Sympathomimetics drugs

Prepared by: Heba Ahmed Hassan
Assistant professor of clinical pharmacology
faculty of medicine, mutah university, JORDEN

Sympathomimetics

- **Drugs that mimic effects of endogenous norepinephrine (noradrenaline) or epinephrine (adrenaline).**
- **Classification**

A) According to the mechanism of action:-

1. **Direct-acting agonists.**
2. **Indirect-acting.**
3. **Mixed agonists: Both direct and indirect actions.**

1) Direct-acting agonists:

They directly activate adrenoceptors e.g. norepinephrine (NE), epinephrine and dopamine

2) Indirect-acting: either by:

i. **Release of stored catecholamines from the adrenergic nerve endings e.g. amphetamine.**

ii. **Inhibit reuptake of catecholamines already released e.g. cocaine and tricyclic antidepressants "TCAs".**

3) Both direct and indirect actions (mixed) e.g. ephedrine.

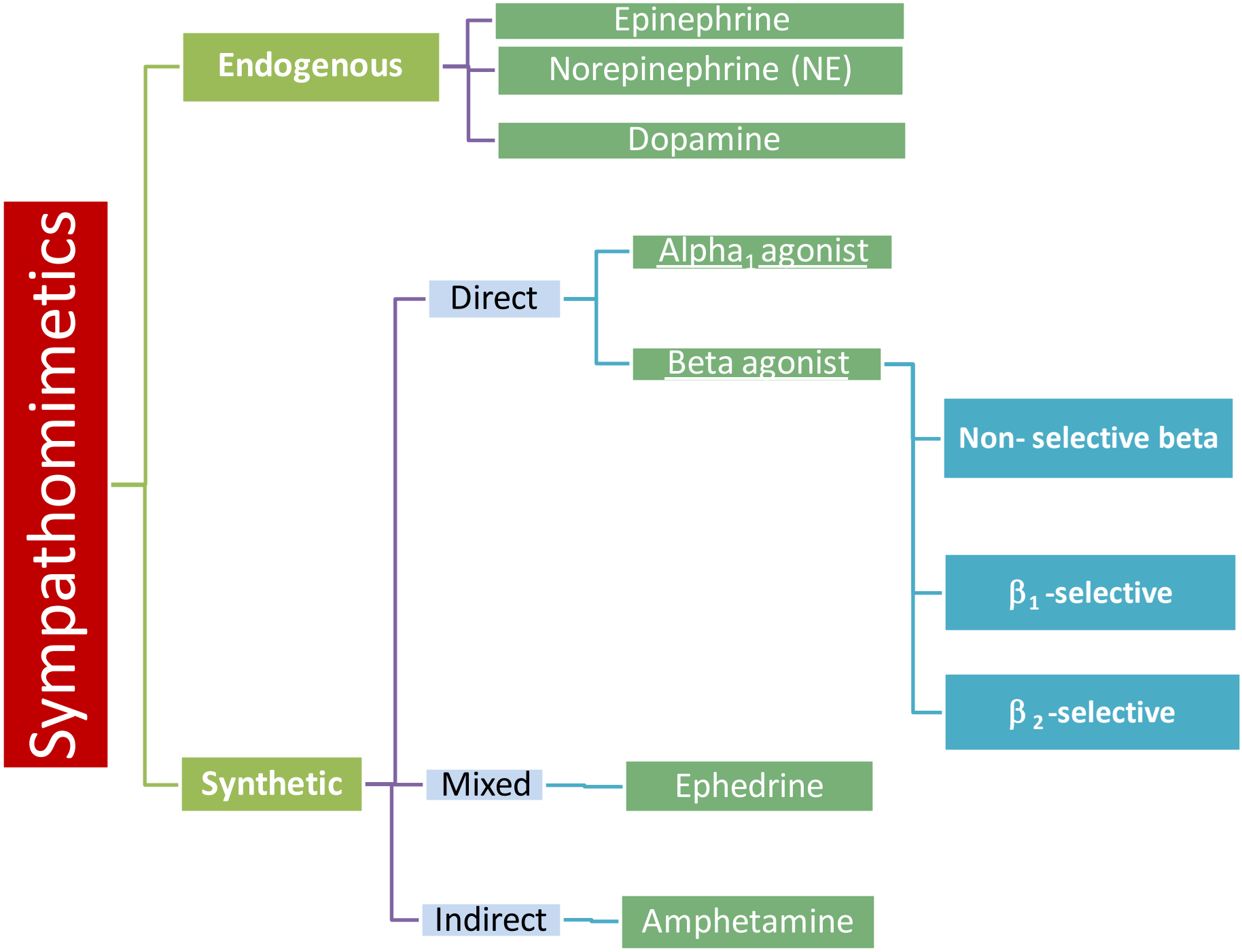
B) Classification according to their chemical structure:

i. Catecholamines:

- ✓ **Rapidly metabolized by COMT and MAO so have short duration of action and not absorbed orally.**
- ✓ **Cannot cross BBB.**

ii. 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.**


Sympathomimetics
Endogenous
Epinephrine
Norepinephrine (NE)
Dopamine
Synthetic
Direct
Alpha1 agonist
Beta agonist
Non- selective beta
β1 -selective
β 2 -selective
Mixed
Ephedrine
Indirect
Amphetamine

Endogenous Catecholamines
(1) Epinephrine (Adrenaline)

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

Pharmacokinetics:

- **Epinephrine has a rapid onset but a brief duration of action (due to rapid degradation by MAO and COMT).**

Pharmacological actions

A- Local actions:

- **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.**
- **Eye: decongestion [VC of conjunctival blood vessels], but no effect on pupil size, because it is destroyed by alkalinity of tears.**

B- Systemic actions:

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

Heart: epinephrine increases all cardiac properties.

Blood vessels: VC of skin and mucous membrane blood vessels and splanchnic area.

VD of skeletal muscle, and coronary blood vessels.

Blood pressure:

- ↑ **Systolic** blood pressure as a result of ↑↑ COP.
- ↓ **Diastolic** BP in therapeutic doses (β_2 stimulation) and increases it in large doses (α_1 stimulation).
- **α_1-adrenoceptor blockers reverse the hypertensive effect of epinephrine.**

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:** variable with species. It causes relaxation of the pregnant uterus.

6) **Sweat glands:** ↑↑ sweat secretion from apocrine sweat glands of the palm of the hand (non-thermoregulatory sweat).

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.

9) Other actions: anxiety, tremors and facilitates neuromuscular transmission.

Therapeutic uses

1) **Anaphylactic shock and angioneurotic edema.**

2) **With local anesthetics to:**

   i. **delay absorption**

   ii. **prolong duration**

   iii. **decrease toxicity**

- **It is not used in fingers or toes → gangrene.**

3) In epistaxis (locally), but not used if the cause is hypertension.

4) In acute bronchial asthma (inhalation).

5) In cardiac arrest (IV or intra-cardiac).

6) In open-angle glaucoma (dipivefrin "prodrug" is preferred).

Adverse effects

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

Contraindications

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

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 ?? (reflex vagal stimulation as a result of increased blood pressure.)**

➢ Blood vessels:

- **VC of skin and mucous membrane blood vessels → ↑↑ PR → ↑↑ SBP & DBP.**

Therapeutic uses:

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

Adverse effects:

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

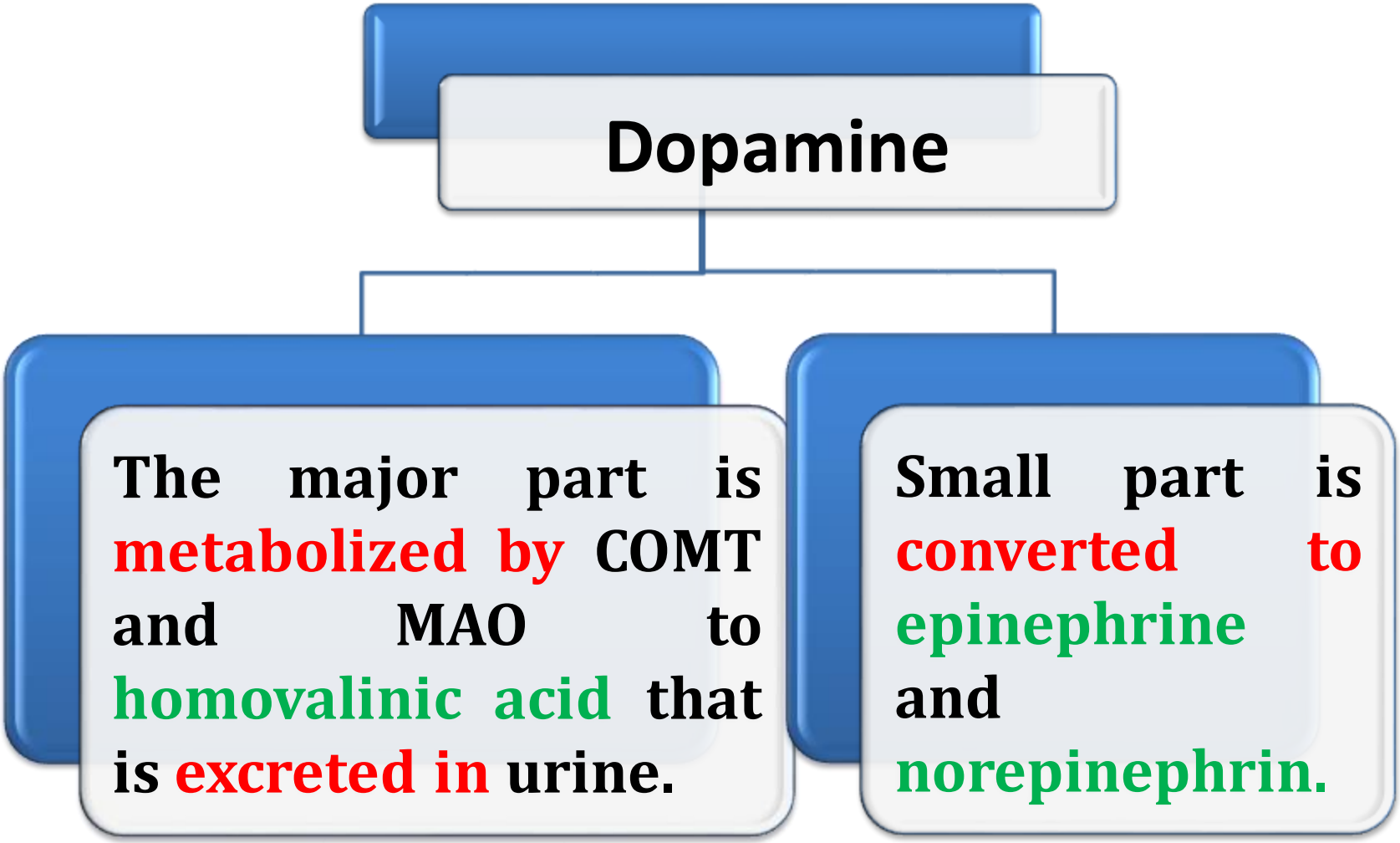
- Treatment: rapid injection of phentolamine locally.

Dopamine

- Dopamine is a precursor of norepinephrine.
- It is present also in CNS and acts as a chemical transmitter in basal ganglia & hippocampus.

Pharmacokinetics:

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



Therapeutic uses:

1) Cardiogenic shock
2) Hypovolemic shock

Adverse effects:

- An overdose of dopamine produces the same effects of sympathetic stimulation.
- Dopamine is rapidly metabolized by MAO and COMT, and its adverse effects (nausea, hypertension, and arrhythmias) are, therefore, of short duration.

Synthetic Sympathomimetics

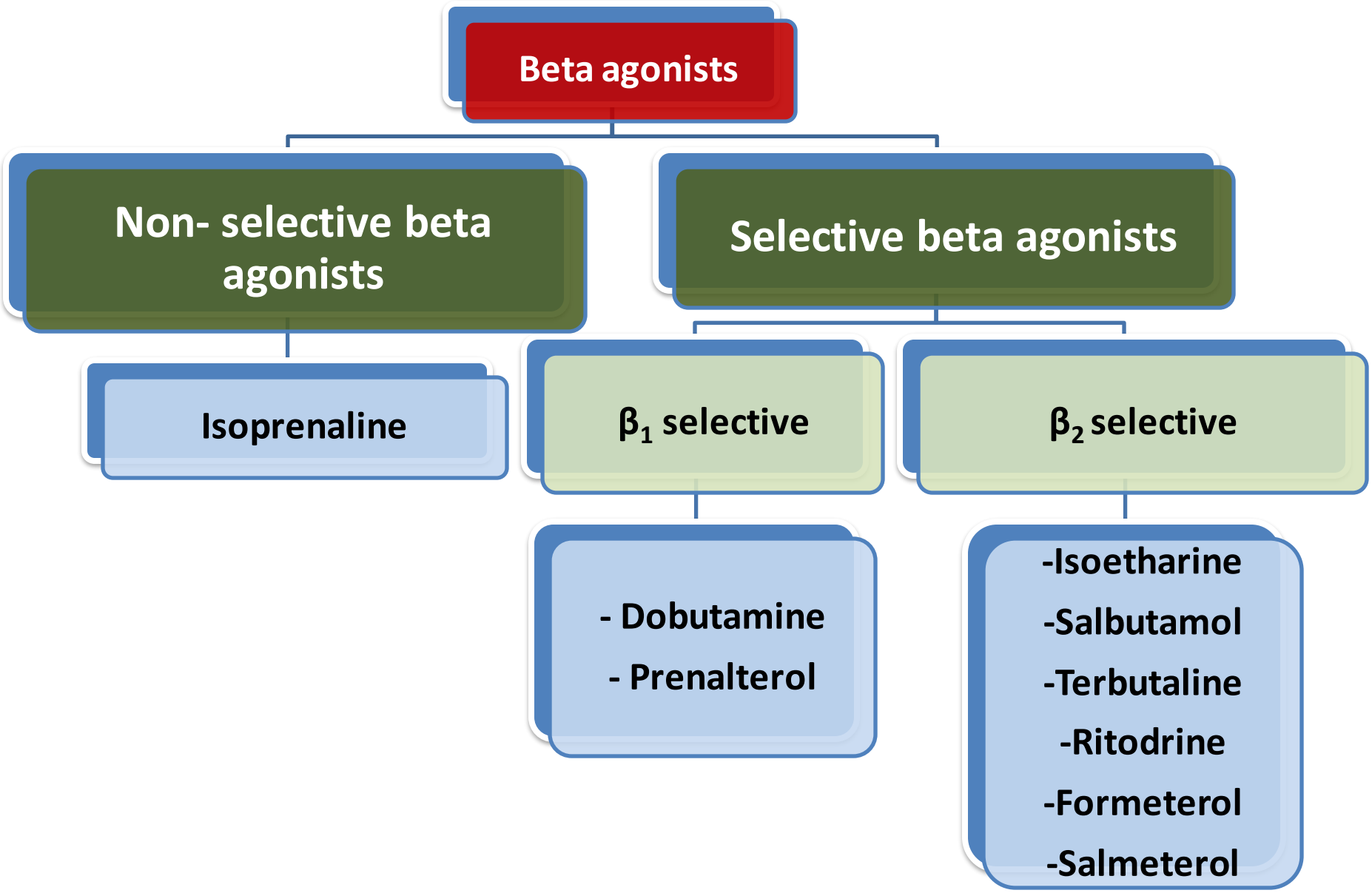
A] Direct-acting Sympathomimetics

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.


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

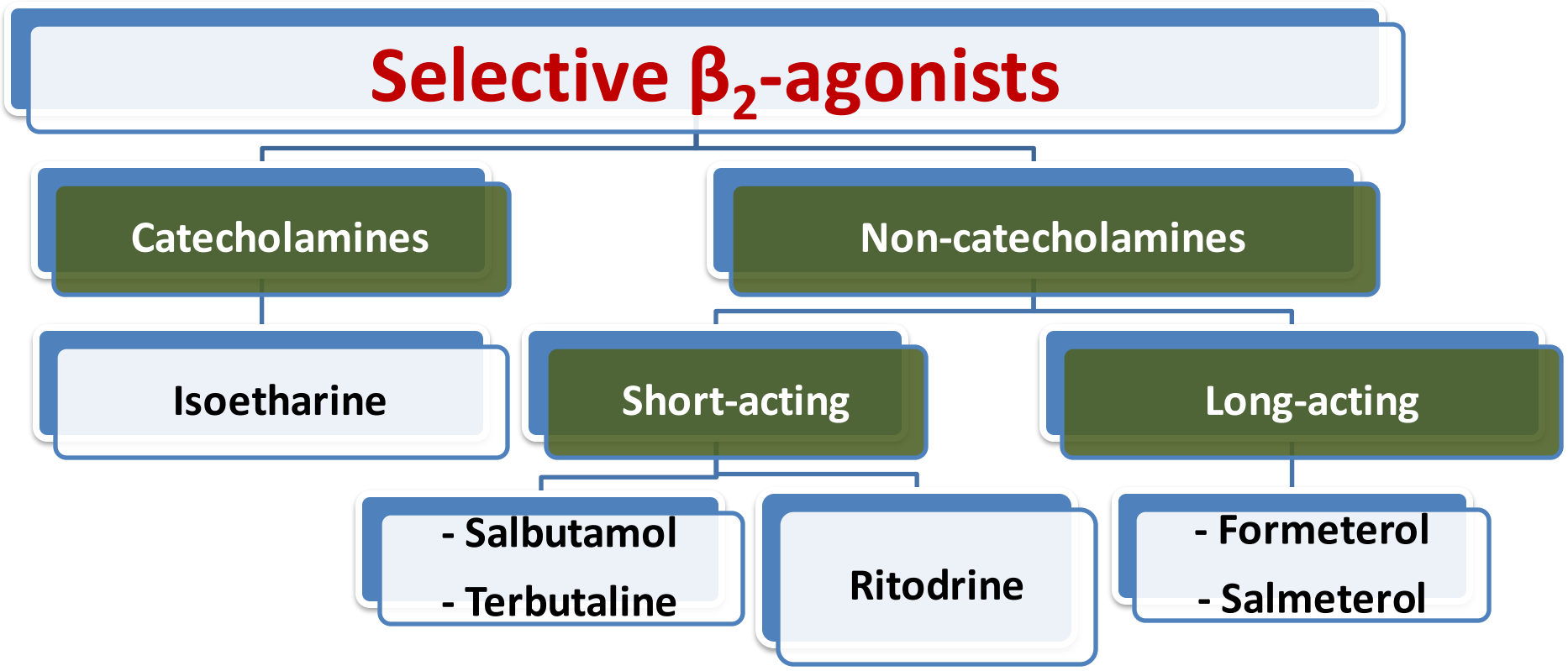
- Catecholamine, directly acting sympathomimetic.
- Selective β_1-agonist.
- Has a major advantage over other sympathomimetic drugs (??)

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 (tocolytic)
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

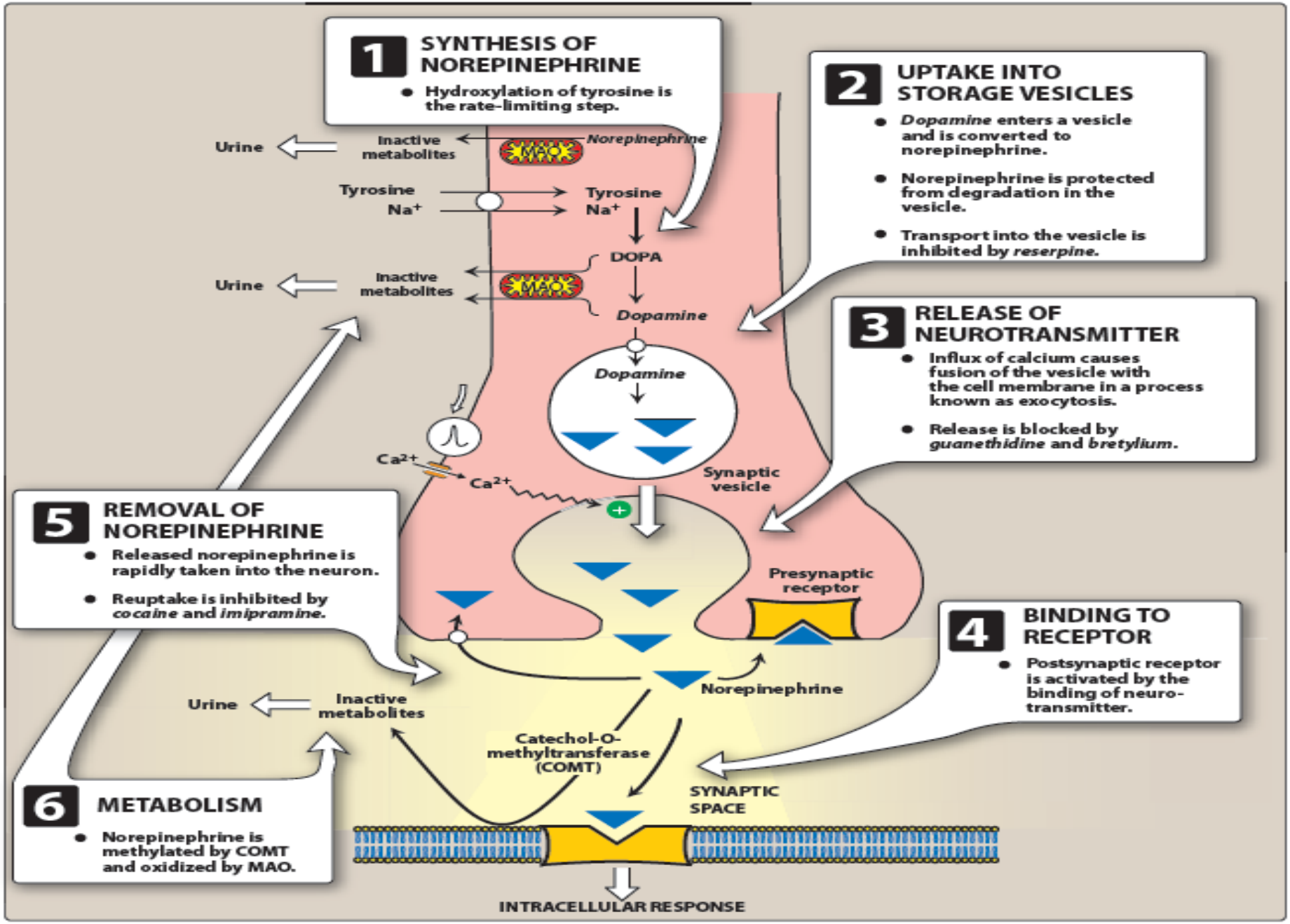
Fenoldopam

- ✓ D_1-receptor agonist causes VD of arterioles → ↓↓ TPR → ↓↓ BP.
- ✓ Its $t_{1/2}$ is 5 min.
- ✓ Used by IV infusion in hypertensive emergencies.
- ✓ **Adverse effects:**
  1) Headache and flushing.
  2) Tachycardia.

Mixed-acting sympathomimetics

&

Indirect-acting sympathomimetics



Synthesis, release & fate of NE in adrenergic neurons

Ephedrine

activates α_1, β_1 and β_2-adrenoceptors.

Pharmacokinetics:

- **It is absorbed orally and can be given parenterally.**
- **It is poor substrate to MAO and COMT, so it has long duration of action.**
- **Distributed all over the body and passes BBB.**
- **Excreted in urine. Acidification of urine by ammonium chloride increases its excretion.**

Pharmacological actions:

- It is a mixed sympathomimetic. It acts mainly indirectly; its actions are slower in onset and have longer duration.
- It shows the phenomenon of tachyphylaxis.

A- Local actions

1) Produces VC of blood vessels.
2) In the eye, it produces active mydriasis.
3) It is decongestant to nasal mucosa; however, it causes rebound congestion.

B-Systemic actions

1) CNS:

-Stimulates cerebral cortex → insomnia, anxiety, tremors and convulsions.

In contrast, it causes sedation in attention deficit hyperkinetic children.

-It stimulates medullary centers and vasomotor center and chemoreceptor trigger zone.

-It stimulates spinal reflexes.

2) CVS:

- **Heart:** Stimulates all cardiac properties.
- **Blood vessels:**
  - VC of skin and mucous membrane Bl.Vs. → increases systolic & diastolic BP [α-blockers can abolish the hypertensive effect of ephedrine].

3) Bronchi:

Bronchodilatation (β_2), and VC of mucous membrane Bl.Vs.

4) GIT and urinary bladder:

- **Contraction of sphincters (α_1)**
- **Relaxation of walls (β_2)**

5) Skeletal muscles:

- **Stimulant more than epinephrine**

Therapeutic uses:

1) Analeptic in toxicity with CNS depressants.
2) Attention-Deficit Hyperkinetic Disorder (ADHD).
3) Mydriatic eye drops 1-3%.
4) Nasal decongestant (pseudoephedrine is better).
5) For reversal of hypotension from spinal or epidural anaesthesia (by I.V ephedrine).
6) Nocturnal enuresis.
7) Myasthenia gravis (adjuvant with neostigmine).

Adverse effects:

1) **CNS stimulation:** insomnia, tremors, anxiety, convulsions and vomiting (CTZ).
2) **CVS:** tachycardia, palpitation, angina, arrhythmia, hypertension.
3) **Urine retention** (in old age with senile enlargement of prostate).
4) **Tolerance and tachyphylaxis.**

Indirect-acting Sympathomimetics

A. Drugs that release the stored catecholamine transmitters:

- Amphetamine
- Tyramine

B. Catecholamine reuptake inhibitors:

- Atomoxetine
- Cocaine

Amphetamine

Pharmacokinetics:

Absorbed and excreted as ephedrine.

Pharmacological actions:

1) **It stimulates cerebral cortex, reticular activating system, midbrain and spinal cord.**
   - **These effects are manifested as euphoria, increased mental activity, alertness and wakefulness.**
2) **Also it has analeptic and anti-fatigue actions.**

3) It decreases appetite (anorexiogenic).

4) It produces sympathomimetic action like ephedrine with little effect on bronchi.

5) Tolerance: occurs to anorexiogenic and psychic effects.

6) Addiction (dependence): on prolonged use.

Therapeutic uses:

1) Narcolepsy.
2) Obesity.
3) Attention-deficit hyperkinetic disorder (ADHD).

Adverse effects:

1) CVS:

- Palpitations, hypertension, arrhythmias.

2) CNS:

i. Anxiety, anorexia, insomnia, hallucination and convulsions.

ii. Dependence.

iii. Psychosis and coma.

Contraindications:

As epinephrine plus:

1) Insomnia.
2) Prostatic enlargement.
3) With MAOIs.

Amphetamine derivatives

- **Methamphetamine:**

More CNS effects with less peripheral actions.

- **Phenmetrazine and diphenmetrazine are used in obesity.**

- **Methylphenidate: used in ADHD.**

➢ Modafinil:

- It acts on α, serotonin (5-HT) and glutamate receptors in CNS.
- It is used in narcolepsy and ADHD.

➢ Fenfluramine and dexfenfluramine:

- Anorexiogenic drugs acts on 5-HT receptors centrally.
- In large doses can cause arrhythmia.

Tyramine

- It is a normal byproduct of tyrosine metabolism in the body and is also found in high concentrations in some fermented foods (such as cheese), chicken liver, chocolate, and smoked fish.
- It is inactivated by MAO in the liver and intestine when taken orally.
- If administered parenterally, it produces an indirect sympathomimetic action.

- In patients treated with non-selective MAO inhibitors, effect of tyramine is exaggerated, leading to severe hypertension (cheese reaction).

Atomoxetine

- It is a selective inhibitor of the norepinephrine reuptake transporter.
- It is used in the treatment of ADHD.

Cocaine

- It is a local anesthetic with a peripheral sympathomimetic action due to inhibition of both:
  i. Neuronal uptake [uptake-1] of catecholamines
  ii. MAO
- It penetrates CNS and produces amphetamine-like psychological effects.


Thank you!