Autonomic Nervous System Pharmacology

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Drugs that produce therapeutic effect by mimicking / altering functions of autonomic nervous system are called AUTONOMIC DRUGS.

CHOLINERGIC AGONISTS

General effects of cholinergic stimulation / intoxication:

Muscarinic effects:
  1. Salivation & sweating & lacrimation
  2. Miosis, accommodation spasm (blurred vision)
  3. Flushing, BP↓, bradycardia
  4. Bronchospasm & bronchorrhea, rhinorrhea
  5. Abdominal pain, nausea, vomiting, diarrhea, fecal incontinence
  6. Urinary urgency & incontinence
N.B. ATROPINE is antidote!

Nicotinic effects:
  1. Skeletal muscle fasciculations → paralysis (due to prolonged nicotinic action) (breathing difficulty, etc).
  2. Pallor, tachycardia, BP↑

CNS effects (if agent can enter CNS) – mimics alcohol intoxication:
  1. Agitation, headache, drowsiness, confusion, ataxia, delirium
  2. Convulsions
  3. Coma
DIRECT ACTING CHOLINERGIC AGONISTS

- directly bind to cholinoreceptors.

In general, little specificity to N or M receptors – limited clinical usefulness!

ACETYLCHOLINE – no therapeutic application:
  1) very shortly acting (rapid inactivation by acetylcholinesterase)
  2) quaternary ammonium compound – cannot penetrate membranes (active only i/v)
  3) multiplicity of actions
- Aech i/v → cardiodepression, vasodilation (→ brief BP↓) → sympathetic ganglia &
  adrenomedullary stimulation → BP↑.
- may be used as myotic in cataract surgery.

BETHANECHOL (synthetic ester of choline – resist hydrolysis by acetylcholinesterase, but slowly
hydrolysed by other esterases)
- MUSCARINIC agent - strongly binds to M receptors, almost no nicotinic activity:
  1) intestinal motility & tone↑
  2) expulsion of urine
- duration of action ≈ 1 hour.
- clinical application:
  1) stimulation of atonic urinary bladder (i.e. nonobstructive retention - postpartum, post
  operation, etc).
  2) esophageal reflux disease

CARBACHOL (synthetic ester of choline – resist hydrolysis by acetylcholinesterase, but slowly
hydrolysed by other esterases)
- has both – muscarinic and nicotinic (ganglionic) – actions.
- duration of action ≈ 1 hour.
- clinical application – eye drops to produce miosis and decrease intraocular pressure.

PILOCARPINE (natural alkaloid, tertiary amine, stable to hydrolysis by acetylcholinesterase)
- preferentially binds to M receptors (MUSCARINIC agent).
- far less potent than other agents.
- clinical application:
  1) eye drops to produce miosis, emergency (!) lowering intraocular pressure (drug
  extremely effectively opens Schlemm canal; effect lasts up to 24 hours)
  2) burnos skalavimas sukelti seilių išsiskyrimą

METHACHOLINE
- pure muscarinic agent.
- clinical application:
  1) vasodilator in peripheral vascular disease
  2) inducing hyperemia (locally by iontophoresis) in arthritis
  3) inducing bronchospasm during PFTs - bronchial asthma diagnosis

CEVIMELINE (Evoxac) - indicated for treatment of dry mouth in Sjögren’s syndrome.

ANTICHOLINESTERASES (s. indirect acting cholinergic agonists)
- prolong lifetime of acetylcholine (→ stimulation of N & M cholinoreceptors).
**REVERSIBLE**

- act as *substrate for acetylcholinesterase*, and form relatively stable enzyme-substrate intermediate.

**PHYSOSTIGMINE** (tertiary amine, alkaloid)
- duration of action 2-4 hours.
- well absorbed from GI tract; can enter (and stimulate) CNS.
- indications:
  1) *intestinal / bladder atony*
  2) producing miosis and *lowering intraocular pressure* (PILOCARPINE is more effective!)
  3) overdosage of *anticholinergics* (e.g. atropine, phenothiazines, tricyclic antidepressants).
- precautions, contraindications – see below (anticholinergic poisoning).

**NEOSTIGMINE** (synthetic quaternary amine)
- duration of action 2-4 hours.
- more polar molecule – not well absorbed orally, does not enter CNS.
- **effects on SKELETAL MUSCLES** (greater than that of PHYSOSTIGMINE; because of additional direct nicotinic stimulation) – indications:
  1) *curare* antidote
  2) *myasthenia gravis* treatment

**PYRIDOSTIGMINE**
- ≈ NEOSTIGMINE; duration of action 3-6 hours (more suitable in *chronic treatment* of *myasthenia gravis*).

**EDROPHONIUM** (Tensilon®)
- ≈ NEOSTIGMINE; duration of action 10-20 min (used in *diagnosis* of *myasthenia gravis*, or as *curare* antidote).

Newer CENTRALLY ACTING agents (**TACRINE, DONEPEZIL, GALANTHAMINE, RIVASTIGMINE**) – used in treatment of *Alzheimer disease* (žr. S11 p.)

**IRREVERSIBLE**

- *covalently bind to acetylcholinesterase & pseudocholinesterase*.
- enzyme molecule is inactivated (activity restoration requires synthesis of new enzyme molecules); “aging” – inactivated enzyme molecule slowly *releases alkyl group* and so becomes *permanently* inactivated (impossible to reactivate).

**CHOLINERGIC POISONINGS**

**ORGANOPHOSPHATES**
- extremely toxic synthetic agents:
  1) *military nerve agents* (convulsions, breathing muscle paralysis); newer military agents “age” in minutes ÷ seconds.
  2) *insecticides* (e.g. PARATHION, CHLORPYRIFOS, DIAZINON, MALATHION, TRICHLOROFON)
- readily absorbed (even through intact skin).
- some are lipid soluble (accumulate).
- **clinical features** – general *cholinergic effects* (muscarinic + nicotinic + CNS);
  - toxicity manifests when > 50% acetylcholinesterase is inactivated.
  - garlic-like / petroleum-like odor in patient’s breath.
1-3 weeks after initial exposure, organophosphate-induced delayed polyneuropathy (OPIDP) may develop - distal dying back axonopathy - cramping muscle pain in legs, paresthesias, motor weakness (e.g. foot drop, weakness of intrinsic hand muscles, absent ankle jerk, weakness of hip and knee flexors).

**Confirmatory diagnosis:**
- erythrocyte (true) cholinesterase – gold standard (reflects enzyme activity in neural tissues) – below 70% of normal.
- plasma (pseudo) cholinesterase – levels affected by many other conditions.
- urine screen for metabolites.

**Treatment:**
1) ABC
2) benzodiazepines for seizures
3) decontamination (avoid self-contamination - wear protective clothing, masks, gloves!)
   - gastric lavage with charcoal, skin flushing with water and soap.
4) **ANTIDOTES:**
   - **ATROPINE** in high doses (1-2 mg IM q1h) can reverse many muscarinic and CNS effects.
     - tachycardia is not contraindication.
     - end point for atropine administration is drying of bronchial secretions.
   - Acetylcholinesterase reactivation – **Pralidoxime (PAM)** 1 g IV:
     - effective only if given before “aging” (but late presentation does not preclude administration).
     - acts at nicotinic receptors; cannot reverse CNS effects (drug molecule has charged group).

**Carbamates**
≈ organophosphates; differences:
- do not penetrate BBB – small CNS toxicity.
- spontaneously hydrolyze.

**Therapeutic Agents**
- **Echotiothophate**
- **Isoflurophate** (s. DFP)
- **Demecarium**
  - used as ophthalmic ointments to treat open-angle glaucoma (effect lasts up to 1 week).
  - DFP “ages” in 6-8 hours.

**Cholinergic Antagonists**
- Antimuscarinic effects:
  1. **Mydriasis** (photophobia - “blind as bat”), **cycloplegia** (blurring of near vision, intraocular pressure↑ - contraindicated in glaucoma and elderly individuals!!!)
  2. **GI activity** ↓↓↓ (most potent antispasmodics!) → constipation, paralytic ileus; HCl production↓ depends specifically on M₁ blockade.
3. Urinary bladder activity ↓ → urinary retention (occasionally used for enuresis treatment)
4. Bradycardia (at small doses – blockade of M₁ on inhibitory prejunctional neurons, medullary stimulation of cardioinhibitory center) → tachycardia (at atropine doses ≥ 1 mg – higher than ordinary doses); BP is unaffected or ↑ (at toxic doses, cutaneous vasodilation – “red as beet”).
5. Xerostomia ("dry as bone"), sweating ↓ (→ body temperature ↑ - “hot as Hades”), xerophthalmia (“sandy eyes”).
6. CNS (at toxic doses, e.g. > 10 mg atropine) – “mad as hatter”: agitation, confusion, delirium with hallucinations, amnesia, psychosis, seizures, coma, cardiorespiratory collapse, death.

**ATROPINE** (racemic mixture of d- and l-HYOSCYAMINE; alkaloid of *Atropa belladonna**, s. deadly nightshade*) – reversible competitive Acch antagonist at M receptors (at very high concentrations – also at N receptors).

* belladonna alkaloids were used in past by women who wanted large pupils as sign of beauty (*bella donna*).

- poorly absorbed orally.
- acts both centrally and peripherally.
- duration of action ≈ 4 hours (if placed topically in eye ≈ days).
- clinical use:
  1) ophthalmology (topical) – **mydriasis & cycloplegia production** for measurement of refractive errors without interference by accommodative lens capacity.
     N.B. if cycloplegia is not required, use α-adrenergic mydriatics.
  2) **antisecretory** (in respiratory tract) before anesthesia induction.
  3) **antidote** for organophosphate, mushroom poisonings.
  4) treatment of **bradyarrhythmias**.
  5) GI, bladder relaxation.

**SCOPOLAMINE**, s. **HYOSCINE** (alkaloid found in *Hyoscyamus niger, Duboisia myoproides, Scopolia japonica, Scopolia carniolica, Atropa belladonna*) ≈ **ATROPINE**; except longer duration of action and greater effect on CNS:

1. Most effective **anti-motion sickness** drug available!!!
2. Sedation (vs. atropine) + blocks short-term memory (useful in anesthetic procedures)

**IPRATROPIUM** (quaternary derivative of atropine), **TIOTROPIUM** – inhaled drugs for treatment of asthma, COPD.

TIOTROPIUM is longer acting (∼ 1 /d).

**PIRENZEPINE** – selective M₁ antagonist; treatment of gastroduodenal ulcers.

Anticholinergic drugs for urinary incontinence treatment: see 2590 p. (UROGENITAL SYSTEM)

1) **PROPANTHELINE**
2) **OXYBUTYNIN, DICYCLOMINE** (combination of smooth muscle relaxant + anticholinergic)
3) **TOLTERODINE** (selective M₃ antagonist)

Anticholinergic drugs for parkinsonism treatment: see Mov10 p.

1) **BENZTROPINE**
2) **TRIHEXYPHENIDYL**
3) **RIPERIDEN**

**ANTICHOLINERGIC POISONINGS**

1. Drugs:
AUTONOMIC NS PHARMACOLOGY

1. OTC antihistamines, OTC cold, OTC sleep medications
2. Atropine ophthalmic drops
3. Phenothiazines
4. Tricyclic antidepressants
5. Scopolamine (used to incapacitate and take advantage of unwary victim)


- poisons delay gastric emptying → prolonged absorption → delayed onset.
- most clinical effects are antimuscarinic.
- **treatment:**
  1) ABC
  2) cooling
  3) benzodiazepines (for agitation, seizures)
  4) bladder catheterization
  5) cardiac support:
     - if QRS is prolonged → sodium bicarbonate i/v
     - avoid class Ia antiarrhythmics!!!
  6) gastric decontamination (multiple doses of activated charcoal) – drug may remain in stomach up to 4 hours!
  7) antidote – **PHYSOSTIGMINE** i/v every 5-100 min up to total 1-3 mg:
     - short duration of action, narrow margin of safety
     - **requirements:** ¹ both peripheral and central anticholinergic toxicity must be present [antidote acts both centrally and peripherally], ² narrow QRS, ³ no conduction abnormalities.
     - **contraindication** – co-ingestion of class Ia-like drugs (incl. cyclic antidepressants) - exacerbates their poisoning.
     - pretreat with benzodiazepines (to avoid seizures).
     - physostigmine also has nonspecific analeptic activities (response to physostigmine does not confirm diagnosis of anticholinergic poisoning!).
     - persistent signs of intoxication can be treated with longer-acting cholinesterase inhibitors (e.g. DONEPEZIL).
     - neuroleptics (anticholinergic activity) are contraindicated!

There is no withdrawal syndrome!

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**GANGLIONIC BLOCKERS**

- competitive N cholinoreceptor blockers in all autonomic ganglia (no selectivity for sympathetic or parasympathetic ganglia).

  COMPLETE AUTONOMIC DENERVATION! – actions are complex and unpredictable – more used in experimental pharmacology than clinically!

  - do not block neuromuscular junction!

1. **TRIMETHAPHAN** - short-acting (skiriamas i/v/i).
   - indication – emergency lowering of blood pressure.

2. **MECAMYLAMINE** - veikia iki 10 val. (skiriamas per os).

3. **NICOTINE** (active component of cigarette smoke) addiction, withdrawal – see Psy23 p.
• not used clinically (except in smoking cessation).
• low doses → ganglionic stimulation; high doses → ganglionic blockade.
• highly lipid soluble – readily crosses BBB (stimulates → blocks N receptors in CNS), readily crosses all barriers (placenta, breast milk, skin, mucosa).
• stimulates hypothalamic corticotropin-releasing factor (CRF), increases levels of endorphins, ACTH, arginine vasopressin (marked antidiuretic activity).
• clinical effects:

**LOW DOSES:**

- CNS stimulation (esp. with small rapid doses): arousal, reduced fatigue, improved attention, learning, problem solving, reaction time; appetite ↓ → weight loss.
- CNS sedation (esp. with long drawn-out doses): relaxation (reduced anxiety), euphoria.

*Tobacco is second only to caffeine as most widely used CNS stimulant!*

peripheral – BP↑ and tachycardia (adrenomedullary and sympathetic ganglia stimulation), bowel hyperactivity & salivary hypersecretion (parasympathetic ganglia stimulation).

Smoking exacerbates hypertension, angina pectoris, peripheral vascular disease

**TOXIC DOSES** (acute nicotine poisoning):

- CNS – irritability, tremors (→ convulsions), respiratory & vasomotor paralysis, coma.
- peripheral – nausea, vomiting, salivation, pallor, hypotension, arrhythmias, cold sweat, abdominal pain, diarrhea, GI & bladder activity↓↓↓.

*Acute lethal dose* is 60 mg (one cigarette contains 6-8 mg; 90% inhaled nicotine is absorbed), but **tolerance develops rapidly** (within days).

death due to paralysis of respiratory muscles

N.B. cigarette smoking increases rate of metabolism of number of drugs (it is not known which over 3000 components of cigarette smoke are responsible for this phenomenon, although BENZOPYRENES have been implicated).

4. **HEXAMETHONIUM** – not used therapeutically.

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### ADRENERGIC AGONISTS (s. sympathomimetics)

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>DIRECT AGONISTS</th>
<th>Selective</th>
<th>Nonselective</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁</td>
<td>phenylephrine, midodrine, methoxamine</td>
<td>NA &gt; A &gt; ISP</td>
<td></td>
</tr>
<tr>
<td>α₂</td>
<td>clonidine, guanfacine, guanabenz, α-methyldopa</td>
<td>A &gt; NA &gt; ISP</td>
<td></td>
</tr>
<tr>
<td>β₁</td>
<td>dobutamine</td>
<td>ISP &gt; A = NA</td>
<td></td>
</tr>
<tr>
<td>β₂</td>
<td>metaproterenol, albuterol, terbutaline, salbutamol, salmeterol, pirbuterol, bitolterol, ritodrine</td>
<td>ISP &gt; A &gt;&gt; NA</td>
<td></td>
</tr>
</tbody>
</table>

ISP - isoproterenol

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### DIRECT-ACTING ADRENERGIC AGONISTS

- adrenergic drugs are derivatives of β-phenylethylamine; most important structural features of molecules:
- number & location of –OH groups on benzene ring (determine catabolism rate);
- substituent nature on amino nitrogen (more bulky substituent, greater potency at β receptors).

**CATECHOLAMINES**

- biosynthesis and catabolism - žr. BIOCHEMISTRY 812 p., ENDOCRINE SYSTEM 2723 p.
- CATECHOL is 1,2-dihydroxybenzene; so catecholamines are amines that contain 3,4-dihydroxybenzene group.
- catecholamines:
  - have high potency for α/β receptors;
  - rapidly inactivated (MAO, COMT in liver) – must be given i/v/i;
  - ineffective when given orally - MAO, COMT in gut wall;
  - poor penetration into CNS.

N.B. non-catecholamine drugs (poor substrates of COMT, MAO) have much longer duration of action; many also have greater access to CNS; all can be administered orally.

**EPINEPHRINE. s. ADRENALINE**

At low doses β effects predominate against α effects!

1) cardiovascular effects (cardiostimulation, systolic BP↑, diastolic BP↓) – žr. 1319 p. (C/V SYSTEM)
2) biochemical effects (hyperglycemia, lipolysis) - žr. 2723 p. (ENDOCRINE SYSTEM)
3) powerful bronchodilation
• clinical uses:
  1) drug of choice in acute bronchospasm (asthma attack, anaphylaxis)
  2) drug of choice in type I hypersensitivity reactions (anaphylaxis)
  3) resuscitation of cardiac arrest.
  4) open-angle glaucoma – 2% solution (humor production↓ due to ciliary body
     vasoconstriction)
  5) component (1:100,000) in local anesthetic solutions – prolonged action, bleeding↓;
     weak solution may also be used topically to control capillary oozing.

• administration – parenterally (i/v*, s/c**, inhalation), topically.
  *risk of heart fibrillation.
  **due to vasoconstriction, subcutaneous absorption is slow.

• adverse effects: anxiety & fear, headache, tremor, BP↑, cardiac arrhythmias (esp. if on digitalis,
  cocaine, hyperthyroidism), pulmonary edema.

NOREPINEPHRINE, s. LEVARTERENOL
• in therapeutic doses α-receptors are most stimulated – strong vasoconstriction (incl. renal),
  systolic & diastolic BP↑, reflex (baroreceptor) bradycardia.
• clinical use – shock treatment (but DOPAMINE is better!)

ISOPROTERENOL
• β1, β2 receptors are stimulated much stronger than α receptors:
  1) strong cardiostimulation, vasodilation, systolic BP slightly↑, diastolic BP↓↓↓
  2) strong bronchodilation (as effective as with epinephrine)
• clinical use – emergency treatment of bradyarrhythmias.
• may be given orally, but absorption is unreliable.
• slowly metabolized by COMT, stable to MAO action.

DOPAMINE
  about central action modulation see A4b p.
• effects depend on DOSE:
  1-3 μg/kg/min – stimulation of D receptors: VASODILATION (renal & splanchnic) →
     natriuresis.
  3-10 μg/kg/min – stimulation of β1 receptors: CARDIOSTIMULATION (ino & chrono) →
     systolic BP↑.
  >10 μg/kg/min – stimulation of α1 receptors: VASOCONSTRICTION (incl. renal) →
     diastolic BP↑.
• clinical use – drug of choice in treatment of shock – rises BP without affecting renal blood flow!
  (vs. norepinephrine).
  N.B. little effect on β2 receptors!
• adverse effect (at overdoses) – sympathetic overstimulation.

DOBUTAMINE - selective β1-agonist – cardiostimulation without vascular effects (slight β2
vasodilation*).
  β1 potency: ISOPROTERENOL > DOBUTAMINE > EPINEPHRINE.
  N.B. inotropy↑↑↑ > chronotropy↑ – myocardium O2 demands not significantly elevated
  (major advantage over other sympathomimetics).
• clinical use – treatment of cardiac failure (e.g. cardiogenic shock).
  *undesirable effect in treatment of noncardiogenic shocks.
• increases AV conductance – risky in atrial fibrillation.

**α1-AGONISTS**

| Vasoconstriction → systolic & diastolic BP↑ → reflex bradycardia |

• not inactivated by COMT – prolonged action.
• clinical uses:
  1) rising BP and so stimulating n. vagus → termination of supraventricular tachycardias.
  2) hypotension during HALOTHANE narcosis treatment (METHOXAMINE – it does not trigger arrhythmias, vs. other sympathomimetics).
  3) topical (PHENYLEPHRINE) - mucosal decongestant, mydriatic.

N.B. contraindicated in decreased cardiac output states!

PHENYLEPHRINE – not very potent (if dose 300 μg/min is reached, switch to more potent vasoconstrictor).

**METHOXAMINE**

MIDODRINE – FDA approved for orthostatic hypotension of various etiologies.
• active metabolite, DESGLYMIDODRINE, is α1-agonist.
• does not cross BBB.
• tablets 10 mg x3/d.
• T1/2 of DESGLYMIDODRINE = 3-4 hours.
• can cause marked elevation of supine blood pressure (> 200 mmHg systolic) – take last dose not later 6 p.m. (i.e. > 4 hours before bedtime).
• in overdosage (hypertension, urinary retention), use PHENTOLAMINE.

<table>
<thead>
<tr>
<th>AGENT</th>
<th>DOSE</th>
<th>CARDIAC</th>
<th>PERIPHERAL VASCULAR</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Heart Rate</td>
<td>Contractility</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2-20 μg/min</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1-20 μg/min</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>1-5 μg/min</td>
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<td>+++</td>
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<td>Phenylephrine</td>
<td>20-200 μg/min</td>
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<tr>
<td>Dopamine</td>
<td>1-4 μg/kg/min</td>
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<td>+</td>
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<td></td>
<td>4-20 μg/kg/min</td>
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<td>+++</td>
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<tr>
<td>Dobutamine</td>
<td>2.5-15 μg/kg/min</td>
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<td>Amrinone*</td>
<td>5-15 μg/kg/min</td>
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<tr>
<td>Milrinone*</td>
<td>0.375-0.75 μg/kg/min</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

*phosphodiesterase inhibitors

**β2-AGONISTS**

METAPROTERENOL
ALBUTEROL*
TERBUTALINE*
PIRBUTEROL*
BITOLTEROL
RITODRINE
SALBUTAMOL
SALMETEROL – longest acting (up to 12 hours).

*most β₂-selective

- clinical uses:
  1) bronchodilation  see 2132 p. (RESPIRATORY)
  2) uterine relaxation

N.B. can have minimal β₁ effects – caution in c/v disease, hyperthyroidism.

**CENTRAL α₂-AGONISTS**

- stimuliuoja presinaptinius α₂ receptorius CNS vazomotoriniame centre - mažina central sympathetic outflow (CENTRAL SYMPATHOLYTICS) - vieniems vyrauja vazodilatacija (GUANFACINE, α-METHYLDOPA), kitiems cardic output↓ (CLONIDINE, GUANABENZ).

**CLONIDINE**

- clinical uses: essential hypertension, withdrawal of opiates / benzodiazepines.
- adverse effects:
  1) sedation
  2) oronasal mucosa drying
  3) negalima staiga nutraukti (rebound hypertension)
  4) nemažina renal blood flow ir glomerular filtration (tinka prie renal diseases), bet linkės sulaikyti Na ir H₂O - todėl skiriamas kartu su diuretikais!

**α-METHYLDOPA** - panašu į CLONIDINE;

- gali sukelti hemolitinę anemiją (direct Coombs' test positive) ir liver damage!

**GUANABENZ** ≈ CLONIDINE

**GUANFACINE** - veikia ilgiausiai (skiriamas 1 k./d.).

**INDIRECT-ACTING ADRENERGIC AGONISTS**

**AMPHETAMINE**

dextroamphetamine
methamphetamine (METH, Ice)
methylenedioxymethamphetamine (MDMA, Ecstasy)

- stimulate NA release into synaptic cleft (i.e. displaces stored norepinephrine), also weakly block MAO.

  CNS – psychomotor stimulation is marked (≈ COCAINE, but 4-8 times longer) → drug abuse.
  – effects are due to dopamine (not norepinephrine) release;
  – entire CNS is stimulated: alertness↑, fatigue↓, euphoria, increased motor and speech activity, appetite↓, insomnia (hypervigilance), medullary respiratory center stimulation (analectic action).

  Periphery – norepinephrine release (“fight or flight”): marked vasoconstriction (α effect), cardiotimulation (β effect), mydriasis (vs. opiates!!!), perspiration.
  – amphetamines typically cause erectile dysfunction in men but enhance sexual desire.
Administration - completely absorbed from GI tract; abusers also use by i/v, smoking “crank” (vs. cocaine – “crack”).

Clinical uses: attention deficit - hyperkinetic syndrome (paradoxical calming effect is produced with long-term therapy), narcolepsy, depression (augmentation of antidepressants [except MAO inhibitors!] in treatment-resistant depression), appetite control.

- clinical use is limited:
  1) psychological / physiological dependence – abuse potential. see Psy23 p.
  2) tolerance to euphoric / anorectic effects occurs within weeks (however, tolerance to toxic effects [e.g. convulsions] develops less).
  3) hazardous in pregnancy!
  4) contraindicated in cardiovascular disease, taking MAO inhibitors.
  5) adverse effects:
     – insomnia, headache, vertigo, confusion, delirium, hallucinations, panic, suicidal tendencies, tremor, convulsions (usually brief, self-limited); prolonged usage → fatigue, mental depression.
     – palpitations, arrhythmias, hypertension, hyperthermia, angina (most common complaint at ED), MI, circulatory collapse.
     – nausea & vomiting, abdominal cramps & diarrhea.
     – chronic use of high doses produces “amphetamine psychosis” (paranoia progressing to frank hallucinatory psychosis that resembles acute schizophrenic attack) or “wash-out” (exhaustion syndrome with mental status↓).
     – Tourette’s syndrome exacerbation.

- DEXTROAMPHETAMINE and METHAMPHETAMINE are preferred to AMPHETAMINE - increased CNS action and reduced peripheral effects.

- MDMA causes changes in strength of emotions (psychiatrists have experimented with MDMA to facilitate psychotherapy in patients with difficulty expressing emotions).

Intoxication (overdosage): agitation, psychotic reactions (confusion, illusions, delusions of being infested with parasites, hallucinations), marked cardiovascular effects (diastolic pressure may reach 120 mmHg), hyperthermia, convulsions → exhaustion, coma.

N.B. even massive doses are rarely fatal (long-term users have reportedly injected as much as 15,000 mg of amphetamine in 24 h without observable acute illness); recovery from even prolonged amphetamine psychosis is usual (recover slowly but completely); deaths may attributed to severe dehydration, DIC, renal failure.

Treatment: 
(1) quiet, cool room - often all that is needed!
(2) antidote – CHLORPROMAZINE or HALOPERIDOL - relieves CNS effects, hypertension (because of α-blocking activity). 
    N.B. such patients are prone to neuroleptic malignant syndrome!
(3) urine acidification (ammonium chloride 1 g PO q2-4h) to increase excretion.
(4) for hypertension and hyperthermia – PHENTOLAMINE.
(5) for seizures – DIAZEPAM.

TYRAMINE
- stimulates NA release into synaptic cleft
- normal by-product of tyrosine metabolism (decarboxylated tyrosine).
- found in fermented foods (e.g. ripe cheese, Chianti wine, beers), putrefied animal matter.
- normally, it is oxidized by MAO; if patient is taking MAO inhibitors, it causes serious vasoconstriction!!!
- also elevated in tyrosinemia type II.
- not used clinically.
COCAINE
- blocks Na⁺/K⁺-ATPase → inhibited NA/dopamine/serotonin reuptake from synaptic cleft → exaggerated & prolonged action of naturally released transmitters.
- CNS & peripheral effects ≈ AMPHETAMINE (but shorter duration).
- T½ ≈ 1 hour.
- clinical use – local anesthetic (only topically on mucosa!!!) – blocks voltage-gated Na⁺ channels. N.B. the only local anesthetic that produces vasoconstriction! (useful in nosebleed treatment)
- inexpensive, widely available, highly addictive – widely abused for intense euphoria (dopaminergic effect in limbic system). see Psy23 p.
- routes of abuse:
  a) smoking (“crack”, “freebasing”) - alkaloidal cocaine (free base) is suitable for smoking; when cocaine crystals are heated, cracking sound is produced; smoking delivers cocaine to vascular bed of lung (effect comparable to IV injection).
    N.B. “crack” is cheapest cocaine form and most addictive substance known – dependence occurs in days or from very first dose of cocaine (one-try addiction - because of incredibly unpleasant withdrawal) (animals choose self-administration of cocaine over food and water until they die)
  b) inhalation (“snorting”); after “snort”, peak occurs after 15-20 min and lasts 1-1.5 hours - nasal mucous membrane vasoconstriction limits absorption (snorting does not provide "rush" generally associated with freebasing).
  c) chewing
  d) i/v – immediate euphoria, but ↑ risk of seizures.
- adverse effects (= AMPHETAMINE):
  1) prolonged use depletes dopamine stores in CNS → severe depression → craving for cocaine to temporally relieve depression (vicious cycle).
  2) chronic inhalation (“snorting”) causes nasal septum necrosis & perforation.
  3) fetal exposure → vasoconstriction of intrauterine vessels → spontaneous abortion / premature labor (cocaine stimulates uterine contractions), abruptio placentae, stillbirth, intrauterine growth retardation → low-birth weight infants, perinatal strokes & seizures; teratogenic effects may result from cocaine-induced vasoconstriction (urogenital malformations, prune-belly syndrome, limb reduction deformities, intestinal atresia, porencephaly, microcephaly).
    - for preterm labor use Mg sulfate (does not stimulate heart as β-mimetics).
    - some newborns may show withdrawal if mother used cocaine shortly before delivery, but symptoms are less common and less severe than for narcotic withdrawal.
  4) at high doses, hyperthermia, convulsions (usually generalized but occasionally partial), arrhythmias, MI, cardiorespiratory failure.
    N.B. 60% patients with chest pain shortly after cocaine use have MI!
    - seizures can occur in repeated cocaine users without overdose (due to "kindling")
  5) cocaine exacerbates bipolar disorder, Tourette syndrome.
  6) all varieties of stroke (vasoconstriction → ischemia; vasoconstriction → hypertension → hemorrhage [intracerebral, SAH]; vasoconstriction → ischemia → reperfusion → hemorrhage).
    see also Vas3 p.
    - cocaine-stroke is one of most important causes of stroke in individuals < 40 yrs.
    - strokes occur with all routes in both first-time and chronic users.
    - cocaine HCl: hemorrhagic > ischemic (2 : 1).
    - crack cocaine: hemorrhagic = ischemic.
    - intracranial hemorrhages: intracerebral (> 50%), SAH (< 50%).
    - strokes occur within minutes ÷ hours of cocaine administration.
    - angiography: normal ÷ vessel occlusion or stenosis, vasospasm, vasculitis (it is unclear whether cocaine can induce vasculitis).
in intracranial hemorrhage, underlying lesions (aneurysm, AVM) are found in 50% (e.g. acute hypertension causes aneurysmal rupture); H: angiography in all cocaine-hemorrhage patients!

- diagnosis - urine toxicology screen (positive for cocaine within first 24 hours; urinary cocaine metabolites [norcocaine, benzoyl ecgonine] may remain positive for several days).

  N.B. urine toxicology screening is indicated in all ED patients who present with acute neurological syndrome!

- treatment of acute intoxication (generally supportive – cocaine is extremely short acting):
  
  DIAZEPAM is drug of choice; HALOPERIDOL (for psychotic symptoms).

  N.B. β-blockers are contraindicated* (unopposed α effects would produce severe hypertension and coronary vasoconstriction); so for c/v features, PHENTOLAMINE (α blocker) is recommended!

  *main difference from treatment of “traditional” heart attacks!!!

**METHYLPHENIDATE, DEXMETHYLPHENIDATE** (pharmacologically active d-enantiomer of racemic METHYLPHENIDATE)

- block NA and dopamine reuptake and increases release.
- indications: narcolepsy, attention deficit – hyperactivity disorder.
- adverse effects: nervousness, insomnia, decreased appetite, abdominal pain, weight loss; may exacerbate psychosis; may lower seizure threshold; may cause visual disturbances and increase BP

**MIXED ACTION (direct & indirect) ADRENERGIC AGONISTS**

- stimulate NA release into synaptic cleft (i.e. displace stored norepinephrine) + directly stimulate adrenergic receptors.

**EPHEDRINE**

- plant alkaloid (Ephedra species), now made synthetically.
- excellent absorption orally; penetrates into CNS; eliminated unchanged into urine.
- effects ≈ EPINEPHRINE, but less potent, slower onset, prolonged action (not substrate for MAO & COMT!!!), stimulates CNS.
- clinical uses (generally declining) – chronic asthma prophylaxis, nasal decongestant, mild CNS stimulation (alertness↑, appetite↓, athletic performance↑), raising BP (e.g. in spinal anesthesia), myasthenia gravis treatment (+ anticholinesterases).
- tachyphylaxis occurs.

**METARAMINOL**

- effects ≈ NOREPINEPHRINE, but less potent; little effect on CNS.
- used to treat shock (when infusion of dopamine, norepinephrine is not possible), topical nasal decongestant.

**HYDROXYAMPHETAMINE** ≈ EPHEDRINE without CNS effects.

**METHAMPHETAMINE** – as AMPHETAMINE in CNS, more potent than EPHEDRINE in periphery.

**MEPHENTERMINE** – as METHAMPHETAMINE without CNS effects.
ADRENERGIC ANTAGONISTS (s. adrenoblockers, sympatholytics)

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>ANTAGONISTS</th>
<th>Nonselective</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁</td>
<td>prazosin, terazosin, doxazosin, trimazosin</td>
<td>phenoxybenzamine, phentolamine</td>
</tr>
<tr>
<td>α₂</td>
<td>yohimbine</td>
<td></td>
</tr>
<tr>
<td>β₁</td>
<td>metoprolol, atenolol, acebutolol, esmolol, betaxolol, bisoprolol, nebivolol</td>
<td>propranolol, nadolol, timolol, oxprenolol, sotalol, pindolol, carteolol, penbutolol, labetalol</td>
</tr>
<tr>
<td>β₂</td>
<td>butoxamine</td>
<td></td>
</tr>
</tbody>
</table>

**β-ADRENERGIC BLOCKERS**

- buvę pirmos eilės vaistai gydant esencialinę hipertenziją (ypač jauniems baltaodžiams)!

**Nonselective (β₁ + β₂)**

1. **PROPRANOLOL** – prototype drug; (turi ir prailginto veikimo formą)
2. **TIMOLOL**
3. **NADOLOL** - T₁/₂ iki 24 val.
4. **PINDOLOL***
5. **PENBUTOLOL***
6. **CARTEOLOL***
7. **OXPRENOLOL**
8. **SOTALOL** (also has K⁺ channel blocking activity)

**β₁-selective (s. cardioselective)**

N.B. selektivyvumas mažėja didinant dozes, nes selektyvumas nėra absoliutus.

1. **ATENOLOL**
2. **METOPROLOL** (turi prailginto veikimo formą)
3. **ACEBUTOLOL***
4. **BETAXOLOL**
5. **BISOPROLOL**
6. **ESMOLOL** - T₁/₂ tik 10 minučių - vartojamas tachiaritmijų abortavimui.
7. **NEBIVOLOL** - veikia ilgai - skiriamas 1 k./d.

* with **intrinsic sympathomimetic activity** (partially stimulate, but prevent full stimulation) - tinka prie bradikardijos, diabetikams, neįtakoja kraujo lipidų, bet neturi kardioprotekcijos (netinka po MI).

- **veikimo mechanizmas:**
  1) **kardiosupresija** (O₂ poreikis↓; bradycardia limits drug dose)
  2) **renino sekrecija↓** → vazodilatacija, volemija↓
  3) **vazokonstrikcija** (uzblokuotas β₂ vazodilatacinis poveikis) → ↓kraujotaka periferijoje, Na⁺ retencija inkstuose.

N.B. **suminis efektas yra VAZOKONSTRIKCIJA**, o AKS↓ dėl kardiosupresijos!
  - nesukelia posturalinės hipotenzijos, nes lieka neblokuoti α₁-receptoriai!
  - ilgą laiką vartojant, jvyksta **receptor upregulation** - gydymą, esant reikalui, galima nutraukti tik pamažu (per 1 sav.) nes gali šoktelėti AKS, išprovokuoti stenokardiją ir aritmijas.

- **clinical uses:**
  1) esencialinė **hipertenzija**
2) supraventricular tachyarrhythmias (ventricular tachyarrhythmias — tik SOTALOL)
3) chronic treatment of CAD, prophylaxis and acute treatment of MI — reduced O₂ demand.
4) chronic treatment of glaucoma (esp. TIMOLOL) — reduced humor production.
5) prophylaxis of migraine (esp. PROPRANOLOL) — blockade of catecholamine-induced vasodilation.
6) blunting sympathetic stimulation in hyperthyroidism (esp. PROPRANOLOL).

- **kontraindikacijos** (reliatyvios kardioselektyviems):
  1) chronic obstructive lung disease (dėl sukeliamо bronchospazmo)
  2) congestive heart failure, bradyarrhythmias (dėl kardiosupresijos)
  3) diabetes (β-blokeriai slopina glikogenolizę — po insulino injekcijos hipoglikemijos pavojus — o jos simptomus β-blokeriai maskuoja)
  4) occlusive peripheral vascular disease (dėl sukeliamos vazokonstrikcijos)

N.B. anafilaksinės reakcijos β-blokerių fone būna sunkesnės!

- **adverse effects**: sexual dysfunction (!!!), bet ne visiems ir neaišku kodėl, mat vyrų sexualinės funkcijos vyksta per α-receptorius), CNS depression (fatigue, insomnia), plasma triglycerides↑, LDL↑, HDL↓.

- **OVERDOSAGE treatment**:
  1) gastric lavage → charcoal
  2) antidotes: glucagon, amrinone, epinephrine / norepinephrine, β₂ agonists.

### α₁-ADRENERGIC BLOCKERS

- competitive blockers of postsynaptic α₁-receptors in blood vessels.

1. **PRAZOSIN**
2. **TERAZOSIN** - veikia ilgiau negu prazosin.
3. **DOXAZOSIN** - veikia ilgiausiai.

- sukelia arterijų ir venų relaksaciją.
- **clinical use** — HYPERTENSION treatment (skiriami kaip antros eilės vaistai su β-blokeriais, diuretikais).
  - vieninteliai iš antihipertenzinių vaistų teigiamai veikia plazmos lipidus (LDL↓, HDL↑).
  - nekeičia cardiac output (ilgalaikės tachikardijos nėra), nemažina renal blood flow (nesukeliamas renino sekrecijos padidėjimas).
  - malšina prostates adenomos simptomus (galima net skirti gydymui!).

- **adverse effects**:
  1) neišvengiama trupalaikė refeleksinė tachikardija (skirk kartu su β-blokeriais) ir first dose syncope (pirmą dozę skirk sumažintą iki ¼ prieš einant gulti).
  2) posturalinė hipotenzija (ypač senukams! - jiems vengtina arba dažnai monitoruok AKS gulint ir stovint!).

**ERGOT ALKALOIDS** (esp. ERGOTAMINE, DIHYDROERGOTAMINE, METHYLSERGIDE) are weak α-adrenoblockers.

- strong vasoconstrictors (due to serotonin-agonist activity + directly stimulate smooth muscles); used for migraine treatment & prophylaxis. see S25 p.
- other ergot alkaloids (ERGONOVINE, METHYLERGONOVINE) lack α-adrenoblocking activity, but strongly directly stimulate uterine muscles; used for postpartum bleeding.

### α₁,₂-ADRENERGIC BLOCKERS
1. **PHENOXYBENZAMINE** - nonselective postsynaptic $\alpha_1$ and presynaptic $\alpha_2$ receptor blocker.
   - receptors are blocked noncompetitively & irreversibly (covalently); vaistų veikimas praėjime tik susintetinus naujus $\alpha$-receptorius (> 24 val.).
   - nors dėl postsynaptinės $\alpha_1$ blokados sukélia stiprią vazodilataciją, bet sukeliama stipri kardiostimuliacija (refleksinė + dėl presinaptinės $\alpha_2$ blokados) - netinka hipertenzijai gydyti!
   - **clinical use:**
     1) feochromocitomos priešoperacinis stabilizavimas ar chroninis gydymas (blokuojamas epinefrino vazokonstrikcijas, bet išlieka vazodilatacinių poveikių per $\beta$-receptorius).
     2) overdosage of sympathomimetics, MAO inhibitors.
     3) Raynaud disease
     4) autonomic hyperreflexia (← predisposes paraplegics to stroke).
   - **adverse effects:** postural hypotension & tachycardia (esp. in hypovolemic patients), nasal congestion, inhibited ejaculation.

2. **PHENTOLAMINE** ≈ **PHENOXYBENZAMINE**, bet receptorų blokada competitive; veikia tik 4 val.
   - **indikacijos:** feochromocitomos diagnostika (dabar ją pakeitė katecholaminų tyrimas šlapiame), cocaine / amphetamines intoxication treatment.

### $\alpha_1$ and $\beta_1,2$-ADRENERGIC BLOCKERS

N.B. visi $\beta$-blokeriai turi galūnę "-olol", bet tie kurie turi papildomų funkcijų (blokuoja $\alpha_1$-receptorius, blokuoja K+ kanalus) turi kitokias galūnes "-alol", "-ilol"!

#### LABETALOL
- vazodilatuoja (vs. pure $\beta$-blockers), bet nesukelia refleksinės tachikardijos, tačiau turi visas neselektyvių $\beta$-blokerių blogybes.
- naudojamas (i/v) in hypertensive emergencies, pregnancy-induced hypertension.

#### CARVEDILOL

### OTHER ANTIADRENERGICS

- hipertenzijai gydyti praktiškai nebenaudojami.

#### RESERPINE (rauwolfia alkaloid)
- veikia ir CNS, ir periferiniuose simpatiniuose nervuose - blokuoja neurotransmifierių (norepinephrine, dopamine, serotonin) Mg$^{2+}$/ATP-dependent transportą iš adrenerginio neurono citoplazmos iš storage vesicles* (citoplazmoje pasilikusį norepinephrine suardo MAO) → catecholamine depletion → simpatinis tonusas↓
  *taip dopaminas transportuojamas į vesicles, kuriose sintezuojamas NA; taip pat, po reuptake iš sinapsės, NA grįžta į vesicles
- pradeda veikti lėtai, bet veikia ilgai (nutraukus vartojimą - dar kelias dienas).
- **adverse effects:** parasympatinis tonusas↑ GI trakte (diarėja, paūmėja opaligė), sexual dysfunction, sedation & depression up to suicide (kontraindukuotina sergantiems depresija!).

#### GUANETHIDINE, GUANADREL (shorter duration of action)
- blokuoja norepinephrine sekreciją, ištumia norepinephrine iš storage vesicles periferiniuose nervuose (į CNS nepatenka!) → simpatinis tonusas↓
- **adverse effects:**
  1) pradžioje ištumia norepinephrine iš storage vesicles → laikiniai AKS↑
  2) orthostatic hypotension
3) male sexual dysfunction
4) dėl norepinephrine depletion atsiranda HYPERSENSITIVITY - galima hipertenzinė krizė (e.g. pavartoju cold preparations containing phenylpropanolamine, sergantiems feochromocitoma)

- contraindicated if taking MAO inhibitors.

**FENOLDOPAM mesylate** - pure dopaminergic agonist.
- naudojamas prie hypertensive emergencies - efektyvumas kaip nitroprusido, bet mažiau pašalinių efektų.
- FDA neaprobuotas.

**BRETYLIUM** - blokuoja norepinephrine sekreciją & reuptake
- used as class II-III antiarrhythmic for potentially lethal refractory VENTRICULAR TACHYARRHYTHMIAS (see 1361 p.)

**BIBLIOGRAPHY** for ch. “Autonomic PNS” → follow this [LINK ]
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