Pharmacology team 436

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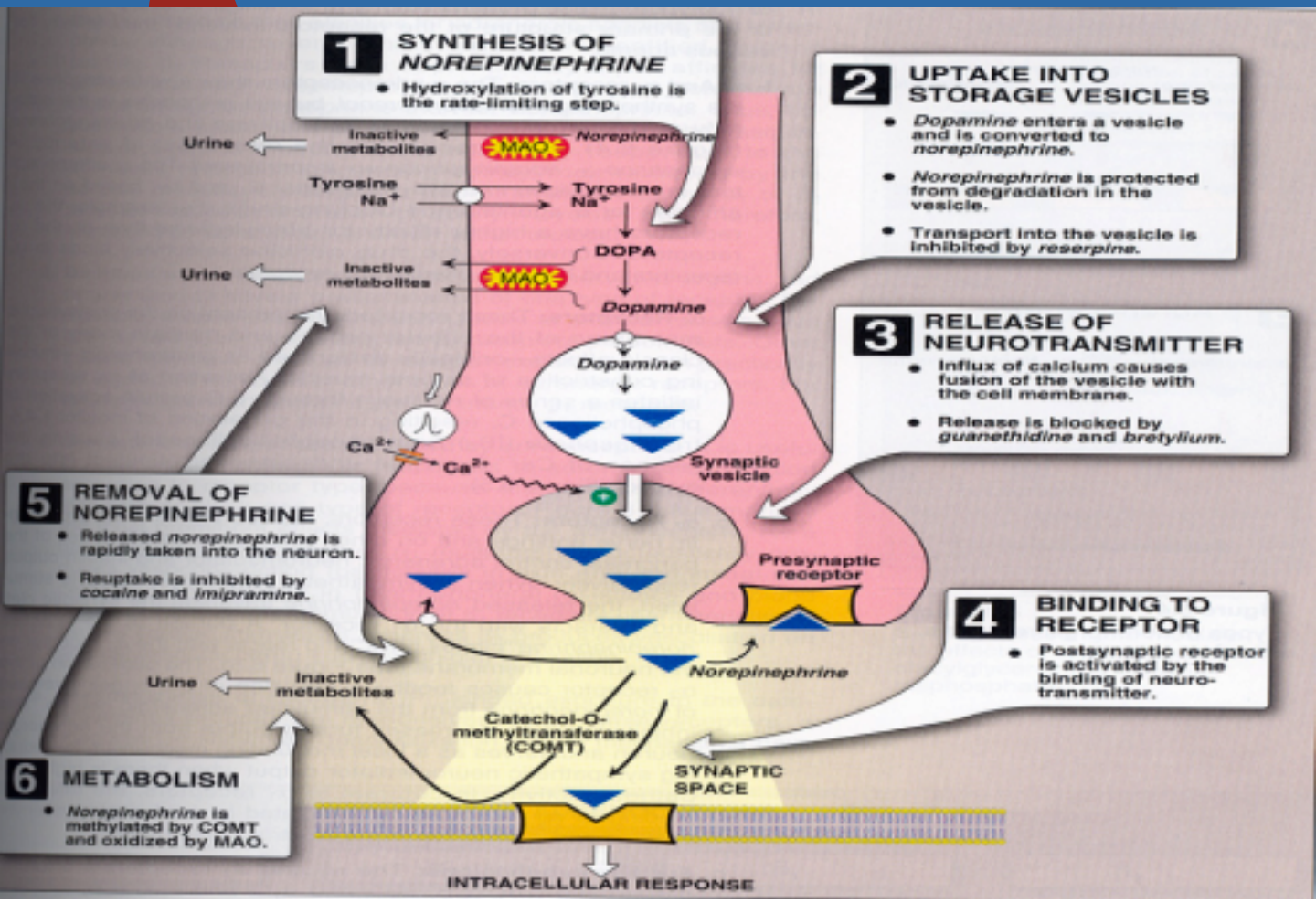
Adrenergic agonists

Objectives:

على قدر الهدف يكون الانطلاق.

- Titles
- Very important
- Extra information
- Doctor's notes

Adrenergic transmission



Adrenergic transmission

1) **Synthesis of norepinephrine**
2) **Storage of norepinephrine**
3) **Release of norepinephrine**
4) **Binding to post synaptic receptors**
5) **Ending of action by**

- ✓ Neuronal reuptake into neuron
- ✓ Monoamine oxidase (MAO) in neuronal mitochondria
- ✓ Catechol -O-methyl transferase (COMT) in synaptic space

Adrenergic receptors

In general we can say
1 → excitatory
2 → inhibitory

α-adrenoceptors			β-adrenoceptors		
α_1	α_2	β_1	β_2		β_3
postsynaptic	Presynaptic	postsynaptic	postsynaptic	Presynaptic	postsynaptic
Present in smooth muscles.	-	mainly in heart قلبي هو بيتك الأول و الأخير	mainly in smooth muscles	-	adipose tissue
excitatory in function except in GIT	Inhibition of NE (Negative feedback) α_2 = (a t)wo	excitatory in function	inhibitory in function present هذا بيتك الثاني ارتاح inhibitory =relaxation	↑ release of NE (Positive feedback) β2 = (P t)wo	
• Vasoconstriction of skin & peripheral blood vessels →↑peripheral resistance → hypertension • Relaxation of GIT muscles • ↑Glycogenolysis • Contraction of: 1- radial muscle of eye → mydriasis 2-pregnant uterus. عشان كذا ما ينفع استخدم أي درق يشتغل على هذا الريسبتور للمرأة المتوقع اجهاضها . 3- sphincter in GIT + urinary bladder راح (أ)جهض طفلي الأول؟ = α_1		↑ heart rate: *+ chronotropic effect, Tachycardia* ↑ force of contraction : *+ inotropic effect* ↑ *conduction velocity : +dromotropic effect* ↑ blood pressure ↑ renin release	• Relaxation of: 1- skeletal & coronary blood vessels (vasodilatation). 2-bronchial smooth muscles 3- GIT muscles (constipation). 4-Urinary bladder 5-Uterus Delay premature labor • ↑blood glucos level(hyperglycemia) • ↑ glucagon release from pancreas • ↑ liver & muscle glycogenolysis • Tremor of skeletal muscles	عكس الفا ١ هنا يفضل استخدامه للمرأة المتوقع اجهاضها لانه يسوي ريلاكسيشن. The 2nd baby is coming. = β_2	↑ lipolysis →↑ free fatty acids

Sympathetic actions

Sympathetic

Dilates pupil

Inhibits flow of saliva

Accelerates heartbeat

Dilates bronchi

Inhibits peristalsis and secretion

Conversion of glycogen to glucose

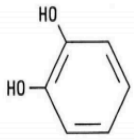
Secretion of adrenaline and noradrenalin

Inhibits bladder contraction

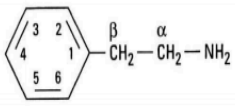
Constipation

Relaxation of the uterus.

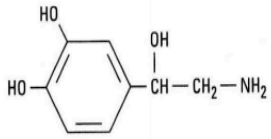
↑ ***conversion of glycogen to glucose (hyperglycemia)***



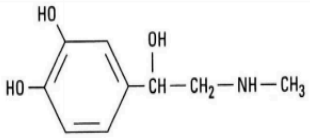
Catechol



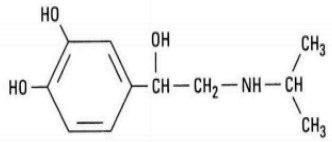
Phenylethylamine



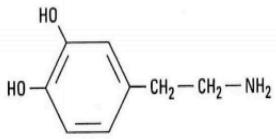
Norepinephrine



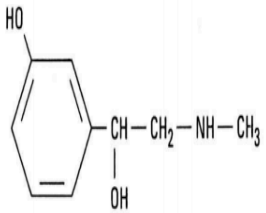
Epinephrine



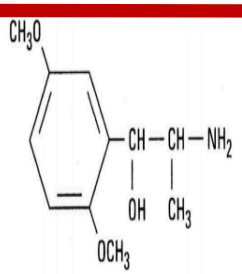
Isoproterenol



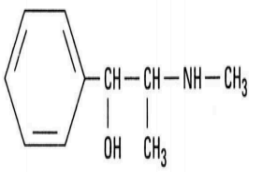
Dopamine



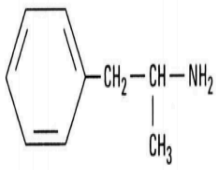
Phenylephrine



Methoxamine



Ephedrine



Amphetamine

Some examples of noncatecholamine sympathomimetic drugs.

Classification of sympathomimetics

Action

- **Direct acting:**
- Direct stimulation of adrenergic receptors -: **Adrenaline - Noradrenaline - Isoprenaline - Phenylephrine - Dopamine - Salbutamol - Methoxamine - Naphazoline - Clonidine – dobutamine**

- **Indirect acting:**
- Increase noradrenaline release from pre-sympathatic adrenergic nerve endings -: **Amphetamine – tyramine.**

مافيه زيادة من نورا Amphetamine increase NA

- Inhibit noradrenaline uptake: **Cocaine - Anti depressants**

- **Mixed "dual acting":**
- Direct and indirect stimulation of adrenergic receptors -: **Ephedrine - Pseudo-ephedrine**

Chemistry

- **Catecholamines:**
- -have catechol rings - Water soluble - Not effective orally - Poor penetration into CNS - Inactinated by COMT and MAO in GIT - Sort half life: **Adrenaline - Noradrenaline – Dopamine - Isoprenaline**

Adre Nora is Dopa ادري نورا از دوبا

- **Non-catecholamines:**
- Lack catechol rings - Lipid soluble - effective orally - cross well BBB - Not inactivated by COMT in GUT wall - Long half life: **- Ephedrine – Amphetamine - Phenylephrine**

Spectrum of action

- **Non-selective adrenergic agonist:**
- Adrenaline (a1, a2, B1, B2, B3)
- -Noradrenaline (a1, a2 B1)

نورا وقفت عند قلبي β_1

- -Isoprenaline (B1, B2, B3)

Isomers of peta receptor

- -Dopamine (a1, B1, D1)

- **selective agonist:**
- Phenylephrine (a1)
- - a-methyldopa – clonidine (a2)
- -Dobutamine (B1)

β_1 والأمانة والضمير محلها القلب Do it But be Amine

- -Salbutamol , terbutaline, ritoderine (B2)

Adrenaline

- non-selective agonist (a1, a2, B1, B2).
- Natural, catecholamine.
- Fast onset of action.
- Short duration of action. "cause inactivated by COMT and MAO in GIT"
- Not effective orally. "inactivated by intestinal enzymes"
- Given by inhalation, SC or IV , topically.

Pharmacological actions:

Heart	β_1	Inotropic / Chronotropic / Dromotropic
Blood Pressure	$\alpha 1$, $\beta 1$	Increase systolic
	β_2	Decrease diastolic
Blood vessele	α_1	Vasoconstriction Of BV in skin and peripheral
	β_2	Vasodilation of BV of skeletal muscle and coronaries
Eye	α_1	Mydriasis (not effect on accommodation)
Lung	β_2	Bronchodilation
GIT	α_1	Contract sphincter
	β_2	Decrease motility
bladder	α_1	Contract sphincter
	β_2	Relaxation of detrusor muscle
Pregnant uterus	β_2	Relaxation tocolytic

Metabolism:

a2	B2	B3	CNS (little)
- ↓ insulin	- ↑ Glucagon - ↑ liver glycogenolysis - ↑ skeletal muscle glycolysis	- Adipose lipolysis	- Headache - Tremors - restlessness

uses

Locally	Hemostatic "Control bleeding" Such as	Nasal pack in epistaxis
		In dental practice
	Combined with local anesthetic to ..	↓ Absorption of local anesthetic
		↑ Duration of action
		↓ Side effect of local anesthetic
		↓ Bleeding from incision
Systemically	In acute asthma "given by inhalation, SC "	$\beta_2 \rightarrow$ bronchodilation $\alpha 1 \rightarrow$ ↓ mucosal edema
	Anaphylactic shock "hypersensitivity reactions"	Is the drug of choice given SC Is the physiological antagonist of histamine ↑ BP and bronchodilation
	Cardiac arrest	Given IV

Adverse effects:

- Tachycardia / Palpation / Arrhythmias / Angina pains
- Headache / Weakness Tremors / Anxiety / Restlessness
- Hypertension → Cerebral hemorrhage and pulmonary edema
- Coldness of extremities → Tissue necrosis and gangrene if extravasation.
- Nasal stuffiness: rebound congestion if used as decongestant

Contraindication

- Hypertyhroidism
- Close angle glaucoma "ciliary relaxation , ↓filtration angle" → ↑ IOP

Cardiovascular disease such as :

- Coronary heart disease (CHD)
- Ischemic heart disease (angina)
- Arrhythmia
- Myocardial infarction
- Hypertension
- Peripheral arterial disease

Norepinephrine (Noradrenaline)

Feature :	Uses :
- Non selective agonist "mainly in a adrenoreceptors a1, a2, week action on B2" - Catecholamine - Sever vasoconstriction (a1) - Increase force of contraction but decrease HR - Reflex bradycardia - Given only by IV - not I.M or S.C → necrosis	In hypotensive state " in septic shock if fluid replacement and inotropics fail" As a local haemostatic with local anesthetic

Isoprenaline

Features:	Pharmacological actions:		Uses	Contraindication
Non selective B agonist "B1 B2 B3" Synthetic, Direct acting Catecholamine Longer effect "no reuptake, no destruction by MAO"	β_1	- Inotropic - Chronotropic - Increase cardiac output	Mainly in cardiac arrest "parenteral" Rarely in acute attacks of asthma " inhalation"	Hyperthyroidism Coronary heart disease
	β_2	- Vasodilation of blood vessels of skeletal muscles and coronaries - Bronchodilation - Relaxation of uterus - hyperglycemia		
	β_3	lipolysis		

Dopamine

Features:	- Natural CNS neurotransmitter - Direct acting, catecholamine - Given parenterally via infusion		
Doses:	Low: "D1"	Vasodilation of: - Muscarinic - Coronary - Renal blood vessel → Improves blood flow to viscera "has diuretic action"	- On heart → " inotropic, chronotropic effects " - On Blood pressure → "according to dose" • First : decrease in BP due D1 effect . • Then : increase in BP due to β_1 Followed by $\alpha 1$ effect
	Intermediate: " β_1 "	+ inotropic +chronotropic	
	High: "$\alpha 1$ "	Vasoconstriction	
Uses :	- Cardiogenic shock "IV infusion" : • Septic • Hypovolemia • Cardiogenic • Increase BP and CO (B1) "without causing renal impairment D1"	- Can be given in acute heart failure "but better dobutamine"	

Dobutamine (selective B1)	
Features:	• Synthetic catecholamine. • Metabolized by COMT • Short duration, given by intravenous infusion • **Selective β_1–receptor agonist.** • Positive inotropic effect, increases cardiac output, with little increase in heart rate.
Uses:	**short term management of cardiac decompensation** after cardiac surgery, in acute myocardial infarction (AMI) & heart failure.

Phenylephrine (selective α1)	
Features:	• A synthetic **non catecholamine, direct acting** • Not inactivated by COMT, longer duration of action • Vasoconstriction ,↑ increased both systolic & diastolic blood pressure, hypertension, reflex bradycardia.
Uses:	**Nasal decongestant** topically, nasal drops in allergic rhinitis, cold **Vasopressor agent:** hypotension & terminate atrial tachycardia (reflex bradycardia). **Local Haemostatic** with local anesthesia **Mydriatic:** In ophthalmic solutions to facilitate eye examination.
Adverse effects:	Hypertension
other	**Midodrine** peaks in 20 min, duration 30 min, used in hypotensive states

ADRENERGIC STIMULANTS
Direct Acting Sympathomimetics

Nasal & Ocular Decongestants

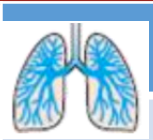
PHENYLETHYLAMINES

- Phenylephrine
- Pseudoephedrine
- Methoxamine

IMIDAZOLINE

- ~~Naphazoline~~
- ~~Oxymetazoline HCl~~ (Afrin)
- ~~Xylometazoline HCl~~ (Otrivine)

Selective β_2 agonists



Salbutamol	Ritodrine	Terbutaline
• selective β2 agonists, non catecholamines • orally or by inhalation or injection. • Produces bronchodilation • **Used for acute attack of asthma & COPD.**	• Selective β2 agonist, non catecholamines. • orally or by injection • Is a tocolytic drug (relaxation of uterus). • **Used** orally and injection to treat **premature labor.** Ritodrine = Tocolytic = Beta Two	• **Bronchodilator** • **Tocolytic** 

Clonidine (selective α2)

Features:	• synthetic, imidazoline • Given orally or as patch. • Is a presynaptic **α_2 agonist**.
Pharmacological action	Acts centrally (a2) at nucleus tractus solitaries to ↓ sympathetic outflow to heart & vessels. Inhibit sympathetic vasomotor centers
Uses:	**Used as antihypertensive in essential hypertension to lower BP.**

Brimonidine

is an imidazoline → **α_2 agonist used in glaucoma**

ADRENERGIC STIMULANTS
Indirect & DUAL acting sympathomimetics

Indirect acting	**Amphetamine** (α & β)	Synthetic non-catecholamine. ○ given orally, longer duration ○ Excreted mostly unchanged (↑ by acidification of urine) ○ Acts indirectly, it depletes vesicles from stored NE → tachyphylaxsis ○ has CNS stimulant effects; mental alertness, wakefulness, concentration & self-confidence followed by depression & fatigue on continued use ○ ↑ euphoria → causes its abuse ○ ↓ Weight → ↓ appetite ↑ increase energy expenditure ○ No more used therapeutically → induces psychic & physical dependence and psychosis.
DUAL Acting	**Ephedrine** (α & β)	Plant alkaloid, synthetic, non-catecholamine, dual acting ○ direct action on receptors → down regulation of receptors ○ indirect by releasing NE from adrenergic endings → depletes stores ○ Tachyphylaxsis ○ Orally, not destroyed by enzymes → prolonged action ○ has CNS stimulant effects (less than amphetamine) ○ No more therapeutically used → but is abused by athletes and prohibited during games.
	Pseudoephedrine	Dual acting < CNS & pressor effects compared to ephedrine. Used as nasal & ocular decongestant & in flu remedies

SUMMARY

- Agents specifically indicated for **hypotension**

  Midodrine, Phenylephrine, Norepinephrine, ~~Phenylpropanolamine~~

- Agents specifically indicated for **cardiogenic shock→AHF**

  Dobutamine, Dopamine, Epinephrine

- Agents specifically indicated for **shock** (Dopamine, Norepinephrine)

- Agents specifically indicated for **cardiac arrest**

  (Epinephrine, Norepinephrine, Dobutamine)

- Agents specifically indicated for **bronchial asthma**

  Salbutamol, Salmeterol, Formoterol, Terbutaline, Isoprenaline

- Agents specifically indicated for **premature labour**

  Ritodrine, Terbutaline

- Agents specifically indicated for **nasal decongestion**

Pseudoephedrine, Naphazoline, Oxymetazoline, Phenylephrine, Xylometazoline

- Agents specifically **abused in sports** → Ephedrine, Amphetamine

SAQ

A 47 years old patient with asthma came to the emergency room with difficulties in breathing, after checking his heart beats it turned out he has tachycardia.

Which drugs could be prescribed to him that will slow his heart and reduce the vasoconstriction in his lung?

Adrenaline and Noradrenaline

Which receptors do that drugs effect ?

Adrenaline (α1, α2 , β1 , β2, β3)
Nor adrenaline (α1, α2 , β1)

What's the traits of that drug that you can conclude if you know its a catecholamine?

- have catechol ring water soluble (polar) Not effective orally.
- Poor penetration into CNS.
- inactivated by COMT & MAO in GIT.
- short half-life.

What's the best route of administration for his case ?

I.V

what are 3 adverse effect that is expected to see in this patient after giving him the drug ?

- Tachycardia.
- Hypertension.
- weakness.

QUIZ


Boys	Girls
عبدالرحمن ذكري	غادة المهنا
عبدالعزيز رضوان	اللولو الصليهم
مؤيد أحمد	روان القحطاني
فيصل العباد	امل القرني
فارس النفيسة	شروق الصومالي
خالد العيسى	سما الحربي
عبدالرحمن العريفي	انوار العجمي
عبدالرحمن الجريان	وتين الحمود
محمد خوجة	رنا باراسين
عمر التركستاني	

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