

***Title of Lecture: ANS***

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

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♥we have talked about the synthetic machinery , essential substances are produced & then stored cause they are essential , such like hormones, its synthesis starts from DNA & chromosomes then complete the processes to transcription →translation→proteins →stored→ & then released . we have releasable pool & storage pool , the importance of these pools are a lot, whats available in the synapse is the release pool & there is a limited amount existed in this pool , when this amount ends ,it takes from the store then released, release is very quick , but synthesis takes time as in stressful conditions for ex. Cortisol will be released immedietly but if we want to make a combination btw storing & releasing at the same time, there won't be a quick response . So in cases of a disorder, we manipulate with the release more than synthesis cause it won't take much time, so when there is an increase in a substance → inhibition of synthesis could be applied but it takes time , on the other hand, the best thing to happen is to decrease the release in these cases of overproduction, & the same concept is applied to decreased production

♥***Ex. NE*** :

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| ***In case of decreased production*** | ***In case of overproduction*** |
| -the uptake will be increased by targets -We have to increase synthesis ,storage & release -give an agonist-inhibiting the deactivation mechanism of NE-inhibiting MAO | -inhibit uptake by targets -inhibit synthesis, storage & release-inhibiting tyrosine hydroxylase (the rate limiting step of making NE), metyrosine helps in inhibiting.-damage stores(reserpine is a mjor depletor for all neurotransmitters) - Using an antagonist |

♥***Note:***

- after producing an effect by NE , its deactivated by high specific uptake mechanism , this process has a value in management of cases related to decreased NE levels , meaning that when inhibiting the high specific uptake , we increase the drug.

-NE could be metabolized also by MAO (monoamine oxidase) in the liver , peripheral tissues or neuronal mitochondria. By inhibiting MAO, NE levels increases.



♥***Excess vs. depletion of NE***

-Excess: such in hypertension . all drugs mentioned that could inhibit NE in synapse, could inhibit also the case of hypertension . drugs used are:

Reserpine (making depletion) – guanethidine (inhibits the release) – specific antagonist (alpha 1, Beta blockers)

-Depletion: such in depression . biochemical effect is that there is no NE in the CNS of patients . the drug used in this case is: Tricyclic antidepressant

♥***NOTE***: drugs that tolerate hypertention have several side effects that would lead to depression , & the same is applied to drugs that tolerate depression which its side effects would be hypertension & something else called orthostatic hypotention caused by alpha 1 receptor blocking effect . as we know, alpha 1 makes vasoconstriction & increase the blood pressure, so in this system only we could control the hypertension ,there is lots of drugs related in management of hypertension through alpha 1 receptor we will talk about them.

What types of drugs could we take to treat….?

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| ***hypertension*** | ***depression*** |
| -tyrosine uptake inhibitors > theoretically, when there is no tyrosine, there will be no NE- inhibitors at any level state of synthesis NE-guanethedine > inhibits NE release-antagonist > when NE is released into the synapse, none of any drugs could help in controlling hypertension now except the antagonist-reserpine > this drug is not preferred to be used cause its not only affects NE, but also Serotonin as well, so reserpine depletes stores for all neurotransmitters leading to depression & Other side effects | -Drugs that: increase release, storage & synthesis of NE- specific agonist-alpha 2 antagonist-inhibitors for the reuptake of NE >the most impotant point , by inhibiting the metabolism , NE will increase- MAO inhibitors > MAO here exists in mitochondria |

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| Major side effect : is decreased the amount of NE leading to depression |  |

♥***Metabolism of E & NE is sympathetic system***

-effect are mediated through different receptors: alpha 1, alpha 2, beta 1, beta 2

-after producing the effect , action has to be terminated . termination happens by high specific uptake , also we have element of metabolism in periphery , liver, GI & in neuron

- we have 2 pathways of inactivation: MAO (oxidation) & COMT (methylation)

NOTE: we don’t have to know the intermediates of metabolism.

-Both E & NE are metabolite by MAO & COMT

- the final end product & major metabolite is: VMA (vanyllil mandilec acid) or named as methoxy hydroxyl mandilec acid. (an exam question)

-VMA could be measured in urine , it’s a diagnostic test to cases associated to excess production of E & NE.

♥***Adrenal pheochromocytoma***

- Adrenal pheochromocytoma > it’s a tumor in the adrenal medulla characterized by excess in E& NE . when E & NE ↑, the metabolism also ↑ by MAO & COMT so as a result, VMA is excreted in the urine with excess. Patients of pheochromocytoma suffer from hypertension

- solution : is difficult , the 2 glands have to be removed if it’s a bilateral condition

♥***Sympathomimetic drugs***: have direct or indirect acting:

-Direct acting: direct means that they are synthesized then released , or giving an agonist that interact with alpha 1 or 2 or beta 1 or 2 receptors. EX : E & NE

-indirectly acting: it means that these drugs don’t interact with the receptors, instead, the drug will cause a release of NE to interact with a receptor. EX: Ephedrine & Amphetamine( an addictive drug).

♥***About NE:***

-it’s a catecholamine > this words means catechol (that has a benzene ring with 2 hydroxyl groups ) + amine group.

♥-***Action of NE*** : the main & obvious action for NE is vasoconstriction. Vasoconstriction → increase in peripheral resistance → increase blood pressure.

NOTE that NE don’t have Beta 2 receptor ,just alpha 1(mainly) & beta 1 .

When we talk about sympathetic system , the main thing that comes in mind is that all systems in the body are going to increase , as blood pressure , heart rate & etc , but according to NE, it may increase the heart rate little bit but its main effect is vasoconstriction & bradycardia . the bradycardia that happens here is explained by:

1. the opposed & over activity of parasympathetic system that companies the use of NE according to what we know that sympathetic & parasympathetic system compensates each others .PS system overacting the action of NE on Beta 1 receptor leading to bradycardia . the evidence of the action of parasympathetic system is when we give an antagonist for the parasympathetic (Atropine) & the result is increasing the heart rate.
2. Bradycardia happens as a reflex for vasoconstriction (physiologically), for more understanding, when there is peripheral vasodilatation & a drop in blood pressure the reflex will be in this case tachycardia to counter act the drug in blood pressure.

♥***Clinical uses of NE:***

-for shock & drop in blood pressure

-local anaesthetics . ( through making a vasoconstriction )

-could be given subcutaneously & as IV infusion … infusion means in the drip with glucose

♥***Side effects of NE:***

-headache , tremors, increase in blood pressure, bradycardia, palpitation & cardiac arrhythmias.

♥***Mechanism of action of catecholamine:***

As a refreshment , we have taken 4 types of receptors: G protein couples receptor, enzyme coupled, ion channel coupled & catecholamines acting intracellulary in transcription & translation . according to catecholamines, we have alpha & beta receptors that we are going to talk about .

-Beta receptors : beta adrenergic receptors are G protein coupled receptor to adenylyl cyclase. The first messenger is catecholamine. Catecholamine + beta adrenergic receptor → G protein transfer signal from the receptor to an enzyme (adenylyl cyclase)→ stimulation to adenylyl cyclase will inhace production of cAMP (second messenger) from ATP . Not only that , but also there is connections enhances openenig little Ca+ channels→ Ca+ bind calmodulin → then phosphorylation of different proteins & kinases in the cell that will mediate catecholamine action on beta adrenergic receptors. Note: cAMP is broken down by phosphodiesterase enzyme .there are 2 ways to increase levels of cAMP in the cell, & they are:

1- stimulation of adenylyl cyclase

2-Or inhibit phosphodiesterase enzyme

 NOTE: when cAMP\* related to Beta receptors \* increase → heart rate will increase & also the contractility , positive chronotropic & positive ionotropic.

♥***Alpha adrenergic receptor:*** has G protein coupled receptor to phospholipase c → activation of phospholipase c increases levels of IP3 & DAG→ these makes phosphorylation to different proteins that mediate the effect of alpha receptor.

As a conclusion , the main differences btw alpha & beta adrenergic receptors :

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| ***Alpha adrenergic receptor*** | ***Beta adrenergic receptor*** |
| Second messenger: IP3 & DAG | cAMP |
| The enzyme: phospholipase C | Adenylyl cyclase |

♥***About Epinephrine :***

-it has alpha 1 & 2 , beta 1 & 2

-because there is alpha 2 receptor , so any elevation wouldn’t be severe as in NE.

♥***-its effects:***

- ↑ heart rate and contractility and ↑ CO

- ↑ systolic BP

- Bronchodilatation

- ↑ blood sugar

- ↓ GIT motility

- Dilatation of pupils

- ↓ salivary secretions

♥***-clinical uses:***

- Anaphylactic shock ( drop in blood pressure)

- Open angle glaucoma (↑ drainage of eye fluid)

- + local anaesthetic

E is ineffective orally; given SC or IM

IV→ administration is contraindicated → fatal ventricular fibrillation

Metabolized by MAO & COMT

NOTE: we couldn’t give the patient E as an IV infusion , but we could give NE as an IV infusion , this is because NE has an opposing system for the sympathetic effect on the heart leading to bradycardia , but E don’t has this although it has alpha 2 receptors , but it doesn’t have that much effect , so the heart will be affected & this will be a fatal condition.

♥***E side effects:***

- Anxiety

- Nervousness

- Sweating

- Headache

- Palpitations

- Cardiac arrhythmias

- ↑BP

♥***NOTE:***

- when a diabetes patient feels nausea or a little sweating, we order him or her to eat a chocolate . all these side effects will disappear quickly after controlling the blood sugar .

- patient with hyperthyroidism are characterized by over activity of sympathetic system , mainly by increase level of cAMP in the heart.

-beta blockers drugs are the solution to control the manifestation of hyperthyroidism .

♥***About Isoprenaline:***

-A catecholamine; β1 & β2 stimulant

- A good bronchodilator

- ↑ heart rate; contractility and CO

-No change or little ↑ in BP (due to ↑ in CO) (beta 1)

♥***Clinical uses:***

- Bronchial asthma given by inhalation

- Shock & cardiac arrest given by an IV infusion

♥***About Dopamine :***

-it’s a unique drug,it’s a neurotransmitter & a hormone, & A catecholamine; precursor to NE

-Present in adrenergic neurons, adrenal medulla and dopaminergic neurons and in the CNS

-following release of dopamine, it interacts with 5 receptors, D1 to D5

-it presents in nervous system mainly

-excess dopamine makes schizophrenia , & deficiency of it is related to Parkinson disease

-to prevent the excess we use dopamine antagonist , & the major side effect of this is Parkinson disease

-it’s the major hormone that regulates prolactin synthesis & release , if we want prolactine, we have to inhibit dopamine

-prolactine is involved in breast development & lactation .

- at the end of pregnancy , dopamine levels decreases ,& after delivery there will be no dopamine exists .

-best inotropic agent in the management of shock

♥***Dopamine***:
- ↑ release of NE

- Interacting with α and β1-receptors

- Interacting with specific dopaminergic receptors

-the action of alpha receptors could be blocked by alpha antagonist,& beta receptors could be blocked by beta antagonist of dopamine

♥***Doses***:

-low dose: increases renal blood flow . (renal blood flow is dependent on dopamine)

-intermediate dose: stimulate Beta 1 receptor

-high dose : activates alpha 1 receptor

***So easy lecture***

***Enjoy ^^***