Adrenergic System

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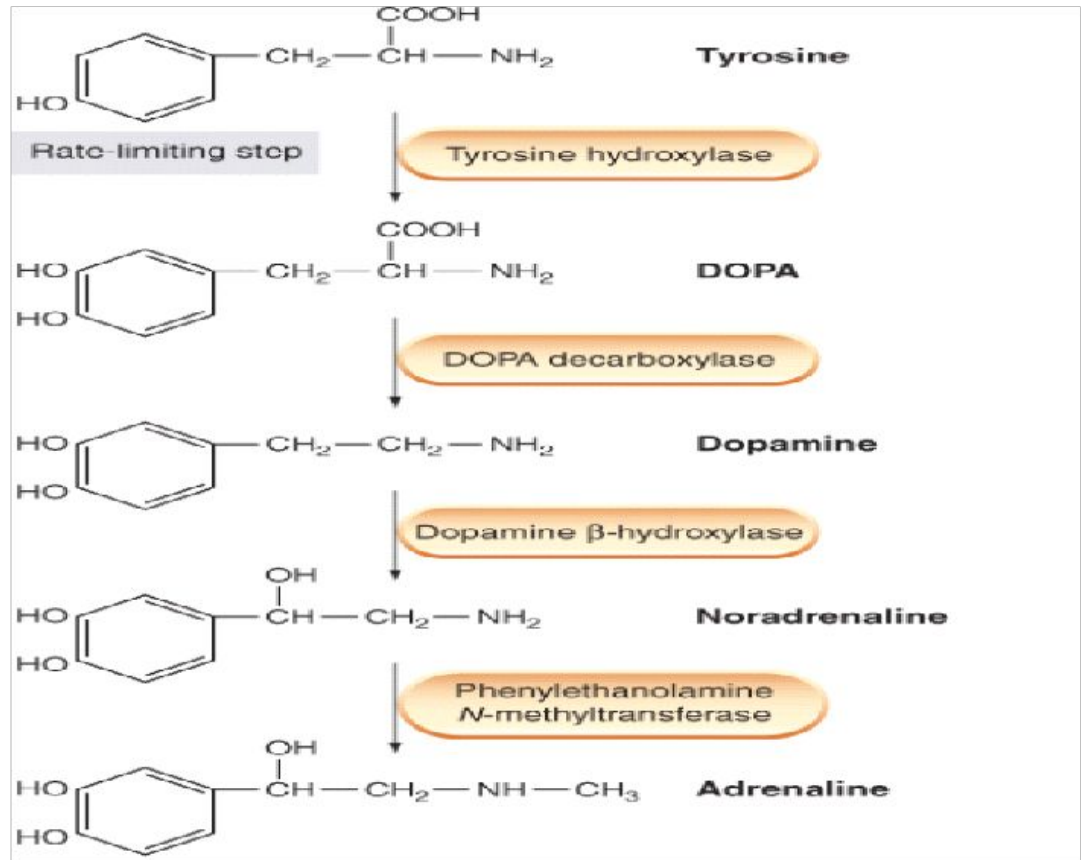
NORADRENERGIC TRANSMISSION
(Adrenergic System)

THE NORADRENERGIC NEURON

Responsible for **synthesis**, **storage** and **release** of **NA** and located in:
- ***ANS*** (postganglionic sympathetic neurons)
- ***CNS***

Noradrenaline synthesis :



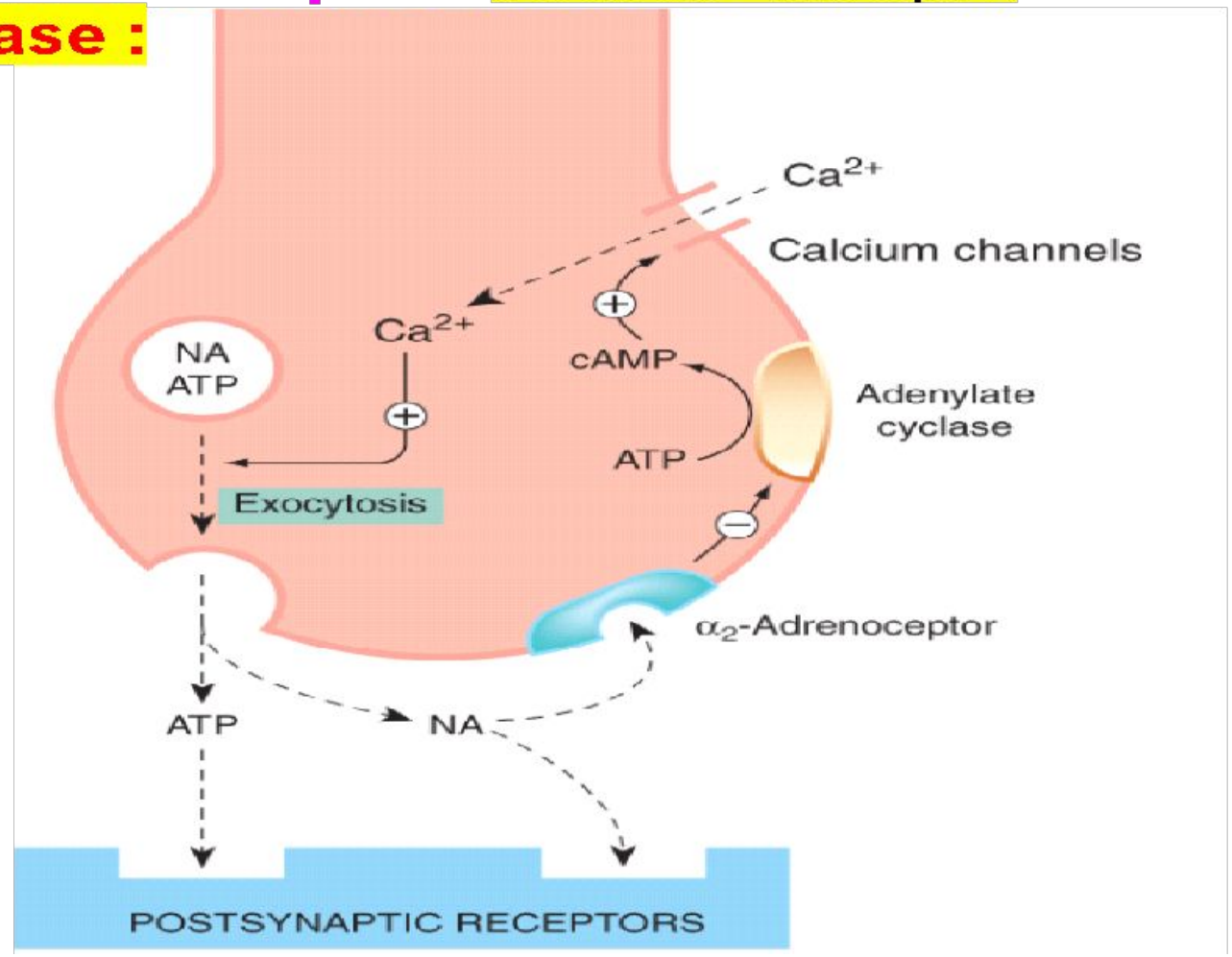
- **DOPA** = dihydroxyphenylalanine
- Adrenaline is synthesized in the adrenal medulla

Noradrenaline storage :

Stored in vesicles in **nerve terminals** or **chromaffin cells** (only a little is free in the cytoplasm) with ATP.

High concentration in the vesicles is maintained by the ***vesicular monoamine transporter***, **Reserpine** block this transport

Noradrenaline release :



•Release can be **blocked** by (***Bretylium***), other drug is ***Guanithidin*** has Bretylium like effect and Reserpine like effect. While release can be **stimulated** by indirect sympathomimetic agents like ***Amphetamine*** and ***Tyramine***.

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•Regulation of noradrenaline release :

•1- By acting on presynaptic receptors (**α_2-adrenoceptors**), released **NA** exerts a **local inhibitory effect** on the terminals from which it came(***autoinhibitory feedback***).

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•2- Uptake of catecholamine : (80% of termination of action)

•The action of released **NA** is terminated mainly by **reuptake**

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A. **Uptake 1 :**

- **Neuronal uptake** (by noradrenergic nerve terminals)
- Represent **75 %** of uptake
- **terminate the action** of the transmitter, and to recycle it.

A. **uptake 2 :**

- **Extraneuronal uptake** (By other cells near the nerve terminal)
- Represent **25 %** of uptake
- **Limit transmitter spread.**

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•Some drugs inhibit noradrenaline uptake e.g. ***Tricyclic Antidepressant*** **and** ***Cocaine***

•**Endogenous** and **exogenous** catecholamines are metabolized mainly by two enzymes: ***monoamine oxidase*** (***MAO***) and ***catechol-O-methyl transferase*** (***COMT***).

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•**MAO** is **intracellular**, (**membrane of mitochondria**).

•It is **abundant in noradrenergic nerve terminals**, also present in **liver** and **intestinal epithelium**.

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•**MAO** converts **catecholamines** to ***aldehydes***

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•**MAO** can also oxidize other monoamines, important ones being **dopamine** and **5-HT**.

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•**COMT** cause **methylation** of one of the **catechol hydroxyl groups** to give a ***methoxy derivative***.

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•**COMT** is **absent from noradrenergic neurons** but present **postsynaptically**, and in **adrenal medulla**, **liver** and **GIT**.

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•The final product of **MAO** and **COMT** is ***vanillyl mandelic acid*** (***VMA***) and excreted in **urine** in this form.

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•In patients with ***pheochromocytoma***, the urinary excretion of ***VMA*** is markedly increased.

ADRENOCEPTORS

•Classification of adrenoceptors:

•Main pharmacological classification into ***α*** and ***β*** types.

•Adrenoceptor subtypes: (G-protein-coupled receptors).

- two main ***α-receptor*** subtypes, α_1 and α_2, each divided into further subtypes (α_{1A}, $_{1B}$, ……)
- three ***β-adrenoceptor*** subtypes (β_1, β_2, β_3)

•Second messengers:

- **α_1-receptors** (G_q) activate phospholipase C, producing **IP_3** and **DAG** as second messengers
- **α_2-receptors** inhibit adenylate cyclase, decreasing cAMP formation (G_i)
- all types of ***β-receptor*** stimulate adenylate cyclase (G_s) and increase intracellular cAMP

The main effects of adrenoceptors activation

A, adrenaline; **ISO**, isoproterenol; **NA**, noradrenaline.

Table 14.1 Distribution and actions of adrenoceptors

Tissues and effects	α_1	α_2	β_1	β_2	β_3
SMOOTH MUSCLE					
Blood vessels	Constrict	Constrict/dilate	–	Dilate	–
Bronchi	Constrict	–	–	Dilate	–
Gastrointestinal tract	Relax	Relax (presynaptic effect)	–	Relax	–
Gastrointestinal sphincters	Contract	–	–	–	–
Uterus	Contract	–	–	Relax	–
Bladder detrusor	–	–	–	Relax	Relax
Bladder sphincter	Contract	–	–	–	–
Seminal tract	Contract	–	–	Relax	–
Iris (radial muscle)	Contract	–	–	–	–
Ciliary muscle	–	–	–	Relax	–
HEART					
Rate	–	–	Increase	Increase[a]	–
Force of contraction	–	–	Increase	Increase[a]	–
OTHER TISSUES/CELLS					
Skeletal muscle	–	–	–	Tremor Increased muscle mass and speed of contraction Glycogenolysis	Thermogenesis
Liver (hepatocytes)	Glycogenolysis	–	–	Glycogenolysis	–
Fat (adipocytes)	–	–	–	–	Lipolysis Thermogenesis
Pancreatic islets (B cells)	–	Decrease insulin secretion	–	–	–
Salivary gland	K^+ release	–	Amylase secretion	–	–
Platelets	–	Aggregation	–	–	–
Mast cells	–	–	–	Inhibition of histamine release	–
Brain stem	–	Inhibits sympathetic outflow	–	–	–
NERVE TERMINALS					
Adrenergic	–	Decrease release	–	Increase release	–
Cholinergic	–	Decrease release	–	–	–

[a]Minor component normally but may become significant in heart failure.

•Activation of α_1 Adrenoceptors:

•G-protein will activate phospholipase C that will act on **PIP_2** membrane phospholipid to produce **IP_3 & DAG** 2nd messengers. **IP_3** will stimulate intracellular Ca^{++} release that cause **smooth muscle contraction**.

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•Activation of α_2 Adrenoceptors:

•G-protein will inhibit adenylate cyclase enzyme (that convert ATP to cAMP 2nd messenger) so **decrease the concentration of cAMP** that will decrease transmitter release by reducing Ca^{++} influx.

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•Activation of *β* Adrenoceptors:

•G-protein will stimulate adenylate cyclase enzyme so **increase the concentration of cAMP** that will produce the following effects:

- In the **heart** cAMP will **increase Ca^{++} influx** (increase HR **(+ve chronotropic** effect**)**, automaticity, contractility **(+ve inotropic)**, conductivity **(+ve dromotropic)**, excitability, cardiac output, cardiac work, and O_2 demand, while decrease refractory period)
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- In **smooth muscles** cause **phosphorylation (inactivation) of myosin light chain kinase** and produce **relaxation**.
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- In the **Liver** cAMP will activate enzymes responsible for **Glycogenolysis and Gluconeogenesis**.
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- In **adipose tissue** cAMP will **activate lipase enzyme**.

ADRENERGIC AGONISTS
(Sympathomimetic drugs)

•CLASSIFICATION

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1. **according to chemical structure: (Catecholamines & Non-catecholamines)**

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•Catecholamine :

•Catecholamines are compounds containing a catechol moiety (a benzene ring with two adjacent hydroxyl groups) and an amine side-chain. Pharmacologically, the most important ones are:

- **Noradrenaline**
- **Adrenaline**
- **Dopamine**
- **Isoproterenol** (**isoprenaline**), a synthetic drug
- **Dobutamine**, synthetic drug, act as selective agonist for β_1 receptors

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1. **according to receptor selectivity:**
   - ***Selective α_1 agonists***
   - ***Selective α_2 agonists***
   - ***Selective β_1 agonists***
   - ***Selective β_2 agonists***

according to the mode of action:

- **Direct-acting agonists:** These drugs act directly on **α** or **β** receptors. Examples include ***adrenaline***, ***noradrenaline***, ***isoproterenol***, ***phenylephrine*** ….etc.
- **Indirect-acting agonists:** These agents may block the uptake of noradrenaline (**uptake inhibitors**) *e.g.:* ***cocaine*** or are taken up into the presynaptic neuron and cause the **release of noradrenaline** e.g. ***amphetamines***.
- **Mixed-action agonists:** Some agonists, such as ***ephedrine*** and ***pseudoephedrine*** have the capacity both to stimulate adrenoceptors directly and to release noradrenaline from the noradrenergic neuron

Catecholamines	Non-catecholamines
High potency	Low potency
Do not readily penetrate into CNS	Readily penetrate into CNS
Metabolized by MAO & COMT	Not metabolized by MAO & COMT
Not given orally (except isoprenaline)	given orally
Short duration of action	Long duration of action
Less lipid soluble	High lipid solubility
e.g. adrenaline, dopamine, isoprenaline	e.g. ephedrine, phenylephrine, amphetamine


thank you!