Pharmacology of the adrenergic system

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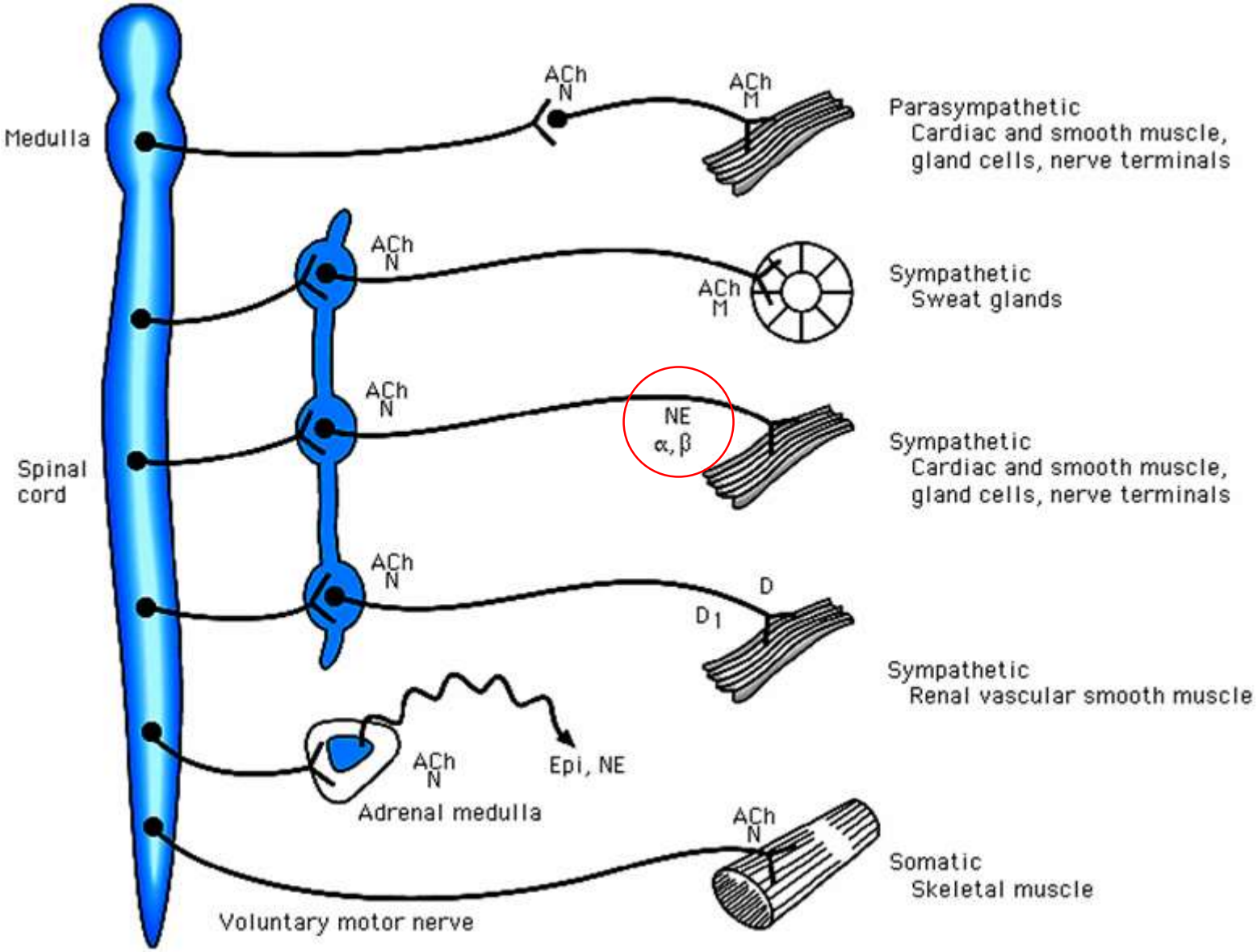
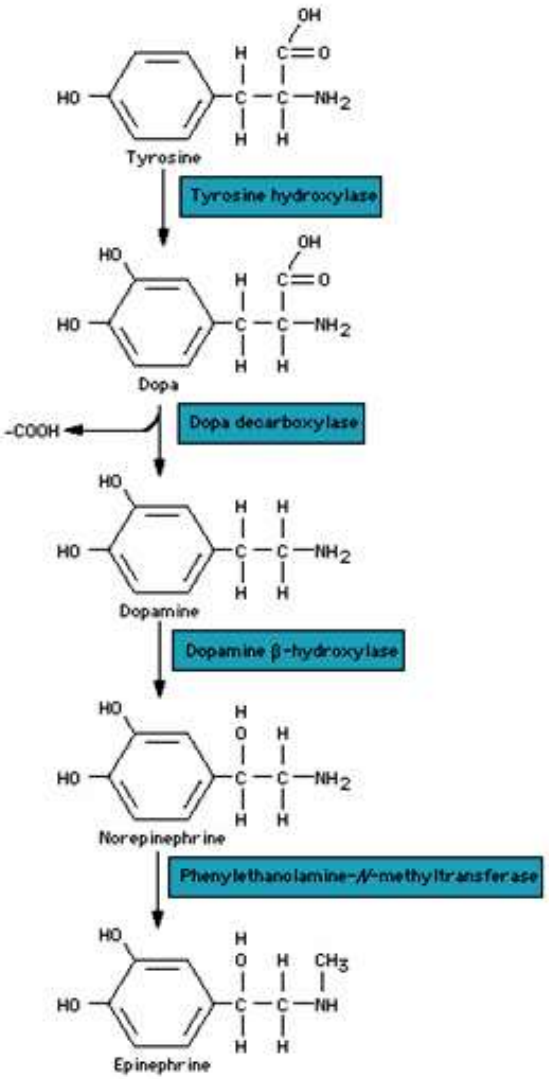
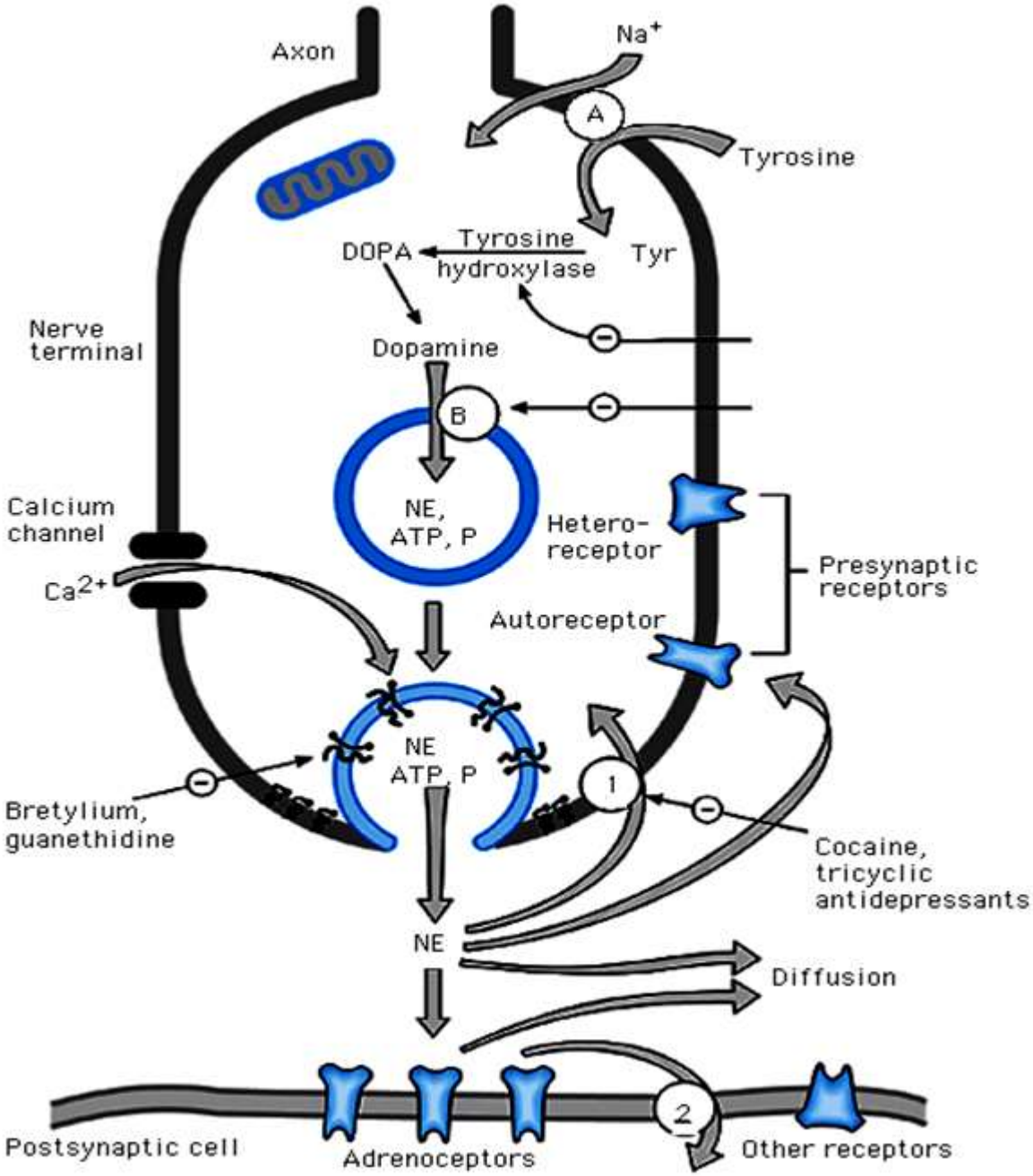


Neurotransmitters of autonomic and somatic motor nerves

The adrenergic nerve terminal





Possibilities to influence the adrenergic transmission

1. Presynaptic stimulation
2. Presynaptic inhibition

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3. Postsynaptic stimulation
4. Postsynaptic inhibition

Sympathomimetics

1. Presynaptic stimulation
2. Presynaptic inhibition

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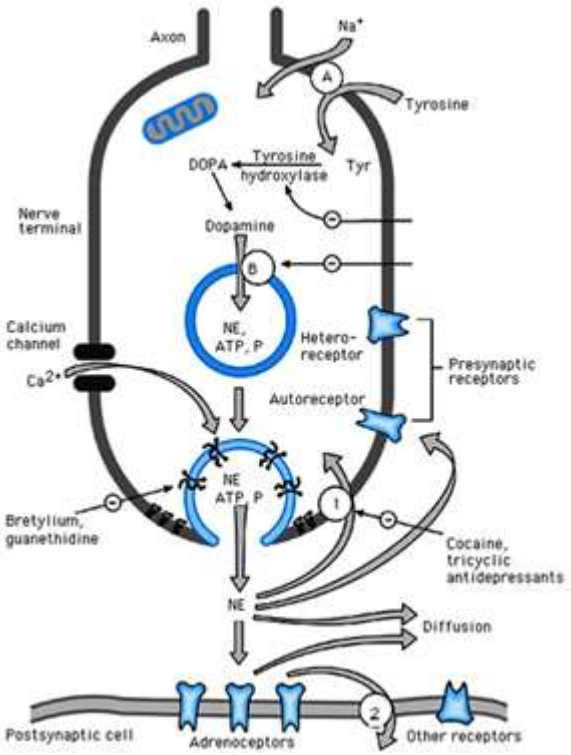
3. Postsynaptic stimulation
4. Postsynaptic inhibition

Presynaptic stimulation



- **Synthesis: Precursor substance – levodopa**
- **Release**
  - **Depolarization: 4-aminopyridine (*Fampridine*) (K^+ channel blocker)**
  - **Increased Ca^{2+} concentration**
  - **Latrotoxin - causes explosive release of norepinephrine**

  - **Presynaptic receptors**
    - **Activation of stimulatory presynaptic β_2 receptors**
    - **Inhibition of inhibitory presynaptic α_2 autoreceptors (yohimbine, *mianserin*)**
    - **Activation of presynaptic stimulatory heteroreceptors (e.g. AT_1 receptors)**
  - ***Indirectly acting sympathomimetics*** **(tyramine, ephedrine, amphetamine) – promote transmitter release**
- ***Reuptake inhibitors*** **(cocaine, tricyclic antidepressants: amitryptyline, desipramine)**
- ***MAO inhibitors*** **(tranylcypromine, selegiline, moclobemid)**

Postsynaptic stimulation

Directly acting sympathomimetics

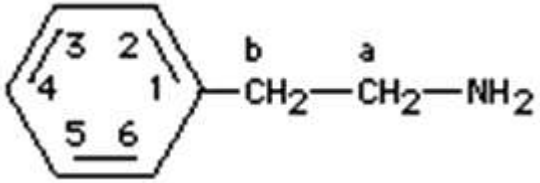
(α and/or β receptor agonists)

Sympathomimetics

- Catecholamines
- β_1 receptor agonists
- (Peripheral D receptor agonists)
- β_2 receptor agonists
- α receptor agonists
- Indirectly acting sympathomimetics
- (Reuptake inhibitors and MAO inhibitors)

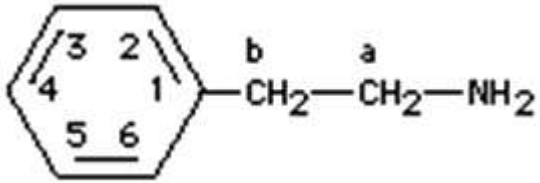
Structure-activity relationships of sympathomimetic agents I.

Sympathomimetics are phenylethylamine (the most drugs) or imidazoline (some α agonists) derivatives



- **Substitutions on the benzene ring**
  - **-OH substitutions (esp. at 3rd and 4th position) increase the potency, but decrease the resorption and the distribution of drugs (↓ lipophility)**
    - ***catecholamines* (3,4-OH substituents)**
      - **are the most potent sympathomimetics (good pharmacodynamics),**
      - **with bad pharmacokinetics: poor absorption, bad distribution, and short duration of action – they must be given parenterally for systemic use, and they don't penetrate the blood-brain barrier**
      - **catecholamines are substrates of COMT, it further ↓ their bioavailability**

Structure-activity relationships of sympathomimetic agents II.

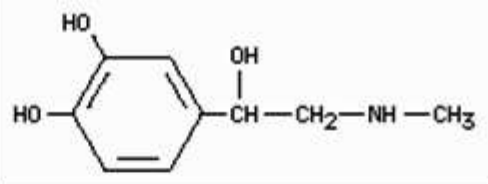


- **Substitutions on the benzene ring**
  - ***3-OH, 4-OH or 3,5-OH derivatives***
    - **are weaker sympathomimetics than the catecholamines but they have better (but still not optimal) pharmacokinetics**
    - **they are not substrates of COMT, but still polar drugs – they may be given even orally with low bioavailability**
  - ***non substituted derivatives***
    - **very weak direct or only indirect (norepinephrine-releasing) sympathomimetic action (bad pharmacodynamics), but a**
    - **very good pharmacokinetics: good absorption and penetration through the blood-brain barrier (CNS effects!)**
- **Substitution on the amino group**
  - **methylation increases the relative potency on β_2 receptors (eg. epinephrine/norepinephrine).**
  - **large substitution on amino groups increases significantly the β_2 receptor affinity**

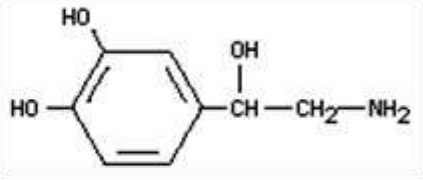
Catecholamines

Catecholamines are the strongest sympathomimetics, but they can't be given orally, they have a short duration of action, and they don't penetrate the blood-brain barrier.

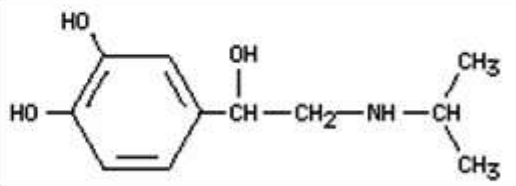
- **Epinephrine (Adrenalin)**



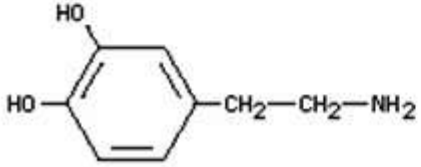
- **Norepinephrine (Noradrenalin)**



- **Isoproterenol (Isoprenaline)**



- **Dopamine**



- **Dobutamine, Dopexamine**

Epinephrine

- Epinephrine activates each adrenergic receptor types.
- It can cause both vasodilation (β_2) and vasoconstriction (α_1), the receptor distribution determines its action on the organs.
- The mean arterial pressure is not changed dramatically.
- It has positive inotropic and chronotropic actions on the heart.
- It causes bronchodilation.
- Indications:
  - anaphylactic shock (0.3-0.5 mg sc. or im.)
  - emergency management of complete heart block and cardiac arrest (1 mg iv.)
  - asthmatic state
  - inhaled epinephrine – treatment of croup (subglottic laryngitis)
  - reduction of regional blood flow
    - local anaesthesia (1:200,000 - combination with local anaesthetics)
    - facial, nasopharyngeal, oral surgery

Norepinephrine

- Norepinephrine activates α and β_1 receptors, but it has a little effect on β_2 receptors.
- It causes vasoconstriction, and elevates the blood pressure.
- Compensatory vagal reflexes can overcome its direct positive chronotropic action on the heart. (It may cause bradycardia in vivo.)
- Indications:
  - neurogenic shock (early phase), septic shock, cardiogenic shock (pressor effect in case of hypotensive emergency)
  - locally to reduce blood flow (diffuse bleeding; combination with local anaesthetics)

Isoprenaline

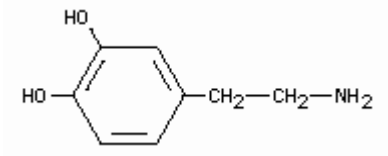
- **Isoprenaline is a potent and selective β receptor agonist (both β_1 and β_2).**
- **It has positive inotropic and chronotropic actions on the heart.**
- **It causes vasodilation, decreases the diastolic and the mean arterial pressure.**
- **It causes bronchodilation.**
- **Possible indications:**
  - **Bradycardia, heart blocks (AV)**

Dopamine

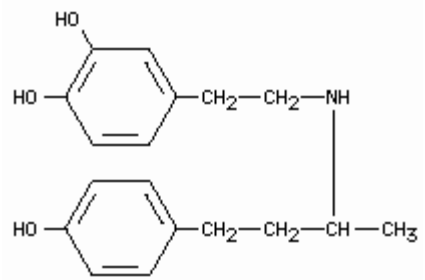
- In low dose (0.5-2.5 µg/kg/min) it activates D_1 dopamine receptors selectively (vasodilation – increased renal blood flow)
- In addition, in medium dose (2.5-5 µg/kg/min) it activates β_1 adrenergic receptors (positive inotropic action on the heart)
- In high dose (more than 5 µg/kg/min) it looses the selectivity, acts like epinephrine.
- Indication: cardiogenic shock (low to medium dose)
- Problems: tachycardia, tolerance, bad pharmacokinetics

Selective β_1 receptor agonists

- **Dopamine** in medium dose (2.5-5 µg/kg/min)



- **Dobutamine**



  - it causes less tachycardia compared with dopamine

- Ibopamine, Prenalterol

- **Indications: - cardiogenic shock**

  - in case of chronic heart failure their usefulness is limited

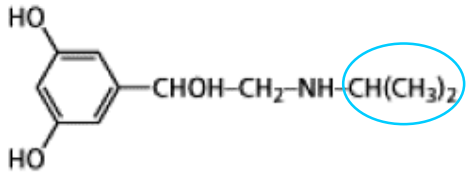
- **Adverse effects: tachycardia**

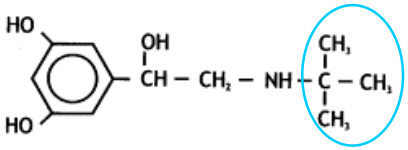
Peripheral D receptor agonists

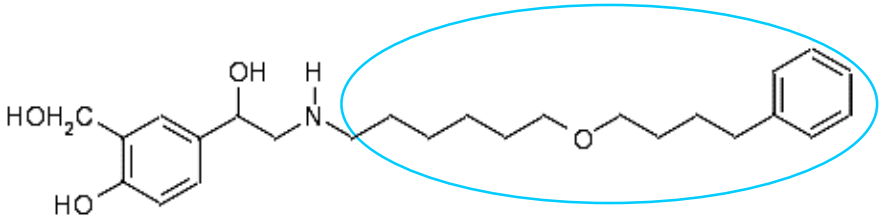
- **Dopamine in low dose**
  - **dilation of mesenterial and renal blood vessels**
    - **it might be a useful action in shock to save the kidneys**
    - **the therapeutic importance is questionable**
- **Fenoldopam**
  - **peripheral vasodilation in mesenterial vascular bed**
    - **administered i.v. for the treatment of severe hypertension**
- **Dopexamin**
  - **D, β_2 (β_1) agonist, (reuptake inhibitor)**

Selective β_2 receptor agonists

- **Main actions and indications**
  - **bronchodilation (treatment of bronchial asthma and COPD)**
    - **SABA:** salbutamol, terbutalin, fenoterol, levosalbutamol (levalbuterol)
    - **LABA:** salmeterol, formoterol, clenbuterol, bambuterol, procaterol indacaterol, olodaterol, vilanterol
  - **relaxation of the pregnant uterus** (terbutalin, ritodrin)
- potential **adverse effects**: tremor, tachycardia, hyperglycaemia, hypokalemia
- no absolute selectivity! – if possible – topical use (bronchial asthma)

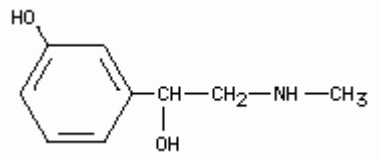






α receptor agonists I.

- **local use – local sympathomimetic action**
  - **as nasal decongestants (nasal drops to reduce mucous membrane congestion caused by hay fever or common cold)**
    - **in this case it is not very important whether a drug α_1 or α_2 (or mixed) agonist**
    - **the local activation of both postsynaptic α receptors (e.g. α_{1A}, α_{2B}) is resulted in local vasoconstriction**
    - **naphazolin, xylometazoline, oxymetazoline, phenylephrine**



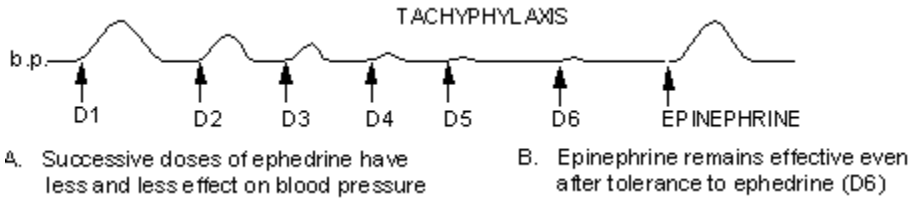
    - **side effects: rebound hyperemia, ischemic changes of the mucous membrane, swallowing might cause systemic side effects – receptor selectivity can be important**
  - **opthalmologic use**
    - **decongestion (phenylephrine)**
    - **mydriasis (phenylephrine)**
    - **treatment of glaucoma (apraclonidine, brimonidine)**

α receptor agonists II.

- **systemic use**
  - **in this case the selectivity of the drug to α_1 or α_2 receptors is extremely important**
- **α_1 selective agonists – sympathetic activation**
  - **cause vasoconstriction, elevate the blood pressure**
  - **e.g. phenyleprine, midodrine, methoxamine**
- **α_2 selective agonists – decrease of sympathetic tone**
  - **reduce the sympathetic tone, decrease the blood pressure (due to the enhancement of the negative feed back of norepinephrine and/or central activation of α_2 receptors involved in blood pressure regulation)**
  - **e.g. clonidine, guanfacin**
  - **they are used as antihypertensive agents**
    - **high systemic doses might activate the postsynaptic α_2 receptors on blood vessels at first, which might be resulted in transient elevation of the blood pressure before the blood pressure falls**

Indirectly acting sympathomimetics

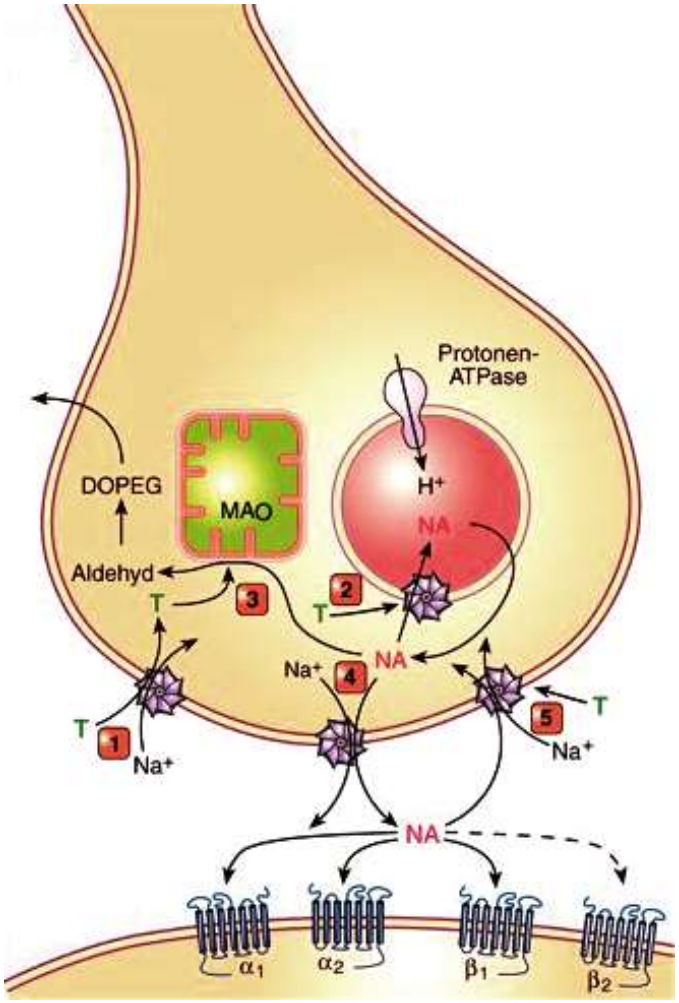
- They release norepinephrine from the nerve terminals
- Rapid development of tolerance (tachyphylaxis) is characteristic to their actions



A. Successive doses of ephedrine have less and less effect on blood pressure

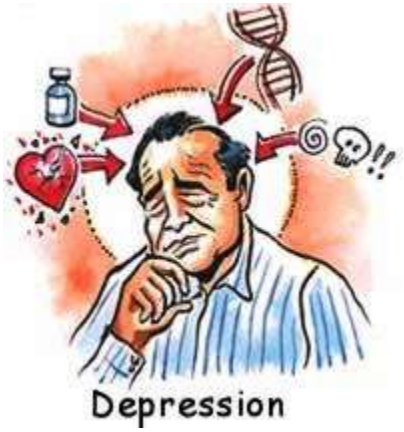
B. Epinephrine remains effective even after tolerance to ephedrine (D6)

- Tyramine, ephedrine and amphetamine belong to this group



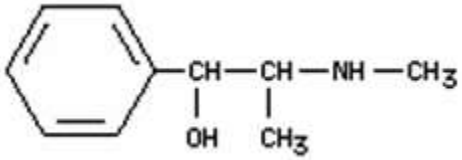
Tyramine

- **It is not used as a therapeutic agent.**
- **It can be found in high concentration in foods (cheese, chicken liver, smoked or pickled fish, red wine).**
- **It is metabolized by MAO-A in the gastroinstestinal tract, and inactivated if ingested.**
- **Cheese-effect:**



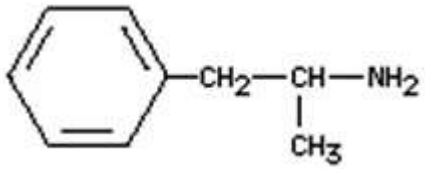
Patients treated with irreversible MAO-A inhibitors must avoid foods containing tyramine. If they don't do that, tyramine reaches the systemic circulation, and increases the sympathetic tone by releasing norepinephrine. It can cause hypertensive crisis.

Ephedrine

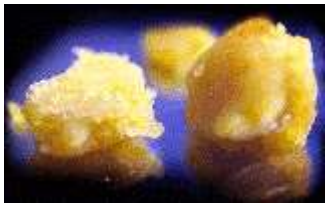


- alkaloid (from Chinese medicine eg. Ma-huang)
- high oral bioavalability, long duration of action
- penetration through the blood-brain barrier, mild stimulant
- mixed sympathomimetic mechanism of action: weak receptor activator and releases norepinephrine
- can be used as a vasoconstrictor or a bronchodilator when weak and prolonged action is needed
- its enantiomer is pseudoephedrine – available over-the-counter as a component of many decongestant mixtures

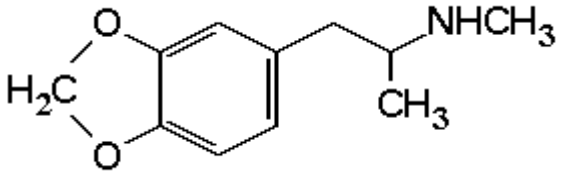
Amphetamine



- orally active compound with long duration of action
- enters the CNS very easily, releases biologic amines and causes a marked stimulant effect on mood and alertness (psychostimulant)



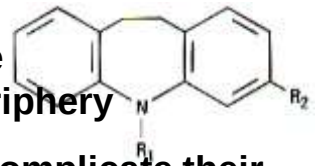
- euphoria leads to abuse of this drug
- decreases the appetite
- on the periphery it is an indirectly acting sympathomimetic
- structurally related drugs: methylphenidate (treatment of ADHD), pemoline, phenmetrazine, metamphetamine, MDMA (ecstasy)



Reuptake inhibitors and MAO inhibitors

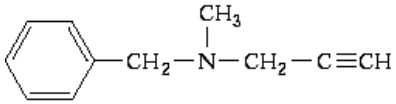
- **Reuptake inhibitors**
  - **Cocaine**


    - **local anaesthetic**
    - **blocks NA and DA reuptake on the periphery and in the CNS, causes sympathomimetic actions, euphoria and drug abuse**
  - **TCA and related compounds**
    - **eg. desipramine, amitriptyline**
    - **used for the treatment of mental depression, block the norepinephrine (and serotonine) reuptake in the CNS and on the periphery**

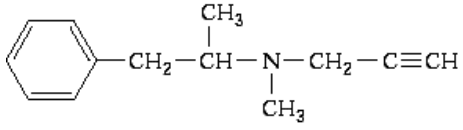


    - **α and M blockade may complicate their autonomic actions; risk of cardial adverse effects**
  - **SNRI, SSNRI**
    - **e.g. reboxetine, venlafaxine**
    - **antidepressants, no receptor blockade**

- **MAO-Inhibitors**
  - **Irreversible non selective MAO inhibitors**



    - **eg. tranylcypromine, pargyline**
    - **old-fashioned antidepressive drugs, their use is not recommended because of severe side-effects (eg. cheese-effect)**
  - **Reversible MAO-A inhibitors**
    - **eg. moclobemid**
    - **used for the treatment of mental depression, doesn't cause cheese effect**
  - **Irreversible MAO-B inhibitors**
    - **selegiline**



    - **used for the treatment of Parkinson's disease**
    - **doesn't cause cheese effect**

Sympatholytics

1. Presynaptic stimulation
2. Presynaptic inhibition

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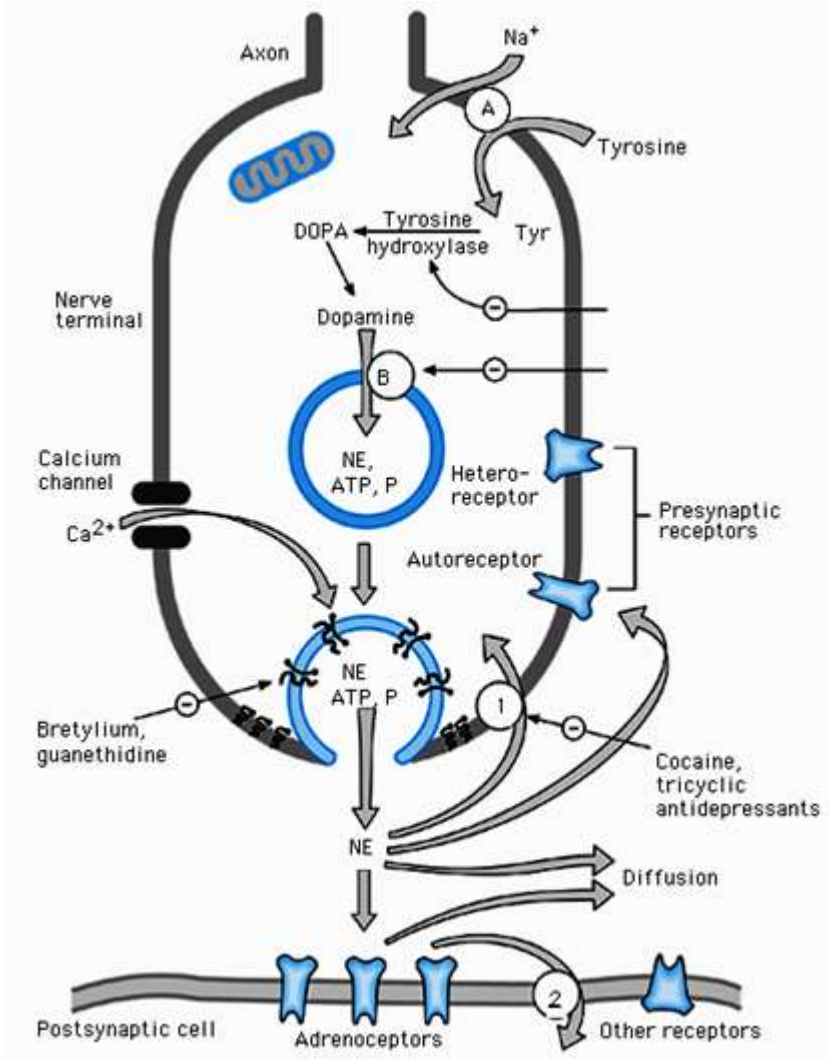
3. Postsynaptic stimulation
4. Postsynaptic inhibition

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

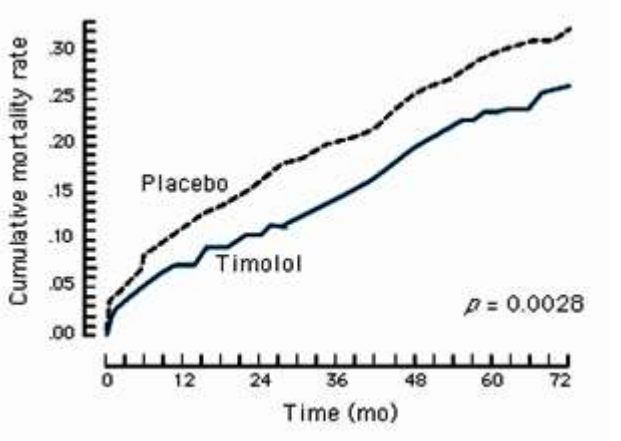
β receptor antagonists

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**

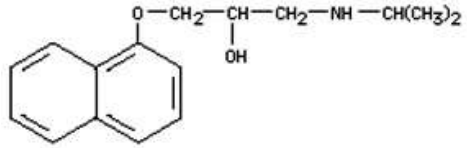
Major differences among the β blockers

- 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

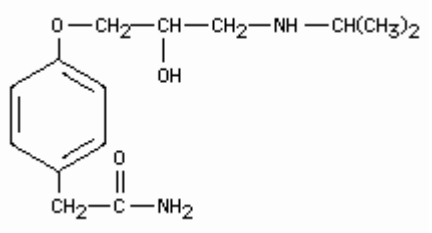
- propranolol



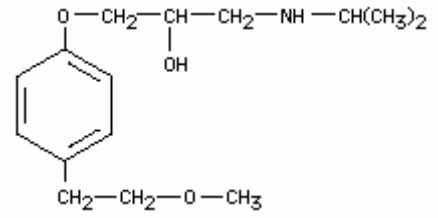
- pindolol
- oxprenolol
- alprenolol
- nadolol
- carteolol
- levobunolol
- penbutolol
- timolol
- sotalol (+K-ch-bl.)
- carvedilol (+α_1-bl.)
- labetalol (+α_1-bl.)

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.**

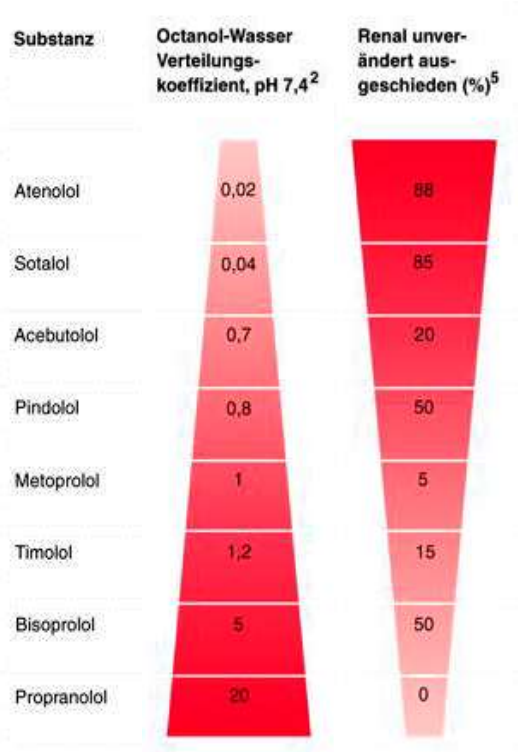
Lipid solubility of the β blockers

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**

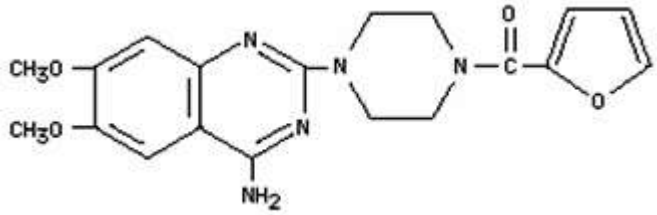
Potential therapeutic interest – smooth muscle relaxation (blood vessels, sphincters) - antihypertensive action, treatment of peripheral vascular diseases, treatment of prostate hyperplasia)

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

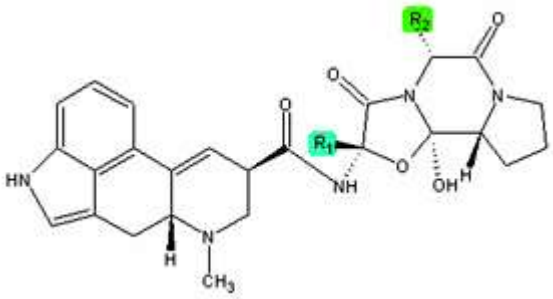
- **reversible α blockers**
- **phentolamine is strong, used in pheochromocytoma (treatment and diagnosis)**
- **tolazoline is a weak blocker, used as a vasodilator in peripheral vascular diseases (very limited indications)**

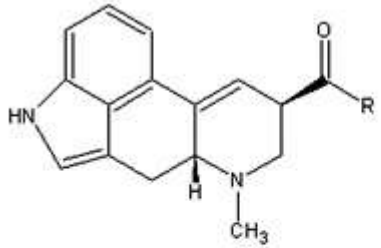
Ergot alkaloids

• **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)**

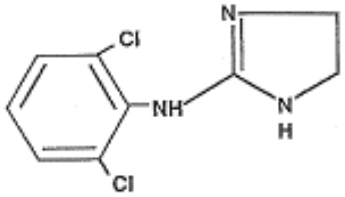
- **possible adverse effects**
  - **nausea, vomiting, diarrhea, prolonged vasospasm, CNS disturbances**

Drugs with α blocking side effect

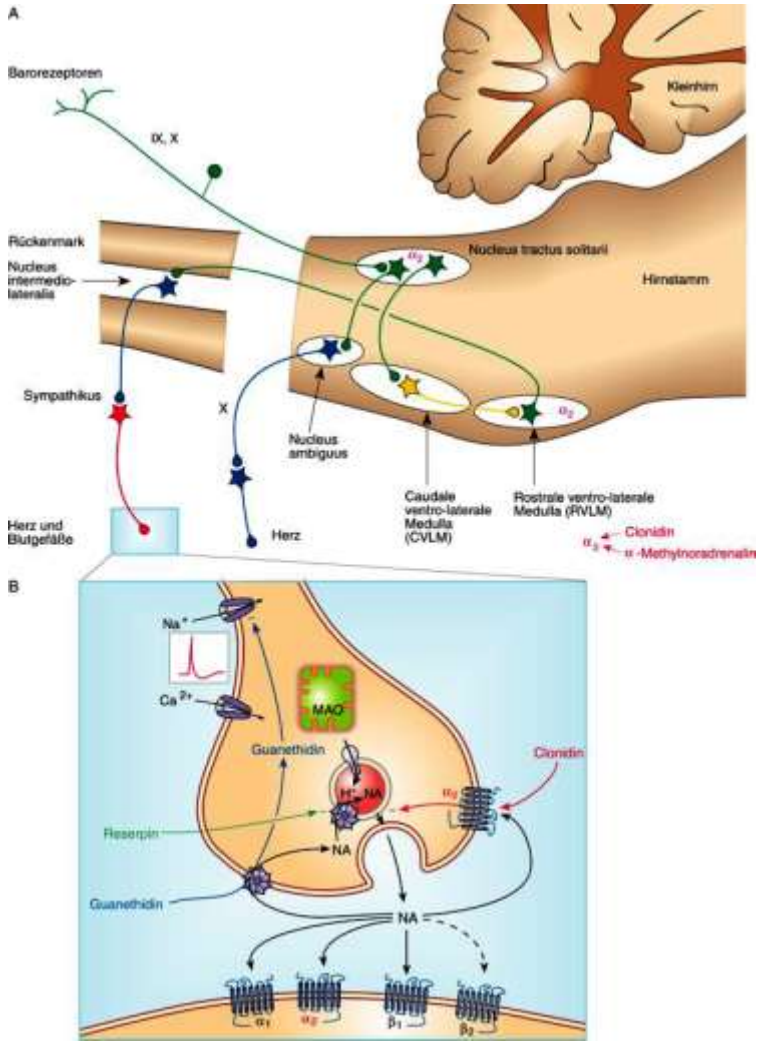
- several (mostly tricyclic) antidepressants (eg. amitriptyline, imipramine)
- several antipsychotics (eg. phenothiazines - chlorpromazine)
  - may cause hypotension, and reflex tachycardia
- quinidine
  - antiarrhythmic drug, too rapid iv. injection may cause blood pressure fall

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**



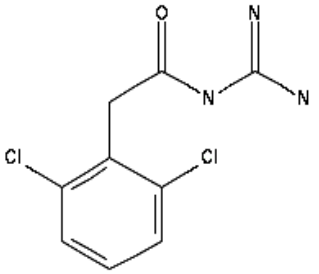
α_2 receptor agonists

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

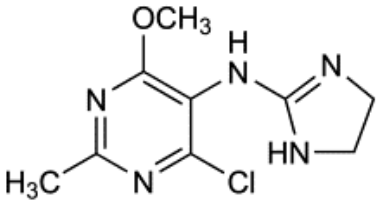
Guanabenz and guanfacine



- 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

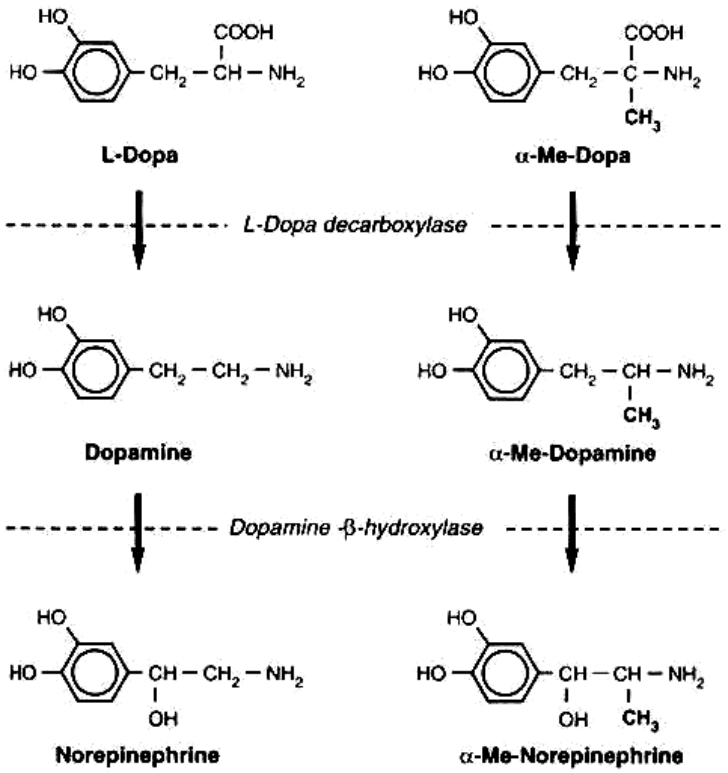


- sedation and dry mouth occurs less frequently than with clonidine ?

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)**

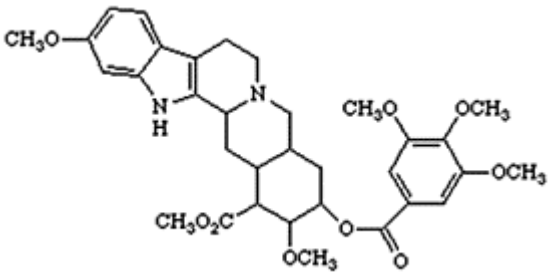
Adrenergic neuron blockers

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

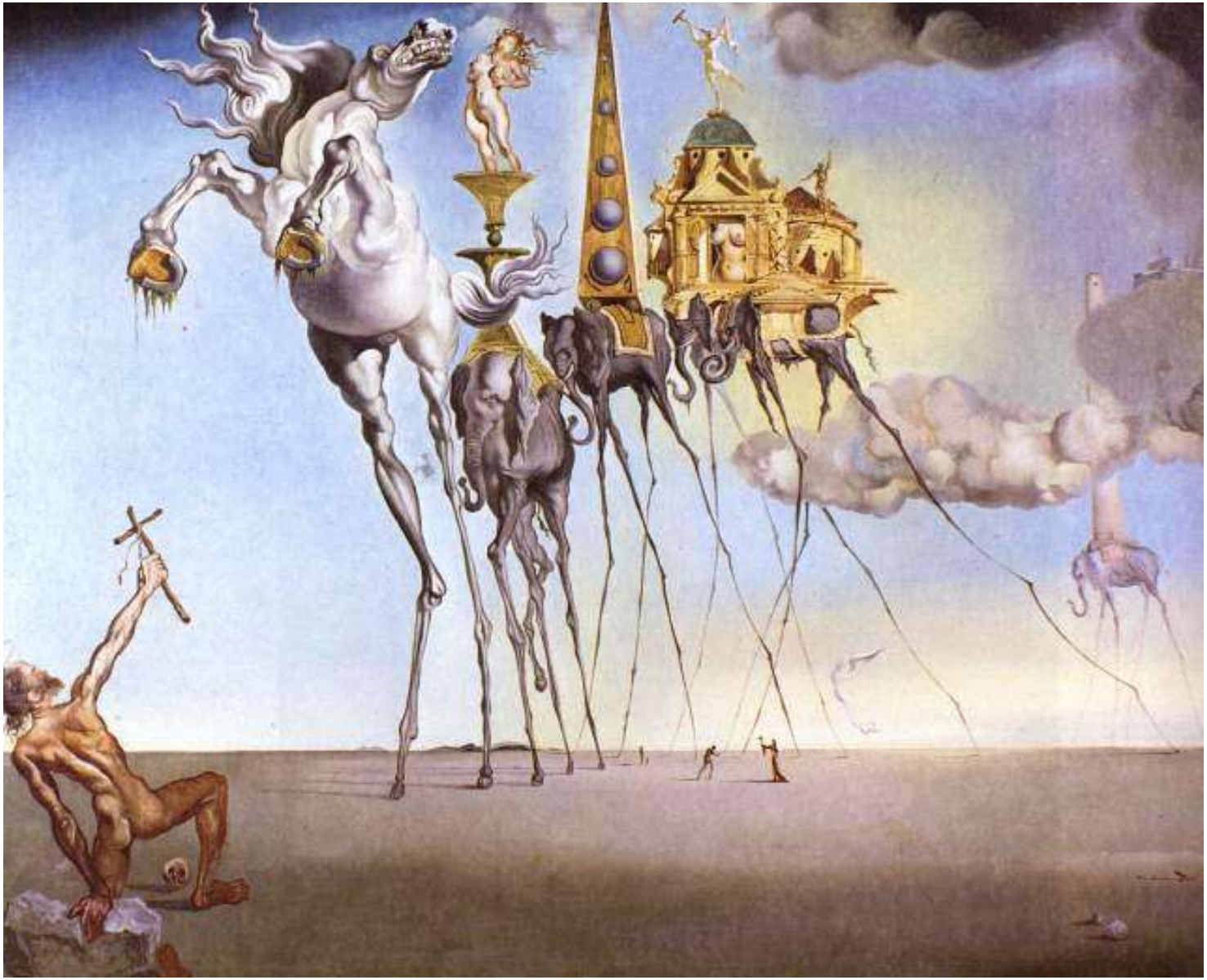
- 857 – Xanten (Rhine Valley, NW Germany) first documented „epidemy"
- 922 severe „epidemy" in Europe – ~40000 deaths
- 1692 – Salem ?
- 1926-27 Sowiet Union (~11000 deaths);
- 1951 Pont-St. Esprit (last „epidemy" in Eurpe, 5-7 deaths);
- 2001 – Ethiopia

Pieter Bruegel: The Beggars 1568

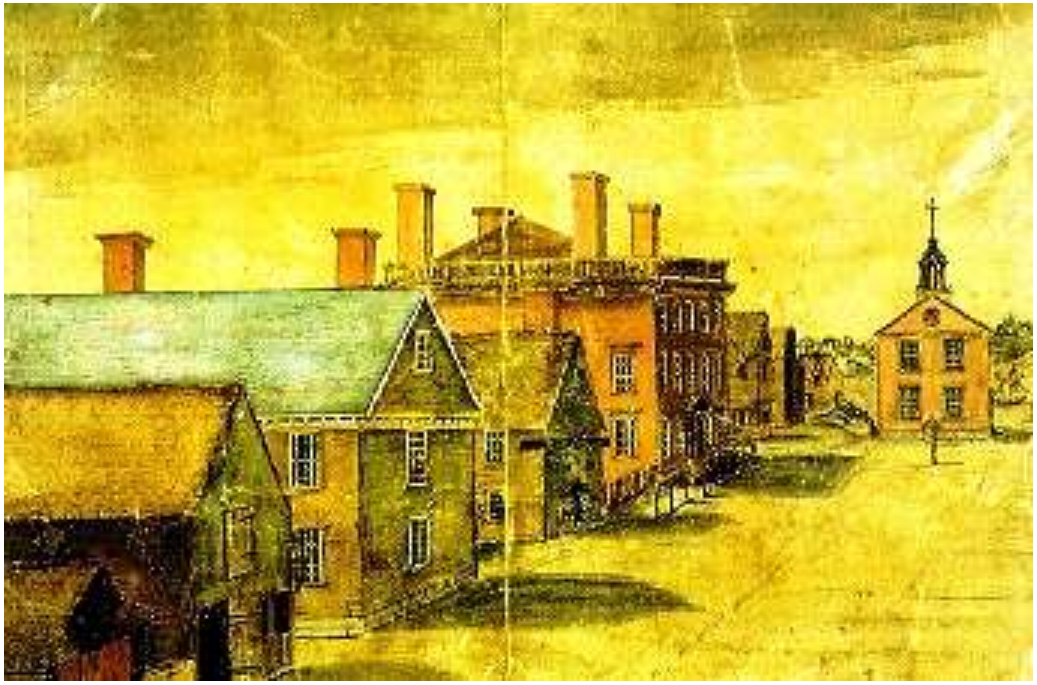
Matthias Grünewald

The Temptation of St Anthony

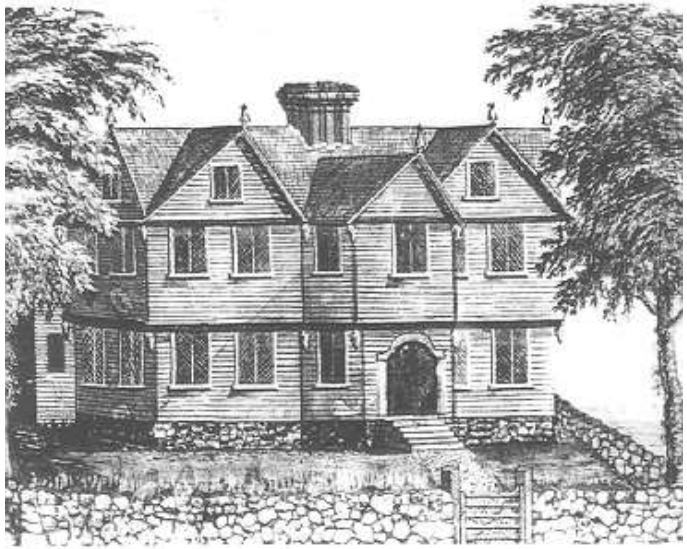
(ca. 1512-16; A panel of the Isenheim Alterpiece)



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)