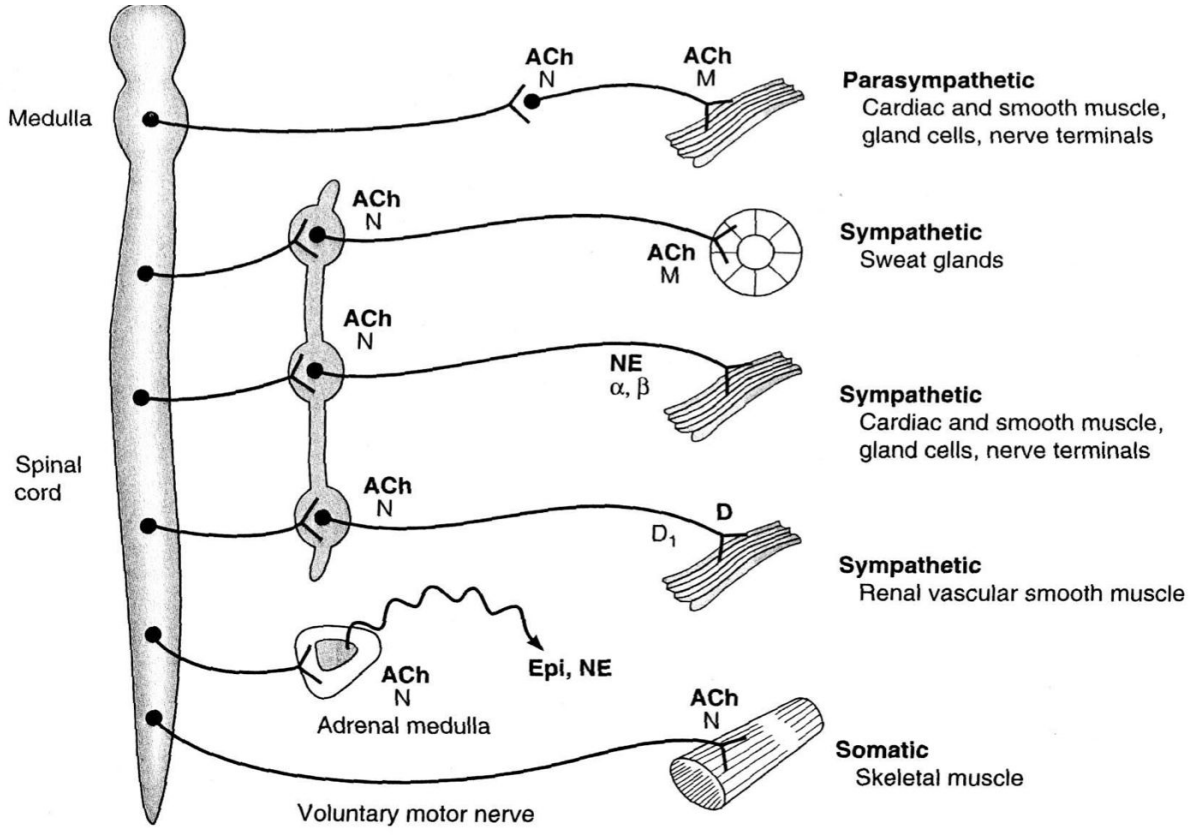
Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Respiratory Block

5 Adrenergic agonists



Color index:
Red: important
Grey: Notes or extra information

Adrenergic transmission

Adrenergic transmission:

1) Synthesis of norepinephrine.

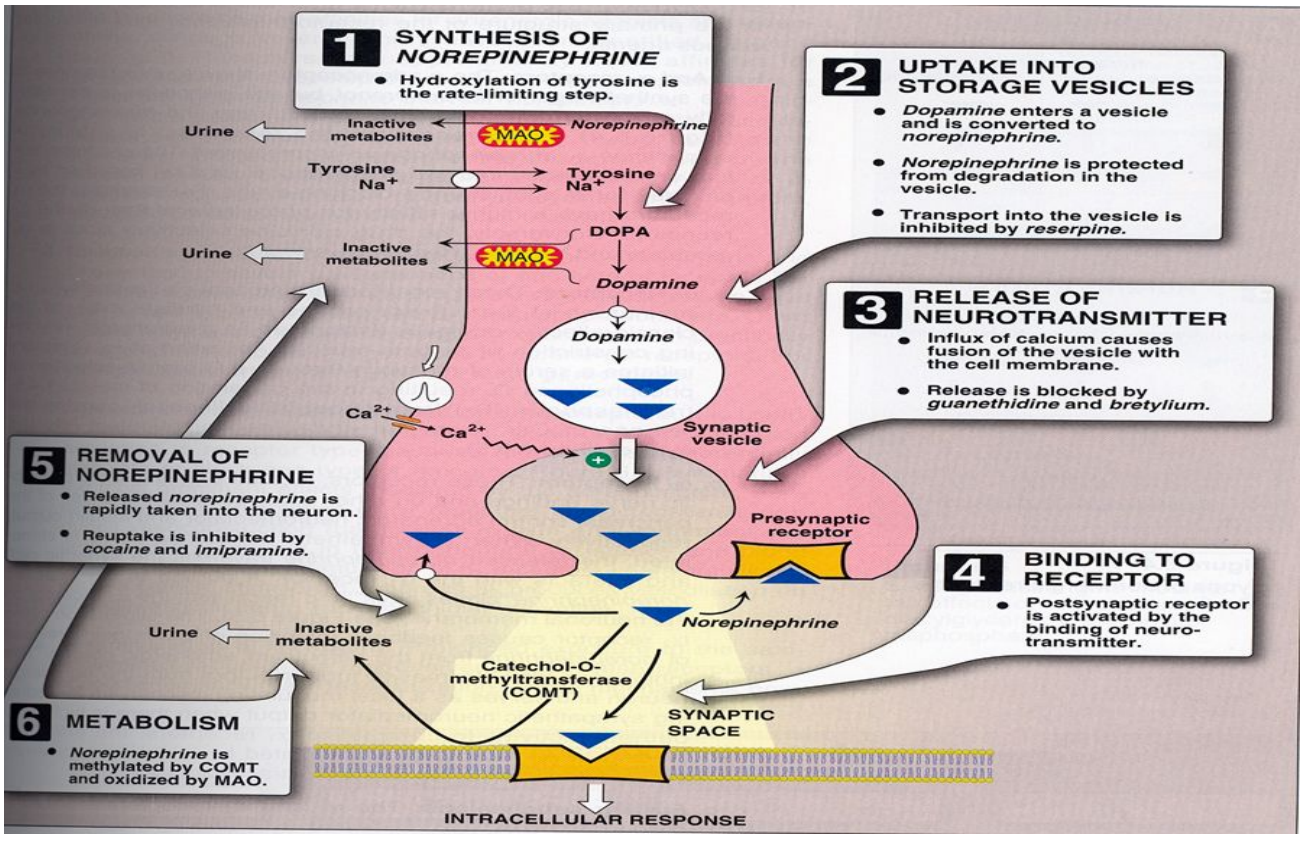
2) Storage of norepinephrine.

3) Release of norepinephrine.

4) Binding to postsynaptic receptors.

5) Ending of action by:

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



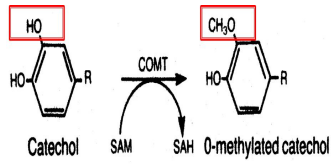
***Mono-amine oxidase (MAO):**

It's enzyme responsible for the metabolism of catecholamines as adrenaline and serotonin by using the Oxygen to remove an amine group (plus the adjacent hydrogen atom) from a molecule.

****Catechol -O-methyl transferase (COMT):**

Enzymes that degrade catecholamines (such as epinephrine, and norepinephrine), catecholestrogens, and various drugs and substances having a catechol structure.

وظيفته أنه ينقل للأكسجين مجموعة ميثايل "CH3"



Epinephrine = adrenaline
Norepinephrine = noradrenaline

Adrenergic receptors

Adrenergic receptors

a-adrenoceptors : Subtypes (a_1 & a_2)

b-adrenoceptors : Subtypes (B_1 , B_2 & B_3)

located postsynaptically are: a_1 and all beta types (B_1 , B_2 & B_3)

located Presynaptically are: a_2& B_2

a-adrenoceptors: (a_1 & a_2

a_1-adrenoceptor "postsynaptic"	**a_2-adrenoceptor "Presynaptic"**
• α_1 are excitatory in function except in GIT (Inhibition) • Present in smooth muscles. • Contraction of radial muscle of eye → mydriasis. • Contraction of pregnant uterus. • Vasoconstriction of skin & peripheral blood vessels → ↑ -peripheral resistance→ hypertension. • Contraction of sphincters in GIT & urinary bladder. • Relaxation of GIT muscles. • ↑Glycogenolysis.	• Inhibition of norepinephrine (negative feedback mechanism).

B_2-adrenoceptor "Presynaptic"

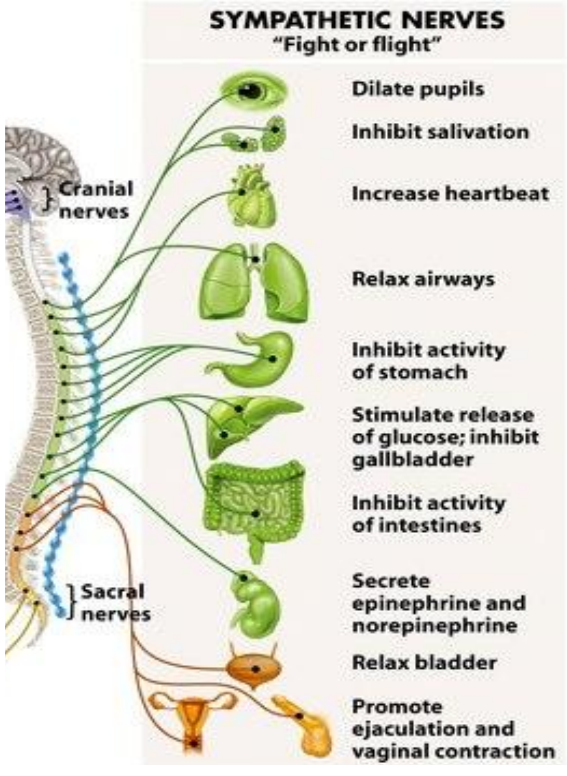
-
↑ release of norepinephrine (Positive feedback mechanism).

β-adrenoceptors

β1	β2	β3
excitatory in function	inhibitory in function	-
Postsynaptic	Postsynaptic and Presynaptic	Postsynaptic
Mainly in the heart	mainly in smooth muscles نفس مكان الفا١ لكن عكسها بالوظيفة	Adipose tissue
• ↑ heart rate: + chronotropic effect, Tachycardia. • ↑ force of contraction : + inotropic effect, arrhythmia. • ↑ conduction velocity: + dromotropic effect. • ↑ blood pressure. • ↑ renin release.	• Relaxation of skeletal & coronary blood vessels (vasodilatation). • Relaxation of bronchial smooth muscles. • Relaxation of GIT muscles (constipation). • Relaxation of urinary bladder. • Relaxation of the uterus (Delay premature labor) • Increase blood glucose level (hyperglycemia) by two ways 1- ↑ glucagon release from pancreas. 2- ↑ liver & muscle glycogenolysis. • Tremor of skeletal muscles.	↑lipolysis ↑ free fatty acids.

Sympathetic Actions

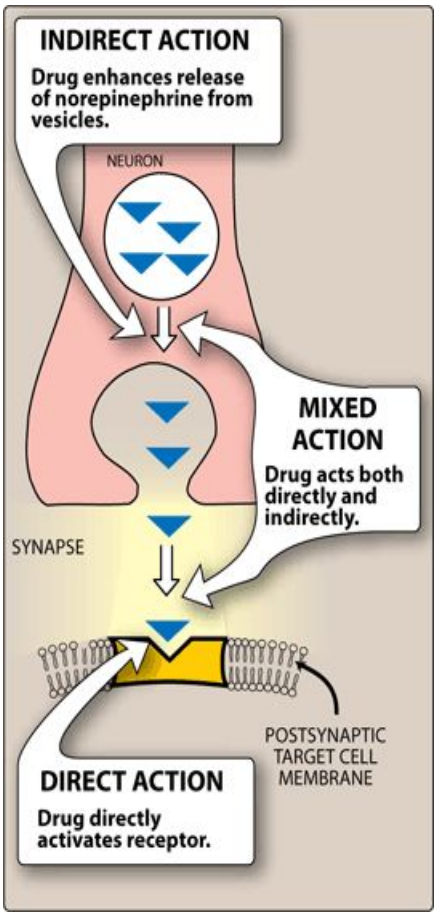
1. Mydriasis (dilatation of eye pupil)
2. Increase heart rate.
3. Bronchodilation
4. Inhibit peristalsis of GIT and secretion.
5. Relaxation of GIT muscles (constipation).
6. Relaxation of urinary bladder.
7. Relaxation of the uterus (Delay premature labor)
8. Increase conversion of glycogen to glucose (hyperglycemia)



Classification of Sympathomimetics
(According to Action)

Direct-acting:

Direct stimulation of adrenergic receptors.
E.g. adrenaline, noradrenaline, dopamine, isoprenaline, salbutamol, phenylephrine, methoxamine, naphazoline, clonidine, dobutamine, etc.

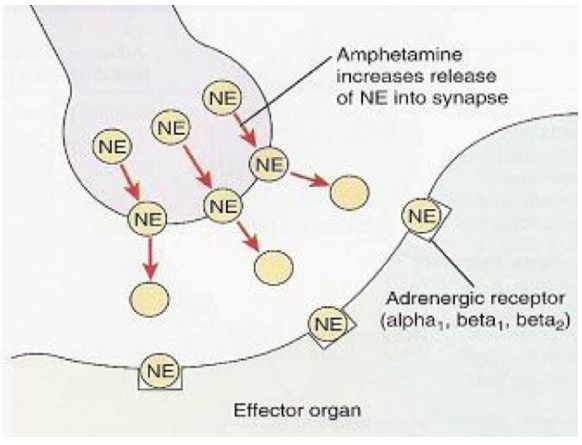


Dual-acting (Mixed):

Direct and indirect stimulation of adrenergic receptors.
E.g. ephedrine, pseudoephedrine.

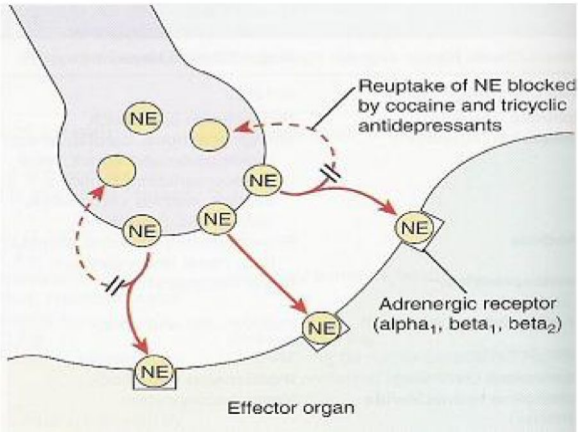
Indirect-acting:

↑NA release from presynaptic adrenergic nerve endings.
E.g. amphetamine, Tyramine.



Or

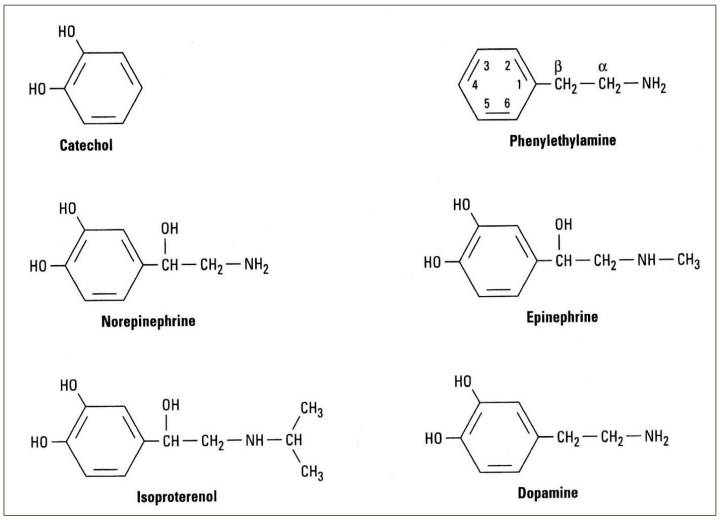
Inhibit NA uptake
E.g. Cocaine, antidepressants.



Classification of Sympathomimetics
(According to Chemistry)

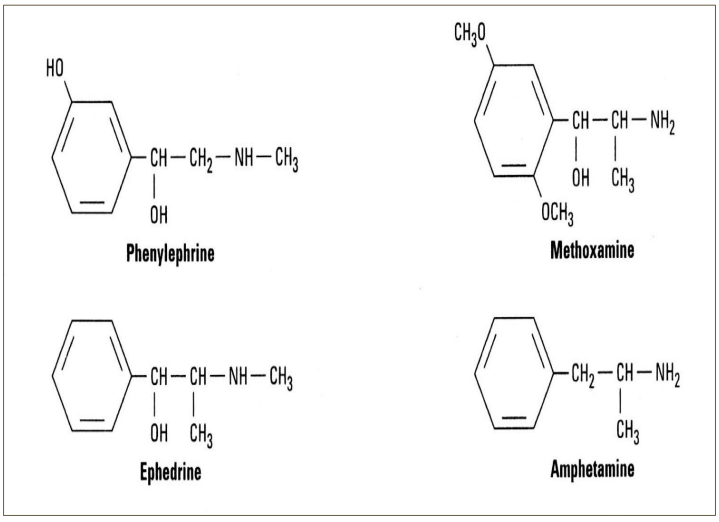
Catecholamines

- Have catechol ring
- Water soluble (polar)
- Not effective orally.
- Poor penetration into CNS
- Inactivated by COMT & MAO in GIT
- Short half-life.
- ***E.g.*** adrenaline, noradrenaline, dopamine, isoprenaline



Non-catecholamines

- Lack catechol ring
- Lipid soluble
- Effective orally.
- Cross well BBB
- Prominent CNS effects
- Not inactivated by COMT in gut wall
- Long half-life.
- ***E.g.*** Ephedrine, amphetamine, phenylephrine.



Classification of Sympathomimetics
(according to spectrum of action)

Non-selective adrenergic agonists

- Adrenaline (α1, α2 , β1 , β2, β3)
- Noradrenaline (α1, α2 , β1)
- Isoprenaline (β1, β2, β3)
- Dopamine (D1, β1, α1)

Selective adrenergic agonists

- Phenylephrine (α1)
- α-Methyldopa - clonidine (α2)
- Dobutamine (β1)
- Salbutamol, terbutaline, ritoderine (β2)

Adrenaline (α, β)

Features:

- Natural, catecholamine
- Non-selective agonist α1, α2 , β1 , β2 , β3
- Fast onset of action & Short duration of action.
- Not effective orally (inactivated by intestinal enzymes).
- Given I.V, S.C, inhalation.

Pharmacological Actions:

Heart	• inotropic, chronotropic, dromotropic (β1)
Blood Pressure	• ↑systolic (β1) (α1) / diastolic↓ (β2)
Blood vessels (Vascular smooth muscle cells)	• Vasoconstriction of b.v. in skin + peripheral (α1) • Vasodilatation of b.v.of skeletal muscles and coronaries (β2)
Eye	• mydriasis (α1) / no effect on accommodation
Lung	• bronchodilatation (β2)
GIT	• ↓motility (β2) / contract sphincter (α1)
Bladder	• relaxation of detrusor muscle (β2) • contraction of sphincter (α1)
Pregnant Uterus	• relaxation tocolytic (β2)
Metabolism	• ↓insulin (α2) ,↑glucagon (β2) • ↑liver glycogenolysis + skeletal muscle glycolysis (β2) • ↑adipose lipolysis (β3)
CNS	• little, headache, tremors & restlessness

Cont. Adrenaline (α, β)

Uses:

Locally	Systemically

• **Haemostatic (control bleeding):**
  ○ Nasal pack in epistaxis and in dental practice.
• **combined with local anesthetic to:**
  ○ ↓ absorption of L.A. & ↑duration of action
  ○ ↓ side effects of local anesthetic.
  ○ ↓ bleeding from the incision.
	• **In acute asthma** S.C., inhalation, emergency bronchodilatation (β2) + ↓mucosal edema (α1)
	• **Anaphylactic shock (Hypersensitivity reactions)** is the drug of choice given S.C. as it is the physiological antagonist of histamine (↑BP & bronchodilation).
	• **Cardiac arrest** (i.v.)

Adverse effects :

- Tachycardia, palpitation, arrhythmias, angina pains
- Headache, weakness, tremors, anxiety and restlessness.
- Hypertension → cerebral hemorrhage and pulmonary edema.
- Coldness of extremities → tissue necrosis
- Nasal stuffiness: rebound congestion if used as decongestant.

Contraindication:

- coronary heart diseases (CHD), Ischemic heart disease (angina)
- Arrhythmia, Myocardial infarction
- Hypertension, peripheral arterial disease.
- Hyperthyroidism.
- Closed-angle glaucoma (ciliary relaxation↓filtration angle) → ↑IOP

NOREPINEPHRINE = NORADRENALINE

Features:

- Catecholamine, non-selective agonist
- mainly on α adrenoceptors (α1, α2, β1).
- Weak action on β2
- Severe vasoconstriction α1
- Increase force of contraction but decrease H.R.
- Reflex bradycardia
- Only administered IV - Not IM or S.C. ⟶ necrosis

Uses :

- In **Hypotensive states** (in septic shock if fluid replacement and inotropics fail).
- As a **local haemostatic** with local anesthetic.

Isoprenaline

Features:

- A synthetic, direct acting catecholamine
- **Longer effect** (no reuptake-no destruction by MAO)
- non-selective b agonist (b1, b2 & β3)
- β1 + inotropic effect, + chronotropic effect, increase cardiac output (CO).
- β2 : -Vasodilatation of blood vessels of skeletal muscles and coronaries.
  -Bronchodilatation .
  -Relaxation of uterus.
  -Hyperglycemia
- β3 lipolysis

Uses :

Used mainly in cardiac arrest (Parenteral).
Rarely in acute attack of asthma (inhalation).

Contraindication:

Contraindicated in hyperthyroidism & CHD

Dopamine (D_1 > β1 > α1)

Features:

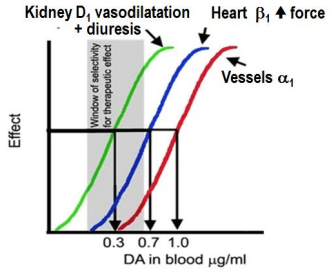
- Natural CNS neurotransmitter.
- Direct acting, catecholamine
- Given parenterally via infusion

Doses :

Low dose: dopaminergic receptors D_1

vasodilatationof mesenteric,coronary, renal blood vessels → improves blood flow to viscera

(Has diuretic action)



Intermediate dose (β1)

+ve inotropic

+ve chronotropic effects

High dose (α1): vasoconstriction

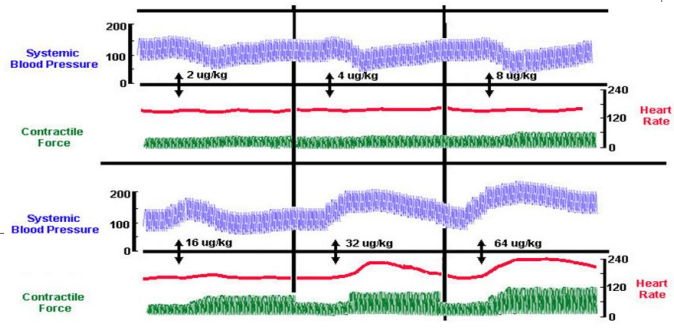
On heart : Inotropic, chronotropic effect

On BP → According to dose

First ↓ D_1

then ↑due to β1

followed by α1 effect



Uses :

Cardiogenic shock:

septic, hypovolemia or cardiogenic (I.V infusion).

↑ BP & CO (**β1**), without causing renal impairment (D1)

Can be given in acute heart failure (HF) but better dobutamine

Dobutamine

Features	- Synthetic catecholamine - Metabolized by COMT - Short duration, given by intravenous infusion - Selective B1-receptor agonist - Positive inotropic effect, increases cardiac output with little increase in heart rate
Uses	1- Short term management of cardiac decompensation after cardiac surgery 2- acute myocardial infarction 3- Heart failure

Phenylephrine (selective α1)

Features	- A synthetic **non catecholamine** - **Direct acting** - Not inactivated by COMT → longer duration of action - Vasoconstriction → increase both systolic and diastolic blood pressure → hypertension → reflex bradycardia (Selective a1 agonist)
Uses	1- **Nasal decongestant**: topical,nasal drops in allergic rhinitis and cold 2- **Vasopressor agent**: hypotension and terminare atrial tachycardia (reflex bradycardia) 3- **Local hemostatic** with local anesthesia 4- **Mydriatic**: in ophthalmic solutions to facilitate eye examination
Adverse effect	Hypertension
Midodrine	Peaks in 20 minutes, duration 30 minutes, used in *hypotensive* states

ADRENERGIC STIMULANTS (Direct acting sympathomimetics)

Nasal and ocular decongestants

Phenylethylamines	Imidazoline
- Phenylephrine - Pseudoephedrine - Methoxamine	- Naphazoline - Oxymetazoline HCl (Afrin) - Xylometazoline HCl (Otrivine)

Drug	Features	Action	Uses
Selective β_2 agonists			
Salbutamol	• selective β_2 agonists • non catecholamines • orally or by inhalation or injection.	Produces bronchodilation	Used for acute attack of asthma & COPD.
Ritodrine	• Selective β_2 agonist • non catecholamines. • orally or by injection	Is a tocolytic drug (relaxation of uterus).	Used orally and injection to treat premature labor.
Terbutaline	-	Bronchodilator & Tocolytic	-
α_2 Agonist			
Clonidine (Selective a_2 agonist)	• Synthetic, imidazoline • Given orally or as patch. • Is a presynaptic **α_2 agonist**	• Acts centrally (a_2) at nucleus tractus solitaries t ↓ sympathetic outflow to heart & vessels. • Inhibit sympathetic vasomotor centers.	Used as antihypertensive in essential hypertension to lower BP.
Brimonidine	is an imidazoline	-	**α_2 agonist** used in glaucoma

ADRENERGIC STIMULANTS (Indirect acting sympathomimetics)

Amphetamine (a&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.

ADRENERGIC STIMULANTS
(Dual acting sympathomimetics)

Ephedrine (a & b)	Pseudoephedrine
• 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.	• 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

MCQs

1- which of the following receptors is postsynaptic and Presynaptic at the same time ?

A. B1
B. B2
C. B3
D. a1

2-which of the following drugs is acting direct and indirect stimulation of adrenergic receptors?

A. Adrenaline
B. Noradrenaline
C. Dopamine
D. ephedrine.

3-which of the following drugs is Not inactivated by COMT in GUT wall

A Adrenaline
B Noradrenaline
C Dopamine
D ephedrine.

4-low Dose of Dopamine cause:

A. Vasodilation of Renal blood vessel
B. Inotropic
C. Vasoconstriction
D. chronotropic

5- which of the following drugs cause Reflex bradycardia?

A Adrenaline
B Noradrenaline
C Dopamine
D ephedrine.

6-drug use as short term management of cardiac decompensation ?

A Adrenaline
B Phenylephrine
C Dobutamine
D ephedrine.

7-drug use as Mydriatic in ophthalmic solutions to facilitate eye examination?

A Adrenaline
B Phenylephrine
C Dobutamine
D ephedrine.

8- drug use as tocolytic drug:

A Terbutaline
B Ritodrine
C both a and b
D ephedrine

SAQ

1. **What is the drug of choice in case of Anaphylactic shock?**
2. **Which receptors do that drug effect ?**
3. **Why this drug Combined with local anesthetic ?**
4. **What are 3 adverse effect that is expected to see in this patient after giving him the drug ?**

Answers:
1. B
2. D
3. D
4. A
5. B
6. C
7. B
8. C

Answers:
1. Adrenaline
2. non-selective agonist (a1,a2,B1,B2).
3.
   a. ↓ absorption of L.A. & ↑duration of action
   b. ↓ side effects of local anesthetic.
   c. ↓ bleeding from the incision.
4. Tachycardia,Hypertension and weakness.

Good Luck & Thank you !

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