Sympathomimetics

Sympathomimetics (SM) are substances that mimic the effects of stimulation sympathetic nervous system. It acts on receptors responsive to adrenaline and noradrenaline. We divide them into **directly acting** (stimulating α or β receptors) and **indirectly acting** (displacing noradrenaline from its bond). Indirect sympathomimetics are always non-selective.

Basic Effects

Cardiovascular system

- positive chrono, dromo, batmo i ino-tropical effect;
- α-sympathomimetics cause local vasoconstriction;
- β-2-sympathomimetics have a dilating effect on coronary vessels.

Bronchial system

- β-2-sympathomimetics relax smooth muscle;
- β-sympathomimetics have bronchodilator effects, but adversely affect the myocardium.

Womb

- stimulation β-2-receptors leads to suppression of uterine contractions

Smooth muscle

- Both α and β ympathomimetics suppress intestinal peristalsis;
- α, β sympathomimetics contract the sphincters of the GIT and bladder.

Metabolism

- norepinephrine suppresses insulin secretion;
- β-sympathomimetics stimulate other mechanical functions.

CNS

- lipophilic substances with indirect action have psychostimulant and anorectic effects.

Adverse effects

- Fear, anxiety, restlessness, insomnia;
- drug addiction;
- hypertension, vasoconstriction, tachycardia, arrhytmia, cardiac arrest, reduced renal blood flow.

Therapeutically used sympathomimetics

Non-selective direct sympathomimetics

It acts on both α and β receptors. Side effects include fear, restlessness, palpitations, arrhythmia, anginal problems, tremors (β 2). Absolute and relative contraindications can be hyperthyroidism (increased number of β 2), sclerosis of coronary and cerebral vessels (due to increased pressure), hypertension, tachycardia, pheochromocytoma and glaucoma.

Noradrenaline (norepinephrine)

- It preferentially stimulates **α-receptory**, β a little less, β 2 practically not at all.
- Effects: **↑ blood pressure** (systolic i diastolic), ↑ peripheral resistance, ↓ renal blood flow – not exactly desirable in patients in shock.
- t is used in shock states and acute hypotension, when it is necessary to increase peripheral resistance to maintain tissue perfusion. Must be administered continuously (noradrenaline half-life approximately 1 minute)

Adrenaline (epinephrine)

- **Non- selective** sympathomimetic, in low doses it preferentially stimulates **β receptors** – low doses increase systolic pressure due to stimulation of β 1 receptors, higher then also diastolic pressure, β 2 stimulation takes place even at very low concentrations (after an initial increase in blood pressure, due to stimulation of β2 receptors, later its decline).
- **It is used as a vasoconstrictor** ingredient in local anesthetics, **in anaphylactic shock** , a cardiostimulant to restore the heart rhythm **during arrest.**
- Half time approximately 2 to 3 minutes.

Dopamine

- Agonist on **D 1** , **β 1** , **α 1 receptors** , also stimulates the release of noradrenaline from nerve endings - individual effects are manifested according to the dose:
  - low doses (1–2 μg/kg/min) – stimulation of D 1 receptors (localized in kidney vessels): v**asodilatation in the kidneys and mesentery** , increased sodium excretion by increasing diuresis;
  - at higher doses (2–10 μg/kg/min) – β 1 stimulation : **heart rate increases** , peripheral resistance does not change or decreases;
  - with a further increase in the dose (above 10 μg/kg/min), α 1 stimulation occurs : vasoconstriction (usually compensated by D 1 stimulation in the kidneys).
- Use: **heart failure with hypotension and reduced cardiac output, shock (cardiogenic, anaphylactic, septic)**
- Half-life 1 to 5 minutes (continuous administration)

Isoprenalin

- non-selective β receptor agonist, used for temporary treatment of bradycardia inadequately responsive to atropine
- kardiostimulans

Selective direct sympathomimetics

Despite the selective effect, they can affect related receptors, especially depending on the dose and other medication

α-1-sympathomimetics

By binding, they activate α1-receptors → local vasoconstriction (decrease of swelling, decongestion), systemic rise in peripheral resistance and pressure, increase in sphincter tone, mydriasis, drop in intraocular pressure. They are used in the **treatment of rhinitis to decongest the nasal mucosa** , further in conjunctivitis, or inducing mydriasis during examination of the fundus of the eye. Adverse effects are headaches and increased pressure, which can also occur with topical application. A **rebound phenomenon** caused by receptor downregulation also often occurs.

- ***nafazolin, oxymetazolin, xylometazolin*** – nasal drops and sprays for
- ***fenylephrin***
- ***metoxamin***
- ***midodrine*** – peripherally stimulates α1 receptors → increase in peripheral resistance; treatment of orthostatic hypotension + increases tone in the proximal part of the urethra and bladder neck → treatment of stress incontinence
- ***ephedrine and pseudoephedrine*** – **indirect** effect– less selective, ephedrine also has central euphoric effects, which is why pseudoephedrine, which lacks these effects, is preferred today, ephedrine is also a vasopressor when administered intravenously, which can be administered (unlike noradrenaline) as a bolus

α-2-sympathomimetics

Activation of α 2 receptors leads to suppression of sympathetic activity. The main indication for α 2 mimetic is **hypertension** , but it is not the drug of choice. The effect does not start immediately after administration. Adverse effects include dry mouth, sedation, **postural hypotension** , bradycardia, sexual dysfunction, constipation. Other side effects are water and salt retention during long-term therapy, parkinsonism and hyperprolactinemia, hepatotoxicity, hemolytic anemia

- ***clonidine*** – can specifically cause contact dermatitis, indicated for glaucoma (not available in the Czech Republic)
- ***metyldopa*** – is a prodrug, its active substance is methylnoradrenaline; absorbed by active transport for amino acids (fasting); is the drug of choice for hypertension **in pregnant women**
- ***rilmendine, moxonidine*** – at the same time agonists of imidazoline receptors, antihypertensives of second choice

β-1-sympathomimetics

The indication is the treatment of **acute** heart failure.

- ***Dopamine***.
- ***Dobutamine*** – has a stronger **positive inotropic effect** than a chronotropic one = increases contractility but does not increase oxygen consumption, explanation unknown; the indication is acute heart failure.
- ***Ibopamin***.

β-2-sympathomimetics

Their selectivity for β 2 receptors is not complete – they increase the release of endogenous catecholamines and in higher doses can also stimulate β 1 receptors. Indications are mainly **bronchial asthma** a **COPD**, disorders of peripheral circulation - intermittent claudication or Raynaud's syndrome or as a tocolytic.

Undesirable effects mainly include **tachycardia** , **arrhythmia** , **anginal conditions** , **skeletal** muscle tremors. With long-term therapy, tolerance develops. Administered parenterally, they increase glycemia and the concentration of free fatty acids in the blood and decrease the concentration of potassium.

Hexoprenaline is used as a *tocolytic*.

According to the duration of the effect, they are divided into short-term (3-6 hours, so-called SABA) and long-term (12 h, so-called LABA) acting. Sometimes a group with rapid onset of effect *RABA (Rapid Acting Beta Agonists)* is singled out.

SABA (Short Acting Beta Agonists)

- ***fenoterol, salbutamol, terbutalin, reproterol***

LABA (Long Acting Beta Agonists)

- ***formoterol*** – The effect starts within 5 minutes and lasts for about 12 hours
- ***salmeterol*** – effect around 12 hours, but slower onset
- ***klenbuterol*** – around 14 hours

Ultra LABA

- ***indacaterol*** – just give it once a day

β3-sympathomimetics

By binding, they activate β3 receptors → relaxation of the bladder muscles, reduction in the frequency of bladder contractions without micturition. The indication is therefore a hyperactive detrusor musce

- ***mirabegron***

Indirect sympathomimetics

They increase the concentration of noradrenaline (NA) in the synaptic cleft. They may **induce the release** of NA from storage vesicles (amphetamines, ephedrine), **inhibit reuptak**e from the synaptic cleft (cocaine), or their effect may be based on a combination of both mechanisms (tyramine).

Hydroxy groups (both in the side chain and on the benzene core) are important for the direct effect, their removal changes the nature of the effect to an indirect one and i**ncreases lipophilicity** . This results in increased concentration in the CNS and **central effects**

Peripheral effects correspond to those of NA (pressure increase, tachycardia). The central effects are then an **increase in attention** , concentration and performance, **a decrease in the feeling of hunger.**

Side effects include anxiety, insomnia, restlessness, dependence on euphoric and psychostimulant effects. Interactions with cardioglycosides or halogenated inhalation anesthetics lead to arrhythmia, with MAO inhibitors there is a risk of hypertensive crisis

Representatives:

Amphetamine like substances:

- ***methylphenidate*** – mild CNS stimulant, treatment of narcolepsy or attention disorders in children with hyperkinetic syndrom
- ***amphetamine*** – passes easily through the blood-brain barrier, significant central stimulating effects, in some countries the treatment of ADHD, in the Czech Republic the amphetamine derivative methylphenidate is used for this purpose → prevents the reputation of NA and dopamine + increases their release.
- ***phentermine*** – anorectic, reducing the feeling of hunger
- ***modafinil*** – treatment for narcolepsy, works similarly to methylphenidate
- ***ephedrine*** – weak bronchodilator, vasopressor (popular in anesthesia for transient hypotension), euphoric effects
- ***pseudophedrine*** – decongestant in rhinitis, without undesirable euphoric effects

MAO, inhibitors, catecholamine reuptake inhibitors:

- ***moclobemide, St. John's wort*** – antidepressants
- ***selegilin, rasagilin*** – antiparkinsonika
- ***tyramine*** – a degradation product of tyrosine formed during food digestion, if the patient is treated with MAO inhibitors → escapes more first pass effect → increases release + agonist of adrenergic receptors
- ***atomoxetine*** – NA reuptake, treatment of ADHD, as NU can lead to orthostatic tachycardia
- ***venlafaxine, duloxetine*** – rreuptake of NA and serotonin, treatment of depression, anxiety, overactive bladder, diabetic polyneuropathic pain
- ***sibutramine*** – reuptake of NA a serotonin, anorectic, not used (bad safety profile)
- ***cocaine***

Links

Related Articles

- Vegetative nerve system (physiology)
- Vegetative nerve system (farmacology)
- Catecholamines
- Sympatolytics
- Parasympatomimetics
- Direct Parasympathomimetics
- Indirect Parasympathomimetics

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Category:Farmacology Category:Physiology