic fibres
- The parasympathetic system includes portions of cranial nerves III, VII, IX and X (oculomotor, facial, glossopharyngeal and the vagus nerves respectively
- In the parasympathetic nervous system, the nerves have long preganglionic fibres and short post ganglionic fibres

Synoptic comparison of the sympathetic and the parasympathetic systems

- The sympathetic and the parasympathetic nervous systems often have opposing effects on the organ function

The sympathetic system

- Activation of the sympathetic system produces the **"Fight or Flight"** reaction in response to threatening situations
- This reaction leads to stimulation of the cardiovascular system which provides oxygen and fuels required to carry out vigorous activity while glycogenolysis and lipolysis activation releases the energy
- The sympathetic system tends to discharge as a unit thereby, producing a diffuse activation of the targeted organs
- The sympathetic system is well placed for its role because of its preganglionic, sympathetic neurons synapse with a large number of post ganglionic neurons
- The release of epinephrine and norepinephrine from adrenal medulla into circulation enables the activation of target tissues through out the body including those not innervated by the sympathetic nerves

The parasympathetic systems

- The parasympathetic system is also referred to as the **"Rest or Digest"** system as it slows heart rate while promoting vegetative functions like digestion, defecation and micturition

- Many parasympathetic effect such as pupil constriction, broncho-constriction and stimulation of the gut and the bladder are caused by smooth muscle contraction

- In contrast to the sympathetic system, the parasympathetic system can discretely activate specific target tissues e.g. it is very possible for the parasympathetic system to slow down the heart rate without simultaneously stimulating the gastrointestinal or bladder function

- This is partly because of the low ratio of postganglionic fibres to preganglionic fibres in the parasympathetic system

Receptors in the peripheral nervous system

- All parasympathetic effects are mediated by muscarinic receptors (M)
- Sympathetic effects are mediated by α-adrenoceptors (α), β-adrenoceptors (β) or muscarinic receptors (M)

Enteric nervous system (ENS)

- The ENS is also referred to as the **third arm** of the autonomic nervous system
- It consists of the network of autonomic nerves located in the gut wall responsible for regulation of GIT motility and secretions
- The ENS is innervated by the sympathetic and the parasympathetic nervous systems
- The parasympathetic stimulation activates the ENS while the sympathetic stimulation inhibits the ENS
- Through its afferent and efferent fibres, the ENS integrate the autonomic input with localized reflexes to synchronise propulsive contraction of the gut called peristalsis

SOMATIC NERVOUS SYSTEM

- The somatic nervous system consists of the motor neurons to the skeletal muscles

- These neurons have a single nerve fibre that releases acetylcholine at the neuromuscular junction

Parasympathetic and sympathetic effects on specific organs or systems

Parasympatic effects		Sympathetic effects
Organ/ system		
Eye, nostril, mouth	Miosis (Pupil constriction – M_3, M_2)	Mydriasis (Pupil dilatation - α_1)
	Accomodation (M_3, M_2)	Vasocontriction within the eye (α_1)
	Lacrimation (M_3, M_2)	Vasoconstriction (Nostrils - α_1)
	Mucus secretion (nostril - M_3, M_2)	Vasoconstrition (below skin - α_1)
	Salivation (M_3, M_2)	Salivation (α_1)
Skin		Sweating (M_3, M_2)
Airway	Bronchoconstriction ($M_2 = M_3$)	Bronchodilation (β_2)
	Mucus secretion (M_3, M_2)	

Parasympathetic and sympathetic effects on specific organs or systems

Parasympathetic effects		Sympathetic effects
Organ/ system		
Heart	↓ Heart rate (M_2)	↑ Heart rate (β_1))
	↓ Atrioventricular conduction (M_2)	↑ Atrioventricular conduction (β_1))
		↑ Contractility (β_1)
GIT	↑ Hydrochloric acid secretion (M_3, M_2)	Glycogenolysis (β_2)
	↑ Motility (M_3, M_2)	↓ Motility (α and β)
Kidney		Renin secretion (β_1)
Airway	Bronchoconstriction ($M_2 = M_3$)	Bronchodilation (β_2)
Bladder	Micturition (M_3)	Urinary retention (α_1)
Reprod uction		Female (Uterine relaxation - β_2)
	Male (Erection - M_3)	Male (Ejaculation - α_1)

Neurotransmitters

- The primary neurotransmitters found in the autonomic nervous system is acetylcholine while the primary neurotransmitter in the somatic nervous system is norepinephrine (Noradrenaline)
- The terms adrenergic and cholinergic refer to neurons that release norepinephrine and acetylcholine respectively
- Acetylcholine is the transmitter at all autonomic ganglia, parasympathetic neuro effector junctions and somatic neuromuscular junctions
- Ach is also the transmitter at few sympathetic neuro effector junctions including nerves in sweat glands and vasodilator fibres in skeletal muscle
- The presence of Ach in several types of autonomic and somatic synapses contribute to the lack of specificity of drugs acting on Ach transmission

Neurotransmitters Cont'd

- Norepinephrine is the primary neurotransmitter at most sympathetic postganglionic neuro effector junctions
- However, epinephrine (adrenaline) is the principal catecholamine released from the adrenal medulla in response to activation of the sympathetic nervous system
- Other neurotransmitters have been identified in autonomic nerves of the ENS of the GIT as well as the genitourinary tract and certain blood vessels
- The transmitters released by these neurons include neuro peptide Y, vasoactive intestinal polypeptide, encephalin, substance P, serotonin, ATP and nitric oxide

Receptors for acetylcholine

- Acetyl choline receptors are divided into two depending on their reaction to two plants alkaloids i.e. muscarine and nicotine
- Muscarinic (M) receptors are activated by muscarine and are primarily located at parasympathetic neuro effector junction
- Nicotinic receptors are activated by nicotine and are found in all autonomic ganglia, somatic neuromuscular junction and in the brain

Subdivisions of muscarinic receptors and general effects of cholinergic receptor stimulation

- Muscarinic receptors are subdivided based on molecular and pharmacological criteria
- Activation of M_3 receptors produces smooth muscle contraction(except sphincters) and grand secretion
- Activation of M_2 mediates cardiac slowing while M_1 is particularly concerned with neurotransmission at central and peripheral sites
- Activation of the nicotinic receptors in the autonomic ganglia excites neurotransmission while activation of these receptors in skeletal muscle causes muscle contraction

Receptors for norepinephrine and epinephrine

- The receptors for norepinephrine and epinephrine at sympathetic neuro effector junction are called adrenoceptors, a name derived from adrenaline, the other name for epinephrine

- The two adrenoceptors are α and β receptors with their subtypes

- These two types of receptors can be activated or blocked by drugs called adrenoceptor agonists and adrenoceptor antagonist respectively
- The α_1 adrenoceptors mediate smooth muscle contraction while the β_2 adrenoceptors mediate smooth muscle relaxation

- Stimulation of β_1 adrenoceptors produces cardiac stimulation

Synthesis and metabolism of acetylcholine

Choline

+ Acetate ↓ Acetyltransferase

Acetylcholine (Ach) – stored in the seminal vessicle

↓ Calcium mediated exocytosis in response to nerve stimulation

Acetyl choline is released

- The enzyme acetylcholinesterase hydrolyzes acetylcholine to form choline and acetate
- Choline is recycled through the process of reuptake by the presynaptic neuron

Drugs affecting cholinergic neurotransmission

1. **Black widow spider vernom –** containing **α - latrotoxin**

- Stimulates vesicular release of acetylcholine thereby producing excessive activation of acetylcholine receptors
- A black widow bite may cause muscle contraction and pain with the abdominal muscle being affected
- Salivation, sweating, lacrimation and changes in heart rate and blood pressure can occur but are uncommon and death is rare
- Administration of an analgesic and an anti-inflamatory may be the only treatment required

2. **Botulinum toxin A** – produced by ***Clostridium botulinum***

- Blocks the exocytotic release of acetylcholine and inhibits neurotransmission
- Botulinum is being used for a number of medical and cosmetic conditions
- It is used to treat localized muscle spasms of the eyes, face and hands and in treatment of tremors, dystonia, excessive salivation and other symptoms of parkinsonism disease, achieving all this by effecting relaxation
- Injection of the preparation of this toxin called BOTOX is used in the reduction of facial wrinkles for cosmetic purposes
- Botulinum is also used in the treatment of excessive sweat (Hyperhidrosis) of the palms or soles, also irrigation of the bladder which provides long lasting relief of bladder spasm
- Common side effects are dry mouth and dysphagia

3. Agonists of the cholinergic receptors

- After acetylcholine is released, it can activate post synaptic muscarinic or nicotinic receptors
- Drugs such as Pilocarpine mimic the effects of acetylcholine at these receptors and they are called direct acting acetylcholine receptor agonists
- Another group of drugs, the cholinesterase inhibitors like neostigmine prevent the breakdown of acetylcholine thus leading to increase in its concentration and the activation of acetylcholine receptors
- These are called indirect acting acetylcholine receptor agonists

4. Antagonists of the cholinergic receptors

- Acetylcholine receptor antagonists drugs inhibit cholinergic neurotransmission
- This includes muscarinic receptors antagonists such as atropine
- Others are nicotinic receptor antagonists such as atracurium that act on the neuromuscular junction and are called neuromuscular blocking agents

Sympathetic neurotransmission – norepinephrine synthesis

Tyrosine

↓

Dopa

↓ Dopa decaboxylase

Dopamine

↓ Dopamine β hydroxylase

Norepinephrine

↓ Calcium mediated exocytosis in response to nerve stimulation

Norepinephrine is released into the synapse

- Neuronal reuptake takes place with the help of catecholamine transport

- The enzymes cathechol- O-methyltransferase (COMT) and monoamine oxidase (MAO) have the role of inactivating norepinephrine that is not taken by presynaptic neurons

Drugs affecting Adrenergic Neurotransmission

1. Metyrosine

- This is the competitive inhibitor of tyrosine and hence it inhibits the synthesis of epinephrine and norepinephrine in persons with phaechromocytoma, an adrenal medulla tumor which secrets excess of these catecholamines resulting in severe hypertension

2. Adrenoceptor antagonists

- These are the most clinically important drugs used to reduce excessive sympathetic stimulation of various organs

- Examples are phentolamine which selectively inhibits α_1 adrenoceptors, propranolol which selectively blocks β – adrenoceptors and labetalol which blocks both receptor types

Adrenoceptor agonists and antagonists

- Drugs that bind and activate the α or β – adrenoceptors are known as direct acting adrenoceptors agonists e.g. albuterol (salbutamol), dobutamine, epinephrine

- Cocaine and amphetamine increase the concentration of epinephrine by inhibiting its reuptake and additionally, their vasoconstrictive effect further enhances the accumulation of epinephrine in the localized area and these are called indirect acting adrenoceptor agonists

- Another group of drugs act by inhibiting the break down of norepinephrine by COMT and MAO and these drugs exert their effects on the CNS

Modulation of the Baroreceptor reflex

- Apart from the primary pharmacological effects, a number of adrenoceptor agonists and antagonists modulate the baroreceptor reflex
- When a drug or a physiological action increases blood pressure, this activates the mechanoreceptors (receptors) located in the aortic arch and the carotid sinus at the bifurcation of the carotid artery
- This initiates the impulses that travel to the brain stem via the afferent nerves
- The stimulation of the vagal motor nucleus leads to vagal (parasympathetic) outflow thus leading to decrease in heart rate and a decrease in the sympathetic nerve outflow
- This effect on the heart is called reflex bradycardia

Modulation of Baroreceptor reflex Cont'd

- If a drug lowers the blood pressure sufficiently, it may reduce the baroreceptor tone
- This produce an acceleration of the heart rate and activation of sympathetic vasoconstriction
- This is referred to as reflex tachycardia

END