



The Brain, Biology and Cognition (BBC)

Biological and Cognitive effects of drug addiction

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Mechanisms of Drug Action

- To have an effect, drugs must pass through blood-brain barrier.
- Drugs affect the nervous system, either in a diffuse manner
- Or specifically bind to particular synaptic receptors, influence synthesis, transport, release, deactivate a neurotransmitter, or influence chain of reactions in postsynaptic neurons.
- Action of most drugs are terminated by enzymes in the liver – called drug **metabolism**.
- Drug metabolism eliminates a drug's ability to pass through lipid membranes of cells so it cannot penetrate the blood-brain barrier
- Small amounts may also be excreted in urine, sweat, feces, breath, and mother's milk.



Pharmacology of Synaptic Transmission

How drugs influence synaptic activity

- Agonists – increase or facilitate activity
- Antagonists – decrease or inhibit activity
- A drug may act to alter neurotransmitter activity at any point in its “life cycle”

Pharmacology examines behavioural effects of neurotransmitters.

Behavioral Pharmacology: Three Influential Lines of Research



- **Drugs selective to specific receptor subtypes may exert different effects**
 - e.g. nicotinic vs. muscarinic acetylcholine receptors
- **Discovery of the endogenous opioids provided insight into brain mechanisms of pleasure/pain**
- **Effects of dopamine agonists and antagonists on psychotic symptoms led to new treatments for schizophrenia**



Agonistic and antagonistic drug effects



Some Mechanisms of Drug Action

Agonistic Drug Effects

Drug increases the synthesis of neurotransmitter molecules (e.g., by increasing the amount of precursor).

Drug increases the number of neurotransmitter molecules by destroying degrading enzymes.

Drug increases the release of neurotransmitter molecules from terminal buttons.

Drug binds to autoreceptors and blocks their inhibitory effect on neurotransmitter release.

Drug binds to postsynaptic receptors and either activates them or increases the effect on them of neurotransmitter.

Drug blocks the deactivation of neurotransmitter molecules by blocking degradation or reuptake.

Antagonistic Drug Effects

Drug blocks the synthesis of neurotransmitter molecules (e.g., by destroying synthesizing enzymes).

Drug causes the neurotransmitter molecules to leak from the vesicles and be destroyed by degrading enzymes.

Drug blocks the release of the neurotransmitter molecules from terminal buttons.

Drug activates autoreceptors and inhibits neurotransmitter release.

Drug is a receptor blocker; it binds to the postsynaptic receptors and blocks the effect of the neurotransmitter.

Some mechanisms of agonistic and antagonistic drug effects

Drug Tolerance

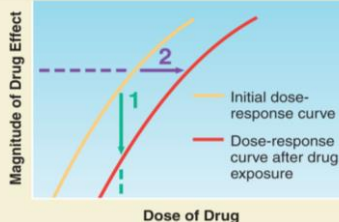


- People can become tolerant of a drug, where they experience decreased sensitivity to the drug due to repeated exposure.
- Demonstrated in 2 ways: either dose has less effect than before, or it takes more of the drug to produce the same effect.
- Drug tolerance = shift in dose-response curve: a graph of the magnitude of effect of different doses of the drug to the right.

Drug tolerance is a shift in the dose-response curve to the right. Therefore,

1 In tolerant subjects, the same dose has less effect.

2 In tolerant subjects, a greater dose is required to produce the same effect.



Drug Tolerance

- 3 aspects about the specificity of drug tolerance

1. **Cross tolerance** – one drug can produce tolerance to similar drugs – e.g., alcohol & benzodiazepines.
2. Tolerance often develops to some effects & not others of a drug. Can also have an “**inverse tolerance**,” or sensitization.
3. Drug tolerance is not a unitary phenomenon – no single mechanism underlies all examples of tolerance

Drug Tolerance

- 2 categories of changes that underlie drug tolerance:

Metabolic

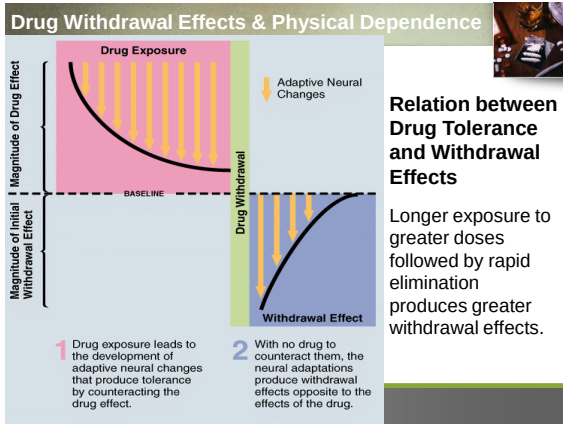
- Reduced amount of drug is getting to the site of action

Functional

- Decreased responsiveness at the site of action; fewer receptors; decreased efficiency of binding at receptors; receptors less responsive

Drug Withdrawal Effects & Physical Dependence

- Sudden elimination triggers adverse physiological reaction: withdrawal syndrome.
- Body makes changes to compensate for drug's presence – functions normally with drug present
- Withdrawal effect is usually opposite to the initial effect of the drug
 - Suggests withdrawal effect may be produced by same neuronal changes that produce drug tolerance.



Addiction: What Is It?

- **"Addicts" continue to use a drug despite adverse effects on health, cognition, and social life and despite repeated efforts to stop.**
- Many equate addiction and physical dependence:
 - They see addicts as trapped in cycle of drug taking, withdrawal, & further drug taking to combat withdrawal
- But this is inconsistent with evidence
- Addicts sometimes take drugs to alleviate/prevent withdrawal symptoms but it is not the major factor.
- However, addicts often start taking their drug again even after months or years without it.

Role of Learning in Drug Tolerance

- Research suggests learning and cognition plays role in drug tolerance
- Focus has been on two phenomena:
 1. **Contingent** drug tolerance: tolerance develops only to drug effects that are actually experienced.
 2. **Conditioned** drug tolerance: tolerance effects are maximally expressed only when a drug is administered in same situation it has previously been administered.

Conditioned Tolerance and Withdrawal



- Situational specificity of drug tolerance
- Siegel et al. addicts are susceptible to lethal effects of drug overdose when the drug is administered in a new context.
- Hypothesis: addicts become tolerant when repeatedly self-administer drug in same environment, thus take larger doses to counteract diminution of drug effect.
- If they administer huge dose in new situation, tolerance effects are not present to counteract effects of the drug.
- Research evidence: Siegel et al. many more heroin-tolerant rats died following high dose of heroin administered in a novel situation than died in the usual injection environment.

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Commonly Abused Drugs:

- Tobacco
- Alcohol
- Marijuana
- Cocaine
- Opiates

Tobacco



- When smoking a cigarette, nicotine (the major psychoactive ingredient of tobacco) & ~4,000 other chemicals referred to as tar are absorbed through the lungs.
- **About 70% of those who experiment with smoking become addicted**
- **Nicotine acts on nicotinic cholinergic receptors in the brain.**
- But because considerable tolerance develops to some of the immediate effects of tobacco, the effect on smokers vs. nonsmokers is remarkably different

Effects of Long-Term Tobacco Use

- **Smoker's syndrome** – chest pain, labored breathing, wheezing, coughing, susceptibility to respiratory infections
- Susceptible to lethal lung disorders – pneumonia, bronchitis, emphysema, lung cancer, cancer of larynx, mouth, kidneys, bladder, pancreas & stomach.
- Increased risk of cardiovascular disorders: can culminate in a heart attack or stroke.
- Can lead to Buerger's disease: blood vessels become constricted, especially those supplying blood to legs & in some cases toes, foot, ankle, leg, need to be amputated.
- Many claim to smoke to reduce tension but studies suggest smokers are more tense than nonsmokers.

Cognitive studies and Nicotine

- **Basic design:** compare performance of smokers who have had nicotine with control group of smokers not given nicotine.
- Short/simple information processing tasks (e.g., search, logical reasoning, digital recall task) show a nicotine benefit (Snyder & Henningfield, 1989).
- Grobe et al. (1998): nicotine enhanced performance on the Sternberg memory scanning task when distracting auditory stimuli were presented concurrently.
- Can also be seen to influence real-world cognition:
 - Sherwood (1995) report positive effects of smoking on tracking and break reaction times in a driving task.

Alcohol

- Alcohol molecules are so small & soluble in fat & water, they invade all parts of the body.
- Classed as a depressant because it reduces neural firing.
- Has a genetic component, heritability estimate for alcohol addiction ~ 55%
- Metabolic & functional tolerance develop
- Experience cognitive, perceptual, verbal, motor impairment as well as loss of control leading to unacceptable actions.

Effects of Chronic Alcohol Consumption

- **Severe withdrawal in 3 phases:**
 - 5-6 hrs post drinking: tremors, nausea, sweating, vomiting, headache, cramps, etc.
 - 15-30 hrs: convulsive activity
 - 24-48 hrs: **delirium tremens** (DTs) disturbing hallucinations, bizarre delusions, agitation, confusion, hypothermia: may last 3-4 days
- **Korsakoff's syndrome: brain damage, memory loss, sensory and motor dysfunction.**
- **Cirrhosis: scarring of the liver**
- Erodes heart muscles & increases risk of heart attack. Irritates lining of digestive tract & increases risk of oral & liver cancer, stomach ulcers, pancreatitis, and gastritis.
- **Fetal alcohol syndrome:** affects children of mothers drinking alcohol during pregnancy



Effects of Alcohol on memory

- People who drink excessively can suffer blackouts and almost total memory loss for all events that occurred while drunk.
- Blackouts indicate a failure to consolidate memories formed during intoxication.
- Moulton et al. (2005):
 - LTM was impaired in Ps who drank alcohol BEFORE learning information.
 - Alcohol consumption shortly AFTER learning led to improved memory.
 - Explanation: alcohol may have inhibited the formation of new memories that would interfere with the consolidation of those formed just before alcohol consumption.



Marijuana

- **Cannabis sativa** – common hemp plant
- **THC** – primary psychoactive constituent – although 80 other cannabinoids are also present.
- Research on THC changed during 1990s with discovery of two receptors for it in the brain: CB1 & CB2.
- CB1: most prevalent G protein-linked receptor in the brain, while CB2 is found in brain stem & cells of the immune system.
- But why would we have THC receptors in our brain?
- This was answered with discovery of a class of endogenous cannabinoid neurotransmitter – called the endocannabinoids.



Adverse Effects of Marijuana Use

- Respiratory problems: cough, bronchitis, asthma
- Impairs STM, speech becomes slurred /conversation lacks meaning, experience unreality, emotional intensification, sensory distortion, paranoia
- Elevated heart rate leading to heart attack.
- Single large doses can trigger heart attacks in susceptible individuals
- Possible correlation with schizophrenia, but no causal link has been shown.
- No evidence for permanent brain damage.

Marijuana Use and Cognition

- But MRI shows prolonged use of large doses (~five joints everyday for ~20 years) reduces hippocampus & amygdala volume (Yücel et al., 2008) – link to memory.
 - But this study is correlational: cannot prove extremely high doses *causes* brain damage.
- Many studies have documented memory deficits, but they tend to be acute and disappear after a few weeks of abstinence (Grant et al., 2003; Jager et al., 2006).
- People who become heavy users in adolescence display memory and other cognitive deficits.
 - However, Pope et al. (2003) found that adolescents with lower verbal intelligence were more likely to become users, which could account for the poor cognitive performance

Cocaine and Other Stimulants

- Increase neural and behavioural activity
- Extracted cocaine (hydrochloride - white powder), is either snorted or injected.
- **Crack:** potent, cheap, smokable form
- Cocaine is an effective local anesthetic
 - But due to associated dangers, synthetic analogues (e.g., procaine and lidocaine) are used today.



Cocaine



- **Binges/sprees may lead to cocaine psychosis**
 - Mistakenly diagnosed as paranoid schizophrenia
 - Effects include tremors, nausea, hyperthermia, seizures, loss of consciousness, respiratory problems, heart attack, stroke.
- **During a spree, users become tolerant to euphoria, so larger doses are needed to feel the same effect.**
- **While tolerance may develop to most effects of cocaine (i.e., to the euphoria), sensitization is seen to its motor and convulsive effects**
- **Although highly addictive, withdrawal is relatively mild**

Other Stimulants



- **Amphetamine (“speed”)**
 - Effects like cocaine – can produce psychosis
 - Other amphetamines include methamphetamine (meth), which is used in an even more potent crystallized form (ice or crystal meth).
- **MDMA (“ecstasy”)**
 - Impairs dopaminergic and serotonergic function in animal studies; human relevance unclear
 - Impairs executive function, inhibitory control, and decision making (as shown by cortex and limbic functional brain scan abnormalities)

Opiates: Heroin and Morphine



- **Opium: dried form of sap exuded by the seed pods of opium poppy**
 - Has several psychoactive ingredients, but most notable are morphine & codeine.
 - Which along with other drugs of a similar structure are referred to as opiates.
- **Medicinal uses**
 - Analgesics (painkillers)
 - Treatment of cough and diarrhea
- **High risk of addiction**



Opiate Addiction

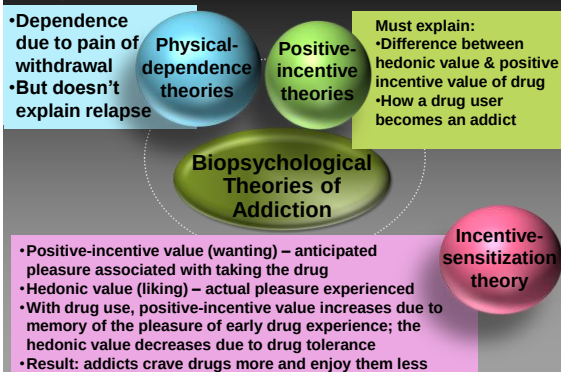


- Desire to avoid withdrawal adds to motivation to use & tolerance encourages use of higher doses.
- Withdrawal symptoms begin 6-12 hours after last dose & include restlessness, pacing, fidgeting, eyes watering, runny nose, yawning, sweating, sleep fits
- Once awake they experience chills, shivering, nausea, vomiting, diarrhea, cramps, dilated pupils, tremor, muscle pains and spasms.
- Many health hazards related to use of dirty needles & poorly processed "street" versions.
- Death from overdose by suppressing breathing

Treatment for Heroin Addiction

- **Main treatment: Methadone (an opiate itself)**
- **Binds to opiate receptors, but....**
 - Produces less pleasure than heroin
 - Administered orally
 - Prevents withdrawal
- **Buprenorphine: similar but longer lasting**
- **Substitute less dangerous drug for abused drug**

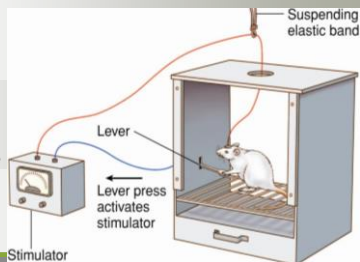
Biopsychological Theories of Addiction



Intracranial Self-Stimulation and Brain "Pleasure Centers"

- In the brain there is circuitry that reinforces behaviour and species (inc. humans) will administer brief bursts of weak electrical stimulation to them.

- Olds and Milner (1954): specific brain sites that mediate self-stimulation are those that usually mediate pleasurable effects of natural rewards (e.g., food and water).



Mesotelencephalic Dopamine System and Intracranial Self-Stimulation

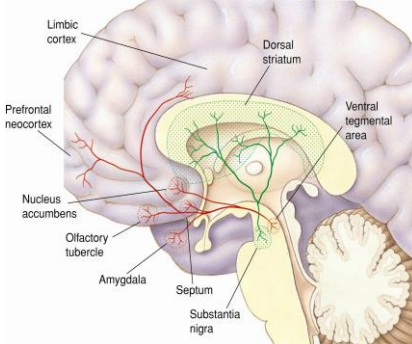


Diagram shows two pathways:

Ventral tegmental area in red projecting to its various areas

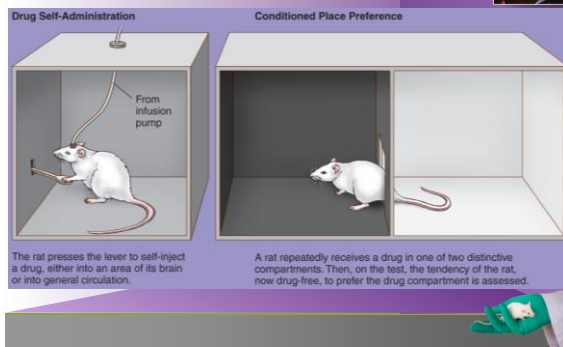
Substantia nigra in green projecting to its various areas.

Mesocorticolimbic Pathway & Reward

- Evidence supports view that mesocorticolimbic pathway of mesotelencephalic dopamine system plays role in mediating intracranial self-stimulation.....

1. Many of the brain sites where self-stimulation occurs are part of the mesotelencephalic dopamine system.
2. Intracranial self-stimulation is often associated with an increase in dopamine release in the mesocorticolimbic pathway.
3. Dopamine agonists tend to increase intracranial self-stimulation, while dopamine antagonists tend to decrease it.
4. Lesions of the mesocorticolimbic pathway tend to disrupt intracranial self-stimulation.

Two Key Methods for Measuring Drug-Produced Reinforcement in Laboratory Animals



Dopamine and Drug Addiction

- Following research on role of dopamine in intracranial self-stimulation, studies implicated dopamine in the rewarding effects of neural reinforces and addictive drugs.
- E.g., in rats dopamine antagonists blocked self-administration of, or the conditioned preference for several types of addictive drugs & reduced reinforcing effects of food.
- Findings from research suggest dopamine signals something similar to reward value or pleasure and the nucleus accumbens appears to play a key role in this.

Nucleus Accumbens (NA) & Drug Addiction

1. Lab animals would self-administer microinjections of addictive drugs directly into nucleus accumbens.
2. Microinjection of drugs into nucleus accumbens produced conditioned place preference for compartment where they were administered.
3. Lesions to either nucleus accumbens or ventral tegmental area blocked self-administration of drugs into general circulation or the development of drug-associated conditioned place preferences.
4. Both self-administration of addictive drugs & experience of natural reinforcers were found to be associated with elevated levels of extracellular dopamine in the nucleus accumbens.

Support for the Involvement of Dopamine in Addiction: Evidence from Imaging Human Brains



- Volkow et al. administered various doses of radioactively labelled cocaine to addicts and asked to rate the high.
 - Used PET to measure degree to which the labelled cocaine bound to dopamine transporters.
 - Intensity of high experienced correlated with degree to which cocaine bound to dopamine receptors
 - No high was experienced unless the drug bound to 50% of the dopamine transporters.
- Healthy non-addicted humans given amphetamine injection.
 - As dopamine levels in nucleus accumbens increased in response to injection, Ps reported increase in euphoria.

Dopamine Release in the NA: What Is Its Function?



- But reward is a complex process with many psychological components – so what exactly is the role in reward of dopamine release in the nucleus accumbens.
- Extracellular dopamine levels in the NA increase following presentation of a natural reward (e.g., food or addictive drug)
- Ventral tegmental neurons, which release dopamine into the NA fire in response to a stimulus at a rate proportional to its reward value.
- Dopamine released in the NA is related to the expectation of reward rather than to the experience itself.



Current Issues in Modern Addiction Research



- Addiction is psychologically complex
- Addicts show poor decision making & lack of self control, suggestive of prefrontal cortex role
- Drug addiction may be related to other non-adaptive behaviors, e.g., compulsive eating, gambling, sexual behavior, klepto-mania, etc.
- Other neurotransmitters also involved: glutamate, endogenous opioids, norepinephrine, GABA, and endocannabinoids

Brain Structures That Mediate Addiction: The Current View



- **Current research not in complete agreement but there is consensus other areas are involved in....**

1. Initial drug taking: mediated in same way as pleasure activity, with the mesocorticolimbic pathway (particularly nucleus accumbens playing a key role).

- But it does not act alone
- Instead it interacts with 3 other areas:
 - Prefrontal lobes (role in decision making);
 - Hippocampus: provides info about previous experiences;
 - Amygdala: coordinates positive and negative reactions.

Brain Structures That Mediate Addiction: The Current View



2. Craving & compulsive drug use: repeated consumption brings major changes in motivation as addict develops habit & compulsion despite adverse effects.

- Due to direct neural response to repeated exposure of drug-induced pleasure and as product of conditioned response to drug-associated cues.
- Several changes in brain's response contribute to development of addiction:
 - Change in how striatum reacts to drugs, which spreads from the NA to the dorsal striatum, which is known to play a role in habit formation.
 - At same time the prefrontal cortex in controlling behavior declines & stress circuits in hypothalamus begin to interact with dorsal striatum.
 - Development of addiction is a pathological neuro-plastic response.

Brain Structures That Mediate Addiction: The Current View



3. Relapse – thought to be triggered by 3 factors:

- Stress – drug use as a coping mechanism
- Priming – a single exposure leads to a relapse
- Environmental cue – certain people, times, places, objects previously associated with the drug
- Evidence from animal studies shows:
 - Prefrontal cortex mediates priming-induced relapse,
 - Amygdala mediates condition cue induced relapse,
 - Hypothalamus mediates stress-induced relapse.
