Understanding the neurobiology of drug addiction and potential future targets for the treatment of drug addiction

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Declarations

- The author has no conflicts of interest or financial relationships to disclose
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Learning objectives

- Commonly abused drugs/medications
- Phases in the development of addiction
- Circuitry involved in mediating acute reinforcing effects of drugs
- Repeated drug exposure and involvement of different brain circuits (leading to development of tolerance, sensitization, withdrawal, relapse)
- Factors which increase vulnerability to the development of drug addiction
- Role of genetics and epigenetics in the development of drug addiction
- FDA-approved medications to treat drug addiction
- Challenges in the treatment of drug addiction
- Articulate potential future targets for the treatment of drug addiction (Potential future therapeutic options)

Addiction

- Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences
- People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences

American Society of Addiction Medicine
(https://www.asam.org/quality-care/definition-of-addiction)

Commonly abused drugs that can lead to addiction

Legal	Illegal
Nicotine	Heroin
Alcohol	Cocaine
Cannabis (Legal in many states)	**Cannabis**
	Methamphetamine
	MDMA
	Bath salts
	Phencyclidine (PCP)
	Lysergic acid diethylamide (LSD)

Which are the most addictive drugs ?

Drug of abuse	Risk of addiction
Nicotine	31.9%
Alcohol	15.4%
Cocaine	16.7%
Cannabis	9.1%
Heroin	23.1%

O'Brien, 2012; Goodman & Gillman: The pharmacological basis of therapeutics

Commonly abused medications that can lead to addiction

Prescription	Examples
Opioids	Oxycodone, Hydrocodone, Oxymorphone Meperidine, Propoxyphene, Codeine, Morphine, Methadone
Barbiturates	Thiopental Sodium, Phenobarbital, Pentobarbital, Amobarbital
Benzodiazepines	Diazepam, Alprazolam, Clonazepam, Lorazepam, Temazepam
Sedative	Zolpidem, Zaleplon, Eszopiclone
Stimulants	Methylphenidate, dextroamphetamine, amphetamine, dextroamphetamine
Anticonvulsant	Gabapentin
Cough suppressant	Dextromethorphan (DXM)

https://nida.nih.gov/sites/default/files/rx_drugs_placemat_508c_10052011.pdf

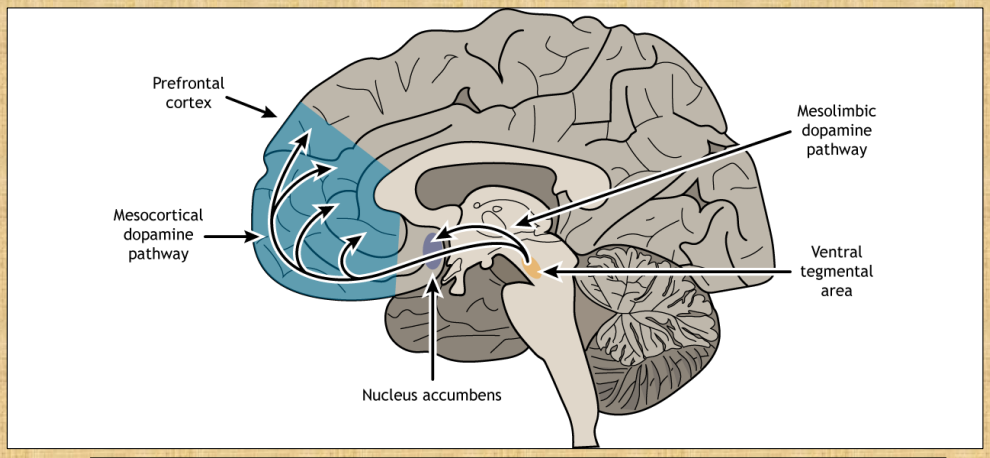
Rewarding effects of drugs of abuse

Reward is something that produces pleasure, elicits attention, and induces behavioral action aimed at obtaining it

- Natural rewards

- Produce pleasure
- Required for survival
- Increase motivation
- Minimally alter the brain and easy to reverse
- Mild cravings
- Mild to no withdrawal effects

Reward pathway



https://openbooks.lib.msu.edu/neuroscience/chapter/motivation-and-reward/

Mesolimbic and mesocortical dopamine neurons

- Both natural and drug rewards increase firing of mesolimbic and mesocortical dopaminergic neurons producing pleasure
- The pattern of firing of dopamine neurons is described as ‘phasic’, which refers to the rapid burst-like firing pattern of dopamine neurons in the brain
- The stimulation of these neurons by drugs of abuse depending on the drug of abuse is 10-100 times that of natural rewards
- Drugs of abuse produce more intense pleasure compared to natural rewards

Natural rewards vs. Drug rewards

Natural reward/ non-addictive behaviors

Squeezing a balloon lightly

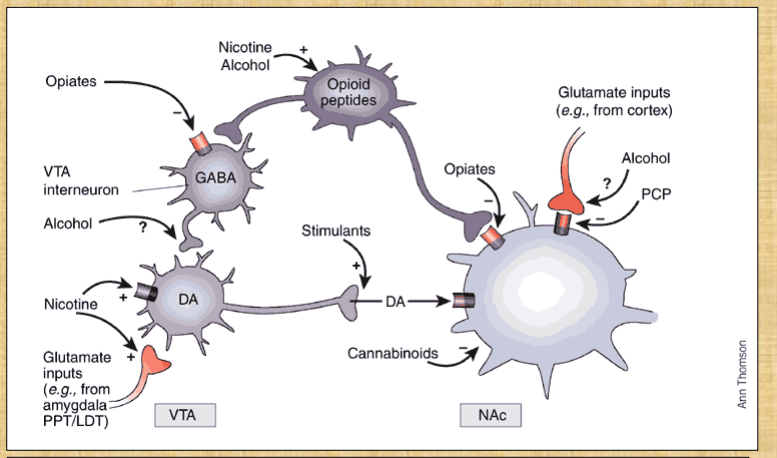
Natural rewards (Brain pathways unchanged or minimal change)

Squeezing soft clay

Drug rewards alter the brain = plasticity

Drug reward/ addictive behaviors

Different drugs of abuse activate mesolimbic dopamine neurons via different mechanisms



Nestler EJ. Nat Neurosci 2005; 8: 1445–1449 .
https://doi.org/10.1038/nn1578

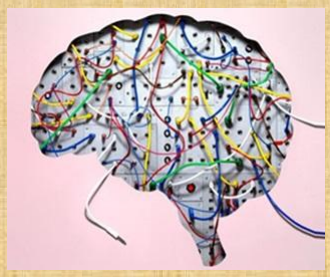
Mechanisms of various drugs of abuse

Drug of abuse	Target	Effects
Opioids	Mu (μ) opioid receptor (MOR)	Activation of mu opioid receptors, decreases activity of inhibitory GABA interneurons and increases activity of dopamine neurons in the VTA and increases dopamine levels in the nucleus accumbens
Nicotine	Nicotinic acetylcholine receptors (nAChRs)	Activates nAChRs located on dopamine neurons in the VTA and increases dopamine levels in the nucleus accumbens
Alcohol	Several targets (MORs, NMDA receptors, GABA-A receptors)	Increases MOR activity, decreases NMDA activity, increases release endogenous cannabinoids, increases GABA levels and increases dopamine in the nucleus accumbens
Stimulants	Dopamine uptake transporters	Increases dopamine in the nucleus accumbens by blocking dopamine uptake transporters
Cannabis	CB1 receptors	CB1 receptors regulate glutamate and GABA release in the VTA and thus modulate firing of dopamine neurons and increase of dopamine in the nucleus accumbens

Volkow ND et al. Physiol Rev 2019; 99: 2115–2140; doi:10.1152/physrev.00014.2018

Neuroadaptations (rewiring) following repeated exposure to drugs



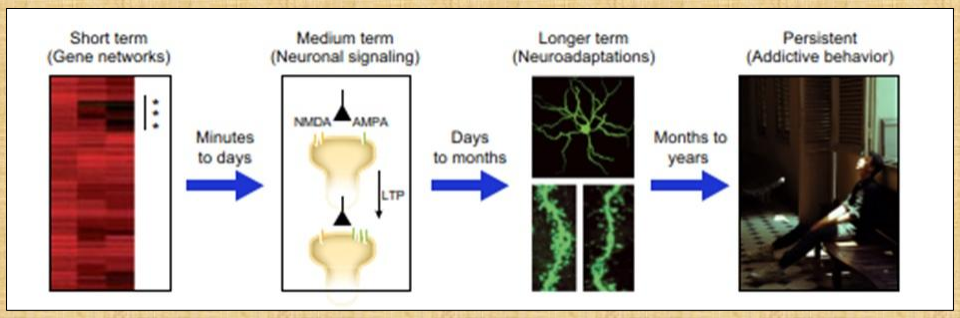


Repeated exposure to drugs of abuse leads to many changes (plasticity) in the brain

Plasticity of the brain can be divided as follows:

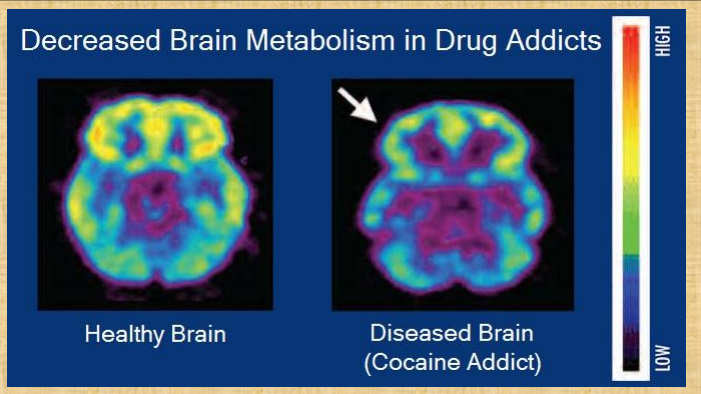
- Acute gene changes
- Synaptic changes
- Structural changes
- Chemical changes
- Behavior change

Summary of plasticity in the brain induced by repeated exposure to drugs of abuse



Volkow et al. Physiol Rev. 2019 Oct 1;99(4):2115-2140.
doi: 10.1152/physrev.00014.2018.

Repeated exposure to drugs of abuse induces plasticity in the brain which can be assessed by changes in brain metabolism using PET scanning



Volkow et al., Am J Psychiatry. 1991 May;148(5):621-6.
doi: 10.1176/ajp.148.5.621.

Effects of brain plasticity

- Development of incentive salience
- Tolerance
- Transition from casual use to abuse to uncontrolled use
- Engagement of different brain regions and circuits
- Craving & Relapse

Development of incentive salience

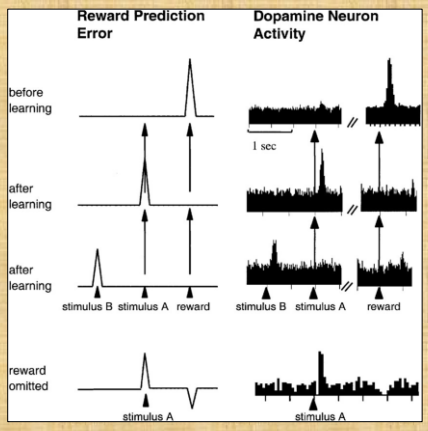
Repeated exposure to drugs of abuse can result in development of incentive salience

- Incentive salience can be defined as motivation for rewards derived from both one's physiological state and previously learned associations about a reward cue that is mediated by the mesocorticolimbic dopamine pathway
- With each drug exposure the rewarding effects experienced by the individual result in development of a state that acquires 'salience'
- This 'salience' then motivates the individual to experience the state repeatedly and builds a sense of anticipation till the state is achieved

Incentive salience (cont'd)

- Drugs of abuse have profound effect on the response to previously neutral stimuli/cues to which drugs become paired to the drug of abuse
- As stimuli/cues acquire 'salience', these cues gain reinforcing/rewarding properties in their own right
- As cues gain 'salience', mesocorticolimbic dopamine neurons start firing on exposure to the cue in anticipation of the drug even before the drug is consumed/administered

Dopamine neurons fire to cues predicting reward instead of the reward itself



Neural Networks 2002; 15:523-533

Suri RE. Neural Networks 2002; 15:523-533
https://doi.org/10.1016/S0893-6080(02)00046-1

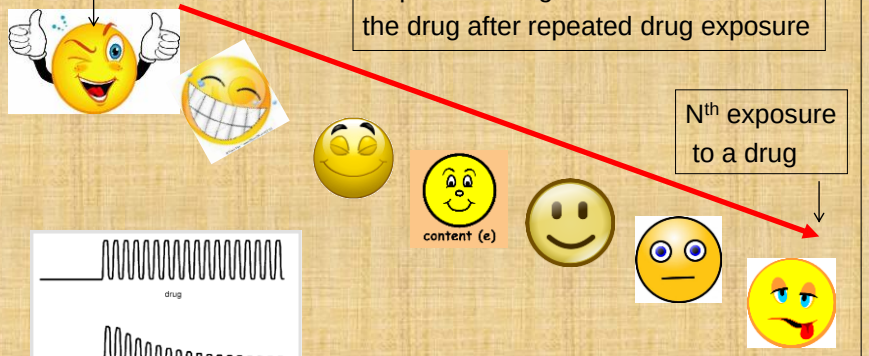
Tolerance

Plasticity can help in the development of tolerance

First exposure to a drug

Tolerance is defined as decreased response to a given dose of the drug after repeated drug exposure

N^{th} exposure to a drug

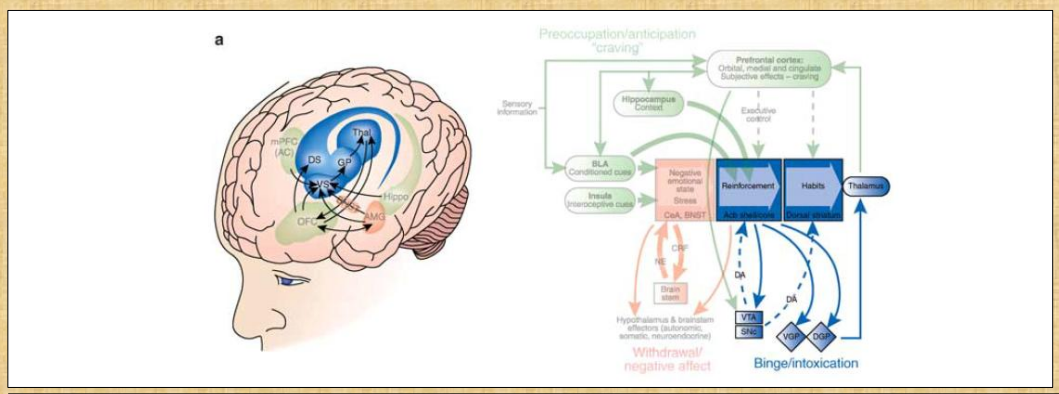


Tolerance (cont'd)

- Tolerance develops to the rewarding effects of the drug
- Rate of development of tolerance varies for each individual and for each drug
- Genetics plays an important role in development of tolerance
- CYP450 enzyme polymorphisms plays an important role in development of peripheral tolerance

Transition from controlled intake to binge intoxication

Repeated exposure to drugs of abuse leads to tolerance, which leads to increased intake transitioning to bingeing/intoxication in vulnerable individuals



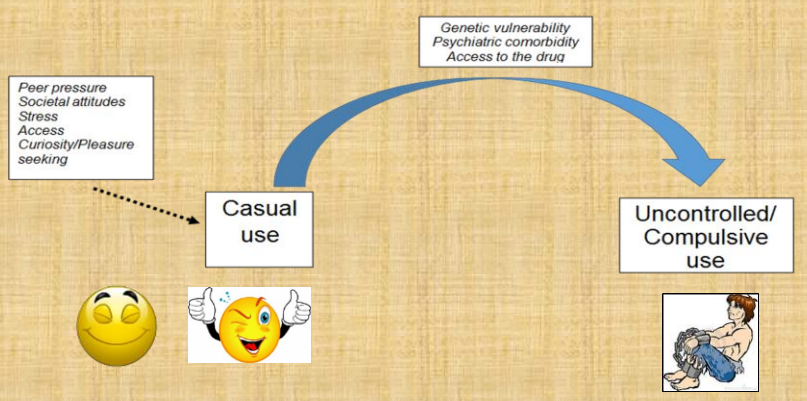
Koob GF & Volkow ND, Neuropsychopharmacology. 2010 Jan;35(1):217-38. doi: 10.1038/npp.2009.110

VGP= ventral globus pallidus; DGP= Dorsal globus pallidus

Transitioning to binge/intoxication involves inclusion of additional brain regions

- Initial exposure to drugs of abuse involves the mesocorticolimbic dopamine neurons
- With repeated exposure, there is development of tolerance to the rewarding effects of the drug
- At the same time, dopamine neurons projecting to the dorsal striatum, which is involved in more habitual responding start getting involved
- The combination of tolerance and involvement of brain circuits involved in habitual responding play a critical role in the transition to binge/intoxication phase from controlled drug taking

Transition from abuse/binge intoxication to compulsive use



Transitioning to compulsive use

- With continued use of drugs in vulnerable individuals there is loss of function of the prefrontal cortex
- Decreased function of the prefrontal cortex results in loss of inhibitory influences on drug taking behavior
- Decreased function of the prefrontal cortex results in poor decision-making
- Involvement of brain stress systems facilitates the transition to compulsive drug use
- Continued drug use results in increased incentive salience for drugs over natural reinforcers
- In vulnerable individuals compulsive use of drugs evolves into full-blown addiction with continued drug use

Withdrawal effects

Abstaining from the drug can produce withdrawal effects due to drug-induced plasticity

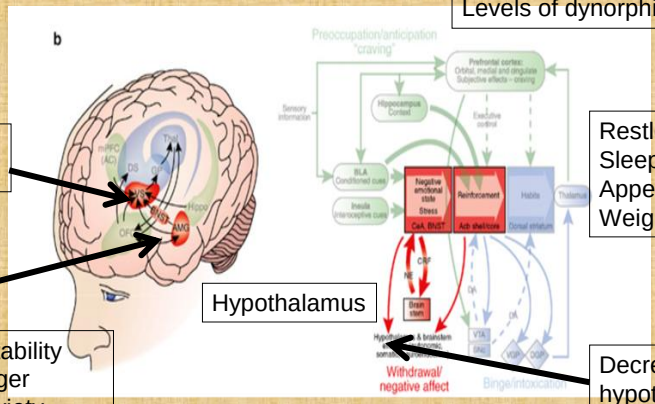
Increase in
Levels of norepinephrine
Levels of CRF
(corticotrophin releasing factors)
Levels of dynorphin

Depressed mood

Decreased activity of the ventral striatum

Increased amygdala activity

Irritability
Anger
Anxiety



Hypothalamus

Restlessness
Sleep disturbances
Appetite changes
Weight gain

Decreased hypothalamic activity

Koob GF & Volkow ND, Neuropsychopharmacology. 2010 Jan;35(1):217-38. doi: 10.1038/npp.2009.110

Preoccupation, craving and relapse

Craving: An abnormal state that is characterized by strong desire/motivation to consume the drug due to a drug dependent brain

Preoccupation

The drug is the focus and the dependent individual avoids or loses interest in other activities

Relapse is the resumption of drug use after one or more periods of abstinence

Biggest challenge to the treatment of addiction

What can precipitate craving and relapse?

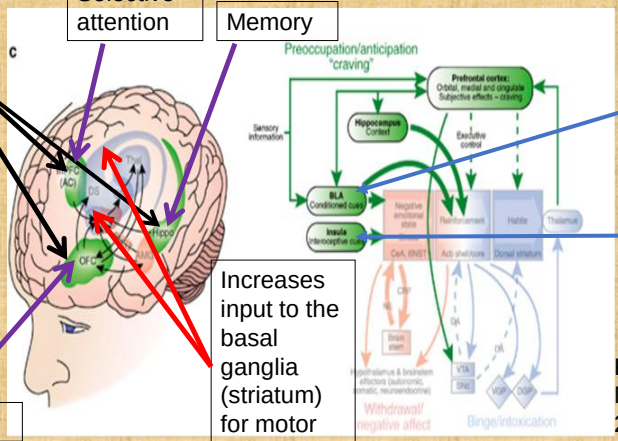
- Stress
- Exposure to paraphernalia
- Friends
- Exposure to places associated with past abuse

Craving and relapse are mediated by several brain regions

Exposure to cues increases activity of prefrontal and hippocampal areas
- Reactivates memory
- Increases attention
- Impulsivity

Selective attention

Memory



Behavioral therapy plays an important role in decreasing craving

Basolateral amygdala

Conditioned cues

Insula

Interoceptive cues

Increases input to the basal ganglia (striatum) for motor action

Impulsivity

Koob GF & Volkow ND, Neuropsychopharmacology, 2020

Summary: Effects of brain plasticity

- Development of incentive salience
- Tolerance
- Engagement of different brain regions and circuits
- Transition from casual use to abuse to uncontrolled use
- Craving & Relapse

Vulnerability factors

- Age of drug exposure
- Comorbidity
- Genetics
- Epigenetics

Drug addiction peaks amongst teenagers

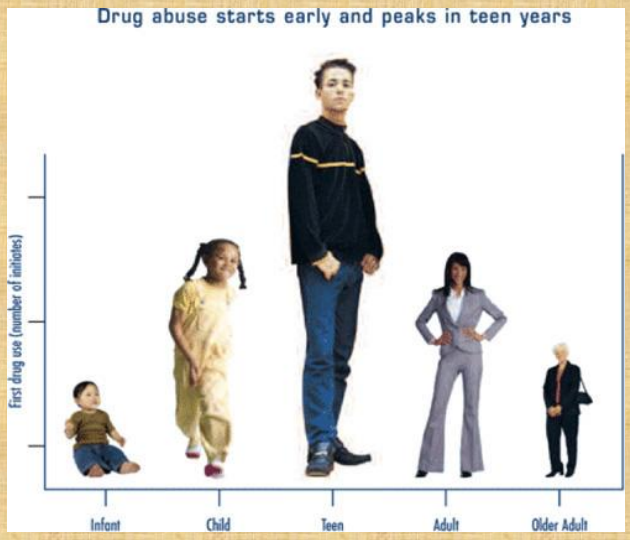
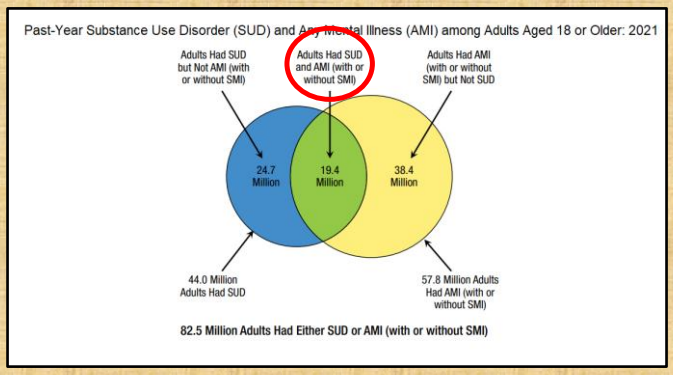


Image from NIDA website

Why?

- The teenage brain is not fully developed
- Explore/experiment
- Inhibitory mechanisms poorly developed
- Drugs of abuse can alter the teenage brain more easily (Plasticity)

Drug addiction & mental illness comorbidity



Common mental disorders associated with drug addiction

- Anxiety
- Depression
- ADHD
- Schizophrenia
- Bipolar disorder

2021 National Survey on Drug Use and Health (NSDUH)

Drug addiction & mental illness: Potential explanations

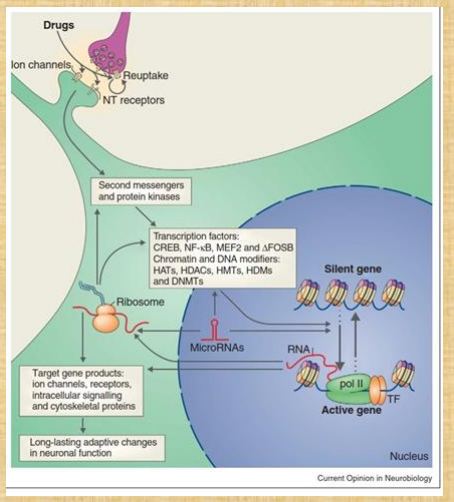
- Mental disorder and drug addiction are separate disorders with common risk factors
- Mental disorder increases vulnerability for drug addiction
- Substance use triggers development of mental disorder
- Mental disorder is temporary during drug use/abuse and is alleviated after discontinuing the drug

Role of genetics in addiction

Genetics and addiction

- Genes play an important role in the development of drug addiction
- Multiple genome-wide association studies have identified genetic variants associated with specific drug addiction
- 40–60% of the population variability in becoming addicted to nicotine, alcohol, or illicit drugs is attributable to genetic factors
- Genes associated with various receptors associated with neurotransmitters, cell signaling proteins, synaptic plasticity and growth factors, proteins involved in cell proliferation, and enzymes involved in drug metabolism
- Some genes are involved in vulnerability to multiple drugs

Epigenetics and drug addiction



Robison AJ & Nestler EJ. Nat Rev Neurosci 2011, 12:623-637.

Epigenetics and addiction

- Epigenetics involves the study of changes in gene expression due to chemical modification of DNA and DNA-associated proteins but not DNA sequence
- Epigenetic changes contribute to unique differential gene expressions in various cells and correlate to changes regulating various biological processes
- Both gene expression and silencing can occur due to unique epigenetic changes in individuals after drug exposure
- The unique epigenetic changes may determine if an individual gets addicted to drugs after exposure to drugs and plays a big role in determining vulnerability to the development of drug addiction

Epigenetics (cont'd)

Gene expression into proteins and other substrates is controlled by different processes such as

- DNA methylation
- Histone acetylation
- Histone methylation
- Histone phosphorylation
- Non-coding RNAs
  - Long non-coding RNAs
  - microRNAs
  - Short interfering RNAs (siRNAs)

Epigenetics and addiction (cont'd)

- However, there are several challenges in targeting epigenetic changes associated in patient dependent on various drugs of abuse.

These challenges include:

- Identification of epigenetic targets
- Identification of effective genetic alteration
- Precision delivery of drugs
- Minimal interaction with unintended regions

Thus, research in developing epidrugs for the treatment of addiction is ongoing

Current pharmacological treatment for drug addiction

FDA-approved medications

Alcohol	Nicotine	Heroin
Naltrexone	Nicotine replacement	Methadone
Acamprosate	Varenicline	Buprenorphine
Disulfiram	Bupropion	Suboxone
		Naltrexone
		Naloxone

Future pharmacological and non-pharmacological treatment for drug addiction

Future therapeutic options

- Vaccines
- GLP-1 agonists
- Non-pharmacological options: Transcranial magnetic brain stimulation

Summary

- Drug addiction treatment continues to be a challenge
- Significant advances have been made in the understanding of neurobiology of drug addiction
- Several new potential targets have been identified that may help in the development of more efficacious medications for the treatment of drug addiction
- Better understanding of genetic and epigenetic changes involving drug addiction will play a significant role in reducing the burden of drug addiction

References

- Fernàndez-Castillo N et al. Molecular Psychiatry 2022; 27:624–639; https://doi.org/10.1038/s41380-021-01256-1
- Guerin AA et al. Neuroscience and Biobehavioral Reviews 2021; 120: 48–74; https://doi.org/10.1016/j.neubiorev.2020.11.001
- Hancock DB et al. Current Psychiatry Reports 2018; 20: 8; https://doi.org/10.1007/s11920-018-0873-3
- Johnson EC et al. Genes, Brain and Behavior 2023;22:e12856; https://doi.org/10.1111/gbb.12856
- Klausen MK et al. Br J Pharmacol. 2022;179:625–641; https://doi.org/10.1111/bph.15677
- Liu M et al. Nat Genet. 2019; 51(2): 237–244. doi:10.1038/s41588-018-0307-5.
- Luo X et al. Current Topics in Medicinal Chemistry, 2023, 23, 1782-1792 DOI: 10.2174/1568026623666230418114133
- Moretti J et al. Front Neurosci. 2020 Mar 6:14:137. doi: 10.3389/fnins.2020.00137
- Nestler EJ. Nat Neurosci 2005; 8: 1445–1449; https://doi.org/10.1038/nn1578
- Koob GF. Biological Psychiatry 2020; 87; 1:44-53; https://doi.org/10.1016/j.biopsych.2019.05.023
- Koob GF et al. 2024, In: Tasman, A., et al. Tasman's Psychiatry. Springer, Cham. https://doi.org/10.1007/978-3-030-51366-5_29
- Koob GF & Volkow ND, Neuropsychopharmacology. 2010 Jan;35(1):217-38. doi: 10.1038/npp.2009.110
- Robison AJ & Nestler EJ. Nat Rev Neurosci 2011, 12:623-637
- Suri RE. Neural Networks 2002; 15:523-533; https://doi.org/10.1016/S0893-6080(02)00046-1
- Towers EB et al. Pharmacol Rev 2023; 75:217–249; dx.doi.org/10.1124/pharmrev.121.000361
- Volkow ND et al., Am J Psychiatry. 1991;148(5):621-6. doi: 10.1176/ajp.148.5.621
- Volkow ND et al. Physiol Rev. 2019 Oct 1;99(4):2115-2140. doi: 10.1152/physrev.00014.2018
- Volkow ND & Boyle M. Am J Psychiatry 2018; 175:729–740; doi: 10.1176/appi.ajp.2018.17101174

Thank you