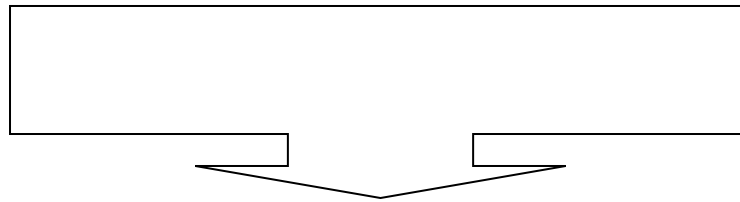


# **SYMPATHOTROPIC DRUGS**

# **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

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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 ( $\alpha_1$ )
- ↓ BP ( $\alpha_2$ )
- cardiostimulation ( $\beta_1$ )
- bronchodilatation, tocolysis, antiallergic effect ( $\beta_2$ )
- psychostimulation
- ↓ 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  $\alpha$  and  $\beta$  receptors
- higher affinity to  $\beta$  receptors, in low concentrations stimulates mainly  $\beta$ -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 –  $\beta$  effect, higher doses –  $\beta$  and  $\alpha$ -effect, high doses –  $\alpha$  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  $\beta_2$ -mimetics (used in *status asthmaticus*)



# Direct sympathomimetics

## Endogenous catecholamines

- **noradrenaline (norepinephrine)**
  - a natural substance (NT in CNS, NT of sympathetic system)
  - stimulates  $\alpha$  and  $\beta$  receptors
  - ineffective in oral administration
  - **Effects:**
    - mainly on the cardiovascular system
    - increase of systolic ( $\beta$  effect) and diastolic BP ( $\alpha$  effect)
    - reflexively by stimulation of n. vagus  $\rightarrow$  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),  $\beta$  receptors, in higher doses  $\alpha$  receptors
- effective only parenteral application
- Use, indications:
  - **Therapy of shock**
    - stimulation of  **$\beta_1$  receptors** = positive inotropic and chronotropic effect
    - higher doses  $\rightarrow$  stimulation of  **$\alpha$  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  $\alpha$  or  $\beta$  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

## $\alpha_1$ sympathomimetics

### Overview of drugs, use:

- imidazolines – naphazoline, oxymetazoline, xylometazoline, tetryzoline, tramazoline
- phenylephrine, midodrine
- methoxamine
  
- Use:
  - local vasoconstriction
  - system vasoconstriction (today not too frequent use)

# Direct sympathomimetics

## $\alpha_1$ selective sympathomimetics

- imidazolines - naphazoline, oxymetazoline, xylometazoline, tetrazyzoline, tramazoline
- stimulation of  $\alpha_1$  receptors  $\rightarrow$  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

## $\alpha_1$ selective sympathomimetics

- **phenylephrine**
- stimulation of  $\alpha_1$  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

## $\alpha_1$ 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)

# 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)



# Direct sympathomimetics

## $\alpha_2$ sympathomimetics

### Overview of drugs, use:

- **clonidine,  $\alpha$ -metyldopa**
- **Use, indications:**
  - for the treatment of hypertension (central and peripheral mechanism of action -  $\alpha$ -metyldopa )
  - rehab for addiction (clonidine – in Czech Rep. non registered)
  - glaucoma (clonidine – in Czech Rep. non registered)

# Direct sympathomimetics

## $\alpha_2$ selective sympathomimetics

$\alpha$ -metyldopa  $\rightarrow$   $\alpha$ -metyldopamin  
 $\rightarrow$   $\alpha$ -metylna (= corbadrine)

/  
= false precursor  $\rightarrow$  NA depletion NA in vesicles

activation of presynaptic  $\alpha_2$  receptors  $\rightarrow$   
inhibition of sympathetic system activity

(+ ligand of I1 receptors)  
**clonidine**

# **Direct sympathomimetics**

## **$\alpha_2$ selective sympathomimetics**

### **Side effects:**

- **confusion, sedation, zmatenost, sedace, decrease of psychomotoric functions**
- **increase in body weight**
- **postural hypotension**
- **abrupt discontinuation of the treatment – hypertensive reaction = „rebound phenomenon“**

# 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

# Direct sympathomimetics

## $\beta_1$ selective sympathomimetics

- **dobutamine**
- *Use, effects:*
  - synthetic substance similar to dopamine
  - stimulation of  $\beta_1$  receptors in heart → strong inotropic effect, relatively poor chronotropic effect
  - oxygen consumption increases less than catecholamines
  - $t_{1/2} = 2.5$  min → should be administered in a continuous infusion
  - indicated for cardiogenic shock in combination with NA

# Direct sympathomimetics

## $\beta_2$ selective sympathomimetics

### Overview of drugs, use:

- salbutamol, fenoterol, hexoprenaline, terbutaline, orciprenaline,...
- *Use, indications:*
  - bronchodilators (asthma bronchiale, status associated with obstruction of the respiratory tract (COPD))
  - tocolytics

# 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

# 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
- $\downarrow$ potassium (enhanced by theophylline and corticosteroids)



# Direct sympathomimetics

## $\beta_2$ selective sympathomimetics

### Use of $\beta_2$ 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)

# Direct sympathomimetics

## $\beta_3$ selective sympathomimetics

- *mirabegron*
- agonism of  $\beta_3$  receptors, relaxes the urinary bladder wall, increases the volume of urine during the storage phase of the micturition cycle
- orally registered in 2012
- Substrate of CYP2D6, PgP

### *Side effects:*

- infection of urinary tract

# 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:

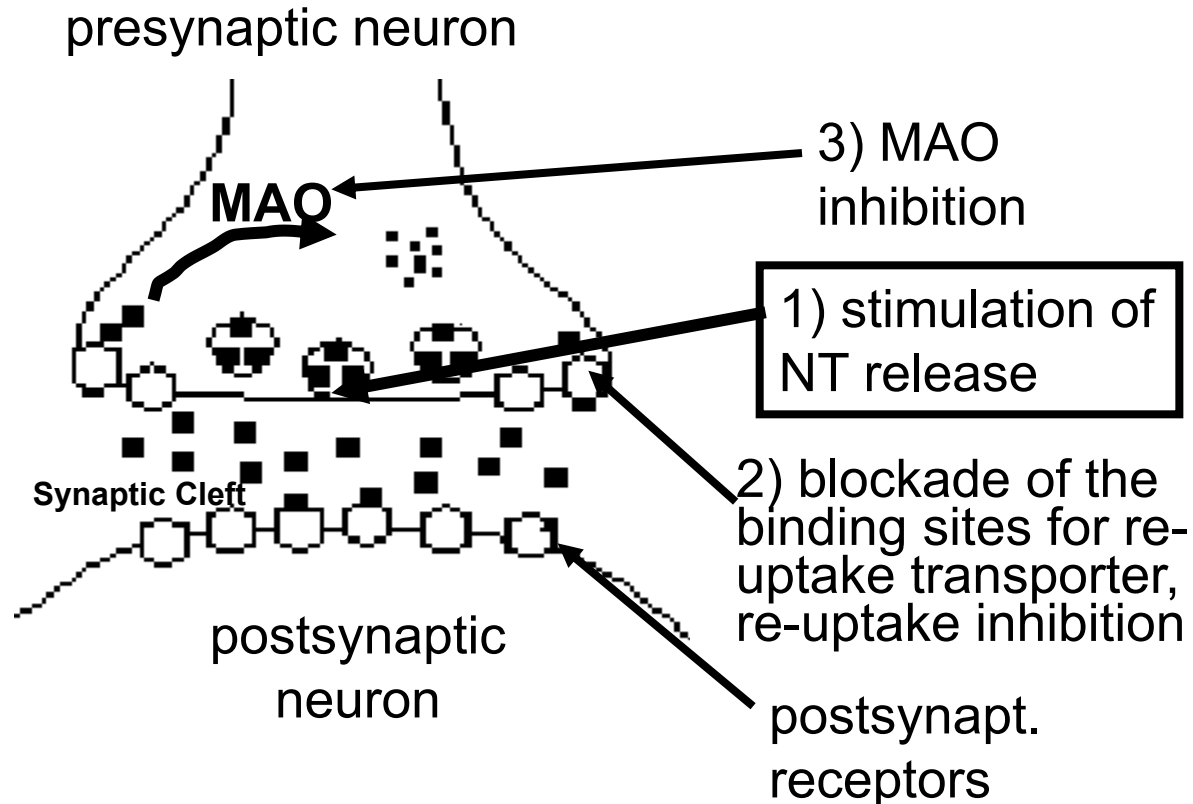
- amphetamine psychostimulants, substances related and other psychostimulants
- ephedrine, pseudoephedrine
- tyramine
- MAO inhibitors (MAOI)
- substances inhibiting re-uptake (TCA, cocaine)
- Use:
  - antidepressants
  - for ADHD treatment
  - for narcolepsia treatment
  - anorectics (antiobesics)
  - mucous membrane decongestion

# Indirect sympathomimetics amphetamine psychostimulants and substances related

## MofA:

amphetamines  
possess wide  
scale of effects on  
**NA, DA, 5-HT**  
neurons:

↑ **activity NT**  
**in brain**



# **Indirect sympathomimetics amphetamine psychostimulants and substances related**

## **Effects on the sympathetic system - stimulation:**

- ↑ HR
- ↑ BP
- ↑ body temperature
- mydriasis
- effects on CNS → psychostimulation

# Indirect sympathomimetics amphetamine psychostimulants and substances related

## AFFECTING THE CNS

### Acute effects

improvement in mood, sense of self-confidence, increased psychomotor activity (doping), dynamogenic effect (an increase in determination to take action), anorexic effect

### Chronic effects

exogenous psychosis – hallucinations, delirium, delusions, aggression, severe major depressive disorder with suicidal behaviour, paranoid states with anxiety symptomatology and agitation, insomnia, risk of „serotonin syndrome“ development

↑ ↑ **psychic addiction and tolerance**

# **Indirect sympathomimetics amphetamine psychostimulants and substances related**

- **amphetamine, methamphetamine  
MDMA (*ecstasy*)**
- ↑↑ psychic addiction and tolerance
- no medical use (in the past yes)
- among abused substances



# Indirect sympathomimetics amphetamine psychostimulants and substances related and other psychostimulants

## Indications

- **modafinil** - narcolepsy
  - **methylphenidate** - ADHD
  - **phentermine** - supportive treatment in diet in patients with BMI > 30 obesity, in which reduction diet is not sufficient to reduce body weight
- 
- **atomoxetine** – ADHD
    - not among the classical stimulants → central SM  
→ selectively inhibits NA re-uptake → ↑ NA concentration  
and indirectly ↑ DA in prefrontal cortex

# **Indirect sympathomimetics amphetamine psychostimulants and substances related and other psychostimulants**

## SIDE EFFECTS – summary:

- tachycardia
- ↑ BP
- sweating
- insomnia
- psychotic attacks
- depressive disorders
- anxiety, panic attacks
- serotonin syndrome
- drug addiction

# Other indirect sympathomimetics

- **ephedrine**

- indirect (+ direct) sympathomimetic effects
- slightly prevalent is  $\beta$ -sympathomimetic effect
- nasal mucosa decongestion ( $\alpha$ -SM effect)
- risk of developing an addiction (psychostimulant)
- methamphetamine production
- obsol.

# Other indirect sympathomimetics

- **pseudoephedrine** (ephedrine stereoisomer)
  - lower risk of addiction in comparison with ephedrine
  - abused for the production of methamphetamine
  - among OTC with restrictions
  - included in preparations for colds
  - in combination with H1-antihistamine loratadine for decongestion

# Other indirect sympathomimetics

- **tyramine**
- metabolit of thyrosine
- product in the synthesis of catecholamines
- tyramine-containing foods → dangerous in patients receiving MAOI → risk of hypertension reaction