

SYMPATHOTROPIC DRUGS

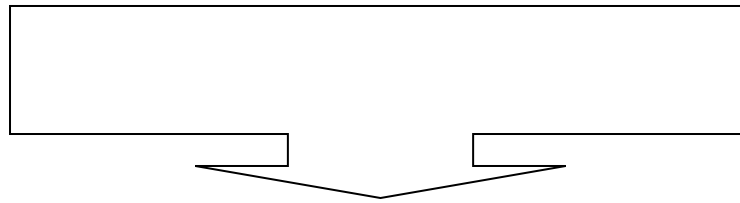
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NEUROTRANSMITTER OF SYMPATHETIC NERVOUS SYSTEM



NORADRENALINE (NOREPINEPHRINE)

Substances affecting the sympathetic nervous system in the meaning of \oplus

SYMPATHOMIMETICS (adrenergics, adrenomimetics)

- DIRECT
- INDIRECT
- SELECTIVE
- NONSELECTIVE

Substances affecting the sympathetic nervous system in the meaning of \ominus

SYMPATHOLYTICS (antiadrenergics, blockers, adrenolytics)

- DIRECT
- INDIRECT
- SELECTIVE
- NONSELECTIVE

Sympathomimetics (direct and indirect)

Effects

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

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

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

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
- \downarrow insulin secretion
- lipolysis

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.)
 - bronchodilatory 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*)

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)

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 \rightarrow stimulation of **α receptors** = constriction of blood vessels (BP increase)
 - stimulation of **D receptors** = vasodilatation in the area of splanchnic system and kidneys \rightarrow increased perfusion (different from noradrenaline! \rightarrow today renoprotective properties of dopamine are being called into question, respectively they are expressed only in high doses of dopamine)

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**

Direct sympathomimetics

α_1 selective sympathomimetics

- imidazolines - naphazoline, oxymetazoline, xylometazoline, tetrazyzoline, 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.)

Direct sympathomimetics

α_1 selective sympathomimetics

- **phenylephrine**
- stimulation of α_1 receptors \rightarrow mydriasis, the mucous membrane decongestion (nasal, conjunctivas), BP increase
- **Use, indication:**
 - the mucous membrane decongestion
 - to induce mydriasis (in conjunctivitis, uveitis, during cataract surgery)
 - peripheral analeptics (in hypotensive conditions) – obsol.

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)

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)

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)

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

Direct sympathomimetics

β_1 selective sympathomimetics

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

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

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
- \downarrow potassium (enhanced by theophylline and corticosteroids)

Direct sympathomimetics

β_2 selective sympathomimetics

Use of β_2 sympathomimetics in gynecology and obstetrics

- **hexoprenaline** → TOCOLYTICS →
→ relaxation of the uterine muscles
- prevention of pre-term birth or risk of abortion during premature uterine activity
- 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)

Indirect sympathomimetics

MECHANISM OF ACTION

increase concentration of catecholamines in synaptic cleft
by:

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

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