Drug addiction.

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Addiction = compulsive drug use despite harmful consequences

is characterized by an inability to stop using a drug (failure to meet work, social, or family obligations; tolerance and withdrawal).

accompanied by unnatural cravings that prompt the compulsive behaviors.

It is a primary, **chronic, neurobiologic disease** with genetic, psychosocial and environmental factors that influence its development and manifestations.

It is characterized by behaviours that include one or more of the following:

loss of control over drug use

continued use despite harm

compulsive use and craving

International Statistical Classification of Diseases and Related Health Problems 10th Revision:

Mental and behavioural disorders due to psychoactive substance use (F10-F19)

F10: Mental and behavioural disorders due to use of alcohol

F11: Mental and behavioural disorders due to use of opioids

F12: Mental and behavioural disorders due to use of cannabinoids

F13: Mental and behavioural disorders due to use of sedatives or hypnotics

F14: Mental and behavioural disorders due to use of cocaine

International Statistical Classification of Diseases and Related Health Problems 10th Revision:

F15: Mental and behavioural disorders due to use of other stimulants, including caffeine

F16: Mental and behavioural disorders due to use of hallucinogens

F17: Mental and behavioural disorders due to use of tobacco

F18: Mental and behavioural disorders due to use of volatile solvents

F19: Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances

Historic context of drug use

Opium known already in neolithic age (8 000 – 5 000 years B.C.)

Coca and resin from hemp – known thousands years

Drugs were first use for their therapeutic purposes, secondary for they narcotic purposes

Isolation of morphine (1805),

caffeine (1820),

nicotine (1828),

cocaine (1859),

ephedrine (1887)

(Dundr, 1995; Miovsky et al., 2008)

19th century: beginning of commercial narcotics production

(e.g. morphine since 1828, cocaine 1862, heroine 1898)

Legal consumption of drugs was ended by opium conventions:

1909 Shanghai,

1912 Haag

1925 Geneva

Illegal way: French Connection (France), Cosa Nostra (USA)

After WWII:

Single Convention on Narcotic Drugs of 1961 - an international treaty to prohibit production and supply of specific (nominally narcotic) drugs and of drugs with similar effects

Council of the Government for Drug Policy Coordination - Annual registr (2012):

CZ – the most frequently abused drugs:

Psychostimulant drugs (particularly methamphetamine, syn. pervitin)

Hemp drugs (particularly tetrahydrocannabinol – THC).

Tolerance x Dependence x Sensitization

Tolerance: a decrease in the effect of a drug as a consequence of repeated exposure (the effectiveness can decrease with continued use).

Mechanisms of Tolerance:

Pharmacokinetic Tolerance (enzyme induction effect)

It occurs because of a decreased quantity of the substance reaching the site it affects.

This may be caused by an increase in induction of the enzymes required for degradation of the drug e.g. CYP450 enzymes.

This is most commonly seen with substances such as ethanol.

This type of tolerance is most evident with oral ingestion, because other routes of drug administration bypass first-pass metabolism.

Tolerance x Dependence x Sensitization

Pharmacodynamic Tolerance (NT depletion, receptor plasticity)

It occurs when the cellular response to a substance is reduced with repeated use.

This may be caused by a reduced receptor response to receptor agonists (receptor desensitization), a reduction in receptor density (usually associated with receptor agonists), or other mechanisms leading to changes in action potential firing rate.

Dependence: a maladaptive pattern of substance use, leading to clinically significant tolerance, impairment, or distress; an adaptive state associated with a withdrawal syndrome upon cessation of repeated exposure to a stimulus (e.g., drug intake).

Tolerance x Dependence x Sensitization

Dependence develops when the neurons adapt to the repeated drug exposure and only function normally in the presence of the drug.

When the drug is withdrawn, several physiologic reactions occur. These can be mild (caffeine) or even life threatening (alcohol).

This is known as the **withdrawal syndrome**.

Tolerance x Dependence x Sensitization

Physical dependence x psychological dependence

Physical dependence (physiologic dependence) referrers to the adverse physical symptoms and signs that result from the withdrawal of the drug.

It results from many of the same mechanisms that produce tolerance.

As with tolerance, homeostatic set-points are altered to compensate for the presence of the drug.
If drug use is discontinued, the altered set-points produce **effects opposite** to those manifested in the presence of the drug.

Psychological dependence

Psychological dependence is a change in emotional state that occurs after using a substance or engaging in a behaviour over a period of time.

i.e. dependency on specific psychological phenomena provoked by the drug (e.g. euphoria)

This change in emotional state is a result of changes in brain chemicals.

It can cause **craving**, motivation to seek out the substance or behavior, irritability, anxiety, or general dissatisfaction when withdrawing from the substance or activity.

Dependence producing substances

Inverse tolerance (sensitization): the drug becomes more effective with repeated doses.

Tolerance

Decreased response to substance effects. A higher dose is required to achieve the same effect.

Substance is usually given in shorter intervals or continuously

Senzitization
(Robinson & Berridge, 1993)

Increased response following repeated drug administration

Intermitent drug administration

Inverse tolerance (sensitization):

There are two hypothesis to explain mechanism of sensitization to psychostimulants:

1) Intermittent exposure to a drug will cause intermittent dopamine release. This will lead to decreased sensitivity or density of pre-synaptic dopamine autoreceptors.

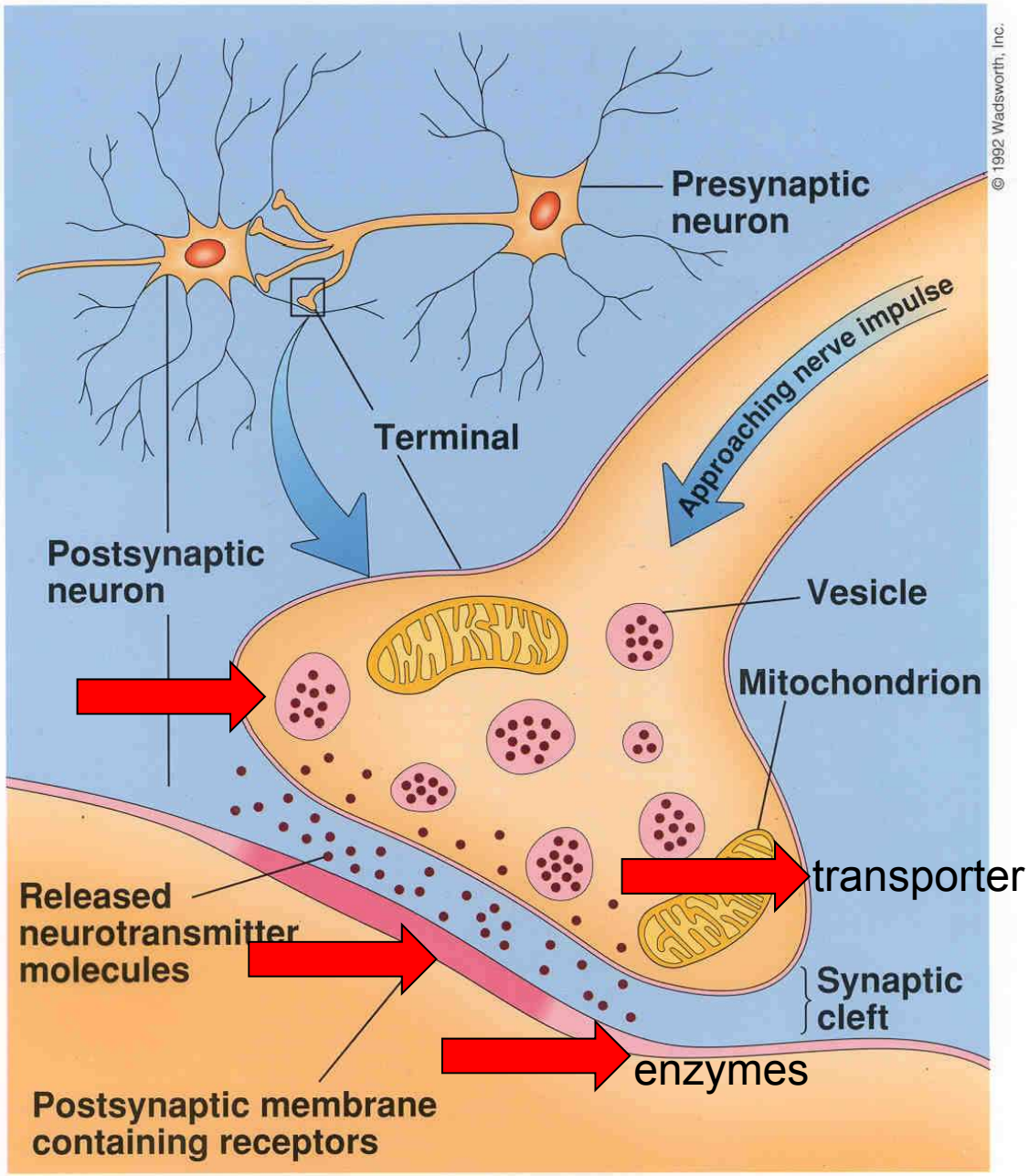
These receptors are responsible for negative feed back → increased dopamine release → increase stimulatory effects of dopamine.

Important rather for development of sensitization than expression.

2) Long-term intermittent exposure to a drug provokes intermittent release of high amounts of dopamine → gradual depletion of dopamine in cytoplasm.

This results in increased sensitivity of D_1 postsynaptic receptor (because they are not stimulated by their natural ligand).

Thus, after challenge dose administration (that acts through activation of the same postsynaptic receptors), an augmented behavioural response can be expected.


Presynaptic neuron
Terminal
Approaching nerve impulse
Postsynaptic neuron
Vesicle
Mitochondrion
transporter
Released neurotransmitter molecules
Synaptic cleft
enzymes
Postsynaptic membrane containing receptors
© 1992 Wadsworth, Inc.

Synapse

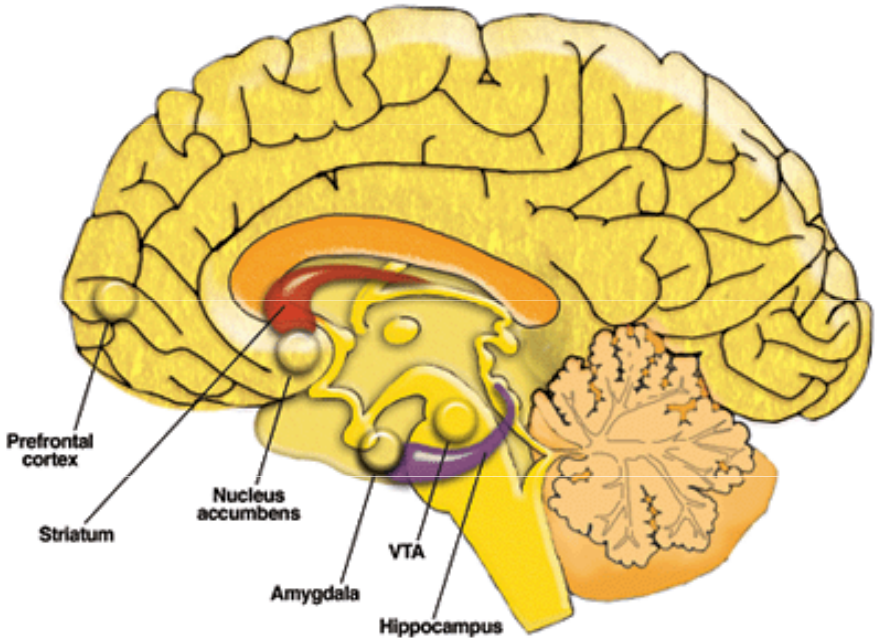
Exposure to alcohol and other drugs (AODs):

Plastic changes associated with AOD use - release of the neurotransmitter dopamine from cells in ventral tegmental area (VTA) induced by addictive drugs.

The VTA is one of the components of the mesolimbic dopamine system – **REWARD PATHWAY**.

Neurons whose cell bodies are located in the VTA, extend long axons most prominently to the nucleus accumbens (NAc) and the prefrontal cortex

Dopamine release in the mesolimbic system is critical for the drive to ingest AODs.



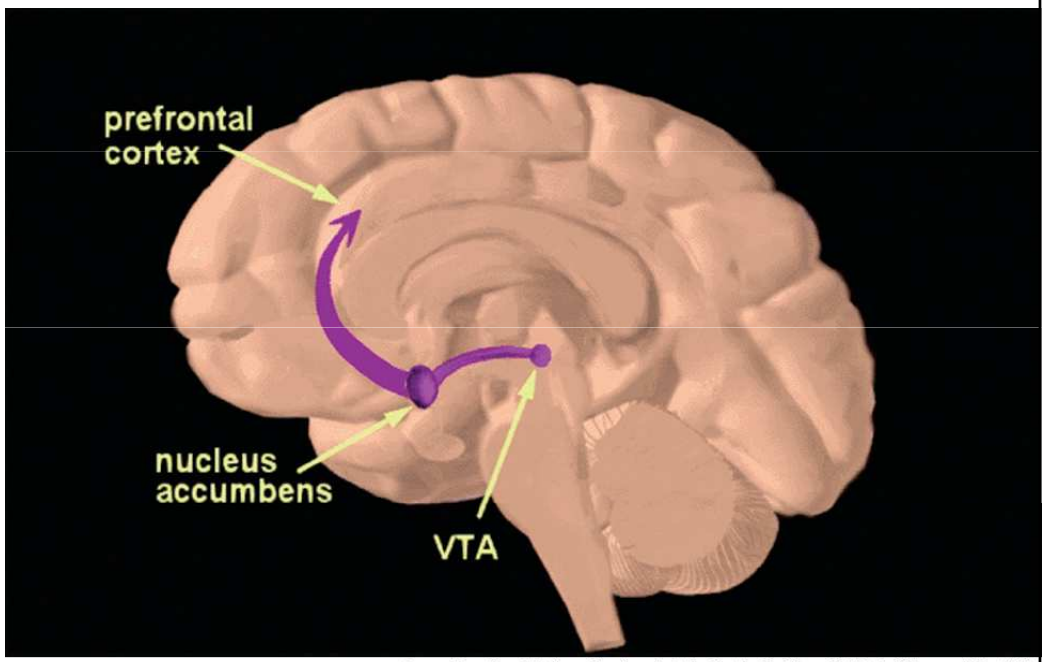


Image retrieved from http://www.nida.nih.gov/pubs/teaching/teaching3/largegifs/slide-4.gif (Accessed 3 Nov 2010).

The mesocorticolimbic dopamine system as an initial target of addictive drugs.

The VTA, at the origin of the mesocorticolimbic system, is composed of dopamine projection neurons that are under inhibitory control of GABA interneurons

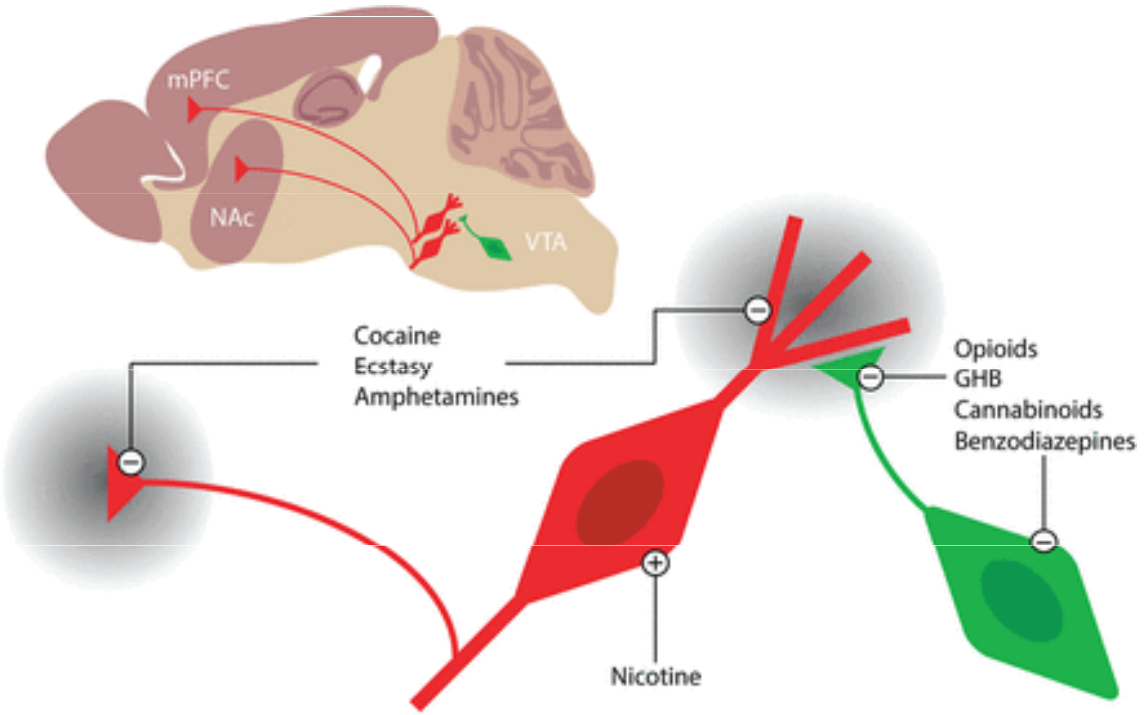
The main targets are the NAc and the mPFC.

Addictive drugs cause an increase in mesocorticolimbic dopamine through:

1) direct activation of dopamine neurons (e.g., nicotine);

2) indirect disinhibition of dopamine neurons (opioids, cannabinoids, benzodiazepines);

3) interference with dopamine reuptake (cocaine, ecstasy, and amphetamines).



Summary of presented substances

alcohol

nicotine

cannabinoids (hemp drugs)

opioids

benzodiazepines

„classical“ psychostimulant drugs

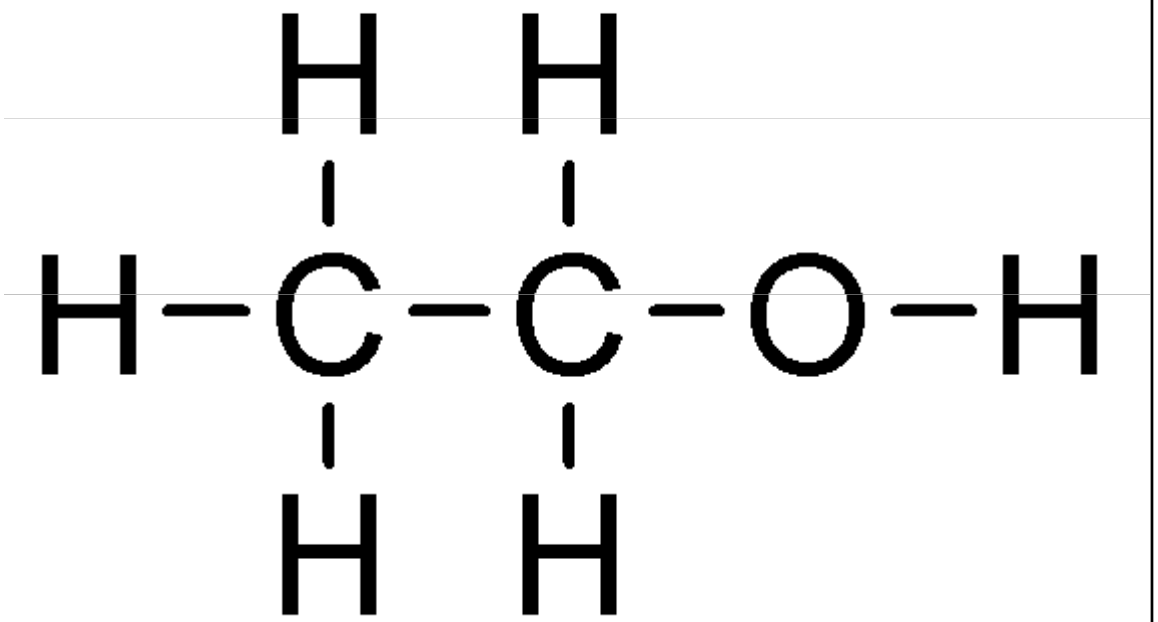
MDMA (exctasy)

„new“ synthetic substances

hallucinogens

Alcohol
syn. ethanol, ethyl alcohol, spirit

Arab. al-kahal (gentle substance)



Alcohol

- is an intoxicating ingredient found in beer, wine, and liquor

- is produced by the fermentation of yeast, sugars, and starches

- it passes directly from the digestive tract into the blood vessels.

  In minutes, the blood transports the alcohol to all parts of the body, including the brain.

Short-term effects of alcohol consumption

improved mood

memory, and insight are impaired.

impairment of judgment, emotional control, and motor coordination

respiratory depression and death can result from overdose

most serious consequences occur when alcohol is combined with other psychoactive agents

Alcohol

Long-term effects of alcohol misuse:

Brain:

Memory loss, blackouts, and exaggerated states of emotion

Problems with coordination and muscle movement

Depressed nerve centers in hypothalamus that control sexual arousal and performance

Korsakoff's psychosis (persistent learning and memory problems)

Learning difficulties

Slowing of neurogenesis, of the growth of new brain cells

Sleep impairment, as alcohol decreases REM sleep and sleep apnea

Peripheral neuropathy, leading to a loss of sensation

https://mmcneuro.wordpress.com/category/amnesia/

Alcohol

Long-term effects of alcohol misuse:

Esophagus:

Increased risk of cancer in esophagus, larynx, and mouth

Vomiting from excessive drinking can tear the esophagus

Pancreas:

Reduced amount of digestive enzymes secreted by the pancreas, which inflames and leaks digestive enzymes that attack the pancreas

Liver:

Liver failure, fat accumulation in liver cells, hepatitis

Cirrhosis

Hepatic encephalopathy, a serious brain disorder that can cause changes in sleep patterns, mood, personality, shortened attention span, anxiety and depression, and problems with coordination such as shaking or flapping hands (called asterixis).

Alcohol

Long-term effects of alcohol misuse:

Stomach:

Ulcers

Gastritis (inflammation of stomach lining)

Acid reflux

Intestinal bleeding

Risk of stomach cancer

Diarrhea and vomiting

Hypoglycemia

Calories in alcohol make chronic drinkers less hungry, leading to malnutrition

Alcohol

Long-term effects of alcohol misuse:

Reproductive system:

Decreased sperm production and testosterone in men due to decreased sex hormone secretion

Decreased estrogen metabolism in the liver, which boosts estrogen levels and can contribute to menstrual irregularities and infertility

Kidneys:

Kidney failure, which affects regulation of fluids and electrolytes in body

Heart:

Heart disease and heart attack

High blood pressure

Enlarged heart (cardiomyopathy)

Irregular or rapid heartbeat

Coronary artery disease

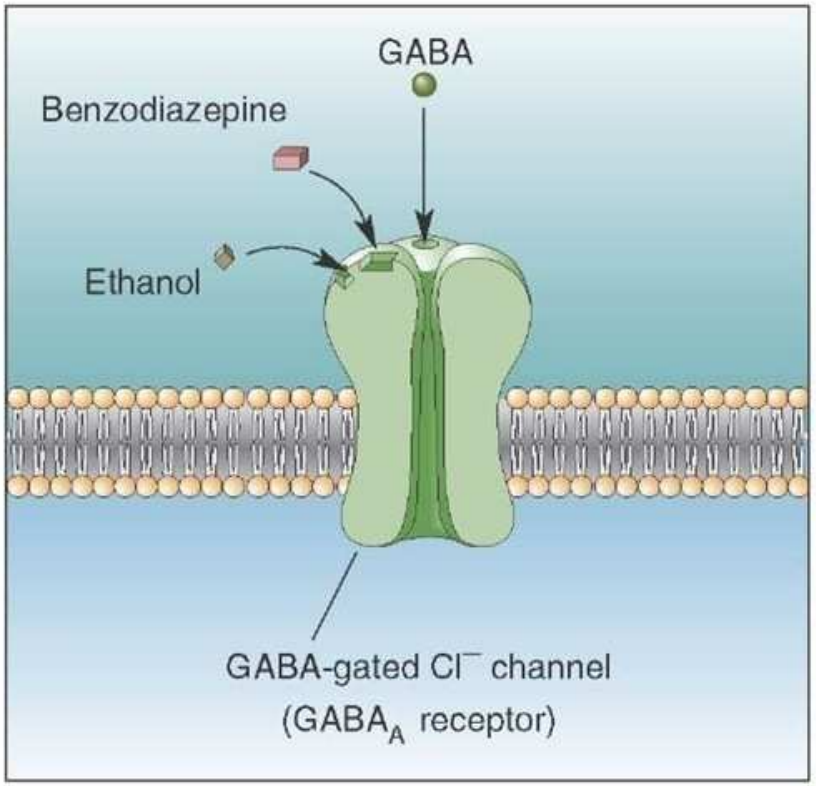
Alcohol – mechanism of action

Two specific neurochemical systems in the brain are implicated in mediating alcohol intoxication:

1) gamma aminobutyric acid (GABA) and its receptor ($GABA_A$)

2) glutamate and N-methyl-D-aspartic acid receptor (NMDA).

GABA: the major inhibitory neurotransmitter in the brain



When these receptors are activated by their specific neurotransmitter, cellular activity changes.
E.g. BZD (which share many behavioural properties with alcohol), enhance chloride ion transport through the $GABA_A$ receptor, causing a decrease in neuronal activity

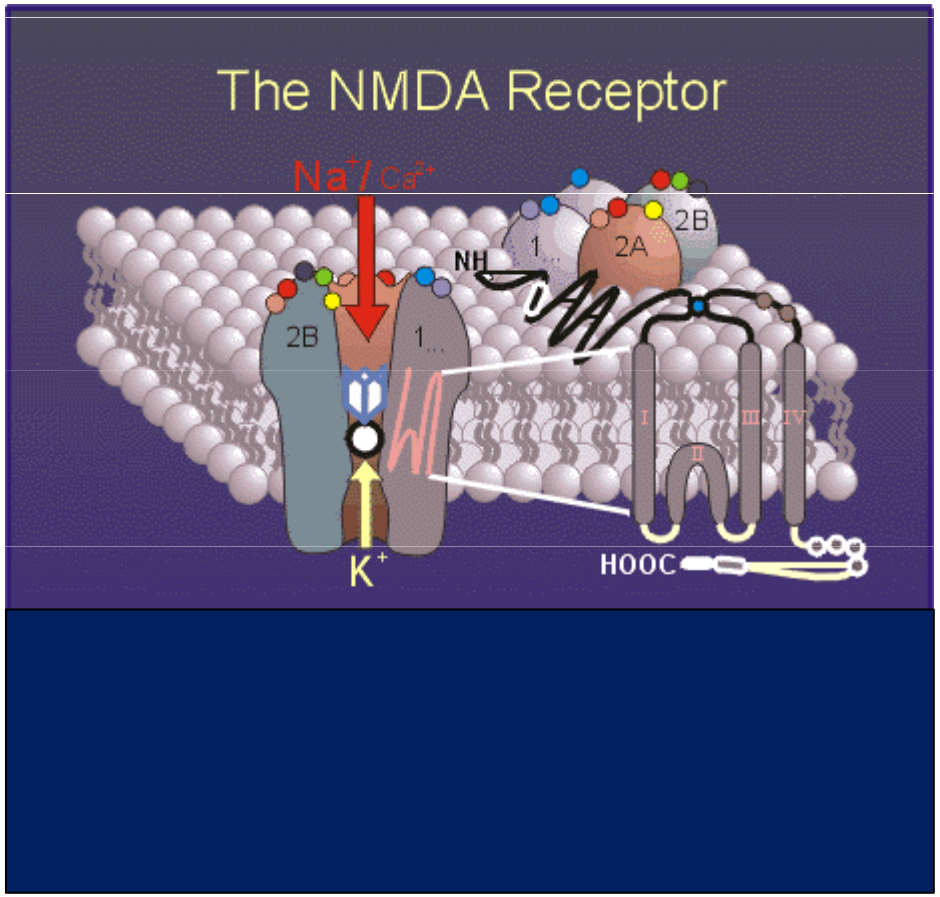
Drugs that mimic the effects of GABA enhance and prolong the behavioral effects of alcohol

Alcohol – mechanism of action

Glutamate: the major excitatory neurotransmitter in the brain, is also believed to play an important role in alcohol intoxication and behaviour

Alcohol antagonizes NMDA-induced behavioral responses

Inhibition of NMDA receptors is an important mechanism by which acute alcohol consumption affects brain function and behaviour



Alcohol – mechanism of action - summary

Alcohol mimics effects of GABA in the brain, binding to $GABA_A$ receptors and inhibiting neuronal signaling.

Alcohol is a positive allosteric modulator of $GABA_A$ receptors. It increases chloride conductance through $GABA_A$ receptors, resulting in cellular hyperpolarization.

Alcohol inhibits the major excitatory neurotransmitter, glutamate, particularly at the NMDA receptor.

It decreases calcium conductance through NMDA receptors, further decreasing cellular excitation.

These dual actions on $GABA_A$ and NMDA receptors contribute to alcohol's anxiolytic, sedative, and CNS-depressant effects

It also releases other inhibitors, such as dopamine and serotonin by a process that is still poorly understood but that appears to involve curtailing the activity of the enzyme that breaks dopamine down.

Alcohol

Withdrawal symptoms

may appear anywhere from six hours to a few days after your last drink.

These usually include at least two of the following:

tremors

anxiety

nausea and/or vomiting

headache

increased heart rate

sweating

irritability

confusion

insomnia, nightmares

Alcohol

Withdrawal symptoms

Symptoms may worsen over two to three days and persist for weeks

They may be more noticeable when you wake up with less alcohol in your blood

The most severe type of withdrawal syndrome is known as **delirium tremens**

Its symptoms include:

extreme confusion and agitation

fever

seizures

tactile hallucinations (e.g., itching, burning, and numbness)

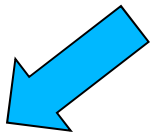
auditory hallucinations (e.g., hearing non-existent sounds)

visual hallucinations (e.g., seeing non-existent images)

Alcohol

Pharmacologic Treatment of Addiction

Dominative psychotherapy
+
Supportive pharmacotherapy



Achievement and maintenance of total abstinence:

DISULFIRAM
ACAMPROSATE
NALTREXONE (NALOXONE)

Decrease in risk consumption:

NALMEFENE

Alcohol

Pharmacologic Treatment of Addiction

DISULFIRAM: irreversibly inhibits acetaldehyde dehydrogenase.

Intake of ethanol during disulfiram therapy will lead to accumulation of acetaldehyde, which is considered the main contributing factor to the disulfiram-alcohol reaction

The disulfiram- alcohol reaction is characterised by:

- Intense vasodilation of the face and neck causing flushing, increased body temperature, sweating, nausea, vomiting, pruritis, urticaria, anxiety, dizziness, headache, blurred vision, dyspnoea, palpitations and hyperventilation.

Alcohol

Pharmacologic Treatment of Addiction

ACAMPROSATE: has a chemical structure similar to that of amino acid neuromediators, such as gamma-amino-butyric acid (GABA)

Acamprosate may act by stimulating GABAergic inhibitory neurotransmission and antagonising excitatory amino-acids, particularly glutamate.

It stabilizes the chemical balance in the brain that would otherwise be disrupted by alcoholism, i.e. it helps to maintain abstinence, **decreases craving**

Alcohol

Pharmacologic Treatment of Addiction

NALTREXONE: opioid antagonist (all opioid receptors).

It reduces alcohol consumption (decreasing „reward“ effect).

The mechanism of action of naltrexone in alcoholism is not completely elucidated, however an interaction with the endogenous opioid system is suspected to play an important role.

Alcohol consumption in humans has been hypothesized to be reinforcing through an alcohol-induced stimulation of the endogenous opioid system.

Hepatic side effects have included hepatocellular injury, hepatitis, and elevated liver transaminases and bilirubin.

Alcohol

Pharmacologic Treatment of Addiction

NALMEFENE: modulator of the endogenic opioid system acting as competitive antagonist at μ a δ receptors and partial agonist at κ receptors with predominant affinity to the μ and κ receptors.

It has similar structure and mechanism to naltrexone. However, it shows better bioavailability after p.o. administration, longer half time of elimination and no hepatic adverse effects.

Nalmefene reduces alcohol consumption, possibly by modulating cortico-mesolimbic functions (there is close association between mesolimbic μ- and δ-opioid receptor activation and dopamine release in nuccleus accumbens) .

Alcohol

Pharmacologic Treatment of Addiction

Clonidine:

α_2 sympatomimetic drug with central effect.

Clonidine is a drug used to lower blood pressure.

Clonidine is now sometimes used in the treatment of alcohol withdrawals.

It is believed to help reduce a number of associated symptoms including:

Tremor

Elevated blood pressure

Anxiety

Tension

Sweating

Alcohol

Pharmacologic Treatment of Addiction

OTHER TESTED SUBSTANCES WITH SIMILAR MECHANISMS:

odelepran (LY2196044; Eli Lilly)

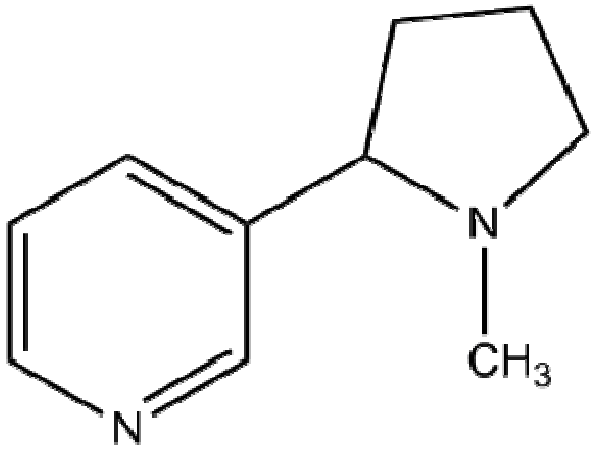
samidorphan (ALKS-33; Alkermes), ALKS-29 (Alkermes).

Alcohol

Clinically used biomarkers:

- Concentration of alcohol in blood (BAC)
- γ-glutamyl transferase (transpeptidase) (GGT)
- Carbohydrate-deficient transferrin (CDT)
- GGT/CDT ratio
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- AST/ALT ratio
- Mean corpuscular volume or mean cell volume (MCV)
- Fosfatidyl ethanol (PEth)
- Triacylglycerols (TAG)
- Immunoglobulin A (IgA)

Nicotine



Nicotine

Nicotine is a tertiary amine found in tobacco. It binds to nicotinic cholinergic receptors.

Nicotine

Pharmacokinetics and metabolism:

Nicotine is a weak base (p*K*a = 8.0).

Absorption through mucous membranes depends on pH.

Chewing tobacco, snuff, and nicotine gum are buffered with an alkaline pH to facilitate absorption through buccal mucosa.

Smoking is a highly efficient form of drug administration, as the drug enters the circulation rapidly through the lungs and moves into the brain within seconds.

Inhaled drugs escape first-pass intestinal and hepatic metabolism.

The more rapid the rate of absorption and entry of a drug into the brain, the greater the rush, and the more reinforcing the drug.

Smoking produces high concentrations of a drug in the brain that are comparable to those seen after intravenous administration.

Nicotine is rapidly and extensively metabolized by the liver, primarily by the liver enzyme CYP2A6.

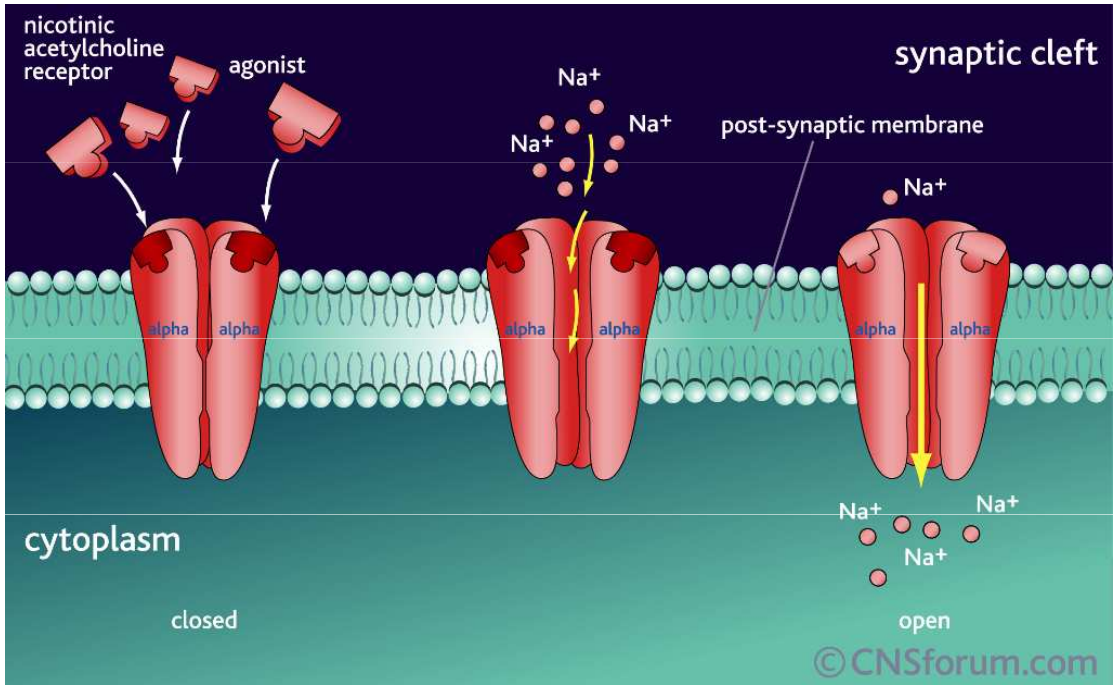
Nicotine – mechanism of action

When a person inhales smoke from a cigarette, nicotine is distilled from the tobacco and is carried in smoke particles into the lungs, where it is absorbed rapidly into the pulmonary venous circulation.

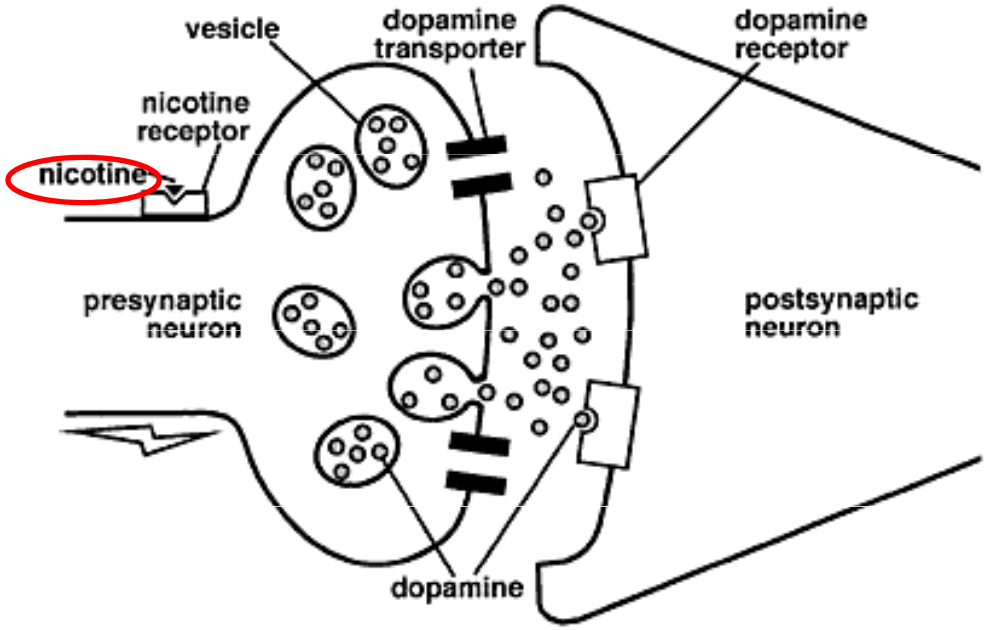
It then enters the arterial circulation and moves quickly to the brain.

Nicotine diffuses readily into brain tissue, where it binds to nAChRs, which are ligand-gated ion channels.

When a cholinergic agonist binds to the outside of the channel, the channel opens, allowing the entry of cations, including sodium and calcium.



Nicotine



Nicotine binds to specific receptors on the presynaptic neuron.

When nicotine binds to receptors at the cell body, it excites the neuron so that it fires more action potentials that move toward the synapse, causing more dopamine release.

When nicotine binds to nicotine receptors at the nerve terminal, the amount of dopamine released in response to an action potential is increased.

Nicotine

Most of the nicotine-mediated release of neurotransmitters occurs via modulation by presynaptic nAChRs.

Chronic cigarette smoking reduces brain monoamine oxidase A and B activity: increase in dopamine and norepinephrine in synapses, thus augmenting the effects of nicotine and contributing to addiction.

Dopamine release signals a pleasurable experience, and is critical to the reinforcing effects of nicotine and other drugs of abuse.

Chemically or anatomically lesioning dopamine neurons in the brain prevents nicotine self-administration in rats.

Nicotine

Effects:

Nicotine from tobacco induces stimulation and pleasure, reduces stress and anxiety.

Smokers come to use nicotine to modulate their level of arousal and for mood control in daily life.

Smoking may improve concentration, reaction time, and performance of certain tasks.

Nicotine releases catecholamines, increases heart rate and cardiac contractility, constricts cutaneous and coronary blood vessels, and transiently increases blood pressure.

Nicotine

Withdrawal symptoms

These include:

irritability

depressed mood

restlessness

anxiety

problems getting along with friends and family

difficulty concentrating

increased hunger and eating

insomnia

craving for tobacco

Nicotine

Withdrawal symptoms

Mood disturbances comparable in intensity to those seen in psychiatric outpatients.

Hedonic dysregulation, the feeling that there is little pleasure in life and that activities that were once rewarding are no longer enjoyable.

Relative deficiency in dopamine release following long-standing nicotine exposure accounts for many of the mood disorders and the anhedonia, as well as the tobacco craving, that may persist in smokers for a long time after they have quit.

Nicotine Replacement Therapy

Nicotine medications act on nAChRs to mimic or replace the effects of nicotine from tobacco.

Nicotine replacement medications are believed to facilitate smoking cessation in several ways.

1) relief of withdrawal symptoms when a person stops tobacco use. Amelioration of these symptoms is observed with relatively low blood levels of nicotine.

2) positive reinforcement, particularly for the arousal and stress relieving effects – it is most relevant to rapid-delivery formulations such as nicotine nasal spray (to a lesser extent, nicotine gum, inhaler, and lozenge).

The use of these products allows smokers to dose themselves with nicotine when they have the urge to smoke cigarettes.

Nicotine Replacement Therapy

3) the last mechanism of benefit is related to the ability of nicotine medications to desensitize nicotinic receptors.

This desensitization results in a reduced effect of nicotine from cigarettes (when a person lapses to smoking while on nicotine replacement therapy, the cigarette is less satisfying and the person is less likely to resume smoking).

Bupropion (Norepinephrine Dopamine Reuptake Inhibitor)

Bupropion was marketed as an antidepressant medication before it was marketed for smoking cessation.

The serendipitous observation of spontaneous smoking cessation among veterans treated with bupropion for depression led to the exploration of bupropion as a smoking cessation medication.

Bupropion increases brain levels of dopamine and norepinephrine, simulating the effects of nicotine on these neurotransmitters.

Bupropion also has some nicotine receptor–blocking activity, which could contribute to reduced reinforcement from a cigarette in the case of a lapse.

Varenicline

Varenicline was synthesized with the goal of developing a specific antagonist for the α4 β2 nAChR.

Varenicline was shown in vitro receptor binding studies to have high affinity for the α4 β2 nAChR, and relatively little effect on other nAChR subtypes or neurotransmitter receptors.

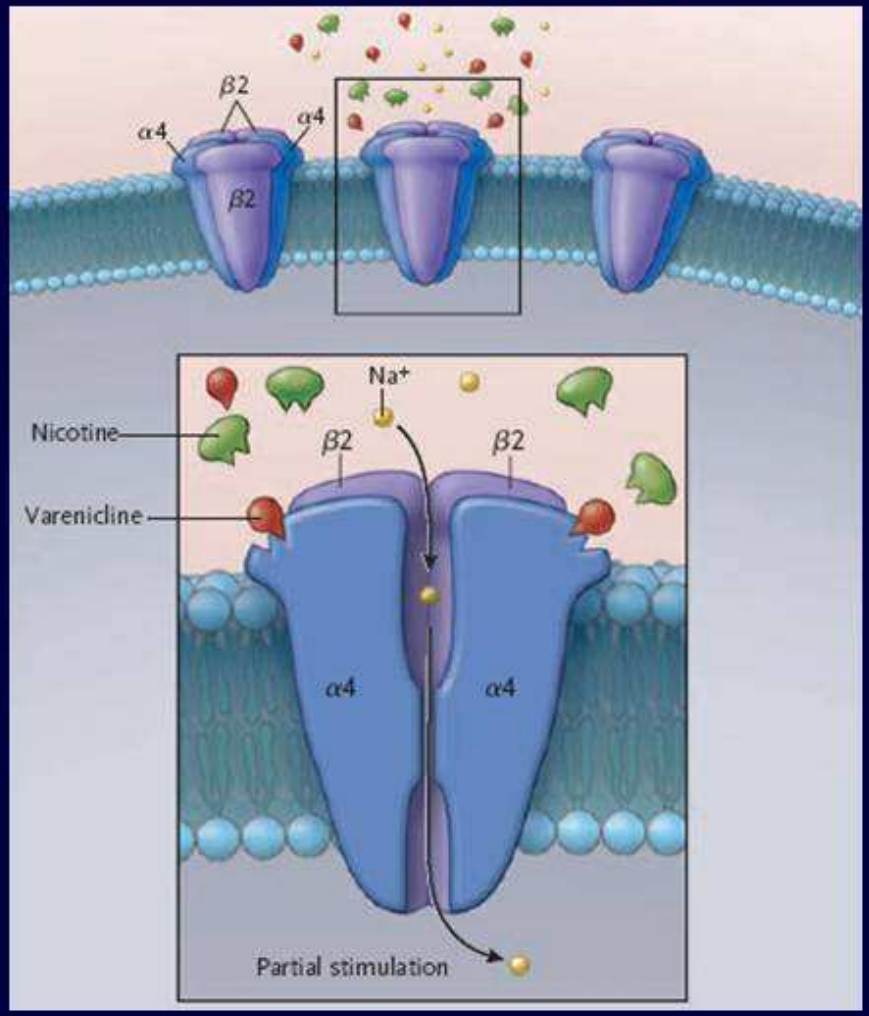
Varenicline

Varenicline is a partial agonist of the α4 β2 receptor.

Nicotine, a full agonist, causes substantial dopamine release. Varenicline produces less of a response than nicotine (~50%) but at the same time blocks the effects of any nicotine added to the system.

Clinical trials have found that varenicline is superior to bupropion in promoting smoking cessation, and prolonged administration of varenicline has been shown to reduce relapse in smokers who were abstinent 12 weeks after initial therapy.

Mechanism of Chantix in Blocking the Effect of Nicotine



From Hays & Ebbert, New Eng J Med, 2008

Chantix (red molecules) block the nicotine receptors on the cell surface well enough to prevent withdrawal from the receptors being empty, but also blocks the binding of nicotine itself (green molecules), which would feed the dependence on tobacco.

GRACE
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Clonidine:

α_2 sympatomimetic drug with central effect.

Clonidine is a drug used to lower blood pressure.

Some studies have reported amelioration of craving, anxiety, restlessness, tension and hunger by clonidine therapy.

Clonidine is probably as effective as bupropion, however with more adverse effects: dry mouth, sedation, dizziness, postural hypotension.

Nortriptyline:

tricyclic antidepressant drug – inhibition of norepinephrine and serotonin reuptake.

Noradrenergic effects probably alleviate withdrawal symptoms.

Other useful effects – anxiolytic.

Medications in Development

Rimonabant: cannabinoid CB_1 receptor antagonist developed for treatment of obesity and the metabolic syndrome.

Clinical studies have also shown rimonabant to be effective as an aid for smoking cessation.

Cannabinoid receptors are believed to contribute to the reinforcing effects of nicotine action. NOT APPROVED SO FAR

Nicotine vaccines: currently undergoing clinical trials.

Acute immunization is performed so as to develop antibodies to nicotine.

The antibody binds nicotine and slows its entry into the brain, thereby reducing the reinforcing effects of cigarette smoking.

Medications in Development

Monoamine oxidase inhibitors: would inhibit the metabolism of dopamine and therefore increase dopamine levels in brain.

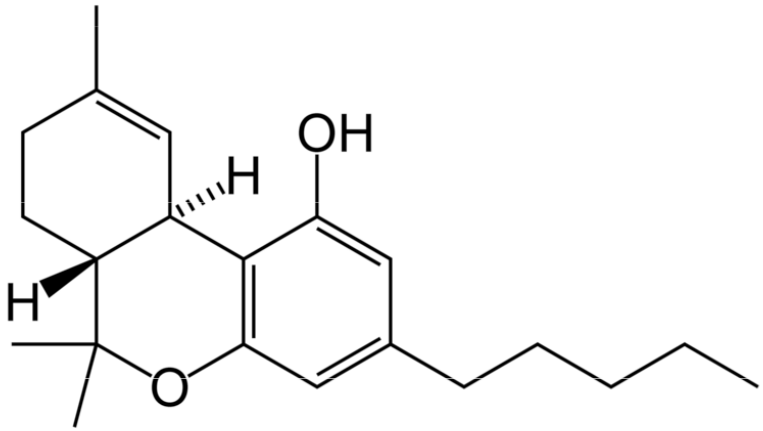
Inhibitors of CYP2A6 activity: increase in nicotine levels from tobacco use and thereby reducing urges to smoke.

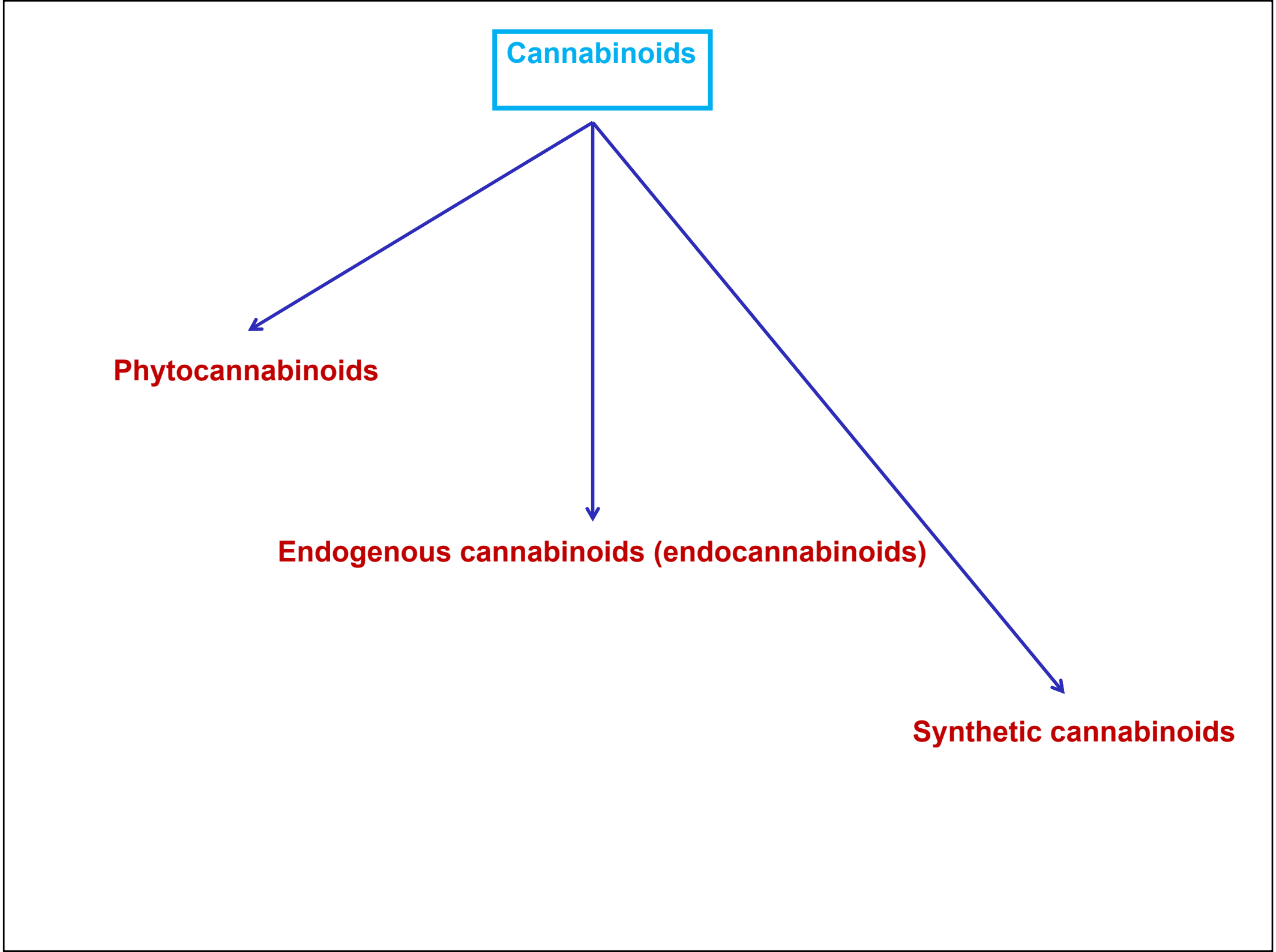
Methoxsalen and tranylcypromine inhibit CYP2A6 activity and slow nicotine metabolism, but both have significant toxicity, making routine clinical use problematic.

Finally, novel selective nicotinic cholinergic receptor agonists and antagonists, in addition to varenicline, are under development.

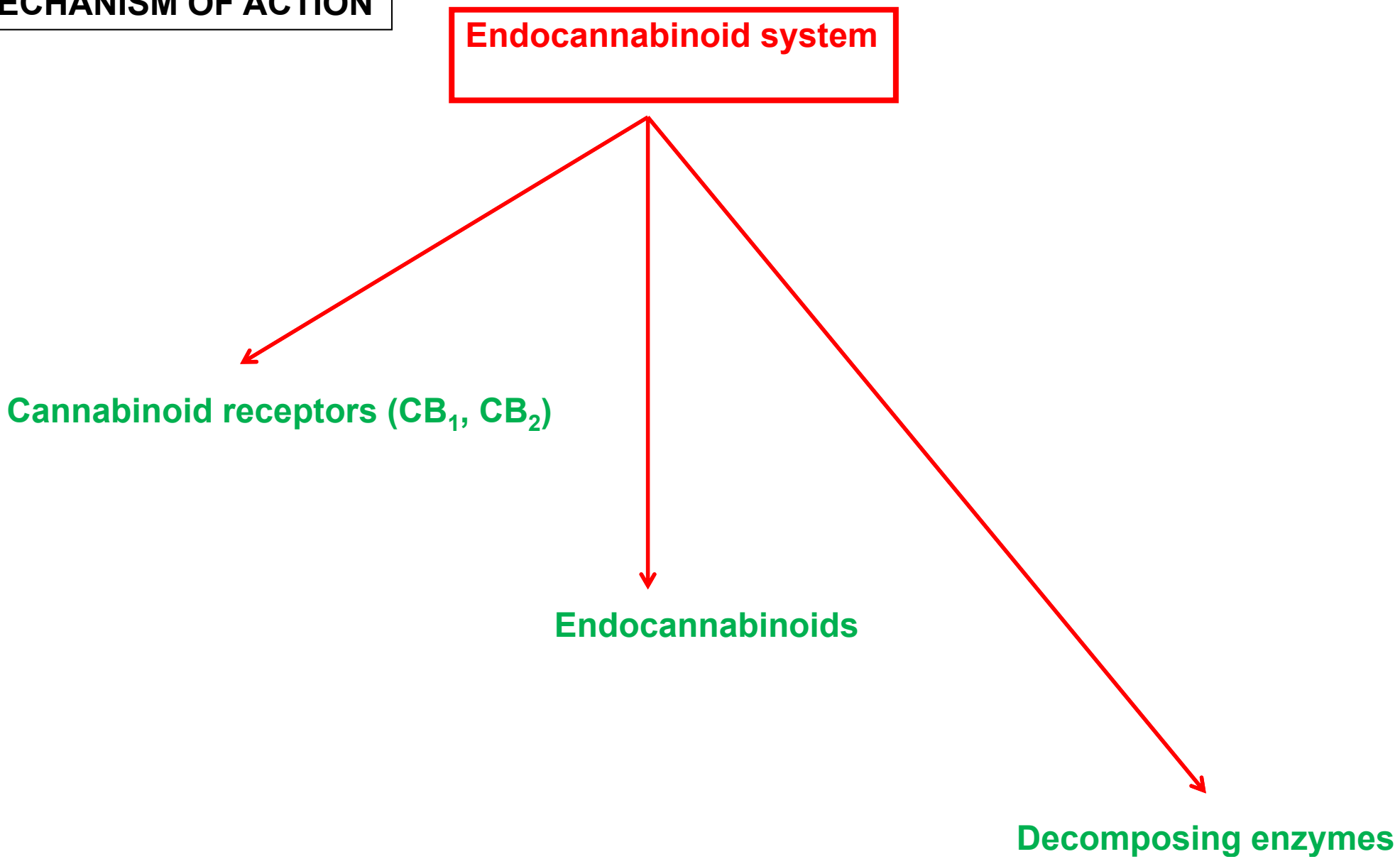
Cannabinoids (hemp drugs)

THC




Cannabinoids
Phytocannabinoids
Endogenous cannabinoids (endocannabinoids)
Synthetic cannabinoids

MECHANISM OF ACTION



Endocannabinoid system

Cannabinoid receptors (CB_1, CB_2)

Subtypes of cannabinoid CB receptors: CB_1 a CB_2 (Howlett a kol., 2002).

CB_1 receptors: nerve endings particularly in CNS (cortex, hippocampus, basal ganglia, hypothalamus, cerebellum, spinal cord)

CB_2 receptors: mainly in peripheral tissues (testicles, sperm, cells of immune system).

Psychoactive effects: CB_1 receptors

Cannabinoids

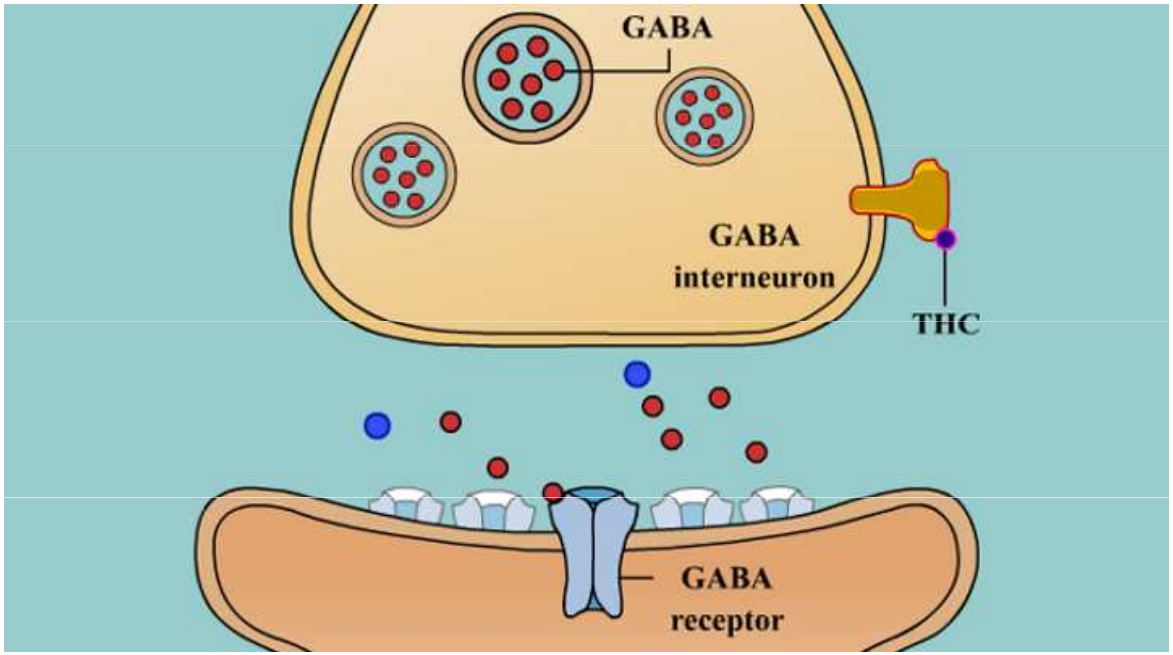
THC stimulates neurons in the reward system to release dopamine.

It inhibits release of GABA, it inhibits release of glutamate, it affects other neurotransmitters.

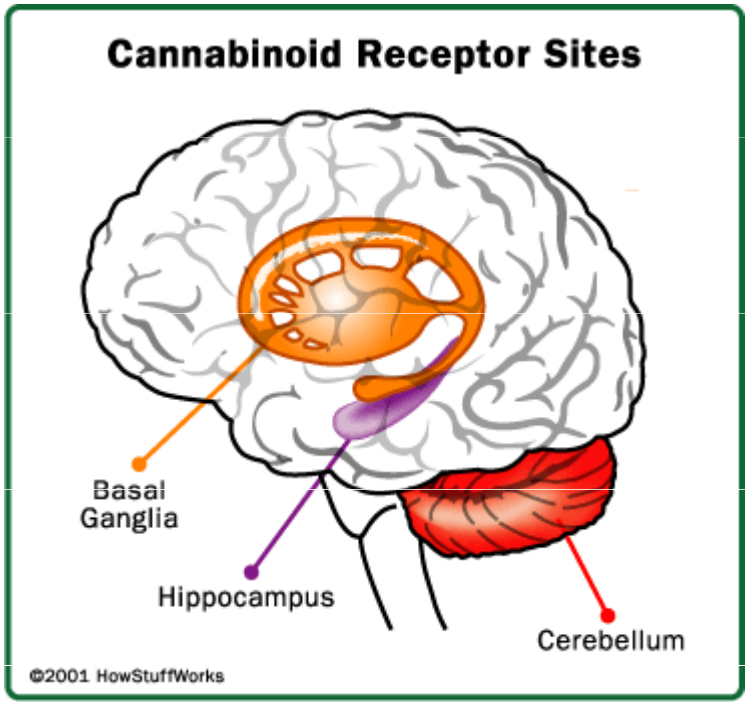
GABA normally acts to dampen the amount of dopamine released in the nucleus accumbens.

When GABA is blocked by THC, the result is an increase in the amount of dopamine released.

GABA is naturally also inhibited by endocannabinoids produced by the brain. They are believed to play an essential role in the release of dopamine in day-to-day functions.



Cannabinoids



IMPAIRMENT OF:

Short-term memory

Co-ordination of movements

Learning

Problem solving

High concentrations of cannabinoid receptors: hippocampus, cerebellum, basal ganglia.

Hippocampus is important for short-term memory.

Cerebellum: short-term memory.

Basal ganglia: motor co-ordination.

Endocannabinoid system

Endocannabinoids

anandamide (N-arachidonoylethanolamine)

noladin ether (2-arachidonyl glyceryl ether)

virodhamine (O-arachidonoylethanolamine)

N-arachidonoyldopamine

Decomposing enzymes

fatty acid amide hydrolase (FAAH)

monoacylglycerol lipase (MGL)

Physiologic functions of endocannabinoid system are very complex.

They involve:

motor coordination

memory

appetite

modulation of pain

neuroprotective effects

homeostasis maintenance (Pacher et al., 2006).

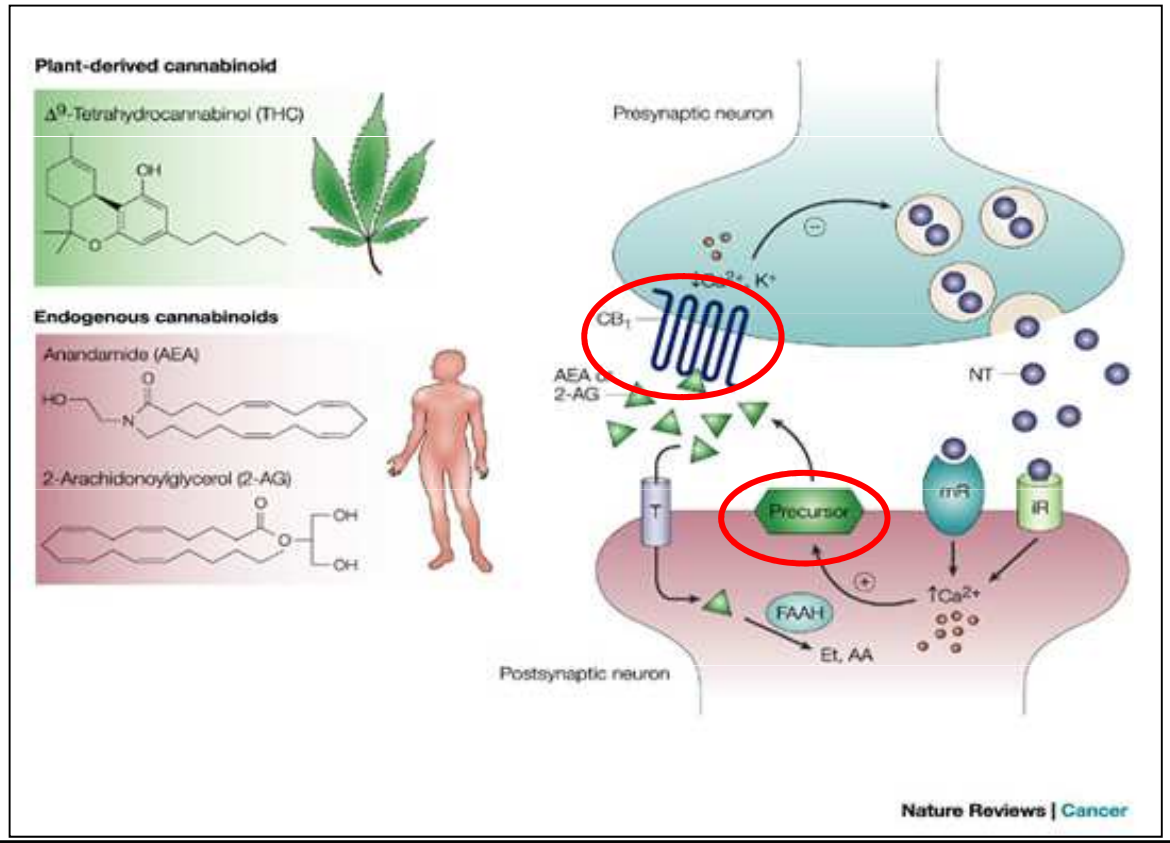
MECHANISM OF ACTION

Cannabinoids

Plant-derived cannabinoids such THC function in the body by activating specific cannabinoid receptors that are normally engaged by a family of endocannabinoids

Exogenous administration of THC will displace bound endocannabinoids from the receptor and furthermore, it will inhibit their production following long-term administration.

Cannabinoid CB_1 receptors are localized presynaptically.



Cannabinoids

Phytocannabinoids

Tetrahydrocannabinol (THC)

Raphael Mechoulam

THC (1964)

Cannabinoids

Tetrahydrocannabinol (THC)

Hemp is the most widespread illegal drug from the point of view of production and commerce.

In EC: the most frequently used illegal drug.

The most significant use: age 5 – 24 years.

The most frequently abused forms of hemp drugs:

marijuana

hashish

hemp (hashish) oil.

Cannabinoids

Tetrahydrocannabinol (THC)

Marijuana: flowers and petals of dried female hemp plant, that can be mixed with larger leafs.

Hashish: hemp resin.
Concentration of THC is in hashish usually 5 times higher than in marihuana. It presents about 20 %.

Hemp oil: extract from hemp. Hashish oil is produced by hashish extraction.

Other terms:

- **bhang** – marihuana (dagga, kif, grass…);
- **ganja** – unpollinated dried and pressed flowers of female plants;
- **charas** - hashish.

Cannabinoids

Tetrahydrocannabinol (THC)

Effects:

may vary dramatically among different users

pleasant euphoria and sense of relaxation/anxiety, fear, distrust, or panic

heightened sensory perception (e.g., brighter colors)

laughter

altered perception of time

increased appetite.

People who have taken **large doses** of marijuana may experience an acute psychosis, which includes hallucinations, delusions, and a loss of the sense of personal identity.

Cannabinoids

Tetrahydrocannabinol (THC)

Adverse Consequences of Marijuana Use:

Impaired short-term memory

Impaired attention, judgment, and other cognitive functions

Impaired coordination and balance

Increased heart rate

Anxiety, paranoia

Psychosis

Cannabinoids

Tetrahydrocannabinol (THC)

Persistent (lasting longer than intoxication, but may not be permanent):

Impaired learning and coordination

Sleep problems

Long-term (cumulative effects of repeated use):

Potential for addiction

Potential loss of IQ

Increased risk of chronic cough, bronchitis

Increased risk of schizophrenia in vulnerable people

Potentially increased risk of anxiety and depression

Cannabinoids

Tetrahydrocannabinol (THC)

Hemp drugs do not provoke physical (somatic) dependence.

Psychic dependence occurs in 8 – 10 % after long-term use.

Withdrawal symptoms

The most common symptom: insomnia (from a few nights of practically no sleep at all, up to a few months of occasional sleeplessness).

Other symptoms: depression

nightmares and vivid dreams

anger, fear or anxiety, loss of concentration

Physical symptoms: headaches

night sweats

Phytocannabinoids

Hemp plants contain at least 483 chemical components and 66 of them are cannabinoids.

We recognize various cannabinoid subclasses:

Type of: cannabigerol (CBG)

cannabichromene (CBC)

cannabidiol (CBD)

delta-9-THC

delta-8-THC

cannabinol (CBN) and cannabidiol

other cannabinoids

Cannabinoids

Therapeutic potential of hemp:

There is a huge number of scientifically well-documented reports on possible beneficial effects of cannabinoids showing their therapeutic potential in treatment of many disorders involving:

different types of pain, inflammation

cancer

asthma

glaucoma

hypertension, myocardial infarction, arrhythmia

rheumatoid arthritis, diabetes, multiple sclerosis, epilepsy

Parkinson's disease, Alzheimer's disease

depression, feeding-related disorders

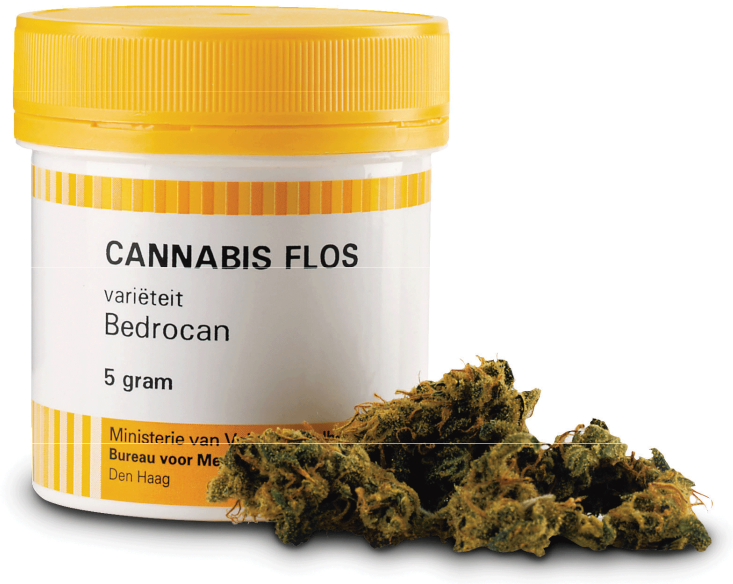
Since March 4, 2013:

Legal possibility to use hemp for therapeutic purposes in the Czech Republic.

Only in pharmacies.

Rx.

Personal cultivation and utilization of hemp for therapeutic purposes is prohibited by law.



Cannabinoids

Endogenous cannabinoids

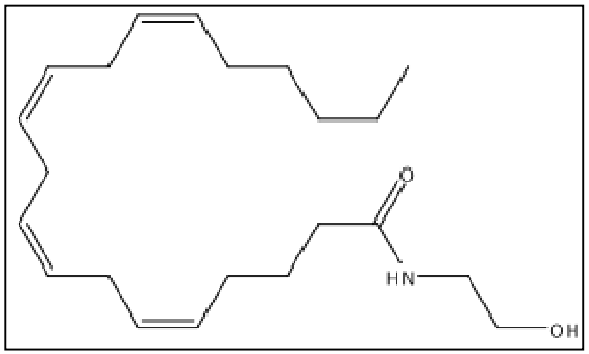
Lumír Hanuš

William Devane

anandamide (1992)

anandamide

Sanskrit word *ananda* = joy, bliss, delight + amide = chemical base of the substance



noladin ether (2-arachidonyl glyceryl ether)

virodhamine (O-arachidonoylethanolamine)

N-arachidonoyldopamine

Cannabinoids

Synthetic cannabinoids

Purposes: study of distribution and pharmacologic properties of cannabinoid receptors in the brain

The best understood synthetic analogue of phytocannabinoids: HU-210 (11-hydroxy-Δ8-THC-dimethylheptyl)

- it has high affinity to both CB_1 i CB_2 receptors (antagonist)

Other synthetic cannabinoids: CP 55,940 (CB_1 and CB_2 receptor agonist)

WIN 55,212-2 (CB_1 receptor agonist)

JWH015 (CB_2 receptor agonist)

SR141716A, so called rimonabant (CB_1 receptor antagonist)

AM251 (CB_1 receptor antagonist)

Significant dates in the research concerning cannabinoids:

1937-1940 identification of the first cannabinoids

1941 synthesis of the first synthetic cannabinoid

1964 discovery of the exact chemical structure of Δ9-tetrahydrocannabinol (Δ9-THC)

1988 identification of cannabinoid receptors in the brain

1990 cloning (= acquiring of DNA copies *in vitro*) of cannabinoid CB_1 receptor

1992 discovery of the first endocannabinoid (anandamide)

1993 cloning of cannabinoid CB_2 receptor

1994 development of the first CB_1 receptor antagonist

Cannabinoids

Pharmacologic Treatment of Addiction

Currently, no medications are indicated for the treatment of marijuana use disorder, but research is active in this area.

Because sleep problems feature prominently in marijuana withdrawal, some studies are examining the effectiveness of medications that aid in sleep.

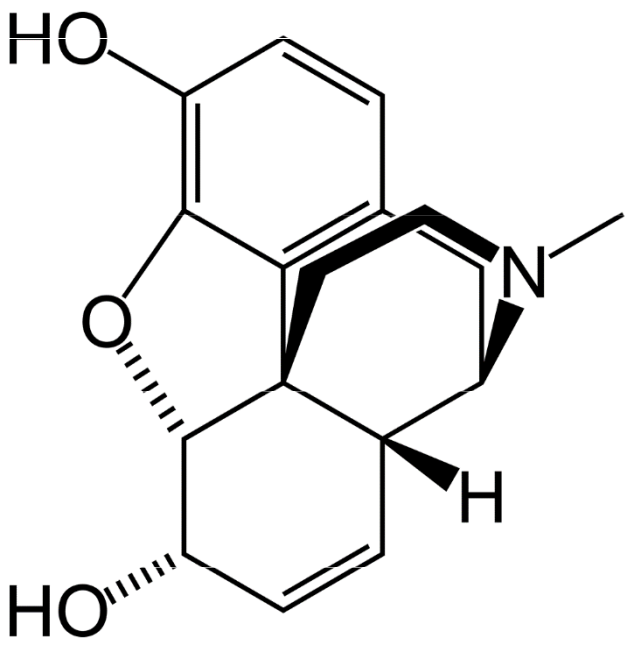
Medications that have shown promise in early studies or small clinical trials include the sleep aid: **zolpidem**

anti-anxiety/anti-stress medication: **buspirone**

anti-epileptic drug: **gabapentin** (that may improve sleep).

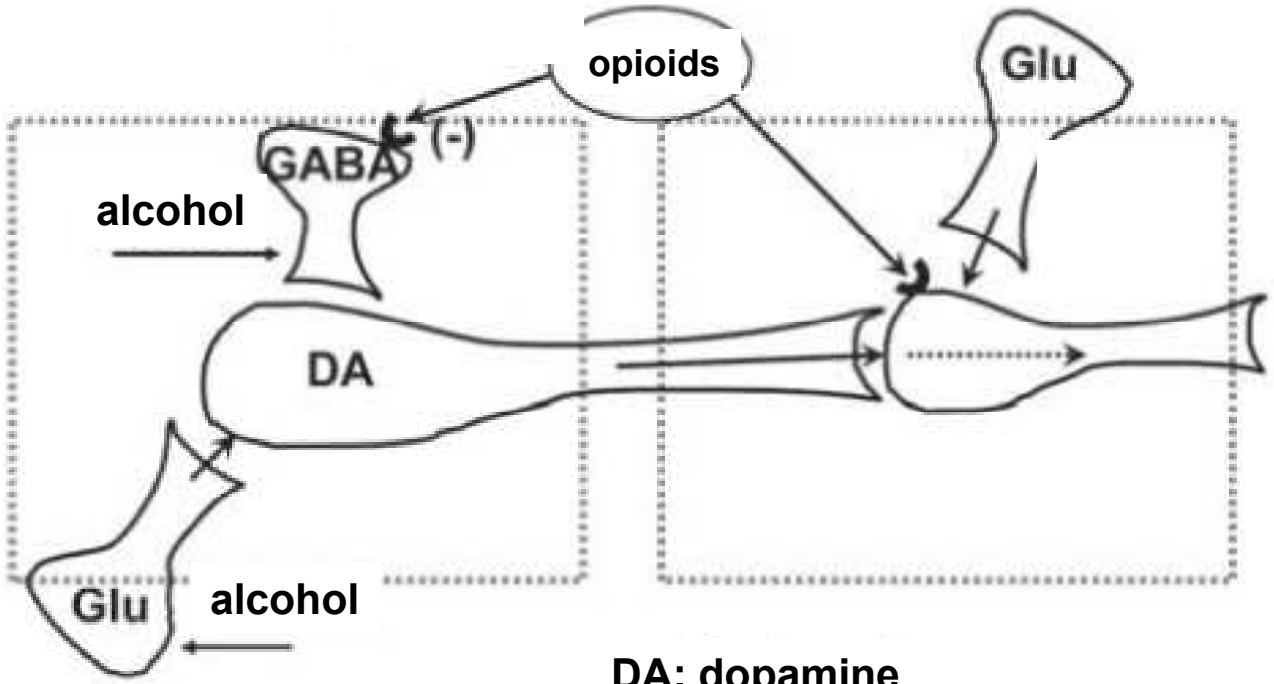
Opioids

morphine



Opioids

VENTRAL TEGMENTUM **NUCLEUS ACCUMBENS**

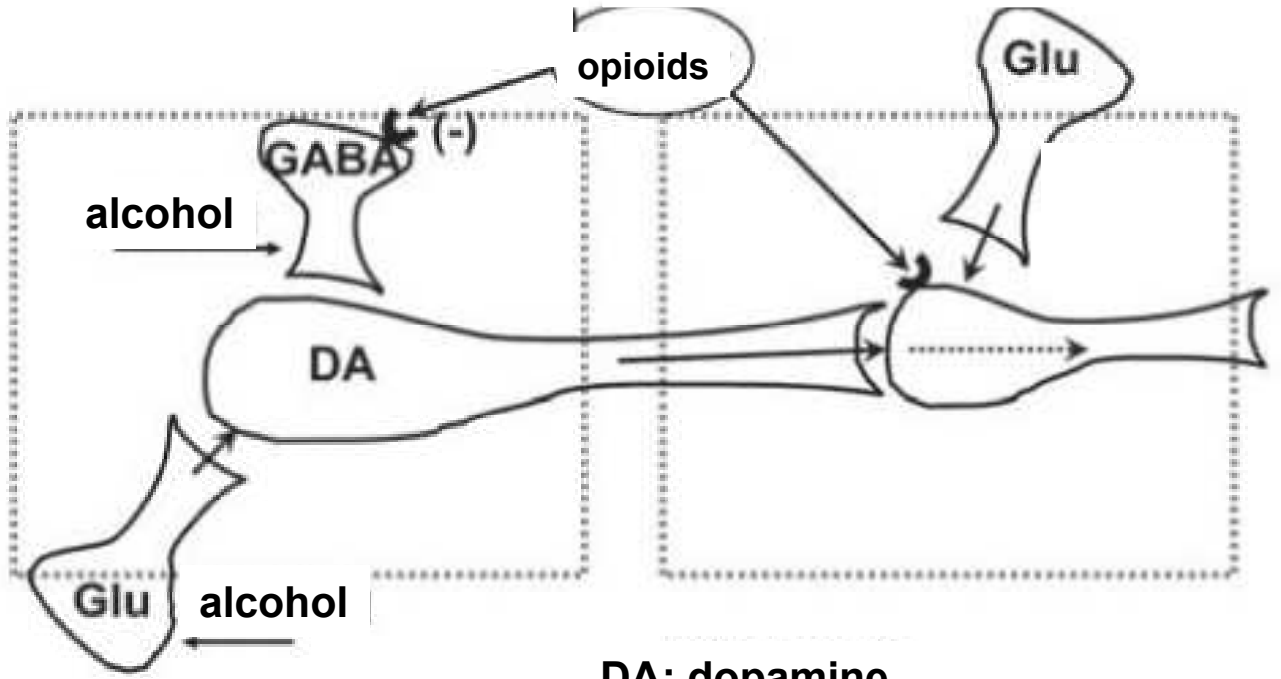


DA: dopamine
GABA: GABA-ergic interneuron
Glu: glutamate
U: opiod receptor

Addictive substances activate dopaminergic pathway: ventral tegmentum – nucleus accumbens.

Opioids act indirectly – they inhibit GABA-ergic interneurons in ventral tegmentum, which suppresses they inhibitory effect on dopaminergic neurons, that are disinhibited.

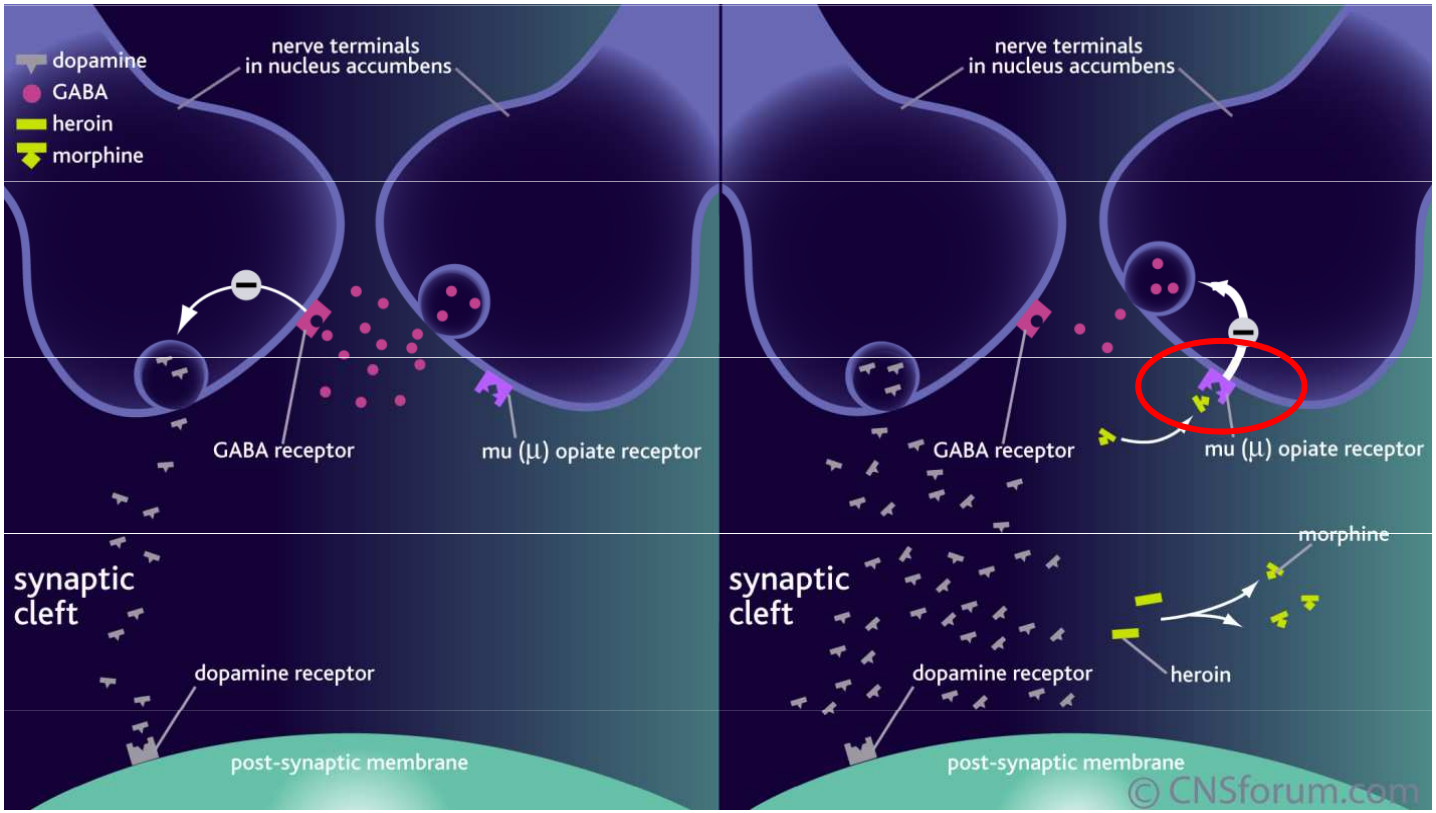
Opioids



DA: dopamine
GABA: GABA-ergic interneuron
Glu: glutamate
U: opiod receptor

However, opioids can act also directly – they bind to opioid receptors in nucleus accumbens.

Opioids


dopamine
GABA
heroin
morphine
nerve terminals
in nucleus accumbens
GABA receptor
mu (μ) opiate receptor
synaptic
cleft
dopamine receptor
post-synaptic membrane
nerve terminals
in nucleus accumbens
GABA receptor
mu (μ) opiate receptor
morphine
synaptic
cleft
dopamine receptor
heroin
post-synaptic membrane
© CNSforum.com

Opioids

Opium

The opium poppy was cultivated in lower Mesopotamia as long ago as 3400 BCE.

Long tradition of both therapeutic and non-therapeutic use of opium (ancient Egypt, Greece, Persia, Rome).

Use in Europe: beginning of the second millennium.

The chemical analysis of opium in the 19th century revealed that most of its activity could be ascribed to two alkaloids, codeine and morphine.

Opioids

Opium

UN (Mai 2013): Afghanistan harvested 5.500 tons of opium (more then the total production in the rest of the world).

Maximum crop in Afghanistan – 2007: 7.400 tons.

Opioids

Opium

Early times in Europe: opium was used as one of the best medical means for a myriad of symptoms.

It was prescribed even for healthy person because it was believed that it optimizes internal balance of human body.

Consumption of opium in England in the first half of the 19th century: 25 kg for 1000 people.

Opioids

Opium

Globally, opium has gradually been superseded by a variety of purified, semi-synthetic, and synthetic opioids with progressively stronger effects.

This process began in 1804, when Friedrich Wilhelm Adam Sertürner first isolated morphine from the opium poppy.

The process continued until 1817, when Sertürner published the isolation of pure morphine from opium.

Morphine represent 10 % of raw opium. It is 10x stronger

Opioids

Fentanyl

Synthetic opioid – therapy of acute and chronic pain, general anesthesia
i.v., transdermal patches

USA: abused particularly by medical staff.

Opioids

Morphine

Natural source: opium.

Use: analgesic drug.

Massive use during wars.

Strong addictive potential (smaller than heroin).

Frequently abused by medical staff.

Not very common as street drug.

Opioids

Morphine

Effects:

may vary dramatically among different users

Respiratory center depression. High doses: respiratory arrest.

After i.v. administration: calm euphoria.

Increased self-confidence.

MECHANISM OF ACTION

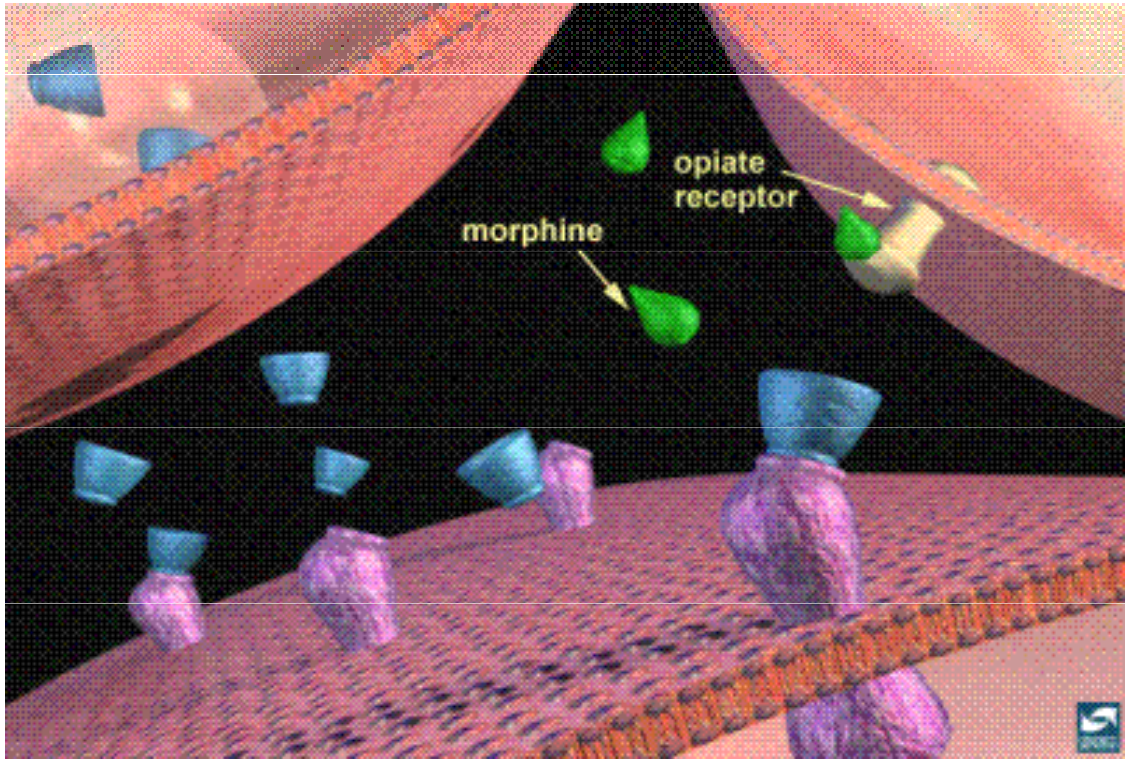
Opioids

Morphine

Opiod receptors: μ, κ, δ in CNS.

Neurons form other receptors, thereby increasing sensitivity.

Increasing tolerance: excessive reaction of neurons following abrupt cessation.



Fast dependence development (physic and psychic).

Opioids

Heroin

Synthetized in 1874.

Chemically: diacetylmorphine

Orall administration: extensive first-pass effect.

Injections: it avoids this first-pass effect, very rapidly crossing the BBB (higher fat solubility than morphine).

Once in the brain, it then is changed to morphine, which bind to opioid receptors.

Administered i.v., heroin is two to four times more potent than morphine and is faster in its onset of action „rush or flash„. .

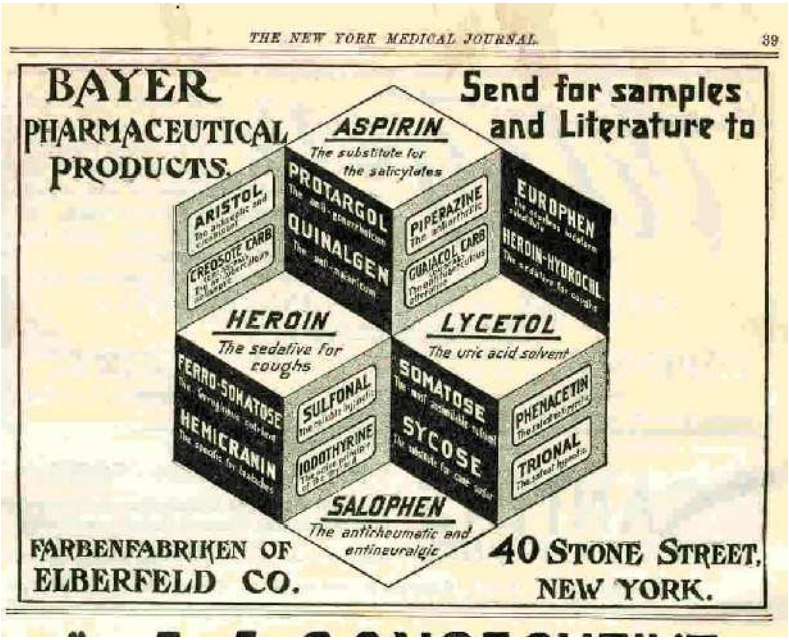
Opioids

Heroin

In 1895, the German drug company Bayer marketed diacetylmorphine as an OTC drug under the trademark name Heroin.

The name was derived from the Greek word *heros* because of its perceived "heroic" effects upon a user.

It was developed chiefly as a morphine substitute for cough suppressants that did not have morphine's addictive side-effects.



Opioids

Heroin

Routes of application:

Orally (first-pass effect)

Injections (risk of infections)

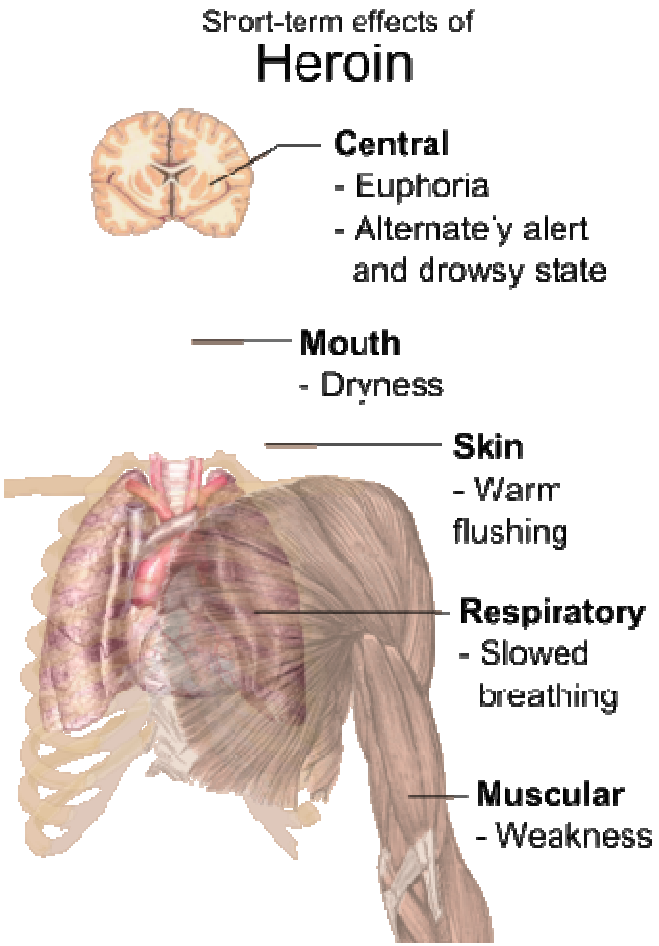
Smoking

Insufflation

Suppositories (limited way)

Opioids

Heroin



Initial effects:

Feeling a surge of pleasurable sensation—a “rush.”

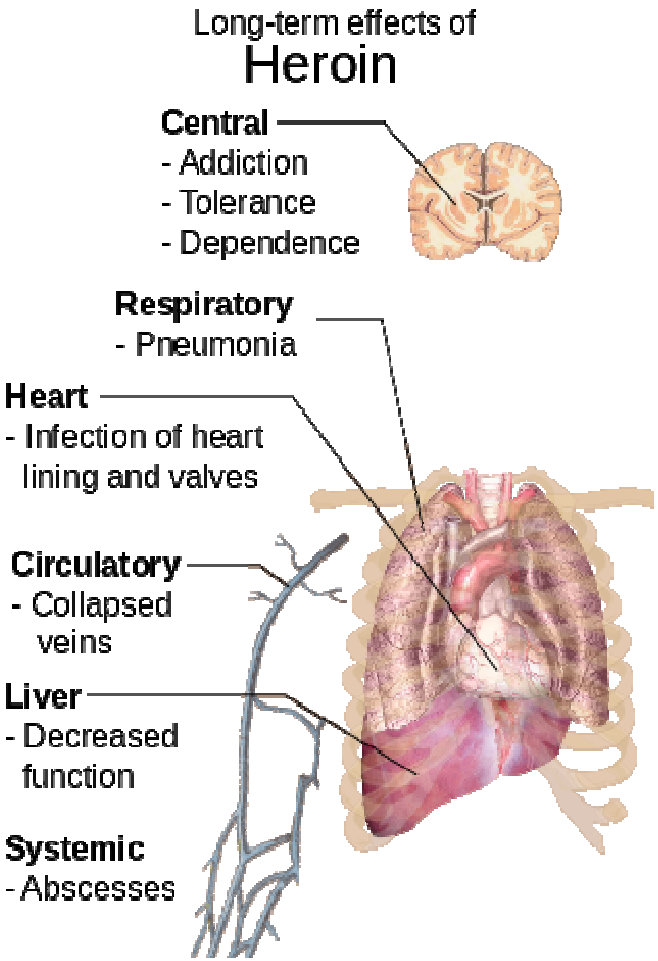
The rush is usually accompanied by:
a warm flushing of the skin
dry mouth
heavy feeling in the extremities
(at beginning) nausea, vomiting, and severe itching.

After the initial effects:

Drowsiness for several hours; clouded mental function
slower heart function
severely slower breathing (enough to be life-threatening)

Opioids

Heroin



Long-term effects:

Repeated heroin use changes the physical structure and physiology of the brain, creating long-term imbalances in neuronal and hormonal systems that are not easily reversed.

Impairment of: decision-making abilities
ability to regulate behavior
responses to stressful situations.

Constipation.

Heroin also produces profound degrees of tolerance and physical dependence.

Opioids

Withdrawal symptoms

Withdrawal may occur within a few hours after the last time the drug is taken.

Symptoms include:

restlessness

muscle and bone pain

insomnia

diarrhea

vomiting

cold flashes with goose bumps (“cold turkey”)

leg movements.

Opioids

Withdrawal symptoms

Major withdrawal symptoms peak between 24–48 hours after the last dose of heroin and subside after about a week.

However, some people have shown persistent withdrawal signs for many months.

Heroin is extremely addictive no matter how it is administered, although routes of administration that allow it to reach the brain the fastest (i.e., injection and smoking) increase the risk of addiction.

Opioids

Pharmacologic Treatment of Addiction

Medications developed to treat opioid addiction work through the same opioid receptors as the addictive drug, but are safer and less likely to produce the harmful behaviors that characterize addiction.

Three types of medications include:

(1) agonists, which activate opioid receptors

(2) partial agonists, which also activate opioid receptors but produce a smaller response

(3) antagonists, which block the receptor and interfere with the rewarding effects of opioids.

Opioids

Pharmacologic Treatment of Addiction

Methadone (Dolophine® or Methadose®): slow-acting opioid agonist.

Oral application - it reaches the brain slowly, dampening the “high” that occurs with other routes of administration. Methadone has been used since the 1960s.

Methadone is only available through approved outpatient treatment programs, where it is dispensed to patients on a daily basis.

Opioids

Pharmacologic Treatment of Addiction

Buprenorphine (Subutex®):
partial agonist at μ-opioid receptors and κ receptor antagonist .

Buprenorphine relieves drug cravings
without producing the “high” or dangerous side effects of other opioids.

Suboxone® is a novel
formulation of buprenorphine that is taken orally or sublingually and contains naloxone (an opioid antagonist) to prevent attempts to get high by injecting the medication. If an addicted patient were to inject Suboxone, the naloxone would induce withdrawal symptoms, which are averted when taken orally as prescribed.

Opioids

Pharmacologic Treatment of Addiction

Buprenorphine	Methadone	Heroin
Partial agonist	Full agonist	Full agonist
Long half-life (24 to 60 hours)	Long half-life (8 to 59 hours)	Short half-life
Ceiling effect; good safety profile	No ceiling effect (useful in patients dependent on high doses of opioids)	No ceiling effect

Opioids

Pharmacologic Treatment of Addiction

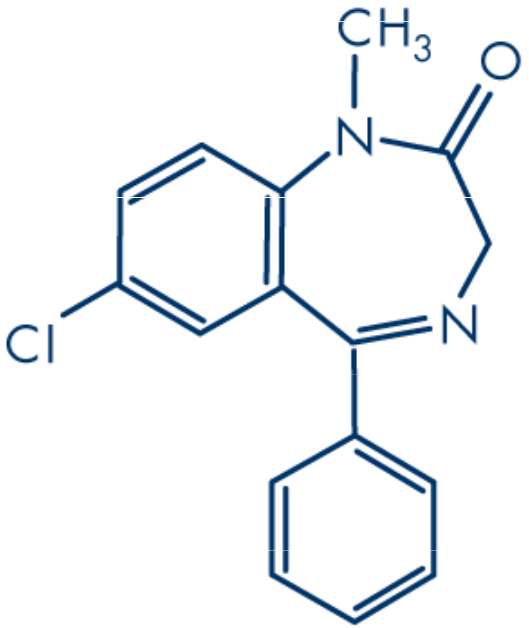
Naltrexone (Depade® or Revia®): opioid antagonist.

Naltrexone blocks the action of opioids, is not addictive or sedating, does not result in physical dependence; however, patients often have trouble complying with the treatment, and this has limited its effectiveness.

An injectable long-acting formulation of naltrexone (Vivitrol®) recently received FDA approval for treating opioid addiction. Administered once a month, Vivitrol® may improve compliance by eliminating the need for daily dosing.

Benzodiazepines

diazepam



Benzodiazepines (BZD)

Frequently used and abused psychotropic drugs.

Often prescribed as anxiolytics, sedatives and hypnotics.

Mostly abused in combination with other substances (alcohol, heroin).

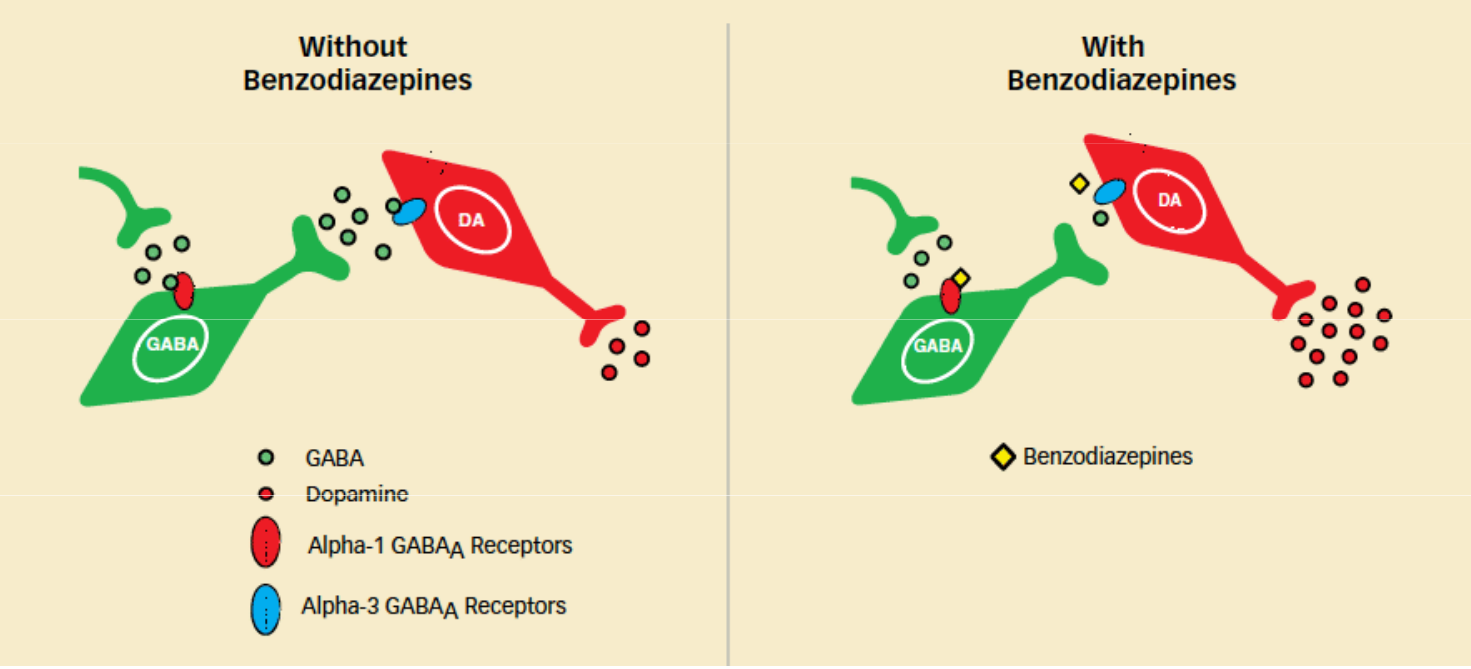
Benzodiazepines (BZD)

(Left Image) Both inhibitory interneurons (GABA) and dopaminergic neurons (DA) are subject to the restraining influence of the inhibitory neurotransmitter GABA.

A key difference, however, is that GABA affects the inhibitory interneurons largely via the alpha-1 subset of $GABA_A$ receptors and the dopaminergic neurons largely via the alpha-3 subtype.

(Right Image) BZD currently on the market do not interact strongly with alpha-3 $GABA_A$ receptors on dopaminergic neurons and so have no direct impact on dopamine release.

However, the drugs do interact strongly with alpha-1 $GABA_A$ receptors, thereby curtailing inhibitory interneurons' release of GABA into synapses with dopaminergic neurons → lessening of GABA restraint on the dopaminergic neurons and an increase in dopamine release.



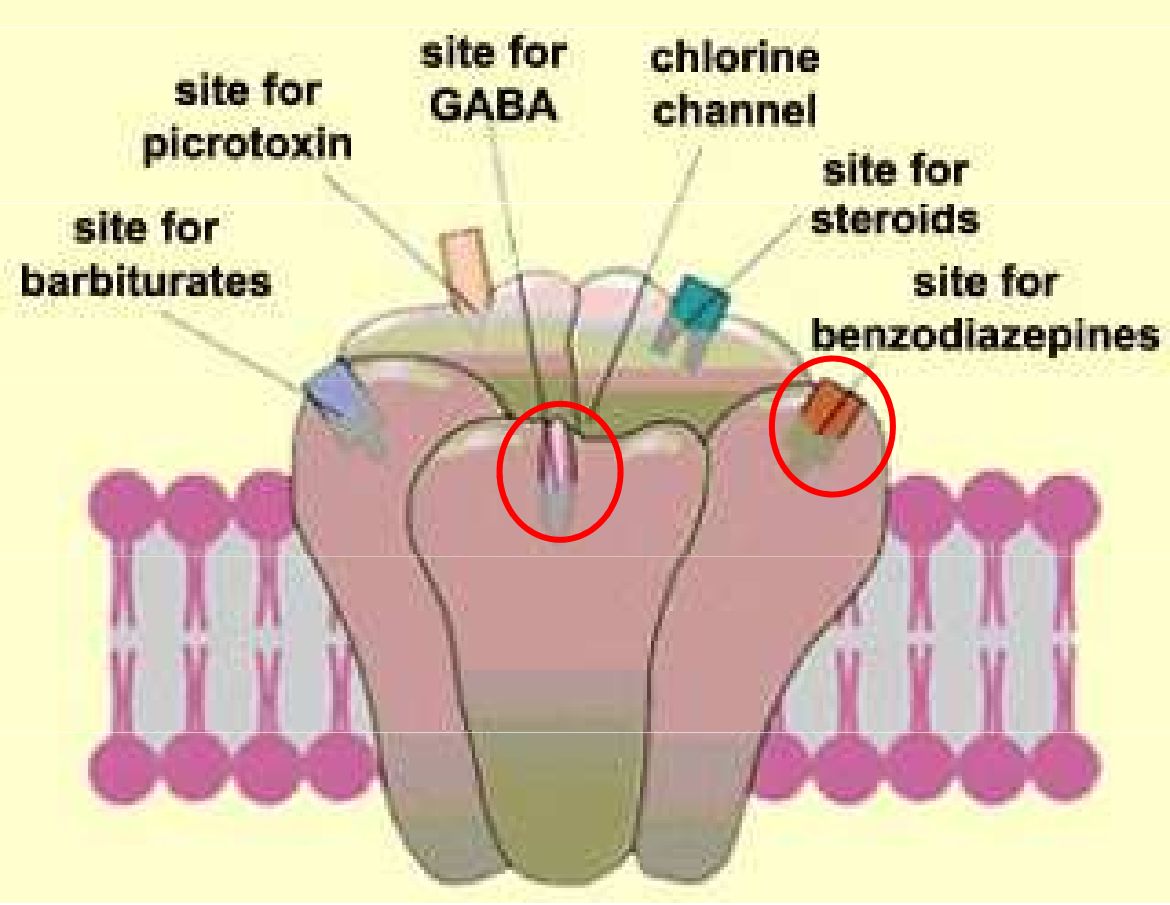
MECHANISM OF ACTION

Benzodiazepines (BZD)

$GABA_A$ receptors in the brain

BZD enhance responses to the inhibitory neurotransmitter GABA by opening GABA-activated chloride channels and allowing chloride ions to enter the neuron.

This action allows the neuron to become negatively charged and resistant to excitation, which leads to the various anti-anxiety, sedative, or anti-seizure activity.



Benzodiazepines (BZD)

Effects:

Sedative-hypnotics for sleep

Adjuncts to anesthesia to induce relaxation and amnesia (procedural memory loss)

To reduce anxiety (anxiolytic)

Panic disorders

To treat or prevent seizures

Muscle relaxant

Benzodiazepines (BZD)

Effects:

Cognitive losses

Short-term memory impairment

Confusion

Increased risk of developing dementia

Benzodiazepines (BZD)

Withdrawal symptoms

Dizziness

Difficulty with concentration

Confusion and cognitive difficulty

Memory problems

Blurred vision or nystagmus

Agitation

Low blood pressure

Respiratory depression

Hallucinations

Coma

Benzodiazepines (BZD)

Withdrawal symptoms

BZD withdrawal can be severe and can provoke **life-threatening withdrawal symptoms**, such as seizures, particularly with abrupt or overly-rapid dosage reduction from high doses or long time users.

Ten to 15 % of people withdrawing from BZD, experience a protracted withdrawal syndrome which can sometimes be severe.

Symptoms may include:
tinnitus, psychosis, cognitive deficits, insomnia, paraesthesia (tingling and numbness), pain (usually in limbs and extremities), muscle pain, weakness, tension, painful tremor, shaking attacks, jerks, may occur even without a pre-existing history of these symptoms

Benzodiazepines (BZD)

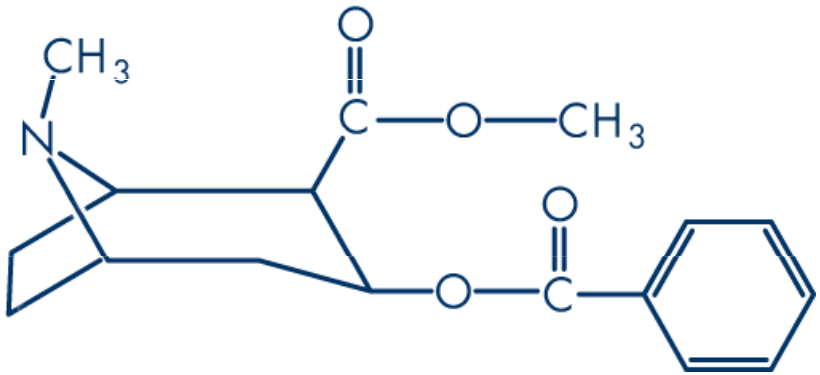
Pharmacologic Treatment of Addiction

Flumazenil was found to be more effective than placebo in reducing feelings of hostility and aggression in patients who had been free of benzodiazepines for 4–266 weeks.

This may suggest a role for flumazenil in treating protracted benzodiazepine withdrawal symptoms.

„Classical“ psychostimulants

cocaine



„Classical“ psychostimulants

Substances with stimulating effects on CNS

Cocaine

Cocaine is a powerfully addictive stimulant drug made from the leaves of the coca plant (*Erythroxolon coca*) native to South America.

It produces short-term euphoria, energy, and talkativeness in addition to potentially dangerous physical effects like raising heart rate and blood pressure.

PLATE XX.—*Erythroxylon coca* (Coca). (From Jackson: *Experimental Pharmacology and Materia Medica.*)

„Classical“ psychostimulants

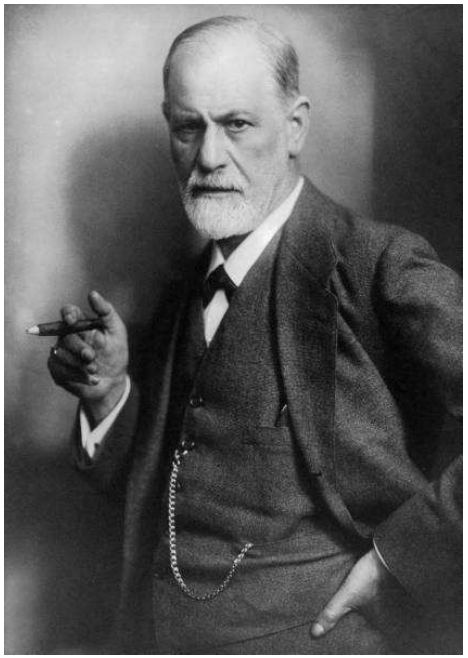
Cocaine

Dr. Albert Nieman extracted and purified the compound naming it cocaine in 1862.

In 1879 cocaine began to be used to treat morphine addiction.

Cocaine was introduced into clinical use as a local anesthetic in Germany in 1884.

Cocaine was pioneered by the young Sigmund Freud, the neuropathologist, as a treatment for postnatal depression



„Classical“ psychostimulants

Cocaine

Use as local anesthetic drug

Karl Koller experimented with cocaine for ophthalmologic usage.

In an infamous experiment in 1884, he experimented upon himself
by applying a cocaine solution to his own eye and then
pricking it with pins.

His findings were presented to the Heidelberg Ophthalmological Society

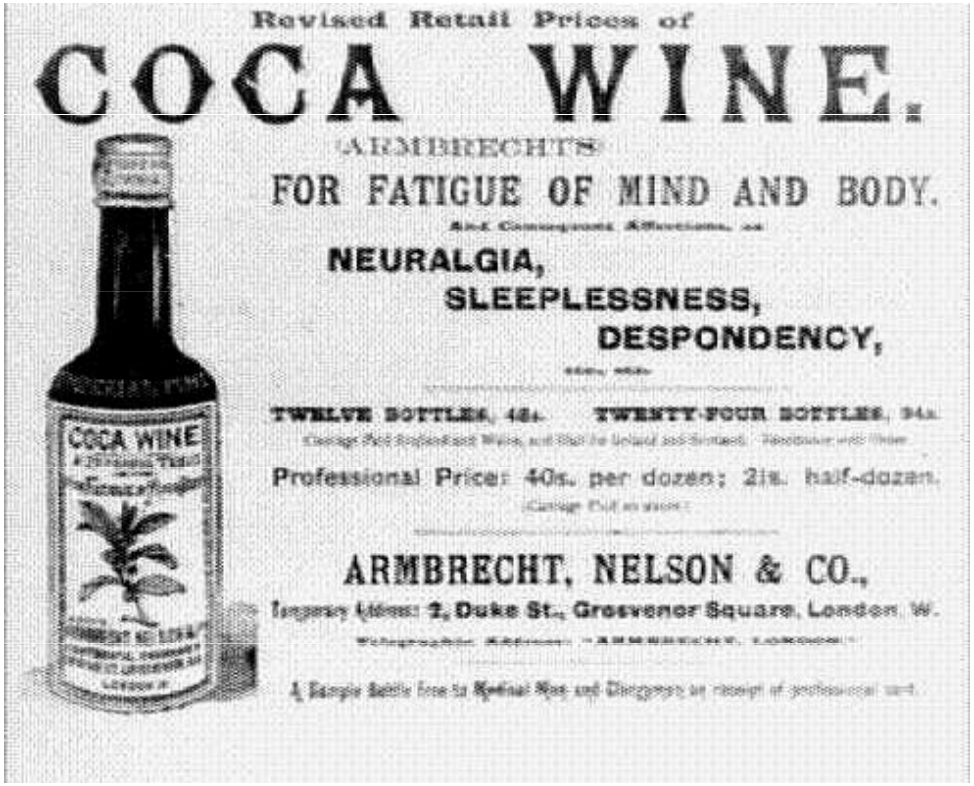
„Classical“ psychostimulants

Cocaine

Cocaine was widely distributed in elixirs (coca wine) and drinks like *Coca-Cola.*

Indeed, *Coca Cola* contained small amounts of cocaine until 1904,
which is how it obtained its name.

(Nowadays stimulatory effects of *Coca-Cola* come from caffeine).



„Classical“ psychostimulants

Cocaine

Routes of administration:

Orally (chewing coca leafs)

Nasal insufflation (so called snorting, sniffing or blowing)

Injection

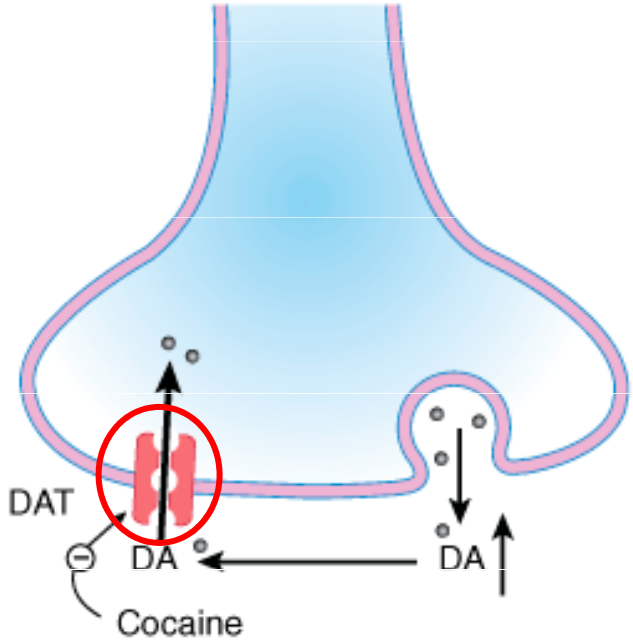
Inhalation (cocaine is smoked by inhaling the vapor by sublimating solid cocaine by heating)

Suppository (limited way called "plugging“)

MECHANISM OF ACTION

„Classical“ psychostimulants

Cocaine



Cocaine inhibits dopamine transporter (DAT), thereby decreasing dopamine reuptake → increase in dopamine extracellular concentration.

„Classical“ psychostimulants

Cocaine

Short-term effects:

Short-term euphoria

Feelings of superiority

Talkativeness

Loss of appetite

Increased heart rate, blood pressure, body temperature

Contracted blood vessels

Increased rate of breathing

Dilated pupils

Disturbed sleep patterns

Hyperstimulation

„Classical“ psychostimulants

Cocaine

Long-term effects:

Disorientation, apathy, confused exhaustion

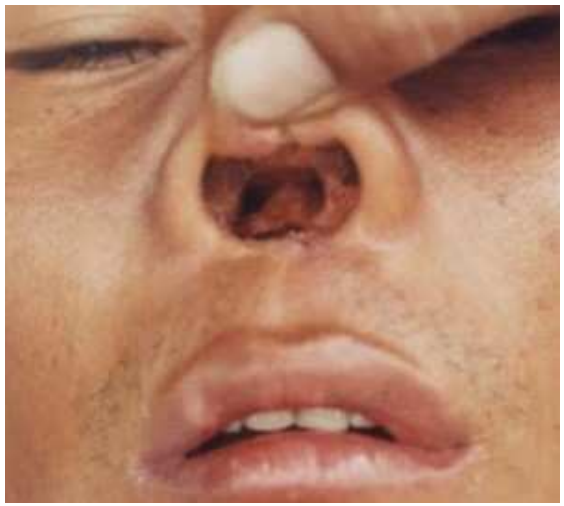
Irritability and mood disturbances

Increased frequency of risky behavior

Delirium or psychosis

Severe depression

High blood pressure, leading to heart attacks, strokes, and death



Destruction of tissues in nose if sniffed

Malnutrition, weight loss

Sexual problems

„Classical“ psychostimulants

Cocaine

Withdrawal symptoms

Symptoms generally last for about a week or two include:

Depression

Anxiety

Sleep disturbances

Tremors and shakiness

Pain

Inability to feel pleasure

Exhaustion

Challenges in concentration

Intense craving → **relapses**

„Classical“ psychostimulants

Cocaine

Pharmacologic Treatment of Addiction

Presently, there are no proven medications to treat cocaine addiction.

Promising substance: **Vigabatrin** – originally for epileptic patients as an anti-convulsant medication.

It increases the amount of GABA in the brain (irreversible inhibition of transaminase)

GABA inhibits the production of dopamine and dopamine is the chemical which cocaine use causes to wash over the brain creating the intense pleasure that users are seeking.

A drug which can temper the effects of dopamine essentially reduces the addictive effects of cocaine

„Classical“ psychostimulants

Cocaine

Pharmacologic Treatment of Addiction

Bromocriptine: agonist of dopamine D_2 receptors (**used with mixed success**).

Originally intended for treatment of Parkinson’s disease.

„Classical“ psychostimulants

Cathinone

Khat (*Catha edulis*)

1980: WHO classified it as a drug of abuse that produces mild-to-moderate psychic dependence (**less than tobacco or alcohol**), although WHO does not consider khat to be seriously addictive

The khat plant is known by a variety of names: e.g.: *qat* and *gat* in Yemen

qaat and *jaad* in Somalia

chat in Ethiopia

Leafs are typically chewed.

MECHANISM OF ACTION

„Classical“ psychostimulants

Cathinone

Cathinone is structually related to amphetamine, and similarly to amphetamine, increases the levels of dopamine in the brain by acting on the cathecholaminergic synaspes.

„Classical“ psychostimulants

Cathinone

Effects:

Alertness

Arousal

Concentration

Confidence

Euphoria

Friendliness

Increased blood pressure

Increased heart rate

Suppressed appetite

Talkativeness

„Classical“ psychostimulants

Cathinone

Withdrawal symptoms (mild)

Emotional ups and downs

Inability to sleep

Inability to focus

Tension

Depression

Lethargy

Irritability

„Classical“ psychostimulants

Cathinone

Pharmacologic Treatment of Addiction

There are very few reports of treatment of khat addition.

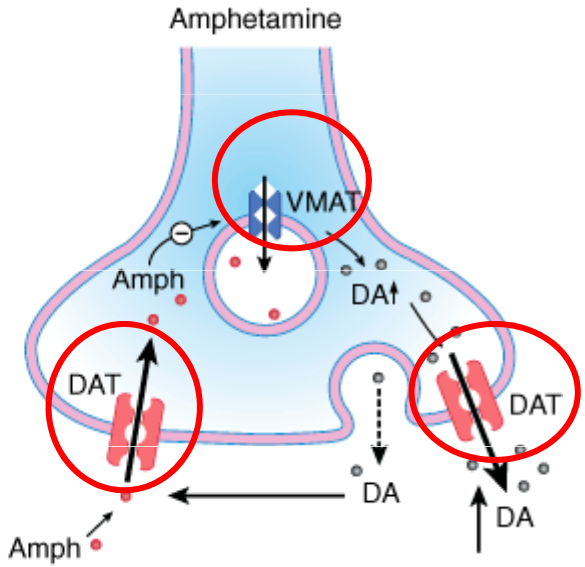
Published possibility:

bromocriptine
using a protocol developed for cocaine addiction.

MECHANISM OF ACTION

„Classical“ psychostimulants

Amphetamine



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Amphetamine is substrate for dopamine transporter (DAT) and inhibits dopamine (DA) transport.

Amphetamine is taken into the presynaptic part by the transporter instead of DA.

Interferes with vesicular monoamine transporter (VMAT) function and prevents filling of synaptic vesicles with DA.

It leads to increase in cytoplasmic DA. Due to increased cytoplasmic dopamine direction of DAT reverses.

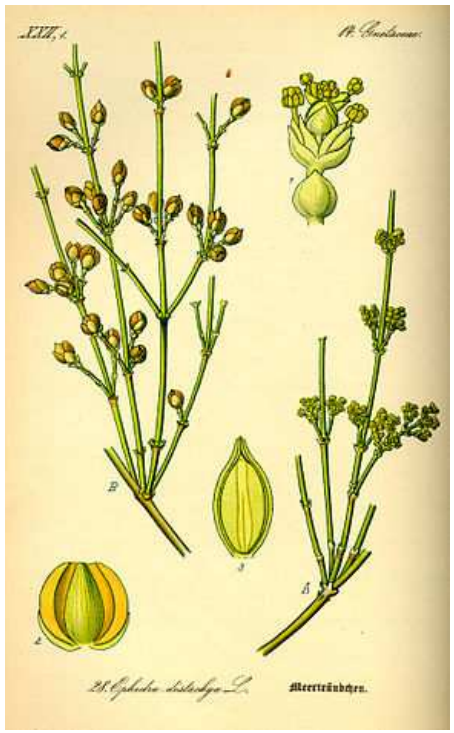
→ increase in extracellular DA

„Classical“ psychostimulants

Methamphetamine (pervitin)

1893: synthesis of methamphetamine from ephedrine by Japanese chemist Nagai Nagayoshi

Ephedrine: substance from Ephedra shrub (*Ephedra vulgaris)*
– used traditionally for hundreds of years in China



„Classical“ psychostimulants

Methamphetamine (pervitin)

WWII:

Pervitin, a methamphetamine brand used by German soldiers was dispensed in tablet containers.

High doses were given to Japanese Kamikaze pilots before their suicide missions.

„Classical“ psychostimulants

Methamphetamine (pervitin)

Application:

Orally

Smoking

Inhalation (snorted)

Injections

„Classical“ psychostimulants

Methamphetamine (pervitin)

Very widespread substance in this country.

Most frequently used route of administration in CR: i.v.

Usual doses: 50 – 250 mg/day (price 800 – 1000 Kč/gram).

Estimation: number of problem drug users (high-risk drug users in CR: 20,5 thousands.

2/3 of the total number of problem drug users in CR.

MECHANISM OF ACTION

„Classical“ psychostimulants

Methamphetamine (pervitin)

Increased dopamine (norepinephrine) release + inhibition of DAT
→ increased levels of monoamines in the synaptic cleft.

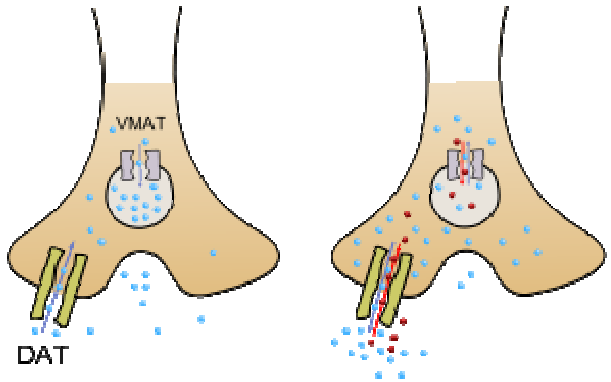
Methamphetamine works by taking advantage of its similarity to dopamine.

It attaches itself to the DAT (it binds to them more powerfully than dopamine, and will push dopamine out). Methamphetamine then gets transported into the cell.

Interferes with vesicular monoamine transporter (VMAT) function and prevents filling of synaptic vesicles with DA.

It leads to increase in cytoplasmic DA. Due to increased cytoplasmic dopamine direction of DAT reverses.

→ increase in extracellular DA



„Classical“ psychostimulants

Methamphetamine (pervitin)

Short-term effects:

Increased attention and decreased fatigue

Increased activity and wakefulness

Decreased appetite

Euphoria and rush

Increased respiration

Rapid/irregular heartbeat

Hyperthermia

„Classical“ psychostimulants

Methamphetamine (pervitin)

Long-term effects:

Addiction

Psychosis, including:
paranoia
hallucinations
repetitive motor activity

Changes in brain structure and function

Deficits in thinking and motor skills

Increased distractibility

„Classical“ psychostimulants

Methamphetamine (pervitin)

Long-term effects:

Memory loss

Aggressive or violent behavior

Mood disturbances

Severe dental problems

Weight loss

„Classical“ psychostimulants

Methamphetamine (pervitin)

Primary neurocognitive deficits associated with long-term methamphetamine use:

Attention/Psychomotor Speed

Learning & Memory

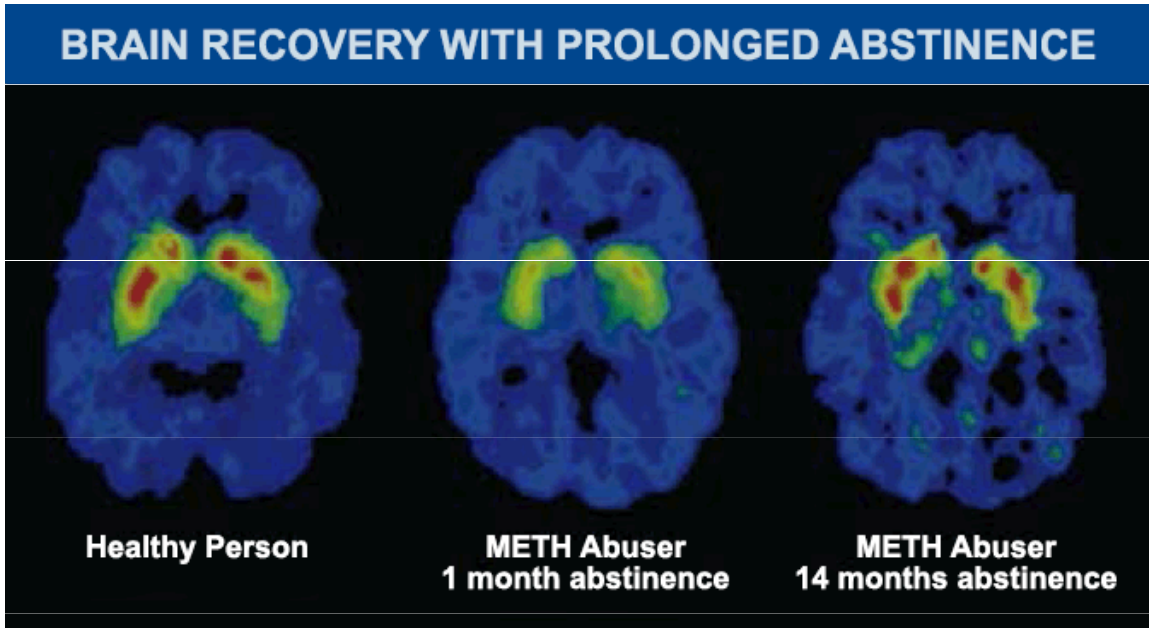
Executive Functions
- Resulting in:
  - Poor judgment
  - Lack of insight
  - Poor strategy formation
  - Impulsivity
  - Reduced capacity to determine consequences of actions

„Classical“ psychostimulants

Methamphetamine (pervitin)

Methamphetamine abuse greatly reduces the binding of dopamine to dopamine transporters (highlighted in red and green) in the striatum, a brain area important in memory and movement.

With prolonged abstinence, dopamine transporters in this area can be restored.



The subject in the middle who is at the greatest risk of relapse.

„Classical“ psychostimulants

Methamphetamine vs. cocaine

Methamphetamine	Cocaine
Stimulant	Stimulant and local anesthetic
Man-made	Plant-derived
Smoking produces a long-lasting high	Smoking produces a brief high
50% of the drug is removed from the body in 12 hours	50% of the drug is removed from the body in 1 hour
Increases dopamine release and blocks dopamine re-uptake	Blocks dopamine re-uptake

„Classical“ psychostimulants

Methamphetamine (pervitin)

Withdrawal symptoms

Depression

Anxiety

Fatigue

Excessive sleeping and lethargy

Increased appetite

STRONG CRAVING

→ RELAPSES

„Classical“ psychostimulants

Methamphetamine (pervitin)

Pharmacologic Treatment of Addiction

There are currently no medications that counteract the specific effects of methamphetamine or that prolong abstinence.

UNDER RESEARCH

Ibudilast: suppresses the neuroinflammatory actions of glial cells.
It has been shown to inhibit methamphetamine self-administration in rats.

Uknown safety and effectiveness in humans with methamphetamine addiction.

MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)

1912: first synthesized and patented by a German pharmaceutical company under the name of “methylsafrylamin”.

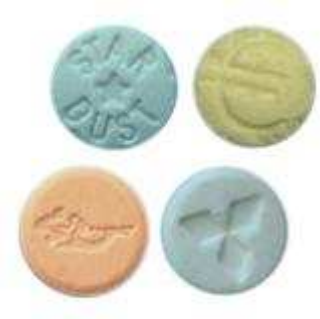
It was not intended for therapeutic use, but only as a precursor for therapeutically active compounds.

Merck had no intentions of using MDMA as an appetite suppressor, as many times erroneously has been written.

The company decided against marketing the drug and had nothing more to do with it.

MDMA acts as both a stimulant and psychedelic, producing an energizing effect, as well as distortions in time and perception and enhanced enjoyment from tactile experiences.

During the 1970s, in the United States, some psychiatrists began using MDMA as a psychotherapeutic tool believing that the drug eliminated the typical fear response and increased communication.



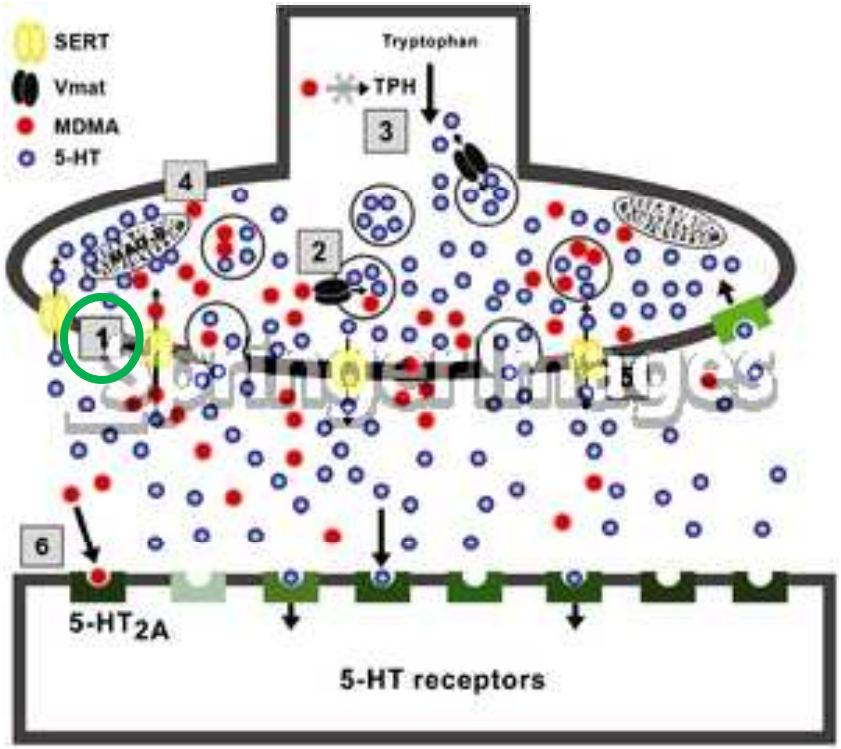
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)

MDMA is taken orally,
usually in a tablet or capsule, and its effects last approximately 3 to 6 hours.

The average reported dose is one to two tablets, with each tablet typically containing between 60 and 120 milligrams of MDMA.

MECHANISM OF ACTION

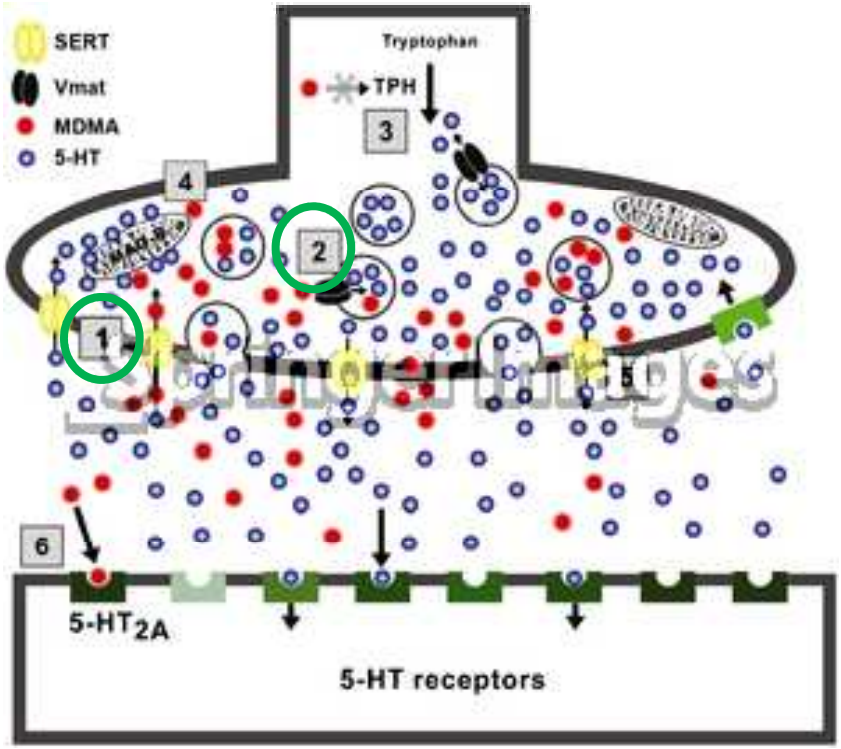
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



1) MDMA, like serotonin (5-HT), is a substrate of the serotonin transporter (5-HTT) and uses the transporter to enter inside the neuronal terminal, although at high concentration (it may also enter by diffusion).

MECHANISM OF ACTION

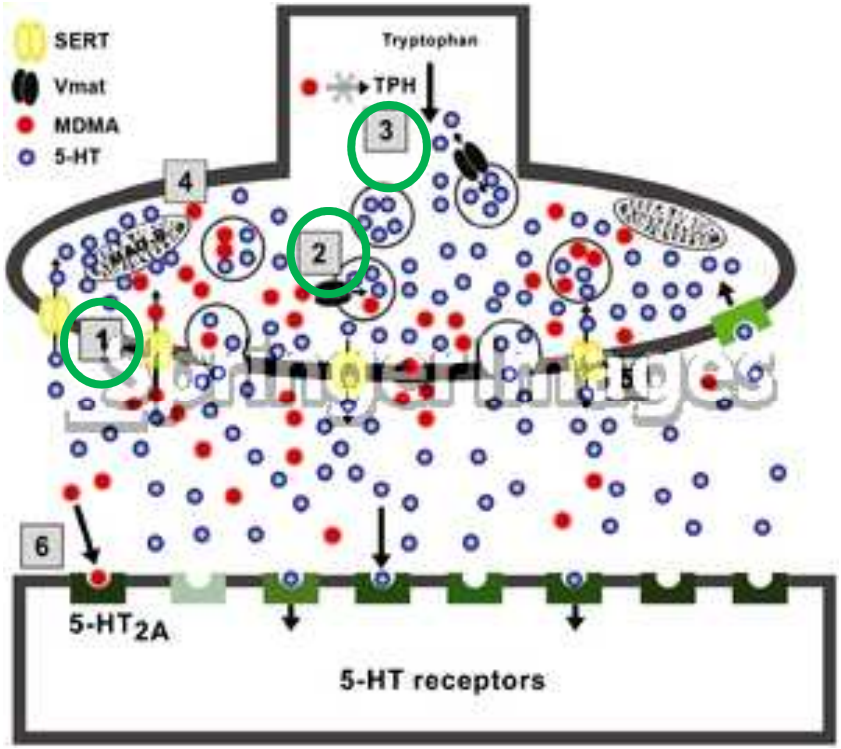
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



2) Once inside, MDMA produces an acute and rapid enhancement in the release of 5-HT from the storage vesicles, possibly by entering the vesicles via the vesicular monoamine transporter (VMAT) and depletes vesicular neurotransmitter stores.

MECHANISM OF ACTION

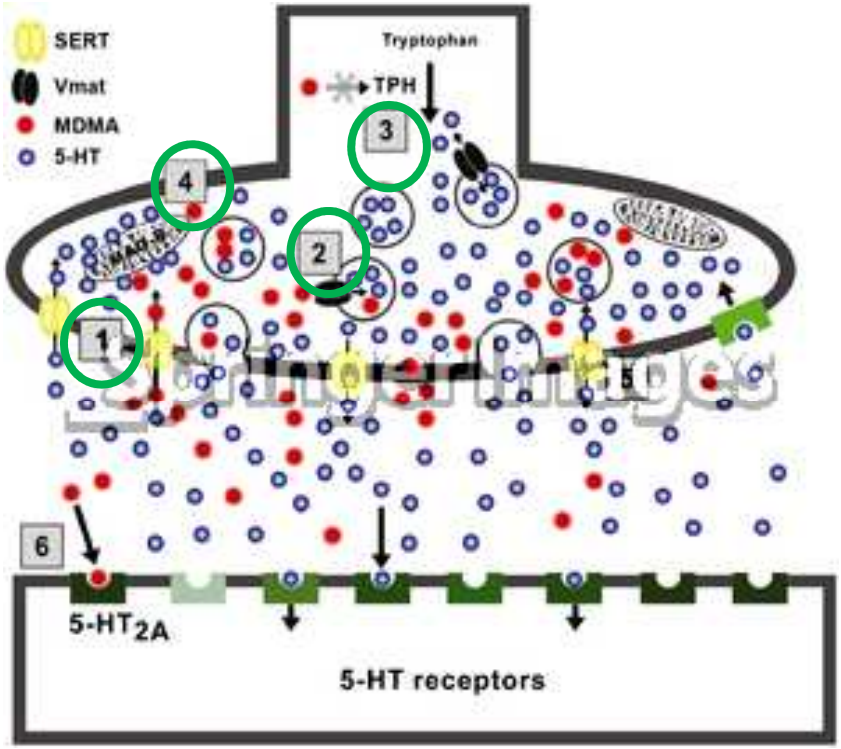
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



3) MDMA also inhibits tryptophan hydroxylase (TPH), the rate-limiting enzyme for 5-HT synthesis.

MECHANISM OF ACTION

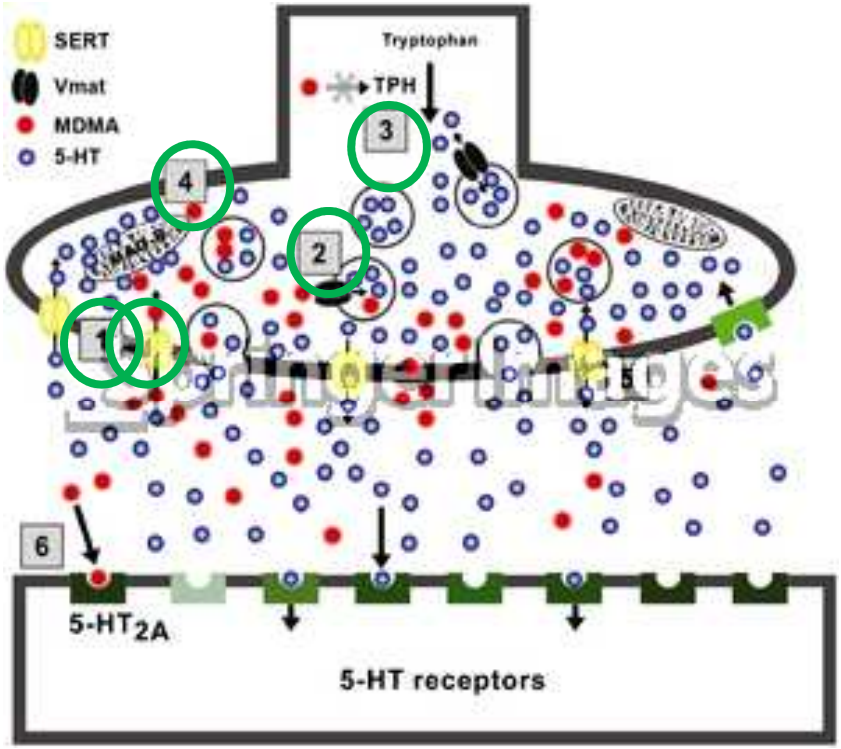
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



4) Monoamine oxidase B (MAO-B), located in the outer membrane of the mitochondria of serotonergic neurons, is the enzyme responsible for 5-HT degradation and its activity is partially inhibited by MDMA.

MECHANISM OF ACTION

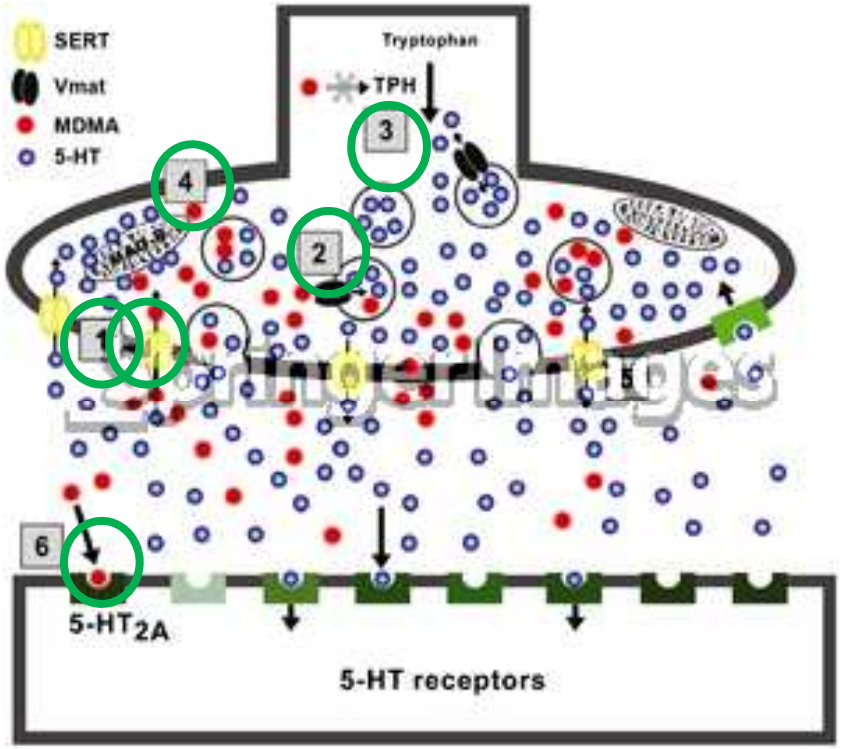
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



5) Due to the increase in the free cytoplasmatic pool of 5-HT, MDMA promotes a rapid release of intracellular 5-HT to the neuronal synapse via reversal of the 5-HTT activity.

MECHANISM OF ACTION

MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



6) MDMA hallucinogenic properties depend on the agonist activity at the 5-HT_{2A}-receptor.

MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)

Effects:

feelings of mental stimulation

emotional warmth

empathy toward others

general sense of well being

decreased anxiety

enhanced sensory perception

MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)

Possible dangerous adverse effect:

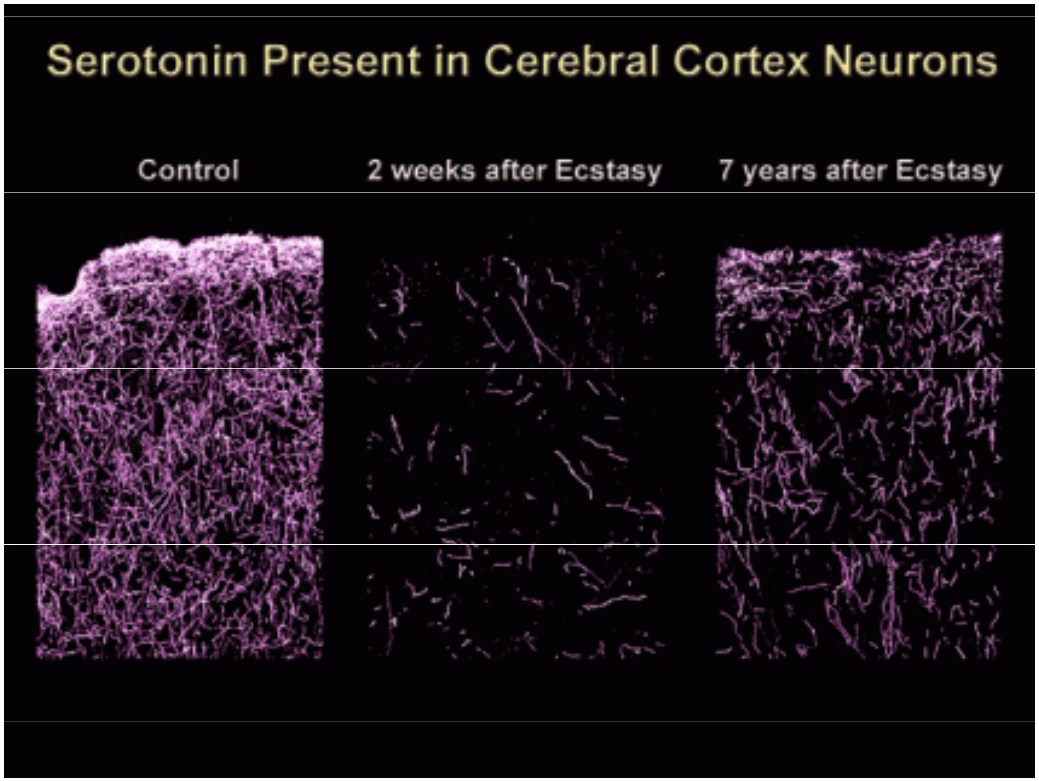
marked rise in body temperature (**hyperthermia**)

- following vigorous physical activity for extended periods

Symptoms of MDMA overdose:

High Blood Pressure
Faintness
Panic attacks
Loss of consciousness
Seizures

MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



Long-term effects in monkeys.

The left panel is brain tissue from a normal monkey.

The middle and right panels illustrate the loss of serotonin-containing nerve endings following MDMA exposure.

MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)

Is MDMA addictive?.

Experiments have shown that animals will self administer MDMA - an important indicator of a drug's dependency potential

- although the degree of self-administration is less than some other drugs of abuse such
- as cocaine

Dependency on MDMA is relatively rare.

There is a risk associated with transition to other stronger stimulants (pervitin, cocaine).

MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)

Withdrawal symptoms (mild)

Fatigue and mood swings.

Craving and irritability.

There are no specific pharmacologic treatments for MDMA abuse.

„New“ synthetic substances

Broad spectrum of substances.

„New“´= new in the market.

Majority o these substances (including their psychotropic properties) is known many years.

Increase in the last 15 years in association with rave parties and MDMA use.

empathogens and entactogens

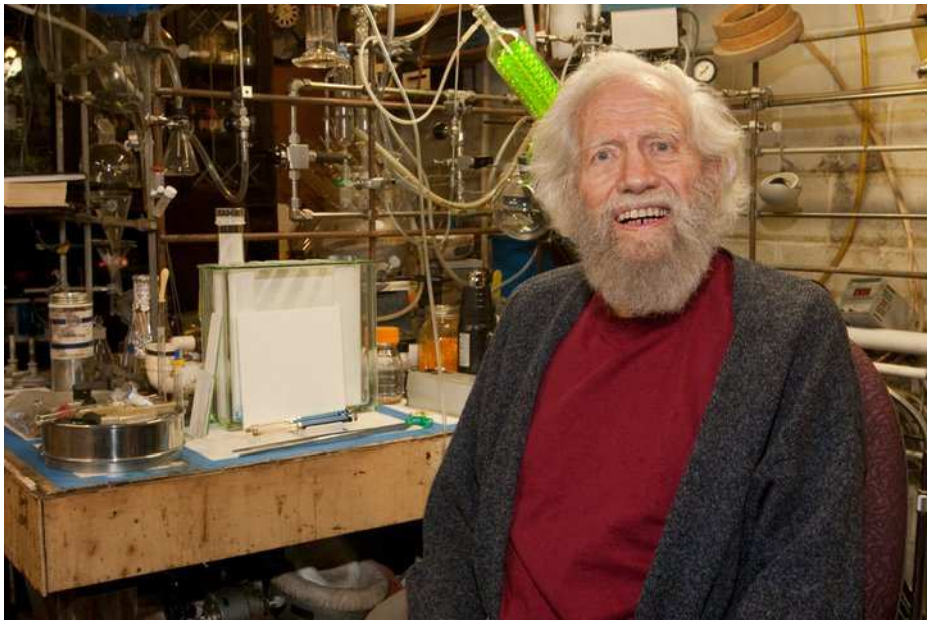
„New“ synthetic substances

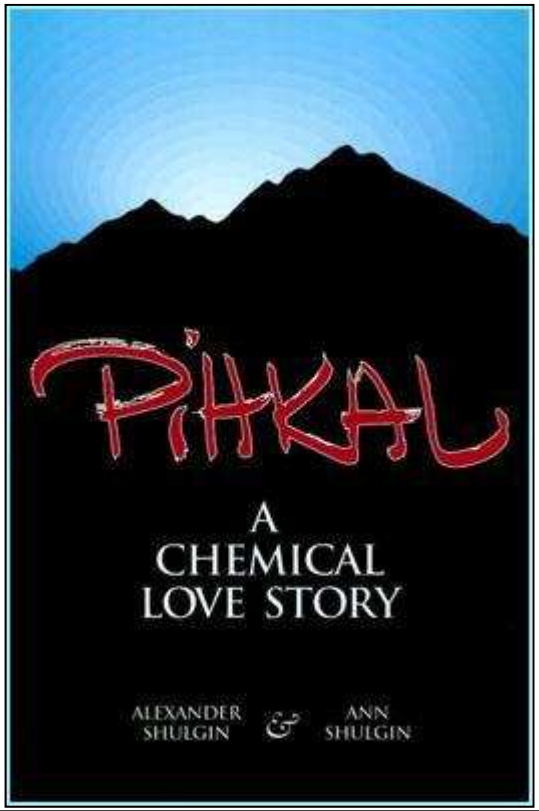
Substances derived from **phenylethylamine** a **tryptamine**.

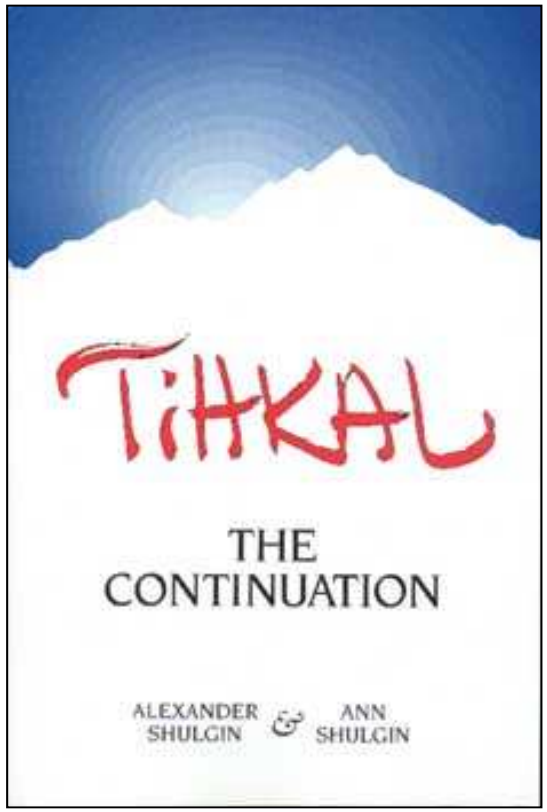
For the first time described in a detailed way by prof. Alexander Shulgin (1925 – 2014) in books:

PIHKAL (Phenylethylamines I Have Known And Loved)

TIHKAL (Tryptamines I Have Known and Loved).







MECHANISM OF ACTION

„New“ synthetic substances

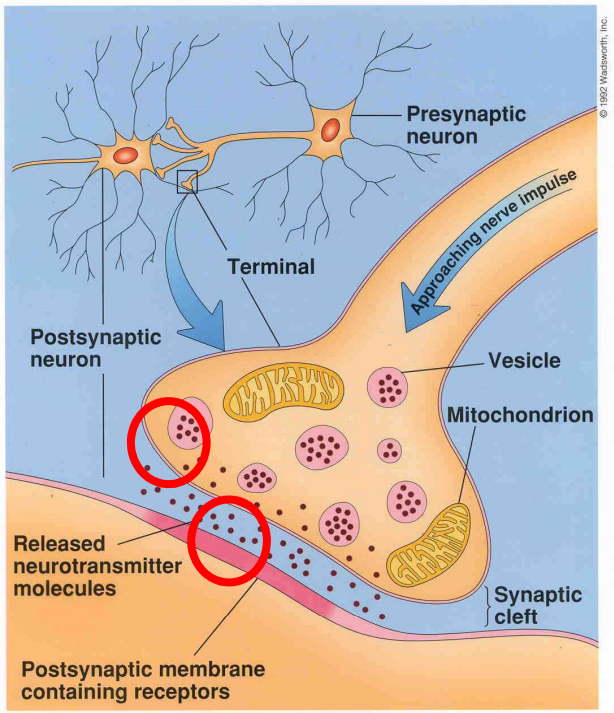
Majority of these substances affects more neurotransmitter systems in the CNS.

Usually the most important system: serotonergic.

Other important systems: dopaminergic and noradrenergic, sometimes cholinergic.

1. mechanism: direct acting at receptors.

2. mechanism: inhibition of neurotransmitter reuptake.



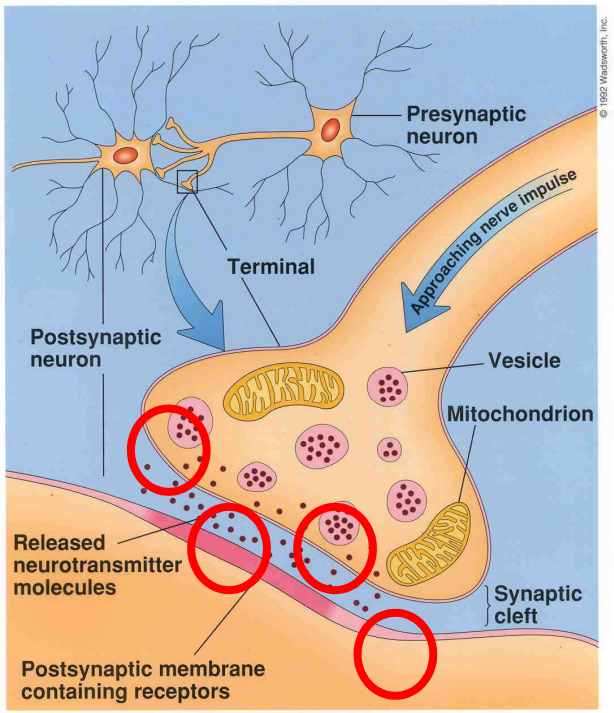
Synapse

MECHANISM OF ACTION

„New“ synthetic substances

3. mechanism: increase neurotransmitter release.

4. mechanisms: inhibition of decomposing enzymes



Synapse

„New“ synthetic substances

Phenylethylamines

PMA (para-methoxy-amphetamine**)**

2,4-DMA (2,4-dimethoxy-amphetamine)

MDA (3,4-methylenedioxy-amphetamine)

MMDA (3-methoxy-4,5-methylendioxy-amphetamine)

TMA (3,4,5-trimethoxyamphetamine)

DMMDA (2,5-dimethoxy-3,4-methylenedioxyamphetamine)

TeMA (2,3,4,5-tetramethoxyamphetamine)

„New“ synthetic substances

Tryptamines

DBT (N,N-Dibutyl-T)

DET (N,N-Diethyl-T)

DiPT (N,N-Diisopropyl-T)

DMT (N,N-Dimethyl-T)

DPT (N,N-Dipropyl-T)


"Blue Mystic" 2C-T-7 Tablets

2C-T-2 Tablets
Photo by Murple, © 2000 Erowid.org

Hallucinogens

Hallucinogenic compounds found in some plants and mushrooms have been used - mostly during religious rituals -for centuries.

Many hallucinogens have chemical structures similar to those of natural neurotransmitters (e.g., acetylcholine-, serotonin-, or catecholamine-like).

While the exact mechanisms by which hallucinogens exert their effects remain unclear, research suggests that these drugs work, at least partially, by temporarily interfering with neurotransmitter action or by binding to their receptor

Hallucinogens

LSD

(d-lysergic acid diethylamide) is one of the most potent mood-changing chemicals.

It was discovered in 1938 and is manufactured from lysergic acid, which is found in ergot, a fungus that grows on rye and other grains.

Sensations and feelings change much more dramatically than the physical signs in people under the influence of LSD.

The user may feel several different emotions at once or swing rapidly from one emotion to another.

If taken in large enough doses, the drug produces delusions and visual hallucinations. The user's sense of time and self is altered.

Experiences may seem to "cross over" different senses, giving the user the feeling of hearing colors and seeing sounds.

These changes can be frightening and can cause panic.

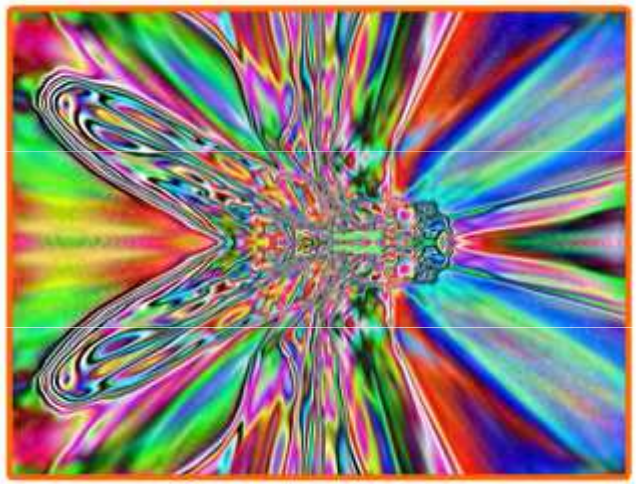
Hallucinogens

Mescaline

principal active ingredient in peyote (small, spineless cactus).

This plant has been used by natives in northern Mexico and the southwestern United States as a part of religious ceremonies.

Mescaline can also be produced through chemical synthesis.



Hallucinogens

Psilocybin:

Mushrooms containing psilocybin are available fresh or dried and are typically taken orally.

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) and its **biologically active form, psilocin** (4-hydroxy-N,N-dimethyltryptamine), cannot be inactivated by cooking or freezing preparations.

The effects of psilocybin, which appear within 20 minutes of ingestion, last approximately 6 hours.

Effects: alterations of autonomic function, motor reflexes, behavior, and perception.

hallucinations, an altered perception of time, and an inability to discern fantasy from reality

Hallucinogens

PCP (phencyclidine) was developed in the 1950s as an intravenous anesthetic.

Its use has since been discontinued due to serious adverse effects (patients often became agitated,delusional, and irrational while recovering from its anesthetic effects).

PCP is a “dissociative drug,” meaning that it distorts perceptions of sight and sound and produces feelings of detachment (dissociation) from the environment and self.

Effects: feelings of strength, power, and invulnerability,
numbing effect on the mind