تفريغ فارما ١

اسم الموضوع: Lec9/Adrenergic Agonist

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لجان الدُفعات

CHARACTERISTICS OF ADRENERGIC AGONISTS

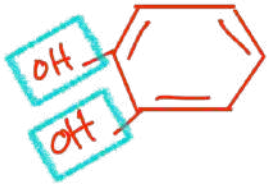
- derivatives of β-phenylethylamine

➢ **Catecholamines**

➢ **Noncatecholamines**

➢ **Substitutions on the amine nitrogen**

Catecholamines



- Sympathomimetic amines that contain the 3,4-dihydroxybenzene group.

1 *Epinephrine*

2 *Norepinephrine*

3 *Isoproterenol*

4 *Dopamine*

-High potency
-Rapid Inactivation : MAO, COMT
-Poor CNS penetration: polar

Noncatecholamines

- Compounds lacking the catechol hydroxyl groups have longer half-lives
- Not inactivated by COMT and they are poor substrates for MAO

✓*Phenylephrine,* (direct)

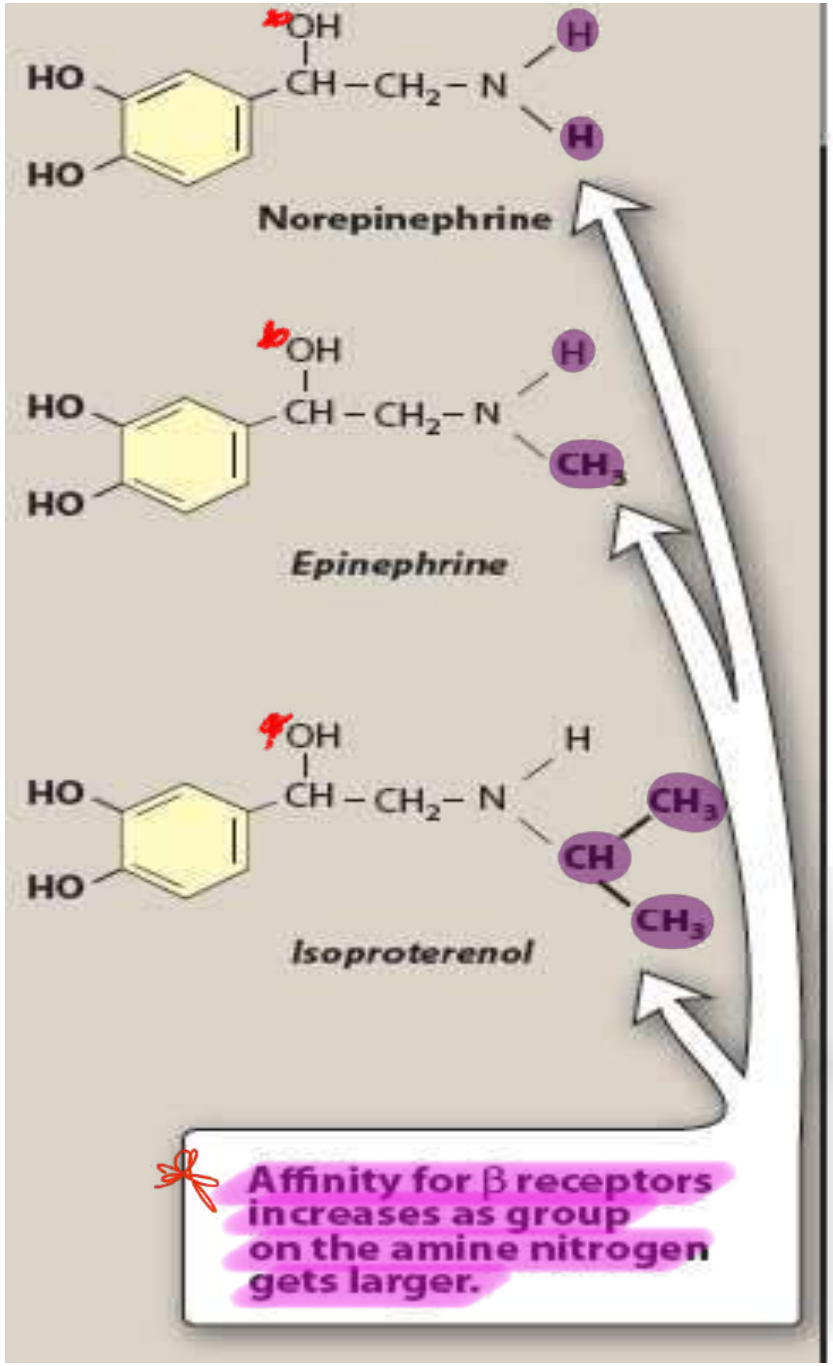
✓*Ephedrine*

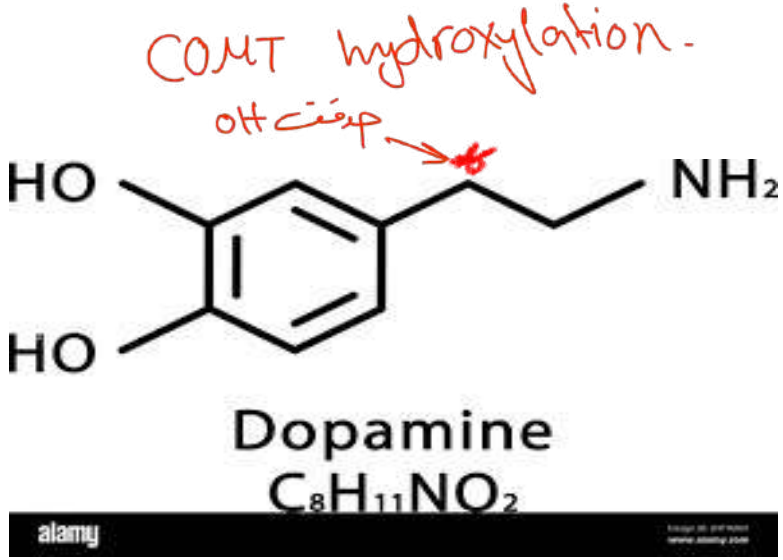
✓ *Amphetamine*

Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

Substitutions on the amine nitrogen

- The nature and bulk of the substituent on the amine nitrogen is important in determining the β selectivity of the adrenergic agonist


HO
HO
OH
CH – CH2 – N
H
H
Norepinephrine
HO
HO
OH
CH – CH2 – N
H
CH3
Epinephrine
HO
HO
OH
CH – CH2 – N
H
CH3
CH
CH3
Isoproterenol
Affinity for β receptors increases as group on the amine nitrogen gets larger.


COMT hydroxylation.
OH
HO
HO
NH2
Dopamine
C8H11NO2
alamy

Mechanism of action of the adrenergic agonists

1. **Direct-acting agonists:** *epinephrine, norepinephrine, isoproterenol, and phenylephrine.*
2. **Indirect-acting agonists:** *amphetamine, cocaine, and tyramine,* يزيد افراز ال norepenphrine
3. **Mixed-action agonists:** *ephedrine and its* stereoisomer, *pseudoephedrine*

deconjestant

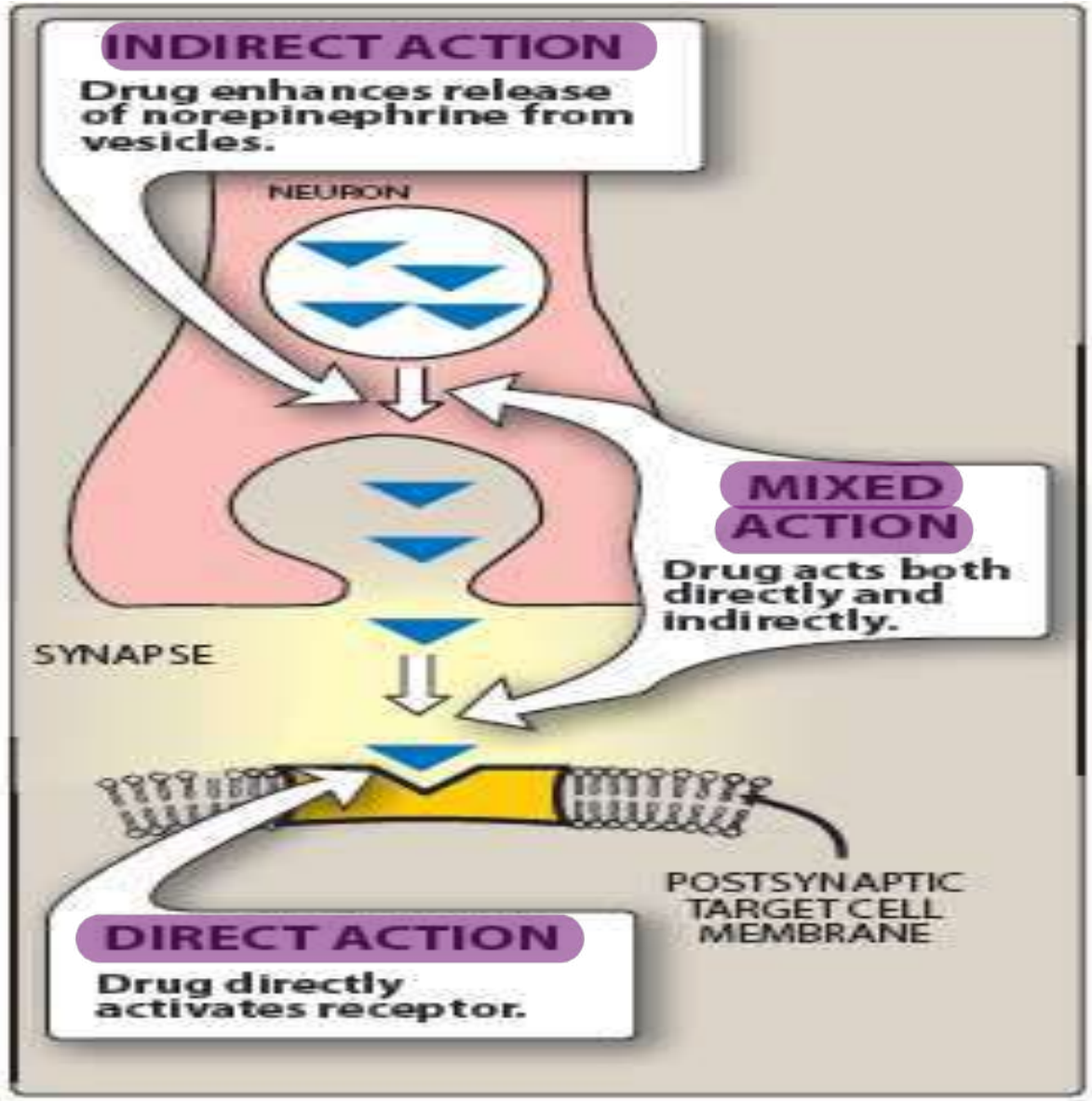


Figure 6.8
Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.

DIRECT-ACTING ADRENERGIC AGONISTS

Epinephrine → Anaphilactic shock

- From catecholamines
- *Epinephrine interacts with* both α and β receptors.
- At low dose –vasodilation effect (β_2 effect)
- At high dose-Vasoconstriction effect (α_1 effect)

Epinephrine Actions

$\alpha_1 \rightarrow G_q \rightarrow IP_3 \rightarrow Ca^{+} \rightarrow$ constriction.

- Cardiovascular :

  - Increase HR (cronotropic) and myocardium contractility(inotropic) via **β1 receptor.** ↑CAMP

  - *Epinephrine activates* β1 receptors on the kidney to cause renin release (vasoconstriction of afferant) → increase blood pressure.

  - Constricts arterioles in the skin, mucous membranes, and viscera (**α effects**)

    * increase sistolic and decrease diastolic.

  - Dilates vessels going to the liver and skeletal muscle (**β2 effects**).

  - Renal blood flow is decreased

  - Increase in SBP

  - Decrease DBP (**β2 effects**).

$\frac{\text{sistolic}}{\text{diastolic}} = \frac{120}{80} \neq \frac{140}{90}$

sistolic → a_1, β_1

diastolic → β_2

diastolic → prephral resistance, V.C and V.D

$\frac{160}{70}$

Epinephrine Actions

Respiratory

- Powerful broncho- dilation by acting directly on bronchial smooth muscle (**β2** action).
- Excellent in asthma , and life saving conditions
- *Epinephrine also inhibits the release of allergy mediators such as* histamines from mast cells

bronchial decongestion

use in anaphylactic shock

in mast cell.

عشان هيك epinephrine بستعمل ك mast cell stabilizer.

Hyperglycemia:

Epinephrine has a significant hyperglycemic effect :

1. Increased glycogenolysis in the liver (β2 effect)
2. Increased release of glucagon (β2 effect), and a decreased release of insulin (α2 effect).

- **Lipolysis:**

  Epinephrine initiates lipolysis through its agonist activity on the β3 receptors of adipose tissue

- **Biotransformations:**

  Epinephrine, like the other catecholamines, is

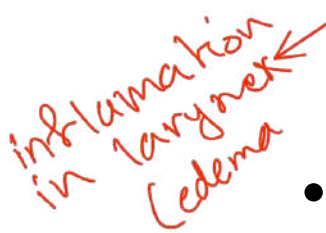
  metabolized by two enzymatic pathways: MAO and COMT

- The preferred route of administration is IM

سعال ديكي
"whooping cough" للأطفال اللي بيكون معهم inhalation ممكن يعطوه

Therapeutic uses of Epinephrine

- **Bronchospasm**



- **Anaphylactic shock:** drug of choice for type I hypersensitivity reactions in response to allergy

- **Cardiac arrest** → vasconstration in circulation.

Adverse events

- CNS effects: anxiety, fear, tension, headache, and tremor
- cardiac arrhythmias
- Pulmonary oedema
- Hyperthyroidism cause increase production of adrenergic receptors which increase sensitivity of sympathetic action.
- Hyperglycaemia in diabetes.

Norepinephrine

- Theoretically it can stimulate all adrenergic receptors
- Therapeutically α receptors are most affected

➢ Cardiovascular effects :

- Vasoconstriction (α1 effect), causes increase peripheral resistance and Increase in SBP & DBP
- Baroreceptor reflex-Bradycardia

" **weak on β2 receptor**, thus not recommended in asthma"

Therapeutic uses

- SHOCK

❑ **Pharmacokinetics:**

Norepinephrine may be given IV for **rapid onset** of action. The duration of action is 1 to 2 minutes following the end of the infusion period

❖**Adverse effects:**

These are similar to those of *epinephrine*

Isoproterenol

شغاله زي epinephrine فتشغل الـ

- Direct-acting synthetic catecholamine
- **Non slecective β1 and β2 Agonist**

- **Actions:**

Cardiovascular: *Isoproterenol produces intense stimulation of* the heart to increase its rate and force of contraction, causing increased cardiac output.

↖ β_1 effect

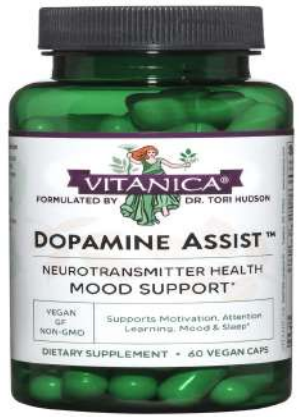
- *Isoproterenol* *dilates* the arterioles of skeletal muscle (β2 effect), resulting in decreased peripheral resistance.
- Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure like epinphrine
- Used in ER to stimulate heart
- Pharmacokinetics: *Isoproterenol is a* ***marginal*** *substrate for COMT* and is stable to MAO action.

Dopamine

hydroxylation

- Immediate metabolic precursor of norepinephrine
- Occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla
- Dopamine can activate α- and β-adrenergic receptors
- *Degraded by COMT & MAO,* ***" short half-life"***

adrenal medulla
↓
norepinephrine
↓ methylation
epinephrine
↓
storage in chromaffin cell in adrenal medulla.



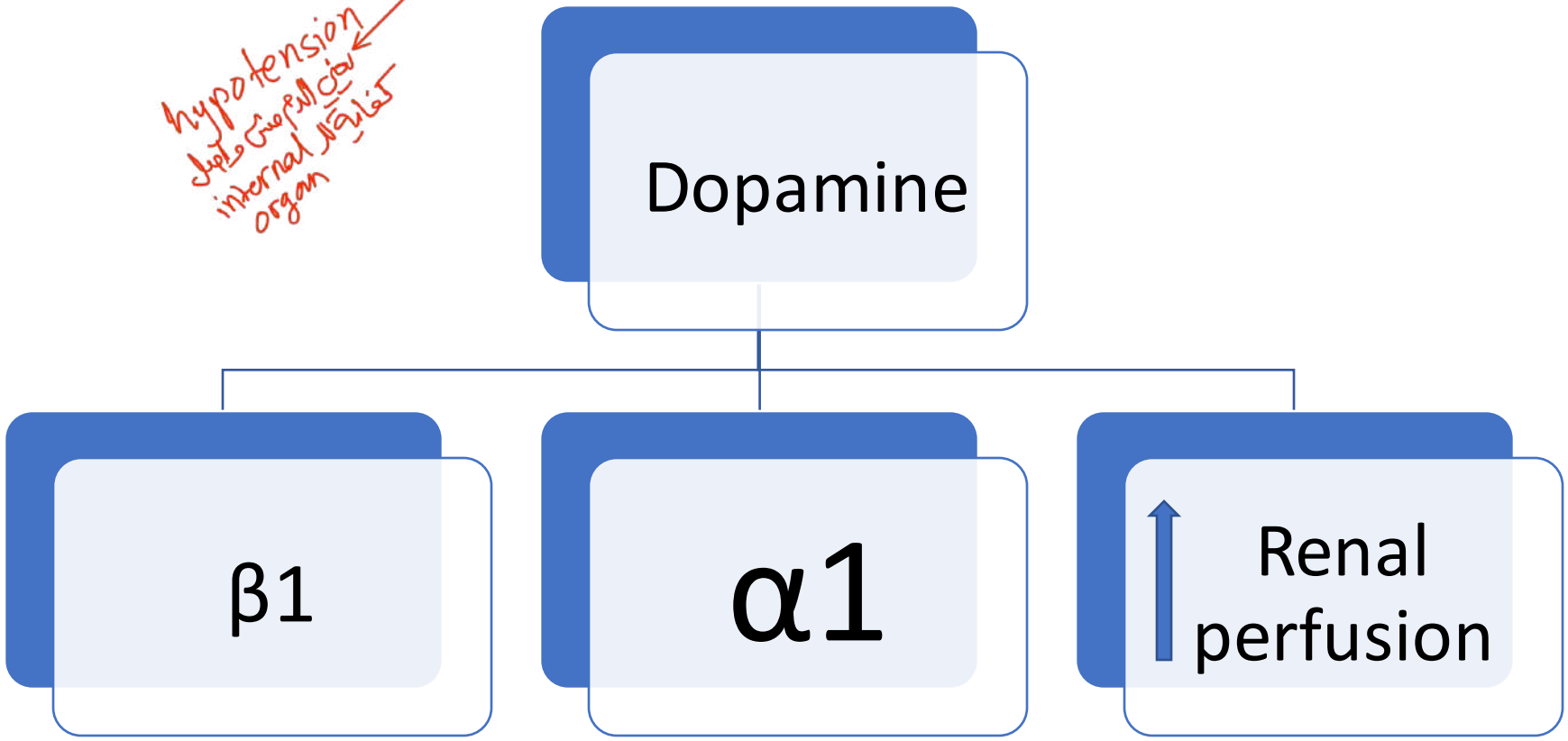
- High doses activate α_1 receptors (Vasocontriction)
- Lower doses activate β_1 cardaic receptors (augment contraction)

- Dopamine activates Dopamenergic receptors in the renal arterioles leading to vasodilation and increase renal blood perfusion

* من أهم الأدوية التي ترفع الضغط .

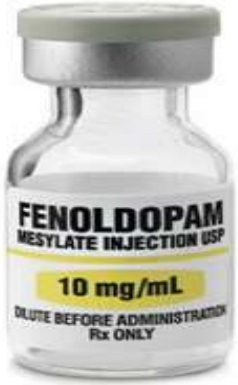
Therapeutic uses of Dopamine

"Septic Shock"



It is also used to treat hypotension and severe heart failure, primarily in patients with low or normal peripheral vascular resistance and in patients who have oliguria

Fenoldopam-R



- *Dopamine D1* receptors agonist
- Moderate affinity for α2 receptors.
- It is used as a rapid-acting vasodilator to treat severe hypertension in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries.
- Extensive first-pass metabolism and
- Has a 10-minute elimination half-life after IV infusion.
- Headache, flushing,dizziness, nausea, vomiting, and tachycardia

Dobutamine

- A synthetic, direct-acting catecholamine β1 receptor agonist
- Increase CO in CHF
- No increase in myocardial oxygen demand !
- Caution in Atrial Fibrilation

Oxymetazoline

Nasa decongestant

- A direct-acting synthetic adrenergic agonist that stimulates **both α1- and α2**-adrenergic receptors
- It is primarily used locally in the **eye** or the **nose as a vasoconstrictor**
- Relieves congestion by decreasing blood supply to the desired tissue

** Systemic ABS. and rebound congestion on LTU.

Absorption

يسبب ارتفاع الضغط (Hypertension)

Long Term Use

يعني سيستخدم فترة معينة هدئه إذا استخدم لفترة طويلة رح يبطل يأثر.

CNS effect / nasal Irritation / sneezing

Phenylephrine

- A direct-acting, synthetic adrenergic drug that binds primarily to α1 receptors
- Not a cathecolamine and not a COMT substrate.
- Raises both systolic and diastolic blood pressures, (no effect on myocardium) like norepinphrine
- Nasal decongestant
- Also used in ophthalmic solutions for mydriasis

Clonidine

- An α2 agonist
- Centrally acting anti hypertensive.

  Acts centrally to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery.

- S/E :lethargy, sedation, constipation
- Abrupt discontinuance must be avoided to prevent rebound hypertension.

Albuterol and Terbutaline

- **Short-acting β2 agonists** used primarily as bronchodilators, and administered by a metered-dose inhaler (MDI)
- **Terbutalin** is used off label as uterus relaxant to inhibit premature labor.
- Tremor, anxiety,
- Tachycardia in systemic administration
- Dose titration may be needed
- C/I with MAOI

another side effect & hypokalemia.

Hyperkalemia

Lasix (furosemide)/ diuretics

Salmeterol and Formoterol

LABA long acting β_2 agonist

- β2-adrenergic selective agonists that are long-acting bronchodilators.
- One dose from inhaler covers 12 hrs compared to SA agonists (3 hrs)
- Combined with Corticosteroids
- Drug of choice for Nocturnal asthma الربو الليلي
- Inhaled powders formulations