number 15

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Corrected by -

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This sheet is intended to give you a general idea about adrenergic receptors (adrenoreceptors) and some drugs affecting them, without going into detail about their subtypes and distribution, if you understood this lecture, the following lectures would be easier in sha’ Allah. I wish you’d find it easy, w sorry if I made any mistake.

The underlined asterisked words* are defined at the end.

Main Lecture Points

- A brief introduction (basic info)
- Overview of adrenergic & cholinergic drugs (this lecture is mainly about adrenergic ones, though)
- Procedures and drugs, that inhibit sympathetic pathways.
- Neurotransmission steps and the effects of some drugs on them. (Lippincott, 6th edition, pages 77-79)

Introduction

- Typical nerve cells (neurons) consist of:
  - Dendrites
  - Cell body (where you can find the nucleus)
  - Axon (where the action potential travels from cell body to reach the terminal)
  - Axon terminals (varicosities): they are bed-like enlargements, in these varicosities, you can find neurotransmitters stored in vesicles (granules), these varicosities are where the neurotransmitter’s synthesis and storage occur and you can also find mitochondria (needed for mitochondriai enzymes and ATP synthesis)
- Synapse (synaptic cleft) is a space between two neurons, anatomically, the neuron which is found before the synapse is called presynaptic, and it delivers the “message” across the synapse to the postsynaptic neuron, “the receiver”
- The same chemical can act as a neurotransmitter in one region and as a hormone elsewhere, one significant difference is the transmission, neurotransmitters’ transmission is across the synaptic cleft, whereas that of hormones is by blood
  - E.g: Norepinephrine (noradrenaline) is released by sympathetic nerve endings as a neurotransmitter, whereas it is released by adrenal gland (medulla)* as a hormone. (will be discussed in detail)
There are cholinergic and adrenergic drugs, in this lecture, we are gonna focus on adrenergic drugs (here is a brief summary of both)

I) **Cholinergic Drugs**

Drugs that affect cholinoreceptors (nicotinic/muscarinic) that are stimulated by Acetylcholine ACh.

1- **Cholinergic agonists**

These agonists can be either direct-acting or indirect-acting cholinergic agents,

- The **direct-acting cholinergic agonists**, (cholinoreceptor stimulants) They mimic the effects of ACh by binding to cholinoreceptors.
- **Indirect-acting cholinergic agonists**: AChE (acetylcholinesterase agents or cholinesterase inhibitors) indirectly provide a cholinergic action by preventing the degradation of acetylcholine (some are reversible, others are irreversible)

2- **Cholinergic antagonist**

The agents that bind to cholinoreceptors (muscarinic or nicotinic) and prevent the effects of ACh and other cholinergic agonists

- Parasympatholytics or antimuscarinic agents
- **Ganglionic blockers**, these show preference for the nicotinic receptors of both sympathetic and parasympathetic ganglia.
- Neuromuscular- blocking agents (mostly nicotinic antagonists), these agents interfere with transmission of efferent impulses to skeletal muscles

II) **Adrenergic Drugs:**

Adrenergic drugs affect receptors (adrenoreceptors/ adrenergic receptors) that are stimulated by norepinephrine or epinephrine, it is important to note that these drugs interfere with one of these active processes (Synthesis, Storage, Release, Binding, Removal of the neurotransmitter) -will be discussed in more detail-

1- **Sympathomimetics**, 
(adrenergic agonists) adrenergic drugs that activate/stimulate adrenergic receptors, they can be either direct-acting or indirect-acting agonists.

- **Direct-acting agonists**, these drugs directly act on adrenergic receptors. *(activating receptor)*
- **Indirect-acting agonists**, these drugs act indirectly by enhancing *(norepinephrine) release* -releasers- or blocking *reuptake* -reuptake inhibitors-

2- **Sympatholytics**
(adrenergic blockers/ adrenergic antagonists), These drugs block the action of adrenergic receptors, by binding without triggering the usual intracellular effects/response (some are reversible and others are irreversible)

Note: by saying blockers of adrenergic receptors, we usually mean that they are competitive blockers which compete with catecholamines*.

**Other Adrenergic Drugs:**
3- Drugs that inhibit the synthesis of catecholamines*
4- Drugs that interrupt the release of catecholamines from neurons
REMEMBER:
- the major classes of adrenergic receptors are: *alpha receptors* and *beta receptors*, there are subtypes for both of them (distribution of these receptors will be discussed in the following lectures)
- adrenergic neurons are *not* only found in the sympathetic nervous system (where they serve as links between ganglia∗ and the effector organ), but these neurons are also found in the central nervous system CNS.

**Slide 3**

we don’t only study the adrenergic drugs to understand how CNS drugs (therapeutic effect) influence the adrenergic system, but also to understand how other drugs can possibly affect adrenergic system (side effects) because our ultimate goal is to maintain **Homeostasis**.

**CNS → Fibers**

Each sympathetic pathway has a nucleus in the CNS (spinal cord), the sympathetic pathways originate in different segments of the spinal cord, thoracic T1-T12 and lumbar L1-L3
- (fibers: neurons for both sympathetic and parasympathetic, but in this sheet we’re focusing on the sympathetic)

- Each sympathetic pathway (goes from the spinal cord to the stimulated/effector organ) is composed of two neurons:
  a- Preganglionic neuron (neuron’s cell body lies in the spinal cord)
  b- postganglionic neuron
• One of its courses, the preganglionic neuron synapses with postganglionic neuron in the ganglion*, and the postganglionic neuron merely touches the cells of the effector organ, where neurotransmitters (such as norepinephrine) are released (this is how sympathetic nervous system works directly).

REMEMBER:
1) all preganglionic neurons are cholinergic -nicotinic-, when applied to the ganglia (whether sympathetic or parasympathetic).
2) the postganglionic neurons of the sympathetic system are adrenergic.

- Recap of (adrenergic neurons release norepinephrine directly by post-synaptic neurons)
  o Preganglionic neuron (from spinal cord to ganglia) ---{ At the sympathetic ganglia (release of acetylcholine to postganglionic neuron) }--- ACh binds to nicotinic receptors to activate postganglionic neuron }--- postganglionic terminals (release (norepinephrine) }---- this norepinephrine binds to adrenergic receptor (on effector organ)

• But it works indirectly on our “two adrenal medullae*”, where preganglionic sympathetic nerves pass, without synapsing with a postganglionic nerve, (meaning that there is no postganglionic fibers), then to the adrenal medulla – as the figure of the previous page shows- , the adrenal (suprarenal) medulla then releases adrenaline and noradrenaline into blood.

- Recap of (release of adrenergic catecholamines indirectly by adrenal (suprarenal) medulla)
  o Preganglionic neuron (its terminals release acetylcholine) ----{ acetylcholine binds to nicotinic receptors of adrenal (suprarenal) medulla ---{ the medulla releases norepinephrine to blood --{ this norepinephrine binds to adrenergic receptors of the effector organ (causing indirect effect on adrenergic receptors)
Note:
When talking about sympathetic system, we can find nicotinic receptors on:
- Sympathetic (ganglia)
- Adrenal (suprarenal) medulla

Slide 2

Inhibition of sympathetic pathway, (disruption of ANS functions) can occur at the following parts as a result of certain procedures:

I) Preganglionic neurons, (the continuous line in the figure below)

the inhibition can occur because of:

1- Spinal Anaesthetic* (procaine is used as anaesthetic*) sympathetic nerves system may be affected, a good anaesthetist should apply it without affecting the patient’s sympathetic system and its activities, this is why he should have a good knowledge of relevant anatomy, physiology and pharmacology.

Note: high spinal anaesthesia may lead to loss of sympathetic activity (at certain sites)

2- Sympathectomy (-ectomy= removal) it is a surgical procedure that removes nerves of sympathetic nervous system, some cancer patients with severe pain undergo such procedure to provide pain relief, but it leads to inhibition of sympathetic system which affects its function
3- **Ganglia** Ganglionic blockers, (e.g: Ecolid) receptors of ganglia are mainly nicotinic receptors (acetylcholine), these drugs block the ion channels of the ganglia, and thus they block the entire output at the nicotinic receptor.

**REMEMBER:**
- All preganglionic nerves are cholinergic (secrete acetylcholine), in both sympathetic and parasympathetic nervous systems.
- Both Nicotinic and Muscarinic Receptors are Cholinergic.

II) **Post-ganglionic neurons (the dotted line in the figure above)**

4- **Drugs preventing the synthesis** (e.g: a-methyl dopa)
5- **Drugs preventing the release** (e.g: guanetidine)
6- **Drugs depleting the stores** (e.g: poserpine)
7- **Drugs inhibiting postsynaptic receptors binding** (on effector cells/or organs) such as alpha-2 inhibitors.

As you can notice, all the previous drugs/procedures lead to prohibiting the neurotransmitters from binding to their receptors, and thus your body tries to compensate, so the previous 7 points induce:

a- Supersensitivity of the receptor, meaning that if we applied the neurotransmitter/something that mimics it, the receptors would hyper-react and attract it (analogous to a hungry man who has just found something to eat)

b- **Upregulation**, increasing the number of receptors, might this increase its opportunity to bind?

**Clinically important:** in such cases, even small doses of the drug can lead to death, the doctor gave an example about a child who was undergoing an
operation to expand (dilate) his pupil, but ended up dead when he was given a little dose of a certain drug (*his receptors are supersensitive to the drug*)

- It is really important to check the patient’s blood pressure and heart rate because it can give you an indication
- this supersensitivity or upregulation induces vasodilation and drop in blood pressure (hypotension), but why? you might find an answer to your “why” in the extra note.

**Extra Note: (not included)** why they induce vasodilation and drop in blood pressure, because parasympathetic nerves are unopposed, take for instance, the spinal anaesthesia as a factor that induces supersensitivity to adrenergic receptors, but spinal anaesthesia does not block the vagal component of the ANS (which is parasympathetic) ,as a result, this leads to decreasing blood pressure( hypotension), heart rate (bradycardia) and other might-be-life threatening effects of parasympathetic stimulation. Source: [https://www.ncbi.nlm.nih.gov/pubmed/7762776](https://www.ncbi.nlm.nih.gov/pubmed/7762776)

**Slides 4-6**

At the beginning, we said that drugs may interfere with one of the following steps, and these steps can explain the different effects of some drugs(adverse and therapeutic) effects, the consequences of drug abuse, Neurotransmission at adrenergic neurons involves the following steps:

1. Synthesis of (norepinpherine)
2. Storage of (norepinpherine) in vesicles
3. Release of (norepinpherine)
4. Binding to receptors
5. Removal of (norepinpherine)

*Note:* the previous processes are active, they need energy and could be inhibited (Note: passive processes are only affected by concentration gradient)

1) **Synthesis + Storage**

Synthesis of catecholamines such as epinepherine, norepinpherine and dopamine (this occurs in a multi-step reaction using many enzymes), *some drugs can inhibit these enzymes (as a side effect/ therapeutic effect)*
Let’s see the multi-step reaction:
- Phenylalanine is a precursor for tyrosine, which actively enters the cell by a carrier dependent on sodium (Na+)

- The rate-limiting step of Norepinephrine synthesis is the Hydroxylation of tyrosine to form DOPA (dihydroxyphenylalanine) - this step can be a target to many drugs-
  - Tyrosine $\rightarrow$ DOPA (hydroxylation by tyrosine hydroxylase)

- Decarboxylation of DOPA occurs to form dopamine
  - DOPA $\rightarrow$ Dopamine (decarboxylation by DOPA-decarboxylase enzyme)

Dopamine is then taken up into storage vesicles by a carrier system (amine transporter system), and then got hydroxylated into norepinephrine, (the storage occurs to inactivate the neurotransmitters, they are stored in vesicles to use them when they are needed, some drugs deplete these stores)
  - Dopamine $\rightarrow$ Norepinephrine (hydroxylation by the enzyme dopamine beta-hydroxylase)

Note: Dopamine can be administered IV, and Dopamine is not significant in peripheral nervous system PNS, its functions are limited to the CNS (central nervous system)

Note: Amine carrier system can be blocked by reserpine.

- Then Methylation occurs, a methyl group (-CH3) is added to norepinephrine, converting it into epinephrine
  - Norepinephrine $\rightarrow$ Epinephrine (mythelation)

Note:
- the adrenal medulla (suprarenal medulla) produces about 20% norepinephrine, and 80% is transformed into epinephrine.
2) Release

Release of neurotransmitters is triggered by arrival of the action potential, the membrane’s permeability to calcium ions increases (calcium comes from the extracellular fluid), this increase in calcium ions leads to fusion of synaptic vesicles with presynaptic membranes undergoing *exocytosis* to expel their contents.

**Clinical Note** about Guanetuidine (antihypertensive drug),

- **Its intended action** is to inhibit the release of neurotransmitter -such as epinepherine and norepinpherine- from the vesicles into the space.
- **One of its contraindications** is, it can lead to a hypertensive crisis (malignant hypertension) in some patients (extra: especially those with phenochromocytoma).

3) Binding

The released neurotransmitters binds to postsynaptic receptors, binding of norepinpherine to receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messangers, adrenergic receptors use both cAMP second messanger system and the phosphatidylinositol cycle to make a particular response, (Norepinpherine also binds to presynaptic receptors that modulate the release of the neurotransmitter, -mainly alpha2-)  

*some drugs prevent this binding*  

4) Removal

Removal of neurotransmitters from the synaptic space to terminate neurotransmitters’ actions.. this removal can occur by one of the following mechanisms:  

A) Destruction of the neurotransmitter by enzymatic metabolism in the synaptic space, 10% of them are removed by this mechanism, e.g: Metabolism of norepinpherine by Catechol-O-Methyl transferase (COMT) enzyme, in the synapse leading to production of O-methylated derivatives (inactive metabolites) which are passed into urine.

B) Diffusion out of the synaptic space, to enter the systemic circulation.
C) Reuptake from the synaptic space back to the presynaptic neuron by alpha receptors (it is the main and primary mechanism accounting for norepinephrine removal of over 90% of neurotransmitter (norepinephrine), it involves a sodium-chloride (Na+/Cl-) dependent norepinephrine transporter NET (this step can be inhibited by tricyclic antidepressants TCA such as imipramine)

**Tricyclic antidepressants’** work,
- by norepinephrine-serotonin reuptake *inhibitors* (such as duloxetine) leading to temporary accumulation of them in the synaptic space such as,
- or by *cocaine*.

**Reuptaken (Recaptured) norepinephrine fates:**

i. stored in vesicles: some are taken up into adrenergic vesicles by amine transporters to synthesise it, they become inactive in vesicles and released when needed - by another action potential- (as mentioned previously)

ii. Free (mobile pool, not captured in vesicles): it may persist in a protected pool in cytoplasm, or some norepinephrine can be oxidized by one of the enzymes which are found in nerve terminals (in the mitochondria), such as monoamine oxidase MAO, MAO inactivates norepinephrine in the mobile pool (not in vesicles), the products of this breakdown are passed to urine, *examples* on these products (*VMA* -vanillylmandelic acid-, metanephrine and nor-metanphrine)

**Note:**
- Reuptake occurs when a neurotransmitter binds to pre-synaptic receptors
- Response occurs when it binds to post-synaptic receptors
- MAO is found in the terminals, COMT is found in the synapse

**Mentioned in the lecture but I could not place it:**

- Some people use beta- blockers for sedation, it is important to note that beta blockers leads to receptor upregulation (*EXTRA NOTE:* during
withdrawal from use, it is important to decrease dose to avoid excessive cardiovascular effects)

(You are not supposed to memorise these:)

- **Anaesthetic**: a substance that induces insensitivity to pain (see also Spinal Anaesthesia)

- **Adrenal medulla (suprarenal)**: the inner part of the adrenal (suprarenal) gland that produces hormones such as adrenaline (the outer part of this gland is known as cortex)

  *Note*: Adrenal glands are located on top of each kidney (suprarenal)

- **Catecholamines**: chemicals that are responsible for the response to stressful situations, they can work as neurotransmitters or hormones, three most known are epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine

- **Exocytosis**: a type of transport that involves secretion of certain molecules outside the cell by fusion of vesicles with plasma membrane, this process requires energy.

- **Ganglion**: it is mainly a cluster of nerve cell bodies (it is where the preganglionic neurons connect with postsynaptic neurons), there are parasympathetic and sympathetic ganglia.

- **Spinal Anaesthesia**: an alternative to a general anaesthetic for some operations, it allows the patient to stay awake without feeling any pain by injecting amounts of local anaesthetic into the CSF - cerebro-spinal fluid- (caesarean section is performed under spinal anaesthetic)

- **Upregulation**: is the process by which the cell increases a cellular component in response to an external stimulus *(the opposite is downregulation* which is the process by which the cell decreases the quantity of a cellular component such as receptors/proteins ..., in response to an external stimulus)

*It is never too late.*

*Good Luck!*