PHARMACOLOGY

◉ Sheets ○ Slides

Number: 8

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Subject: Autonomic nervous system 2

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- In the previous lecture we discussed adrenergic transmission and cholinergic transmission and in this lecture we are going to talk about :
    1. Norepinephrine synthesis, storage and release.
    2. Metabolism of catecholamines.
    3. Cholinoceptors, Adrenoceptors and Dopamine receptors.
    4. Baro receptor reflex (in brief).
    5. Direct effect of autonomic nerve activity.

Synthesis of Norepinephrine: (refer to the slides for the figures)

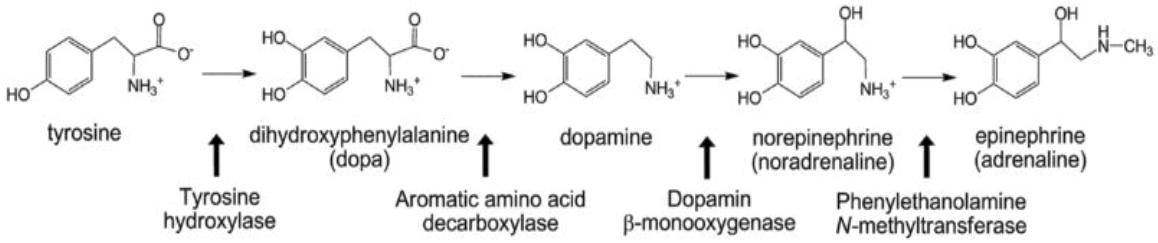
- The first step after the entry of **tyrosine** to the neuron (by active transport) is converting it into **dopa** by the enzyme **tyrosine hydroxylase**, it is the most important step (rate-limiting step) and tyrosine hydroxylase is the most important enzyme [it is also very important in the synthesis of other catecholamines {E,NE,Dopamine}], when it is inhibited, the whole synthesis stops (it can be inhibited by end product inhibition [when too much NE is released]).

  Note: Researchers who want to study the turnover of catecholamines study the activity of Tyrosine hydroxylase, if it is active it means that the whole sympathetic nervous system is active.

- The second step is decarboxylation of dopa into **dopamine** by the enzyme **monoamine decarboxylase**, previously it was referred to as dopa decarboxylase, but it was found out that it decarboxylates other amines and not just dopa.

- The third step is hydroxylation of dopamine into **norepinephrine** by the enzyme **dopamine β-hydroxylase** that is found inside the vesicles, it adds OH group to β-carbon (the carbon next to the carbon bound to amine group).

- The previous step is the last one in the synthesis of NE, but in the chromaffin cells of adrenal medulla there is one further step, which is the synthesis of **epinephrine** by the **enzyme phenyl ethanolamine -N- methyltransferase (PNMT)** which takes methyl group from S-adenosylmethionine (SAM)and adds it on theamine group.



Storage of NE:

- NE is stored in vesicles bound to cAMP (4 molecules of NE for one molecule of cAMP "4:1") and protein.

Release of NE:

There are two major types of release, unlike Ach which has only one type**:**

1. Calcium dependent exocytosis (the major type):
    - We talked about it before, (it is the method by which Ach is released).
    - All the content of the vesicle is thrown out (NE , cAMP , protein and dopamine-β- hydroxylase).
    - This release is blocked by:
        - Bretylium (antiarrhythmic agent) and Guanethidine(antihypertensive) inhibit SNAPs proteins (docking proteins in the membrane that direct the movement of the vesicles), thus preventing the release of NE by exocytosis.{they are no longer used because of their severe side effects}.
        - Omega "ω" conotoxin GVIA(produced by specific types of marine snails and is used to causeparalysis of fish to feed on them) blocks Ca ion channels causing obstruction of the movement of vesicles, thus inhibition of exocytosis as well as the release of NE and Ach.

- Latrotoxin (black widow spider venom) : acts on vesicles causing explosive release of NE&Ach.

2. Calcium independent release:
    - It is caused by products called "indirect active sympathomimetic", the most important ones are: Thyramine and Amphetamine.
    - They use the same transporters that NE uses to enter the neuron "NET: norepinephrine transporter".
    - They are also transported into the vesicles by VMAT (vesicular monoamine transporter) displacing NE (they take the place of NE, so NE is released).
    - Part of the released NE is metabolized in the mitochondria by monoamine oxidase (MAO) but most of it will be released from the neuron by reverse transportation (via NET) [we said "reverse" because the normal way is from the outside to the inside].
    - Once it is outside the nerve, It will cause a sympathomimetic effect (the blood pressure will rise) but it is indirect effect because they don't cause stimulation of adrenoceptors, they (Thyramine and Amphetamine) only release NE from vesicles, thus considered "indirectly active drugs".

Metabolism of Catecholamines (NE, E, Dopamine): (Refer to the slides for figures)

- Metabolism is not the major route for terminating(انهاء) the effect of catecholamines, because even if we inhibited the enzymes required for their metabolism we will not get potentiation(تقوية) of action (unlike Ach, if we inhibit Ach asterase we cause great potentiation of Ach effect), because the majority of catecholamines are transported back to the neuron (about 80%) (uptake 1), and the rest will be transported inside the tissue (uptake 2), and others will diffuse with the blood and then will be metabolized in the liver.

- We have two enzymes responsible for metabolism:
  1. Monoamine oxidase (MAO) in the mitochondria, produces oxidative deamination of monoamines (such as; E,NE,Serotonin, Dopamine).
  2. Catechol-O-methyl transferase (COMT) : transfers methyl group to one of the OH groups of the catecholring, from S-adenosyl methionine (SAM)(SAM, it is a metal donor) on meta position of catecholamine .

- Both of the previous enzymes produce the same product, VMA :"Vanillyl mandelic acid" and it is secreted in the urine. But the difference between them is that MAO is located inside the neuron (in the mitochondria), while COMT is present outside the neuron(around the sympathetic neuron and in the liver, plus other tissues).

- VMA is viable to diagnose pheochromocytoma which is a cancer (tumor) in the chromaffin cells of adrenal gland causes the production of large amount of epinephrine and norepinephrine resulting in different symptoms, like sudden increase in blood pressure. The diagnosis takes place by testing the urine of a whole day for VMA :{3-5 mg/ day is normal, 15-20 mg/day is a sign of pheochromocytoma}
- Dopamine, same enzymes act on it, but the difference is in the final product, it is Homovanillic acid instead of VMA (it has less OH group).

  Note: abnormal high amounts of Dopamine can cause many disease such as; Parkinson (الرعاش) and Schizophrenia (الانفصام في الشخصية)

  **Study the figure in slide #18 for further understanding (the structures are not for memorizing)

Receptors:

❖ cholinoceptors:

Muscarinic &Nicotinic

** They both have several subtypes that have different functions and distributions:

- ✓ **Muscarinic Receptors: (subtypes with different functions and different distribution)**
  - Muscarinic M1: CNS Neurons, sympathetic postganglionic neurons, some presynaptic sites.
  - Muscarinic M2 : Heart (myocardium), smooth muscles, some presynaptic sites and CNS.
  - Muscarinic M3 "Secretion, mainly glands" : exocrine glands , vessels (smooth muscle and endothelium) and CNS.
  - Muscarinic M4 (exclusively in the brain) : CNS neurons and possibly vagal nerve endings.
  - Muscarinic M5 : Vascular endothelium, especially cerebral vessels and CNS nervous.

Note: M1,M2,M3 are mainly located in the peripheral nervous system but still can be found in the CNS and M4,M5 are mainly located in the CNS.

- ✓ **Nicotinic Receptors:**

**In the previous lecture we mentioned that they are located in the autonomic ganglia as well as in the skeletal muscle which are stimulated by acetylcholine as well. But they are not the same. Although they are both stimulated by Ach and Nicotine, they are blocked by different blockers.

- Nicotinic NN "the second N stands for neuronal": Postganglionic neurons, Autonomic ganglia.
- Nicotinic NM "M stands for muscle": Skeletal muscle neuromuscular end plates.

❖ Adrenoceptors:

- Alpha 1 (α1):
  - postsynaptic = on the tissue not the neuron.
  - when we say alpha receptors we usually mean α1.
  - promotes vasoconstriction.
  - especially found on smooth muscles (causes increasing in the intracellular Ca resulting in muscle contraction.
  - promotes formation of IP3 & DAG.

- Alpha 2 (α2):
  - presynaptic adrenergic nerve terminals.
    **Remember when we talked about autoreceptors that inhibit further release of NE when there is excess amount of NE in the synaptic gab, they are α2 receptors.
  - Found in: platelets, lipocytes, smooth muscle.
  - it may be found postsynaptic but it doesn't play a major role.
  - inhibits adenylyl cyclase and decreases cAMP "the second messenger".

- Beta 1 (β1):
  - in the heart (postsynaptic): increases heart rate and constriction.
  - lipocytes, brain, Juxtaglomerular apparatus of renal tubule (kidney) ,ciliary body, epithelium.
  - acts by stimulation of adenylyl cyclase, increasing cAMP {cAMP is the second messenger of β1 receptors}.

- Beta 2 (β2):
  - postsynaptic, lungs (bronchi relax to carry more oxygen),blood vessels of the skeletal muscles (dilate to deliver more blood to the muscles in order to contract),smooth muscles of the lungs.
    **Notice that we need more O_2 and blood because we are in a fight-or-flight situation.
  - acts by stimulation of adenylyl cyclase, increasing CAMP.

- Beta 3 (β3):
  - postsynaptic, especially in the lipocytes.
  - acts by stimulation of adenylyl cyclase, increasing CAMP (increases fatty acids to provide energy to the body).

❖ Dopamine Receptors:

- D1, D5 : Same function (with small differences).
  - brain, effector tissues; especially smooth muscle of the renal vascular bed.
  - acts by stimulation of adenylyl cyclase, increasing CAMP.

- D2:
  - brain, effector tissues; especially smooth muscle, presynaptic nerve terminals.
  - **inhibition** of adenylyl cyclase, increasing potassium conductance.
- D3:
  - brain.
  - inhibition of adenylyl cyclase.

- D4:
  - brain, cardiovascular system.
  - inhibition of adenylyl cyclase.

Note that: D2, D3, D4 have a similar function and they are all found in the brain.

**Remember that any organ that have dual innervations (parasympathetic and sympathetic), the balance between their tones is what regulate the function.

Baro receptor reflex:

- Baro receptors: stretch receptors found in the major arteries, detect any change in the tension in the wall of the great arteries then sends signals to the hypothalamus. For example,
    1. increasing the tension (peripheral resistance) causes signals to be sent to the hypothalamus, activating vagus nerve (parasympathetic), slowing the heart rate.
    2. If there is any decrease in peripheral resistance (decrease in blood pressure), it will be detected and managed by Tachycardia (increase heart rate)(sympathetic effect) .

Direct Effect of Autonomic Nerve Activity:

❖ It is EXTREMELY important to memorize slides #22,23 about this topic (all the receptors types plus actions). And here are some illustration that the doctor have mentioned:

- **The Eye:**
    - There is two types of muscles that control the pupil size:

1)constrictor pupillae	Radial muscle	Mydriasis (increase the size of pupil "when it's dark")	Sympathetic, α1
2) dilator pupillae	Circular muscle	Miosis (decrease the size of pupil)	Parasympathetic, Muscarinic

**The state of our eye in any moment is determined by the balance between both sympathetic and parasympathetic system.

- Ciliary muscle: controls the focal length (البعد البؤري), only parasympathetic effect.M3 receptors (example: some ligaments -that are attached to the lens-contact to accommodate the lens for near vision .

- **The Heart:**

  - SA node contain β1 receptors that, when stimulated, increase heart rate as well as the contractility.
  - Vagus nerve contain M2 receptors that decrease the heart rate and decrease contractility. Found in the atria only and not in the ventricles.

- **Blood vessels**:

  - the endothelium (epithelium lining blood vessels) does not have parasympathetic nerves but have muscarinic receptors which are stimulated if a drug that work as an agonist is added (causes the release of nitric oxide thus dilation of blood vessels).

- **Genitourinary smooth muscle**: (related to genital and urinary organs)

  - notice that sympathetic inhibits urination while parasympathetic induces urination.

- **Skin:**

  - pilomotor smooth muscle is located at the root of the hair, its contraction is very important in animals.
  - remember that sweat glands are regulated by sympathetic only, and stimulated by Ach (have muscarinic receptors).

- **Metabolic function:**
  - Glycogenolysis (converting glycogen into glucose).
  - Glyconeogenolysis (converting other compounds into glucose).

Note: Knowing these receptors is very important clinically to treat many symptoms by agonist or antagonist drugs. For example:

- Asthma symptoms are treated by β2 receptor agonists, causing the bronchi to relax.
- If the uterus is over contracted and there is a risk of miscarriage, β2 receptor agonist drugs are given to relax it.

Good luck ☺

Special thanks to Joud al-Majali