Disordered Behavior:
The Neurobiology and Underlying Basis of
Craving, Relapse and Addiction

Addiction Medicine Academy
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NO COMMERCIAL INTERESTS, NO FINANCIAL RELATIONSHIPS, NO CONFLICTS OF INTEREST, NO OFF-LABEL USES OF MEDICATIONS
Addiction – A primary, chronic disease of brain reward, motivation, memory, and related circuitry

1) Addiction is a disease.
2) Addiction is chronic.
3) Addiction involves the brain’s pleasure circuitry.
4) Addiction involves the brain’s motivation circuitry.
5) Addiction involves the brain’s memory circuitry.
6) What do we know about these brain circuits?
7) Is neurobiological knowledge about addiction helping to improve treatment for addiction?
Stunningly Few Chemicals are Addictive

• ~30,000,000 chemical compounds are known
  \( (Chemical\ Abstracts\ substance\ count) \)
• ~100 are addictive

  Nicotine
  Alcohol
  Psychostimulants (cocaine, amphetamines)
  Opiates
  Cannabinoids
  Barbiturates
  Benzodiazepines
What makes these 100 chemicals addictive?

- They are rewarding, reinforcing, pleasurable
- Animals self-administer them, like humans do
- Rank order of appetitiveness in animals parallels rank order of appetitiveness in humans
- They activate the reward circuitry in the brain
- Degree of activation of reward circuitry in brain correlates with addictiveness
The Pleasure/Reward Circuitry of the Brain

- Prefrontal cortex
- Nucleus accumbens
- Ventral tegmental area
The Pleasure/Reward Circuitry of the Brain
• How Do We Know This?
  
  — Electrical Brain-Stimulation Reward
    • In Laboratory Animals
    • In Human Patients
The crucial reward neurotransmitter is dopamine (DA)
• How Do We Know This?

  – Virtually all addictive drugs are DA agonists
    • The one common feature they share

  – Mic injections of DA agonists
    • Conditioned place preference
    • Intracranial self-administration

  – Effects of DA antagonists
    • Negative reinforcers in animals
    • Subjective effects in humans (neuroleptics)

  – Effects of DA antagonists on drug self-administration
    • Compensatory increase in drug intake
    • Extinction

  – Nucleus Accumbens (NAcc) neurochemistry during self-administration
    • In vivo brain microdialysis
IV heroin self-administration
Catecholamine Synthesis Pathway
Blockade of BSR by Dopamine Synthesis Blockade and Restoration of BSR with ICV Dopamine

“PROPONENT” AND “OPPONENT” BRAIN REWARD PROCESSES IN ADDICTION
DRUG WITHDRAWAL
BRAIN REWARD PROCESSES
IN ADDICTION
Percent Enhancement or Inhibition of Brain-Reward (Alteration in $\theta_0$ or $M_{50}$ Brain-Reward Threshold)

<table>
<thead>
<tr>
<th>Brain-Reward Inhibition</th>
<th>Brain-Reward Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>0</td>
</tr>
<tr>
<td>-10</td>
<td>10</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>

- THC Withdrawal (24 Hrs Post-THC)
  - $M_{50}$
  - $\theta_0$

- Acute THC (20 Mins Post-THC)
  - $M_{50}$
  - $\theta_0$
“REWARD DEFICIENCY” AS A DRIVING FORCE IN ADDICTION
NORMAL STATE

VTA

D2

G1

D1

DA

TH

NFS

VP

VP

AMYG

OLF

CTX

NAC

AC

ATP

creb

fos

jun

ion channels

PKA

D2

D1

G3

TH

D1

DA

TH

NFS

VTA

NAC

ion channels
“Is it possible, then, that some substance abusers have a defect in their ability to capture reward and pleasure from everyday experience, as postulated by some clinicians and as postulated by Blum and colleagues in the context of their formulation of ‘reward deficiency syndrome’? Interestingly, this very concept – of a basal hypofunctionality in brain mechanisms subserving normal reward and pleasure functions – was originally postulated by Dole and colleagues nearly 40 years ago during the development of methadone maintenance for heroin addiction. If these conceptions have merit, they have profound implications: (a) our goals are not only to rescue addicts from the clutches of their addictions, but also, more importantly, (b) to restore their reward functions to a level of functionality that enables them to ‘get off’ on the real world; and (c) pharmacotherapeutic interventions for treatment of substance abuse that are based on simple blockade of brain reward functions are doomed to failure.”

The “Hijacked” Brain Hypothesis

- Addictive drugs act on the same brain-reward substrates and mechanisms as do natural biologically-essential rewards (e.g., food, sex, etc)
- Addictive drugs derive much of their addictive power by activating these brain-reward substrates and mechanisms more powerfully than natural biologically-essential rewards (e.g., food, sex, etc)
- There is solid experimental evidence for this
## Risk of Addiction

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ever Used (%)</th>
<th>Addicted (%)</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>75.6</td>
<td>24.1</td>
<td>31.9</td>
</tr>
<tr>
<td>Heroin</td>
<td>1.5</td>
<td>0.4</td>
<td>23.1</td>
</tr>
<tr>
<td>Cocaine</td>
<td>16.2</td>
<td>2.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Alcohol</td>
<td>91.5</td>
<td>14.1</td>
<td>15.4</td>
</tr>
<tr>
<td>Cannabis</td>
<td>46.3</td>
<td>4.2</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Contributions to the Disease of Addiction

• 50% Genetic
• 50% Environmental

• NOT biology versus environment
• They act together to produce the addiction behavioral phenotype
• Substantial evidence that environmental and social factors can influence neurobiological (brain) substrates of addiction
Genetic Component

- Surprisingly plastic and changeable
- Rat breeding experiments
- Behavioral phenotypes breed true in ~15 generations
  - Lewis versus Fischer 344 rat strains
  - Other drug-seeking drug-liking strains
    - Scandinavian AA
    - Sardinian Alcohol-preferring
    - Others
Individual Variations

- High reactivity to stress
- High novelty-seeking
- High impulsivity
Vulnerability Factors for Disease of Addiction

- Lack of homeostatic reward regulation
- Sensation/novelty seeking
- Impulsivity
- Antisocial conduct disorder (especially in adolescence)
- Depression
- Attention Deficit/Hyperactivity Disorder (ADHD)
- Reward “deficiency”
Fig. 3. $[^{18}F]$FCP binding potential increases in dominant monkeys. Normalized, co-registered PET images (percent injected dose per ml) of $[^{18}F]$FCP binding in the basal ganglia of a dominant and a subordinate monkey, while individually housed and socially housed.
PET Images of [18F]Fluoroclozapine in Cocaine-Naive and Cocaine-Experienced Monkeys

Cocaine-naive monkey

Cocaine-experienced monkey after 227 days of abstinence
Behavioral measures of trait impulsivity in high-impulsive and low-impulsive rats

**Fig. 1.** Behavioral attributes of trait impulsivity on the 5-CSRT task. (A) Impulsive rats exhibit high levels of premature responding on days when visual targets are presented either 5 s after trial initiation (days 1, 2, 4, and 5) or 7 s after trial initiation (day 3), as compared to non-impulsive
Reduced D2/D3 receptor binding in nucleus accumbens of drug-naïve trait-impulsive rats
Black circles – High impulsive rats
White circles – Non-impulsive rats
Progression of drug-seeking behavior from reward-driven to habit-driven

• Long history of involvement of dorsal striatum in habit formation

• Pavlovian-to-Instrumental transfer (PIT)
  – Animals trained to associate CS with a reward (Pavlovian learning)
  – Animals then trained to lever-press for same reward (Instrumental)
  – Test: Ability of CS to enhance lever-pressing in extinction (models addiction)
    • Lesions of CeA and NAc core abolish PIT
    • Lesions of BLA or NAc shell have no effect on PIT
    • Dopamine D2/D3 receptor antagonism abolishes PIT
    • Amphetamine potentiates PIT

• Robbins and Everitt, *Neurobiology of Learning and Memory* 78:625-636, 2002

• Ascending spiral of striato-nigral-striato loop pathways from NAc shell to dorsolateral striatum

• Haber et al, *Journal of Neuroscience* 20:2369-2382, 2000
“Compulsive drug-seeking behavior is inflexible, since it persists despite considerable cost to the addict, becomes dissociated from subjective measures of drug value, becomes elicited by specific environmental stimuli, and involves complex goal-directed behaviors for procurement and self-administration of drugs. Limbic cortical-ventral striatopallidal circuits that underlie goal-directed drug-seeking actions may eventually consolidate habitual, S-R drug seeking through engagement of corticostriatal loops operating through the dorsal striatum. This progression from action to habit may have its neural basis within the “spiraling” loop circuitry of the striatum, by which each striatal domain regulates its own DA innervation and that of its adjacent domain in a ventral-to-dorsal progression (Haber et al, 2000). Thus, the NAc shell regulates its own DA innervation via projections to the VTA and also that of the NAc core. The NAc core in turn regulates its own DA innervation via projections to the VTA and also that of the next, more dorsal tier of the dorsal striatum via projections to the substantia nigra pars compacta and so on. Chronically self-administered drugs, through their ability to increase striatal DA, may consolidate this ventral-to-dorsal striatal progression of control over drug-seeking as an habitual form of responding.”

- Robbins TW and Everitt BJ. Limbic-striatal memory systems and drug addiction. Neurobiology of Learning and Memory 78:625-636, 2002
Addiction is not physical dependence

- Many drugs produce physical dependence without addiction
- Some drugs produce addiction without physical dependence
- Animals take addicting drugs in absence of physical dependence
- Pain significantly reduces addictive liability
- Brain sites of addiction differ from brain sites that mediate physical dependence
Real problem in addiction medicine is relapse

**Question:** Do patients suffering from addiction have an abnormal, aberrant propensity to relapse to drug-seeking behavior?

**Answer:** Yes
TRIGGERS TO RELAPSE

• Re-exposure to DRUG
  – Cross-triggering between drug classes

• Exposure to STRESS
  – Mild stress extremely effective

• Exposure to environmental CUES
  – Sights, sounds, smells associated with drug use
  – “People, places, things” – Alcoholics Anonymous
IMPLICATIONS FOR TREATMENT
Incubation of Relapse Vulnerability Over Time
CRUCIAL TAKE-HOME MESSAGE
DISTINCTIONS BETWEEN:

• Drug-Induced Reward ("High" "Hit" "Blast")
  - VTA-Accumbens Reward/Pleasure Circuit

• Craving and Relapse
  - 3 Separate Craving and Relapse Circuits
    • Drug-Triggered Craving and Relapse
    • Stress-Triggered Craving and Relapse
    • Cue-Triggered Craving and Relapse

• Physical Dependence and Withdrawal
  - Dorsal Mesencephalon (in vicinity of dorsal raphé nucleus)

• Analgesia
  - Periaqueductal/Periventricular Gray and Raphé Nuclei
  - Lateral reticular nucleus, lateral centre-median & lateral parafascicular & lateral intralaminar Thalamic nuclei
ANOTHER CRUCIAL TAKE-HOME MESSAGE:

One CANNOT produce addiction by medically-appropriate long-term treatment of pain with opiates (except in patients with a strong pre-existing vulnerability to addiction)
Chronic pain inhibits opioid-seeking behavior in animal models

• Narita et al, *Life Sciences* 74:2655-2673, 2004
• Narita et al, *Neuropsychopharmacology* 30:111-118, 2005
• Oe et al, *Psychopharmacology* 177:55-60, 2004
• Ozaki et al, *Journal of Neurochemistry* 82:1192-1198, 2002
• Ozaki et al, *Journal of Neurochemistry* 88:1389-1397, 2004
• Suzuki, *Yajugaku Zasshi* 121:909-914, 2001
Chronic pain inhibits opioid-enhanced dopamine in the VTA-MFB-NAc reward/relapse circuitry

• Narita et al, *Life Sciences* 74:2655-2673, 2004
• Narita et al, *Neuropsychopharmacology* 30:111-118, 2005
• Ozaki et al, *Journal of Neurochemistry* 82:1192-1198, 2002
• Ozaki et al, *Journal of Neurochemistry* 88:1389-1397, 2004
• Suzuki, *Yajugaku Zasshi* 121:909-914, 2001
Chronic pain inhibits electrical brain-stimulation reward in animal models

Chronic pain inhibits development of opioid-induced physical dependence in animal models

When opioids are used – even at heroic doses – in the appropriate medical control of chronic pain, addiction and drug abuse are not a major concern.”

What about memory?
“Addiction is a chronic, relapsing disorder, characterised by the long-term propensity of addicted individuals to relapse. A major factor that obstructs the attainment of abstinence is the persistence of maladaptive drug-associated memories, which can maintain drug-seeking and taking behaviour and promote unconscious relapse of these habits. Thus, addiction can be conceptualised as a disorder of aberrant learning of the formation of strong instrumental memories linking actions to drug-seeking and taking outcomes that ultimately are expressed as persistent stimulus-response habits; of previously neutral environmental stimuli that become associated with drug highs (and/or withdrawal states) through pavlovian conditioning, and of the subsequent interactions between pavlovian and instrumental memories to influence relapse behaviour. Understanding the psychological, neurobiological and molecular basis of these drug memories may produce new methods of pro-abstinence, anti-relapse treatments for addiction.”


(Behavioural and Clinical Neuroscience Institute, Department of Experimental Psychology, University of Cambridge, Cambridge, UK)
Sometimes memory is very directly involved in addiction, as in the phenomenon of “chasing the first wonderful ‘high’” (yet never – or very rarely – again achieving it).

The brain loci involved in addiction-related memory functions (or, more correctly, dysfunctions) are the hippocampus (especially the ventral regions) and the amygdala (strongly implicated in emotional memories).
MEMORY

Amphetamine
Cocaine
Opiates
Cannabinoids
Phencyclidine
Ketamine
What about executive functions?
“Executive functioning” (decision-making, willingness to delay short-term gratification for long-term benefit, impulsivity, etc) is also very directly and very importantly involved in addiction. At present, there is no consensus among either researchers or theoreticians in addiction medicine as to the exact way(s) in which “executive functioning” is implicated in:

- Initial vulnerability to addiction
- Ease of achieving abstinence and sobriety
- Vulnerability to relapse to drug-seeking and drug-taking behavior(s)

Animal models derived from the field of behavioral economics (e.g., reward-delay discounting; reward-magnitude discounting) are currently providing researchers with interesting, compelling, and (probably) clinically-relevant laboratory animal models with which to study “executive functioning.”

The brain loci involved in addiction-related “executive functioning” include (at the very least) the frontal cortex and the anterior cingulate cortex.
EXECUTIVE FUNCTIONS

Amphetamine
Cocaine
Opiates
Cannabinoids
Phencyclidine
Ketamine

Opiates
Ethanol
Barbiturates
Benzodiazepines
Nicotine
Cannabinoids

To dorsal horn

ANTERIOR CINGULATE CX

Acc  VTA

FCX

AMYG

GLU

CRF

5HT

DYN

DA

GABA

BNST

HYPOTHAL

ABN

ICSS

BNST

OFT

VP

GABA

ENK

5HT

OPIOID

GABA

GABA

DYN

5HT

HYPOTHAL

DA

NE

LC

PAG

END

RETIC

LAT-TEG

Raphé

To dorsal horn
Effective Current Pharmacotherapies for Drug Addiction

- Methadone – opiate addiction
- Buprenorphine – opiate addiction
- Heroin maintenance – opiate addiction
- Naltrexone – opiate addiction
- Naltrexone – alcohol addiction
- Acamprosate – alcohol addiction
- Varenicline – nicotine addiction
- Nicotine maintenance (nicotine patch, etc) – nicotine addiction
- Bupropion – nicotine addiction
- Baclofen – alcohol addiction (case reports), possibly cocaine
Current promising medication development strategies

- Dopamine D3 receptor antagonists
- Slow-onset, long-acting DAT inhibitors
- Baclofen (GABA\(_B\) agonist)
- Gamma-vinyl-GABA (GABA\(_B\))
- Drugs acting on endocannabinoid system
- Drugs acting on glutamate system
- Central CRF antagonists
The Future of Addiction Treatment:

Neurobiology mechanism-based, hypothesis-driven medication development for treating addiction
The Future of Addiction Treatment:

Predicting vulnerability to addiction by neuro-imaging
Thank You!
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