Drugs of Abuse

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Drugs of Abuse

- Drugs are abused when they are used in ways that are not medically approved.
- Usually because they produce a strong feeling of euphoria, or alter perception.
- Repetitive exposure induces widespread adaptive changes in the brain.
- As a consequence drug use may become compulsive (the hallmark of addiction).

Drugs of Abuse

- Once the abused drug is no longer available, signs of withdrawal become apparent, which defines dependence.
- Dependence is not always a correlate of drug abuse.
- It can also occur with many classes of nonpsychoactive drugs such as vasoconstrictors, bronchodilators, and organic nitrates.

Drugs of Abuse

- **As a general rule, all addictive drugs activate the mesolimbic dopamine system → increase in dopamine (?).**
- **Mesolimbic dopamine codes for the difference between expected and actual reward, and thus, constitutes a strong learning signal.**

Addiction

- Is a disease of maladaptive learning.
- It is characterized by a high motivation to obtain and use a drug despite negative consequences.
- With time, drug use becomes compulsive "wanting without liking".
- Addicted individuals are at high risk of relapsing.

Addiction

Relapse is typically triggered by one of the following three conditions:

A. Re-exposure to the drug of abuse.

B. Stress.

C. A context that recalls prior drug use.

Addiction

- **Large individual differences exist in vulnerability to addiction.**
- **Whereas one person may become “addict" after a few doses, others may be able to use a drug occasionally during their entire lives without ever having difficulty in stopping.**
- **Even when dependence is induced with chronic exposure, only a fraction of dependent users will go on to become addicted.**

Cocaine

- **The prevalence of cocaine abuse is high and represents a major public health problem worldwide.**
- **Cocaine is highly addictive, and its use is associated with a number of complications.**
- **It can be used by injection or inhalation.**

Cocaine

- **In the peripheral nervous system, cocaine inhibits voltage-gated sodium channels, thus blocking initiation and conduction of action potentials.**
- **This action is NOT responsible for the acute rewarding or the addictive effects.**

Cocaine

- In the central nervous system, cocaine blocks the uptake of dopamine, norepinephrine, and serotonin through their respective transporters.
- The block of the dopamine transporter (DAT), & increasing dopamine concentrations in the nucleus accumbens, has been implicated in the rewarding effects of cocaine.

Cocaine

- **Block of the norepinephrine transporter (NET) leads to an acute increase in arterial pressure, tachycardia, and often, ventricular arrhythmias.**
- **Cocaine exposure increases the risk for intracranial hemorrhage, ischemic stroke, myocardial infarction, and generalized or partial seizures.**

Cocaine

- **Subjects typically loose appetite, are hyperactive, and sleep little.**
- **Cocaine overdose may lead to hyperthermia, coma, and death.**
- **Susceptible individuals may become dependent and addicted after only a few exposures to cocaine.**

Cocaine

- **Although a withdrawal syndrome is reported, it is not as strong.**
- **Tolerance may develop, but in some users a reverse tolerance is observed; that is, they become sensitized to small doses of cocaine.**
- **This behavioral sensitization is in part context-dependent.**

Cocaine

- **Cravings are very strong and underline the very high addiction liability of cocaine.**
- **To date, no specific antagonist is available.**

Amphetamines

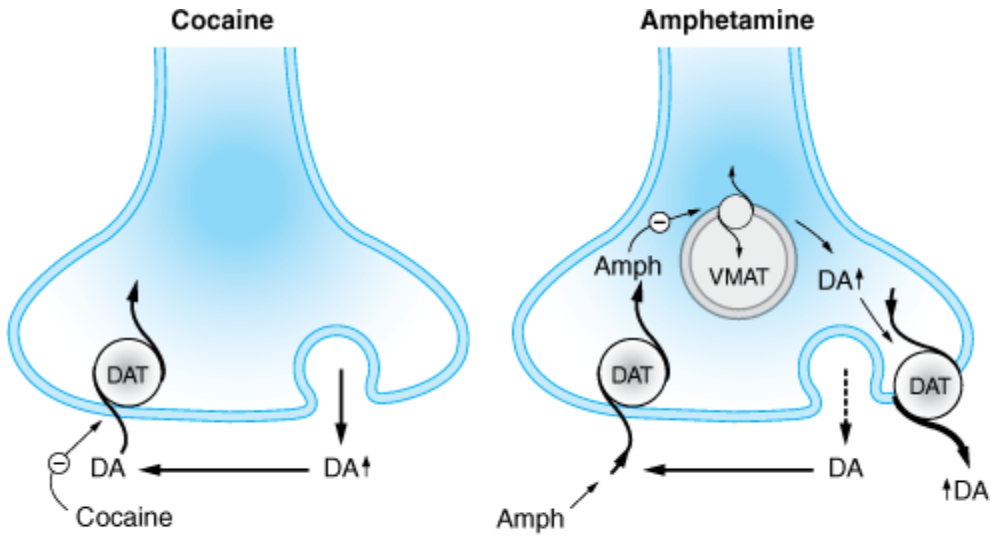
- **Amphetamines are a group of synthetic, indirect-acting sympathomimetic drugs that cause the release of endogenous biogenic amines, such as dopamine, serotonin and norepinephrine.**
- **Amphetamine, methamphetamine, and their derivatives reverse the action of biogenic amine transporters at the plasma membrane.**

Amphetamines

- **Amphetamines are substrates of these transporters and are taken up into the cell.**
- **Once in the cell, amphetamines interfere with the vesicular monoamine transporter (VMAT), depleting synaptic vesicles of their neurotransmitter content.**

Amphetamines

- **As a consequence, levels of dopamine (or other transmitter amine) in the cytoplasm increase and quickly become sufficient to cause release into the synapse by reversal of the plasma membrane DAT.**
- **Normal vesicular release of dopamine consequently decreases, while nonvesicular release increases.**



Mechanism of action of cocaine and amphetamine on synaptic terminal of dopamine (DA) neurons. *Left:* Cocaine inhibits the dopamine transporter (DAT), decreasing DA clearance from the synaptic cleft and causing an increase in extracellular DA concentration. *Right:* Since amphetamine (Amph) is a substrate of the DAT, it competitively inhibits DA transport. In addition, once in the cell, amphetamine interferes with the vesicular monoamine transporter (VMAT) and impedes the filling of synaptic vesicles. As a consequence, vesicles are depleted and cytoplasmic DA increases. This leads to a reversal of DAT direction, strongly increasing nonvesicular release of DA, and further increasing extracellular DA concentrations.

Amphetamines

- **In general, amphetamines lead to elevated catecholamine levels that increase arousal and reduce sleep, while the effects on the dopamine system mediate euphoria but may also cause abnormal movements and precipitate psychotic episodes.**

Amphetamines

- **Effects on serotonin transmission may play a role in the hallucinogenic and anorexigenic functions as well as in the hyperthermia often caused by amphetamines.**

Amphetamines

- **Unlike many other abused drugs, amphetamines are neurotoxic. The exact mechanism is not known, but neurotoxicity depends on the NMDA receptors and affects mainly serotonin and dopamine neurons.**
- **Can be taken by abusers orally or smooked, and ultimately by intravenous administration.**

Amphetamines

- Within hours after oral ingestion, they increase alertness, and cause euphoria, agitation, and confusion.
- Bruxism (tooth grinding) and skin flushing may occur.
- With increasing dosage these agents often lead to tachycardia and dysrhythmias.
- Hypertensive crisis and vasoconstriction may lead to stroke.

Amphetamines

- **Spread of HIV and viral hepatitis infection has been associated with needle sharing by intravenous users of methamphetamine.**
- **With chronic use, tolerance may develop, leading to dose escalation.**
- **Withdrawal consists of dysphoria, drowsiness, insomnia, and general irritability.**

Ecstasy (MDMA)

- **Ecstasy is the name of a class of drugs that includes a large variety of derivatives of the amphetamine-related compound methylenedioxymethamphetamine (MDMA).**
- **The main effect of ecstasy appears to be fostering feelings of intimacy (ألفة) and empathy (تعاطف) without impairing intellectual capacities.**

Ecstasy (MDMA)

- **MDMA causes release of biogenic amines by reversing the action of their respective transporters.**
- **It has a preferential affinity for the serotonin transporter (SERT), and therefore, increases the extracellular concentration of serotonin.**

Ecstasy (MDMA)

- This release is so profound that there is a marked intracellular depletion for 24 hours after a single dose.
- With repetitive administration, serotonin depletion may become permanent.
- Several studies report long-term cognitive impairment in heavy users of MDMA.

Ecstasy (MDMA)

- **MDMA has several acute toxic effects, in particular hyperthermia, which along with dehydration, may be fatal.**
- **Other complications include serotonin syndrome (mental status change, autonomic hyperactivity, and neuromuscular abnormalities, and seizures).**

Ecstasy (MDMA)

- Following warnings about the dangers of MDMA, some users have attempted to compensate for hyperthermia by drinking excessive amounts of water, causing water intoxication involving severe hyponatremia, seizures, and even death.
- Withdrawal is marked by a mood "offset" characterized by depression lasting up to several weeks.

Ecstasy (MDMA)

- **There have also been reports of increased aggression during periods of abstinence in chronic MDMA users.**
- **The evidence for irreversible damage to the brain, implies that even occasional recreational use of MDMA cannot be considered safe.**

Cannabinoids

- **Endogenous cannabinoids that act as neurotransmitters include 2-arachidonyl glycerol (2-AG) and anandamide, both of which bind to CB_1 receptors.**
- **These very lipid-soluble compounds are released at the postsynaptic somatodendritic membrane.**

Cannabinoids

- **Then they diffuse through the extracellular space to bind at presynaptic CB_1 receptors, where they inhibit the release of either glutamate or GABA.**
- **Because of such backward signaling, endocannabinoids are called retrograde messengers.**

Cannabinoids

- **Exogenous cannabinoids (in marijuana or cannabis الحشيش), comprise several pharmacologically active substances including Δ^9-tetrahydrocannabinol (THC), a powerful psychoactive substance.**
- **THC causes disinhibition of dopamine neurons, mainly by presynaptic inhibition of GABA neurons in the ventral tegmental area (VTA).**

Cannabinoids

- The half-life of THC is about 4 hours.
- The onset of effects of THC after smoking marijuana occurs within minutes and reaches a maximum after 1–2 hours.
- The most prominent effects are euphoria and relaxation.
- Users also report feelings of well-being, grandiosity, and altered perception of passage of time.

Cannabinoids

- **Dose-dependent perceptual changes (visual distortions), drowsiness, diminished coordination, and memory impairment may occur.**
- **Cannabinoids can also create a dysphoric state and in rare cases, following the use of very high doses, may result in visual hallucinations, depersonalization (a state in which one no longer perceives the reality of one's self or one's environment), and frank psychotic episodes.**

Cannabinoids

- **Additional effects of THC include: increased appetite, attenuation of nausea, decreased intraocular pressure, and relief of chronic pain, have led to the use of cannabinoids in medical therapeutics.**
- **Chronic exposure to marijuana leads to dependence.**

Cannabinoids

- **withdrawal syndrome (distinctive, but mild and short-lived): Restlessness, irritability, mild agitation, insomnia, nausea, and cramping.**

- **Synthetic agents include Δ^9-THC analogs dronabinol and nabilone. [Used in therapeutics].**

Nonaddictive Drugs of Abuse

- Some drugs of abuse do not lead to addiction.
- This occurs with substances that alter perception without causing sensations of reward and euphoria, such as the hallucinogens and the dissociative anesthetics.
- These agents primarily target cortical and thalamic circuits, unlike addictive drugs which primarily target the mesolimbic dopamine system.

LSD, Mescaline, and Psilocybin

- **They are commonly called hallucinogens because of their ability to alter perceptions such that the individual senses things that are not present.**
- **They induce, often in an unpredictable way, perceptual symptoms, including shape and color distortion.**

LSD, Mescaline, and Psilocybin

- **Subjects have impaired ability to make rational judgments and understand common dangers, which puts them at risk of accidents and personal injury.**
- **Psychosis-like manifestations (depersonalization, hallucinations, distorted time perception) have led some to classify these drugs as psychotomimetics.**

LSD, Mescaline, and Psilocybin

- They also produce somatic symptoms (dizziness, nausea, paresthesias, and blurred vision).
- Some users have reported intense reexperiencing of perceptual effects (flashbacks) up to several years after the last drug exposure.

LSD, Mescaline, and Psilocybin

- They induce neither dependence nor addiction.
- However repetitive exposure still leads to rapid tolerance.
- These drugs also fail to stimulate dopamine release, further supporting the idea that only drugs that activate the mesolimbic dopamine system are addictive.

LSD, Mescaline, and Psilocybin

- **Instead, hallucinogens increase glutamate release in the cortex.**
- **The molecular target of hallucinogens is the 5-HT_{2A} receptor.**

Phencyclidine (PCP) & Ketamine

- **Ketamine and PCP were developed as general anesthetics.**
- **They produce use-dependent, noncompetitive antagonism of the NMDA receptor.**
- **They are sold as a liquids, capsules, or pills, which can be snorted, ingested, injected, or smoked.**

Phencyclidine (PCP) & Ketamine

- **Psychedelic effects last for about 1 hour and also include increased blood pressure, impaired memory function, and visual alterations.**
- **At high doses unpleasant out-of-body and near-death experiences have been reported.**

Phencyclidine (PCP) & Ketamine

- **Although ketamine and phencyclidine do not cause dependence and addiction, chronic exposure, particularly to PCP, may lead to long-lasting psychosis closely resembling schizophrenia, which may persist beyond drug exposure.**