

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*,

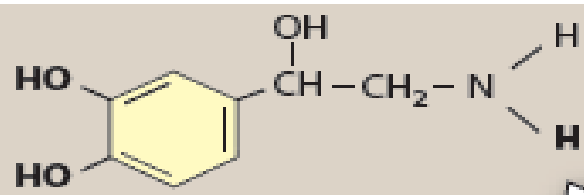
✓ *Ephedrine*

✓ *Amphetamine*

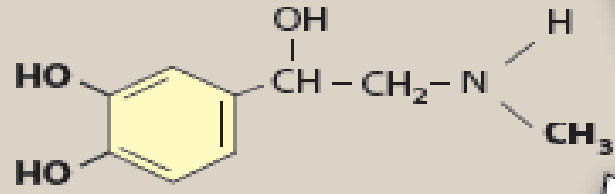
Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

Substitutions on the amine nitrogen

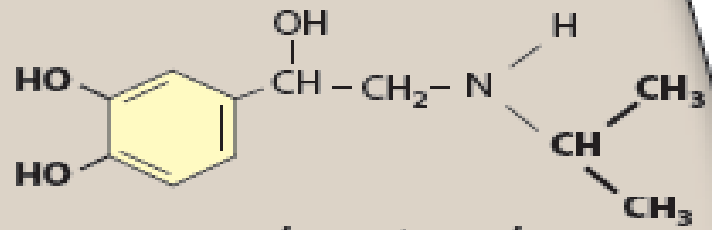
- The nature and bulk of the substituent on the amine nitrogen is important in determining the β selectivity of the adrenergic agonist



Norepinephrine



Epinephrine



Isoproterenol

Affinity for β receptors increases as group on the amine nitrogen gets larger.

Mechanism of action of the adrenergic agonists

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

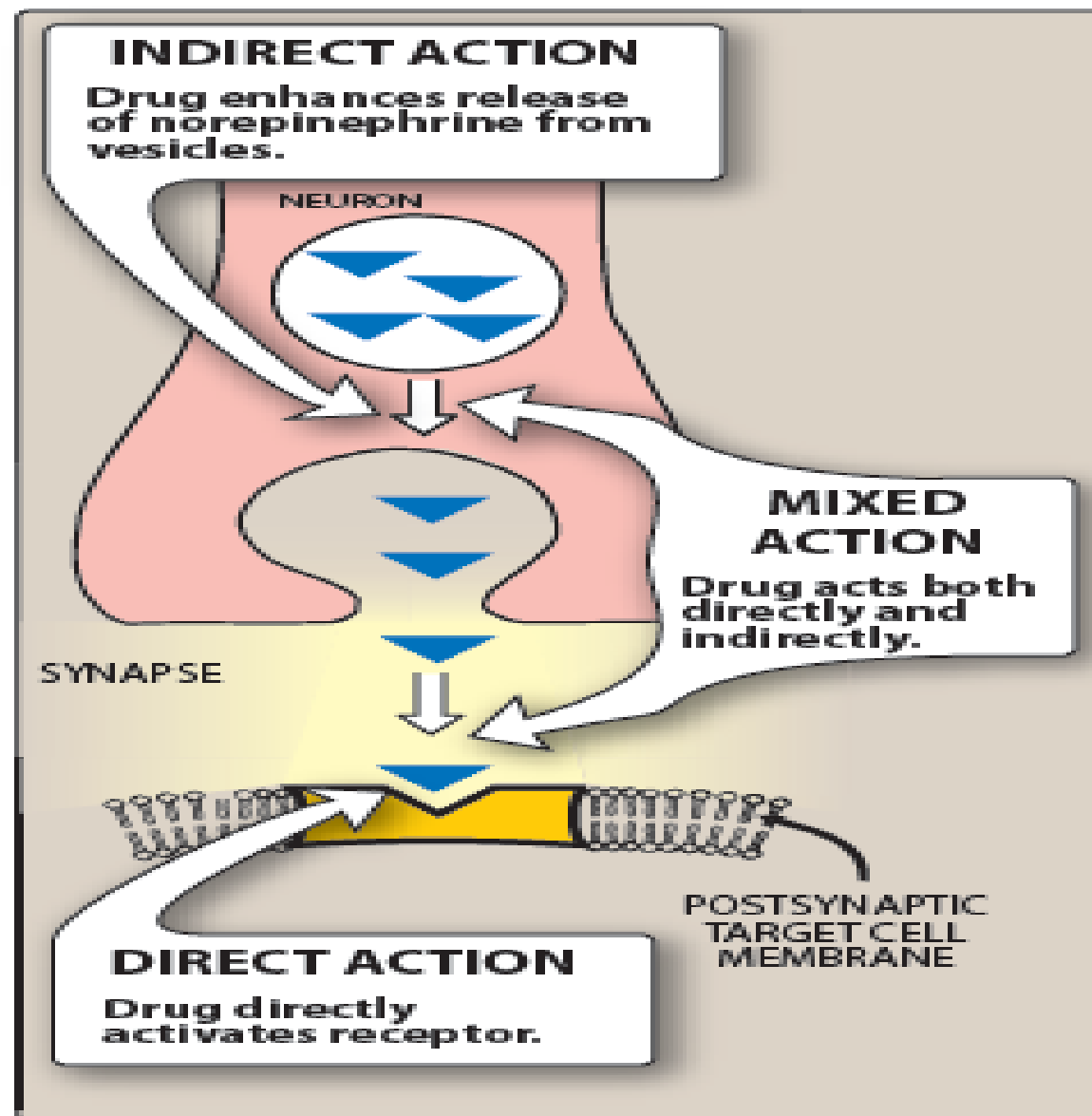


Figure 6.8
Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.

DIRECT-ACTING ADRENERGIC AGONISTS

Epinephrine

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

Epinephrine Actions

☐ Cardiovascular :

- Increase HR (chronotropic) and myocardium contractility (inotropic) via β_1 receptor.
- *Epinephrine activates* β_1 receptors on the kidney to cause renin release
- Constricts arterioles in the skin, mucous membranes, and viscera (α effects)
- Dilates vessels going to the liver and skeletal muscle (**β_2 effects**).
- Renal blood flow is decreased
- Increase in SBP
- Decrease DBP (**β_2 effects**).

Epinephrine Actions

Respiratory

- Powerful broncho- dilation by acting directly on bronchial smooth muscle (**β_2** action).
- Excellent in asthma , and life saving conditions
- *Epinephrine also inhibits the release of allergy mediators such as histamines from mast cells*

Hyperglycemia:

Epinephrine has a significant hyperglycemic effect :

1. Increased glycogenolysis in the liver (β_2 effect)
2. Increased release of glucagon (β_2 effect), and a decreased release of insulin (α_2 effect).

- **Lipolysis:**

Epinephrine initiates lipolysis through its agonist activity on the β 3 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

Therapeutic uses of Epinephrine

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

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 (α_1 effect), causes increase peripheral resistance and Increase in SBP & DBP
 - Baroreceptor reflex-Bradycardia
- “ **weak on β_2 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

- Direct-acting synthetic catecholamine
- **Non selective β_1 and β_2 Agonist**

- **Actions:**

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

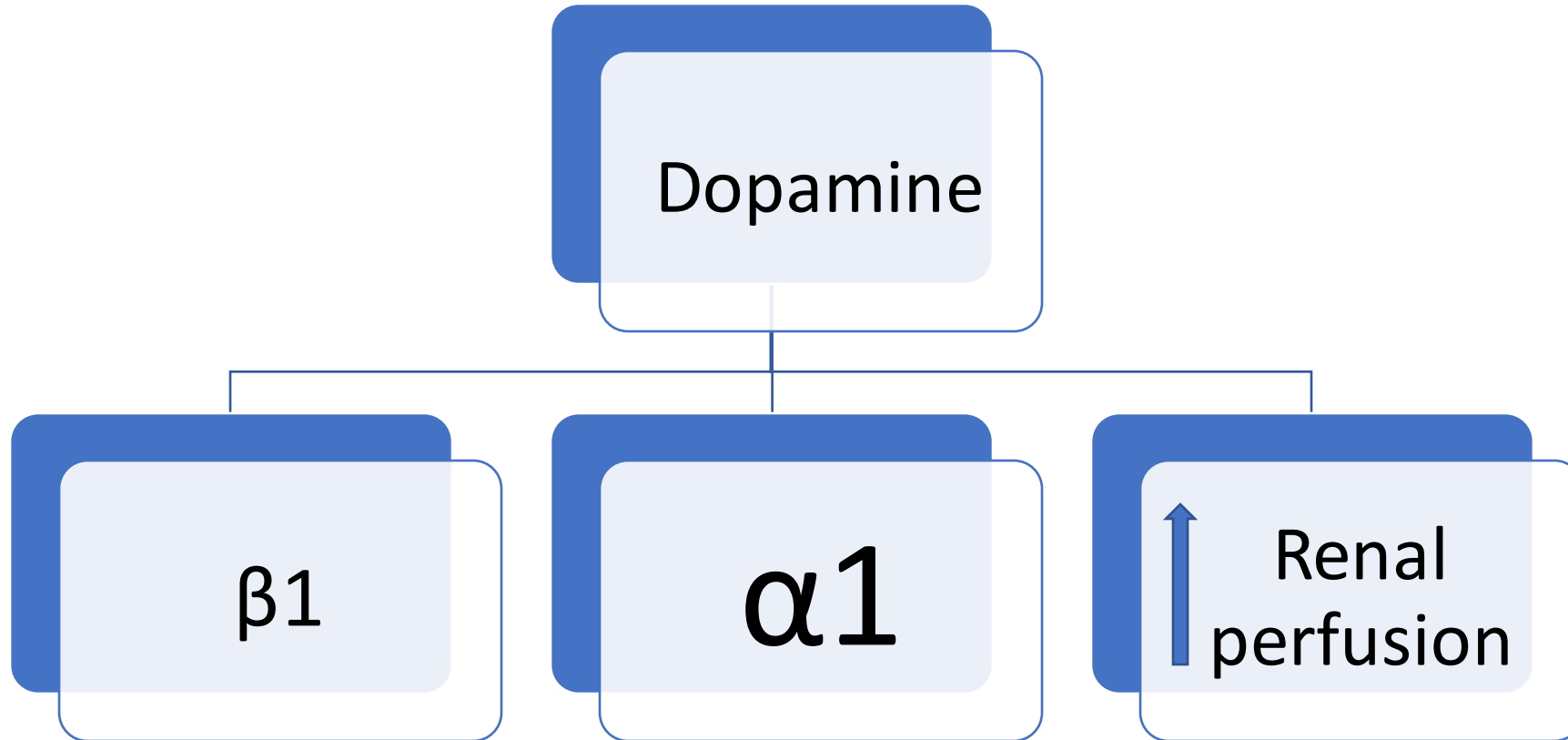
- *Isoproterenol dilates* the arterioles of skeletal muscle (β_2 effect), resulting in decreased peripheral resistance.
- Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure
- Used in ER to stimulate heart
- Pharmacokinetics: *Isoproterenol is a **marginal** substrate for COMT* and is stable to MAO action.

Dopamine

- 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**”*

- High doses activate α_1 receptors (Vasoconstriction)
- Lower doses activate β_1 cardiac receptors (augment contraction)
- Dopamine activates Dopamenergic receptors in the renal arterioles leading to vasodilation and increase renal blood perfusion

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 $\alpha 2$ 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 β_1 receptor agonist
- Increase CO in CHF
- No increase in myocardial oxygen demand !
- Caution in Atrial Fibrillation

Oxymetazoline

- A direct-acting synthetic adrenergic agonist that stimulates **both $\alpha 1$ - and $\alpha 2$ -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.**

Phenylephrine

- A direct-acting, synthetic adrenergic drug that binds primarily to α_1 receptors
- Not a catecholamine and not a COMT substrate.
- Raises both systolic and diastolic blood pressures, (no effect on myocardium)
- Nasal decongestant
- Also used in ophthalmic solutions for mydriasis

Clonidine

- An α_2 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 β_2 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

Salmeterol and Formoterol

- β 2-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
- Inhaled powders formulations