Neuroscience of Addiction
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Definition: Research designed to determine changes in the brain that occur in conjunction with the development of addiction.

At the present time, the research is primarily in rats.
Approaches with little behavioral involvement

• Nestler: $\Delta$FosB accumulation following chronic, passive drug administration

• Robinson and Berridge: drug-induced sensitization reflecting neuronal changes.
Approaches with more emphasis on behavior

• Robbins and Everitt: Impulsive behavior changes to compulsive behavior as reflected in resistance to punishment following chronic, extended self-administration.

• Ahmed and Koob: Increased drug intake following chronic, extended self-administration – opponent processes of drug withdrawal; stress systems
Neuroscience of Addiction

• These each have very different models of addiction. How can we decide what drug addiction is in rats in order to be certain that brain changes that accompany this are relevant?
• We need to be quite certain of what addiction is in humans in order to produce it in animals.
• Yet the meaning and use of the term addiction, even in humans, is controversial.
Should we use the term addiction in humans?

• Sure. The pre-eminent textbook on pharmacology (Goodman and Gilman) has had a chapter entitled Drug Addiction and Drug Abuse since its First Edition (1955).

• Not so fast -- “It is possible to describe all known patterns of drug use and abuse without employing the terms *addict* or *addiction*. In many respects this would be advantageous.” Jerome Jaffe in Fifth Edition of G & G, 1965.
Should we use the term addiction in humans?

- Sometimes the same authors can change their minds:

- Winger, Hofmann, & Woods, Third Edition of A Handbook on Drug and Alcohol Abuse (1992): "Addiction...has taken on a perjorative meaning that is inappropriate in a scientific text; it is used infrequently."

Should we use the term addiction in humans?

• “The reason for these…disagreements is that abuse and addiction are behavioral syndromes that exist along a continuum.” “…there is an arbitrary aspect to the definitions of the overall behavioral syndromes of abuse and addiction.” Charles O’Brien in the Eleventh Edition of G&G, 2006.

• O’Brien goes on to say, “The term addiction…refers to compulsive drug use…”
What is addiction in humans?

- The DSM IV of the APA is silent on addiction, using the terminology *substance dependence* for the overall “behavioral syndrome.”
- Does this help? If we look for an animal model of *substance dependence* rather than an animal model of *addiction*, do we look in a different place?
DSM-IV definition of substance dependence

• Taking the substance in larger amounts or over a longer period than intended
• Failing attempts to reduce or stop use
• Spending a great deal of time obtaining, using, and recovering from using the substance
• Giving up important activities in order to use the substance
• Continued use despite recognition of the negative side-effects
• (how much of this can be applied to animals?)
Two overlooked aspects to drug addiction

• It does not develop in all exposed individuals.

• There is a strong pediatric aspect to the disease.
‘We are animals in a world no one knows’

A LIFE SERIES IN TWO PARTS

Pretty girl named Jane, pleasant young man named John. They could be yesterday or tomorrow.

But they are drug addicts, headed for heroin.

Photographed by BILL EPIDGE
• So, drug addicts take drugs; perhaps the best model of addiction in animals also revolves around drug-taking.

• Animals (monkeys are shown here) have been prepared with indwelling i.v. catheters and given the opportunity to respond and receive drugs throughout the day.

• This permits the study the reinforcing effects of drugs.
Morphine

No. 830 Male 4.4 kg
2.5 mg/kg/inj.

Average daily dose (mg/kg/day)

Week
• For the well being of the animals, it was necessary to restrict access to the drug.

• But something may have been lost in this action.
• Drugs became “simply” reinforcers, not much different behaviorally from other reinforcers.

• Are drugs “simple” reinforcers in non-addicted organisms and more than “simple” reinforcers in addicted organisms?

• Is there a compulsive nature to their reinforcing effects in “addicted” animals that is lacking in most other reinforcers?

• If so, what are the conditions that change the drug from “simply” a reinforcer to a compulsively administered reinforcer?
This approach to addiction

Addiction occurs when drugs move from “simple” or “normal” reinforcers and become “compulsively” taken reinforcers; the reinforcing effects remain critical.

Compulsive behavior can be defined as behavior that is controlled more by the stimuli previously paired with the drug.

Compulsive behavior develops as a consequence of a history of drug administration, but other than this is poorly understood.
Is extensive drug self-administration necessary and sufficient for addiction?

• No – you can place an i.v. catheter in a human and encourage her to push a button to obtain infusions of morphine, nearly as often as she wishes, and she does not become an addict.

• No – you can give a child stimulants twice daily for years and years and he does not have an increased likelihood of becoming an addict.

• No – students, truck drivers, airplane pilots take stimulants on a regular basis, but rarely develop addiction.
Is drug administration necessary and sufficient for the development of compulsive disorders?

- Yes – administration of D3/D2 agonists to individuals with Parkinson’s disease, restless leg syndrome, or fibromyalgia can result in compulsive disorders.
Compulsion and Addiction

• What are the similarities and differences between addiction to drugs and “addiction” to gambling, food, sex, computer gaming?
• Do you need a drug in order to develop an addiction?
• Yes, if your definition of addiction involves brain changes that are drug induced.
• But if your definition is behavioral, then one can have a drug that does not produce addiction (e.g., caffeine) and a non-drug that does (e.g., gambling).

• This definition would focus on behaviors that become excessive, are difficult to reduce or eliminate, and have unwanted effects on the addicted individuals and their environment.
What is drug addiction?

• Behaviorally: drug self-administration – responding to the reinforcing effects of a drug.

• Development of compulsive aspects of the behavior, so that the stimuli associated with the drug become more important.

• Compulsion may be related to brain receptor changes due to drug history and perhaps drug withdrawal.
Drug Addiction Requirements

• Drug with reinforcing effects
  – These are different for different drugs
  – Rate of onset plays a critical role in reinforcing effects of drugs
  – Availability (legality) is also critical
  – Importance of drug withdrawal?

• Pattern of drug-taking that results in compulsive behavior – the big unknown

• Susceptible individuals
  – Genetics undoubtedly play a role
  – Environment may influence susceptibility – drug exposure

• Susceptible age
Apply these

• Ethanol:
  – A fairly poor reinforcer
  – A fairly slow onset of action
  – But widely available; a huge majority of the population has consumed ethanol at some time.
  – If this exposure occurs in susceptible individuals at a susceptible time, problems can occur.
Further application

• Nicotine
  – Appears to function poorly as a reinforcer
  – But has an immediate onset of action
  – Widely available
  – Compulsive use may be linked to nicotine withdrawal
  – The drug has an unusual capacity to induce compulsive behavior.
How about

• Cocaine?
  – Powerful reinforcer
  – Much more addictive when smoked (fast onset) than when snorted (slower onset)
  – Not as widely available, and more social concerns about use
  – No withdrawal signs
Impact of the reinforcement concept of addiction on treatment

- It is possible that treatment for drug abuse is now feasible.
- It requires slow-release formulations of agents that block the effects of the drug.
- Slow release reduced the serious problem of compliance.
- The effects of the drug that are blocked include the reinforcing effects.
Antagonist treatment

- **Opioids:** Naltrexone or other long-lasting opioid antagonists prepared in a slow-release formulation. Currently available, just need to get them into heroin addicts.

- **Cocaine:** Cocaine esterase enzymatically degrades cocaine very, very quickly and can remove it from the blood and brain within second. Slow-release formulation is being developed.
Antagonist treatment

• Nicotine: Dihydroβerythroidan may be a “pure” nicotine antagonist. A long-lasting formulation might be useful for treating tobacco use.

• Marijuana: Remonibant and similar drugs are Δ⁹ THC antagonists that have been approved for human use. Issues point out difficulties in drug company production.
In the Meantime:

• Contingency Management is the most effective way to reduce drug use.
• CM provides non-drug reinforcement for drug avoidance.
  – Provide vouchers for cocaine-negative urines.
  – Monetary value of the voucher increases for each consecutive drug-free urine sample.
  – Reset value of voucher following a positive sample.
• CM is expensive.
Conclusions

• Drug addiction is a chronic, remitting, relapsing behavioral disorder.

• It has been treated by drastic changes in the environment, but this is nearly impossible to accomplish.

• Any treatment, methadone, drug antagonists, CM, or counseling, will need to be continued indefinitely.
Questions

• Anything that was not answered on site but holds your interest:

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