SYMPATHOTROPIC DRUGS

SYMPATHOLYTICS

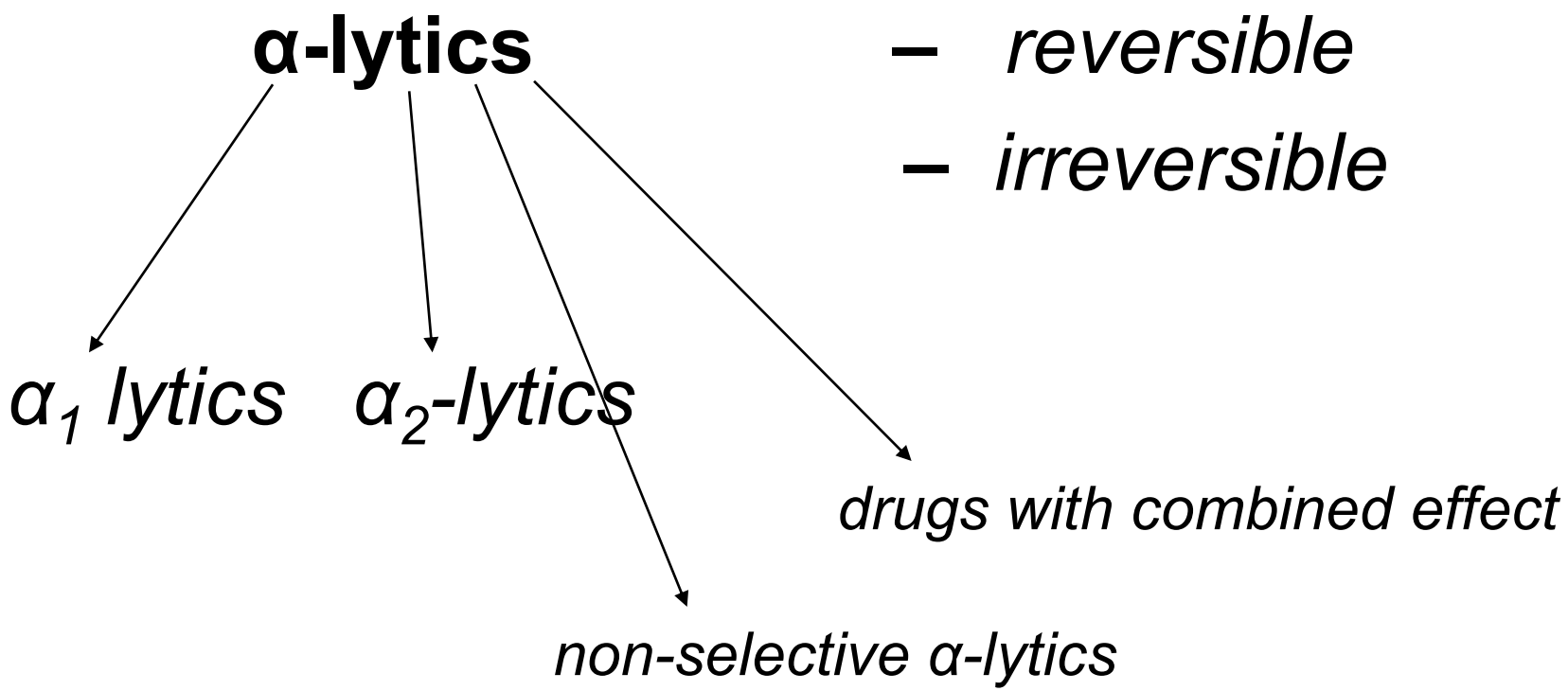
Sympatholycs (direct and indirect)

Indications:

- hypertension (mild and moderate)
- antimigraine drugs
- disorders of peripheral vascularity
- benign prostatic hyperplasia
- urinary obstruction – postoperative atonia
- pheochromocytoma

Direct sympatholytics

α



Direct sympatholytics
α non-selective

- **ergot alkaloids** (ergotamine, ergometrine, ergotoxine, methylergometrine, dihydroergotamine, dihydroergotoxine, dihydroergocristine)

Direct sympatholytics
α non-selective

Ergot alkaloids and their derivatives ➔ reversible α-lytics

- in *Secale cornutum*, product of *Claviceps purpurea*, fungus that infects cereal crops
- derivatives of lysergic acid
- effects:

- CNS (halucinations, ↓ prolactine secretion)
- smooth muscle of blood vessel (effects mimetic or **lytic**)
- uterine muscle → contractions

Direct sympatholytics
α non-selective
Ergot alkaloids

<u>INDICATIONS AND USE</u> (today rare use, in gynekology, sometimes in individually prepared prescription):

- uterotonics
- antimigraine drugs
- (vasodilators)
- (hypertension)

Direct sympatholytics
α non-selective
Ergot alkaloids

- **ergotamine, ergometrine**

  - parcial α-agonistic effects

  - uterotonic effect, amplified by methylation of derivatives (methylergometrine)

- **ergotoxine**

  - mixture of alkaloids, mainly **ergocristine, ergocriptine** and **ergocornine** - especially α-lytic effects

- **<u>α-lytic effects are increased in dihydro-derivatives</u>** ***(dihydroergotamine, dihydroergotoxine, dihydroergocristine)*** **!**

Direct sympatholytics
α non-selective
Ergot alkaloids

- **methylergometrine**

uterotonic effect (amplified by methylation of derivatives derivátů)

• therapy and prevention of uterine bleeding after childbirth (in hypotony and atony of myometrium)
• therapy and prevention of uterine bleeding after evacuation or revision of the uterus after a miscarriage
• subinvolution of uterus in the postpartum period
• gynecological operations – for the ↑ uterine tone
• III. time of birth after birth limbs

Direct sympatholytics
α non-selective
Synthetic drugs

INDICATIONS AND USE

- pheochromocytoma
- mild and moderate hypertension
- peripheral vasospastic diseases: (Raynaud phenomena)
- urinary obstruction
- today almost not used

Direct sympatholytics
α non-selective

- **phentolamine** (in Czech Rep. non registered)
- **blocks α_1 and α_2 receptors** – decrease of peripheral vascular resistance
- cardiostimulatory effect (↑ HR,tachy or arrhytmia)➞
  resulted from α_2-adrenergic blockade → non-regulated noradrenaline releasing

- GIT stimulation ➞ HCl hypersecretion and diarrhea
- parenteral administration
- obsol.

- **phenoxybenzamine** (in Cz. Rep. non registered)
- irreversible α-receptor antagonist
- covalent binding to the receptor – need of receptor synthesis *de novo*

Use:

- pheochromocytoma therapy

Direct sympatholytics
α_1 selective

$\alpha_1$sympatholytics

Overview of drugs, use

- **terazosin, doxazosin, alfuzosin, tamsulosin…**
- **prazosin (in Czech Rep. non registered)**

- **Use:**

  - hypertension (relaxation of arterial and venous smooth muscle)

  - benign prostatic hyperplasia

  - urinary obstruction

Direct sympatholytics with combined effect

- **urapidil**

- combined central and peripheral action, blocks α_1 receptors, in CNS blocks H_1 receptors, activates 5-HT_{1A} receptors

- **Use:**
  - hypertension (hypertension crisis, severe, respectively, very severe forms of hypertension and hypertension resistant to standard therapy)

Direct sympatholytics
α_2 selective

α_2 sympatholytics

- **yohimbine** (in Czech Rep. non registered)
- vasodilation in the pelvic area, afrodisiac effect
- it is contained in some dietary supplements

Direct sympatholytics
β-blockers, β-sympatholytics

- **competitive antagonists** (intrinsic aktivity = 0) or **partial agonists**

  (ISA - *intrinsic sympathomimetic activity*) = dualists

- **nonselective** or **cardioselective** (selectively block í β_1 receptors)

- sufficient solubility in fats → penetration across HEB

Direct sympatholytics
β-blockers, β-sympatholytics

Organ effects

cardiovascular system: negatively chronotropic and inotropic effect →

↓ **BP** and **HR**

- inhibition of vasodilation by β_2-receptor blockade → **peripheral vascular resistence increase**

- renine secretion reduction

bronchi: bronchoconstriction

eye: intraocular pressure decrease

metabolic effects: glycogenolysis reduction, lipolysis inhibition

Direct sympatholytics
β-blockers, β-sympatholytics

NONSELECTIVE (β_1 + β_2)	**propranolol, metipranolol**
(CARDIO)SELECTIVE (β_1)	**atenolol, metoprolol**
NONSELECTIVE (β_1 + β_2) WITH ISA	**pindolol, bopindolol (in Czech Rep. non registered)**
(CARDIO)SELECTIVE (β_1) WITH ISA	**acebutolol**
WITH COMBINED EFFECTS α + β	**labetalol carvedilol**

Direct sympatholytics
β-blockers, β-sympatholytics

Use, indications:

- hypertension
- Ischemic heart disease, non-stabil *angina pectoris*, status after acute myocardial infarction
- arrhytmia
- glaucoma
- hyperthyreosis
- anxiety (moderate effect)

Direct sympatholytics
β-blockers, β-sympatholytics

Side effects:

- *asthma bronchiale*, dyspnoea
- heart insufficiency
- bradycardia, blockade of heart impuls conduction
- masking of hypoglycemia symptoms
- disorders of peripheral blood circulation
- sleep disorders, depression (lipophilic drugs)
- rash, fever and other allergic symptoms (rarely)
- abrupt discontinuation of therapy – „**rebound phenomena“**

Nondirect sympatholytics

<u>decreases catecholamine concentratio in the synaptic cleft by:</u>

- inhibition of NT synthesis
- inhibition of NT storage
- inhibicí of NT release
- false precursors

Nondirect sympatholytics

- blockators of nerve endings ➔ block catecholamine uptake to the nerve endings and cause stabilization of the membranes (representatives: guanethidine, bretylium, debrisoquine)
- false precursors (α-methyldopa – see above – ranked among SM but the resulting effect is sympatholytic!)
- drugs causing catecholamine depletion (reserpine)
- drugs inhibiting NT synthesis (methyltyrosine = metyrosine)

- **today rare medical use**