What can animal studies tell us about drug addiction?

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The beginning.......
Early studies used Weeks’ design to determine which drugs were self-administered by laboratory animals

Thompson T, Schuster CR Psychopharmacologia 5, 87-94 (1964) Morphine Self-Administration, Food-reinforced, and Avoidance Behaviors in Rhesus Monkeys

Deneau G, Yanagita T, Seevers M. H. Psychopharmacologia 16, 30-48 (1969) Self-Administration of Psychoactive Substances by the Monkey A Measure of Psychological Dependence


Main take-home messages from the early studies

• All drugs that are abused by humans are self-administered by laboratory animals (some examples)
  • Opiates-morphine, heroin, methadone, meperidine, codeine, pentazocine
  • Stimulants- amphetamine, methamphetamine, cocaine, MDMA, nicotine. methylphenidate
  • Cannabinoids- THC, CB1 agonists
  • Alcohol
  • Sedative hypnotics-barbital, phenobarbital, pentobarbital, diazepam, chlordiazepoxide

Yanagita T UNODC 1973
What about the new so-called designer drugs?

• Designer drugs are produced in laboratories, the majority resembling drugs legally restricted for distribution and possession. They share one common trait, producing psychoactive effects that can range from cannabis-like, psychomotor stimulation, dissociative anesthesia to hallucinogenic.

• Examples include mephedrone, methylone, MDPV, ethylphenidate, synthetic cannabinoids, 2,5-dimethoxy-4-(n)-propylphenethylamine (2C-P), N-adamantyl-1-pentylindole-3-carboxamide (2NE1), methiopropamine, and methoxetamine.

• ALL ARE SELF-ADMINISTERED BY LABORATORY ANIMALS
“Self-administration tests assess the rewarding properties of a drug. If animals actively work at a behavioral task to receive a dose of the drug, it is likely that the drug will be rewarding in humans.”

“When comparing findings from rat self-administration studies independently with each clinical indicator of abuse liability, findings from rat studies were concordant with reports of positive subjective-effects in 41 of 54 (75.9%) drug cases and were concordant with drug scheduling status in 49 of 70 (70%) cases.” (O’Connor et al., Neurosci Biobehav Rev (2011) 35:912-938)
So, one thing that animal studies can tell us is whether drugs have abuse liability

- Important consideration when scheduling new drugs that come onto the market
- Important consideration when deciding whether drugs pose a minimal risk of harm
Drugs with high abuse liability also pose the greatest risk of harm.

How prevalent is drug addiction?

• We have a lot of information on drug use but what about problem drug use consistent with a substance use disorder?
Data from USA: National Survey on drug use and health- Drug dependence is a real problem

https://www.drugabuse.gov/publications/drugfacts/nationwide-trends
But.......Not everyone who uses drugs becomes addicted
Is the variability in response to drugs of abuse related to environmental factors?

**Human studies suggest that it is**

- Cadoret RJ et al., Arch Gen Psychiat 43 (1986) 1131-1136. An Adoption Study of Genetic and Environmental Factors in Drug Abuse
- Schenk S. in Kandel DB Stages and pathways of drug involvement: Examining the gateway Hypothesis. Sensitization as a process underlying the progression of drug use via gateway drugs 318-337
Is the variability in response to drugs of abuse related to genetic factors?

**Human studies suggest that it is:**


- Pascale et al., Alcohol Alcohol 50 (2015) 259-265 Alcohol dependence and serotonin transporter functional polymorphisms 5-HTTLPR and rs25531 in an Italian population.

- Odgerel Z et al., Transl Psychiatr 3(2013) e307 Genotyping serotonin transporter polymorphisms 5-HTTLPR and rs25531 in European- and African-American subjects from the National Institute of Mental Health's Collaborative Center for Genomic Studies.

- Yang Z et al., Drug Alc Dep 129 (2013) Serotonin transporter and receptor genes significantly impact nicotine dependence through genetic interactions in both European American and African American smokers.


What can animal studies tell us about the why some subjects become addicted and others appear resistant? Is there a way to alter the sensitivity to understand environmental and genetic factors that might impact drug-taking?
Studies from my laboratory have shown that sensitivity can be increased by certain treatments

- Rats preexposed to nicotine, caffeine, amphetamine, methylphenidate (Ritalin) all more readily self-administered cocaine-the variability in cocaine self-administered was decreased by prior exposure to other drugs
Are these findings relevant to humans?

• Yes!

• Adults who were treated with Ritalin as children were more likely to abuse cocaine even when a large number of potential confounds were considered

Animal studies can help us to understand why sensitivity to drugs is altered by preexposure by looking at brain changes that occur and that can explain the enhanced sensitivity to the positive reinforcing effects of cocaine.
Sensitization and Tolerance in Psychostimulant Self-Administration

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Review

MDMA ("ecstasy") abuse as an example of dopamine neuroplasticity

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Other questions of interest: Do certain traits predispose to drug addiction? Impulsivity?

- [http://www.impulsivity.org](http://www.impulsivity.org)
  International Society for Research on Impulsivity
- [Barratt Impulsiveness Scale](http://www.impulsivity.org)
- [BIS11 Translations](http://www.impulsivity.org)
- [Balloon Analogue Risk Task](http://www.impulsivity.org)
- [Cued Go No-Go](http://www.impulsivity.org)
- [Immediate and Delayed Memory Tasks](http://www.impulsivity.org)

- Drug addicts are impulsive as indicated by all of these tasks
  - Perry, JL and Carroll ME The role of impulsive behavior in drug abuse. Psychopharmacology 2008 Sep;200(1):1-26
But….were they more impulsive to start with or did drug use make them impulsive----chicken and egg question


• Studies in Laboratory animals can help to answer this question
First, measured impulsivity using 2 different tasks (5-CSRT and delayed reward task)

Do a median split to determine high and low impulsive animals

Measure time to extinction following acquisition of cocaine self-administration (a measure of strength of addiction)

Impulsivity determines extinction of responding- High impulsive rats tend to be resistant to extinction of drug-taking behavior
Impulsivity was a good predictor of drug-seeking following abstinence from MDMA self-administration in a model of relapse.

Is the variability in response to drugs of abuse related to genetic factors?

Studies in laboratory animals suggest that the answer is “yes” and help to identify specific genetic components:

- Hanrahan JR et al., PLoS One. 9(2014):e85525 **GABAA receptors** containing ρ1 subunits contribute to in vivo effects of ethanol in mice.

- And many, many more using knock-out or knock down technologies that interfere with the expression of a specific receptor gene.
A genetic deletion of the Serotonin Transporter increased MDMA self-administration in rats

More information that is available from animal studies

• Animal studies allow us to determine how the brain has changed as a result of repeated exposure to drugs of abuse
Drug addiction proceeds as a result of neuroadaptations resulting from repeated drug exposure

• Where in the brain?
• What changes?

• Animal studies are well-suited to answer these questions
The mesocorticolimbic dopamine system as target of addictive drugs

Simple version

More complicated version
Molecular Biology has provided techniques to study changes in intracellular signalling that occur with repeated exposure to drugs (eg morphine)

And new techniques are increasing our ability to understand relevant changes in brain that occur as a function of repeated exposure to drugs of abuse

- Optogenetics allows selective activation or inactivation of brain cells that use a specific neurotransmitter

**Channelrhodopsin**

- Cation channel
- Activated by blue light (470nm)
- Allows Na$^+$ influx across the membrane and depolarizes the neuron, thus activating it
- Acts as the on switch

**Halorhodopsin**

- Chloride pump
- Activated by yellow light (580 nm)
- Triggers influx of Cl$^-$ which hyperpolarizes the cell and inhibits the neuron
- Acts as the Off switch

3 If addiction rewires the brain, can we short the circuit?

Scientists know that the use of addictive substances causes physical changes in the brain that can lead to addiction. What they are just beginning to understand is how those changes can be reversed to treat the disease.

Using optogenetic-guided brain surgery in mice, researchers have been able to identify a type of dopamine receptor that seems to have a crucial role in addiction. Blocking this receptor has reversed the symptoms of cocaine addiction in mice ($50).

For practical and ethical reasons, optogenetic methods cannot be used in humans, but their increasing use in the lab could speed the discovery of drugs to target and reset the reward circuits that are overloaded in addiction.
Optogenetics is gaining momentum as a tool to understand the neurobiology of drug abuse and is paving the road to novel treatments

Summary and Conclusions

• Studies in laboratory animals provide an indication of abuse potential of drugs
• Studies in laboratory animals allow us to experimentally manipulate environmental and genetic variables to determine the role of these variables in the acquisition and maintenance of drug taking
• Animal studies allow us to assess the role of specific preexisting traits in drug-taking and to determine effects of drug exposure on the expression of specific traits
• Studies in laboratory animals provide us with the tools to determine and to manipulate brain mechanisms that are relevant to the development and maintenance of drug taking