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Neuropharmacology

Nervous system is divided into two anatomical parts:

1. **The central nervous system (CNS)** which is composed of brain and spinal cord.
2. **The peripheral nervous system (PNS)** which includes neurons located outside the brain and the spinal cord. PNS s subdivided to:-

- The efferent division: includes the neurons which carry the signals away from the brain and the spinal cord to the peripheral tissues. This division also divided into:

A- **The somatic efferent neurons**: they are involved in the voluntary control function such as contraction of skeletal muscles.

B- **The autonomic efferent neurons** (Autonomic nervous system ANS): they regulate the daily involuntary needs and the requirements of the vital body functions without the conscious participation of mind.

- The afferent division: includes the neurons which bring the information from periphery to the CNS.

Autonomic nervous system

The autonomic nervous system consists of two large divisions:

 Parasympathetic (craniosacral) outflow, which include the motor roots of the{occulomtor (III), facial (VII), glossopharyngeal (IX) and vagus (X)}; cranial nerves and the 2^{nd}, 3^{rd}, and 4^{th}.

 Sympathetic (thoracolumbar) outflow, which include the motor roots of 1-12thoracic, 1-5 lumber and 1 sacral nerves.

According to the Neurotransmitters (endogenous chemical substances which transmit the impulses through the nerve) we can classify the efferent nerve fibers to:

1. **Cholinergic N.:** include the somatic and parasympathetic nerves
2. **Adrenergic N.:** include the sympathetic nerves.

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- Functions of ANS are attributed to presence of specific receptors on affected cells or tissues which either classified to:

1- Cholinoceptors.

2- Adrenoceptors.

Tissues which contain these receptors and sensitive to Acetylecholine (Ach) are called cholinoceptive, while nerves that are sensitive to the Noradrenaline (NA) are called adrenoceptive.

The Parasympathetic Nervous System

The Parasympathetic Nervous System is a part of the autonomic nervous system; it helps in conserving of body energy and is partly responsible for activities such as slowing of the heart rate, food digestion processes, and elimination of body waste.

The Parasympathetic Nervous System has two neurohormones (neurotransmitters):

Acetylcholine (ACh) and acetylcholinesterase (AChE).

ACh is a neurotransmitter responsible for the transmission of nerve impulses to effector cells of the parasympathetic nervous system. ACh plays an important role in the transmission of nerve impulses at synapses and myoneural junctions. ACh is quickly destroyed by the enzyme AChE, thereby allowing the nerve impulse to pass, but not remain in an excited state Acetylcholine acts on two types of receptors:-

1. **Muscarinic receptors**: On which the pharmacological effect of acetylcholine is seems to those of the alkaloid "Muscarine" e.g. stimulation of secretion of exocrine glands like salivary and lachrymal glands, contract plain muscle, slow and weaken heartbeat, dilate arterioles.

2. **Nicotinic receptors**: which the pharmacological effect of acetylcholine is seems to those of the alkaloid "Nicotine" these cholinoceptives are exist in the neurons of sympathetic and parasympathetic ganglia, motor end palate of voluntary muscles and adrenal medulla.

Parasympathomimetic (Cholinergic agonists)

Drugs with Ach like activity and its divided to two types:

I- Direct acting: this type of the drugs is mimic to the effect of the Ach by binding directly to the cholinoceptors this group includes:

Acetylcholine: is a quaternary amine compound that cannot penetrate the membranes therapeutically it has no benefits due to its unspecified action and its sensitivity to hydrolyzed by the AchE.

- Ach has both muscarinic and nicotinic activity.
- It decreases the cardiac output and the heart rate due to its mimic effect on the Ach on the vagal stimulation.
- Its decrease blood pressure although no innervation of the vasculature by the parasympathetic system, there are cholinoceptors on the blood vessels that respond to cause vasodilatation.
- GIT: Ach increase salivary secretion and stimulate intestinal secretion and motility, bronchiolar secretions also are enhanced.
- Genitourinary tract: the tone of the (detrusor urinae) muscle will increase
- The eye: Ach stimulates ciliary muscle contraction for near vision also cause miosis (marked constriction of the pupil).

Pilocarpine: it's a tertiary amine alkaloid and its stable to hydrolysis of by AchE, pilocarpine exhibit the muscarinic receptor and its used primarily in ophthalmology.

Carbachol: its carbamylcholine has strong nicotinic and weak muscarnic activates, asingle administration can last as long as one hour. Therapeutically it used only as miotic agent and in cases of glaucoma.

II- Indirect acting: this group of cholinomimitc drugs has no direct effect on the cholinoceptors and its effect is represented by inhibition of AchE and this effect lead to increase the level of Ach. This group is divided to two subtypes those are:

- Reversible anticholinestrase: this group will inhibit AchE but reversibly and it include:

Physostigmine (Eserine): physostigmine is an alkaloid (a nitrogenous compound
found in the plant) and a tertiary amine which reversibly inhibits AchE and the result is potentiation of cholinergic activity throughout the body.

Physostigmine has a wide range of effects as a result its action and its effect is extend to the nicotinic receptor of the neuromuscular junction in addition to its effects on the muscarinic and nicotinic sites of the ANS its duration of action is about 2 - 4 hrs.
physostigmine can enter and stimulate cholinergic sites of the CNS.

Therapeutic uses of Physostigmine

1- Physostigmine increases the intestinal and urinary bladder motility which serveas its therapeutic action in atony of each organ.

2- In the eye physostigmine produce miosis as well as lowering of the intraocular Pressure so that it's used to treat glaucoma but pilocarpine is more effective.

3- Physostigmine is also used in treatment of overdoses of drugs with anticholinergic effects like atropine.

Adverse effects:

1- physostigmine can cause convulsions with high doses.
2- Bradycardia and fall in cardiac output.
3- Paralysis of skeletal muscle due to accumulation of Ach.

- **Neostigmine** (Prostigmine) synthetic analogue of physostigmine but cannot pass to the CNS (quaternary amine)

Pyridostigmine (Mestinone) its similar to neostigmine but with longer duration of Edrophonium (Tensilon) rapid effect with short duration of action.)

- **Irreversible anticholinestrase**: this group will inhibit AchE irreversibly and this type of chemicals are non-specific AchE inhibitors, leading to increase all sites were its released almost of these chemicals are extremely toxic and used as chemical warfare agents like (Tupan, Sarine) some of these chemicals are used as pesticides or insecticides like diazenone and chloridine while a little types of these chemicals are used as medicines specially in ophthalmologic purpose like Echothiophate and Isoflurophate.

Parasympatholytic or Anticholinergic (Blockers):

This class of drugs is bind to the cholinoceptors but they do not trigger the usual receptor mediated intracellular effect and the effect distributed among muscarinic blocking agent or nicotinic (Neuromuscular blocking agents) or dual effect on the ganglia of sympathetic and parasympathetic systems.

I-Antimuscarinic agents: these agents block muscarinic receptors causing inhibition of all muscarinic functions. Antimuscarinic agents are beneficial in a variety of clinical cases because they are don't close nicotinic receptors. Also antimuscarinic have little or no action on skeletal neuromuscular junctions or autonomic ganglia.

Atropine: an alkaloid derived from *Atropa belladonna* this plant contain two alkaloids those are L- hyoscine and L- hyocyamine (Atropine) where it:

1- binding competitively preventing Ach from binding to these sites.

2- atropine acts both centrally and peripherally.

3- Its general action last about 4 hrs. except when placed topically in the eye where the action may last for days.

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Actions and therapeutic uses of atropine:

- Ophthalmic: in the eye topical atropine exerts the mydriatic effect (Mydriasis: marked dilatation of the pupil). Atropine is contraindicated in glaucoma patients.
- Antispasmodic agent: its used as antispasmodic agent to relax the GIT and urinary bladder.
- Antidote for treatment overdose of AchE inhibitors like insecticides and poisoning with some types of mushroom.
- Antisecretary agent: atropine is used as pre-surgical operations drug in order to reduce (minimizing) secretion of upper and lower respiratory tracts.

***Adverse effect*:** depending on the dose atropine may cause:

1- Dry mouth.
2- Blurred vision (sand fly).
3- Tachycardia.
4- Constipation.
5- CNS disturbances include: restlessness, confusion, hallucinations and delirium which may progress to depression, collapse of the circulatory and respiratory system then death.

Scopolamine: is another *Atropa belladonna* (Hyoscine) produce peripheral effects similar to those of atropine. Scopolamine has greater action on the CNS. It has larger duration of action in comparison to those of atropine. Therapeutically scopolamine is used to treatment of motion sickness.

Ipratropium: A quaternary amine derivative of atropine, Inhaled ipratropium is useful to treat asthma in patients who are unable to take adrenergic agonists. It's also beneficial in the management of chronic obstructive pulmonary diseases.

II- Ganglionic blockers:

These groups of the drugs act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.

Nicotine: its an alkaloid derived from tobacco.

- Nicotine has many undesirable actions, its with out therapeutic benefits and its deleterious to health.
- depending on the dose, nicotine depolarize ganglia resulting first in stimulation and then paralysis of all ganglia the stimulatory effect includes:

* Increased blood pressure and cardiac rate.

** Increased peristalsis and secretions.

*** At high doses the blood pressure falls because of the ganglionic and activity both in GIT and urinary bladder (atony).

Trimethophane:

- Short acting competitive nicotinic ganglionic blocker.
- It used in emergency lowering blood pressure via i.v. route only.

Mecamylamine:

- produce competitive nicotinic blockade of the ganglia.
- Duration of action is about one hour after single administration.
- It can be uptakes via oral route in contrast to trimethophane due to its good absorption.

III- Neuromuscular blocking drugs:

- These drugs block cholinergic transmission between/motor nerve ending and the nicotinic receptors on the neuro-muscular end palate of skeletal muscle.
- These neuro-muscular blocking blockers are structural analogs of Ach.
- These drugs are act as antagonists (non-depolarizing type) or agonists.

- **Non-depolarizing competitive blockers:**

- Not effect on neural permeability to ions.
- first agent has been discovered was the curare which was used from the native tribes of Africa and south America as a tip of arrow to paralyze the victim.
- These drugs are combining with nicotinic receptor and prevent the binding of Ach lead to preventing of muscular contraction.
- Example\ D-tubocurarine, Galamine and pancuronium.
- These agents are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscles.

- **Depolarizing agents:-**

- Attach to the nicotinic receptors and act like Ach, (but they resist hydrolyzing by AchE) to depolarize the neuro-muscuIar junction instead of released Ach.
- The resultant effect is the paralysis but not necessarily relaxation.
- They are very useful agents when rapid endotracheal intubation is required during the induction of anesthesia.
- Ex. Succinylcholine.

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Sympathetic Nervous System

 Sympathetic nervous system is the second compartment of the autonomic nervous system.

 The **chemical neurotransmitter** which responsible of transmitting the impulses through the adrenergic nerves is the Norepinephrine (a catecholamine synthesized in the nerve endings of the adrenergic nerves and in the adrenal medulla)

 The chemical substances which responsible of norepinephrine degradation are:

- Catechol O–methyltransferase (COMT) which responsible of norepinephrine methylation.
- Then norepinephrine will be oxidized by Monoamine oxidase (MAO).

 Norepinephrine has shown his effect via two types of receptors (Adrenoceptors)

A- **α- adrenoceptor** which divided to two subunits those are :

1- **α_1 receptor (post synaptic):**

- **Blood vessels:** vasoconstriction (arterioles of skin viscera and mucosa)which increase peripheral resistance leading to increase blood pressure.
- **Eye**: dilatation of pupil (Mydriasis).
- **Sphincters smooth muscles**: contraction, no digestion.

2- α_2(mostly presynaptic):

- Decrease norepinephrine release (feedback mechanism).
- Decrease Insulin release.

B- **β- adrenoceptor** which divided to two subunits those are :

1- $\beta_1$receptor:

- **Heart**: increase contractability (+ inotropic) and increase heart rate (+ chronotropic)
- **Metabolism**: lipolysis, increase free fatty acids in the blood.

- **Glands**: increase rennin secretion from juxtaglomerular system.

2- **β_2 receptor**:

- **Blood vessels**: dilatation of coronary arteries and the vessels of skeletal muscles.
- **Smooth muscles**: relaxation of bronchioles, GIT, urinary bladder and uterus.
- **Metabolism**: cause glycogenolysis leading to hyperglycemia.

Adrenergic agonists (sympathomimetics): drugs with norepinephrine like effects, and it's divided to:-

A- Direct acting agonists: these drugs act directly on the receptor and include:-

Epinephrine (Adrenaline): one of naturally existing catecholamines in the body. Affects all types of adrenergic receptors.

- **Therapeutic uses of Adrenaline:**

1. **Asthma**: in emergency cases of asthmatic attracts, adrenaline rapidly relieves the dyspnea and increase tidal volume.
2. **Glaucoma**: adrenaline can be used to decrease aqueous humor formation through constriction of ciliary blood vessels.
3. **Anaphylactic shock**: it's used in treatment of hypersensitivity (type I) in response to allergen.
4. **Local anesthesia**: it's combined with local anesthetics in order to cause local vasoconstriction to slowing the absorption of local anesthetics and to control the oozing of the blood.

- **Adverse effects:**

1.CNS: anxiety, fear, tension, headache, tremor and cerebral hemorrhage.

2.Heart: it can cause arrhythmias in patients who receive digitalis.

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Norepinephrine:

- One of the natural catecholamines analogous to epinephrine in its action.
- Its effect on α more than β receptor
- Therapeutically norepenephrine is not satisfactory because its has many adverse effects , sometimes its used in treating of shock.

Dopamine:

- Another natural catecholamine
- It has general effect on both adrenergic receptors. Also on the dopaminic receptors (D_1, D_2).
- Therapeutically its considered the drug of choice in treatment of shock (shock, is a serious, life-threatening medical condition where insufficient blood flow reaches the body tissues).

Phenylephrine:

- Direct acting on $\alpha_1$receptor.
- It is not a catechole derivative therefore it's not a substrate for COMT.
- Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressure.
- Pharmacological uses of this drug include nasal decongestant, producing prolonged vasoconstriction and also it's used to raise blood pressure.
- Large doses can cause hypertensive headache and cardiac irregularities.

Clonidine:

- Direct acting on $\alpha_2$receptor. (Not a catechole derivative).
- Clonidine acts centrally to produce inhibition of sympathetic vasomotor center, therefore it's used as central antihypertensive.
- Is used to minimize the symptoms that accompany withdrawal from opiate or benzodiazepines.

Dubutamine:

- Synthetic direct acting catecholamine that is a β_1 receptor agonist.
- Therapeutically, dubutamine is used to increase cardiac output in congestive heart failure.
- The main adverse effect represented by arterial fibrillation due to increase atrio-ventricular conduction.

Salbutamol (Ventoline), Albuterol:

- Direct acting β_2 agonist. (Not a catechole derivative).
- These drugs are very beneficial in treating the broncho-constriction and the cases of asthma.

B-Indirect acting agonists: these drugs are not act directly on the receptor and they are act on the neurotransmitter like:-

Amphetamine:

- This drug has CNS stimulation action.
- It increases blood pressure through $\alpha_1$and β_1 receptors.
- It has abused CNS effect but it is useful in cases of depression, hyperactivity of children, sleeping sickness also termed by Narcolepsy (neurological condition most characterized by Excessive Daytime Sleepiness (EDS), in which a person falls asleep during the day at inappropriate times).and in treatment of obesity (appetite controller).

C- Mixed action: these drugs have dual effect and they work on releasing of stored norepinephrine and in the same time they effect directly on the adrenoceptors.

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Ephedrine: alkaloid, cause release of stored catecholamines and in the same time it effects on α and β receptors.

- Less potent than epinephrine.
- It is poor substrate for COMT and MAO (long duration of action).
- Pharmacologically it's used for prevent attacks of asthma, also in treatment of Myasthenia gravis with ChE. Inhibitors, also in CNS stimulator and produce alertness, decrease fatigue and prevent sleep, improve athletic performance and it is used in as decongestant.

Adrenergic antagonists (also called blockers or sympatholytic agents):-

Adrenergic receptor antagonists inhibit the interaction of norepinephrine, epinephrine, and other sympathomimetic drugs with α and β receptors.

α - adrenergic blockers:-

+ phynoxybenzamine:

- Its non selective α receptor blocker (effect on α_1 and α_2 receptor)
- Its effect is irreversible and noncompetitive and only mechanism of reactivation of the adrenergic effect is by re-synthesis of adrenoceptors.
- Action of phenoxybenzamine last about 24 hrs. After a single dose of administration.
- The most therapeutic use of this medicine in treatment of phenocytochrma (a catecholamine – secreting tumor of cells derived from adrenal medulla.)
- Side effects include: hypotension, nasal stiffness, nausea and vomiting.

+ prazosin, terazosin, doxazosin and tamsulosin:

- selective competitive blockers of α_1 receptor
- decrease peripheral vascular resistance (relax the smooth muscles of arterioles and veins) leading to decrease in arterial blood pressure.
- **Tamsulosin** is more potent inhibitor of α_1(subtype A) which exist in the smooth muscles of prostate therefore its used in the treatment of benign prostatic hyperplasia.

β – adrenergic blockers:-

+ Non- selective β adrenergic blocker

propranolol (Inderal):

- its non- selective β adrenergic blocker (effect on β_1 and β_2 both)
- it has both negative inotropic (force of heart contraction) and chronotropic (heart rate) therefore it cause bradycardia and hypotension.
- Another pharmacological uses are, treatment of angina pectoris, myocardial infarction and treatment of migraine.
- The main side effect of propranolol is the bronchoconstriction due alteration of drug with β_2 receptors which mainly exist in the bronchial ramification of the lung.
- Other side effects are cardiac arrhythmias and metabolism disturbances.

+ **Selective β_1 blockers**:

- this group of drugs has an important role in treatment of chronic hypertension
- This group of drugs has less effect on the bronchial ramification. due to its selective blocking of β1 receptors only.
- this group includes: Acebutolol, atenolol (tenormine), esmolol and practolol (Eralidin).

 Drugs affecting neurotransmitter release or uptake :

+ Reserpine:-

- A plant alkaloid inhibits of the mechanism transport of monoamines from the cytoplasm of the nerve cell and chromaffin cells to the storage vesicles.
- In consequence lead to depletion of norepinephrine levels in the adrenergic neuron.
- The only therapeutic use of reserpine in treatment of hypertension that fails to respond to treatment with other drugs.

+ **Cocaine**:-

- has the ability to block the mechanism of norepinephrine uptake across the cell membrane of adrenergic neuron.
- Consequently norepinephrine accumulates in the synaptic cleft resulting in enhancement of sympathetic activity and potentiation of catecholamine effects.