AUTONOMIC NERVOUS SYSTEM

Pharmacology Department

2024

Adrenergic nervous system

Role: regulates the activities of structures that are not under voluntary control (respiration, circulation, digestion, body temperature, metabolism, sweating, secretion of endocrine glands).

Neurotransmitters:

Acetchylcholine – preganglionic sympathetic fibers

Norepinephrine - postganglionic sympathetic fibers

Epineprine – released from the adrenal medulla

Dopamine – is formed from DOPA and converted to norepinephrine in the adrenergic neurons.

Adrenergic receptors (α1 and α2 , β1, β2 and β3) are coupled to G proteins (**G protein–linked receptors)**. G-protein is transmembrane domain receptor that is involved in two principal signal transduction pathways: the cAMP signal pathway and the phosphatidylinositol signal pathway.

Adrenergic receptor	G protein	Biochemical effectors
β1	Gs	↑ adenylyl cyclase
β2	Gs	↑ adenylyl cyclase
β3	Gs	↑ adenylyl cyclase
α1	GQ	↑ phospholipase C, ↑ Ca^{2+} channels
α2	Gi	↓ adenylyl cyclase, ↓ Ca^{2+} channels

Receptor Type	Prominent Effector Organs	Response to Receptor Activation
β1	**Heart**	**Increased heart rate** **Increased force of contraction**
β2	**Arterioles (and arteries in skeletal muscle)**	**Dilation**
	Bronchial and uterine smooth muscle	**Relaxation**
β3	**Several sites**	**Metabolic effects**
α1	**Arterioles in skin, mucosa, viscera, and kidney (resistance vessels)**	**Contraction**
	Veins	**Contraction**
	Uterus	**Contraction**
α2	**Presynaptic nerve endings**	**Inhibit NE release**
	Postsynaptic in CNS	**Decreased sympathetic tone**
Dopamine	**Arterioles in kidney, brain, and mesentery**	**Dilation**

Adrenergic agonists:

- Direct-acting:

- selective (α1- phenylephrine, β1-dobutamine, β2-salbutamol),

- non-selective (**α1 and α2**- xylometazoline, oxymetazoline, naphazoline, tetryzoline; **β1, β2**- isoproterenol, **α1, α2, β1, β2**- epinephrine; **α1, α2, β1**- norepinephrine)

Epinephrine (α and β stimulant)

- **Local vasoconstriction** (↓ cutaneous blood flow, marked decrease in blood flow in the hands and feet) - after subcutaneous injection
- **Cardiac effects** (↑ heart rate, ↑↑↑ cardiac output, ↑↑ stroke volume, ↑↑↑ left ventricular work per beat, ↑↑ coronary blood flow) → β1 stimulation → increased venouse return to the heart and arterial pressure, increased heart rate
- **Vascular effects** (vasoconstriction of veins and arteries) → α stimulation → ↑↑↑ muscle blood flow, ↑↑↑ splanchnic blood flow, ↑ cerebral blood flow, cutaneous blood flow −,

- **Blood pressure** (↑↑↑ systolic arterial, ↑ diastolic arterial) → direct myocardial stimulation , ↑ ventricular contraction, ↑ heart rate, vasoconstriction in vascular beds (skin, mucosa, kidney)
- **Metabolic effects** (↑↑ myocardial oxygen consumption, ↑↑↑ blood glucose, ↑↑↑ blood lactic acid)
- **Central nervous system** (↑ respiration, ↑ subjective sensations) ,
- **Smooth muscle** (effect depends on the type od adrenergic receptor) → GI, bronchial tree– relaxation, prostate – contraction, uterus – depends on the sexual cycle, state of gestation and dose given

Therapeutic uses: hypersensitivity reactions, in restoring cardiac rhythm, to prolong the action of local anesthetics, for temporary relief symptoms of severe asthma.

Routes of administration:

- intravenously – must be diluted, except for cardiac arrest;
- subcutaneously
- intramuscularly
- topically

Norepinephrine (α and β stimulant, less potent than epinephrine on the β receptors)

- ↑ systolic and diastolic pressure,
- cardiac output ↓ or ↑ or −
- total peripheral resistance ↑
- coronary flow ↑

Metabolic effects – similar to epinephrine only after large dose

Used in serious hypotensive states, cardiogenic shock, septic shock, to prolong the action of local anesthetics

Dopamine (D1 and D2 agonist)

- **Cardiovascular effects:**

  2–10 μg/kg b.w/min - positive inotropic, chronotropic, dromotropic effect in the myocardium (β1 activation and release of norepinephrine),

  > 10 μg/kg b.w. /min - vasoconstriction (vascular α1 receptors activation)
- **Renal activity:** at low doses (0,5–2 μg/kg b.w./min) ↑ GFR, ↑ renal blood flow, ↑ Na excretion (inhibition Na-H exchanger and the Na-K-ATPase pump)

Therapeutic uses: cardiogenic and septic shock, severe congestive failure in patients with oliguria and low or normal peripheral vascular resistance

Adverse reactions: nausea, vomiting, tachycardia, anginal pain, arrhythmias, headache, hypertension

α-adrenergic receptor agonist

Phenylephrine (selective α1 receptor, in high concentration β-receptor agonist, used in various nasal and ophtalmic formulations)

β adrenergic receptor agonists

Isoproterenol (non-selective agonist with very low affinity for α receptors)

Dobutamine (β receptor agonist, α1 receptor antagonist (-) isomer or agonist (+) isomer)

- ↑ heart rate, ↑ cardiac out put, mild vasodilation
- t0,5= 2 min. (used by i.v. infusion)

Use: cardiac decompensation (acute myocardial infarction, congestive heart failure, cardiac surgery)

Side effects: tachycardia, skin rash, bronchospasm, eosinophilia, increase in the ischemic area of the heart muscle (increases the oxygen demand at high dose), phlebitis

β2-selective adrenergic receptor agonists

Salbutamol, fenoterol, formoterol, salmeterol – used as bronchodilators (asthma, COPD) by cAMP activation.

Adverse effects: tolerance, tachycardia, tremor, hypokalemia

Ephedrine (α and β receptor agonist, ↑ release of NE)

- ↑ heart rate, ↑ cardiac out put,
- ↑ peripheral resistance
- bronchidilation,
- potent CNS stimulant,

Use: urinary continance, hypotension with spinal anesthesia, for the relive of nasal congestion

Side effects of adrenergic agonists:

- **Tachyarrhythmias, palpitations** and even ventricular fibrillation (agents with β1 activity)
- **Hypertension** (agent with α1 activity)

- **Localized ischemia** (infusion site of α1 agonists)
- **localized vasoconstriction and necrosis** (if the site of an i.v. infusion is not changed periodically),
- **Precipitous hypotension -** if a patient is suddenly withdrawn from an infusion of an α1 agonist. Such infusions must be discontinued gradually to allow receptor and reflex regulation mechanisms to readjust.
- **CNS stimulation** in the form of nervousness, anxiety, insomnia, and drug dependence can result from the use of adrenergic agonists that cross the blood-brain barrier (the amphetamines are notable in this respect).

α receptor antagonists

Non-selective α-antagonists: phentolamine

α1- selective: prazosin, terazosin, doxazosin, tamsulosin

α1 receptor antagonists: vasodilation (↓ vessels resistance, ↓ **blood pressure**)

α2 receptor antagonists: ↑ NO release ↓ **blood pressure –** predominant effect

Prazosin

Pharmacological effects: ↓ peripheral vascular resistance, ↓venouse return to the heart, ↓ LDL and TG, ↑ HDL,

Therapeutic uses: primary hypertension, prostatic hypertrophy,

Adverse effects: postural hypotension (especially with the first dose) and syncope

Tamsulosin

Pharmacological effects: relaxation of prostate and urethra smooth muscle

Therapeutic use: prostatic hypertrophy

Side effects: headache, abnormal ejaculation, postural hypotension

β-adrenergic receptor antagonists

Non-selective β-adrenergic antagonists: propranolol, nadolol, timolol, pindolol, labetalol, carvedilol,

Selective β1-adrenergic antagonists: metoprolol, atenolol, acebutolol, nebivolol, esmolol

Additional α1 receptor antagonism: carvedilol, labetalol

Pharmacological effects:

- cardiac effects: - inotropic, - chronotropic, - bathmotropic, - dromotropic
- vascular effect: vasoconstriction (exc. nebivolol, carvedilol, labetalol)

Therapeutic uses: hypertension, angina, heart failure, supraventricular and ventricular arrhythmia, glaucoma, acute panic symptoms, prophylaxis of migraine attack, hyperthyroidism
Adverse effects: bradycardia, A-V block, orthostatic hypotension, bronchoconstriction, dysglycaemia, masking of hypoglycaemia symptoms, ↑ TG, ↑ LDL, ↓ HDL, impotence

Contraindications:
- relative contraindications: asthma, COPD, peripheral vascular diseases
- absolute contraindications: vasospastic angina, bradycardia, A-V block

Centrally acting adrenomimetics: clonidine, methyldopa

Clonidine:
- is selective postsynaptic α2 receptor and imidazoline receptor agonist (in brainstem) and presynaptic α1 receptor - ↓ NE release
- orally – 100% bioavailability
- onset of action – 30min., duration of action – 8 h

Therapeutic uses:
- Hypertension (as a second line drug), pain in cancer patients, anesthesia

Adverse effects:
- dry mouth
- **sedation,**
- sexual dysfunction,
- contact dermatitis (TTS)
- **bradycardia**
- **hypotension**

Methyldopa:
- stimulates α2-adrenergic receptors and inhibits the NE release
- blocks DOPA decarboxylase - decrease in NE synthesis
- ↓ peripheral resistance, ↓ blood pressure

Use: hypertension in pregnant women (as a first-line drug in chronic therapy in pregnant women)
Side effects: drowsiness, dizziness, orthostatic hypotension, parkinsonism, dry mouth, diarrhea, ↑ Alat, ↑ Aspat, ↑ prolactin, impotence

<u>Cholinergic nervous system</u>
Neurotransmitter – acetylcholine

Receptors;

- muscarinic M_1 (neural), M_2 (cardiac), M_3 (glandular), M_4, M_5 (G protein linked receptors)

- nicotinic N_1 (neural), N_2 (muscular) (receptors coupled ion channels, increased sodium influx)

Muscarinic effects - stimulation of smooth muscle, bronchoconstriction, stimulation of secretion in glands, ↑ ureteral peristalsis, hypotension, bradycardia

Nicotinic effects – skeletal muscle contraction, neuronal excitation

Cholinomimetics (direct-acting):

Choline esters (acetylcholine, carbachol, bethanechol, metacholine)

Plant alkaloids (pilocarpine, muscarine, arecoline)

Synthetic drugs (cevimeline, varenicline)

Therapeutic uses

- gastric atony or gastroparesis, megacolon – bethanechol,
- urinary retention - bethanechol,
- xerostomia – pilocarpine, cevimeline,
- Sjögren syndrome – cevimeline,
- glaucoma – pilocarpine

Adverse effects - diarrhea, intestinal cramps, urinary incontinence, miosis, sweating

Contraindications – asthma, peptic ulcer, hyperthyroidism, coronary insufficiency

Cholinomimetics (indirect-acting):

Carbamates (reversible) – pirydostigmine, neostigmine, rivastigmine, galantamine, edrophonium, donepezil, physostigmine

Organophosphates (irreversible) – paraoxon, parathion, malathion, echothiophate

Pharmacological effects - miosis, block of accommodation, smooth muscle - ↑ contraction, ↑secretion, skeletal muscle - ↑ neurotransmision , ↑ contraction

Uses:

- postoperative atony of the bowel or bladder – neostigmine,
- myasthenia gravis (treatment) – pyridostigmine, neostigmine,
- myasthenia gravis (diagnosis) – edrophonium,
- to reverse the neuromuscular blockade during surgery – neostigmine, pyridostygmine
- physostigmine - as an antidote in poisoning with parasympatholytic drugs,
- Alzheimer's disease – rivastigmine, galantamine, donepezil

Cholinolytics – acetylcholine receptor antagonists

Belladonna alkaloids: atropine, scopolamine

Semisynthetic and synthetic: ipratropium, homatropine, tropicamid

Cholinolytics : prevent the effects of ACh by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on: smooth muscle, cardiac muscle, gland cells, in peripheral ganglia and in CNS

Pharmacological effects

- relaxation of smooth muscle (bronchi, GI, ureter and bladder)

- cardiac muscle – stimulation, remove vagal influence on the sinoatrial and atrioventricular nodes, ↑ heart rate
- exocrine glands - ↓ secretions of the nose, mouth, pharynx, bronchi, ↓ gastric secretions, ↓ salivary secretions, inhibition of sweating (reduce heat loss and lead to hyperthermia)
- eye - mydriasis – pupillary dilation (relaxation of iris sphincter muscle)

USES:

- spastic states in GI: scopolamine
- overactive urinary bladder, urinary incontinence – oxybutynin, solifenacin, tolterodine
- excessive salivation (drug-induced, parkinsonism, heavy-metal poisoning)
- sinus bradycardia - atropine, only for short-term intervention
- CNS (scopolamine, in the prevention of motion sickness)
- anesthesia (atropine, to block responses to vagal reflexes induced by surgical manipulation of visceral organs, atropine, scopolamine-premedication)
- poisoning with organophosphates or mushrooms containing muscarine- atropine
- COPD, asthma, chronic bronchitis (ipratropium bromide, tiotropium bromide, umeclidinium bromide – in inhalation provide protection against bronchoconstriction)
- mydriasis – tropicamide (short-term), atropine (long-term)

Adverse effects - dry mouth, blurring of vision, photophobia, rapid heart rate

Contraindications - glaucoma (relaxation of the pupillary sphincter, intraocular pressure rises), prostatic hypertrophy with impaired micturition.