

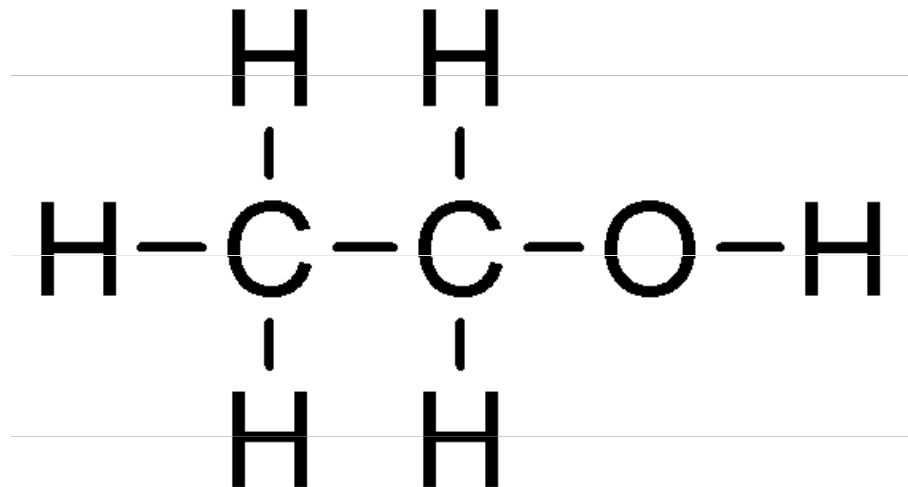


Drug addiction to the individual substances

Alcohol



syn. ethanol, ethyl alcohol,
spirit



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



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 asterix).

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

Irregular or rapid heartbeat

Coronary artery disease

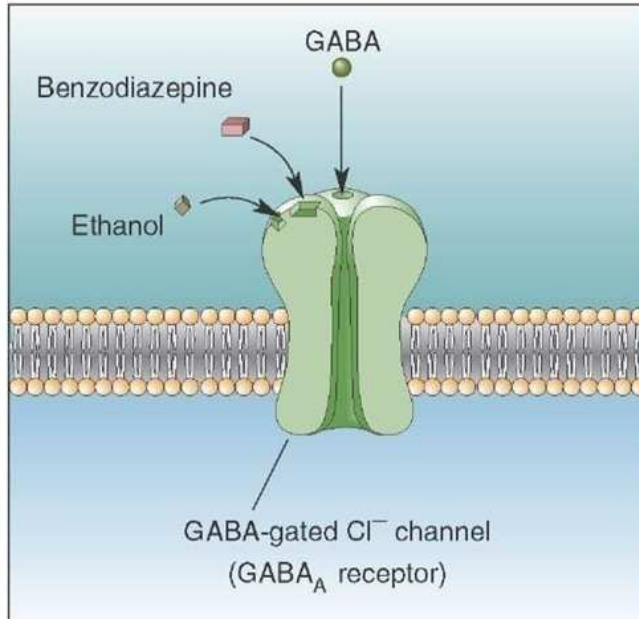
Alcohol – mechanism of action



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

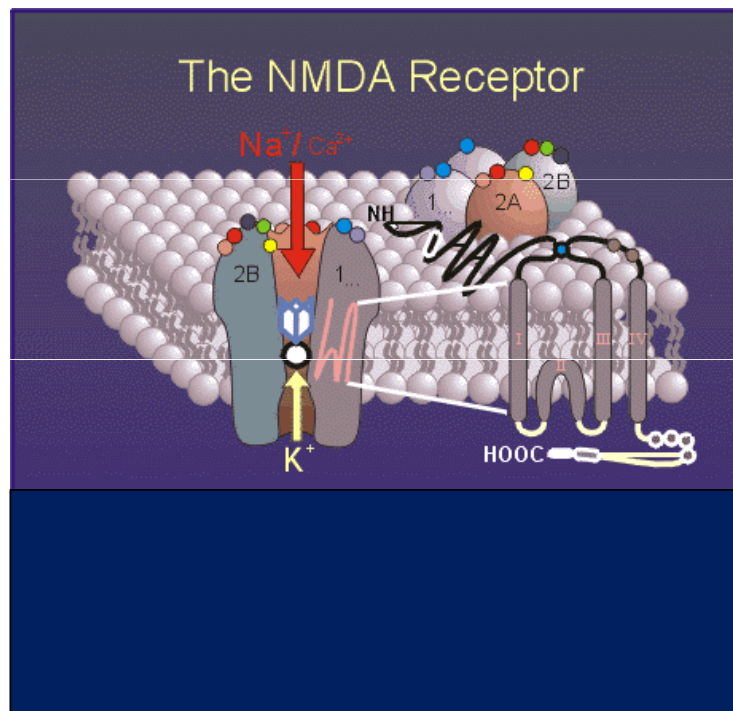
Alcohol – mechanism of action



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 and 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 nucleus 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

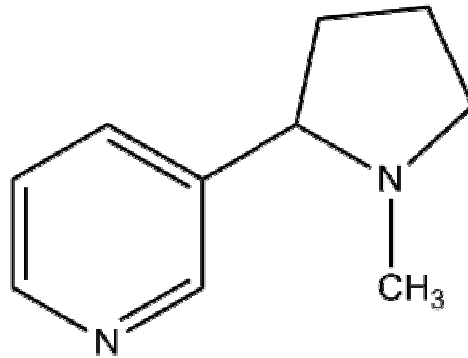
Elevated blood pressure

Anxiety

Tension

Sweating

Nicotine



Nicotine

Pharmacokinetics and metabolism:

Nicotine is a weak base ($pK_a = 8.0$).

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

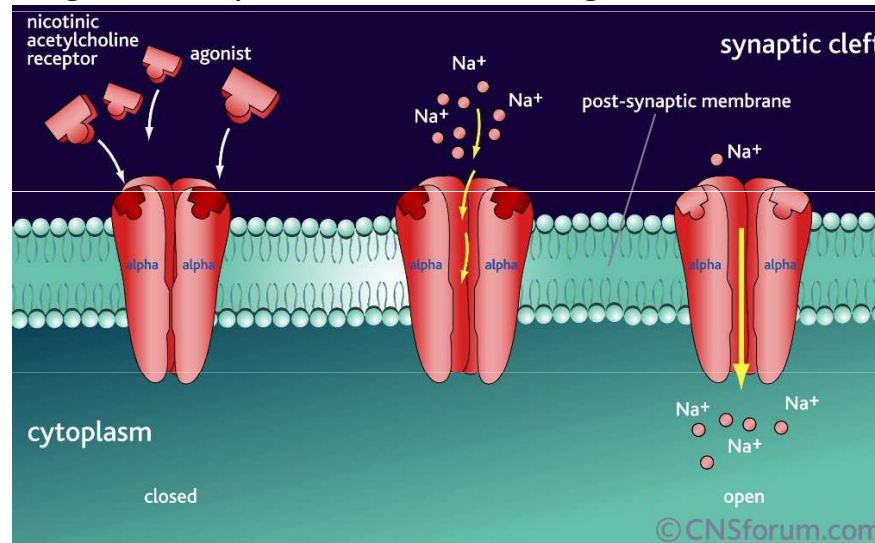


When a person inhales smoke from a cigarette, nicotine is distilled from the tobacco and is carried in smoke particles into the lungs, where it is absorbed rapidly into the pulmonary venous circulation.

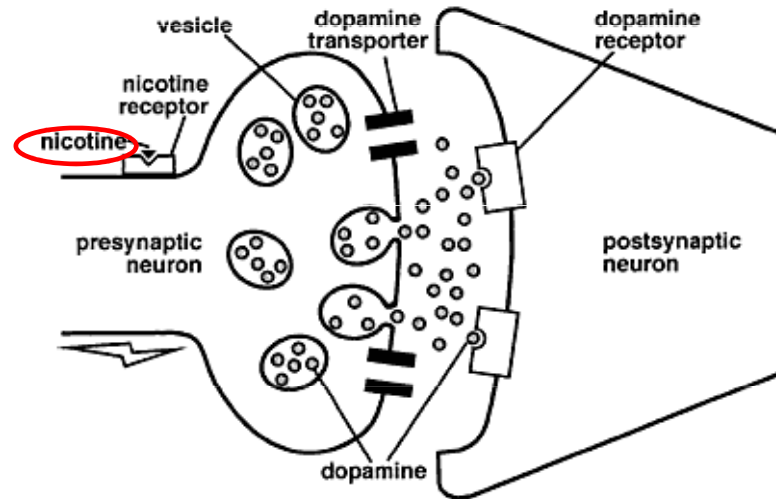
It then enters the arterial circulation and moves quickly to the brain.

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



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 $\alpha 4 \beta 2$ nAChR.

Varenicline was shown in vitro receptor binding studies to have high affinity for the $\alpha 4 \beta 2$ nAChR, and relatively little effect on other nAChR subtypes or neurotransmitter receptors.



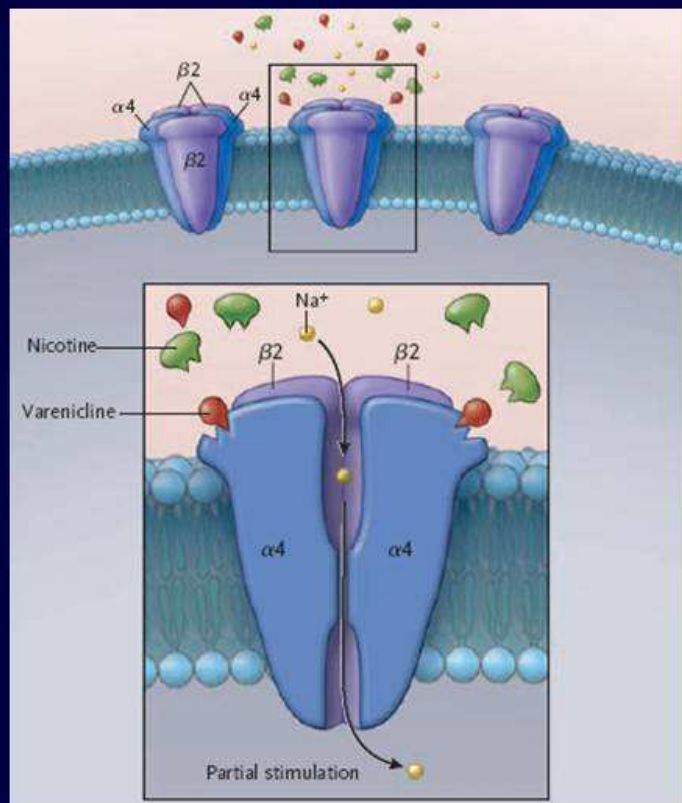
Varenicline

Varenicline is a partial agonist of the $\alpha 4 \beta 2$ 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



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.

From Hays & Ebbert, *New Eng J Med*, 2008

Nicotine **Pharmacologic Treatment of Addiction**



Clonidine:

α_2 sympathomimetic 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.

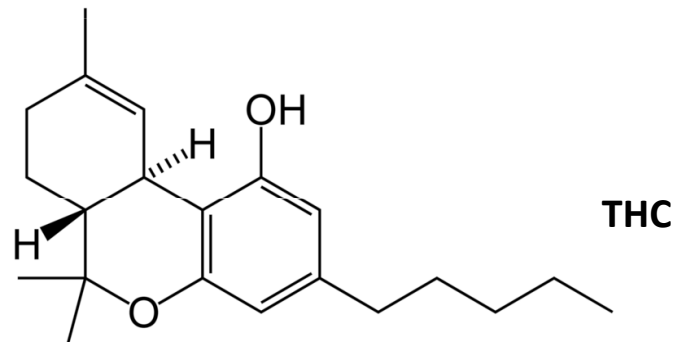
Nortriptyline:

tricyclic antidepressant drug – inhibition of norepinephrine and serotonin reuptake.

Noradrenergic effects probably alleviate withdrawal symptoms.

Other useful effects – anxiolytic.

Cannabinoids (hemp drugs)



Cannabinoids

Phytocannabinoids

Endogenous cannabinoids (endocannabinoids)

Synthetic cannabinoids



MECHANISM OF ACTION

Endocannabinoid system

Cannabinoid receptors (CB₁, CB₂)

Endocannabinoids

Decomposing enzymes



Endocannabinoid system



Cannabinoid receptors (CB₁, CB₂)

Subtypes of cannabinoid CB receptors: CB₁ a CB₂ (Howlett a kol., 2002).

CB₁ receptors: nerve endings particularly in CNS (cortex, hippocampus, basal ganglia, hypothalamus, cerebellum, spinal cord)

CB₂ receptors: mainly in peripheral tissues (testicles, sperm, cells of immune system).

Psychoactive effects: CB₁ receptors

Endocannabinoid system

Endocannabinoids

anandamide (N-arachidonylethanolamine)

noladin ether (2-arachidonyl glyceryl ether)

virodhamine (O-arachidonylethanolamine)

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).

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.

MECHANISM OF ACTION

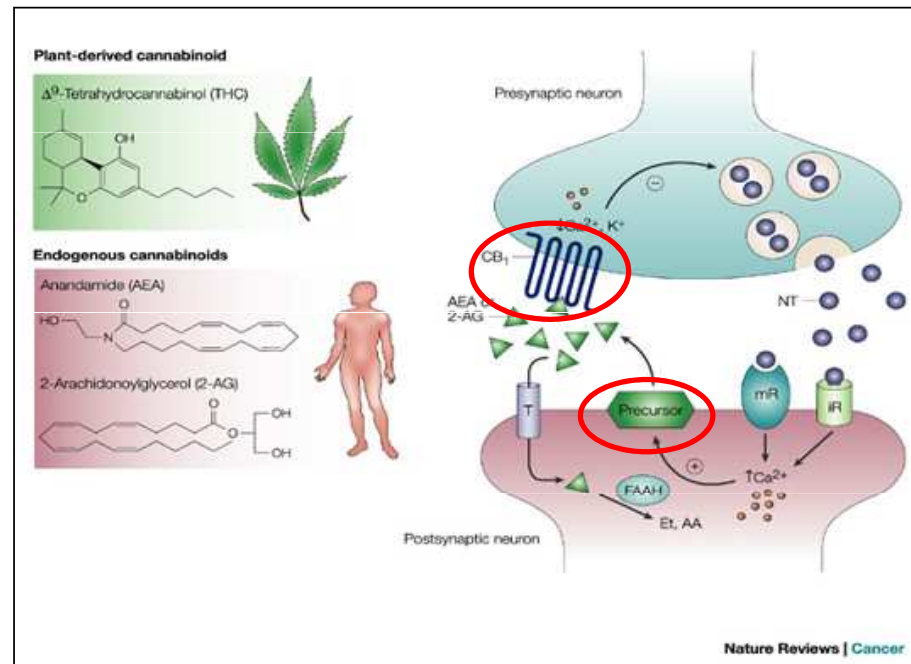
Cannabinoids



Plant-derived cannabinoids such as 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 CB₁ receptors are localized presynaptically.



Cannabinoids



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)

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.

Cannabinoids



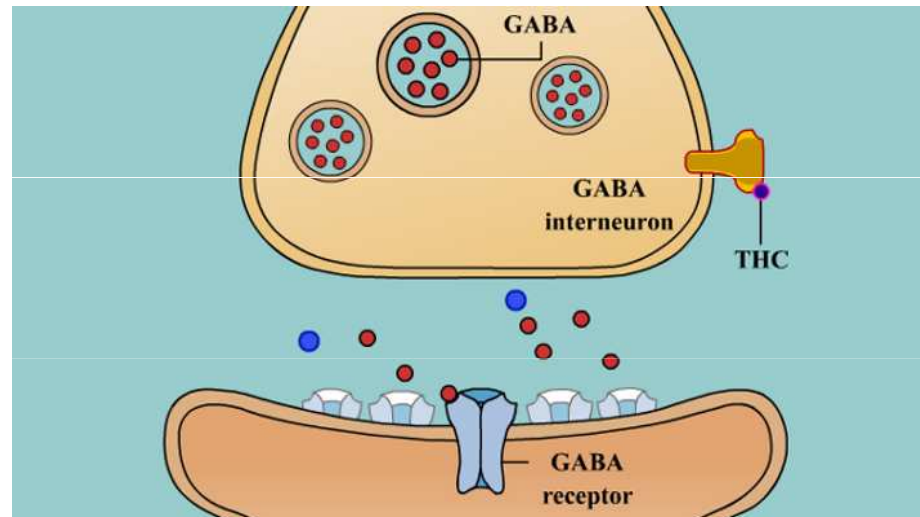
THC stimulates neurons in the reward system to release dopamine.

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.



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



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



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**

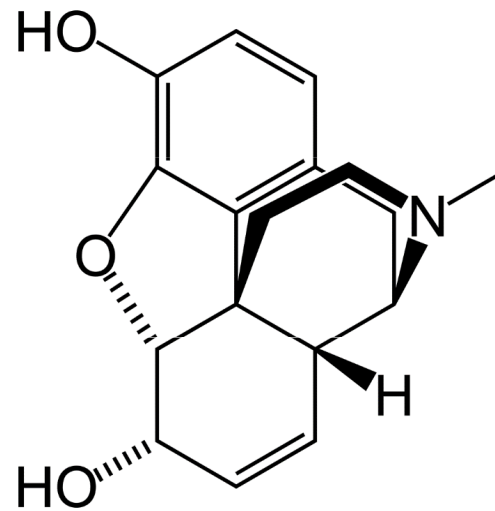
anti-anxiety/anti-stress medication: **buspirone**

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

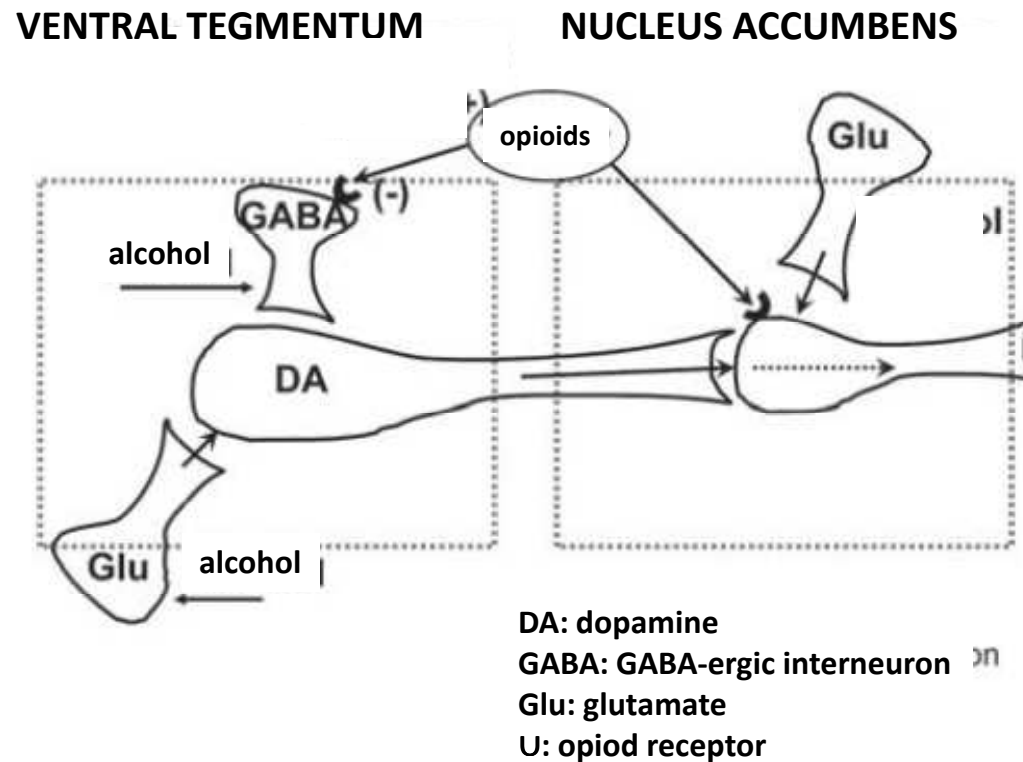
Opioids



morphine



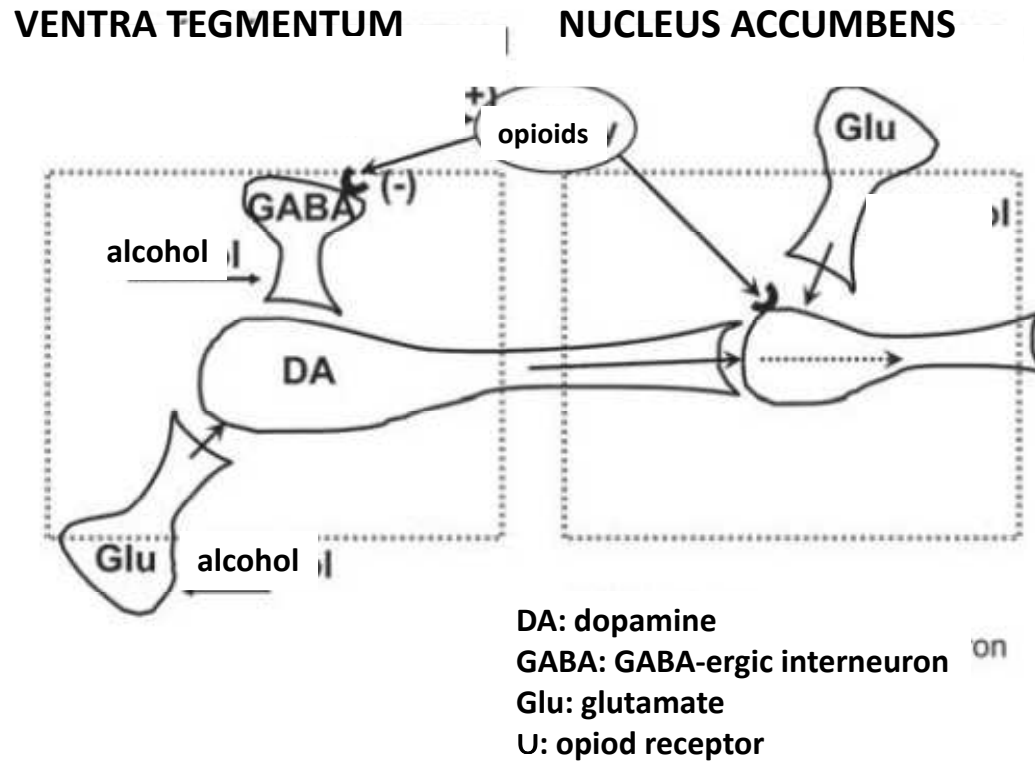
Opioids



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



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

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



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

Opioid 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

Fentanyl



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

USA: abused particularly by medical staff.

Opioids

Heroin

Synthesized in 1874.

Chemically: diacetylmorphine

Oral 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



Routes of application:

Orally (first-pass effect)

Injections (risk of infections)

Smoking

Insufflation

Suppositories (limited way)

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

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).

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

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

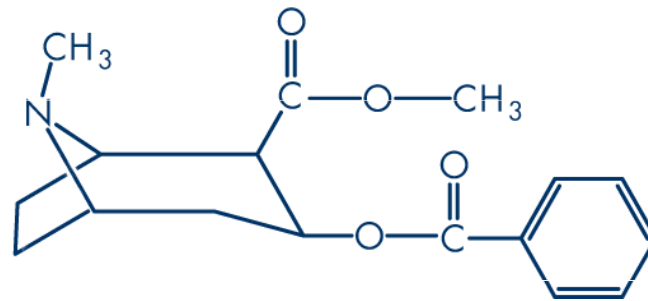
Flumazenil was found to be more effective than placebo in reducing feelings of hostility and aggression in patients who had been free of benzodiazepines for 4–266 weeks.

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.

„Classical“ psychostimulants

Cocaine

Routes of administration:

Orally (chewing coca leaves)

Nasal insufflation (so called snorting, sniffing or blowing)

Injection

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

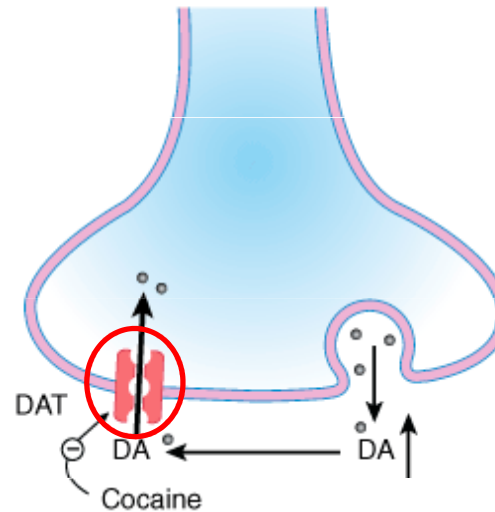
Suppository (limited way called "plugging")

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

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

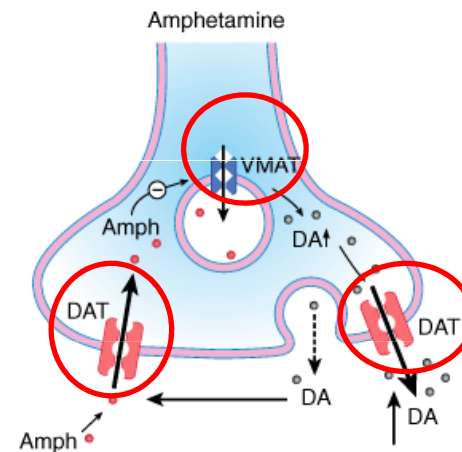
Bromocriptine: agonist of dopamine D₂ receptors (**used with mixed success**).

Originally intended for treatment of Parkinson's disease.

MECHANISM OF ACTION

„Classical“ psychostimulants

Amphetamine



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

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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

MECHANISM OF ACTION

„Classical“ psychostimulants

Methamphetamine (pervitin)

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

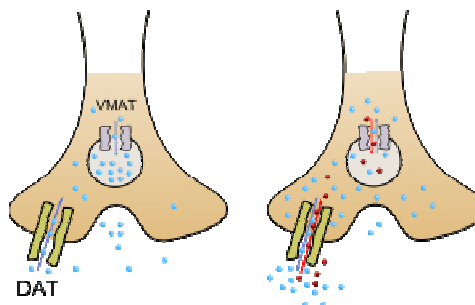
Methamphetamine works by taking advantage of its similarity to dopamine.

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)

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.

„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)

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

Ibuprofen: suppresses the neuroinflammatory actions of glial cells.

It has been shown to inhibit methamphetamine self-administration in rats.

Unknown 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.

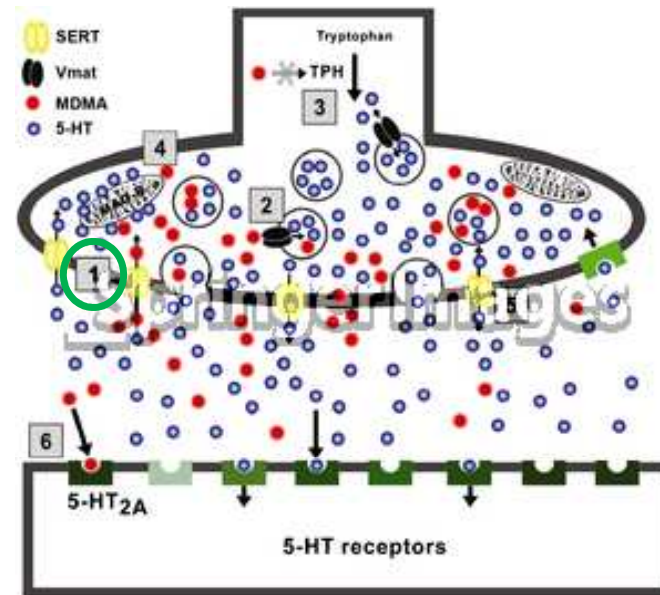
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)

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

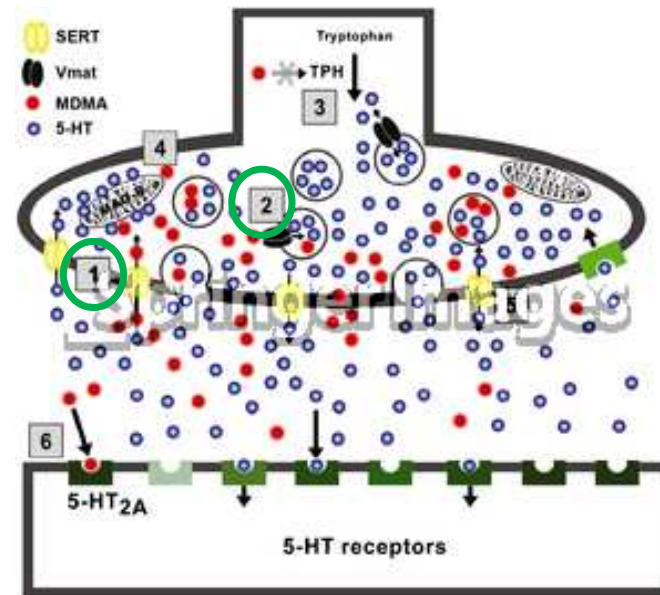
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



- 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

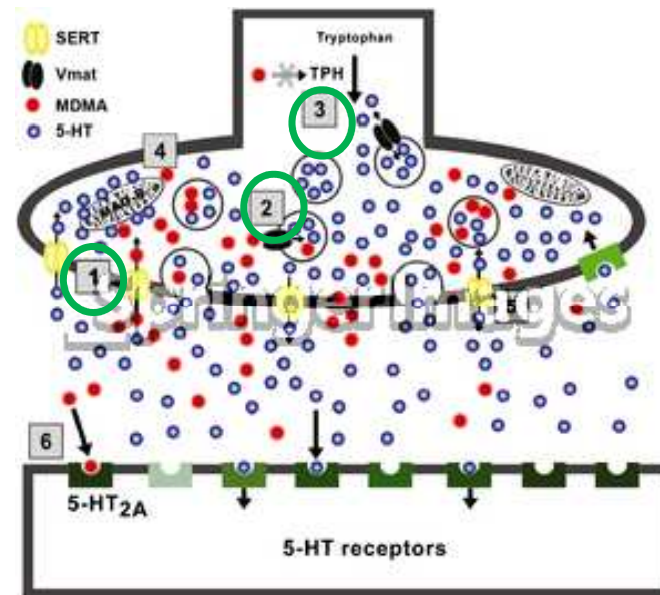
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



- 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

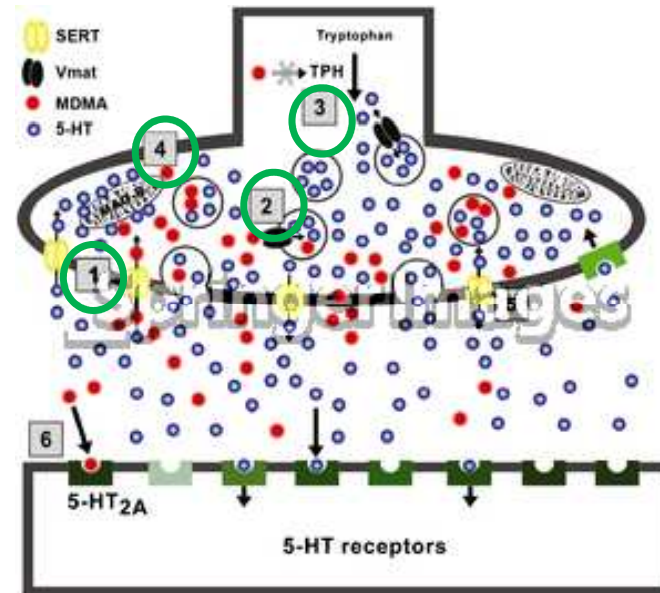
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



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

MECHANISM OF ACTION

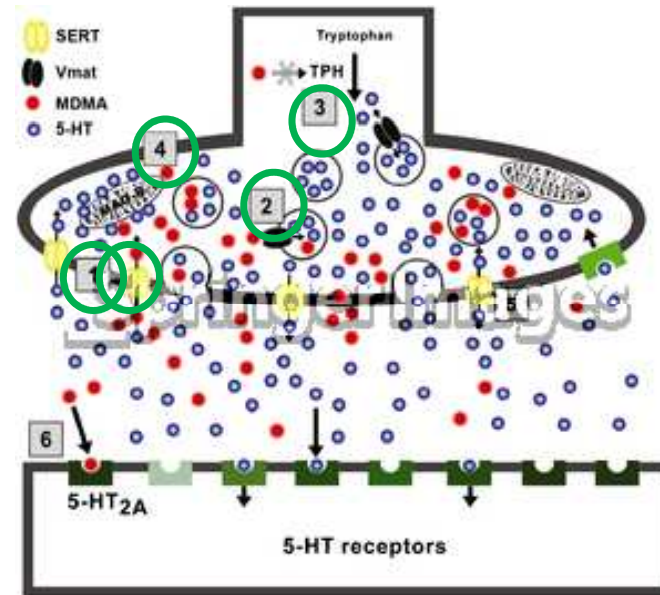
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



- 1) SERT
- 2) Vmat
- 3) Vmat
- 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.
- 5) 5-HT
- 6) 5-HT_{2A} and 5-HT receptors

MECHANISM OF ACTION

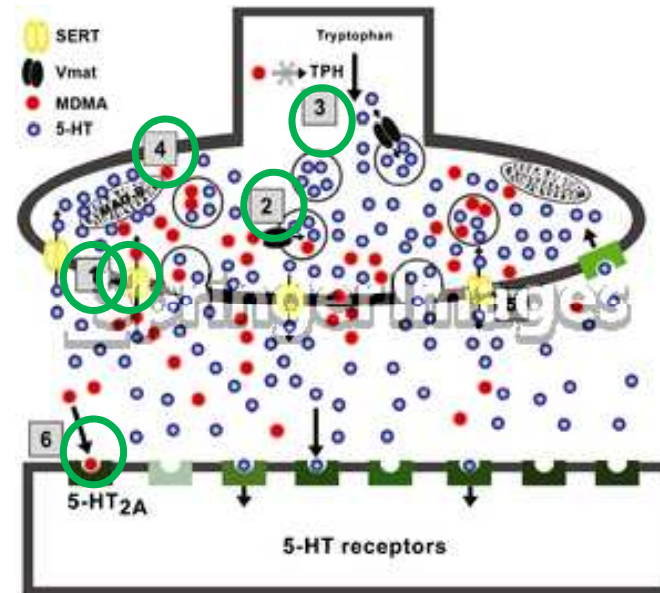
MDMA (3,4-methylenedioxy-methamphetamine, ecstasy)



5) Due to the increase in the free cytoplasmic 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)



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 of 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

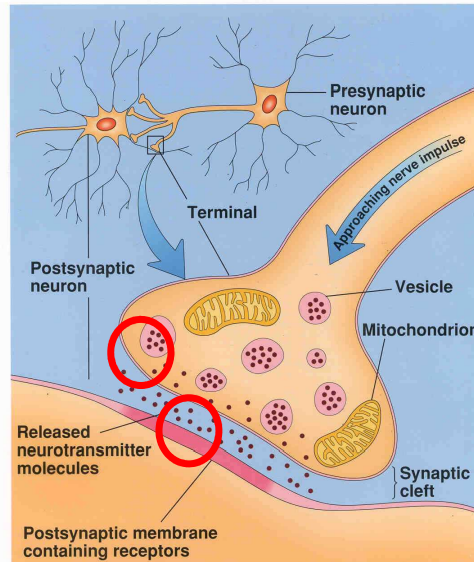
Majority of these substances affects more neurotransmitter systems in the CNS.

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.

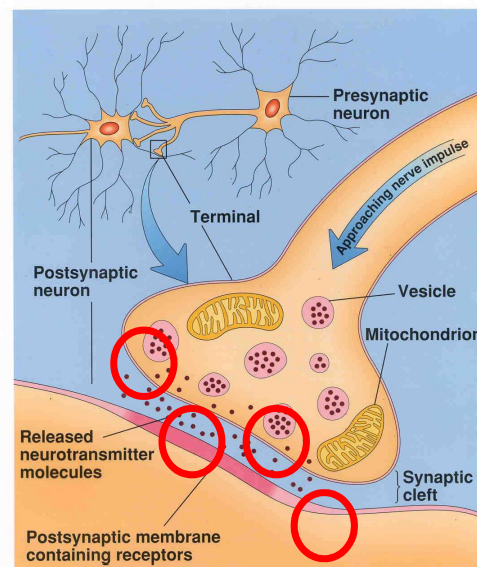


Synapse

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-methylenedioxy-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)

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