(Direct Acting Agonist) SYMPATHOMIMETICS

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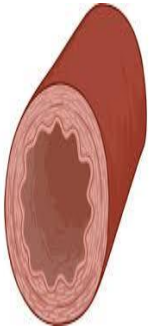
Adrenergic Agonists

- Agents that **mimic actions of sympathetic system & stimulate adrenergic receptors**
- Adrenergic neurons release NE as primary neurotransmitter

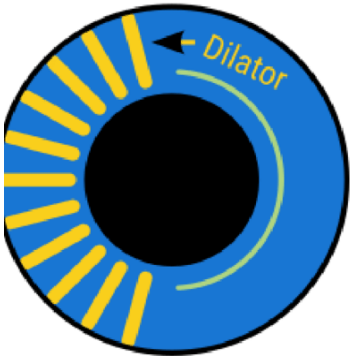
Stimulation of adrenergic receptors

- **Alpha (1 and 2)**
- **Beta (1, 2 and 3)**
- **Dopamine (D1,2,3,4,5)**

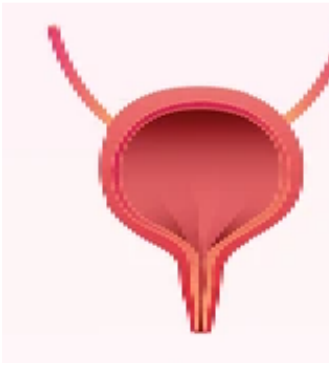
α 1 stimulation



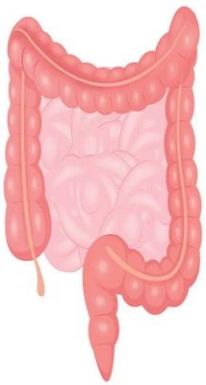
V.C

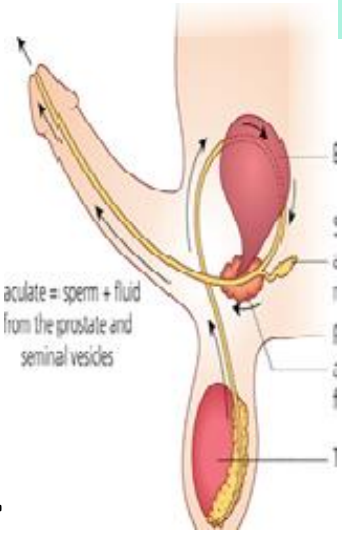


Mydriasis

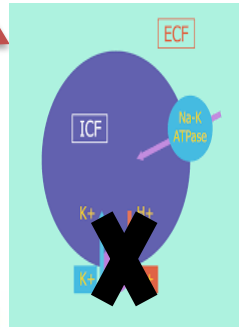


Contraction of sphincter



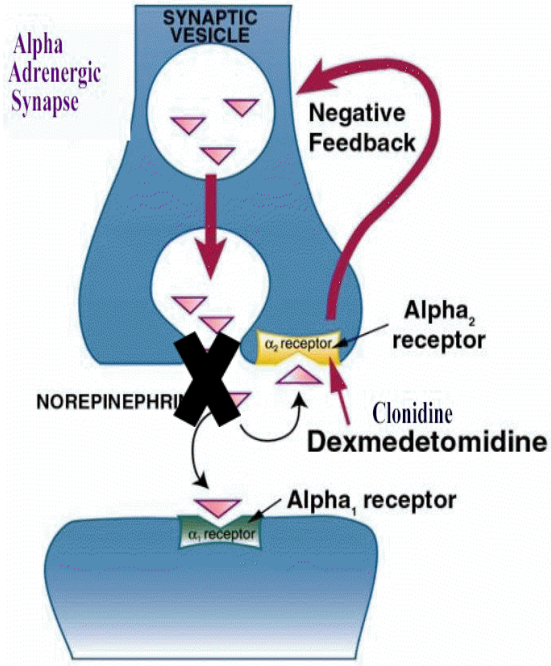


ejaculation

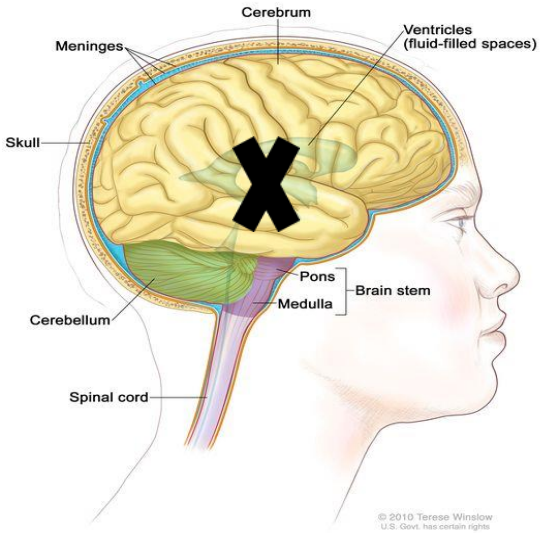


hyperkalemia

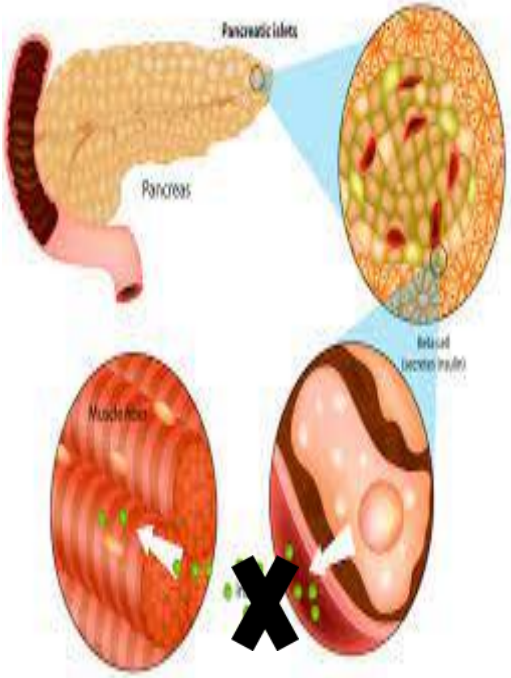
α 2 stimulation(inhibitory)



Inhibit NE, epinephrine and Ach

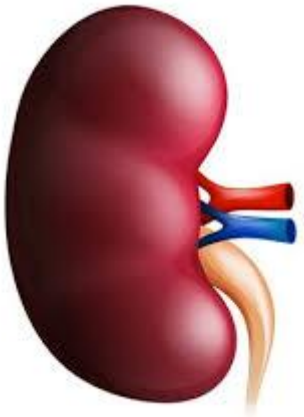


- Sympathetic flow



Inhibit insulin release

β 1 stimulation

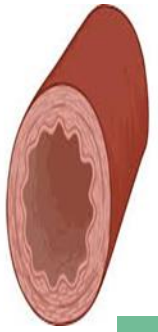


↑ renin release

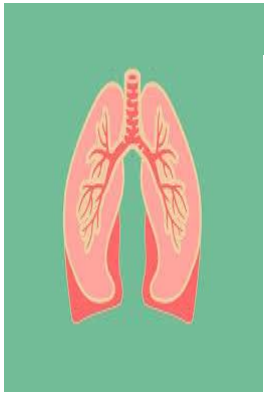
↑ all cardiac properties

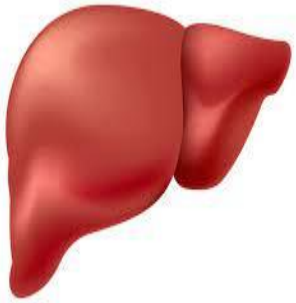
β 2 stimulation

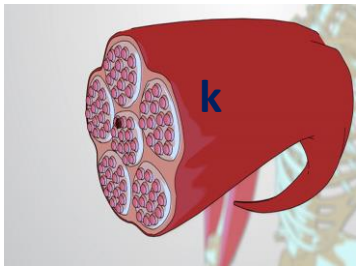
(coronary and skeletal)

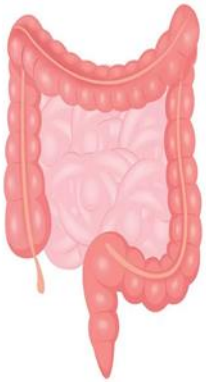


V.D









Relaxation

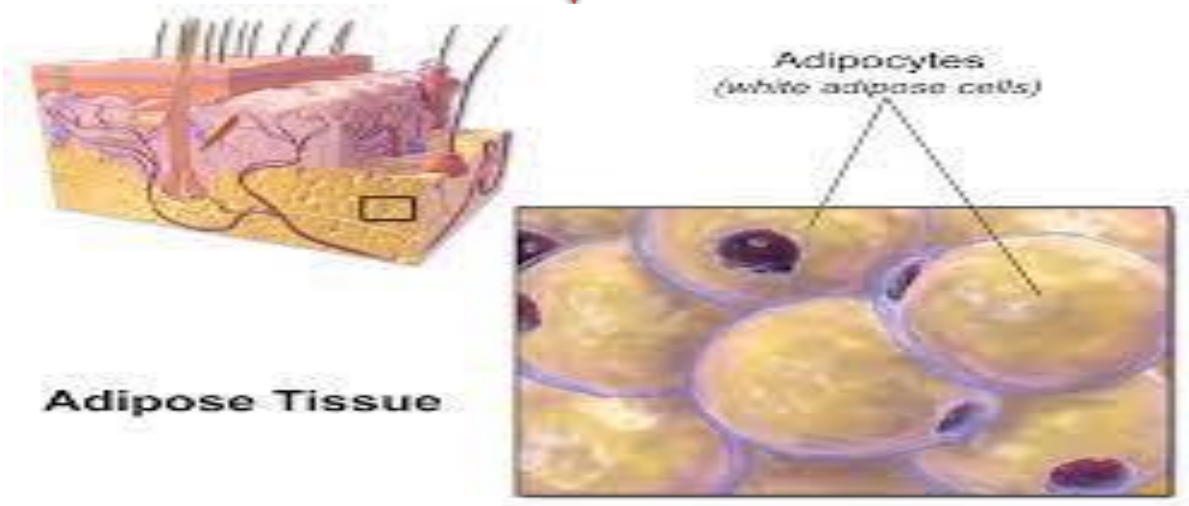
Bronchodilatation

Glycogenolysis: ↑ glucose blood level

Gluconeogenesis: ↑ glucose blood level

↑K uptake by muscles : hypokalemia

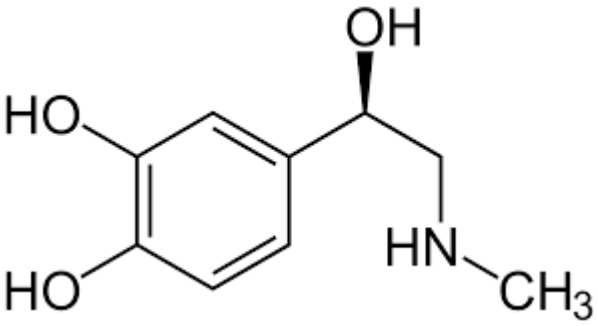
β 3 stimulation

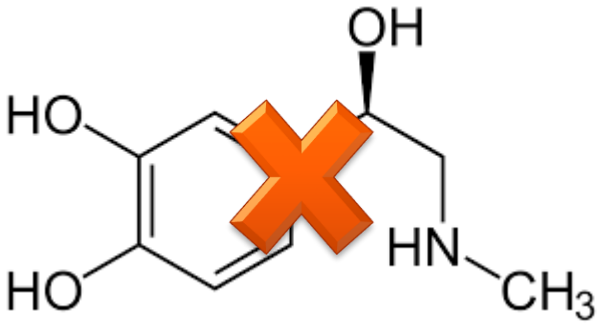


+ lipolysis

Classifications of Sympathomimetics

1- According to their chemical structure





2-According to mechanism of actions

Classification according to their chemical structure:

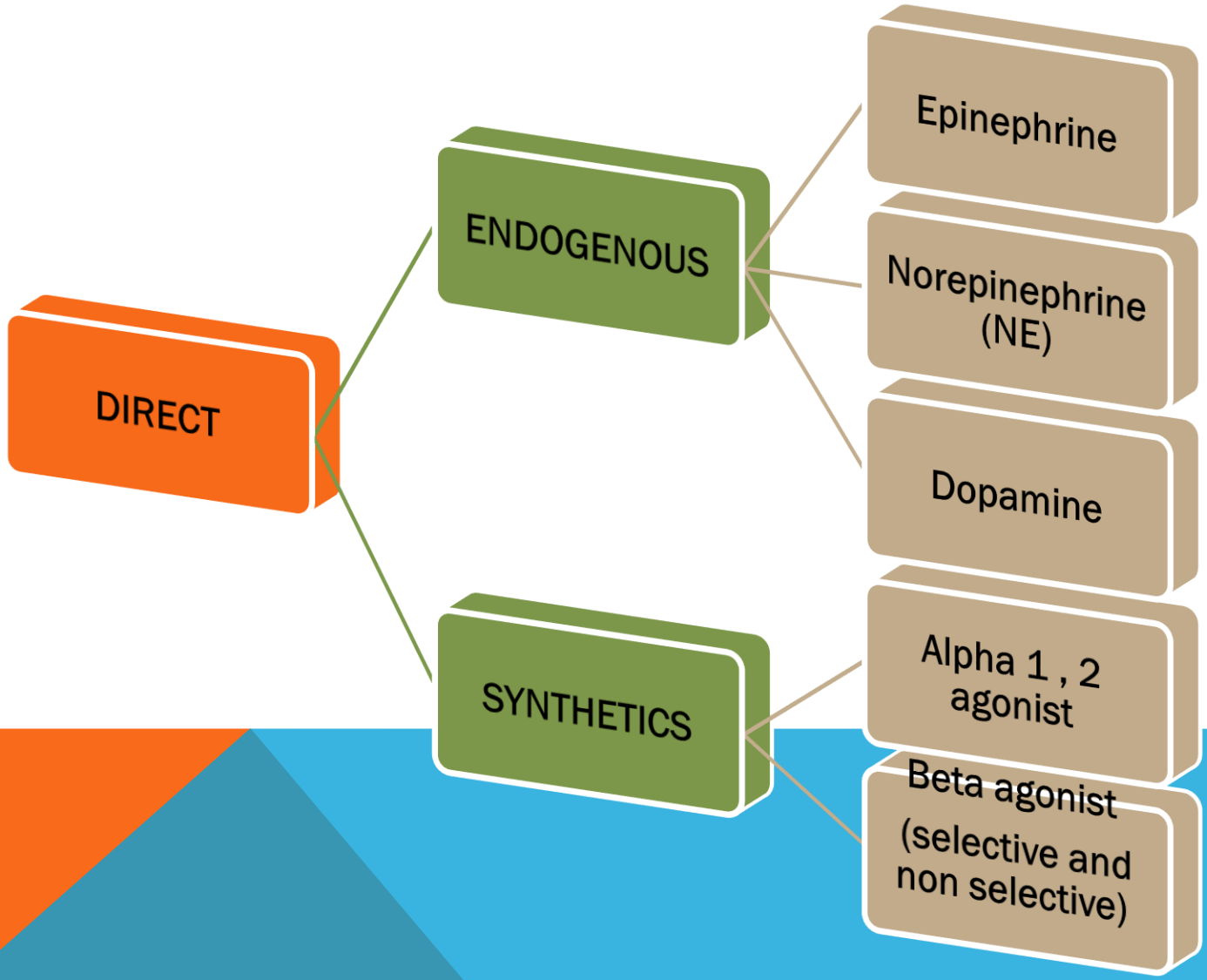
Catecholamines:

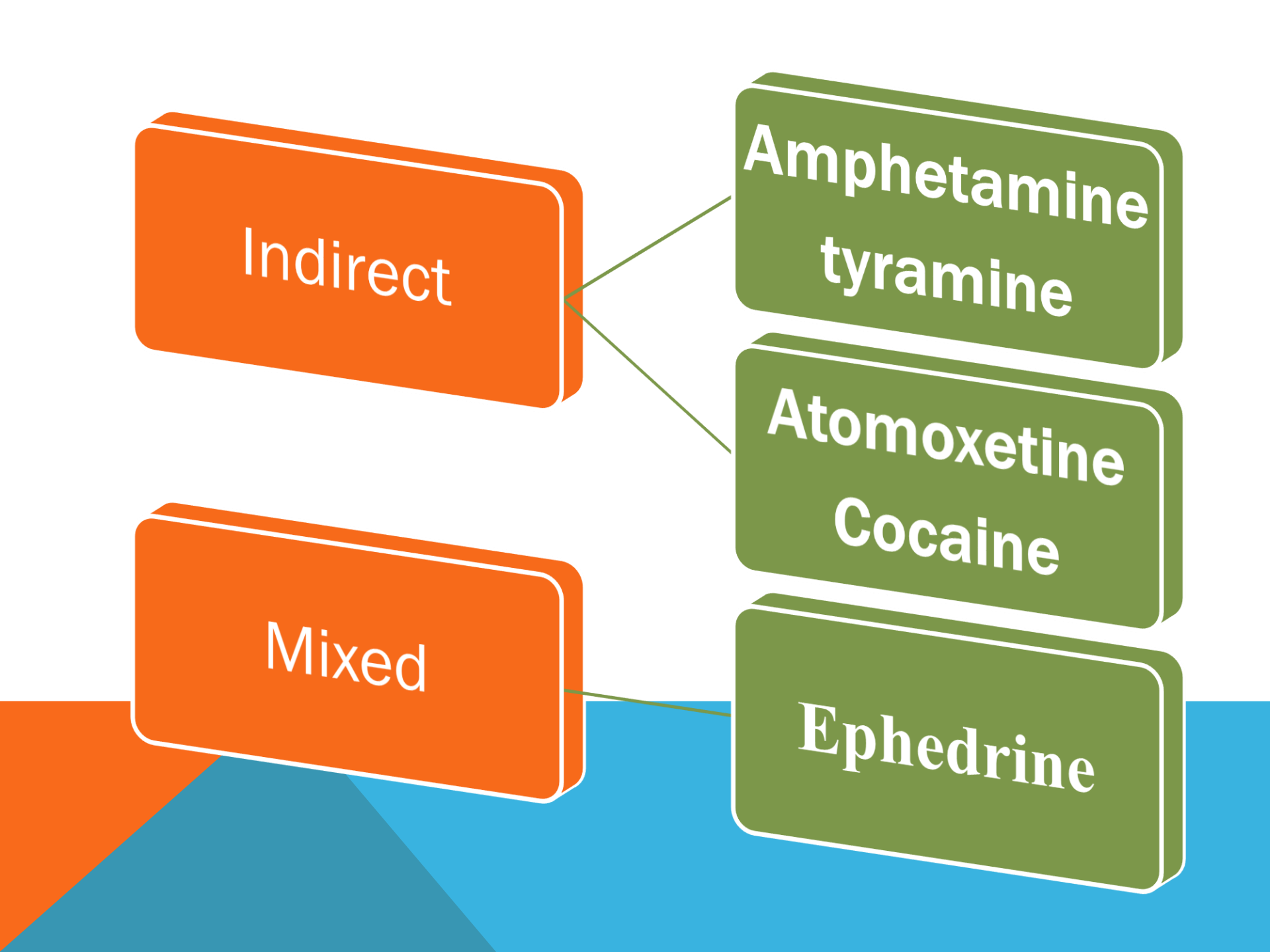
- ✓ **Rapidly metabolized by COMT and MAO so have short duration of action and not absorbed orally.**
- ✓ **Cannot cross BBB.**
- ✓ E.g: adrenaline, NA, dopamine, dobutamine, isoprenaline

Non-catecholamines:

- ✓ **Not metabolized by COMT and MAO so, have longer duration of action and are absorbed orally.**
- ✓ **Can pass BBB and have CNS effects.**
- ✓ **E.g:** synthetic alpha-agonists & beta- agonists, e.g. phenylephrine, ephedrine, amphetamine

MECHANISM OF ACTION




Indirect
Amphetamine
tyramine
Atomoxetine
Cocaine
Mixed
Ephedrine

Endogenous Catecholamines

(A) Epinephrine (Adrenaline)

– **Direct agonist acts on α_1, α_2, β_1, β_2, β_3**

Pharmacokinetics:

- **The preferred route is intramuscular route.**
- **It may be given subcutaneously, by endotracheal tube and by inhalation.**
- **Can be given I.V or intracardiac in cardiac arrest**

Pharmacological actions

- Local actions
- Systemic actions

A- Local actions

Eye: decongestion [VC of conjunctival blood vessels] with no mydrasis ????.

Decongestion and hemostasis because of its VC of skin and mucous membrane blood vessels.

Delay absorption of local anesthetics and prolong their duration.

- **By inhalation → Bronchodilatation, so can be used in bronchial asthma.**

B- Systemic actions:

1) Cardiovascular system (CVS) {β1 receptors}:

Heart

epinephrine increases all cardiac properties

- **positive inotropic effect**
- **positive chronotropic effect**
- **positive dromotropic.**
- **Increases automaticity.**

Blood vessels

- **VC of skin and mucous membrane blood vessels and splanchnic area.**
- **VD of skeletal muscle, and coronary blood vessels.**

Blood pressure:

According to dose and rout of administration

Small dose (S.C or I.M)	Large dose(I.V)
1-↑ Systolic blood pressure as a result of ↑↑ COP **2-↓ Diastolic BP in therapeutic doses (β_2 -stimulation)**	**↑ both SBP & DBP** (predominant **α1 effect).**

2) **Respiration:** bronchodilatation (β_2) and decongestion (α_1).

3) **GIT:** inhibits tone and motility (β_2) and contracts sphincters (α_1).

4) **Urinary bladder:** relaxes wall (β_2) and contracts sphincter (α_1).

5) **Uterus:** It causes relaxation of the pregnant uterus(β_2).

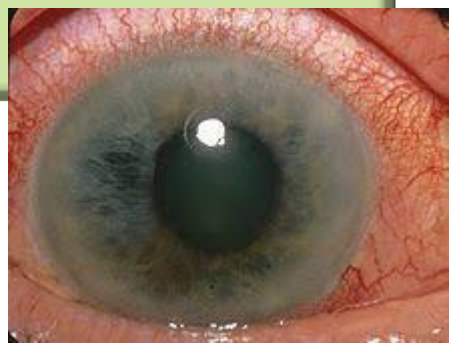
6) **Kidney:** increase renin release

7) Metabolic actions:

- **Hyperglycemia:** due to enhanced liver glycogenolysis (β_2).
- **Increased fatty acids concentration** (β_3).
- **Hypokalemia:** ↑↑ potassium uptake by skeletal muscle cells.

8) Anti-allergic action: it is a physiologic antidote to histamine.

Therapeutic uses
local uses



Eye:

In open-angle glaucoma (dipivefrin "prodrug" is preferred). Cause vasoconstriction; reduces aqueous humor production & IOP

Skin and mucous membranes:

With local anesthetics to:

i. delay absorption
ii. prolong duration
iii. decrease toxicity

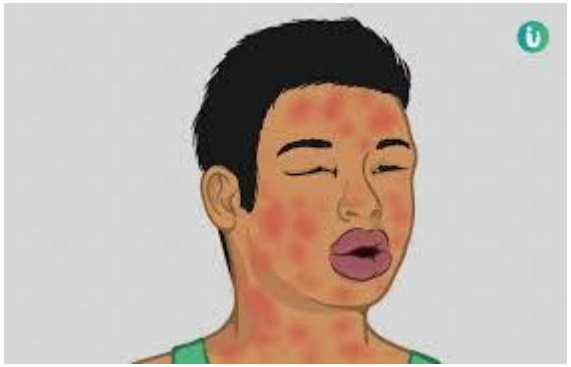
- It is not used in fingers or toes ???
- In epistaxis (locally), but not used if the cause is hypertension ????.

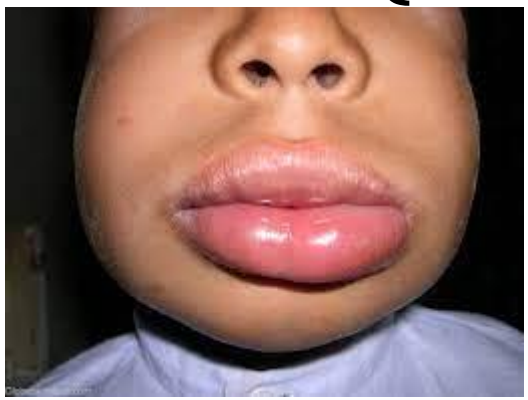
In acute bronchial asthma (inhalation).

Systemic uses

1. **In cardiac arrest (IV or intra-cardiac).**

2- Anaphylactic shock and angioneurotic edema (IM).





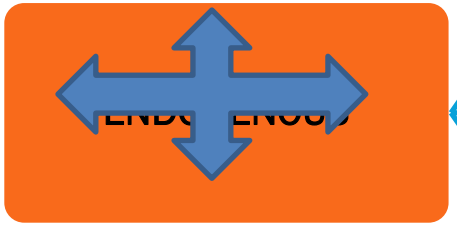
Adverse effects

1) **CNS: Restlessness, anxiety & headache.**
2) **CVS: Tachycardia and arrhythmia, Anginal pain and myocardial infarction.**
3) **Hypertension and cerebral hemorrhage.**

Contraindications

1) Coronary heart disease.
2) Hypertension.
3) Arrhythmias.
4) Peripheral vascular diseases.
5) Hyperthyroidism.

DIRECT



Norepinephrine (NE)

Dopamine

SYNTHETICS

Alpha 1 , 2 agonist

Beta agonist
(selective and non selective)

Norepinephrine (Noradrenaline)

- **Directly acting on α_1, α_2 and β_1 adrenoceptors**

Pharmacokinetics:

- **Not absorbed after oral administration due to its intense VC →→ So, ineffective orally.**
- **It is given only by slow IV infusion.**

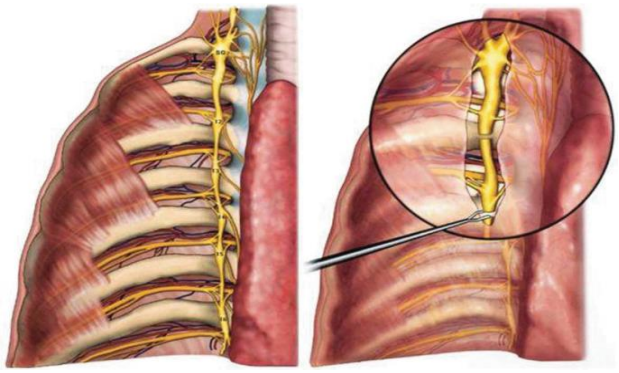
Pharmacological actions:

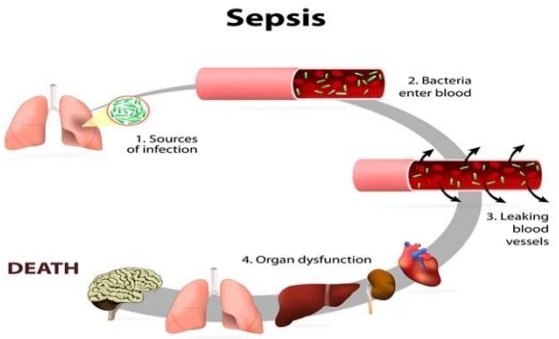
Cardiovascular System:

- **Heart:**
- **Increases contractility (β_1) but heart rate is slowed ??**
- **Blood vessels:**
- **VC of skin and mucous membrane blood vessels → ↑↑ PR → ↑↑ SBP & DBP.**

Therapeutic uses ☹3 s

- **Hypotensive states :**
  1. **After sympathectomy.**
  2. **In spinal anesthesia**
  3. **In Septic shock.**





Adverse effects:

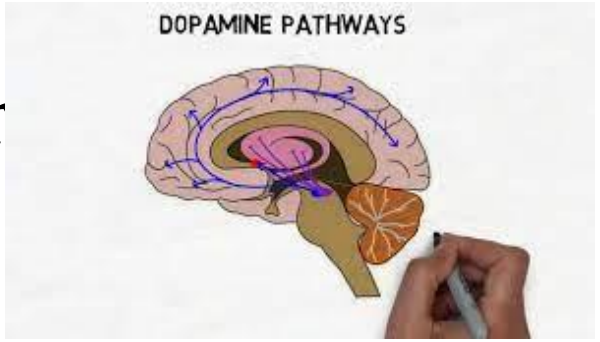
1) **Anxiety and headache.**
2) **Bradycardia and hypertension.**
3) **Extravasation → severe VC → gangrene and sloughing of skin.**

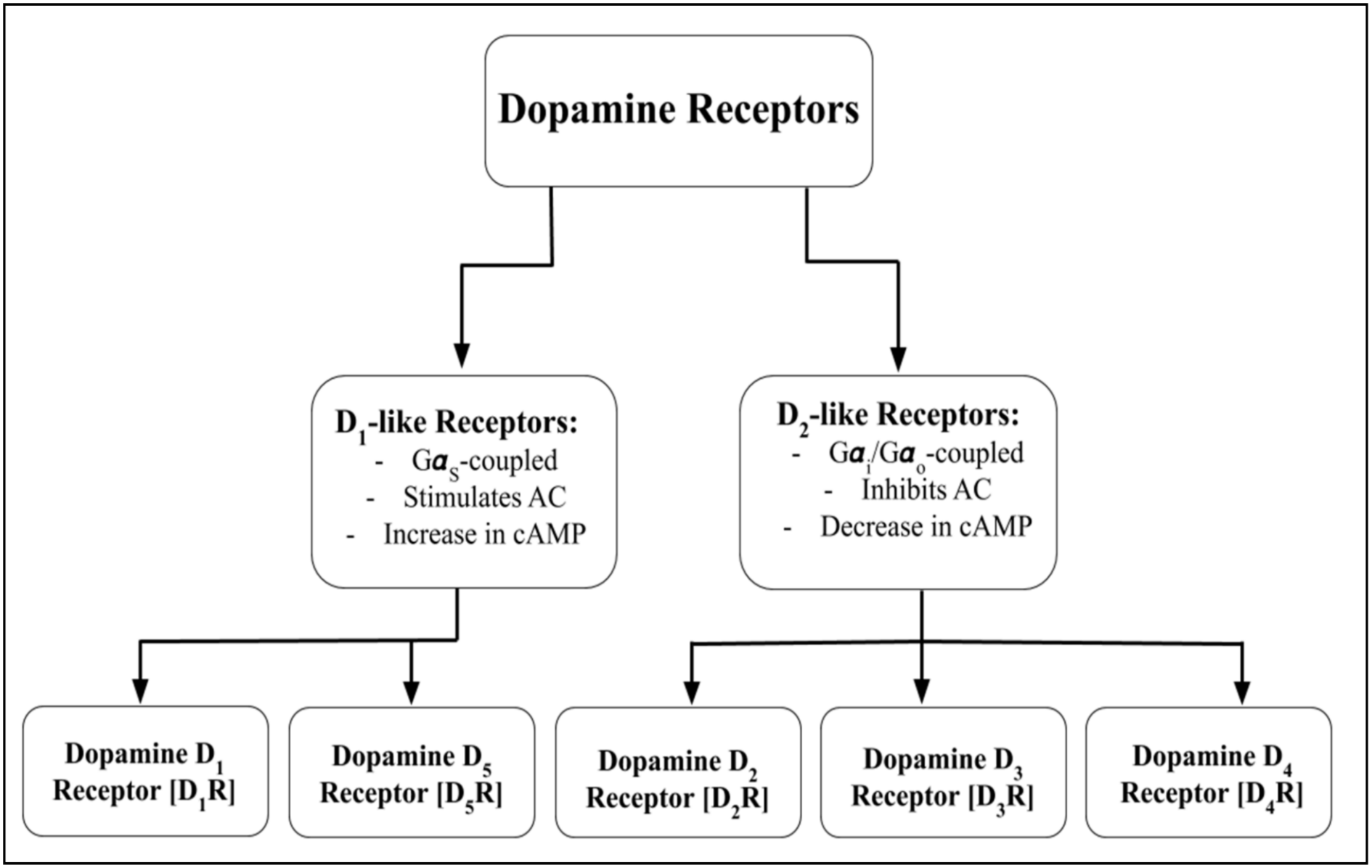
- **Treatment: rapid injection of phentolamine locally.**

Dopamine

- Precursors of adrenaline and noradrenalin.

- It act in CNS as neurotransmitter




Dopamine Receptors
D1-like Receptors:
- Gαs-coupled
- Stimulates AC
- Increase in cAMP
D2-like Receptors:
- Gαi/Gαo-coupled
- Inhibits AC
- Decrease in cAMP
Dopamine D1 Receptor [D1R]
Dopamine D5 Receptor [D5R]
Dopamine D2 Receptor [D2R]
Dopamine D3 Receptor [D3R]
Dopamine D4 Receptor [D4R]

Pharmacokinetics:

– **Ineffective orally, so must be given by IV infusion because it has very short $t_{1/2}$ (2 min).**

Pharmacological actions:

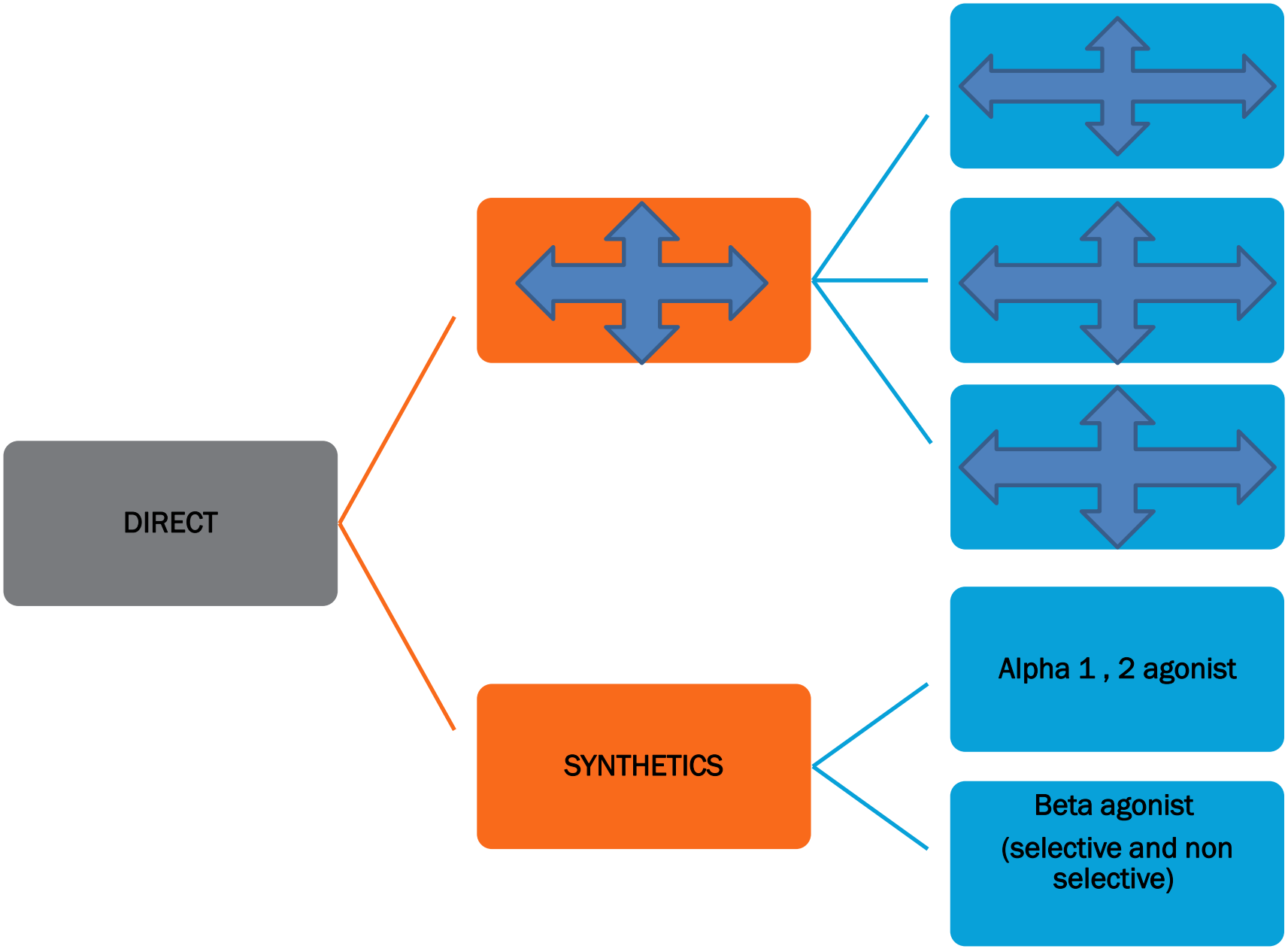
Dose	Receptor stimulated	Site of Receptor	Pharmacological action
Slow rate of infusion [2- 5µg/kg/min]	D_1-receptors	Renal, splanchnic, coronary and cerebral circulation	VD in the renal vasculature. ↑↑renal blood flow and urine output.
Moderate rate of infusion [5-10µg/kg/min]	β_1-adrenoceptors	Heart	Positive inotropic and chronotropic effects → ↑↑ cardiac output.
High rate of infusion [>10µg/kg/min]	α_1-adrenoceptors	Blood vessels of skin and mucous membrane	VC → ↑↑ BP.
Dopamine via D_2 presynaptic receptor stimulation → ↓↓ NE release.			

Therapeutic uses:

1) Cardiogenic shock
2) Hypovolemic shock (??)

N.B.:

- Blood transfusion and physiological solutions must be given either prior to or concomitantly with dopamine in the case of hypovolemic shock with monitoring of BP, HR and urine flow.


DIRECT
SYNTHETICS
Alpha 1 , 2 agonist
Beta agonist
(selective and non selective)

Synthetic Sympathomimetics

A] Direct-acting Sympathomimetics

1- Alpha$_1$ selective agonists

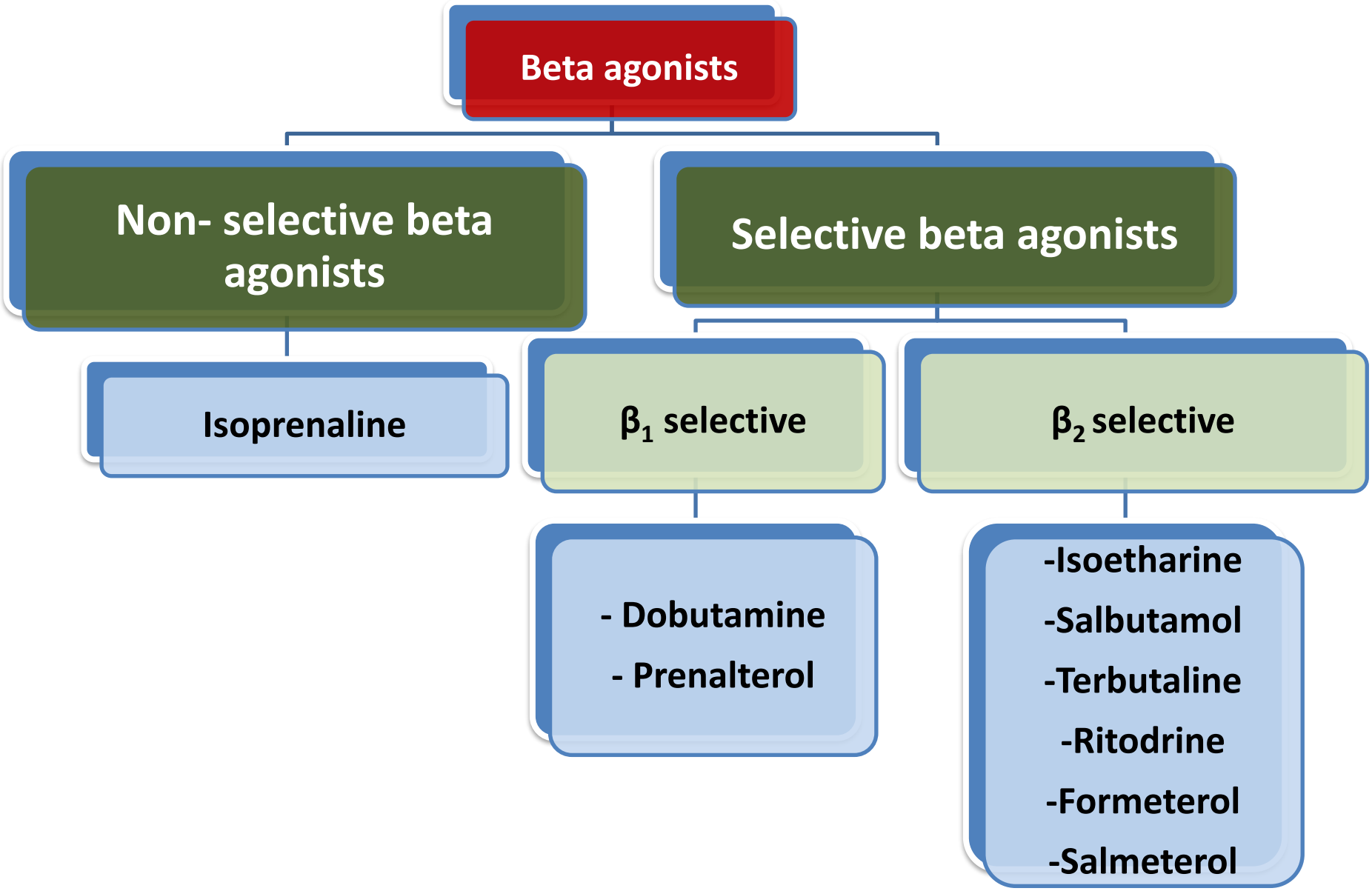
Phenylephrine:

- **Non-catecholamine (not inactivated by COMT →→ long duration)**
- **Uses:**
  1. **Mydriatic**
  2. **Decongestant**
  3. **Treatment of hypotension**

- **Methoxamine:** like phenylephrine.
- **Midodrine:** used in treatment of orthostatic hypotension.
- **Xylometazoline & oxymetazoline:** used as topical decongestants.

2-Alpha 2-agonists:

- Clonidine & alpha-methyldopa


Beta agonists
Non- selective beta agonists
Selective beta agonists
Isoprenaline
β1 selective
β2 selective
- Dobutamine
- Prenalterol
-Isoetharine
-Salbutamol
-Terbutaline
-Ritodrine
-Formeterol
-Salmeterol

Non- selective β-agonists

Isoproterenol (Isoprenaline)

A catecholamine in its chemical structure.

- **Pharmacological actions:**

1) C.V.S:

- **Heart: stimulates β_1 → increase all cardiac properties.**
- **Blood vessels: VD of skeletal muscle and coronary BV (β_2) → ↓↓ diastolic BP → reflex tachycardia.**
- **BP: diastolic BP is decreased but the systolic BP may increase slightly.**

2) Bronchi: bronchodilatation (β_2).

3) Uterus: relaxation (β_2).

4) Metabolic: hyperglycemia.

Therapeutic uses:

1) Bronchial asthma
2) Heart block.

Adverse effects:

1) Tachycardia, palpitation, and arrhythmia.
2) Angina and myocardial infarction.
3) Tremors.

β_1-selective agonists

Dobutamine

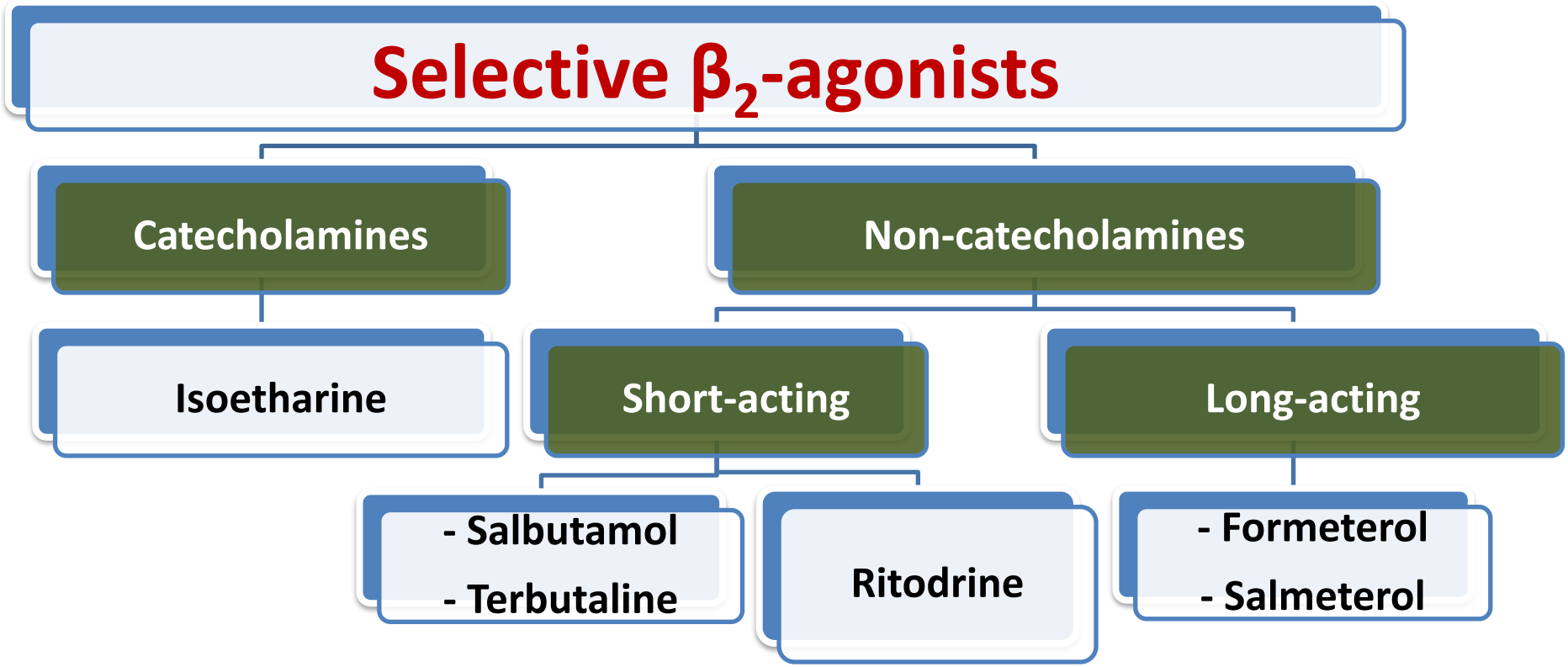
- Catecholamine, directly acting sympathomimetic.
- Selective β_1-agonist.
- Has a major advantage over other sympathomimetic drugs (??)

1) Increasing contractility with minimal increase in hear rate.
2) Increases cardiac output and does not significantly elevates oxygen demands of the heart.

- **Dobutamine** is given by **IV infusion** 2.5-10 ug/kg min.
- **Used in:**
  1) Acute heart failure
  2) Cardiogenic shock
- **Adverse effects:**
  1) Tachycardia, palpitation, angina and arrhythmia
  2) Hypertension
  3) Nausea
  4) Headache

Prenalterol:

Like dobutamine but non-catecholamine and can be used orally.


Selective β2-agonists
Catecholamines
Non-catecholamines
Isoetharine
Short-acting
Long-acting
- Salbutamol
- Terbutaline
Ritodrine
- Formeterol
- Salmeterol

β_2-selective agonists

Pharmacological actions:

- They stimulate β_2>>>>$\beta_1$adrenoceptors:

1) Bronchodilators
2) Uterine relaxant
3) Hyperglycemia
4) Vasodilators of skeletal muscle Bl.Vs.

Therapeutic uses:

1) Bronchial asthma
2) Uterine relaxant to prevent preterm labor (Ritodrine)

Adverse effects:

1) Skeletal muscle tremors.
2) In large doses, stimulate β_1 receptors $\rightarrow$ tachycardia, palpitation and hypokalemia.

D_1-selective agonists

Fenoldopam

- ✓ D_1-receptor agonist causes VD of arterioles → ↓↓ TPR→ ↓↓ BP.
- ✓ Its $t_{1/2}$ is 5 min.
- ✓ Used by IV infusion in hypertensive emergencies.


Thank you!