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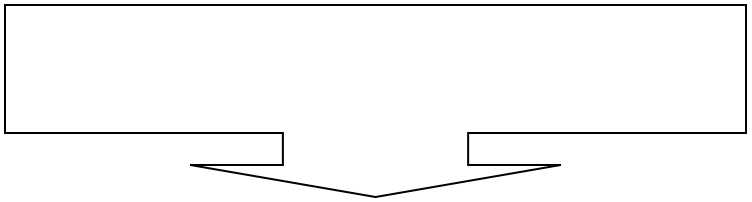
# SYMPATHOTROPIC DRUGS



Department of Pharmacology

# NEUROTRANSMITTER OF SYMPATHETIC NERVOUS SYSTEM



## NORADRENALINE (NOREPINEPHRINE)

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# Substances affecting the sympathetic nervous system in the meaning of (+)

**SYMPATHOMIMETICS (adrenergics,** adrenomimetics**)**

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

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# Substances affecting the sympathetic nervous system in the meaning of (-)

**SYMPATHOLYTICS (antiadrenergics, blockers,** adrenolytics)

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

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# Sympathomimetics (direct and indirect)

***Effects***

- vasoconstriction, mydriasis *($\alpha_1$)*
- ↓ BP *($\alpha_2$)*
- cardiostimulation *($\beta_1$)*
- bronchodilatation, tocolysis, antialergic effect *($\beta_2$)*
- psychostimulation
- ↓ appetite - anorectic effect *(nondirect mechanism of action)*

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# 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

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# 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

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# 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

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# 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 $\beta_2$-mimetics (used in *status asthmaticus*)

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# 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)

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# 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 **$\beta_1$ 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)

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# 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**

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# Direct sympathomimetics
# $\alpha_1$ selective sympathomimetics

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

- stimulation of $\alpha_1$ 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.)

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# Direct sympathomimetics
# $\alpha_1$ selective sympathomimetics

- **phenylephrine**

- stimulation of $\alpha_1$ 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.

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# Direct sympathomimetics
# $\alpha_1$ 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 $\alpha_1$ receptors in the area of urinary bladder sphincter ➔ sphincter contraction)

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# Direct sympathomimetics
# $\alpha_1$ selective sympathomimetics

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

stimulates $\alpha_1$ 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)

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# Direct sympathomimetics

## $\alpha_2$ sympathomimetics

## Overview of drugs, use:

- **clonidine, α-metyldopa**

- ***Use, indications:***

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

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# Direct sympathomimetics

## $\beta_1$ 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

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# Direct sympathomimetics
# $\beta_1$ selective sympathomimetics

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

- syntetic substance similar to dopamine
- stimulation of $\beta_1$ receptors in heart → strong inotropic effect, relatively poor chronotropic effect
- indicated for cardiogenic shock in combination with NA

# Direct sympathomimetics
# $\beta_2$ selective sympathomimetics

***Effects:***

- stimulation of $\beta_2$ 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

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# Direct sympathomimetics
# $\beta_2$ selective sympathomimetics

## ***Use of $\beta_2$ 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)

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# Direct sympathomimetics
# $\beta_2$ selective sympathomimetics

***Use of $\beta_2$ 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)

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# 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*

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# 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

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