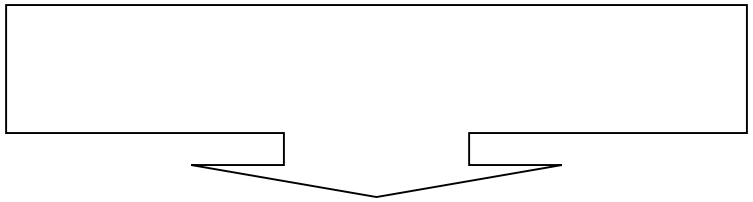
MUNI
MED

SYMPATHOTROPIC DRUGS

Department of Pharmacology

NEUROTRANSMITTER OF SYMPATHETIC NERVOUS SYSTEM



NORADRENALINE (NOREPINEPHRINE)

MUNI MED

Substances affecting the sympathetic nervous system in the meaning of +

SYMPATHOMIMETICS (adrenergics, adrenomimetics**)**

- **DIRECT**
- **INDIRECT**
- **SELECTIVE**
- **NONSELECTIVE**

Substances affecting the sympathetic nervous system in the meaning of -

SYMPATHOLYTICS (antiadrenergics, blockers, adrenolytics)

- **DIRECT**
- **INDIRECT**
- **SELECTIVE**
- **NONSELECTIVE**

MUNI MED

Sympathomimetics (direct and indirect)

Effects

- vasoconstriction, mydriasis *(α_1)*
- ↓ BP *(α_2)*
- cardiostimulation *(β_1)*
- bronchodilatation, tocolysis, antialergic effect *(β_2)*
- psychostimulation
- ↓ appetite - anorectic effect *(nondirect mechanism of action)*

MUNI MED

Direct sympathomimetics

Endogenous catecholamines and their derivatives

Overview of drugs, use:

- adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine, isoprenaline (obsol.)
- non-selective against adrenergic receptors

Use, indications:

- peripheral analeptics
- topical vasoconstriction
- cardiostimulation

MUNI MED

Direct sympathomimetics

Endogenous catecholamines

- **adrenaline (epinephrine)**

- a natural substance (hormone of the adrenal medulla, NT in the CNS, NT in the sympathetic system), stimulates α and β receptors
- higher affinity to **β** receptors, in low concentrations stimulates mainly β-receptors
- ineffective in oral administration
- metabolized like other catecholamines by MAO and COMT, final products – normetanephrine, acid vanilmandelic

MUNI MED

Direct sympathomimetics

Endogenous catecholamines

- **adrenaline (epinephrine)**

Effects:

- heart, blood vessels (vasoconstriction)
- changes of BP (according to the amount of dose – lower doses – β effect, higher doses – β and α-effect, high doses - α effect)
- bronchodilatation
- mast cells – inhibition of release of the allergic reaction mediators (histamine)
- hyperglycemia – glycogenolysis, glucagone secretion
- ⇩ insulin secretion
- lipolysis

MUNI MED

Direct sympathomimetics

Endogenous catecholamines

- **adrenaline (epinephrine)**

Use, indications:

• **resuscitation** during cardiac arrest, tonisation of myocard (1mg repeatedly in the 3 to 5min intervals – intravenously or intraosseously (= very rapid onset of action, intracardial application (very rarely))

• **anaphylactic shock** (1mg in 10ml saline sol.)

- bronchodilatatory effect
- the mucous membrane decongestion
- positive inotropic
- vasoconstriction in higher doses
- blockade of mast cells degranulation

• **additive to local anaesthetic agents** → by vasoconstriction prolongs anaesthesia, reduces toxicity of LA

• **antiasthmatic agent**: today usually replaced selective β_2-mimetics (used in *status asthmaticus*)

MUNI MED

Direct sympathomimetics

Endogenous catecholamines

- **noradrenaline (norepinephrine)**

- a natural substance (NT in CNS, NT of sympathetic system)
- stimulates **α** and β receptors
- ineffective in oral administration

- ***Effects:***
  - mainly on the cardiovascular system
  - increase of systolic (β effect) and diastolic BP (α effect)
  - reflexively by stimulation of n. vagus → bradycardia

- ***Use, indications:***
  - therapy of hypotension
  - therapy of shocks (peripheral analeptics), today drug of the first choice in patients with failing blood circulation
  - (vasoconstrictor additive to LA)

MUNI MED

Direct sympathomimetics

Endogenous catecholamines

- **dopamine** (today not common use)

- a natural substance (NT in CNS, in peripheria, precursor in NA synthesis)
- stimulates **dopaminergic receptors** (kidney and intestinal arterioles), β receptors, in higher doses α receptors
- effective only parenteral application

- ***Use, indications:***
  - **Therapy of shock**
    - –stimulation of **β_1 receptors** = positive inotropic and chronotropic effect
    - –higher doses → stimulation of **α receptors** = constriction of blood vessels (BP increase)
    - –stimulation of **D receptors** = vasodilatation in the area of splanchnic system and kidneys → increased perfusion (different from noradrenaline! → today renoprotective properties of dopamine are being called into question, respectively they are expressed only in high doses of dopamine)

MUNI MED

Side effects of catecholamines

- low distribution across HEB → low CNS toxicity
- toxic peripheral effects result from increased from α or β receptor stimulation

Side effects (mainly on the cardiovascular system):

- **significant vasoconstriction → BP increase**
- **tachycardia**
- **heart arrhythmia**
- **increased demands of the myocardium for oxygen**

MUNI MED

Direct sympathomimetics
α_1 selective sympathomimetics

- **imidazolines - naphazoline, oxymetazoline, xylometazoline, tetryzoline, tramazoline**

- stimulation of α_1 receptors → the mucous membrane decongestion

Use, indications:

- substances used primarily to decongest hyperemic mucous membranes (they are contained in the nasal and eye drops, sprays, gels, etc.)

MUNI MED

Direct sympathomimetics
α_1 selective sympathomimetics

- **phenylephrine**

- stimulation of α_1 receptors → mydriasis, the mucous membrane decongestion (nasal, conjuctivas), BP increase

- ***Use, indication:***
  - the mucous membrane decongestion
  - to induce mydriasis (in conjunctivitis, uveitis, during cataract surgery)
  - peripheral analeptics (in hypotensive conditions) – obsol.

MUNI MED

Direct sympathomimetics
α_1 selective sympathomimetics

- **midodrine**

- drug with prolonged effect (vasoconstrictor action possesses its metabolite)
- can be administered orally or parenterally

- ***Use, indications:***
  - hypotensive status
  - incontinentia urinaria (stimulation of α_1 receptors in the area of urinary bladder sphincter → sphincter contraction)

MUNI MED

Direct sympathomimetics
α_1 selective sympathomimetics

- **methoxamine (in Czech Rep. non registered)**

stimulates α_1 receptors in blood vessels → generalized vasoconstriction → increase of BP = **PERIPHERAL ANALEPTICS**

Use, indications:

- therapy of hypotensive states (during spinal anaesthesia, therapy of shock; today, however, preferred NA)

MUNI MED

Direct sympathomimetics

α_2 sympathomimetics

Overview of drugs, use:

- **clonidine, α-metyldopa**

- ***Use, indications:***

  - for the treatment of hypertension (central and peripheral mechanism of action - α-metyldopa)

MUNI MED

Direct sympathomimetics

β_1 sympathomimetics

Overview of drugs, use:

- **dobutamine**
- **ibopamine (dopamine derivative for oral administration; in Czech Rep. non registered)**

- ***Use, indications:***

  - heart failure, stimulation of conductive heart system

  - cardiogenic shock (today combination NA + dobutamine preferred)

  - severe forms of heart failure

MUNI MED

Direct sympathomimetics
β_1 selective sympathomimetics

- **dobutamine**
- ***Use, effects:***

- syntetic substance similar to dopamine
- stimulation of β_1 receptors in heart ➞ strong inotropic effect, relatively poor chronotropic effect
- indicated for cardiogenic shock in combination with NA

MUNI MED

Direct sympathomimetics
β_2 selective sympathomimetics

Effects:

- stimulation of β_2 receptors in bronchial smooth muscles of → relaxation of smooth muscles and bronchodilatation
- inhibition of inflammation mediators (leucotriens) release and allergic reaction mediators (histamine) release from mast cells
- stimulation of mucociliar functions

- relaxation of the uterine muscles

MUNI MED

Direct sympathomimetics
β_2 selective sympathomimetics

Use of β_2 sympatomimetics for bronchodilatation

Short-term effect (4 – 6 h)

orciprenaline (less selective than others)

fenoterol, salbutamol, terbutaline, hexoprenaline…

Long-term effect (8 – 15 h)

clenbuterol, procaterol, formoterol, salmeterol

Routes of administration: orally, **by inhalation**, by injection (intravenous infusion)

Side effects:

- tremor
- palpitation, nervousness
- ↓potassium (enhanced by theophyline and corticosteroids)

MUNI MED

Direct sympathomimetics
β_2 selective sympathomimetics

Use of β_2 sympatomimetics in gynekology and obstetrics

- **hexoprenaline** → TOCOLYTICS →

→ relaxation of the uterine muscles

• prevention of pre-term birth or risk of abortion during premature uterine aktivity

• calming the uterus before, during and after the cerclage and in operations in the abdominal cavity

• calming the uterus at the time between the decision on the implementation of the sectio caesarea (see point 1)

MUNI MED

Indirect sympathomimetics

MECHANISM OF ACTION

<u>increase concentration of catecholamines in synaptic cleft by:</u>

- releasing from the storage vesicles
- inhibition of neurotransmitter re-uptake presynaptically
- inhibition of catecholamine metabolism (inhib. MAO)
- *increasing of neurotransmitter synthesis*

MUNI MED

Indirect sympathomimetics

Overview of drugs, use:

- **amphetamine psychostimulants, substances related and other psychostimulants**
- **ephedrine, pseudoephedrine**
- **tyramine**
- **MAO inhibitors** (MAOI)
- **substances inhibiting re-uptake** (TCA, cocaine)

- ***Use:***
  - antidepressants
  - for ADHD treatment
  - for narcolepsia treatment
  - anorectics (antiobesics)
  - mucous membrane decongestion

MUNI MED