pharmacology

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ADRENERGICPHARMACOLOGY

The sympathetic system is an important regulator of activities of the heart & peripheral vasculature especially in response to stress.
Adrenergic neurotransmitters are responsible for transmission at all postganglionic sympathetic neurons, except those of sweat glands.

We said before that adrenergic system mainly sympathetic except sweat glands (sympathetic nerve but ACH transmitter)

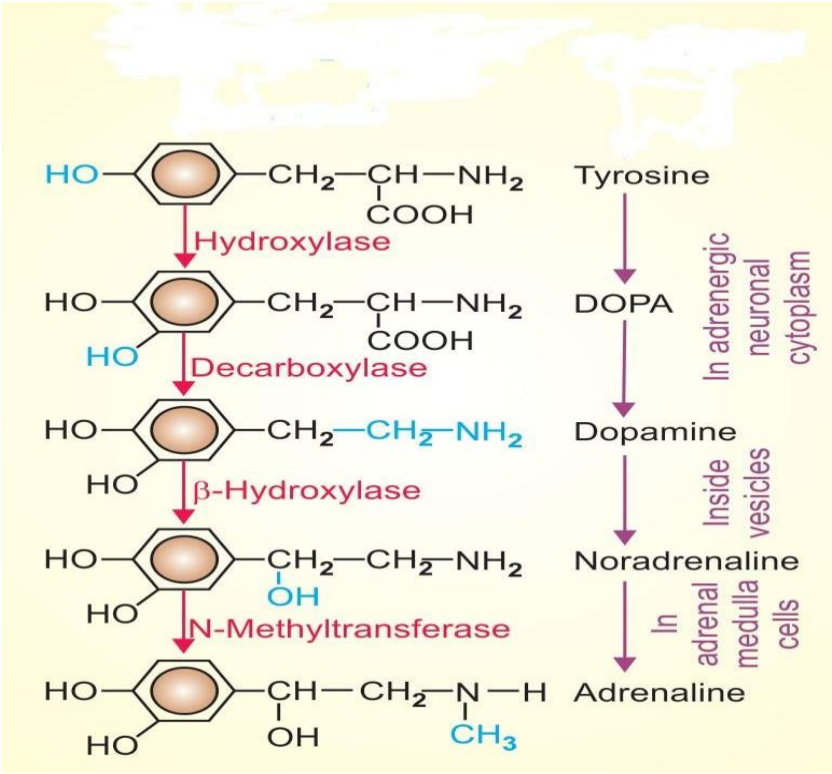
Adrenergic Neurotransmitters (endogenous catecholamines)

1-Norepinephrine (NE)= noradrenaline: The transmitter of postganglionic sympathetic fibers & of certain tracts in the CNS.

2-Epinephrine= adrenaline: major hormone of adrenal medulla. The adrenal medulla receives preganglionic cholinergic neurons & releases epinephrine.

3-Dopamine (DA): Central transmitter in the extrapyramidal, mesolimbic & tuberoinfundibular pathways & in the CTZ. It is also a peripheral transmitter.

Synthesis of CAs(Catecholamines):



The steps above are important and the enzyme required in each step :(
Let me tell you catecholamine synthesis cycle in simple English before reading more details in the upcoming page(PS the blue pic is very good for understanding)
#tyrosine is the precursor for all catecholamines, it enter the nerve ending with Na
#tyrosine is converted into dopa then dopamine in the cytoplasm
dopamine enter the vesicle where it is transformed into NE (in the vesicle)
After action potential reaches the nerve ending …NE is released to act on the adrenergic receptor of the specific tissue
#Where is Epinephrine then?? It is not formed in the nerve ending it is only formed in the adrenal medulla via methyl transferase (glucocorticoids are imp 4 this enzyme)
After NE act on the specific receptor .. reuptake occurs to terminate its action right! It may be stored in the vesicle again or metabolized by MAO enzyme (also the uptake may occur by other tissues other than nerve endings in this case it is metabolized by COMT enzyme)

Tyrosine hydroxylase is a specific and the rate limiting enzyme.
-Its inhibition by α-methyl-p-tyrosine → depletion of CAs → can be used in 1) pheochromocytoma before surgery(tumor of adrenal gland esults in the release of too much epinephrine and norepinephrine)
&2) in inoperable cases.

#NE is synthesized in the nerve cell & is stored in synaptic vesicles at the terminal end of the adrenergic neurons

#Synthesis of Adrenaline occurs only in the adrenal medullary cells. It requires high concentration of glucocorticoids for induction of the methylating enzyme.

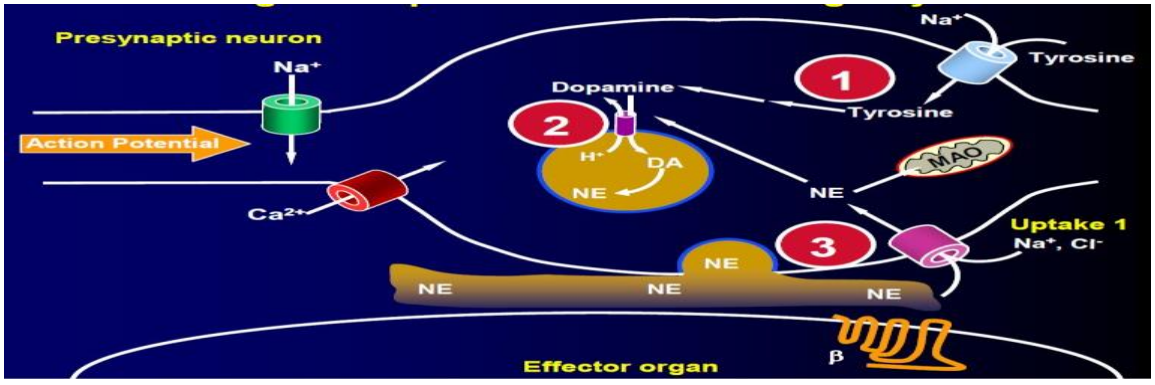
Storage of CAs

- NA is stored in synaptic vesicles or 'granules' within the adrenergic nerve terminal.
- The vesicular membrane actively takes up DA from the cytoplasm and the final step of synthesis of NA takes place inside the vesicle which contains dopamine β- hydroxylase.
- NA is then stored as a complex with ATP & a protein chromogranin

So we can tell the contents of the vesicle which are (Dopamine/NE/beta hydroxylase /ATP/Chromogranin)

Release of CAs

- The nerve impulse → release of CA by exocytosis
- All the vesicular contents (NA or Adr, ATP, dopamine β hydroxylase, chromogranin) are released



Drugs Affecting NE Release

NE release is controlled centrally by nucleus tractus solitarus (NTS) & peripheral by presynaptic neurones

Drugs ↑ release

- Low conc. of NE → activates presynaptic beta 2 receptors.(as a feedback)
- Tyramine(when taken with MAO inhibitors >>>HT crisis because it increase catecholamine synthesis)
- Amphetamine (we will talk more about them)
- Ephedrine. (we will talk more about them)
- Nicotine (presynaptic Nn) (heterogenous autoreceptor)

Drugs ↓ release

#High conc. of NE → activates presynaptic alpha2 receptors→ -ve feedback.

- ACh (presynaptic M_2).
  (heterogenous autoreceptor)

Clonidine. Methyldopa } Central alpha2 agonists

Fate of catecholamines

I. Uptake

A. Uptake 1 (amine pump): actively transports NE from synaptic cleft **into neuronal cytoplasm** to be stored in granules or metabolized by MAO enzyme (the main fate of released NE).

- **Blocked by:** tricyclic antidepressants (TCA) - cocaine.

B. Vesicular: from neuronal cytoplasm to **storage vesicles** for re-use.

- **Blocked by:** Reserpine (depletes stores).(vesicle has no NE)

C. Uptake II: to **target organs** for metabolism.(COMT enzyme)

- **Blocked by:** glucocorticoids.(Remember that they increase synthesis of adrenaline ..and here they inhibit uptake so they increase catecholamines in synaptic cleft ..more action)

II. Enzymatic Degradation of catecholamines

- The monoamines, epinephrine, NE & DA are catecholamines (contain catechol nucleus (a benzene ring with 2 OH groups)).
- They are degraded mainly by oxidative deamination by monoamine oxidase (MAO) & to a lesser extent by methylation by catechol-o- methyl transferase (COMT).
- The end product; vanilylmandelic acid (VMA) is excreted in urine → ↑ in pheochromocytoma (used in diagnosis).**imp (remember also methacholine used too in diagnosis)**

Classification of Adrenergic Receptors:

I- ALPHA (α): we are talking about postsynaptic receptors

α_1	α_2
Coupled to Gq .. ⊕PLC ↑IP3& DAG.. ↑Ca2+ & ⊕PKC	Coupled to Gi adenylate cyclase ↓cAMP ↓PKA
1. Vasoconstriction (skin mucus mem. Splanchnic vessels) 2. Relaxation of walls & Contraction of sphincters of GIT & urinary tracts. 3. Contraction of prostate & vas deferens. (help in ejaculation) 4. Active mydriasis. (stimulate d.pupillae) 5. Liver glycogenolysis & K+ release. 6. (from cell to blood hyperkalemia)	1. ↓ Central sympathetic outflow → ↓BP. (present in nucleus solitaris and when stimulated decrease sympathetic outflow) 2. ↓ Lipolysis. 3. ↓ Insulin secretion (predominant). 4. ↓ Renin release. 5. ↑ Platelet aggregation. When we will talk about this group we will consider them from the sympatholytic not sympathomimetic because they are inhibitory for sympathetic system

II- BETA (β):

β_1	β_2
Coupled to Gs protein . . . ⊕adenylate cyclase ↑cAMP . . . ⊕ PKA	
1. Cardiac stimulation. Imp (all properties) 2. Lipolysis ↑ plasma free fatty acids (**β1 and β3**). 3. ↑Renin secretion. (predominant)	1. Bronchodilation & mast cell stabilization. 2. Vasodilation of skeletal & coronary blood vessels. (I need blood to go to skeletal muscle and coronaries in stress !!!) 3. Uterine and intestinal relaxation. (we didn't talk about sphincters here focus :: Sphincters contraction only in alpha1 but walls relaxation in alpha1 and beta2 impp) 4. Liver & muscle glycogenolysis & k+ uptake. hypokalemia 5. Stimulate insulin release (weak effect). 6. Skeletal muscle tremors (because we increased blood supply and metabolism in muscle)

Presynaptic α2: (presynaptic or postsynaptic ….always inhibitory)
1. Inhibit NE release from sympathetic nerves.
2. ↓ Ach release in the heart & intestine.

Postsynaptic β3: ↑ Lipolysis → ↑ plasma FFA

III. DOPAMINE RECEPTORS

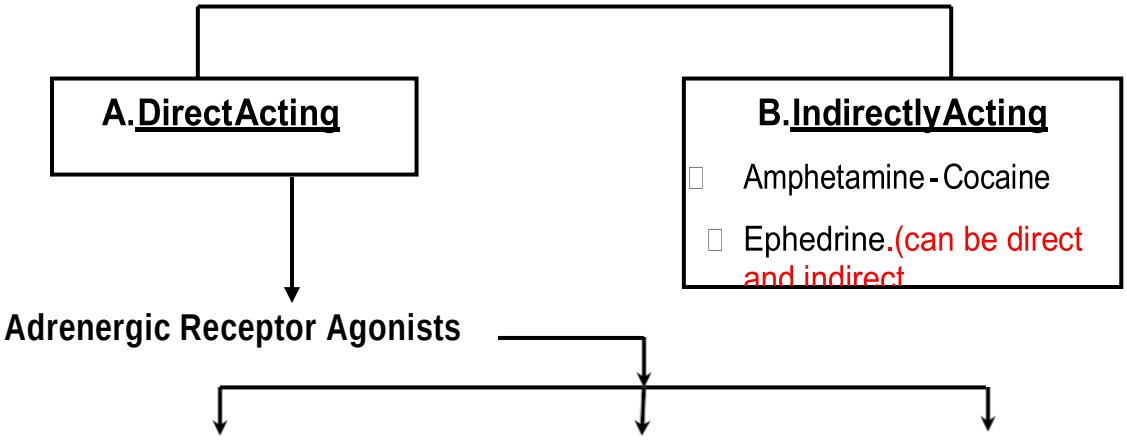
D_1: vasodilation of renal, coronary, cerebral & mesenteric blood vessels.

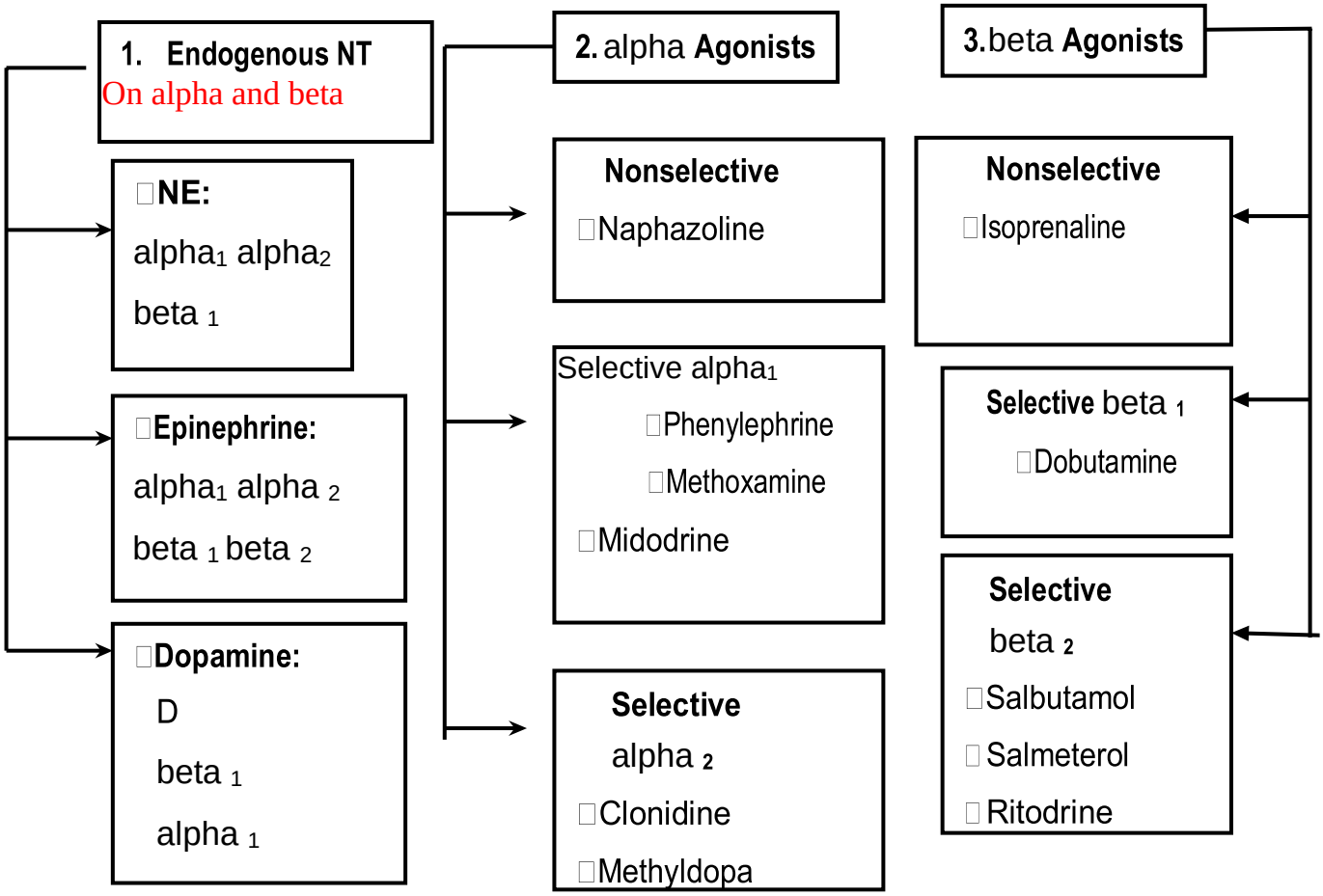
D_2: **Postsynaptic**: central in the extrapyramidal, tuberoinfundibular(hypothalamic pituitary pathway), & mesolimbic pathways & in the CTZ.(center responsible 4 vomiting outside BBB)

Presynaptic: ↓ DA & NE release from nerve endings.

Sympathomimetic Drugs just a "Brain map" and more details about the drugs will be in next lectures :)

Classification According to Mechanism of Action




1. Endogenous NT
On alpha and beta
NE:
alpha1 alpha2
beta 1
Epinephrine:
alpha1 alpha 2
beta 1 beta 2
Dopamine:
D
beta 1
alpha 1
2. alpha Agonists
Nonselective
Naphazoline
Selective alpha1
Phenylephrine
Methoxamine
Midodrine
Selective
alpha 2
Clonidine
Methyldopa
3.beta Agonists
Nonselective
Isoprenaline
Selective beta 1
Dobutamine
Selective
beta 2
Salbutamol
Salmeterol
Ritodrine

DA agonists: Dopexamine (D1 D2 B2) **–(not imp a lot)**

fenoldopam (D1) **vasodilator**

bromocriptine (D2).**(used in parkinsonism ttt)**

N.B.:

Selective α2- agonists are sympatholytics as they ↓ NE release.

Best of wishes <3