

***Title of Lecture: ANS***

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***Refer to slide no. : 6***

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Autonomic nervous system is an important involuntary system – whereas somatic nervous system is voluntary-.

Nervous system in general is divided into Central nervous system, which consist of brain and spinal cord, and Peripheral nervous system.

Peripheral nervous system consist of somatic, sympathetic and parasympathetic. Sympathetic system is also known as adrenergic system -because adrenaline is involved in it- it's thoracolumbar since the nerves compose this system originate from thoracic and lumbar vertebra – this is important to know for physicians and neurosurgeons in tumor removal, electrical stimulation and local anesthesia for conditions associated with over activity of the nervous system.

The parasympathetic system is known as cholinergic ( depend on acetylcholine) it's craniosacral –the associated nerves originate from cranial ( cranial nerves especially vagus nerve which has a big role in the parasympathetic system) and sacral regions- . So as a conclusion in any nervous system we have different nerves and major neurotransmitters "NT".

The nervous system controls most of the body physical functions and biological activities hence it's considered to be the most important system in our body, and the endocrine system follow it in its importance. Even the endocrine system part of it – the hypothalamus, which is a group of specific nuclei- is a part of the central nervous system; so internal stimuli and inhibitors effect the CNS can reflect on the endocrine system and thus the whole body.

Physiology of the ANS:

Starting with the parasympathetic system, it's neurons are very thin and unmyelinated so it's relatively weak and because of its weakness it has some sort of rest stops in its way to the targeted cells which are called ganglion. It can exist near the targeted cells or even imbedded in them. The ganglion consists of pre and postganglionic neurons, preganglionic neurons are usually longer than post neurons.

The major neurotransmitter inside the ganglion is acetylcholine, therefore ganglionic transmission is cholinergic. And then from the cell body of postganglionic parasympathetic neuron through its terminals the major neurotransmitter released is acetylcholine. Acetylcholine mediates the effect of the parasympathetic system on the effector cells.

Synapse is a space, junction and connection signal can pass through, like the one between nerve terminals of a specific system and the effector cells where neurotransmitter is released in this space then interact with the receptor that mediate its effect. Also a synapse in the ganglion between the pre and post ganglionic neurons where ach is released from the terminals of the pre neuron to the junction between them till it reach the nicotinic receptor on the cell body of the postganglionic neuron.

We have different receptors for ach, in the ganglia it's nicotinic receptors and in the effectors are muscarinic receptors.

Sympathetic system: it also contain a ganglion:

* preganglionic neurons release ach
* ganglionic receptor is nicotinic

( so as you observe in all ganglia Ach is the major NT and receptors are nicotinic)

* postganglionic neurons release norepinephrine NE (noradrenaline NA) the major NT of the sympathetic system. It's released in the synapse between the postganglionic neuron and the effectors and interact with different adrenergic receptors on them (α1, α2, β1 , β2)

the sympathetic effect on sweat glands follows the same mechanism except that Ach is the major (final) sympathetic NT released by the postganglionic neuron. Also in adrenal gland we have an exception; it doesn't have a ganglion –the innervating neurons travel for only a short distance relatively so it doesn't need one- , And Ach is the major NT released from the terminals of the sympathetic neurons, which will result in the releasing of epinephrine (adrenaline) from the adrenal gland where it's synthesized.

Nerve terminals lack the enzymes used in synthesizing epinephrine, it only synthesize NE - in the synthetic machinery which we'll discuss later a methylase enzyme is missing in nerve terminals-. So NE is specific to sympathetic nerves and E is for adrenal glands "medulla".

The final nerve system involved with the contraction of voluntary muscles is motor (somatic) system. The junction between motor neurons and voluntary muscles is neuromuscular. We mentioned this along with sympathetic and parasympathetic systems because we have related drugs connects motor nerves with parasympathetic system specially because the major NT in both of them is Ach but they differ in motor system that the receptor type on the effector cells is nicotinic. Even nicotinic receptors of the ganglia are different than those of the motor system (different subtypes). This is important in pharmacology in choosing the right agonist and antagonists.

Example that highlight the specificity and selectivity of different agonists and antagonists; Atropine reverse the effect of parasympathetic system, it's anticholinergic, antimucarinic. So it will work on the receptor of the effectors –not on the receptors of the ganglia nor neuromuscular junction-. So it's selective and specific to only muscarinic receptors.

Sympathetic system is usually involved with stressful conditions , in such conditions E and NE (and also cortisone) concentration increase in the blood to counteract the effect of stress. Cortisone and sympathetic system are essential in reversing the actions of stress. Stressful conditions involving sympathetic system triggers what's known as "flight or flight response". Such as people with certain phobias, once they face that stimulus ( for example a dog in dogs phobias) they go through certain events:

* yellowish face due to the vasoconstriction on the facial muscles; upon stress blood pressure drops so the sympathetic system try to elevate the pressure by vasoconstriction on unessential muscles. Hence hypertensive people upon sympathetic response may suffer exaggerated effect more intense and more dangerous so relaxation is highly recommended.
* Increased heart rate.
* sweating
* Pupils dilate
* Increased blood flow to skeletal voluntary muscles of the legs by vasodilation to the supplying vessels.( Run response)
* Bronchodilation (to cover the increased need for oxygen)

Parasympathetic triggers "feed and breed response" , it acts in restful conditions. maintains essential bodily functions, such as digestive processes and elimination of wastes, increase salivation. It acts in opposite to sympathetic system or in a harmony and balance. And if any reason caused imbalance between them that leads to a pathophysiological process.

Receptors:

Receptors regarding Ach are called cholinergic receptors which divide into muscarinic receptors , at nerve terminals of the parasympathetic neurons and sympathetic nerve terminals of sweat glands , and nicotinic receptors in , in the ganglia and in sympathetic nerve terminals to adrenal glands and are called Nn and second nicotinic type called Nm for motor somatic nerves innervating voluntary muscles.

Adrenergic receptors are (α1, α2, β1 , β2, β3) but β3 is not much significant. Subtypes of adrenergic receptors must be memorized and don't worry about muscarinic and nicotinic subtypes.

Dopamine we'll talk about it here as NT used in specific dopaminergic neurons. Dopamine is also a hormone that inhibit prolactin we'll talk about it in endocrine system. It's essential in the nervous system whether in the peripheral or central nervous system. Any defect involving its secretion or synthesis specially in CNS is associated with many diseases, excess develop schizophrenia and deficiency develop Parkinson's disease. Dopamine is also a β1 agonist.

Sympathetic receptors (responses):

α1-receptors:

activation of this receptor by specific agonist like NE or E mediates:

* Vasoconstriction of cutaneous; visceral; pulmonary; coronary arteries and arterioles and veins. It also can occur by activation of α1agonists and specific antagonists of parasympathetic system and on the other hand specific agonists of parasympathetic system and α1 antagonists triggers the opposite effect ( vasodilation)
* Dilatation of pupils (mydriasis); it's associated with a disease called glaucoma, this disease is involved with a lot of cholinergic and adrenergic receptors

You have to connect the effects with clinical issues; for example vasoconstriction is related to blood pressure anything that leads to it elevate the peripheral resistance and increase blood pressure "hypertension" so α1 antagonists are very valuable in controlling hypertension.

Any effect mediated by subtypes of receptors we have agonists and antagonists that can be used in the management of the over activity of that receptor or system as a whole.

**α2- receptors** are inhibitors for NE so upon stimulation it end up with decreasing blood pressure. Clonidine is an agonist for α2- receptors inhibits NE so it can be used in hypertension.

**β1- receptors** (NE; E, Isoproterenol = Isoprenaline are agonists for this receptors they mediate:

* Increased heart rate (+ve chronotropic effect)
* Increased heart contractility (+ve inotropic effect)
* Increased conduction velocity (+ve dromotropic effect)

The past three effect leads to increase cardiac output possible uses in hypertension; blood pressure is in direct proportion with cardiac output, increased cardiac output leads to increase in blood pressure .

* Increased cardiac output
* Increased lipolysis
* Increased renin release

It also increase aldosterone and it retains salt and water which increase blood pressure, so beta 1 blockers or antagonist would have a great use in controlling hypertension and in the other hand beta 1 agonist treat pressure drop " shock" likewise alpha 1 agonists.

**β2-receptors** E; Isoprenaline; Salbutamol = Albuterol are its agonists mediate :

* Bronchodilation 🡪 which can be beneficial in bronchial asthma we use beta2 agonists, beta blockers cause bronchoconstriction
* Decreased GIT motility increase constipation 🡪 while cholinergic system increase its motility and secretions so over activity cause diarrhea
* Increased glycogenolysis 🡪 it regulate and increase blood sugar level in fight or flight response as energy is needed because glues is the major fuel for the cells
* Relaxation of uterus 🡪 that’s why β2 agonists are used in premature labour
* Relaxation of skeletal and coronary blood vessels

**β3-receptors** it's newly discovered. Amibegron; Mirabegron are its agonists and are also newly used drugs that have the following effects:

* Increased lipolysis in adipose tissue and decrease deposition of fat in adipose tissue. 🡪 so it decrease body fat concentration.
* Thermogenesis in skeletal muscle 🡪 increase body temperature.
* Anxiolytic effect, anti anxiety effect likewise Beta 1 and 2 blockers
* Increase insulin effect possible use in the management of diabetes mellitus.
* Beta3-Receptors are also found in the gallbladder and urinary bladder. Their role in gallbladder physiology is unknown but cause relaxation of the urinary bladder and prevent urination

Possible uses:

* Obesity (also thyroid hormones could be used for obesity)
* treatment of overactive bladder because the relax urinary bladder and prevent urination.
* diabetes mellitus 🡪 increase insulin effect

Table in slide 11 summarizes different effects mediated thro different receptors only focus on the previous mentioned adrenergic receptors. Like when a question ask which receptor increase heart rate upon stimulation? Beta1 vasoconstriction of cutaneous muscle ? alpha 1 , bronchodilatation? Beta2

Specific antagonist for Beta receptors: (beta blockers)

* Cardioselective (e.g. Atenolol...)

Block only β1-receptors so they decease HR , contractility, cardiacoutput and blood pressure ( reverse the effect of stimulated beta 1 receptor) and don't lead to bronchoconstriction (don't effect beta 2 receptors)

* Nonselective (Propranolol…)

Block β1 & β2-receptors so it's dangerous for people suffer from bronchial asthma.

Synthetic machinery of neurotransmitters: Sympathetic system:

Begins in the neuron nerve terminals starting with precursors; the major precursor in the synthesis of NE is Tyrosine, non essential amino acid obtained from diet, converted by Tyrosine hydroxylase to DOPA "Dihydroxyphenylalanine" which is the rate limiting step, DOPA is converted to Dopamine " the first resulting NT which can work on dopaminergic receptors" by l-aromatic a.a decarboxylase. Then it's converted to NE by Dopamine β-hydroxylase enzyme. NE is the major stimulator or precursor for E in the adrenal medulla by Methyltransferase enzyme and this enzyme is only present in the adrenal medulla and absent in sympathetic nerve terminals.

In slide 14 representing the synthetic machinery where Tyrosine is taken up into the neuron where it's converted to NE. Following this synthesis of NE it's stored in vesicles. What's released in the synapse interact with the receptors on effectors cell known as the releasable amount, so we have storage pool and releasable pool. The releasable pool has immediate response but if we reached extent of complete depletion of this releasable pool, stored pool will undergo mobilization to releasable pool in order to provide NE. so we need to have good storage of NE.

Synthesis usually takes time, initiation or inhibition of synthesis is long process, but released pool is quick. So if we have excess of NE we should inhibit release and block it which is quicker than inhibiting synthesis or if it was already released we can use antagonists.

So after releasing NE it interacts with different adrenergic receptors alpha 1, beta 1 and 2 post synaptic while alpha2 is presynaptic ( they are inhibibitory) they either increase the reuptake of NE or block the release of NE.

After producing the desired effect, NE effect is terminated mainly by highly specific uptake mechanism back to the neuron. The major inactivating pathway of NE.

Other mechanism used for deactivating NE(metabolism) is by MAO " mono amino oxidase enzyme"(oxidation pathway1 ) and COMT catechol o methyltransferase enzyme (pathway 2)

There is also mitochondrial MAO inside the neuron itself if we have excess NE. and all these previous processes are in balance.

So if we have a hypertensive clinical issue due to excess of NE in the synapse area possible targets of drugs that could be used in this condition:

* Regarding synthesis: could be by preventing the entrance of tyrosine to the neuron, inactivation of any enzyme involved in the synthesis machinary of NE, destruction of the NE stores like Reserpine (vesicle depletor for all neurotransmitters stores )
* Releasing: inhibit the release of NE
* In Synapse area: we can use antagonist for alpha 1 and Beta receptors or alpha 2 agonists
* In metabolism: enhance the uptake of NE to the neuron and increase the activity of MAO or COMT

All the previous drugs decrease NE concentration, major side effect is depression. Depression is a disease which has a biochemical defect result in low levels of NE so in order to increase the NE levels we reverse the previous drugs like increasing the uptake of tyrosine and most importantly inhibit high specific uptake of NE by TCA’s (tri cyclic antidepressants) & Cocaine block NE & E reuptake.