

Autonomic Nervous System (ANS)

Major portion of the NS (involuntary, unconscious, autonomic portion of the nervous system).

General Organization:

- 1- Central ANS (hypothalamus).
- 2- Peripheral ANS, which consists of :
 - a- Sympathetic (SNS).
 - b- Parasympathetic (PSNS).

A- Sympathetic Nervous System (SNS)

❑ Spinal Roots of Origin: (Thoraco-lumber)

The sympath. preganglionic fibers originate in the thoracic (T1-T12) & Lumber (L1-L5) segments of the spinal cord.

❑ Location of the ganglia:

Most of the sym. ganglia in 2 para-vertebral chain located along spinal cord.

- *The pre-ganglionic fibers short*
- *The post -ganglionic fibers long*

Preganglionic neurons

- Short
- Synapse with postganglionic neurons near spinal cord
- Release acetylcholine (ACH) to activate nicotinic receptors on postganglionic neurons

Postganglionic neurons

- Long
- Synapse on the target organ
- Release norepinephrine to activate adrenergic receptors on target organs

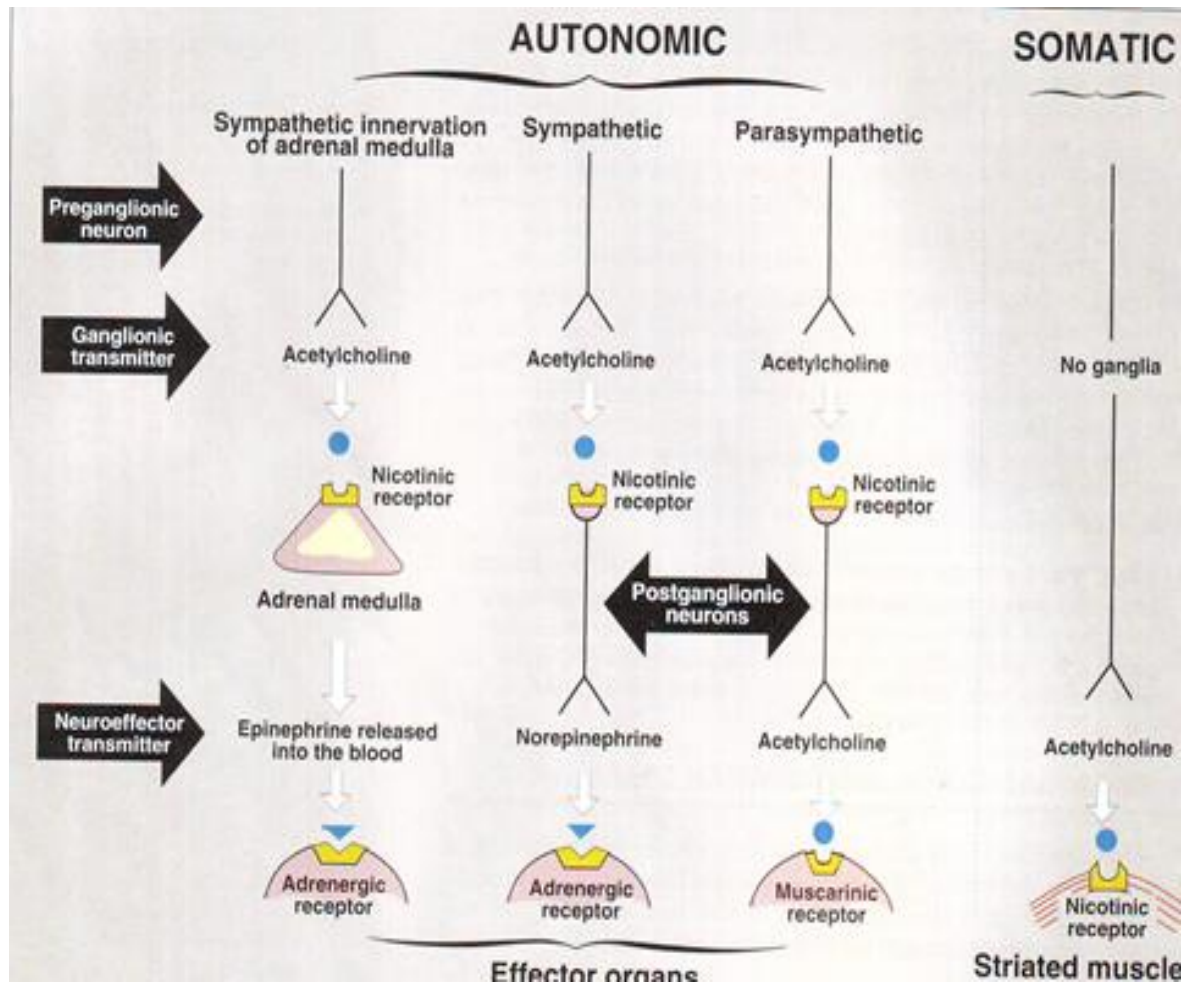
Exceptions in the sympathetic nervous system:

- **Sweat glands:**
 - » Postganglionic neurons involved with stress-related excretion release **norepinephrine** (“sweaty palms”)
 - » Postganglionic neurons involved with thermoregulation release **acetylcholine**
- **Kidneys:**
 - » Postganglionic neurons to the smooth muscle of the renal vascular bed release dopamine
- **Adrenal gland:**
 - » Preganglionic neurons do not synapse in the paravertebral sympathetic ganglion
 - » Preganglionic neurons synapse directly on the adrenal gland, release acetylcholine, and activate nicotinic receptors on the adrenal gland
 - » Adrenal glands release epinephrine into systemic circulation

Neuro-transmitters of SNS

Catecholamine

- Primary transmitter at symp. postganglionic neuron effector cells.
 - a compound containing a catechol nucleus (Benzene ring + 2 adjacent hydroxyl group) + amino-containing side-chain.
- 1- Noradrenaline (NA) Natural
 - 2- Adrenaline (A) Natural
 - 3- Dopamine Natural.
 - 4- Isoprenaline (Isoproterenol) Synth.



Stages of Catecholamines Transmission at symp Synapses

1. Synthesis

Tyrosine $\xrightarrow{\text{Tyrosine hydroxylase}}$ Dopa $\xrightarrow{\text{Decarboxylase}}$ Dopamine
 Dopamine $\xrightarrow{\text{Dopamine hydroxylase}}$ Noradrenaline (NA)

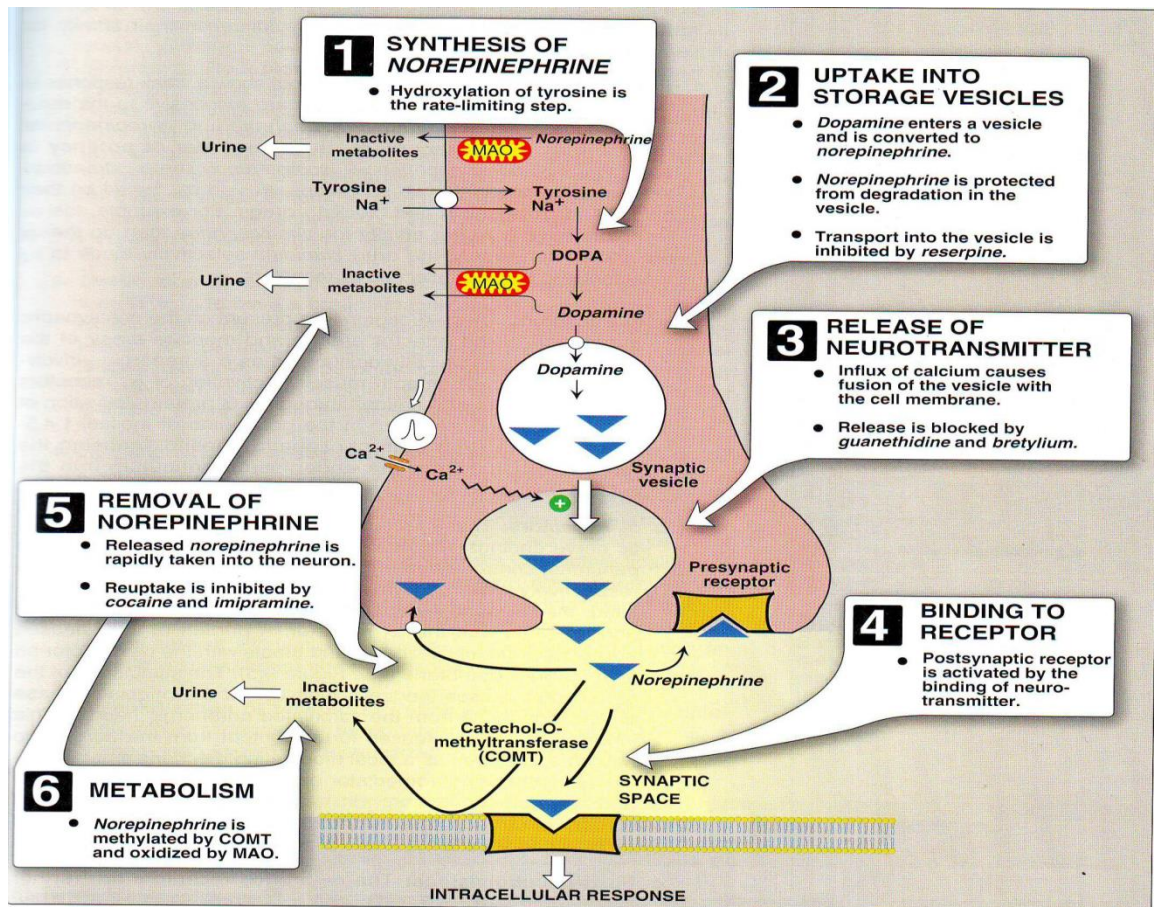
2- Storage of the transmitters at storage granules (inhibited by **Reserpine**).

3- Release of the transmitters from the storage sites (Inhibited by **Guanethidine & Bretylium**).

4- Activation of postsynaptic receptors leading to stimulation or inhibition of the effector organ.

5- Termination of action of Catecholamines by Inactivation of the transmitters.

Stages of Catecholamine Transmission



* In adrenal medulla

NA Enz. Phenylethanolamine-N methyl transferase (PNMT) →
Adrenaline (A).

Termination of action of Catecholamines (Inactivation of the transmitters)

1- Re-uptake into nerve terminals

a- Uptake 1: After release, NA diffuse out of the cleft or is transported into the cytoplasm of the terminal & bind them within storage granules (inhibited by **Cocaine & TCA**).

b- Uptake 2: Taken into the post-junctional cell.

2- Dilution by diffusion out of the junctional cleft and uptake at extraneuronal sites.

3- Metabolic transformation by:

a-MAO(Monoamino oxidase Enz.): mainly on the outer surface of mitochondria of the nerve terminal.

b-COMT(Catechol-O-methyl transferase Enz.):found (outside synaptic neuron) in the cytoplasm of liver & kidney mainly.

Classification of adrenoceptors

I- α Receptors:

A > NA > Isoprenaline

α 1:

- Present at the postganglionic nerve fibers of (Sm.m of Bl. vessels of skin, mucosa, splanchnic area).
- Constriction of most sphincters.
- Radial muscle of iris of the eye (causes its contraction), which lead to mydriasis.

α 2:

- In Presynaptic nerve ending, causing inhibition of the release of NA.
- In B cell of pancreas, causing decrease release of insulin.

II- β Receptors:

• Isoprenaline > A > NA

1- β 1 R (cardiac): Increase heart rate (HR) & contraction of heart.

2- β 2 R (Bronchial sm.m., Bl. vessels of Sk.m.) Bronchodilatation, vasodilatation, relaxation of visceral sm.m uterus & hepatic glycogenolysis.

3- β 3 R.

- Lipolysis, Thermogenesis.
- **III- Dopamine receptors:**
- D1, D2, D3, D4, D5

Symp NS responsible of the changes experienced during emergencies , called (fight or flight response).

1- CVS:

A- Heart: β 1 Receptor.

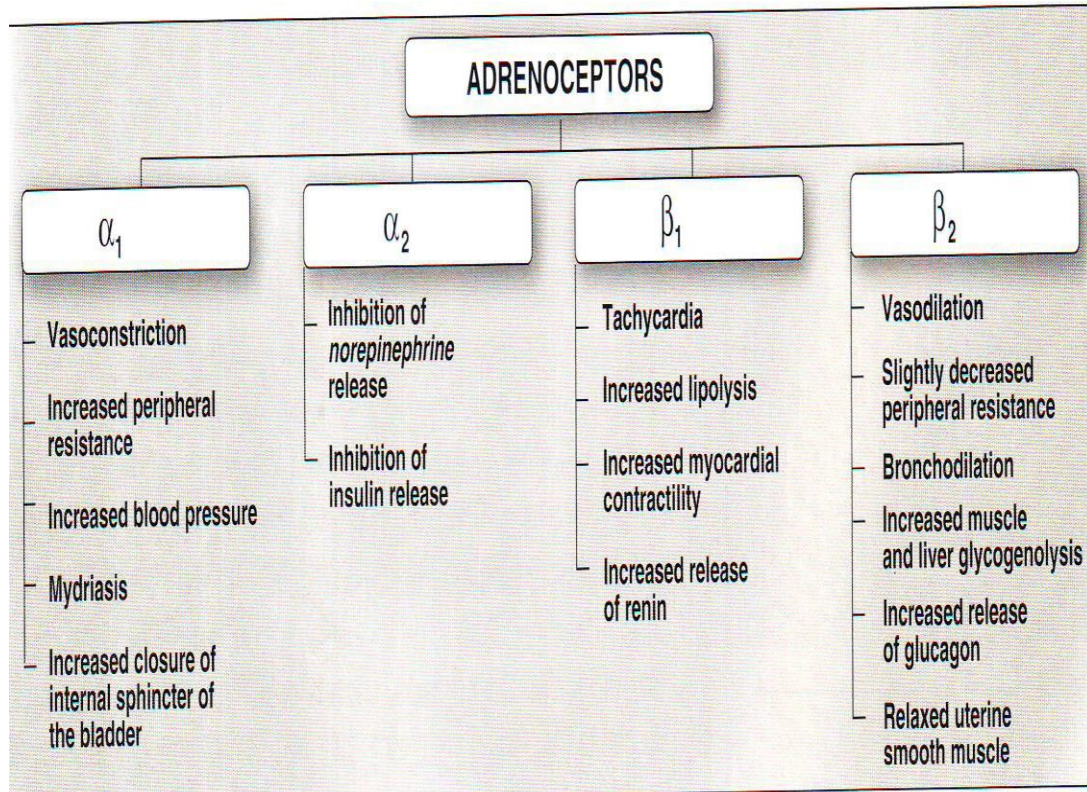
Increase heart rate & contraction of heart.

B- Sm.m of Bl.vessels:

- **Of skin, mucus membrane, & splanchnic area. (α 1 R):** causes Constriction.
- **Of Skeletal muscle (β 2 R):** causes Dilatation.

c- Blood Pressure: α 1 R

Increase BP due to increase PR (by contraction of the arterioles) & vasoconstriction.



2- Eye:

a- Contraction of iris radial muscle (α 1 R): causing papillary dilatation (mydriasis).

b- Decrease IOP (in open angle glaucoma) by:

- α -agonist:
Increase outflow of aqueous humor.
- β -antagonist:
Decrease production of aqueous humor by vasoconstriction of ciliary body bl. vessels.

3-Bronchioles: β 2 : Bronchodilatation.

4- Ureters & Urinary bladder: Relaxes detrusor (β 2) & Contraction of trigone & sphincter (α 1)

5- Genitalia:

- Female: Uterine relaxation (β 2).
- Male: Stimulate ejaculation (α 1).

6- GIT:

- Decrease in muscle motility & tone (**β 2**)
- Contraction of sphincters (**α 1**)
- Salivary gland (**α 1**): thick viscid secretion & decrease K-secretion.

7- Metabolic effects:

a- Liver: Glycogenolysis (**β 2**) & increase release of Glucagons with rise in blood sugar (**β 2**).

b- In B cell of pancreas

- causing decrease release of insulin (**α 2**).
- Increase lipolysis: **β 3**

Adrenergic Agonists Drugs

According to the structure:

1- Catecholamine: compound containing a catechol nucleus (Benzene ring with 2 adjacent hydroxyl group) + amino-containing side-chain.

Noradrenaline (NA), Adrenaline (A), Dopamine, Isoprenaline (Isoproterenol)

2- Non Catecholamine: compound not containing a catechol nucleus.

Phenylephrine, Ephedrine, Amphetamine.

Classifications

(According to the mechanism of action)

I-Direct acting adrenergic agonists:

- Adrenaline (A)
- Noradrenaline (NA),
- Isoproterenol(isoprenaline)
- Dopamine
- Phenylephrine
- Methaxamine
- Salbutamol, Terbutalin, Clonidine, Xylometazoline, Fenoldopam.

II- Indirect acting adrenergic agonists:

- 1- Amphetamine.
- 2- Tyramine.

III- Mixed-action adrenergic agonists.

- 1- Ephedrine.
- 2- Metaraminol.

Sympathomimetics (Direct acting adrenergic agonists)

- These bind to adrenergic (postsynaptic) receptors & causes intracellular signals & initiate action.
- These agents are widely used clinically.

1- Epinephrine (Adrenaline) A:

- Natural catecholamine, commonly used.
 - In therapeutic low doses : β R effect :
 - α R effect - At high dose

Biotransformation:

metabolized by **COMT** & **MAO** & result in production of metanephrine & vanillyl-mandelic acid (VMA) in urine.

* Destroyed by acid of stomach & so not effective orally & usually given SC or IM injection

Action of Adrenaline**1- C.V.S:****Adrenaline**

- increase HR & contraction of heart which lead to increase CO + increase systolic BP.
- But decrease PR, which lead to slight decrease Diastolic BP.

(Adrenaline increase systolic BP & Slight decrease Diastolic BP).

2- Respiratory:

Bronchodilatation (β_2).

3-Metabolic:

a-hyperglycemia by increase glycogenolysis in liver (β_2) & increase release of glucagon (β_2) + decrease release of insulin (α_2).

b- Lipolysis: due to agonist effect on β R of adipose tissue.

Clinical uses of Adrenaline

1- Acute asthma.

2- Anaphylactic shock (1st type hypersensitivity reaction).

3- Anesthesia:

a- With LA (dilution of A 1:10000 parts), as A lead to increase duration of LA by vasoconstriction at the site of injection.

b- Topically (topical haemostatic agent).

4- Glaucoma (2% topically) due to decrease production of aqueous humor by vasoconstriction of ciliary body blood vessels.

Side effects of Adrenaline

1-C.N.S: anxiety, fear, tension, headache, tremor.

2-Hemorrhage: (increase cerebral BP)

3-Cardiac dysarrhythmia: (+ **digoxin**), Large dose lead to V.fibrillation (fatal).

4- Pulmonary oedema.

Drug interaction with Adrenaline

a- Hyperthyroidism:

Adrenaline (hypertension due to increase adrenergic R on vasculature of the hyperthyroid patients).

b- Cocaine:

Cocaine increase CV response of adrenaline (prevent reuptake of Catecholamine into adrenergic neurons).