Lecture 7: Pharmacological influence of smooth muscle activity

There are drugs that:
1. inhibit constriction of smooth muscle (= smooth muscle relaxants)
2. stimulate constriction of smooth muscle

Classification:

I. Drugs that inhibit constriction of smooth muscle (smooth muscle relaxants):

I.1. Non-selective (on different types of smooth muscle):

I.1.1. Calcium channels antagonists (Calcium channels blockers):
- Action on Calcium channels from blood vessels and heart:
  - Dihydropyridine: Nifedipine, Amlodipine, Nicardipine, Nitrendipine
  - Phenylalkylamine: Verapamil
  - Benzothiazepine: Diltiazem
- Specific action on Calcium channels from blood vessels:
  - Dihydropyridine: Felodipine, Isradipine, Nisoldipine, Lacidipine, Lercanidipine
- Specific action on Calcium channels from cerebral blood vessels:
  - Dihydropyridine: Nimodipine
  - Piperazine: Cinnarizine
- Specific action on Calcium channels from heart: Bepridil

I.1.2. Isoquinoline derivatives from opium: Papaverine, Eupaverina, Moxaverine, Ethaverine, Proxyfylline

I.1.3. Methylxanthines:
- Natural sources: Theophylline (1,3,dimethylxanthine), Theobromine (3,7,dimethylxanthine), Caffeine (1,3,7,trimethylxanthine),
- Synthetic: Pentoxiphylline, Dyphylline, Propentophylline, Pentiphylline,

I.1.4. Substances acting on vegetative nervous system

I.2. Selective on vessels (vasodilatation drugs)

I.2.1. Substances acting on vegetative nervous system

I.2.2. Substances with other mechanisms of action except acting on nervous vegetative system:
  a) Nonspecific mechanism:
     - Nonselective (arteriolar and venous):
       - Nitrates and nitrates: Nitroglycerine, Isosorbide mononitrate (ISMN), Isosorbide dinitrate (ISDN), Penta erythrol tetranitrate (PETN), Amyl nitrite, Sodium nitroprusside
       - Other structures: Nicorandil, Molsidomine
       - Selective (arteriolar): Hydralazine, Minoxidil, Diazoxide
  b) Specific mechanisms:
     - Inhibitors of 5-phosphodiesterase: Sildenafil, Tadalafil, Vardenafil
     - Prostaglandine derivatives of:
       - PGE1 analogs: Alprostadil, Prostin
       - PGI 2 analogs: Eproprostenol, Iloprost.
     - Antagonists of histamine receptors H1 and stimulants of release of PGE1 and PGI2: Ciclestatine
     - Other vasodilatation drugs: ethanol, nicotinic acid

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II. Drugs that stimulate constriction of smooth muscle

II.1. Substances stimulating visceral smooth muscle:

II.1.1. Uro-genital tract:
- Substances acting on vegetative nervous system;
- Substances acting on histamine receptors: Histamine;

II.1.2. Gastro-intestinal tract:
- Bulk forming: dietary fibers; colloidal hydrophilic derivatives;
- Stimulant purgatives: castor oil; antraquinones.

II.1.3. Gallbladder: cholecystokinin; food cholecystokinin-like substances

II.2. Substances stimulating vascular smooth muscle (vasoconstrictors)

II.3. Contrast agents in radiology: barium salts

I. Drugs that inhibit constriction of smooth muscle (smooth muscle relaxants):

I.1. Non-selective (on different types of smooth muscle):
I.1.1. Calcium channels antagonists (Calcium channels blockers)
These are drugs that can inhibit the transfer of membrane calcium in cardiac muscle cells and vascular.

Types of voltage-dependent calcium channels (depending on location and electrophysiological characteristics):
- Type L: level of smooth muscle and cardiac muscle
- higher conductance and long open time ("Long-lasting"): eg: couplation excitation – contraction
- Types N, P, Q and R: the neural level (neurotransmitter release)
- Type T: in smooth muscle, cardiac muscle and neurons
- low conductance and short open time ("Transient"): eg: automation of sinoatrial-node

There are two types of calcium antagonist depending on the affinity of the calcium antagonist for vascular and cardiac channels:
- the vascular effect is predominant
- cardiac effect is predominant.
Classification:
- Action on Calcium channels from blood vessels and heart:
  - Dihydropyridine: Nifedipine, Amlodipine, Nitrendipine, Nicardipine
  - Phenylalkylamine: Verapamil
  - Benzothiazepine: Diltiazem
- Specific action on Calcium channels from blood vessels:
  - Dihydropyridine: Felodipine, Isradipine, Nisoldipine, Lacidipine, Lercanidipine
- Specific action on Calcium channels from cerebral blood vessels:
  - Dihydropyridine: Nimodipine
  - Piperazine: Cinnarizine
- Specific action on calcium channels from heart: Bepridil

Mechanism of action:
- Block of voltage sensitive L-type Ca\(^{2+}\) channels (reducing Ca\(^{2+}\) flux through the channel):
  - Inhibition of calcium entry into the cell:
    - in myocardial cells \(\rightarrow\) decreased myocardial contractility, slowed AV conduction, decreased heart rate, decreased myocardial oxygen consumption
    - in smooth muscle cells of artery walls \(\rightarrow\) decrease in arteriolar resistance
    - in bronchial cells \(\rightarrow\) bronchodilatation.
  - Inhibition to form complexes calcium – calmodulin;
  - Stimulation of the kinase inactivation of myosin light chain
- Low intensity inhibition of Ca\(^{2+}\) channels: Verapamil, Diltiazem
- Nifedipine block also Na\(^{2+}\) channels.

Pharmacodynamic effects:
- Are due to reduction of calcium entry:
  - long-lasting relaxation of vascular smooth muscle (very important effect):
    - peripheral vessels (explains the decrease of blood pressure - reduction of systolic and diastolic BP except for selective calcium channel blockers on the heart), explains the decrease in peripheral vascular resistance;
      This reduction in blood pressure causes a reflex sympathetic stimulation and stimulation of the renin angiotensin system (by compensatory mechanisms).
    - coronary vessels;
    - cerebral vessels (explains the reduction of cerebral ischemic lesions): Nimodipine, Cinnarizine;
  - heart muscle (very important effect):
    - inotrop negative effect (reduction in contractility throughout the heart);
    - cronotrop negative effect (decreases in sinus node pacemaker rate);
    - dromotrop negative effect (decreases in atrioventricular node conduction velocity);
    - reduction in myocardial oxygen consumption due to negative chronotropic and inotropic effects (= anti-ischemic effect).
  - bronchial muscle: relaxation (bronchodilatation): Verapamil and Diltiazem
  - low analgesic effects: Verapamil, Diltiazem, Nifedipine
  - for Verapamil:
    - inhibit insulin release in humans;
    - block the P-glycoprotein responsible for the transport of many foreign drugs out of cancer (and other) cells (explains the loss of resistance to anticancer agents)
    - may attenuate the atherosclerotic process: reduce storage of calcium in vascular wall, increase HDL cholesterol;
    - can be effective in decreasing left ventricular hypertrophy.
Lecture 7: Pharmacological influence of smooth muscle activity

Nifedipine has a greater effect on smooth muscle in the peripheral vessels, Verapamil has mainly effect on the myocardium, Diltiazem has intermediate effect on vessels and myocardium.

The calcium channel blockers are agents of Class IV antiarrhythmics (exception: calcium channel blockers selective on the vessels) are effective in supraventricular and ventricular tachyarrhythmias.

**Pharmacokinetics:**
- Absorption (after oral administration): 50% for Nifedipine and Diltiazem, 80% for Verapamil.
- Binding on plasma proteins: more than 90%.
- Cross blood-brain barrier.
- Metabolism: hepatic (by conjugation). Norverapamil is the active metabolite of Verapamil, with stronger vasodilatatory effects.
- First pass effect is stronger for Verapamil and Diltiazem, but not present for Isradipine.
- Elimination is mainly renal (Nifedipine, Verapamil) or through feces (Diltiazem).

**Indications:**
- hypertension (except Nimodipine, Cinnarizine)
- angina pectoris;
- arrhythmias (calcium channels antagonists are class IV antiarrhythmic agents):
  - supraventricular tachyarrhythmia: Verapamil (drug of choice), Diltiazem,
  - atrial fibrillation and flutter: Verapamil, Diltiazem;
- Raynaud's syndrome: Nifedipine, Felodipine, Isradipine, Nicardipine;
- prevention of ischemic sequelae in cerebral vasospasm associated with subarachnoid hemorrhage, vertigo: Nimodipine, Cinnarizine;
- hypertrophic cardiomyopathy: Verapamil;
- migraine prophylaxis: Verapamil;
- adjuvant to reverse the resistance of cancer cells to chemotherapeutic drugs: Verapamil.

**Adverse effects:**
- excessive vasodilatation (especially with dihydropyridines of short-acting):
  - orthostatic hypotension (except: Bepridil, Nimodipine, Cinnarizine);
  - dizziness, headache,
  - flushing,
  - peripheral edema (oedema of the lower limbs / ankle edema) unresponsive to diuretics and occurs after several weeks of treatment,
  - reflex tachycardia (due to this effect, the administration of sublingual nifedipine should be avoided – risk of ventricular fibrilation).
- allergic reaction type I: facial flushing, hot flashes
- inotrop negative effects, arrhythmic side effects, AV block (except: Felodipine, Isradipine, Nisoldipine, Lacidipine, Lercanidipine), bradycardia and exacerbation of heart failure: Verapamil, torsades de pointes (polymorphic ventricular tachycardia): Bepridil;
- gingival hyperplasia;
- hyperglycemia: Verapamil;
- sedation: Cinnarizine;
- constipation (due to intestinal relaxant effect), nausea.

**Contraindications:**
- heart failure (except: Felodipine, Isradipine, Nisoldipine, Lacidipine, Lercanidipine);
- bradycardia, AV block;
- acute myocardial infarction;
- severe arterial hypotension;

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- pregnancy, breast-feeding;
- association with beta-adrenergic blockers.

I.1.2. Isoquinoline derivatives from opium: Papaverine, Eupaverine, Moxaverine, Ethaverine, Proxifylline

**Mechanism of action:**
- inhibits phosphodiesterases in smooth muscle cells, which produces increased tissue levels of cyclic adenosine monophosphate and cyclic guanosine 3,5-monophosphate (also inhibits phosphodiesterase-5 or PDE-5);
- block calcium ion channels in cell membranes, resulting in a reduction of release of calcium from the intracellular spaces.
Papaverine does not act on opioid receptors (does not determine analgesia and euphoria, does not determine addiction).

**Pharmacodynamic effects:**
- relaxation of smooth muscle → vasodilatation and relaxation of other smooth muscles.

**Pharmacokinetics:**
- Papaverine is rapidly absorbed from the GIT, T1/2 = 1-2 hours, plasma protein binding is 90%. It is metabolized in the liver to inactive metabolites, which are excreted in the urine.

**Indications:**
- antispasmodic (intestinal, biliary, genito-urinary collicative pain);
- ischemic conditions associated with arterial vasospasm (Pre-eclampsia, eclampsia, cerebral and peripheral ischemia associated with arterial spasm and without vascular injuries);
- erectile dysfunction (alone, or in combination with phentolamine, or with phentolamine plus alprostadil).

**Adverse effects:**
- “arterial steal” in arterial obstructions;
- quinidine-like effects: QT prolongation, ventricular arrhythmias, and torsade de pointes;
- hepatotoxicity (after high doses / administration prolonguee);
- after intracavernosal injection of papaverine: local administration by injections into the corpus cavernosum → may lead to the development of injection site reaction: local penile fibrosis (loss of elasticity of the tissue), transient penile pain, ecchymosis, and priapism (painful prolonged erection).

**Contraindications:**
- chronic arterial obstructions;
- atroventricular block, bradicardia;
- heart failure;
- pregnancy, breast-feeding.

I.1.3. Methylxantines

**Classification:**
- Natural sources: Theophylline (1,3,dimethylxanthine), Theobromine (3,7,dimethylxanthine) and Caffeine (1,3,7,trimethylxanthine)

Tea contains caffeine and small amounts of theophylline and theobromine when it is prepared from leaves of Thea sinensis, a bush native to southern China and now cultivated also in other countries. Coffee contains caffeine and it is extracted from fruits of Coffea Arabica. Cocoa and chocolate contains theobromine and some caffeine and it is extracted from seeds of Theobroma cacao. Cola-flavored drinks contain considerable amounts of caffeine added during their production and extracted from nuts of Cola acuminate.

- Synthetic: Pentoxiphylline, Propentophylline, Penthiphylline, Dyphylline

Theophylline is among the least expensive drugs used to treat asthma.
Mechanism of action:
- competitive antagonists at adenosine receptors A1 and A2;
- non-selective inhibition of phosphodiesterases (PDE) – the enzymes that degrades cyclic 3',5'-adenosine monophosphate (cAMP). (also inhibit phosphodiesterase-4 or PDE-4)

Pharmacodynamic effects:
- CNS effects (central stimulant effects):
  - vasoconstriction of cerebral vessels (hence the anti-migraine properties of caffeine);
  - psychoanaleptic effect (especially caffeine cause mild cortical arousal with increased alertness and decrease of fatigue, and stimulate intellectual work);
  - psychic dependency (especially caffeine);
  - larger doses cause nervousness, insomnia and fine tremor of hands, anxiogenic effect and in high doses, convulsant effect;
  - very high doses cause medullary stimulation and convulsions;
- peripheral effects:
  - cardiovascular system:
    - positive chronotropic and inotropic effects, increase in cardiac output, increase in peripheral resistance (in sensitive individuals, consumption of a few cups of coffee may result in arrhythmias);
    - large doses relax vascular smooth muscle (except in cerebral blood vessels, where they cause contraction): reduction of systolic and diastolic BP; dilates coronary, pulmonary, renal, and general systemic arterioles and veins;
    - Pentoxifylline: reduction of platelet aggregation and thrombus formation, decrease blood viscosity, increase the deformability of red blood cells;
  - pulmonary system:
    - bronchodilating effect (due to adenosine receptor antagonism and PDE inhibition) – Theophylline is the most effective bronchodilator;
    - strengthen the contractions of diaphragmatic muscle (improve the ventilatory response to hypoxia and diminish dyspnea);
    - stimulation of mucociliary transport (increase clearance mucociliare);
  - renal system: weak diuretic effect (vasodilatation determines the increase in glomerular filtration rate and decrease in tubular reabsorption of sodium and chloride in proximal tubule);
  - antiinflammatory action (inhibits synthesis and secretion of inflammatory mediators from numerous cell types, including mast cells and basophils, due to PDE inhibition);
  - digestive system: stimulate secretion of both gastric acid and digestive enzymes;
- immunosupressory effects;
  - antialergic effect due to decrease of pre- and post- capillary permeability;
  - analgesic effect.

Theophylline has narrow therapeutic index and requires monitoring of drug levels.

Pharmacokinetics:
- Absorption: readily after oral or parenteral administration (caffeine is absorbed more rapidly, food slows the rate of absorption of theophylline).
- Distribution: into all body compartments, cross the placenta and pass into breast milk.
- Metabolism: hepatic.
- Elimination: a small part is eliminated renally unchanged.
Indications:
- Theophylline is used as Aminophylline (which is a 2:1 complex of theophylline and ethylenediamine):
  - asthma (in emergencies and for maintenance treatment);
  - chronic obstructive pulmonary disease;
  - apnea of premature infants;
  - adjunct in the treatment of pulmonary edema or paroxysmal nocturnal dyspnea caused by left-sided heart failure (in iv administration);
- Pentoxiphylline:
  - intermittent claudication (arterial obstructive disease, Raynaud syndrome) – symptomatic treatment, drug of choice;
    - stasis ulcer, phlebitis, thrombophlebitis, hemorrhoidal disease;
    - vascular disorder of inner ear;
    - multiple myeloma, polycythemia, hyperlipidemia
- Caffeine:
  - psychostimulant (reduces fatigue, increases alertness).

Adverse effects:
- cardiovascular effects: tachycardia (palpitations), angina, high blood pressure;
  - there is a coronary vasodilation, but the pacing increases the oxygen needs of the heart → chest pain
- CNS effects (related to excessive consumption): tremor, irritability, insomnia, headache, anxiety, nervousness, convulsive effect;
  - for caffeine: chronic consumption determines phenomenon of tolerance and dependence
  - withdrawal symptoms: headache, dizziness, fatigue, irritability, depressive ideas.
- digestive effects: anorexia, nausea, vomiting, abdominal discomfort, aggravation of peptic ulcer, gastro-esophageal reflux;
- respiratory effects: tachypnea;
- immunosuppressory effects (during prolonged treatment).

Theophylline administration by rapid intravenous → hypotension, tachyarrhythmias, convulsant effect..
Toxic doses of theophylline:
- concentrations of 20–40mg/L in blood determine: agitated maniacal behavior, frequent vomiting, extreme thirst, slight fever, tinnitus, palpitation, and arrhythmias;
- concentrations > 40 mg/L in blood determine: seizures, arrhythmias, death.

Contraindications:
- angina pectoris or acute myocardial infarction, tachyarrhythmias, thromboembolia;
- seizure disorders, insomnia, epilepsy, people with mental labile;
- active peptic ulcer;
- liver failure;
- immunosuppressory diseases, herpes disease;
- children;
- association with platelets antiagregant drugs, psychostimulant drugs, fluoroquinolones.

For children and elderly doses must be adjusted.
I.2. Substances acting selective on the vessels (vasodilatation drugs)

I.2.1. Vasodilatation drugs acting by nonspecific mode of action

I.2.1.1. Nonselective action (on both arteries and veins)

Nitrates and nitrite (collectively termed *nitrovasodilators*)

Nitroglycerin is the prototype of the group and was used in the manufacture of dynamite

**Mechanism of action:**

- NO release (these agents are prodrugs that are sources of NO). NO react with sulfhydryl groups to form thiol-nitroso groups which activate guanylyl cyclase, thereby increasing intracellular levels of cyclic GMP. In turn, this promotes the dephosphorylation of the myosin light chain and the reduction of cystolic (Ca^{2+}), which leads to the relaxation of smooth muscle cells.
- stimulate production of prostacyclin (PGI2) which leads to the relaxation of smooth muscle cells. The antiplatelet effect of nitrates is due to stimulation of prostacyclin (PGI2).

**Pharmacodynamic effects:**

- hemodynamic effects: vasodilation (preferentially dilate the veins more than the arterioles),
  - dilatation of large veins diminishes preload and reduces work of the heart (decrease O2 demand);
  - dilation of coronary vessels increase blood supply in the heart muscle;
- relaxation of smooth muscle form other levels: bronchodilation, gastro-intestinal tract relaxation.

Nitroglycerin, *Isosorbide mononitrate* (ISMN), *Isosorbide dinitrate* (ISDN), *Penta erythritol tetranitrate* (PETN), *Amyl nitrite*

**Pharmacokinetics:**

- Absorption:
  - Nitroglycerin and Isosorbide dinitrate have very low oral bioavailability, for this reason it is preferred sublingual route (which avoids the first-pass effect and achieves a therapeutic blood level rapidly within a few minutes). Sublingually administered nitroglycerin has the most rapid onset of antianginal and hemodynamic effects compared to the other organic nitrates. Sublingual or buccal nitroglycerin and sublingual or chewable isosorbide dinitrate have a more rapid onset of action than when given orally or topically.
  - Nitroglycerin is well absorbed with delay through intact skin when applied topically as an ointment or transdermal system.
  - Amyl nitrite is a highly volatile liquid (the ampule can be crushed with the fingers, resulting in rapid release of inhalable vapors and very rapid absorbed), with unpleasant odor and short duration of action.
- Distribution: highly lipophilic nitrates (nitroglycerin, isosorbide dinitrate) are widely distributed into vascular and other peripheral tissues, less lipophilic nitrates (isosorbide mononitrate) are not widely distributed
- Metabolism: liver (Isosorbide-mononitrate is the active metabolite of isosorbide dinitrate).
- Elimination: kidney.

**Indications:**

- angina pectoris:
  - acute angina: Nitroglycerin (sublingual), Amyl nitrate (highly volatile liquid)
- hypertension (control blood pressure in perioperative hypertension, in patients with severe hypertension or crises, patients with coronary complications such as acute myocardial infarction, pulmonary edema associated with acute myocardial infarction);
- heart failure (acute and chronic heart failure).

**Adverse effects:**
- postural hypotension (may cause dizziness, weakness and other signs of cerebral ischemia), followed by tachycardia due to excessive stimulation of baro-reflex;
- sometime nitrate syncope;
- cutaneous vasodilation with facial flushing
- pulsatile bitemporal headache (at the beginning of the treatment);
- tachyphylaxis;
- methemoglobinemia, anemia;
- increase intraocular pressure (acute attack of glaucoma).

**Contraindications:**
- arterial hypotension, hypovolemia;
- obstructive cardiomyopathy;
- closed angle glaucoma;
- increased intracranial pressure (head trauma, cerebral hemorrhage);
- pregnancy.

Association with inhibitors of phosphodiesterase 5 (Sildenafil, Tadalafil, Vardenafil) ⇒ increase NO (severe hypotension, sometimes fatal).

**Sodium nitroprusside**

**Pharmacokinetics:**
- sodium nitroprusside molecule is unstable (decomposes under strongly alkaline conditions or when exposed to light). The drug must be given by continuous intravenous infusion to be effective. Onset of action is immediate and when the infusion of the drug is stopped, the effect disappears within few minutes (because the half life is very short) and blood pressure returns to initial level.
- rapidly metabolized by liver to thiocyanate, which is eliminated almost entirely in the urine.

**Indications:**
- hypertensive emergencies (pheochromocytoma) – iv administration;
- to induce controlled hypotension during certain surgical procedures;
- acute congestive heart failure.

**Adverse effects:**
- excessive hypotension (determines headache, retrosternal discomfort due to coronary blood stealing phenomenon, palpitation);
- cyanogenic effects;
- methemoglobinemia;
- thiocyanate accumulation;
- others: anxiety, nausea.
Other structures: Nicorandil, Molsidomine

Mechanisms of action:
Nicorandil: NO release + potassium channel-opening action (additional mechanism for causing vasodilation).
Molsidomine: direct activation of guanylyl cyclase + NO release.

Pharmacodynamic effects: vasodilation.
Indications: angina pectoris (maintenance treatment).
Adverse effects: headache.
Advantage: don’t determine tachyphylaxis because have multiple mechanisms of action.

I.2.1.2. Selective (arteriolar) vasodilators: Hydralazine, Minoxidil, Diazoxide,

Hydralazine

Mechanism of action:
- powerful direct vasodilatory effect on arteriolar smooth muscle;
- may stimulate the release of norepinephrine from sympathetic nerve terminals;
- direct action on myocardial muscle.

Pharmacodynamic effects:
- direct vasodilation \(\rightarrow\) reduces blood pressure, reduces peripheral resistance and it is associated with reflexes stimulation of the sympathetic nervous system \(\rightarrow\) results in increased heart rate and contractility, increased cardiac output, increased plasma renin activity, and fluid and sodium retention;
- augment myocardial contractility directly: inotropic, chronotropic, dromotropic positive effects.

Pharmacokinetics:
- Absorption: readily after oral.
- It is concentrated into arteriolar smooth muscle.
- Metabolism: liver (by acetylation), has important first pass effect, entero-hepatic cycle.
- Elimination: kidney.

Indications: moderate or severe hypertension not controlled by first-line drugs (maintenance treatment).

Adverse effects:
- after first doses: headache, flushing, postural hypotension, tachycardia, allergic reactions (skin rash, fever);
- long-term administration:
  - drug-induced lupus syndrome (autoimmune-like reactions – after at least 6 months of continuous treatment);
  - polyneuropathy (paresthesia) due to the ability of hydralazine to combine with pyridoxine;
  - hematologic effects: hemolytic anemia, leukopenia, agranulocytosis, thrombocytopenia;
  - other adverse effects: fluid retention and edema, headache, dizziness, tachycardia may precipitate angina pectoris, nasal congestion, lacrimation, conjunctivitis, diarrhea.

Contraindications:
- renal failure, pregnancy, breastfeeding, seizures, polyneuropathy, peptic ulcer, anemia
- careful administration: coronary artery disease, tachycardia.
Minoxidil

**Mechanism of action:**
- direct vasodilating effect on arterial smooth muscle by opening $K^+$-channels.

**Pharmacodynamic effects:**
- direct vasodilation → reduces peripheral resistance and blood pressure and it is associated with reflexes stimulation of the sympathetic nervous system (results in increased heart rate and contractility, increased cardiac output, increased plasma renin activity, and fluid and sodium retention);
- stimulate regrowth of hair in patients with androgenetic alopecia (by dilating blood vessels).

**Indications:**
- systemic administration: severe hypertension (maintenance treatment) – not controlled by first-line drugs;
- local administration: to combat hair loss (androgenic alopecia).

**Adverse effects:**
- fluid and sodium retention, edema;
- cardiovascular effects: tachycardia, angina pectoris, myocardial infarction in patients with very severe hypertension, pericardial effusion;
- hypertrichosis (elongation, thickening, and increased pigmentation of fine body hair on the face, back, arms and legs) - within 3-6 weeks after initiating minoxidil therapy.

Diazoxide

**Mechanism of action:**
- direct vasodilating effect on arterial smooth muscle by opening $K^+$-channels;
- direct relaxation effect on uterine muscle;
- inhibits pancreatic insulin secretion.

**Pharmacodynamic effects:**
- direct vasodilation – reduces peripheral resistance and blood pressure and it is associated with reflexes stimulation of the sympathetic nervous system (results in increased heart rate and contractility, increased cardiac output, increased plasma renin activity, and fluid and sodium retention);
- inhibition of contractions in both the term uterus during labor and the nongravid uterus;
- increase blood glucose concentration and it has low capacity to inhibit peripheral glucose utilization by muscle and to stimulate hepatic gluconeogenesis.

**Indications:**
- hypertensive crises for emergency (not effective in pheochromocytoma crises).

**Adverse effects:**
- fluid and sodium retention, edema;
- hyperglycemia (transient after the first dose, high long-term administration);
- hirsutism (= hypertrichosis = overabundance of hair in women and children, especially on the forehead, the back and limbs) after prolonged oral therapy.

I.2.2. Vasodilatation drugs acting by specific mode of action

**Inhibitors of 5-phosphodiesterase:** Sildenafil, Tadalafil, Vardenafil

**Mechanism of action:**
- selective inhibition of phosphodiesterase type 5 (PDE5 from the corpora cavernosa) → determines increase of cGMP
- additionally inhibits phosphodiesterase type 6 (PDE6).

**Pharmacodynamic effects:**
- inhibition of PDE5 determines:
- relaxation of the nonvascular smooth muscle of the corpora cavernosa (which result in the achieve and maintain penile erection);
- low intensity systemic vasodilatory effects (transient modest reductions in systolic and diastolic blood pressure is usually clinically unimportant when the drug is taken alone);
- reduction in lower esophageal sphincter tone;
- inhibition of PDE6 in the retina determines consecutive visual disturbances (e.g., blue/green vision, changes in light sensitivity).

**Indications:**
- erectile dysfunction;
- pulmonary arterial hypertension;
- Raynaud syndrome;
- non-medical use: aphrodisiac.

**Adverse effects:**
- moderate adverse effects:
  - cardiovascular effects: headache, flushing, palpitations
  - photophobia, sudden vision loss or visual disturbances (blue/green vision, changes in light sensitivity);
  - sudden decrease or loss of hearing;
  - adverse GI effects (e.g., reflux-induced dyspepsia and heartburn, nausea, vomiting);
  - myalgia.
- severe adverse effects:
  - prolonged erection (> 4 hours) and priapism (painful erection > 6 hours) are medical emergencies;
  - orthostatic hypotension, myocardial ischemia and infarction, ventricular arrhythmia, sudden cardiac death;
  - transient ischemic attack, cerebrovascular hemorrhage.

**Contraindications:**
- cardiovascular diseases: myocardial infarction or active coronary ischemia, with congestive heart failure, with borderline low blood pressure or low blood volume;
- hepatic or renal severe impairment;
- degenerative diseases of the retina (retinitis pigmentosa);
- anatomical deformation of the penis;
- association with HIV protease inhibitors;
- association with nitrates (because induce severe hypotension).

**Prostaglandin analogues**
- PGE1 analogs: Alprostadil, Prostin
- PGI2 analogs: Epoprostenol, Iloprost.

**Indications:**
- Alprostadil: patent ductus arteriosus, peripheral arterial disease (leg), Raynaud's syndrome;
- Prostin: the erectile dysfunction;
- Epoprostenol: peripheral arterial disease;
- Iloprost: peripheral arterial disease, Raynaud's syndrome.
II. Drugs that stimulate constriction of smooth muscle

II.1. Substances stimulating visceral smooth muscle:

II.2. Substances stimulating vascular smooth muscle (vasoconstrictors)

Oxytocin

Oxytocin is a nonapeptide hormone secreted by the neurons of the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior pituitary gland.

**Mechanism of action:**
- agonist on oxytocin receptors → increase influx and concentration of intracellular Ca\(^{2+}\) in the myometrium and the myo-epithelial cells.

**Pharmacodynamic effects:**
- contraction of uterine smooth muscle → induction and augmentation of labor;
- contraction of myoepithelium that surrounds alveolar channels in mammary gland → milk ejection;
- weak antidiuretic effect in high doses.

Oxytocin effects on uterus is influenced by other hormones:
- estrogens stimulate Oxytocine activity;
- progesteron inhibits Oxytocine activity.

During the second half of pregnancy, uterine smooth muscle shows an increase in the expression of oxytocin receptors and becomes increasingly sensitive to the stimulant action of endogenous oxytocin.

Oxytocine activity is:
- absent → in non-pregnant women;
- maximum → near-term uterus.

**Pharmacokinetics:**
- Administration: iv or im to initiate or enhance rhythmic uterine contractions for induction and augmentation of labor and for control postpartum hemorrhage, spray in both nostrils 2–3 min before feeding to promote milk letdown in lactating women. It is rapidly inactivated by digestive enzymes.
- Distribution: no plasma protein binding. T1/2 = 5 minutes.
- Metabolism: rapidly destroyed in the liver.
- Elimination: in urine.

**Indications:**
- antepartum uses:
  - induction of labor in term or near-term pregnancies (when it does not occur spontaneously),
  - augmentation of labor during the first and second stages of labor;
  - sometimes used during second-trimester abortions;
- postpartum uses
  - control postpartum hemorrhage (stimulate immediate contractions of the uterus and control uterine bleeding);
  - stimulation of milk ejection in lactating women (nasal spray, 3-5 minutes before nursing);
  - prevention of mastitis.

Uterine contractions induced by Oxytocin may be antagonized by:
- beta2-adrenergic agonists,
- inhalatory volatile liquid general anesthetics,
- magnesium sulphate i.v.
Adverse effects:
- uterine rupture, prolonged uterine contractions;
- maternal or fetal death;
- excessive fluid retention (water intoxication) and hyponatremia;
- oxytocin-induced thrombocytopenia, afibrinogenemia, and hypoprothrombinemia.

Contraindications¹:
- cephalopelvic disproportion;
- abnormal fetal presentation;
- predispositions for uterine rupture (uterine or cervical scarring from previous cesarean section or major cervical or uterine surgery);
- placenta previa;
- premature labour;
- fetal distress;
- severe hypertension (preeclampsia or eclampsia);
- impaired hepatic or renal function.

**Ergometrine (Ergonovine) and Methylergometrine (Methylergonovine)**

Ergometrine (Ergonovine) is a amino-alcohol ergot alkaloid. Methylergometrine (Methylergonovine) is a semisynthetic derivative of Ergometrine.

**Mechanism of action:**
- directly strong stimulation of uterine smooth muscle;
- agonist of α-adrenergic receptors;
- agonist of dopamine receptors;
- partial antagonist of 5-HT2 receptors.

**Pharmacodynamic effects:**
- intense uterine contractions (increases the basal tone, frequency and amplitude of contractions), followed by periods of relaxation;
- low vasopressor effects;
- prokinetic effects;
- hallucinatory effects.

**Indications:**
- subinvolution or atony of the uterus after expulsion of the child
- postpartum hemorrhage (prevention and treatment of postpartum or postabortion hemorrhage caused by uterine atony or involution) ➔ drug of choice because produce more sustained contractions and higher uterine tonus than does oxytocin.

If the placenta was not expelled, it is necessary to give oxytocin. Do not give ergometrine because it causes tonic uterine contractions that could delay delivery of the placenta.

- Test the Ergometrine (=Ergonovine): performed during coronary angiography, which allows to lift the coronary spasm in variant Prinzmetal angina.

**Adverse effects (of ergot derivatives):**
- nausea and vomiting, abdominal pain, diarrhea;
- vasoconstriction (mainly of capacitance vessels: coronary insufficiency with precipitation or aggravation of angina pectoris and possibly myocardial infarction, cold, numb, painful extremities with or without paresthesia, weakness in the legs, muscle pain or stiffness in the extremities, neck or shoulders, numbness and tingling of fingers and toes)

¹ Are the indications for cesarean delivery.
- Hypertension may occur less frequently with methylergonovine than with ergonovine;
- Endothelial toxicity: vascular stasis, thrombosis, gangrene of extremities;
- Hepatotoxicity, nephrotoxicity;
- Acute ergot toxicity (ergotism) in high doses: arterial spasm (may affect any blood vessel) and ischemia of the extremities, hallucinations.

**Contraindications:**
- Pregnancy, breastfeeding;
- Severe hypertension, peripheral vascular disease, coronary artery disease, heart failure;
- Impaired hepatic or renal function,
- Mental diseases;
- Collagen diseases;
- Sepsis.

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**II.2. Substances stimulating vascular smooth muscle (vasoconstrictors)**

**Ergotamine and Dihydroergotamine**

Ergotamine is a naturally occurring peptide ergot alkaloid. Dihydroergotamine is a semisynthetic peptide ergot alkaloid that is structurally and pharmacologically related to ergotamine.

**Mechanism of action:**
- Partial agonist of α-adrenergic receptors from vessels (and partial agonist of α-adrenergic receptors pre- and post-synaptic);
- Ergotamine: partial antagonist of 5-HT2 receptors, Dihydroergotamine: agonist of 5-HT1D receptors;
- Stimulation of uterine smooth muscle (oxytocic activity).

**Pharmacodynamic effects:**
- Vasoconstrictor effects (may affect any blood vessel): vasoconstriction of peripheral and cranial arteries, increase in venous tone.

**Indications:**
- To prevent or abort vascular headaches (including migraine and cluster headaches).

*Ergotamine is associated with Caffeine for the enhancement of Ergotamine absorption and for the augmentation of vasoconstrictor effect in cerebral vessels. Dihydroergotamine effectiveness is lower than that of Ergotamine.*

**Adverse effects:**
- Nausea and vomiting, abdominal pain, diarrhea;
- Due to vasoconstriction: intermittent claudication, paresthesia, cramps and pain phenomena, high blood pressure;
- Endothelial toxicity: vascular stasis, thrombosis, gangrene of extremities;
- Hepatotoxicity, nephrotoxicity;
- Acute ergot toxicity (ergotism) in high doses;
- Mental depression, fatigue and increased frequency of headache (after prolonged use).

**Contraindications** (similar to Ergometrine):
- Pregnancy, breastfeeding;
- Severe hypertension, peripheral vascular disease, coronary artery disease;
- Impaired hepatic or renal function,
- Mental diseases;
- Collagen diseases;
- Sepsis.
Methysergid

Methysergid is an amine ergot alkaloid.

**Mechanism of action:**
- strong partial antagonist of 5-HT2 receptors;
- weak partial agonist of α1 and α2-adrenergic receptors;
- weak partial antagonist of dopamine receptors;
- weak stimulation of uterine smooth muscle.

**Indications:**
- migraines resistant to other treatments (prevent or abort vascular headaches including migraine and cluster headaches)
- alternative for carcinoid tumors that secrete serotonin.

**Adverse effects:**
- chronic administration: retroperitoneal fibrosis, pleural fibrosis, endocardial fibrosis; it can be reduced this risk if the treatments do not exceed six months and is repeated after intervals of 3 to 4 weeks;
- occasional central nervous system stimulation and hallucinations (it was used as a substitute for LSD);
- nausea and vomiting, abdominal pain, diarrhea;
- high blood pressure;
- endothelial toxicity: vascular stasis, thrombosis, gangrene of extremities;
- hepatotoxicity, nephrotoxicity;
- acute ergot toxicity (ergotism) in high doses.

**Contraindications:** similar to Ergotamine.

**Vasopressin (antidiuretic hormone), Terlipressin, Desmopressin**

Vasopressin (antidiuretic hormone) is a polypeptide hormone secreted by the neurons of the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior pituitary gland.

Terlipressin is a synthetic vasopressin analog with similar efficacy to vasopressin, but with fewer adverse effects.

Desmopressin is a synthetic polypeptide structurally related to vasopressin.

Vasopresin receptors: V1 (mediate vasoconstriction), V2 (mediate antidiuretic effect) and V2-like (=V3, stimulate release of coagulation factor VIII and von Willebrand factor)

**Mechanism of action:**
- Vasopressin and Terlipressin: agonist of vasopresin receptors V1, V2 and V2-like.
- Desmopressin: agonist of vasopresin receptors V2 and V2-like.

**Pharmacodynamic effects:**
- Vasopressin and Terlipressin
  - intense vasoconstriction (particularly of capillaries and of small arterioles, mediated by V1 receptors); Terlipressin has preferential splanchnic vasoconstrictor; the vasopressor effects are less pronounced than those of vasopressin.
  - antidiuretic effect (maintain serum osmolality within a normal range, mediated by V2 receptors);
- Desmopressin
  - potent antidiuretic effect;
  - stimulation of release of coagulation factor VIII (antihemophilic factor) and von Willebrand factor (mediated by V2-like receptors).
Pharmacokinetics:
- Absorption:
  - Vasopressin is administered intranasal (very good absorption) or parenteral.
  - Desmopressin (used as acetate salt) is administered intranasally, orally, by subcutaneous injection, direct IV injection, or slow IV infusion.
- Distribution: in extracellular fluid, but no plasma protein binding.
- Metabolism: rapidly destroyed in the liver and kidneys.
- Elimination: small quantity → unchanged in urine.
- T1/2 = Vasopressin: 10-20 minutes, Desmopressin: 8 - 24 hours.

Indications:
- Vasopressin and Terlipressin
  - diabetes insipidus (it is drug of choice) caused by a deficiency of endogenous posterior pituitary antidiuretic hormone;
  - gastro-intestinal hemorrhage: esophageal variceal hemorrhage, colonic diverticulosis hemorrhage, intestinal perforation;
  - cardiac arrest (may replace the first or second dose of epinephrine in the treatment of ventricular fibrillation arrest, pulseless ventricular tachycardia, asystole, or pulseless electrical activity in advanced cardiovascular life support);
- Desmopressin
  - diabetes insipidus caused by a deficiency of endogenous posterior pituitary antidiuretic hormone (drug of choice);
  - primary nocturnal enurezis;
  - to evaluate the ability of the kidneys to concentrate urine;
  - hemophilia A and von Willebrand disease.

Adverse effects:
- Vasopressin and Terlipressin
  - skin pallor;
  - increased blood pressure (can lead to hypertension, myocardial ischemia or infarction, mesenteric infarction), bradycardia, minor arrhythmias;
  - nausea, vomiting, abdominal cramps;
  - severe hyponatremia (“water intoxication” = overhydration → in infants and children): headache, confusion, anuria, and weight gain;
  - type I allergic reactions (urticaria, angioedema, bronchoconstriction, fever, rash, wheezing, dyspnea, circulatory collapse, cardiac arrest, and anaphylaxis).
- Desmopressin
  - severe hyponatremia;
  - unlike vasopressin, usual doses of Desmopressin do not cause skin pallor, vasoconstriction or abdominal cramps.

Contraindications:
- Vasopressin and Terlipressin
  - hypertensive disease,
  - coronary arteries diseases;
  - pregnancy;
  - renal failure.
- Desmopressin
  - pregnancy;
  - renal failure.

Lecturer Cristina GHICIUC, MD, PhD
Drugs used to treat asthma and chronic pulmonary obstructive disease

1. Substances with stimulatory action on the sympathetic nervous system:
   1.1. non-selective: α, β-adrenergic receptor agonists
      - direct action (adrenergic receptor agonists): Adrenaline (Epinephrine).
      - indirect action (release of norepinephrine cell deposits): Ephedrine.
   1.2. semi-selective β1, β2-adrenergic receptor agonists: Isoprenaline (Isoproterenol), Orciprenaline
   1.3. selective β2-adrenergic receptor agonists:
      - with medium duration of action and rapid effect: Salbutamol (= Albuterol\(^2\)), Terbutaline, Fenoterol, Clenbuterol, Pirbuterol, Procatrol;
      - with long duration of action and late effect: Salmeterol, Formoterol;
      - with super-long duration of action: Bambuterol.

2. Methylxanthines: Theophylline
   - used as Aminophylline (a combination of theophylline and ethylenediamine).

3. Antimuscarinic drugs:
   - The natural alkaloids: Atropine;
   - synthetic substances:
     • with short duration of action: Ipratropium, Oxitropium
     • with long duration of action: Tiotropium.

4. Leukotriene receptor antagonists: Montelukast, Zafirlukast, Pranlukast.
5. Inhibitor of 5-lipoxygenase: Zileuton.
6. Inhibitors of histamine release: Cromolyn (cromoglicate), Nedocromil.
7. Glucocorticoids: Betamethasone, Budesonide, Fluticasone, Flunisolide, Mometazona, Triamcinolone, Prednisone, Prednisolone, Methylprednisolone.
8. Calcium channel blockers: Nifedipine Verapamil.
9. Anti-histamine H1 receptor: Ketotifen.

\(^2\) Salbutamol, which is the World Health Organization recommended name for the medication. In the US this same drug is called Albuterol. In some books it is written that Albuterol has short action, in other books it is written that Salbutamol has medium duration of action. I consider that Salbutamol (= Albuterol) has medium duration of action, to avoid endless confusion.