

Drugs of abuse, Skeletal muscle relaxants

Balázs Varga Pharm.D., PhD

Department of Pharmacology and Pharmacotherapy

University of Debrecen

Definition of „DRUG” and abuse

„drugs” are active substances (usually psychoactive!) that are consumed not because being advised by a doctor, but are self-administrated for various other reasons

- ▶ The cause is mostly: satisfaction/pleasure (hedonic)
- ▶ Drug Abuse: The use of a medication or any other chemical substance
 - ▶ without a prescription;
 - ▶ in a way other than as prescribed;
 - ▶ or for the experience or feeling elicited

Stats

Opiates

- ▶ 50 million permanent user
- ▶ 200 000 deaths/year
- ▶ Opium-production: 7000 tons/year

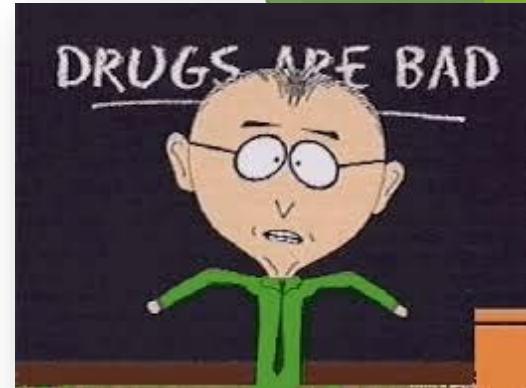
▶ United Nations Office on Drugs and Crime stat

- ▶ Hungary:
- ▶ 50 000 addicts
- ▶ 4000 heroinist (Bp.)

▶ Fürst: Farmakológia

In Hungary the big problem is the drug use of people living in extreme poverty (designers, herbal, green, „no matter what just get high”)

DRUG HARM



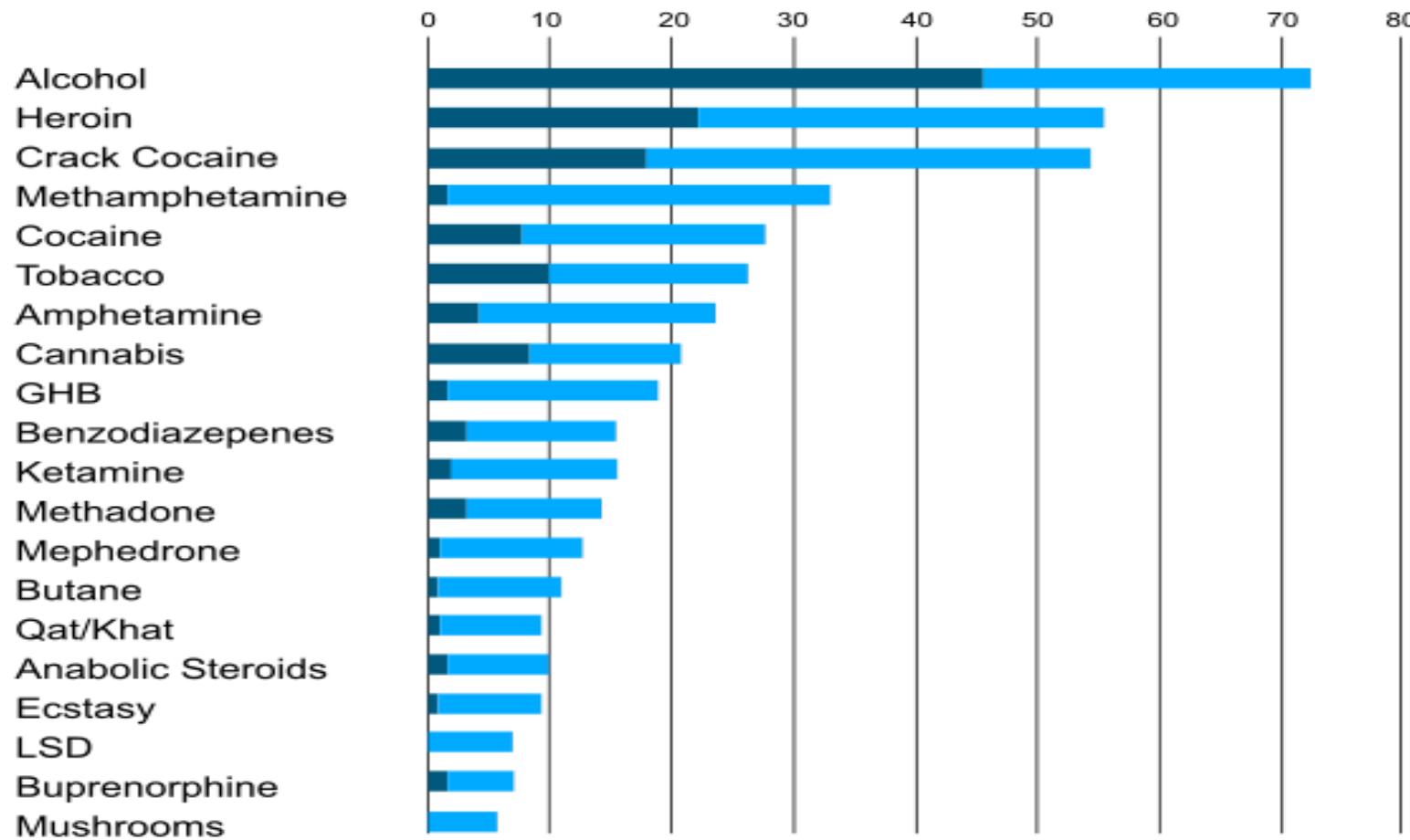
- ▶ All drugs of abuse are *harmful* to a varying extent
- ▶ Drug harm on the user is the result of
 - ▶ actions under narcotic-effect
 - ▶ drug overdose effects on tissues other than the brain
 - ▶ the route of administration (i.v.: HIV)
 - ▶ effects unrelated to the specific actions of the drug (e.g. carcinogenicity)
 - ▶ use for illegal purposes (rape drugs)

"Drug harms in the UK: a multi-criteria decision analysis", by David Nutt

Harm Caused by Drugs

Harm to others
Harm to users

*With a maximum possible harm rating of 100



DRUG DEPENDENCE

When drug taking becomes compulsive (over other needs)

- ▶ Psychological/mental

- ▶ drug seeking behaviour. CRAVING for sthg = irresistible desire, appetite
- ▶ The individual may desire to repeat the experience.
The memory of previous drug-induced experiences can be very intense and long lasting

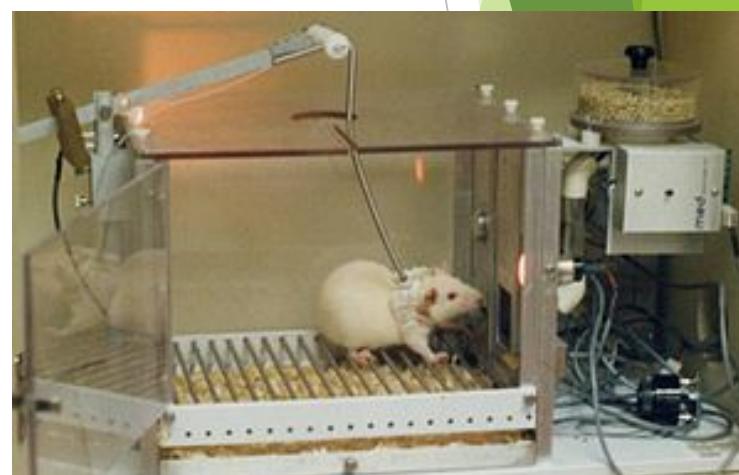
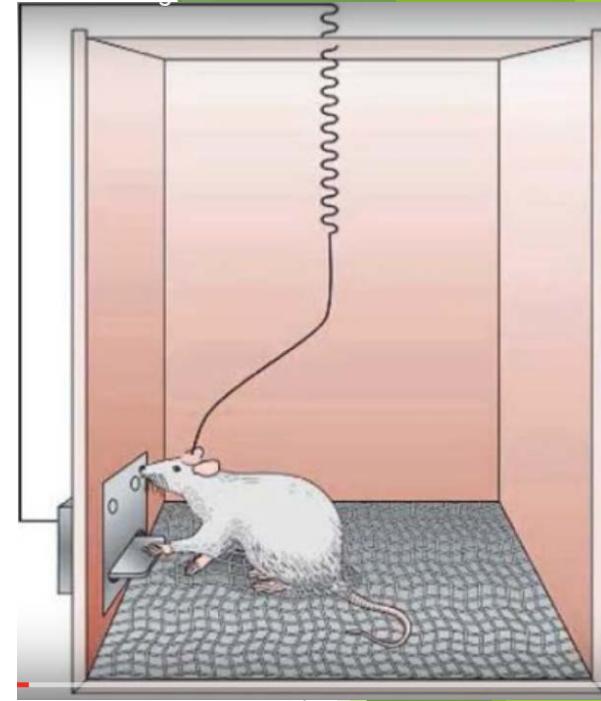
- ▶ Physical

- ▶ when drug withdrawal leads to physical withdrawal symptoms, rebound effects.
- ▶ Withdrawal responses are characteristic of the type of drug taken.
- ▶ little doses of the substance can eliminate these symptoms

- ▶ Addiction: When the patient have both

DRUG-INDUCED REWARD

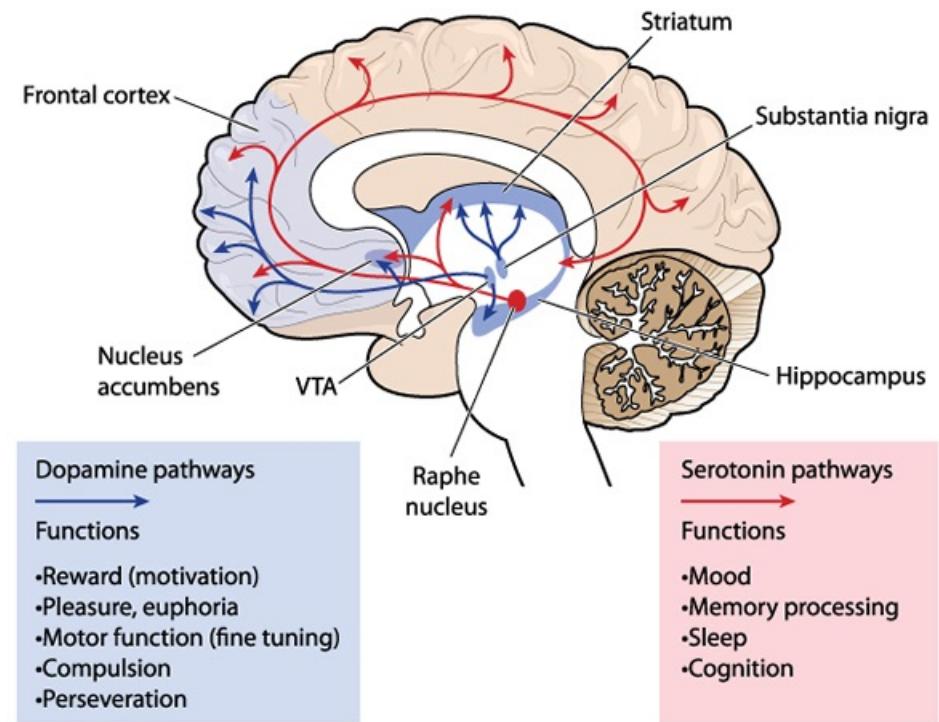
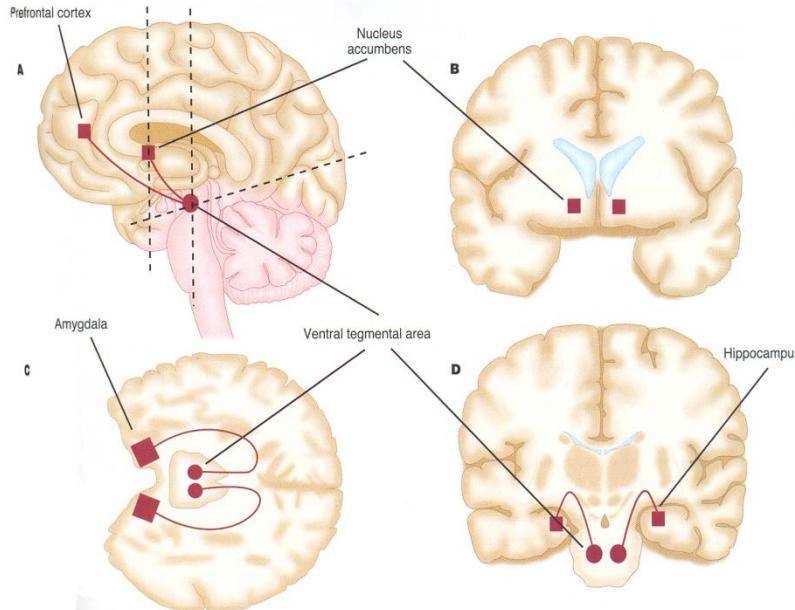
- ▶ psychoactive drugs produce a *rewarding* experience
 - ▶ e.g. an elevation of mood
 - ▶ a feeling of euphoria
 - ▶ or even calmness
- ▶ In animal studies, where the state of mood cannot be inferred directly, reward is manifest as *positive reinforcement*
- ▶ The administration of the drug induces a positive experience or feeling which is called positive reinforcement or self-reward
- ▶ All addictive drugs are self-administered by experimental animals, (e.g.: by pressing a lever (pedal))



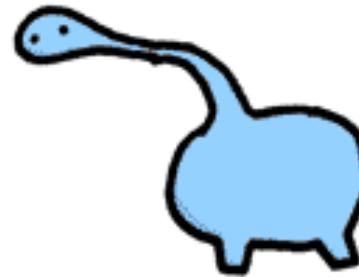
Neurobiology of drug-induced reward

Psychoactive drugs activate the reward pathway

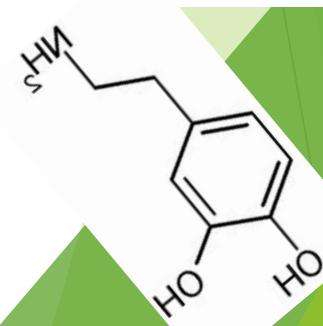
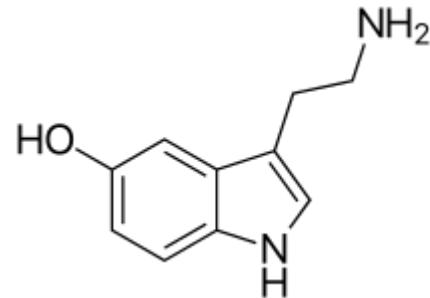
- ▶ the mesolimbic dopaminergic pathway
- ▶ that runs, from the mesencephalon (ventral tegmental area (VTA)) to the nucleus accumbens and limbic region (hippocampus, amygdala)
- ▶ D2 < D3 receptors are involved;
- ▶ serotonine receptors may also be implicated



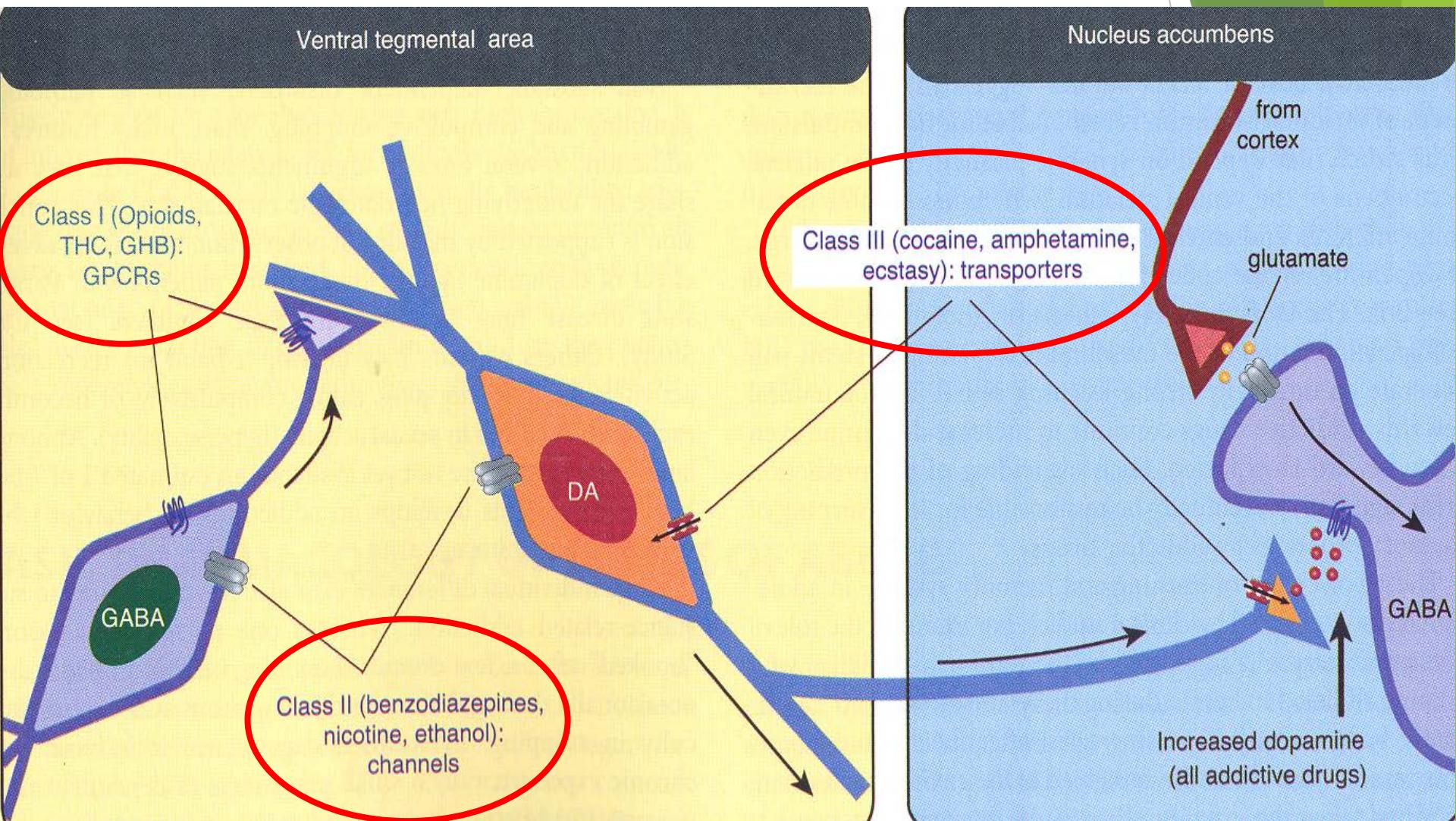
SEROTONIN & DOPAMINE



Technically, the only two things
you enjoy



Neuropharmacologic classification of addictive drugs by primary target



Tolerance

- ▶ Tolerance describes the **decrease in pharmacological effect** on repeated administration of a drug
- ▶ Pharmacodynamic: receptor down-regulation, desensitization after long-term exposure
- ▶ Pharmacokinetic: less active molecule reaches the target - increased rate of metabolism

Most important psychoactive drugs

By pharmacological classes

Pharmacological classes - Drugs of abuse

- ▶ Opioids
 - (topic of next seminar)
- ▶ Central depressants (sedato-hypnotics, anxiolytics + alcohol)
 - (topic of 1st seminar)
- ▶ Stimulants (psychomotor stimulants)
- ▶ Caffeine and nicotine (legal stimulants)
- ▶ Cannabinoids
- ▶ Psychedelics (psychotomimetics, hallucinogenic drugs)
- ▶ Prescription only medicines (anxiolytics, sedatives, (anti-Parkinson drugs), antidepressants)
 - (topic of 1st, (2nd) & 3rd seminar)

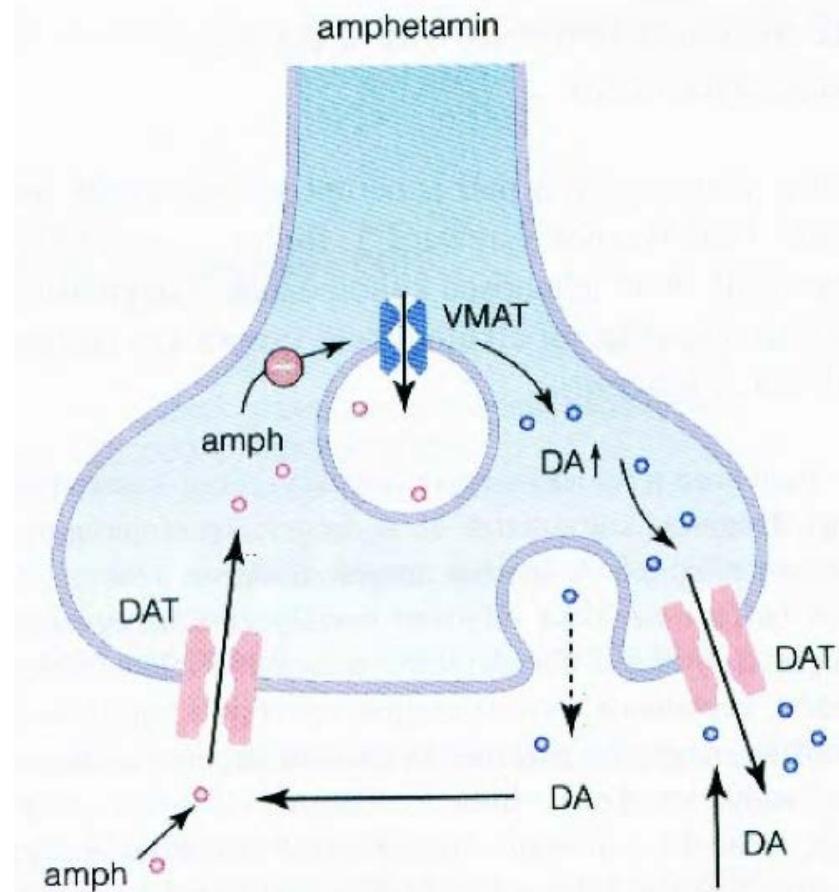
Stimulants

CNS stimulants/Psychomotor stimulants

Psychomotor stimulants

- ▶ have a marked effect on mental function and behaviour,
- ▶ producing excitement and euphoria,
- ▶ reduced sensation of fatigue,
- ▶ and an increase in motor activity

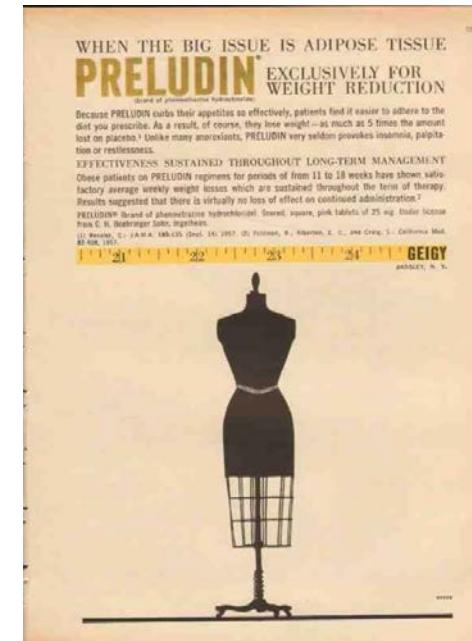
- ▶ They release monoamines, primarily dopamine and noradrenaline, from nerve terminals in the brain
 - ▶ reuptake inhibition + reverse transport
 - ▶ + MAO-inhibition



CNS stimulant molecules

Amphetamines

- ❖ D-amphetamine
- ❖ Methamphetamine („Speed”)
- ❖ Phenmetrazine (Preludin)
- ❖ Methylphenidate (Ritalin)
- ❖ DOM („STP”; dimethoxy-4-methylamphetamine)
- ❖ MDA (methylene-dioxy-amphetamine)
- ❖ **MDMA (ecstasy; methylene-dioxy-methamphetamine)**
- ❖ Other: „designer drugs” (modified moieties)
- ❖ Catha edulis (plant) drugs
 - ❖ cathinone (=hydroxy-amphetamine)
 - ❖ Mephedrone = 4-methyl-meth-cathinone (4-MMC) („miau-miau” „Mephisto”, „Kati”, „Zsuzsi”) (only in 2010 was it added to narcotics’ list in Hungary)



Cocaine

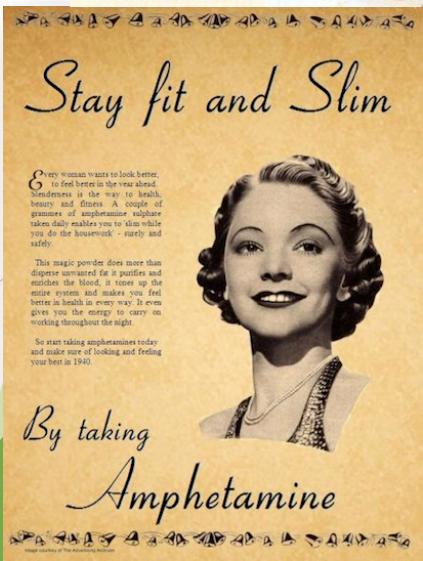
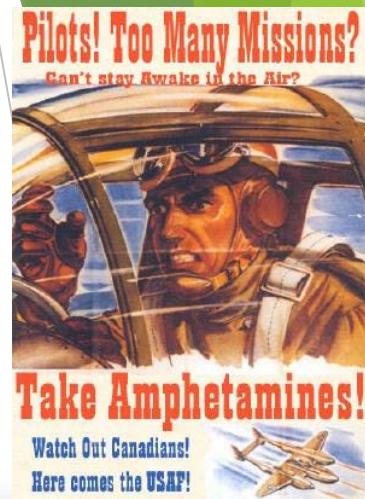
Effects of amphetamines

Acute effects

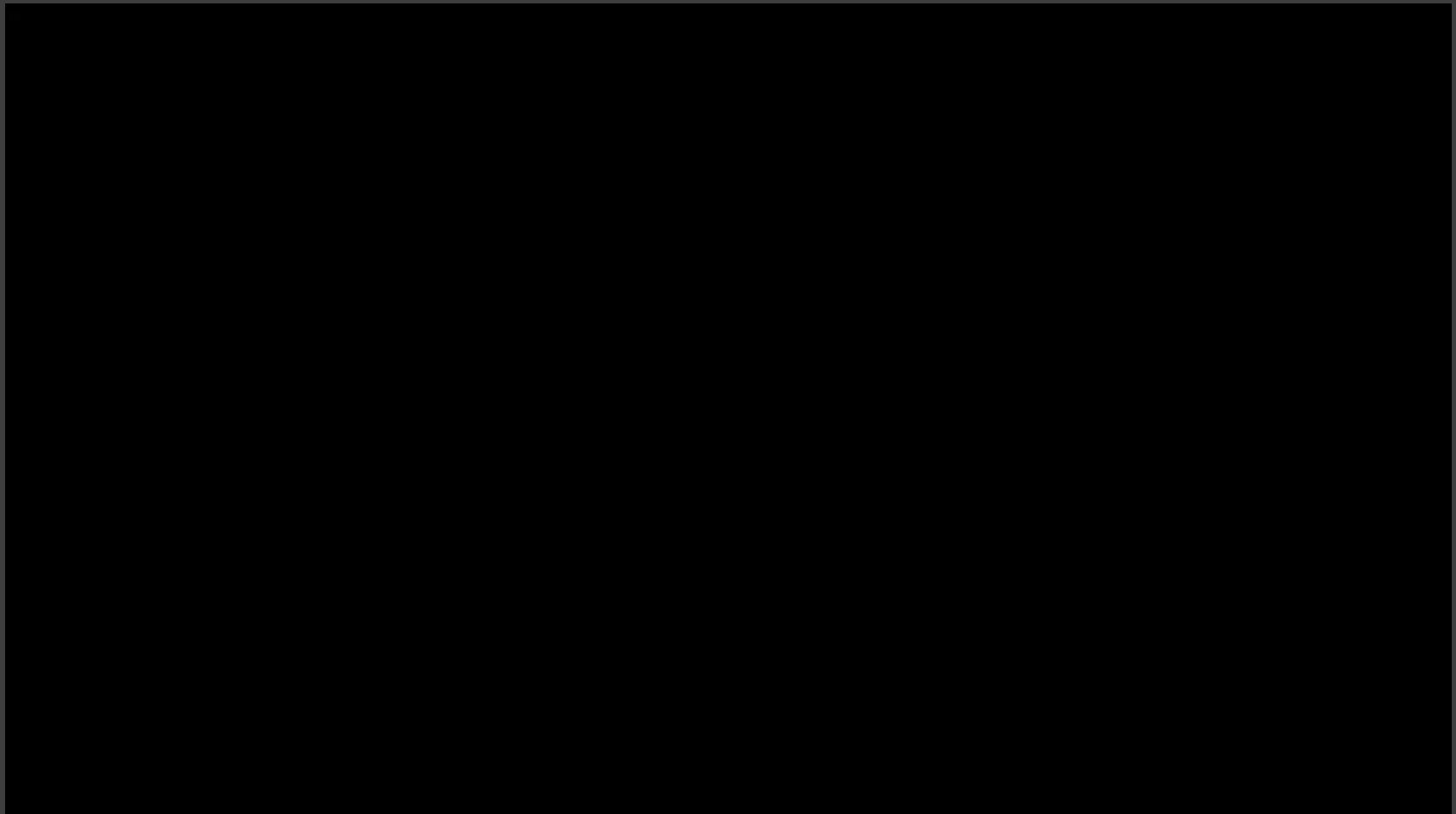
- ▶ Euphoria; with intravenous injection, this can be so intense to be described as 'orgasmic'
- ▶ Subjects become confident, hyperactive and talkative,
- ▶ Sex drive (lust) is said to be enhanced
- ▶ Fatigue, both physical and mental, is reduced → used in narcolepsy (VIDEO) (and formerly for soldiers)
- ▶ Amphetamine-like drugs cause marked anorexia → used as appetite suppressants (formerly)
- ▶ Mental performance is enhanced → in attention deficit hyperactivity disorder (ADHD) for children (Ritalin)

Adverse effects

- ▶ "Dance drugs" (they reduce heat loss+dance=hyperthermia!)
- ▶ anxiety, nervousness
- ▶ irritability
- ▶ restlessness, as the body's energy stores are run down.
- ▶ At high doses, amphetamines may induce panic and paranoia



Narcolepsy (0:42-1:35)



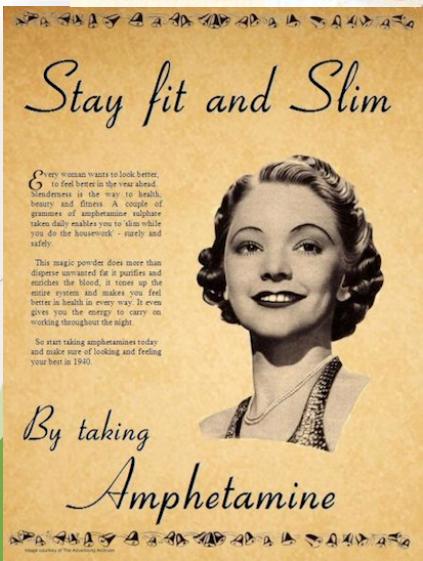
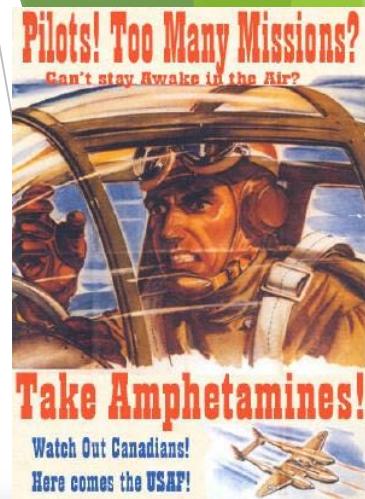
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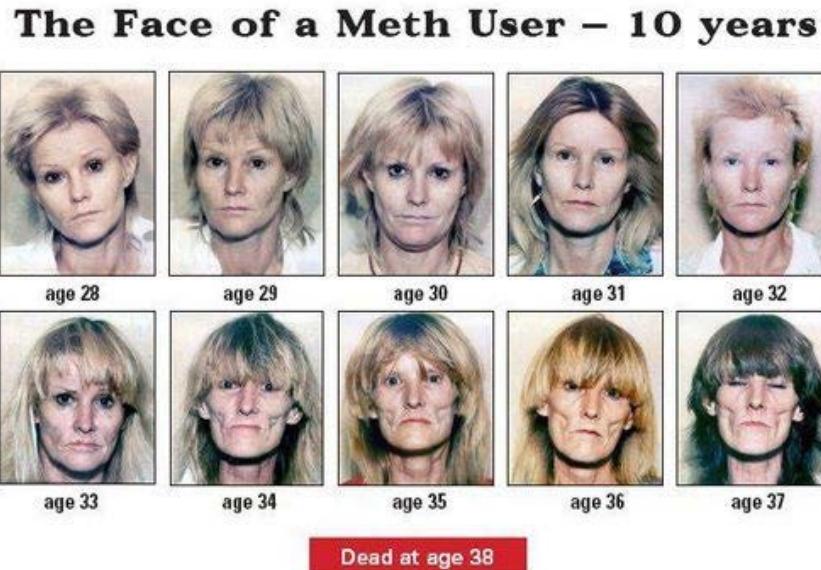
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Chronic CNS stimulant use, tolerance, dependence

Chronic effects

- ▶ With prolonged use, they are **neurotoxic**
 - ▶ cell death especially of 5-HT- and DA-neurons
 - ▶ Probably due to accumulation of reactive metabolites (+ prolonged hyperpyrexia)
- ▶ amphetamine psychosis ~ schizophrenic attack (even after a few days of taking)
- ▶ Tolerance develops rapidly to euphoric and anorexic effects but more slowly to the other effects



Withdrawal symptoms

- ▶ deep sleep and on awakening:
- ▶ Lethargy
- ▶ Depression
- ▶ anxiousness (sometimes even suicidal thoughts)
- ▶ hunger
- ▶ No clear physical and psychical dependence

Therapy of MDMA intoxication

supportive therapy:

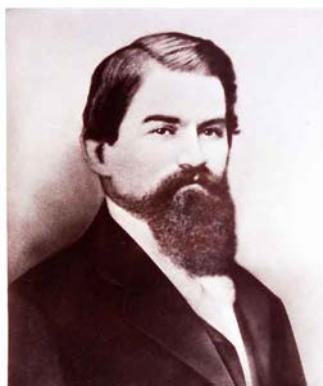
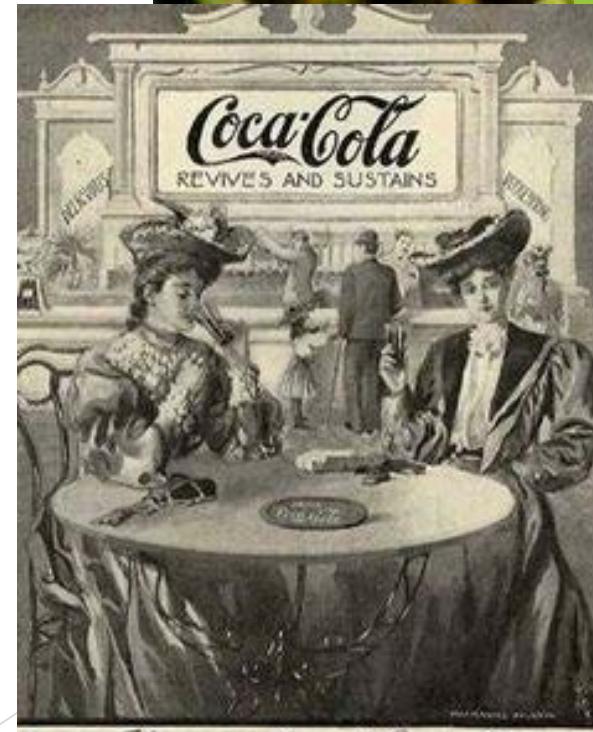
- ❖ agitation/convulsions: *diazepam*
- ❖ gastric lavage together with active carbon
- ❖ support of ventilation
- ❖ hypotension: supplementation of fluid and ions
- ❖ temperature control: above 42° C no survive!
(cooling blankets; ice bag; ice cold infusion etc.)
- ❖ neuromuscular blockade: *dantrolen* (inhibits Ca⁺⁺ release from SR)
- ❖ metabolic acidosis (arrhythmia) →
 sodium bicarbonate - glucose-insulin therapy
- ❖ DIC: severe bleeding - supplementation of clotting factors

specific therapy

selective 5-HT₂ receptor antagonist: ketanserin
- chlormethiazole (sedato-hypnotic) AND inhibits thermogenesis

Cocaine history

- ▶ Coca plant (Erythroxylon coca) - Andean mountains
- ▶ Incas - the first recorded sports doping (leaf chewing)
- ▶ 1860 - Isolation of cocaine
- ▶ Freud tested it extensively on his patients and his family, publishing an influential monograph in 1884 advocating its use as a psychostimulant
- ▶ His ophtalmologist colleague discovered its local anesthetic effect (it was used as mydriatic in ophthalmology)
- ▶ Cocaine was the ingredient of the first Coca-Cola, invented by John Stith Pemberton pharmacist in 1886



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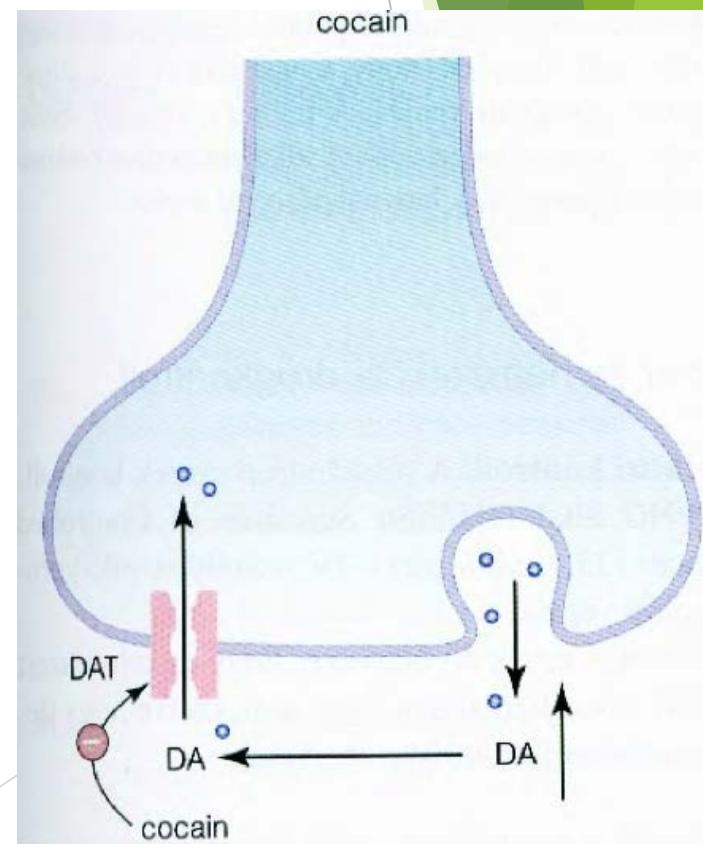
John Stith Pemberton
Inventor of Coca-Cola in 1886

Historic Personalities

R Take one glass of Coca-Cola when weary with shopping. It imparts energy and vigor.

Cocaine - Mechanism of effect

- ▶ inhibits dopamine reuptake (= dopamin-transporter DAT)
→ activation of mesolimbic pathway
- ▶ 5-HT₃ antagonist (→ unknown role)
- ▶ 5-HT₂ agonist → locomotor-activating
- ▶ σ-receptor agonist → euphoria
- ▶ Na-channel blocker → local anaesthetic



Effects of cocaine -

Cocaine = „superamphetamine”

- ❖ Acute Effects: like amphetamines

- euphoria
- hyperactivity
- reduced fatigue
- anorexia

- ❖ similarly „Cocaine psychosis”

- vivid imagery
- acoustic illusions
- tactile illusions

- ❖ strong psychic dependence („cocaine craving”)

- ❖ does not cause severe physical dependence, but withdrawal symptoms:
(like with amphetamine) fatigue, somnolence, depression, bradycardia

- ❖ tolerance may develop

- ❖ Among cocaine sniffers (nasal use):

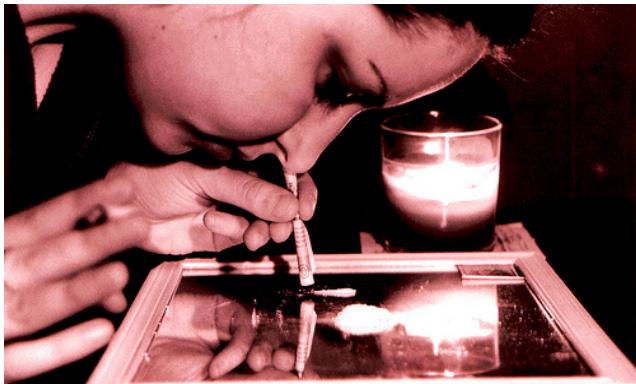
- frequent nose bleeding
- chronic hoarseness
- inflammation of nasal septum

Relative Risk
of addiction
(RRA): 5
(on a 5-scale)



Cocaine high doses

- ▶ tremors and convulsions,
- ▶ respiratory and vasomotor depression
- ▶ Peripheral sympathomimetic actions:
 - ▶ tachycardia
 - ▶ vasoconstriction
 - ▶ increase in blood pressure.
- ▶ Body temperature may increase



Main physiological effects of Crack cocaine

Systemic:

- Increased temperature

Pupils:
- Dilation

Sense of balance:

- Vertigo

Blood vessels:

- Constriction
- Increased blood pressure

Heart:

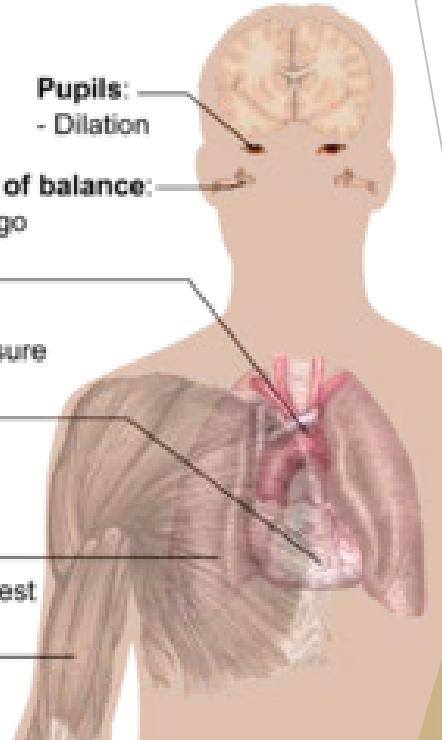
- Increased heart rate
- Risk of cardiac arrest

Lungs:

- Risk of respiratory arrest

Muscles:

- Tremor
- Twitches



Cocaine overdose

- ❖ with high lipidsolubility form („crack”)
- ❖ circulatory collapse
 - ❖ arrythmia
 - ❖ infarct
 - ❖ ischaemies
 - ❖ convulsions
 - ❖ stroke
- ❖ migraine
- ❖ hypertermia

CNS symptoms

anxiety

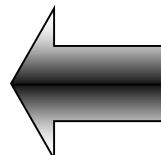
paranoia

fear of death

fatal outcome

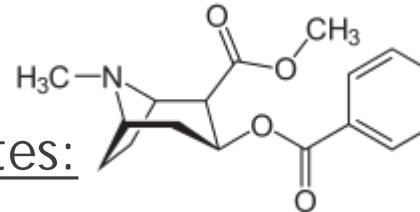
respiratory depression
nose bleeding
headache
fatigue/depression
hoarseness
circulatory disturbances

This syndrome is of
diagnostic importance



Routes of administration, Pharmacokinetics

Cocaine is readily absorbed by many routes:



- ▶ Chewing the coca leaves or pasta (crude extract of coca leaves)
- ▶ Nasal inhalation (sniff)
- ▶ Intravenous
- ▶ Inhaled ('crack') cocaine + NaHCO₃ = Free-base cocaine, that vaporises at around 90°C → can be smoked - rapid onset)
$$\text{Coc-H}^+\text{Cl}^- + \text{NaHCO}_3 \rightarrow \text{Coc} + \text{H}_2\text{O} + \text{CO}_2 + \text{NaCl}$$
- ▶ A cocaine metabolite is deposited in hair, → from the hair shaft cocaine-exposition can be monitored
(even in neonates)



Cocaine and pregnancy

Pregnancy/breast feeding complications:

- ▶ spontaneous abortion
- ▶ teratogenicity
- ▶ microcephaly
- ▶ Withdrawal symptoms in the neonate
 - ▶ a high-pitched crying,
 - ▶ tremors,
 - ▶ sweating,
 - ▶ GI disturbances



Caffeine and Nicotine

Legal stimulants

Caffeine

- ▶ Methylxantines
Naturally occurring alkaloids in plants
- ▶ caffeine, theophylline, theobromine
- ▶ *Coffea arabica*, *Thea sinensis*,
Theobroma cacao, *Mate folium*, Guarana
- ▶ A cup of coffee: 85-200 mg caffeine
Average caffeine consumption from beverages
is about 200 mg/day.



coffee



tea



tea



guarana



cacao



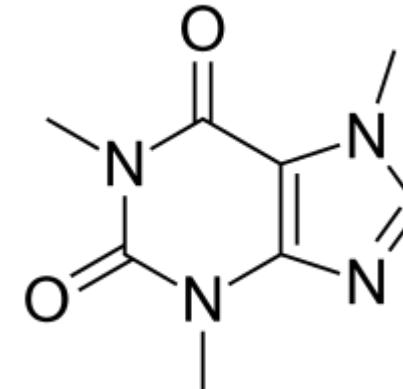
mate folium



Metilxantines - caffeine

- ▶ Caffeine produce psychomotor stimulant effects

- ▶ reduced fatigue
- ▶ improved mental performance
- ▶ without euphoria



- ▶ Mechanism of effect:

- ▶ non-selective competitive antagonism at adenosine receptors
 - A₂-antagonism is responsible for wakefulness
- ▶ non-selective competitive phosphodiesterase (PDE) inhibitor
- ▶ IP3 rec antagonist
- ▶ ryanodin receptor agonist
- ▶ glicin rec competitive antagonist

PDE-specificities						
BOTH	1	2	3	10	11	
cAMP	4	7	8			
cGMP	5	6	9			

- ▶ Peripheral actions are exerted mainly on heart, smooth muscle and kidney.

In pharmacy



Tobacco

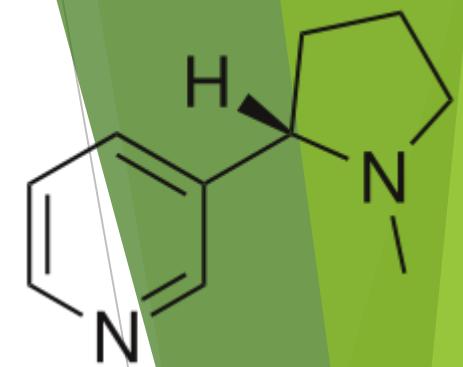


- ▶ The worldwide prevalence of smoking is now about 18% of the adult population, each smoker using on average 5000 cigarettes per year.
- ▶ Nicotine is the main pharmacologically active agent in tobacco-smoke, apart from carcinogenic tars and carbon monoxide.
- ▶ Nicotine absorbed from an average cigarette is about 1-1.5 mg, which causes 130-200 nmol/l plasma-concentration.



Nicotine - Pharmacodynamics

- ▶ Mechanism of effect:
 - ▶ agonism on nACh receptors, mainly of the $\alpha 4-\beta 2$ subtype →
 - ▶ causes neurotransmitter release
(e.g. dopamin (nucleus accumbens) → craving!)
 - ▶ increases neuronal excitation
- ▶ At the behavioural level, nicotine produces a mixture of inhibitory and excitatory effects.
- ▶ Nicotine shows reinforcing properties, associated with increased activity in the **mesolimbic dopaminergic pathway**, and self-administration can be elicited
- ▶ Peripheral effects of nicotine are due mainly to ganglionic stimulation:
 - ▶ tachycardia,
 - ▶ increased blood pressure
 - ▶ reduced gastrointestinal motility
- ▶ Tolerance develops rapidly



Nicotine - Pharmacokinetics

- ▶ Nicotine is metabolised mainly in the liver (CYP2A6), within 1-2 h.
- ▶ The inactive metabolite, **cotinine**, has a long plasma half-life (18-20h) → can be used as a measure of smoking habits.
- ▶ metabolism of nicotine is inhibited by menthol → an additive to mentholated cigarettes → thus increasing the half-life of nicotine in vivo.
- ▶ Causes tolerance, **physical and psychological dependence (craving)**.
Attempts at long-term cessation succeed in only about 20% of cases.

Smoking-cessation - treatment of nicotine-dependence

- ▶ Nicotine replacement therapy (chewing gum or skin patch preparations) improves the chances of giving up smoking

- ▶ Bupropion (Wellbutrin)
 - ▶ Norepinephrin+dopamin reuptake inhibitor (NDRI) → antidepressant
 - ▶ Antagonist on nicotinic receptors → smoking-cessation
 - ▶ As effective as nicotine-replacement therapy (less than varenicline)

- ▶ Vareniclin (Champix)
 - ▶ a high-affinity partial agonist for the $\alpha 4\beta 2$ nACH-R → no dopamin-release → reduce the feelings of craving and withdrawal caused by smoking cessation



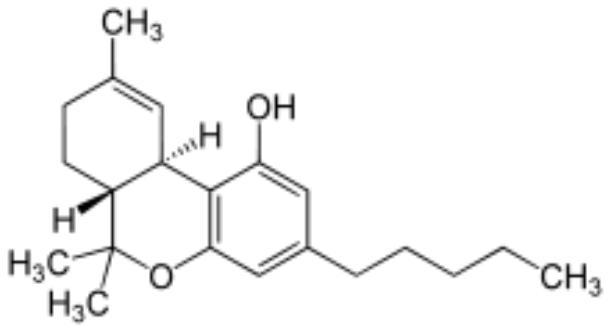
Cannabinoids

Cannabis sativa L. ssp (variegata indica, sativa etc.)

- ▶ Also known as: grass, joint
 - ▶ - marijuana
 - ▶ - Ganja, hasis
 - ▶ - spacecake

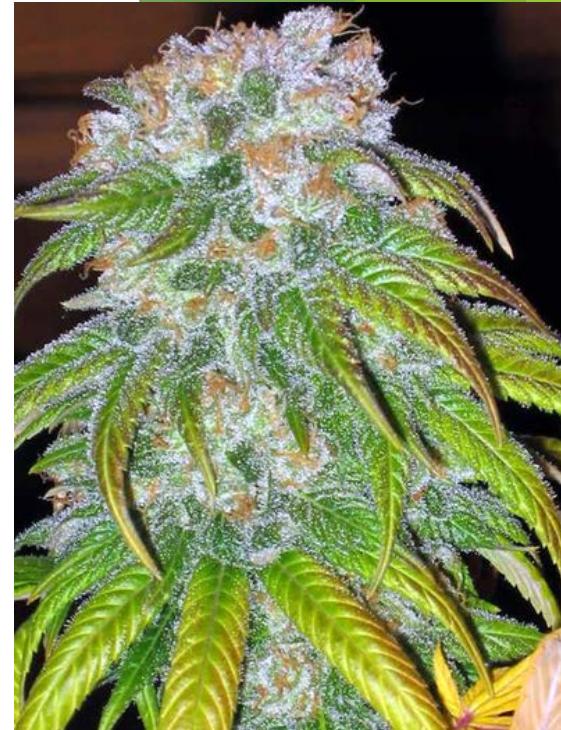


Cannabis



Components:

- ▶ The THC (1-delta-9-tetrahydrocannabinol) is responsible for the psychoactive effects of cannabis.
- ▶ The Cannabis plant produces 60 different substances called **cannabinoids**, such as cannabidiol, cannabigerol, cannabiolic acid etc.
- ▶ THC-content:
 - ▶ 0.5-3% cannabis,
 - ▶ hashish (powder of the resin of the plant) 2-10%,
 - ▶ the hash oil (oil-extract of hashish) contains 30-70% of THC



Cannabis

► The cannabis-induced symptoms:

- ▶ euphoria, drowsiness
- ▶ happiness, disintegration
- ▶ Confusion in the sense of time
- ▶ short-term memory problems
- ▶ inhibits the learning process,
- ▶ Increased hunger
- ▶ tachycardia
- ▶ red conjunctivas



Cannabis

Pharmacodynamics

- ▶ There are two endocannabinoid receptor (both G_i)
 - ▶ CB1 in CNS
 - ▶ CB2 on T/B-lymphocytes and on periferal nerve terminals ↙ antinociception
- ▶ endogenous cannabinoids are derivates of arachidonic acid:
anandamide (= Arachidonoyl-ethanolamine), 2-Arachidonoylglycerol,
N-Arachidonoyl dopamine (NADA) etc.
- ▶ Rimonabant: synthetic CB1 receptor antagonist
- ▶ Effects of endocannabinoid system:
 - ▶ affect hippocampal GABAergic neurons so may have a role in the short-term memory and learning → inhibiting learning processes / extinction of old memories
 - ▶ increase the appetite
 - ▶ reward effects (drug-seeking behavior and relapse)

Cannabis withdrawal

- ▶ Cannabis considered to be safe = less toxic than alcohol or smoking
- ▶ Addiction does not occur (rarely psychic dependence perhaps)
- ▶ It has only mild withdrawal symptoms
- ▶ Main hazards:
 - ▶ "gateway" drug
 - ▶ amotivational-syndrome

Potential therapeutic use of Cannabinoids

Nowadays there is a serious debate about the legitimate of medical use of the plant Agonists

- ❖ Reduce intraocular pressure in the eyes (glaucoma)
- ❖ Bronchial smooth muscle relaxation (asthma)
- ❖ Antinociceptive effect (chronic pain: fibromyalgia, rheumatoid arthritis)
- ❖ Orexigenic effect (AIDS)
- ❖ Antiemetic effect (chemotherapy! Nabilone (Cesamet®): THC analog)
- ❖ Muscle-relaxation (sclerosis multiplex)
- ❖ Anticonvulsive effect
- ❖ Tourette syndrome („tic”)

On the market: Nabilone (Cesamet®), Dronabinol (= synthetic THC) (Marinol®), Nabiximol (=cannabis extract =THC+cannabidiol) (Sativex®)

Antagonist

Rimonabant (Acomplia®) CB₁ antagonist (inverse agonist)

- decreases hunger
(for weight loss in „risk” patients: Type 2 DM; >30 kg/m² BMI; dislipidemia)
- decreases relapse of smokers
- adverse effects: severe depression, suicide!! withdrawn from market

Psychedelics

Hallucinogenic drugs

Psychedelics

- ▶ Psychotomimetics = they "mimic psychosis"
- ▶ also referred to as *psychedelics* = "soul-manifesting"
 - ▶ derived from the Greek words psyche ("soul, mind") and delein ("to manifest") = can access the soul and develop unused potentials of the human mind
- ▶ or *hallucinogenics* = produce hallucinations (not all of them!)
- ▶ *thought, perception is distorted and they affect mood in a complex way,*
- ▶ without causing marked psychomotor stimulation or depression
- ▶ Importantly, psychotomimetic drugs **do not cause addiction**,
 - ▶ these are largely not self-administered by experimental animals
 - ▶ act not on dopamin-reward system
- ▶ Drugs act on **serotonine (5-HT)** receptors (agonists) and/or reuptake transporters (inhibition).

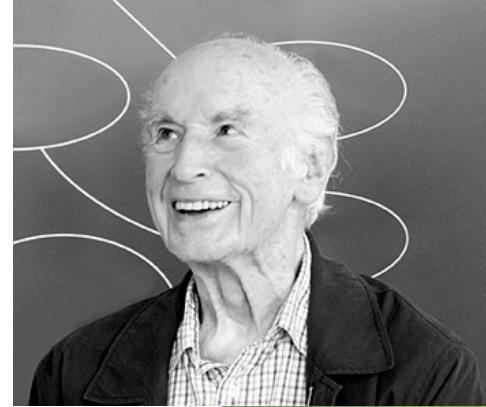
Claviceps purpurea - Anyarozs

Also known as:

- ▶ Secale cornutum
(literally: horned rye)
- ▶ Cereal parasite fungus
- ▶ History: ergotismus
 - ▶ St. Anthony's fire
 - ▶ gangrenous symptoms
(due to vasoconstriction)
 - ▶ Other symptom-type:
Salem witches, 1692
 - ▶ cramps, diarrhea,
vomiting, hallucinations,
mania, psychosis,
hallucinations

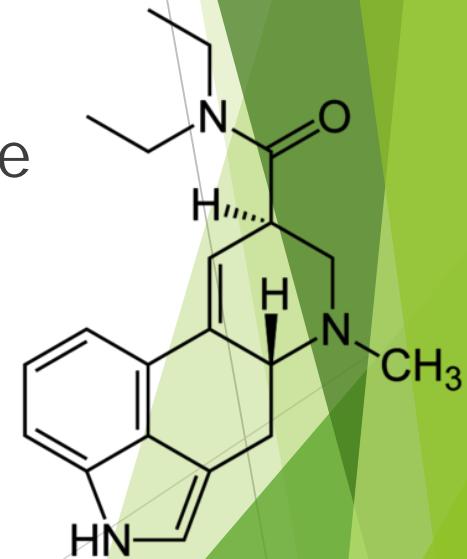


LSD

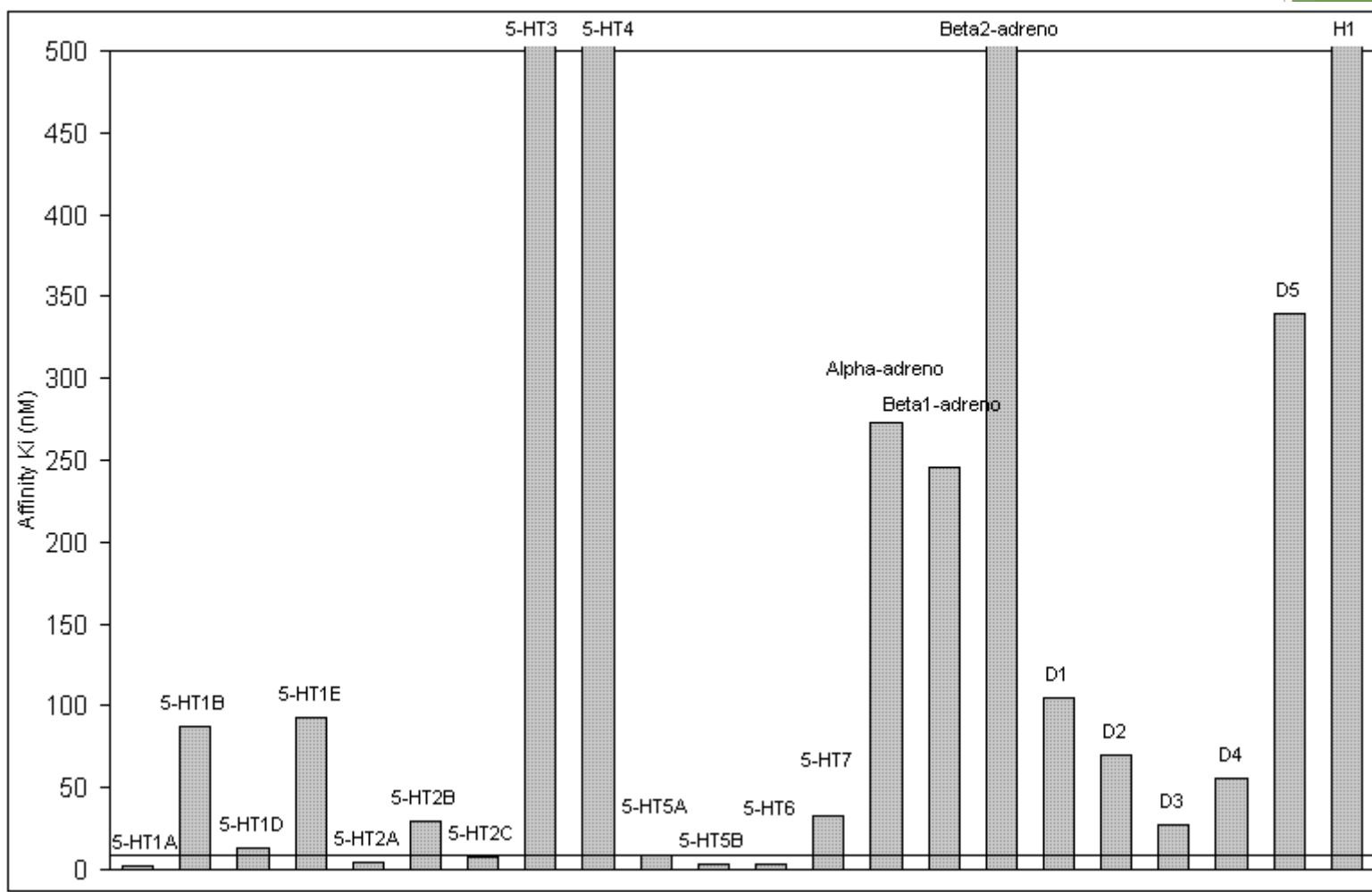


- ▶ Lysergic acid diethylamide
- ▶ - Semi-synthetic material, synthesized by **Albert Hoffman**, Swiss chemist
(LSD - My Problem Child entld. book)
- ▶ - In 1943 he accidentally tried it (famous scene when Hoffman bikes home from work)
- ▶ - The CIA has dealt with the matter as a possible truth serum
- ▶ - The hippies popularized it in the sixties
(Hendrix - Woodstock 1969
Beatles 1967 - Lucy in the Sky with Diamonds ...)

L S D



LSD Mechanism of Effect



Dissociation constants for LSD on different receptors
the lower means the stronger bond

The line is the usual plasma-concentration of LSD for recreational use →
below/near this line receptors may produce the effect = 5-HT_{1A}; 2A ; 2C ;5A etc

LSD



- ▶ Dosage: in a very small amount of 0.5 ug /kg
- ▶ Street names of LSD: acid, paper, Trip
- ▶ Visual hallucinations, colors, shapes becoming more powerful, moving objects, see yourself from the outside (depersonalization)
- ▶ Acoustic hallucinations, loss of sense of time, synesthesia
- ▶ Dizziness, nausea, tremor
- ▶ Bad Trip: Adverse reactions: panic attacks, hallucinations, horror, fear of death,
▶ -> like acute schizophrenia
- ▶ Flashback: months later, the bad trip returns
- ▶ Dependence is rare, no withdrawal symptoms
- ▶ Polydrug abuse is not typical in psychedelics-users
- ▶ Therapy: antipsychotic, if necessary

Peyote

- ▶ The „magic power” of peyote cactus (*Lophophora williamsii*), was discovered somewhere in Mexico by huichol indians

- ▶ The main active ingredient is mescaline (also found in other cactuses)
- ▶ The effect of mescaline (and psilocybin) are roughly the same as LSD, but the experience is less strong

- ▶ 300-500 mg mescaline is required
- ▶ Consumption: chewing the dried cut slices

- ▶ The mechanism of action:
 - ▶ It is very similar to the LSD (5HT-rec agonist)
 - ▶ It is proved by partly the similar psychic effects and partly the cross-tolerance



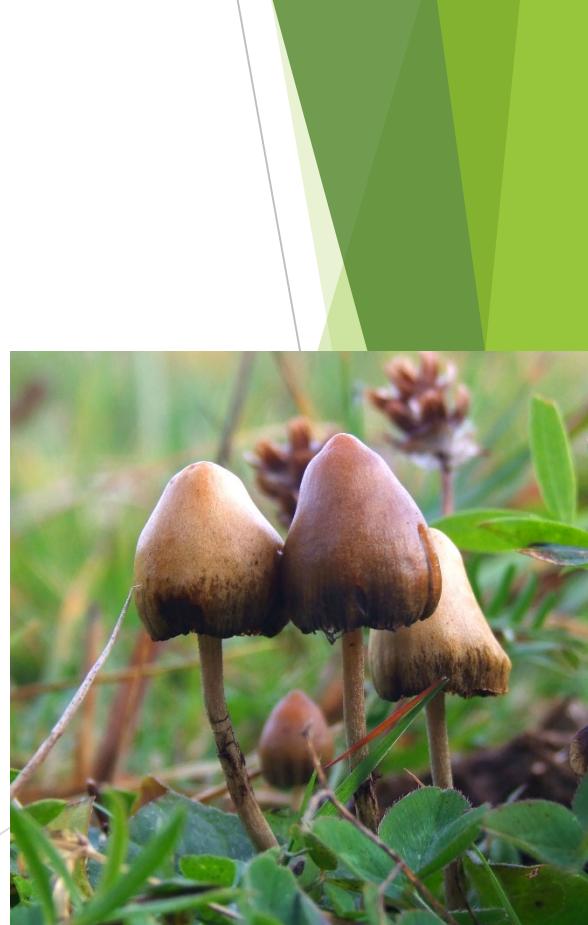
Psilocybe ssp.

- ▶ Synonym: magic mushrooms
- ▶ Active substance: psilocybin
- ▶ Similar to the story of Peyote: The Indians discovered psilocybin-containing mushrooms that are causing hallucinations (teonanacatl=meat of the gods)
- ▶ psilocybin was also isolated by Hoffmann (as LSD)

- ▶ 10-50 mg are required, it takes about 2-5 g of dried mushrooms
- ▶ Consumption: edible or as tea

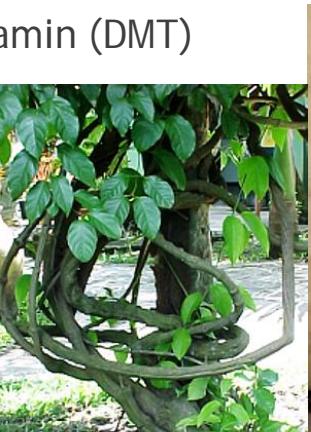
- ▶ The mechanism of action:
 - ▶ It is very similar to the LSD (5HT-rec agonist)

- ▶ Medical use: cluster headache



Ayahuasca (ayawaska)

- ▶ A brew made out of *Banisteriopsis caapi* vine and leaves of the shrub *Psychotria viridis*, both endemic in South America.
- ▶ Meaning of the quechua word ayahuasca is ~"spirit liana"
- ▶ Effects:
 - ▶ mystical or religious experiences
 - ▶ spiritual revelations/awakening ~ rebirth
 - ▶ Vomiting, diarrhoea
- ▶ Mechanism of effect:
 - ▶ *Banisteriopsis caapi* → b-carbolines (harmaline and harmine)
 - ▶ Strong MAO-A-inhibitors (MAO would metabolize DMT)
 - ▶ Tetra-hydro-harmine is also a serotonin reuptake inhibitor
 - ▶ *Psychotria viridis* → dimethyl-triptamin (DMT)
 - ▶ Serotoninergic hallucinogenic
 - ▶ 5-HT_{1A} ← anxiolytic
 - ▶ 5-HT_{2A} ← psychedelic
- ▶ Experimental experiences:
 - ▶ Stimulates neurogenesis
 - ▶ Has anti-ischemic effect



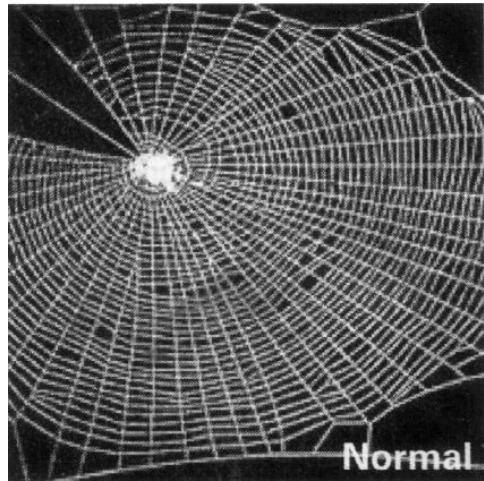
Banisteriopsis caapi



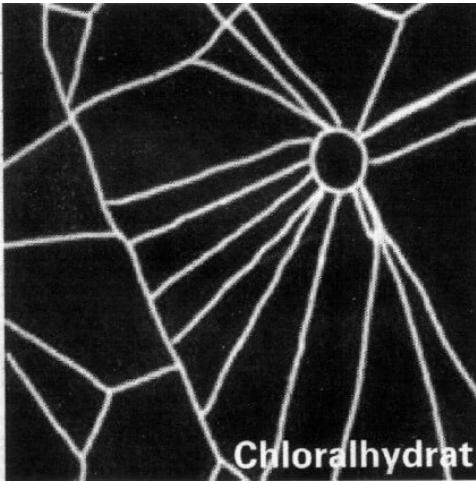
Psychotria viridis



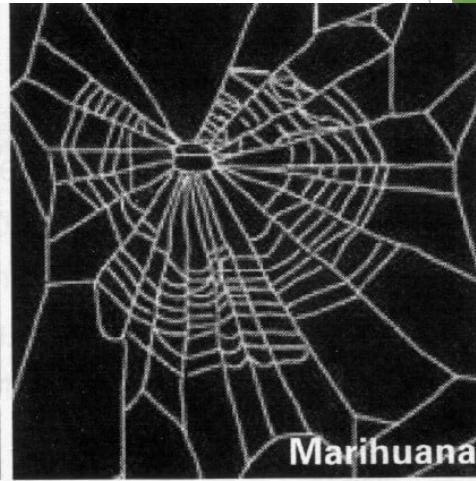
Spider on drugs



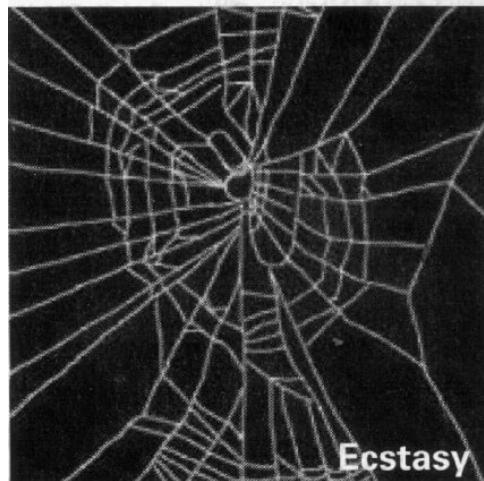
Normal



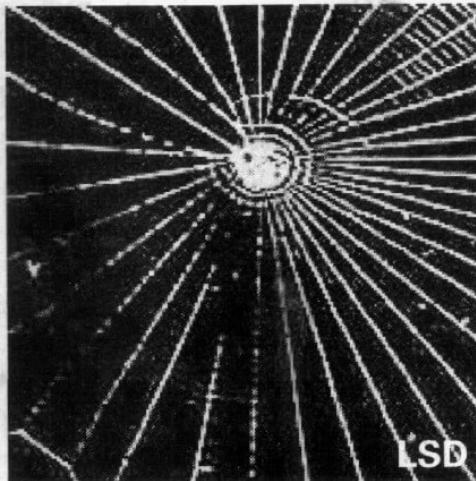
Chloralhydrat



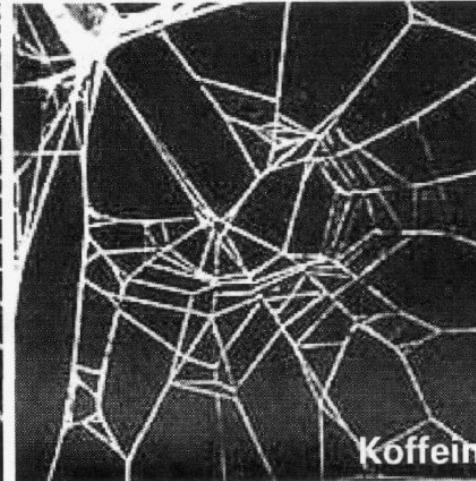
Marihuana



Ecstasy



LSD



Koffein

Central and peripheral skeletal muscle relaxants

Central skeletal muscle relaxants

The muscle-tone

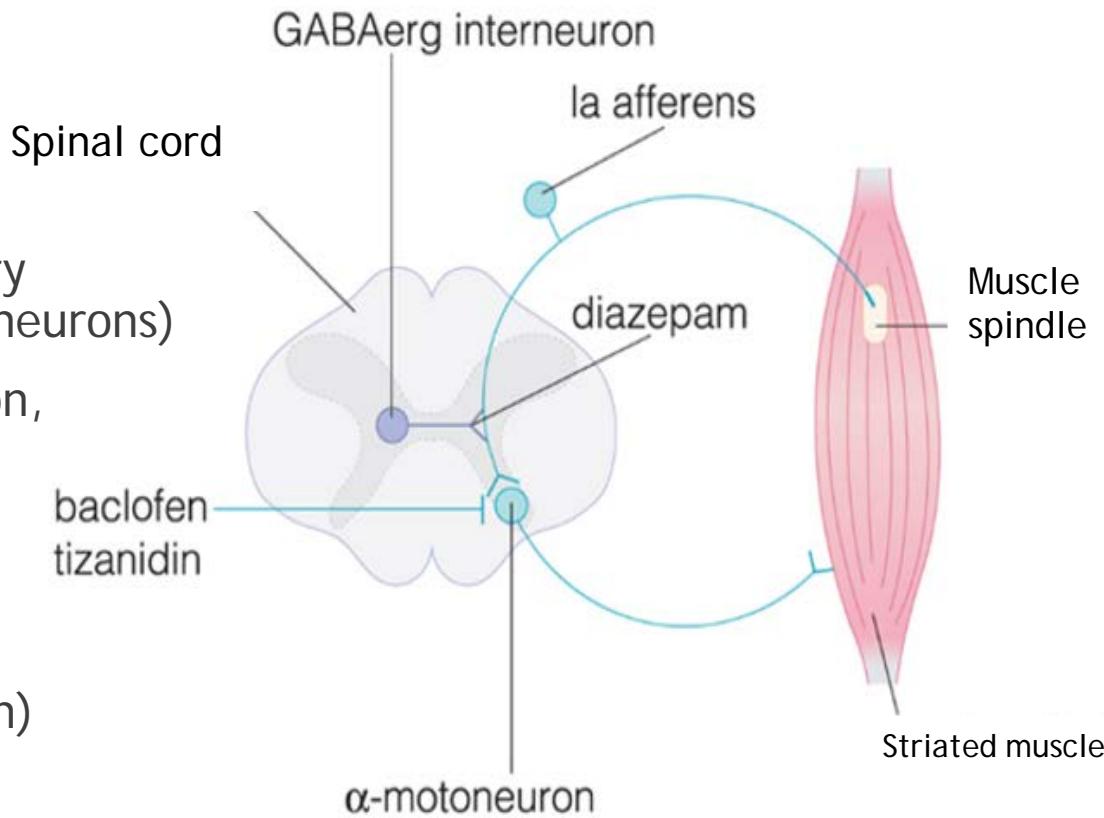
- ▶ Muscle tone: stretch reflex or myotatic reflex or proprioceptive reflex (monosynaptic)
 - ▶ Type Ia primer afferent neurons (carry information from muscle spindle to ventral horn of spinal cord)
 - ▶ Glutamatergic (excitatory) synapse with
 - ▶ efferent α -motoneurons (carry information from ventral horn back to the muscle's neuromuscular junction (n-ACh receptor))

Spasticity: chronic disorder of regulation of muscle tone

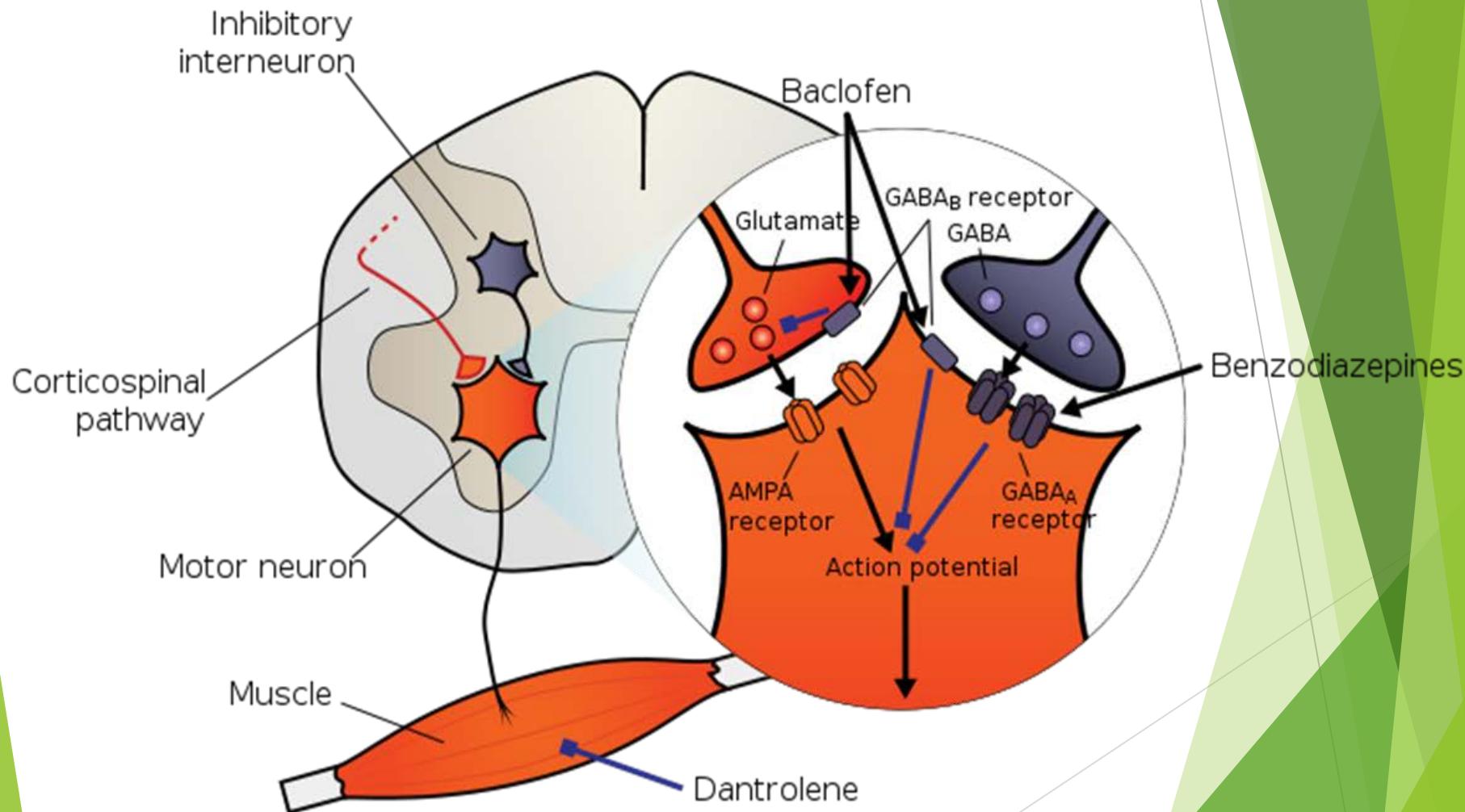
Due to injury/damage of inhibitory motoric pathways (GABAergic interneurons)

(e.g. stroke, chronic inflammation, demyelinisation
(Sclerosis Multiplex))

Acute musclespasms: reversible
(due to e.g. trauma, inflammation)



Other motoric pathways - voluntary movement



Definition of central skeletal muscle relaxants, mechanism of action and indications

Aim: to decrease the basal tone of skeletal muscles by inhibiting *α -motoneurons*

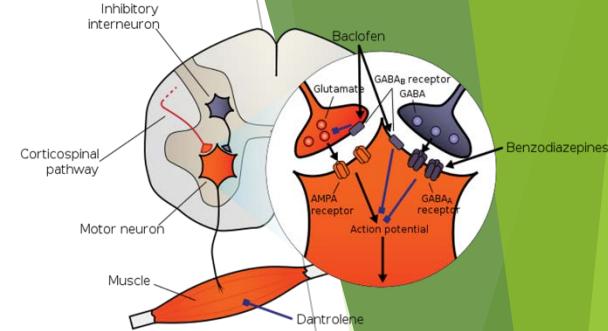
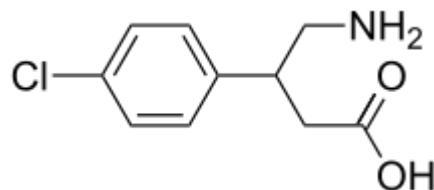
- ▶ decreasing release of excitatory transmitters (mainly glutamate)
- ▶ increasing effect of inhibitory transmitters (mainly GABA)

Indications:

- ▶ these drugs are used to control spastic muscle tone as in epilepsy, multiple sclerosis, spastic cerebral palsy, stroke, etc
- ▶ also in acute muscle spasms: spinal cord injury, myelitis, Spinal disc herniation etc.

Agents effective only in spasticity

Baclofen



- ▶ selective agonist of GABA_B receptors
(mostly presynaptically on excitatory neurons)
 - ▶ Gi signal transduction & opens K⁺ channels & inhibits Ca²⁺ channel → hyperpolarisation & reduces Ca²⁺ influx → decreased release of excitatory neurotransmitters (glutamate)
- ▶ inhibits monosynaptic (myotatic) and polysynaptic (flexor-) reflexes as well
- ▶ acts on nociceptive afferents as well
(by the inhibitory neurotransmitter substance-P)
- ▶ It is rapidly and completely absorbed orally; half life is 3- 4 hours

Under try-out

Gabapentin

Progabid

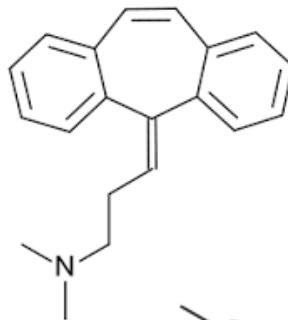
Glicin



Agents effective primarily in acute spasms

Cyclobenzaprine

- ▶ Mechanism of effect: unknown
 - ▶ 5HT2 receptor antagonist at brainstem
- ▶ Antimuscarin adverse effects



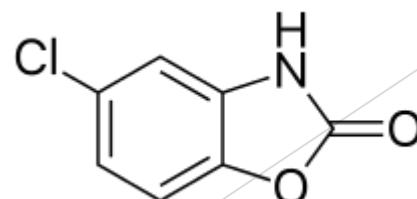
Guaifenesin

- ▶ im. or iv. injection is skeletal muscle relaxant
 - ▶ Due to NMDA-antagonistic effect
- ▶ orally expectorant: increasing the volume and reducing the viscosity of secretions in the trachea and bronchi



Chlorzoxazone

- ▶ Depresses spinal cord with unknown mechanism
- ▶ usual dose is 250 mg 3 times daily

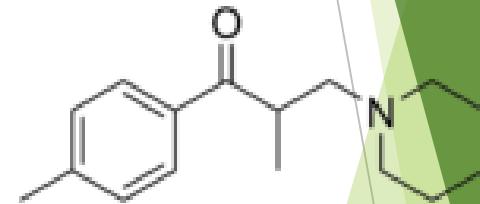


Agents effective in spasticity and in acute muscle spasms as well

- ▶ Diazepam (usual daily dose 5-20 mg divided into 2-4 times) (see 1st seminar)
- ▶ Tizanidin (clonidine-like, α_2 -agonist)
- ▶ Tolperison (Mydeton, Miderizon; 3x50-150 mg)



*inhibits voltage-gated Na⁺-channels like local anaesthetics
→ inhibits spreading of action potential*

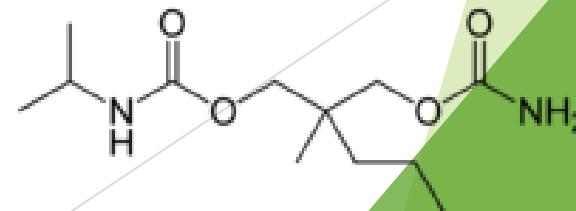


- ▶ Carisoprodol (Scutamil C tbl), Meprobamat

Both carisoprodol and meprobamat has abuse-potential

Mechanism of action:

not completely known
meprobamate is a GABA-A agonist

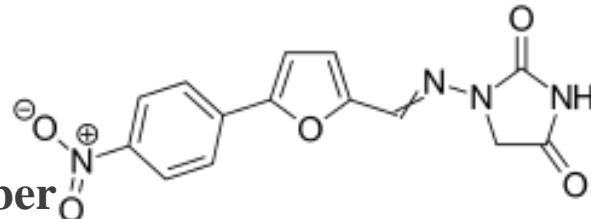


Other agents against increased spasticity

- ▶ „Peripheral“ muscle relaxant,
but indications are as central muscle relaxants

- ▶ **Dantrolene**

- ▶ It acts directly: on muscle fiber
- ▶ inhibits ryanodine receptors =
inhibits Ca²⁺ release from sarcoplasmic reticule →
decreases muscle contraction



Indications:

- ▶ It is very useful in the treatment of malignant hyperthermia (caused by depolarizing muscle-relaxants and inhalational general anaesthetics)
- ▶ Also in any cases of hypertermia including serotonin syndrome (caused by antidepressants, CNS stimulants/psychedelics etc.)
- ▶ administration: orally or intravenously.
Oral absorption is only one third.
- ▶ Half life of the drug is 8-9 hours.
- ▶ **Botulinum toxin** - neurotoxic protein

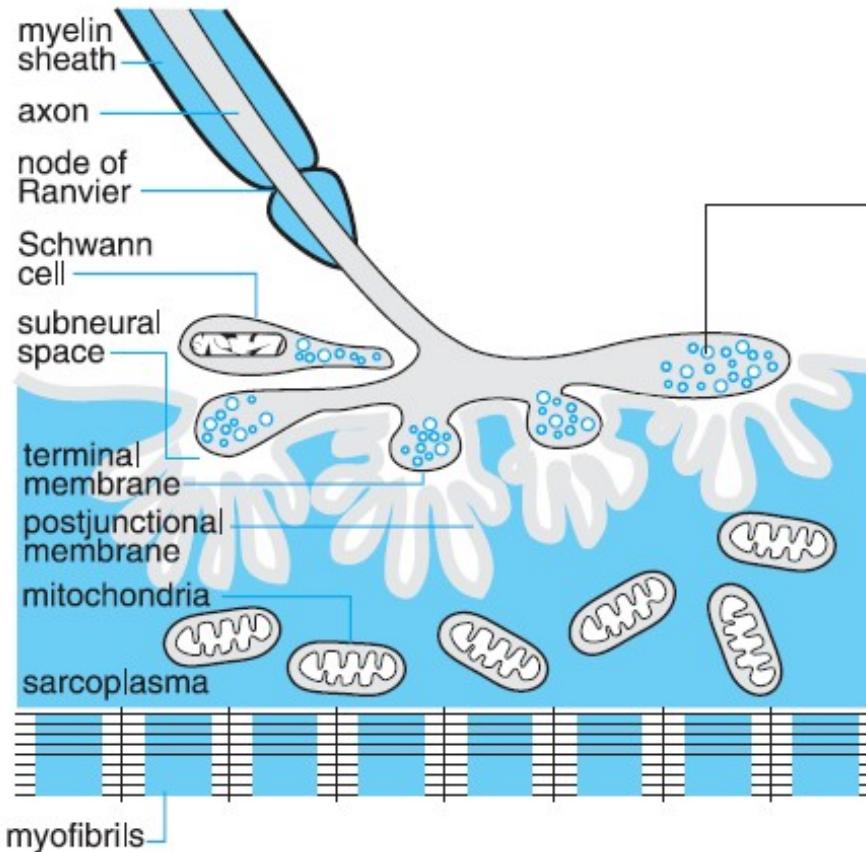


Clostridium botulinum bacterium, inhibits the release of ACh in neuromuscular synaptic cleft

Peripheral skeletal musclerelaxants

Peripheral muscle relaxants

ANATOMY of the Motor End Plate



PHYSIOLOGY

nerve action potential (AP)

vesicular acetylcholine release

depolarization (EPP)
(increased permeability to Na^+ and K^+)

hydrolysis of acetylcholine by cholinesterase

muscle action potential

spread of excitation in muscle

muscle contraction

PHARMACOLOGY

tetrodotoxin
batrachotoxin
local anesthetics

hemicholinium (Ach synthesis inhibition)
botulinus toxin
procaine, Mg^{2+}
4-aminopyridine
lack of Ca^{2+}

excess of Ca^{2+}
curare alkaloids
snake α -toxins
succinylcholine
decamethonium

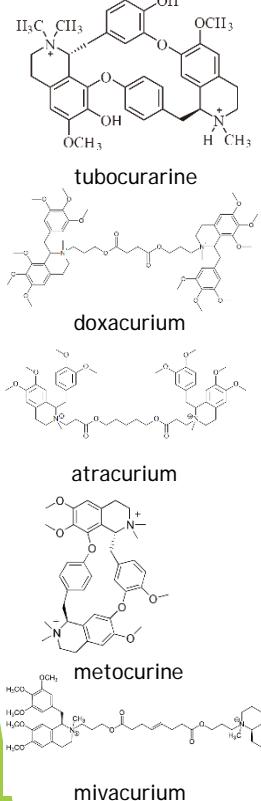
cholinesterase inhibitors
 Ca^{2+}
veratridine

quinine
tetrodotoxin (VG Na^+ inhibition)

metabolic poisons
lack of Ca^{2+}
procaine
dantrolene (uncoupling of RyR)

- ← enhancement
- ← X blockade
- ←---- depolarization and phase II block

Peripheral muscle relaxants



Definition: they act peripherally, blocking the neuromuscular junction

Two main groups:

► Non depolarizing agents

Isoquinoline derivatives

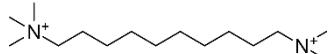
- Tubocurarine
- Doxacurium
- Atracurium
- Metocurine
- Mivacurium

Steriod derivatives

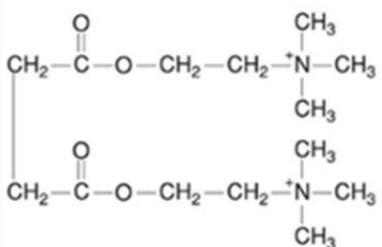
- Pancuronium
- Vecuronium
- Pipecuronium
- Rocuronium
- Rapacuronium

► Depolarizing agents

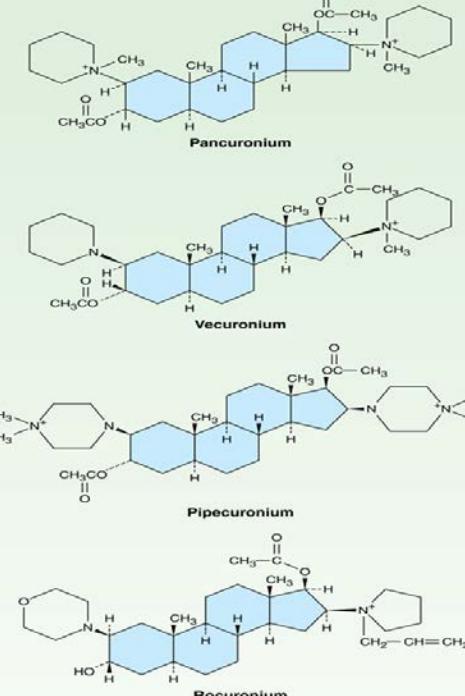
- Suxamethonium (Succinylcholine)
- Decamethonium



Decamethonium

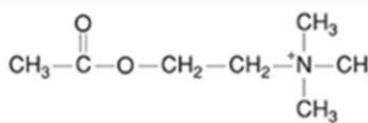


suxamethonium

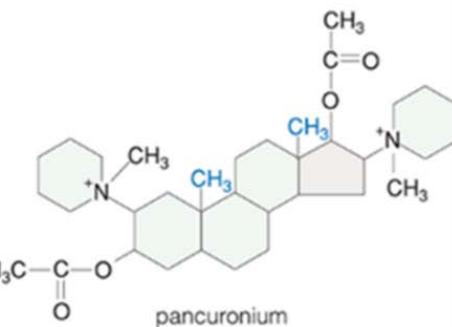


Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 12th edition: www.accessmedicine.com

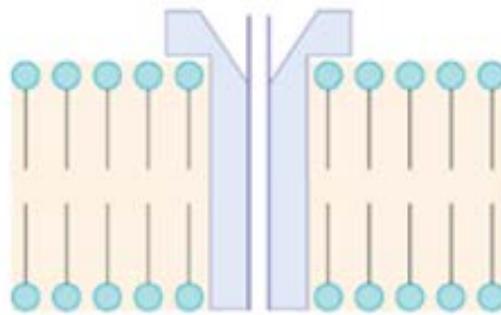
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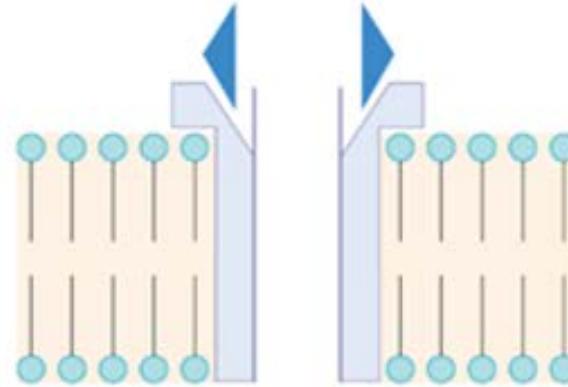
acetilkolin



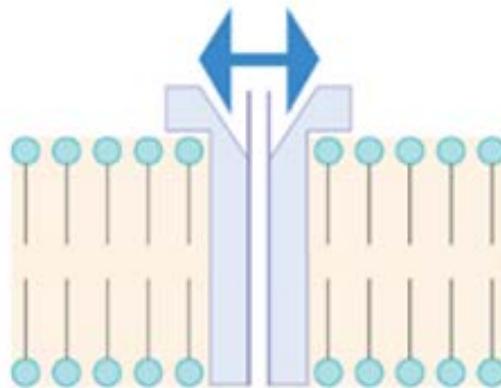
pancuronium



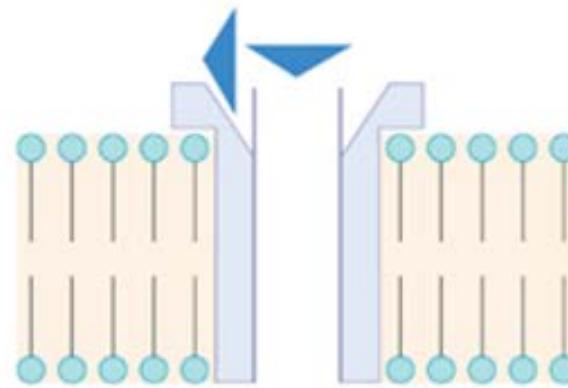
a zárt csatorna



b nyitott csatorna



c nem depolarizáló
izomrelaxáns hatása



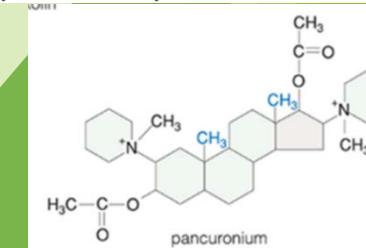
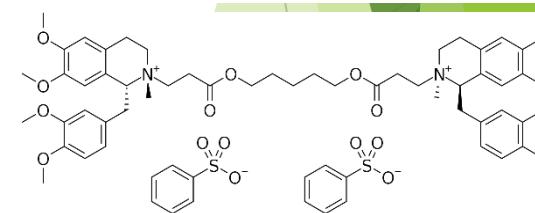
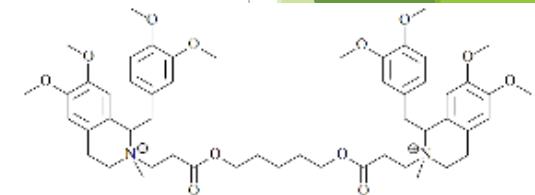
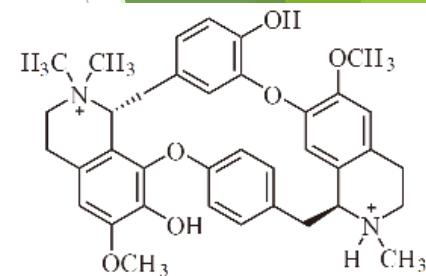
d depolarizáló
izomrelaxáns hatása

Actions

- ▶ All the muscles are not equally sensitive to blockade.
- ▶ Small and rapidly contracting muscles are paralyzed first.
- ▶ Respiratory muscles are last to be affected and first to recover.

Peripheral muscle relaxants

- Non depolarizing muscle relaxants
 - competitive antagonism on muscular type nAChR
 - structural resemblance to ACh
 - antidote: increasing ACh levels
 - e.g. with cholinesterase inhibitors (e.g. physostigmin, neostigmin)
 - flaccid paralysis
 - administered i.v.
 - highly water soluble → cross blood-brain-barrier poorly
 - d-tubocurarin (curare)
 - arrow poison, blocked motorium – but! intact sensory functions
 - no enteral absorption
 - hypotension (symp.ggl.block)
 - atracurium (Tacrium®)
 - spontaneous degradation
 - active metabolite: laudanosin (CNS effects, tachycardia)
 - cisatracurium
 - „most commonly used”
 - no laudanosine
 - pancuronium (Pavulon®)
 - no sympathomimetic effect
 - no histamin release



Peripheral muscle relaxants

- Depolarizing muscle relaxants (Dual phase blockade)
 1. Depolarisation block (just like large dose of Ach):
Fasciculation = muscle twitching
 2. Desensitisation block: the receptor is desensitized → paralysis
- succinyl-choline:
 - ultrashort effect (5-10 min - 0,5-1mg/bwkg) → continuous infusion
 - BChE/PChE metabolizes it only (which is not present at synaptic cleft) Ceasing of effect = redistribution to plasma (there low cc. exist)
 - adverse effects:
 - hyperkalemia (K+ release from ic. sites)
 - arrhythmia (digitalis th.)
 - malignant hyperthermia
- Clinical use of muscle relaxants
 - surgical relaxation, immobilization
 - endotracheal intubation
 - control of ventilation (to reduce the chest wall resistance)
 - treatment of convulsions

