Drugs acting at the sympathetic nervous system

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Lexis
- **ergic** – connected with a certain transmitter
  - adren*ergic* receptor
- **mimetic** – stimulating a certain type of receptor
  - adreno*mimetic* drug
- **lytic** – blocking a certain type of receptor
  - cholino*lytic* drug
- **ceptive** – connected with specific kind of perception
  - nocio*ceptive*

Anatomy of the ANS
- **Sympathetic (thoracolumbar)**
  - Preganglionic neurons – lateral horns of gray matter of the T1–L2 segments of the spinal cord
  - Ganglia – sympathetic trunk
  - Postagnglionic fibers – long, reach the target organs
- **Parasympathetic (craniosacral)**
  - Preganglionic neurons – nuclei of cranial nerves III, VII, IX, X; gray matter of S2-S4 segments of the spinal cord
  - Ganglia – near the target organs
  - Postagnglionic fibers – short

Functional significance of ANS
- Sympathetic: fight or flight
- Parasympathetic: rest and digest

<table>
<thead>
<tr>
<th>Organ / function</th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
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</thead>
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<tr>
<td>Pupil</td>
<td>dilatation</td>
<td>constriction</td>
</tr>
<tr>
<td>Bronchi</td>
<td>dilatation</td>
<td>constriction</td>
</tr>
<tr>
<td>Bladder</td>
<td>relaxation</td>
<td>contraction</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Digestive activity</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
Central control of the ANS

- Hypothalamus – regulation of temperature, alimentary behavior, sexual behavior
- Reflexes from baro- and chemoreceptors – blood pressure regulation

Predominant tone

<table>
<thead>
<tr>
<th>End Organ</th>
<th>Predominant Tone</th>
<th>Effect of Ganglionic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriolar</td>
<td>Sympathetic-adrenergic</td>
<td>Vasodilatation, increased peripheral blood flow, Hypotension</td>
</tr>
<tr>
<td>Heart (SA node)</td>
<td>Parasympathetic-cholinergic</td>
<td>Tachycardia (HR &gt; 100)</td>
</tr>
<tr>
<td>Iris</td>
<td>Parasympathetic-cholinergic</td>
<td>Dilatation of the pupil</td>
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<tr>
<td>Ciliary muscle</td>
<td>Parasympathetic-cholinergic</td>
<td>Paralysis of accommodation (adjustment)</td>
</tr>
<tr>
<td>GI tract</td>
<td>Parasympathetic-cholinergic</td>
<td>Reduced tone and motility</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Parasympathetic-cholinergic</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>Sympathetic-cholinergic</td>
<td>Absence of sweating</td>
</tr>
</tbody>
</table>

Endogenous catecholamines

- Norepinephrine (NE; noradrenaline) – neurotransmitter; released from adrenal medulla
- Epinephrine (E; adrenaline) – released from adrenal medulla
- Dopamine (D)

Catecholamines – synthesis

- Tyrosine → L-DOPA → Dopamine → NOREPINEPHRINE → EPINEPHRINE
- Tyrosine hydroxylase (TH) 
- Aromatic amino acid decarboxylase (AAAD)
- Dopamine β-hydroxylase (DBH)
- Phenylethanolamine N-methyltransferase

Adrenergic receptors – substrate specificity

- α → epinephrine ≥ norepinephrine >> isoproterenol
- β → isoproterenol > epinephrine ≈ norepinephrine

Adrenergic receptors – signalling pathways

- α1 → Gs → PLC → IP3 → ↑ Ca++ 
- Ca++/CAM → active complex
- ↑ myosin kinase activation → smooth muscle contraction
- α2 → Gi → ↓ AC → ↓ cAMP
- β → Gi → ↑ AC → ↑ cAMP: 
  - ↑ myosin kinase activation → smooth muscle relaxation (β1)
  - ▼ ino-, dromo-, chrono-, bathmotropic (+) effect on the heart (β2)
  - ↑ glycogenolysis, lipolysis → ↑ plasma levels of glucose, fatty acids
Adrenergic receptors–mediated effects

- \( \alpha_1 \)
  - vasoconstriction -> ↑ peripheral resistance -> ↑ blood pressure
  - mydriasis
  - ↑ closure of the internal sphincter of the bladder
- \( \alpha_2 \)
  - ↓ NE release
  - ↓ insulin release

- \( \beta_1 \)
  - tachycardia
  - ↑ lipolysis
  - ↑ myocardial contractility
- \( \beta_2 \)
  - vasodilation
  - ↓ peripheral resistance
  - bronchodilation
  - ↑ glycogenolysis in muscle and liver
  - ↑ glucagon release
  - relaxation of uterine smooth muscle

Adrenergic agonists

- Direct-acting – directly bind to receptors and activate them
- Indirect-acting – increase the amount of norepinephrine available to stimulate adrenergic receptors
- Mixed-acting agonists

Structure–activity relationship

- Direct agonists – form hydrogen bonds with receptor
- Indirect agonists – better penetrate blood-brain barrier
- Mixed agonists – features of DA and IA
- Slight modifications in chemical structure can confer significant differences in pharmacodynamics and pharmacokinetics

Pharmacologic effects

- Mode of action – direct, indirect, mixed
- Receptor selectivity
- Relative predominance of CNS and peripheral effects
- The density of receptor population in a particular organ or organ system

Direct acting A-ergic agonists

Epinephrine

- Vasoconstriction in skin, mucosa, and viscera (\( \alpha_1 \))
- Chronotropic (+) and inotropic (+) effect -> ↑ cardiac output; ↑ cardiac oxygen demand (\( \beta_1 \))
- Vasodilation in liver and skeletal muscles (\( \beta_2 \))
- Powerful bronchodilation (\( \beta_2 \))

- PK: metabolism by COMT (postsynaptic membrane) and MAO (mitochondria of presynaptic neuron)
- PK: rapid onset; short duration of action
- PK: oral administration ineffective -> inactivation in the intestine
**Direct acting A-ergic agonists**

*Epinephrine – pharmacokinetics*
- rapid onset; short duration of action
- oral administration ineffective → inactivation in the intestine
- Given s.c., i.m., i.v.
- metabolism by COMT (postsynaptic membrane) and MAO (mitochondria of presynaptic neuron)

*Epinephrine – indications*
- bronchospasm → first choice for emergency (SC in anaphylactic shock), for chronic treatment → selective β₂-agonists
- open-angle glaucoma (topical adm.)
- local anesthetics → vasoconstriction → absorption → local effect

*Epinephrine – adverse effects*
- CNS disturbances: anxiety, tension, headache, tremor
- blood pressure → hemorrhage
- cardiac arrhythmias (esp. with digitalis)
- pulmonary edema

*Norepinephrine*
- A: intense vasoconstriction → peripheral resistance → systolic and diastolic blood pressure
- A: inotropic (+) effect; NO chronotropic (+) effect (counteracted by baroreceptor reflex)
  - if pretreated with atropine → chronotropic (+) effect
- TA: few → shock (α vascular resistance), but dopamine better (NE renal blood flow)

*Isoproterenol (isoprenaline)*
- β₁ ≈ β₂ >> α
- A: inotropic (+), chronotropic (+) effect
- A: vasodilation in skeletal muscles
- A: slight ↑ systolic BP, large ↓ diastolic BP → ↓ mean arterial BP
- A: bronchodilatation (as strong as E) ~ 1h
- PK: inhalation or parenteral administration; no MAO metabolism, little COMT metabolism
- TA: bronchodilator in asthma (acute effect), emergency heart stimulation
- ADE: like epinephrine

*Dopamine*
- D₁, D₂ : β₁ at low doses; α at high doses
- A: inotropic (+), chronotropic (+) effect
- A: at high doses → vasoconstriction (α₁)
- A: vasodilation in kidney, viscera (D receptors)
- PK: very quick metabolism into HVA
- TA: shock → IV infusion → ↑ blood pressure;
  - perfusion of kidneys (unlike epinephrine)
- ADE: like epinephrine (short due to quick metabolism)
Direct acting A-ergic agonists

**Dobutamine**
- $\beta_1$ selective
- A: inotropic (+) effect, weak chronotropic (+)
- A: weak effects on vasculature
- A: $\uparrow$ cardiac output; little effect on cardiac oxygen demand
- PK: tolerance after prolonged use
- TA: congestive heart failure
- CI: atrial fibrillation (atrioventricular conduction)
- ADE: like epinephrine

**Phenylephrine**
- $\alpha_1$ selective
- A: strong vasoconstriction
- A: reflex bradycardia after parenteral administration
- PK: not metabolized by COMT
- TA: mydriasis
- TA: nasal decongestant
- ADE: large doses $\to$ hypertensive headache, arrhythmias

**Methoxamine**
- $\alpha_1$ selective
- A: strong vasoconstriction
- A: reflex bradycardia after parenteral administration
- TA: $\Box$ hypotension in surgery (halothane)
- TA: $\Box$ arrhythmogenic as other A-ergic agonists
- TA: $\Box$ paroxysmal supraventricular tachycardias
- ADE: large doses $\to$ hypertensive headache, vomiting

**Clonidine**
- $\alpha_2$ selective
- A: vasodilation through central sympathetic vasomotor inhibition
- TA: antihypertensive; withdrawal of opiates and BZDs

**Metaproterenol, terbutaline, albuterol, fenoterol**
- $\beta_2$ selective
- A: bronchodilation
- PK: quick onset of action, relatively short duration
- TA: asthma attacks – mainly as inhalations

**Formoterol**

**Salmeterol**
- PK: slow onset of action, relatively long duration
- TA: asthma attack prevention (chronic)

Sympathomimetic drugs

- **Direct acting**
  - stimulate adrenergic receptors
  - E, NE, isoprenaline, phenylephrine

- **Indirect acting**
  - release of NE into synaptic space
  - amphetamine, tyramine

- **Mixed-action**
  - act both directly and indirectly
  - ephedrine, metaraminol
Indirect acting S-mimetic drugs

*Amphetamine, methylphenidate*

- $\uparrow$ release of NE in the synapse
- $\emptyset$ MAO
- $\emptyset$ NE reuptake
- A: CNS $\rightarrow$ euphoria, $\uparrow$ alertness (insomnia), $\downarrow$ fatigue, $\downarrow$ appetite
- A: (+) action on the heart, vasoconstriction
- PK: absorption in GI tract, metabolism in the liver, renal excretion
- TA: attention deficit syndrome
- TA: narcolepsy

ADE: physical and psychological addiction
ADE: insomnia, irritability, weakness, dizziness, tremor, hyperactive reflexes
ADE: confusion, delirium, panic states, suicidal tendencies (exacerbation of mental illness)
ADE: chronic use $\rightarrow$ amphetamine psychosis
ADE: palpitations, cardiac arrhythmias, hypertension, anginal pain, circulatory collapse
ADE: headache, chills, excessive sweating
ADE: anorexia, nausea, vomiting, abdominal cramps, diarrhea

Indirect acting S-mimetic drugs

*Tyramine*

- found in ripe cheese and wine
- if not metabolized by MAO (in MAO inhibitor – taking patients) can cause severe hypertension by $\uparrow$ NE release
- not a drug

Cocaine

- $\uparrow$ reuptake of NE, 5-HT, and DA
- TA: local anesthesia $\rightarrow$ blocks Na$^+$ channels, vasoconstriction
- ADE: few if applied topically
- ADE: cardiac arrhythmias (block of K$^+$ channels)

Sympathomimetic drugs

- Direct acting
  - stimulate adrenergic receptors
  - E, NE, isoprenaline, phenylephrine
- Indirect acting
  - $\uparrow$ release of NE into synaptic space
  - amphetamine, tyramine

Mixed-action S-mimetic drugs

*Ephedrine*

- $\uparrow$ release of NE to synapse (primary action)
- direct action on $\alpha$ and $\beta$ receptors
- PK: well absorbed from GI tract, not metabolized, well distributed in CNS, excreted by urine
- A: vasoconstriction, cardiac (+) $\rightarrow$ blood pr.
- A: slow and weak bronchodilation
- A: $\uparrow$ alertness, $\downarrow$ fatigue, insomnia
- TA: asthma (chronic tmt, rarely)
- TA: myasthenia gravis (+ AChE inhibitors)
- ADE: like epinephrine
Mixed-action S-mimetic drugs

Metaraminol
- A: (+) heart, vasoconstriction
- TA: shock, acute hypotension (IV bolus)
- TA: myasthenia gravis (+ AChE inhibitors)
- ADE: like epinephrine

Sympatholytic drugs

Direct acting
- antagonize adrenergic receptors
- α-adrenergic blockers: phenoxybenzamine, phentolamine, prazosin, terazosin, doxazosin
- β-adrenergic blockers: propranolol, atenolol, metoprolol, labetalol, timolol, ...

Indirect acting
- storage and release of NE in presynaptic vesicles
- reserpine, guanethidine

Nonselective α-adrenergic antagonists

Phenoxybenzamine
- irreversible, covalent binding to α₁ and α₂ (noncompetitive antagonism)
- reversion by resynthesis → duration 24h after single administration
- PK: biotransformation into active molecule → slow onset of action
- A: vasodilation → reflex tachycardia (no effect on blood pressure)
- TA: pheochromocytoma (before surgery to prevent hypertensive crisis; chronic treatment)
- TA: Raynaud’s disease
- TA: autonomic hyperreflexia in paraplegics
- ADE: postural hypotension, nasal stuffiness, nausea, vomiting, Ø ejaculation
- ADE: baroreceptor reflex tachycardia → CI in patients with decreased coronary perfusion

Phentolamine
- competitive α₁ and α₂ blocker
- PK: duration of action ~4h
- A: vasodilation → reflex tachycardia
- TA: pheochromocytoma diagnostics
- ADE: postural hypotension, nasal stuffiness, arrhythmias
- ADE: baroreceptor reflex tachycardia → CI in patients with decreased coronary perfusion

α₁-adrenergic antagonists

Prazosin, terazosin, doxazosin
- competitive α₁ blockers
- PK: metabolism, excretion by urine (doxazosin → feces)
- A: vasodilation, but no reflex tachycardia, changes in renal perfusion, and glomerular filtration
- TA: antihypertensive (no tolerance)
- TA: symptomatic benign prostatic hypertrophy (better urine flow by smooth muscle tone)
- ADE: postural hypotension, esp. first-dose effect (! give at bedtime, smaller dose)
- ADE: nasal congestion, headache, drowsiness
- ADE: Na+ and fluid retention
- IN: diuretics → hypotension (often used together)

β-adrenergic antagonists - features

- nonselective vs. β₁-selective (cardioselective)
- intrinsic activity vs. no intrinsic activity
- lipophilic (CNS penetration) vs. hydrophilic
- additional α-adrenergic blockade
- pharmacokinetics
**β-adrenergic antagonists**

- TA: antihypertensive
- TA: angina
- TA: arrhythmias
- TA: myocardial infarction
- TA: glaucoma
- TA: migraine prophylaxis

**β-adrenergic antagonists**

*Propranolol*

- nonselective → prototype drug
- A: (+) chronotropic and inotropic effect → ↓ cardiac output → ↓ cardiac $O_2$ demand
- A: peripheral vasodilation
- A: ↓ diastolic and systolic pressure
- no postural hypotension
- A: bronchoconstriction
- A: ↑ Na$^+$ and fluid retention (used in combination with diuretics)
- A: glycogenolysis and glucagon secretion → hypoglycemia (at the same time attenuates physiological response → risk of coma in insulin-dependent diabetics)

**β-adrenergic antagonists**

*Propranolol*

- TA: hypertension
- TA: migraine (chronic treatment, for attack more commonly sumatripan)
- TA: (mostly timolol) glaucoma (↑ secretion of aqueous humor)
- TA: hyperthyroidism (chronic and acute)
- TA: angina pectoris (↑ $O_2$ demand of the heart; chronic use)
- TA: myocardial infarction (prophylaxis; cardioprotective effect)
- TA: CHF (more often labetalol, carvedilol)
- TA: stress before performance

**β-adrenergic antagonists**

*Propranolol*

- ADE: asthma attack in susceptible patients (COPD, asthma → relative CI)
- !: do not stop β-blocker therapy abruptly → may cause arrhythmias, angina, hypertension (up-regulation of receptors)
- ADE: sexual impairment, coldness of extremities
- IN: cimetidine, furosemide, chlorpromazine → ↓ metabolism of propranolol → ↓ hypotension
- IN: barbiturates, phenytoin, rifampin → ↓ metabolism → ↓ hypotension

**β-adrenergic antagonists**

*Nadolol*

- more potent than *propranolol*
- longer duration of action

**Cardioselective β-adrenergic antagonists**

*Acebutolol, atenolol, metoprolol, esmolol*

- much higher doses required for bronchoconstriction → useful for asthmatics
- little effect on carbohydrate metabolism → useful for diabetics
- no coldness of extremities

*Esmolol*

- short duration of action → IV in surgery and diagnostic procedures
**β-blockers with intrinsic sympathomimetic activity**

*Acebutolol, pindolol*

- ISA → ability to weakly stimulate β receptors → partial agonists
  - decreased effect on heart
  - decreased effect on lipid and CH metabolism
- TA: hypertension in patients with moderate bradycardia and diabetics


**β-blockers with α₁-blocking properties**

*Labetalol, carvedilol*

- decrease peripheral resistance
- TA: hypertension (including pregnancy-induced hypertension)
- TA: CHF (cardioprotective effect → carvedilol)
- ADE: orthostatic hypotension, dizziness

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**Indirect acting sympatholytic drugs**

*Reserpine*

- alkaloid of *rauwolfia*
- blocker of Mg²⁺/ATP-dependent biogenic amines transporter → Ø of NE, 5-HT and DA transport into synaptic vesicles →
  - MAO activity → NE depletion → impairment of adrenergic signalling
- TA: hypertension → slow onset and long duration of action (for many days)

**Indirect acting sympatholytic drugs**

*Guanethidine, guanadrel*

- Ø NE release
- displacement of NE from storage vesicles (false neurotransmitter) → transient hypertension
- gradual depletion of NE, except CNS
- TA: rarely hypertension
- ADE: orthostatic hypotension (less frequent with guanadrel), male impotence, diarrhea (less frequent with guanadrel)
- ADE: hypertensive crises in supersensitive patients (pheochromocytoma)