Sympatholytics

2019

Laszlo KÖLES
koles.laszlo@med.semmelweis-univ.hu

semmelweis.hu/pharmacology

Sympatholytics

1. Presynaptic stimulation
2. Presynaptic inhibition

---

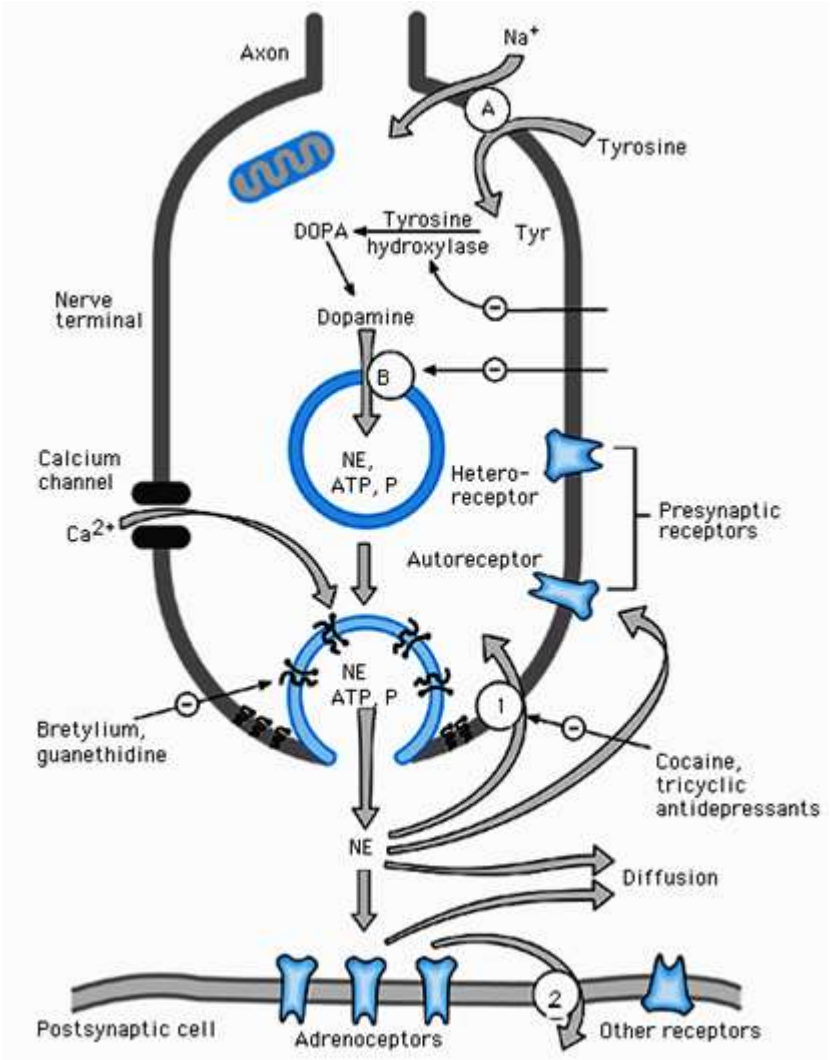
3. Postsynaptic stimulation
4. Postsynaptic inhibition

Presynaptic inhibition

- α-Methyltyrosine (methyrosine) – blocks the tyrosine hydroxylase enzyme
- *Reserpine* – prevents transmitter storage
- Tetrodotoxin, saxitoxin, local anaesthetics (blockade of voltage sensitive Na^+ channels)

- ω-Conotoxin – blocks calcium channels

- *Activation of inhibitory presynaptic α_2 autoreceptors (clonidine, methyldopa)*
- Activation of presynaptic inhibitory heteroreceptors (M_2, D_2, H_3, adenosine, neuropeptide Y, EP_3 prostaglandine, μ, κ, δ opioid receptors)
- *Adrenergic neuron blockers* (guanethidin, bretylium) – inhibit transmitter release
- 6-OH-dopamine – destroys the nerve terminal



Postsynaptic inhibition

α and/or β receptor blockers

Drugs decreasing sympathetic activity

- β receptor antagonists
- α receptor antagonists
- α_2 receptor agonists
- adrenergic neuron blockers
- reserpine
- methyltyrosine

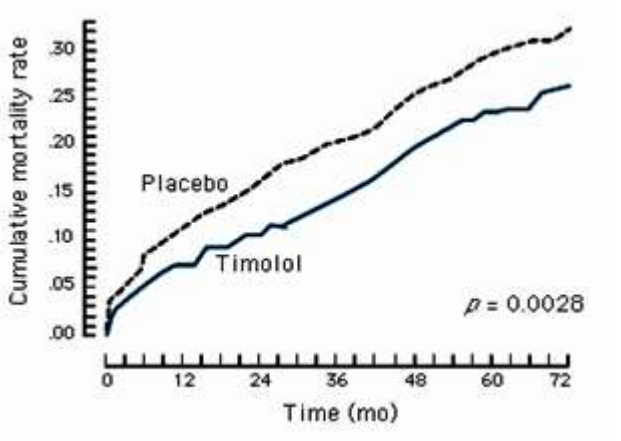
β receptor antagonists

Major consequences of β receptor blockade:

- **negative chronotropic and inotropic actions on the heart (β_1)**
- **decreased blood pressure (in part due to the inhibition of renin release - β_1)**
- **bronchoconstriction (β_2)**
- **local vasoconstriction – end-arteries, and diseased peripheral vessels (β_2)**
- **decreased aqueous humor production in the eye**
- **impaired recovery from hypoglycemia (β_2)**
- **increased plasma concentrations of VLDL and decreased concentrations of HDL**

Potential indications of β blockers

- **hypertension**
- **angina pectoris** (exc.: vasospastic)
- **tachyarrhythmias** (supraventricular)
- **congestive heart failure** (long-term use prolongs survival – acutely they may worsen heart failure!)
- **after myocardial infarction** (secondary prophylaxis)
- **hypertrophic obstructive cardiomyopathy**
- **hyperthyreoidism, pheochromocytom**



- **portal hypertension, esophagus varices** (reduce risk of bleeding)
- **glaucoma** (eye drop)
- **somatic manifestations of anxiety (performance anxiety)**
- **migraine headache** (prevention: propranolol, pindolol – as 5-HT_2-antagonists?)
- **essential tremor, proliferating hemangiomas in newborns** (propranolol)

Adverse effects of β blockers

- **bronchoconstriction (worsening of bronchial asthma)**
- **cardiac decompensation -** if cardiac output is critically dependent on increased sympathetic drive (interaction with other negative inotropic drugs is dangerous, combination is contraindicated)
- **bradycardia, decreased AV-conduction**
- **cold extremities, worsening of peripheral vascular diseases**
- **uterus contractions in pregnancy**
- **hypoglycaemia**
- **hyperlipidemia**
- **contribution to increased potassium level**
- **sleep disturbances (nightmares), mental depression**
- **abrupt discontinuation of therapy after chronic use – increased risk of ischemic heart disease**

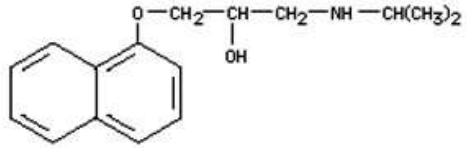
Major differences among the β blockers

- selectivity
- intrinsic avtivity (partial agonistic activity - ISA)
- lipid solubility
- additional actions on ion channels
- additional vasodilatory action
- half-life

Selectivity of the β blockers

Nonselective β blockers

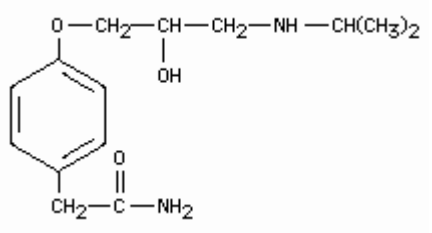
- propranolol



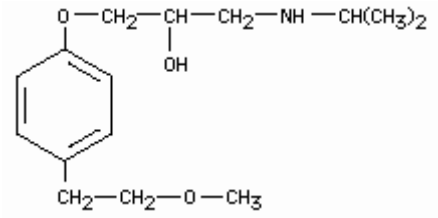
- pindolol
- oxprenolol
- alprenolol
- nadolol
- carteolol
- levobunolol
- penbutolol
- timolol
- sotalol (+K-ch-bl.)
- carvedilol (+α_1-bl.)
- labetalol (+α_1-bl.)

β_1 selective (cardioselective) blockers (2nd generation)

- atenolol



- metoprolol



- bisoprolol
- esmolol
- betaxolol
- nebivolol (+ NO)
- celiprolol
- acebutolol

β_1 selective blockers cause less bronchoconstriction, hypoglycaemia and peripheral circulatory problems.

CAUTION: β_1 selectivity is never absolute!

Partial agonistic (ISA) activity of the β blockers

β blockers with ISA (intrinsic sympathomimetic activity)

- **pindolol**
- **acebutolol**
- **oxprenolol**
- **alprenolol**
- **celiprolol (ISA at β_2 receptors)**

- **β blockers with ISA are less likely to cause bradycardia and abnormalities in plasma lipids.**
- **However, the clinical significance of the ISA is not clear.**
- **Celiprolol may cause less bronchoconstriction.**

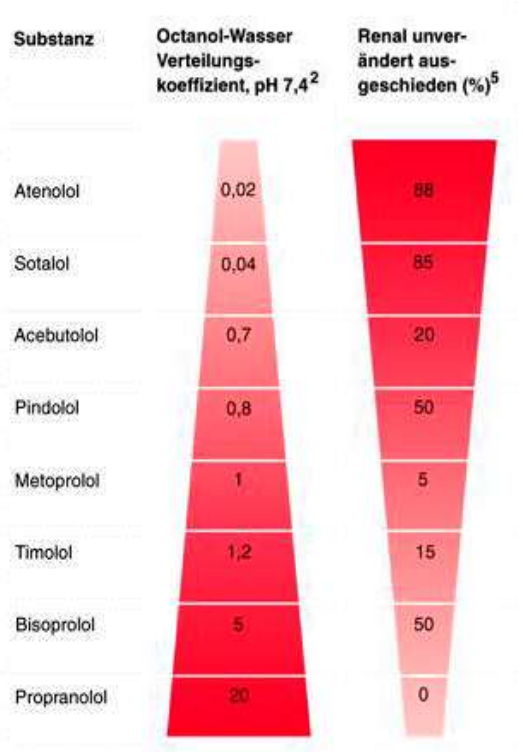
Lipid solubility of the β blockers

β blockers with the highest lipid solubility

- **propranolol**
- **nebivolol**

lowest lipid solubility

- **atenolol**
- **sotalol**
- **acebutolol**



- **Pharmacokinetics**

lipophilic drugs – must be metabolized in the liver
hydrophilic drugs – can be excreted unchaged
(importance of kidney/liver diseases in elimination)

- **Only lipid soluble β blockers can be used for CNS indications (e.g. tremor)**

- **Drugs with low lipid solubility cause less CNS adverse effects (e.g. nightmares, mental depression).**

Action of the β blockers on ion channels

- **Some β blockers possess weak local anesthetic (Na^+ channel blocking) effect**
  - **propranolol**
  - **metoprolol**
  - **pindolol**
  - **acebutolol**

It is unlikely that this effect is important in case of systemic use.

Eye drops mustn't possess this action - timolol doesn't block Na channels - that is one reason why it is used for glaucoma.

- **Sotalol blocks K^+ channels – a class II + III. antiarrhythmic drug**

β blockers with additional vasodilatory action (3rd generation)

- additional blockade of α_1 receptors
  - labetalol, carvedilol
    - racemic mixtures: one isomer is a selective α_1 blocker, another isomer is a β blocker
  - indications: hypertension, congestive heart failure, stable angina
    - synergistic antihypertensive actions without tachycardia
    - less (no) changes in lipid profile
- NO-mediated vasodilation
  - nebivolol
    - antihypertensive indication
    - racemic mixture: one isomer is a selective β_1 blocker, another isomer induces NO release

Half-life of the β blockers

- **Ultrashort-acting**
  - **esmolol**
    - **β_1 selective blocker, 10 min. half-life**
    - **It contains an ester linkage broken down by esterases**
    - **It is much safer in critically ill patients who require β blocker therapy (e.g. supraventricular arrhythmias, perioperative hypertension)**

- **β blockers with long half-life (more than 10 hours)**
  - **nadolol (16-20 h)**
  - **betaxolol (14-20 h)**
  - **bisoprolol (10-12 h)**
  - **nebivolol (~10 h)**

α receptor antagonists

- **Selective α_1 receptor antagonists**
- **Non-selective α receptor antagonists**
  - **Synthetic compounds**
    - **phenoxybenzamine**
    - **phentolamine**
    - **tolazoline**
  - **Ergot alkaloids**

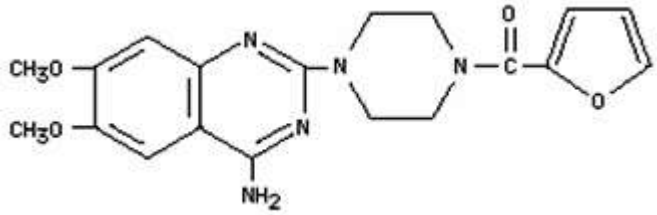
Potential therapeutic interest – smooth muscle relaxation (blood vessels, sphincters) - antihypertensive action, treatment of peripheral vascular diseases, treatment of prostate hyperplasia)

Selective α_1 receptor antagonists cause less tachycardia than the non-selective α-blockers.

Selective α_1 receptor antagonists I.

- their major advantage over the non-selective α-blockers:

less tachycardia



Prazosin

- clinical indications:
  - chronic treatment of mild to moderate hypertension
  - benign prostate hyperplasia
- orally active, short half-life (3x/day)
- side effects
  - first-dose phenomenon (in the beginning of the therapy - severe postural hypotension and syncope)

    to avoid: treatment should be started at bedtime, with a low dose
  - additional side effects are mild and nonspecific: dizziness, palpitations, headache

α_1 blockers are not first line antihypertensive agents, but they can have important advantages: they can be given in case of hyperlipidaemias and diabetes

Selective α_1 receptor antagonists II.

Terazosin and doxazosin

- prazosin-like drugs with longer half-life
- indications: hypertension, benign prostate hyperplasia

Alfuzosin, tamsulozin and silodosin

- Tamsulozin and silodosin are selective blockers of α_{1A} receptor, which is expressed mainly in the urinary tract ?
- used for the treatment of benign prostate hyperplasia with less cardiovascular actions ?

Urapidil

- α_1 antagonist, with weak α_2 agonist, 5-HT_{1A} agonist and β antagonist actions
- antihypertensive agent mostly for hypertensive crisis

Labetalol, carvedilol

- α_1 and β antagonists

Non-selective synthetic α blockers

Phenoxybenzamine

- **irreversible α blocker, long duration of blockade (14-48 hours)**
- **indication: treatment of pheochromocytoma**

Phentolamine and tolazoline

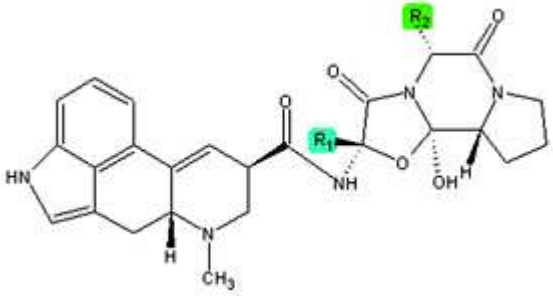
- **reversible α blockers**
- **phentolamine is strong, used in pheochromocytoma (treatment and diagnosis)**
- **tolazoline is a weak blocker, used as a vasodilator in peripheral vascular diseases (very limited indications)**

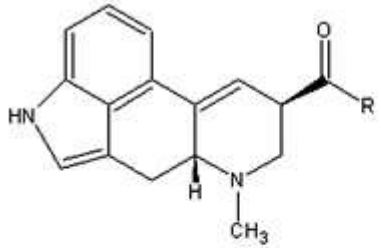
Ergot alkaloids

• **produced by Claviceps purpurea, a fungus that infects grain (esp. rye)**




• **lysergic acid derivatives**





R = OH	Lysergsäure
R = NH_2	Lysergsäureamid
R = $N(C_2H_5)_2$	Lysergsäurediethylamid (LSD)
R = $NHCH(CH_3)CH_2OH$	Ergometrin

• **two major families of natural compounds:**
amine alkaloids (ergometrine)
peptide alkaloids (ergotamine, ergocryptine, ergocrystine, ergocornine)

• **agonist, partial agonist or antagonist actions on several receptors, especially: α, 5-HT, D**

Ergot alkaloids

- main actions
  - vasoconstriction, vasospasm,
  - powerful stimulation of the pregnant uterus,
  - CNS actions

- semisynthetic or synthetic, structurally related drugs
  - dihydro-derivatives: more selective for α receptors (antagonists)
  - methysergid: more selective for 5-HT receptors (antagonist)
  - bromocryptine, cabergoline: more selective for D receptors (agonist)
  - lysergic acid diethylamide (LSD): partial agonist at 5-HT receptors in CNS

Ergot alkaloids

- **therapeutic indications (ergot alkaloids)**
  - **postpartum hemorrhage (ergometrine, ergotamine);**
    NEVER before delivery!
  - **migraine therapy (ergotamine)**

- **therapeutic indications (ergot derivatives)**
  - **hyperprolactinemia (bromocryptine, cabergoline)**
  - **Parkinson's disease (bromocryptine, cabergoline)**
  - **migraine therapy (dihydroergotamine, methysergide)**
  - **peripheral vascular diseases (dihydro-derivatives)**

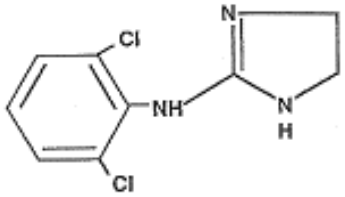
- **possible adverse effects**
  - **nausea, vomiting, diarrhea, prolonged vasospasm, CNS disturbances**

Drugs with α blocking side effect

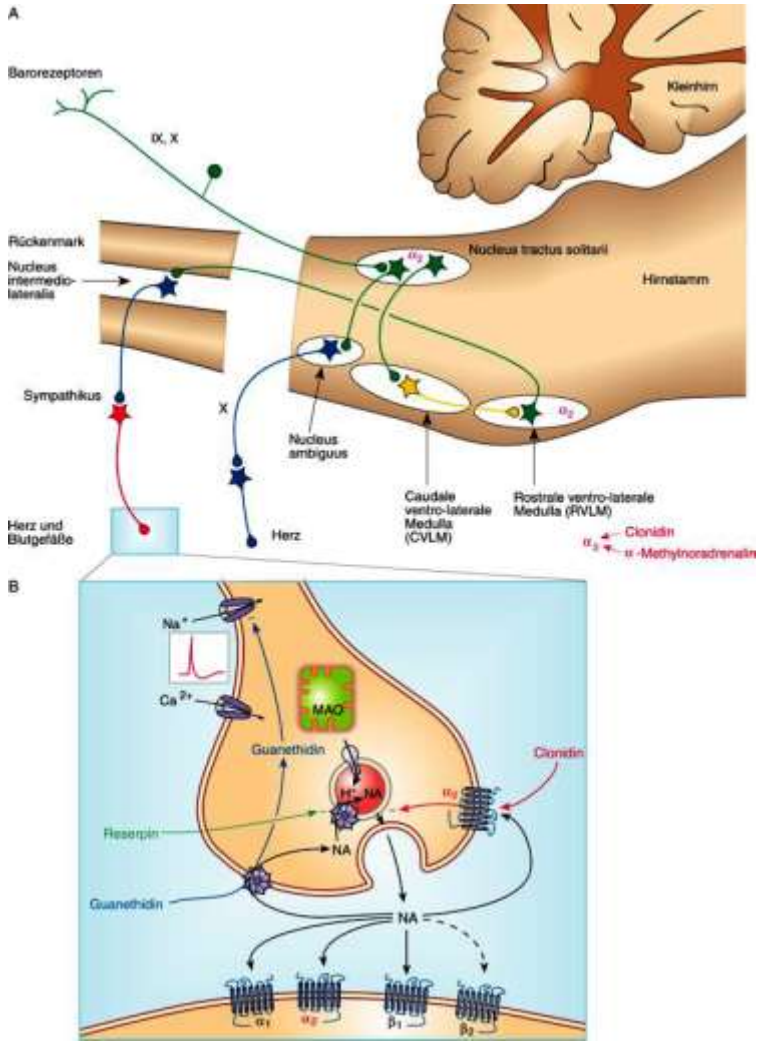
- several (mostly tricyclic) antidepressants (eg. amitriptyline, imipramine)
- several antipsychotics (eg. phenothiazines - chlorpromazine)
  - may cause hypotension, and reflex tachycardia
- quinidine
  - antiarrhythmic drug, too rapid iv. injection may cause blood pressure fall

α_2 receptor agonists

Clonidine



- **imidazoline derivative,**
  originally was tested
  as a nasal decongestant
- **mechanism of action:**
  - **enhances the negative feed back**
    stimulates peripheral presynaptic α_2 receptors at noradrenergic nerve terminals
  - **stimulates central postsynaptic α_2 receptors located in the medulla involved in blood pressure regulation (decreased sympathetic and icreased vagal activity)**
  - **stimulates I_1 imidazoline receptors located in the medulla, which is considered to be the final common pathway for sympathetic vasomotor outflow**



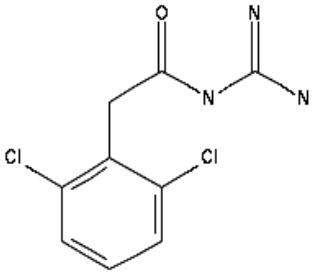
α_2 receptor agonists

Clonidine

- potential indications (clonidine or derivatives):
  - treatment of mild to moderate hypertension (mostly in acute cases)
  - alcohol and opiate withdrawal; cessation of smoking;
  - perianesthetic mediaction
  - sedation and analgesia in intensive care, adjuvant analgesic (epidural, intrathecal)
  - diarrhea in diabetics
  - ADHD
  - glaucoma
- adverse effects: sedation, dry mouth, bradycardia, orthostatic hypotension (rare), mental depression (rare), too rapid iv. administration might be resulted in a transient systemic vasoconstriction
- abrupt withdrawal can cause hypertensive crisis and increased sympathetic activity, if the drug must be stopped, this should be done gradually

α_2 receptor agonists

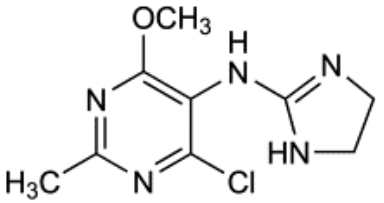
Guanabenz and guanfacine



- centrally acting antihypertensive drugs, with clonidine-like action, but different structure (they are not imidazoline-derivatives)

Moxonidine and rilmenidine

- newer imidazoline-derivatives, with clonidine-like structure
- bind more selectively to I_1 receptors ?
- less affinity to α_2 receptors ?
- indication: treatment of hypertension

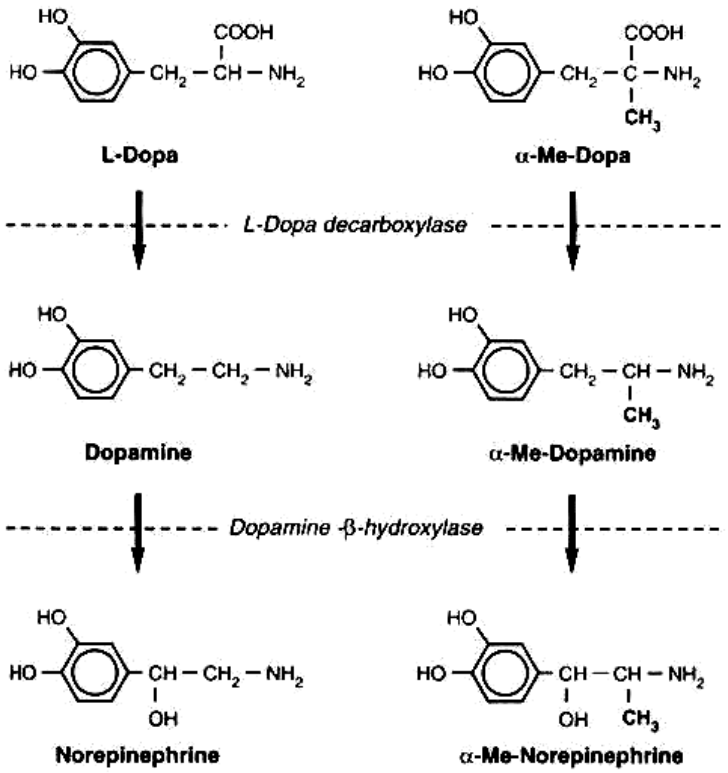


- sedation and dry mouth occurs less frequently than with clonidine ?

α_2 receptor agonists

Methyldopa

- **mechanism of action**
  - **false substrate of the DOPA-decarboxylase → „false transmitter”**
  - **methylnorepinephrine is an α_2 agonist**
  - **slow onset of action**



- **indication: treatment of mild to moderate hypertension, hypertension in pregnancy**
- **adverse effects:**
  - **like clonidine + hyperprolactinaemia, extrapyramidal symptoms, mental depression, positive Coombs test, immune haemolysis, liver toxicity**

α_2 receptor agonists

Further drugs with special indications:

- **dexmedetomidine – sedation (perianesthetic medication, intensive care)**
- **tizanidine – centrally acting skeletal muscle relaxant**
- **nasal decongestant can have mixed α receptorial actions (topical) – previuos lecture**
- **apraclonidine, brimonidine – glaucoma (topical)**

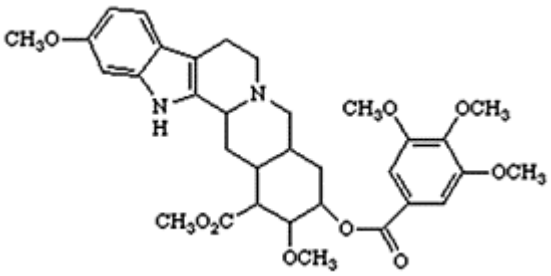
Adrenergic neuron blockers

Guanethidine and debrisoquine

- inhibit norepinephrine release from sympathetic nerve terminals
- antihypertensive indication (limited use because of side effects)
- adverse effects: postural hypotension, diarrhea, impaired ejaculation, Na and water retention, nasal stuffiness

Bretylium

- acts like guanethidine in noradrenergic nerve terminals
- blocks potassium channels on the heart (antiarrhythmic action)
- antiarrhythmic indication (i.v. - in emergency settings - during resuscitation from ventricular fibrillation after lidocaine and cardioversion)
- adverse effects: initial release of norepinephrine can precipitate ventricular arrhythmias, sympatholytic action (e.g. postural hypotension)



Reserpine

- blocks the uptake of biogenic amines into the synaptic vesicles, they are not stored in the vesicles, broken down by MAO
- enters the brain – depletion of norepinephrine, dopamine, serotonine in both central and peripheral neurons
- theoretic (historical) indications
  - treatment of hypertension (peripheral norepinephrine depletion)
  - treatment of psychosis (dopamine depletion in the mesolimbic system)
- main side effects
  - sympatholytic actions (diarrhea, postural hypotension – norepinephrine depletion in the periphery)
  - mental depression (norepinephrine and serotonine depletion in CNS)
  - Parkinsonism (dopamine depletion in the nigrostiatal system)
- **Tetrabenazine (similar mechanism of action) – Huntington, Tourette**

Methyltyrosine

- **blocks the norepinephrine synthesis (rate limiting step, catalyzed by tyrosine hydroxylase)**
- **may act synergistically with phenoxybenzamine in the treatment of pheochromocytoma – that is the only indication (inoperable or metastatic pheochromocytoma)**

St. Anthony's fire: chronic ergot poisoning

- poisoning by ergot-contaminated flour - like epidemics
  - main symptoms:
    - hallucinations, convulsions (Ergotismus convulsivus)
    - prolonged vasospasm, gangrene, burning pain (Ergotismus gangrenosus, Ignis sacer)
    - abortion in pregnancy

St. Anthony (251-356, Egypt), the abbot

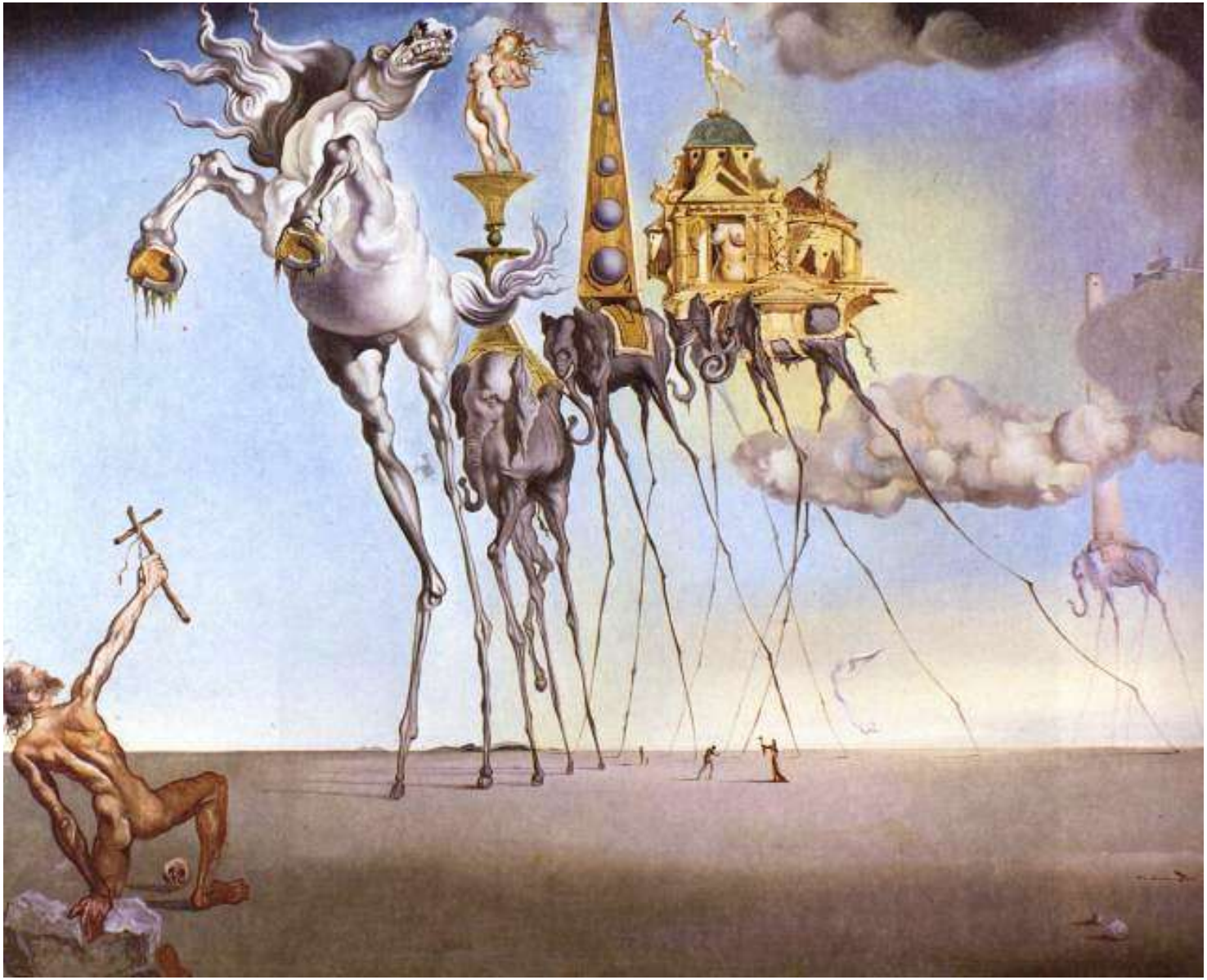
- 857 – Xanten (Rhine Valley, NW Germany) first documented „epidemy"
- 922 severe „epidemy" in Europe – ~40000 deaths
- 1692 – Salem ?
- 1926-27 Sowiet Union (~11000 deaths);
- 1951 Pont-St. Esprit (last „epidemy" in Eurpe, 5-7 deaths);
- 2001 – Ethiopia

Pieter Bruegel: The Beggars 1568

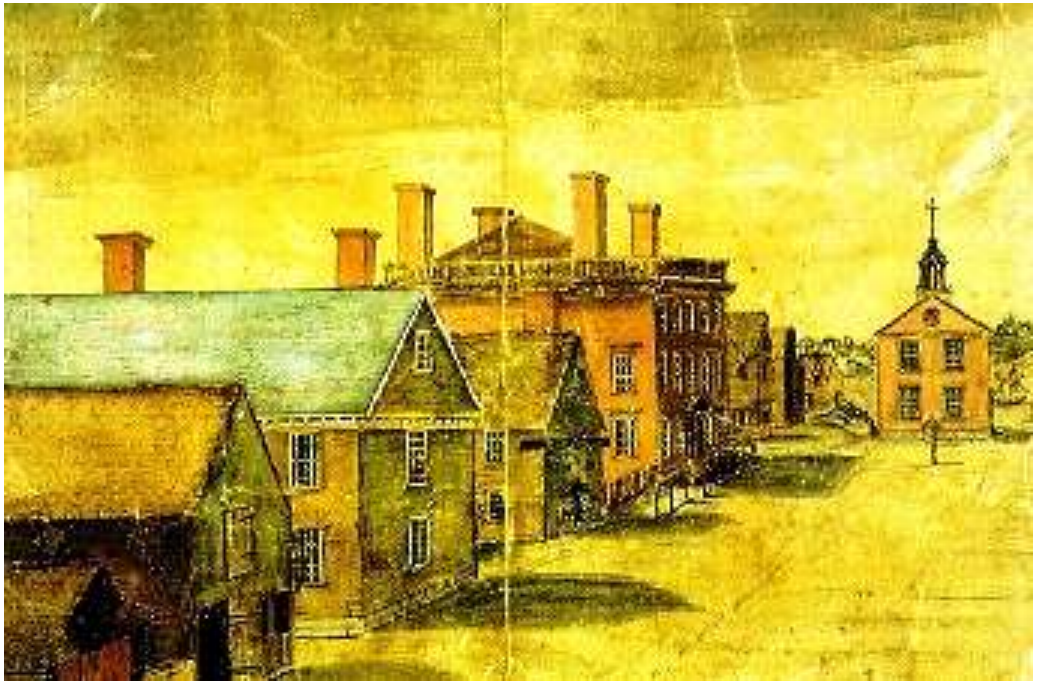
Matthias Grünewald

The Temptation of St Anthony

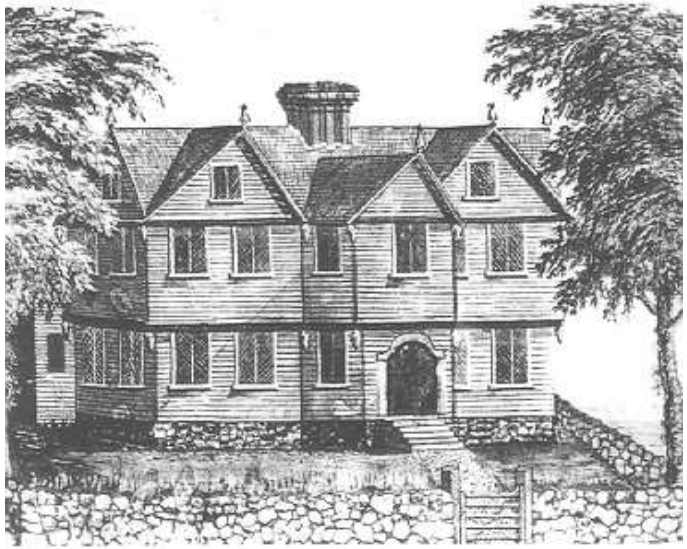
(ca. 1512-16; A panel of the Isenheim Alterpiece)



Salvador Dali The Temptation of Saint Anthony 1946



Salem (Massachusetts) – 1692



The Witch House, 310 Essex Street

T.H. Matteson Examination of a Witch 1853.
(Witches' mark indicated that an individual was a witch)