Neurobiology of Addiction

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Addiction is as old as humankind

And Noah planted a vineyard. And he drank of the wine, and became drunken. And he was naked and dirty in his tent. And Ham saw the nakedness and filthy condition of his father, and told his two brothers. And Shem and Japheth took a garment...and covered the nakedness of their father; and they turned their faces away, so as to avert their eyes from their father's nakedness and shame.

- Genesis 9:20-23
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 basic reward circuitry of the brain is a 3-neuron in-series synaptic circuit
  – Descending Link ABN → VTA, via Medial Forebrain Bundle
  – Ascending Link VTA → NAcc, via Medial Forebrain Bundle
  – Further Ascending Link NAcc → VP
• How Do We Know This?

– Electrical Brain-Stimulation Reward
  • In Laboratory Animals
  • In Human Patients
Representative Stimulation-Response Curves

Lever Presses / 30 Sec vs. Stimulation Frequency (Hz)

- Control
- THC 1.0 mg/kg
- THC 5.0 mg/kg
• Also:

– Conditioned Place Preference to Intracranial Microinjection of Rewarding Drugs

– Self-Administration of Rewarding Drugs Directly into Brain Sites
## Risk of Addiction

<table>
<thead>
<tr>
<th></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>Cocaine</td>
<td>16.2</td>
<td>2.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Heroin</td>
<td>1.5</td>
<td>0.4</td>
<td>23.1</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>

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

  – Microinjections 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

- Diagram showing changes in dopamine levels (% of baseline) over time (min).
SELF-ADMINISTERED VOLUNTARY INTRAVENOUS DRUG "HIT"
“PROPONENT” AND “OPPONENT” BRAIN REWARD PROCESSES IN ADDICTION
Rat Striatal Dopamine Release (% Change from Baseline)

- **Saline**
- $\bar{x}$ Change after morphine (1st hr)
- $\bar{x}$ Change after morphine (2nd and 3rd hr)
- Maximum change after morphine (2nd and 3rd hr)

*\( p < 0.05 \)

**\( p < 0.02 \)
DRUG WITHDRAWAL
BRAIN REWARD PROCESSES
IN ADDICTION
Percent Enhancement or Inhibition of Brain-Reward (Alteration in $\theta_0$ or $M_{50}$ Brain-Reward Threshold)

Brain-Reward Inhibition    Brain-Reward Enhancement

$\theta_0$  $M_{50}$

(20 Mins Post-THC)  (24 Hrs Post-THC)
“REWARD DEFICIENCY” AS A DRIVING FORCE IN ADDICTION
"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? If this be so, then our goals are really two-fold: First, to rescue addicts from the clutch of their addictions, and second, to restore their reward systems to a level of functionality that will enable them to 'get off' on the real world. We surely have our work cut out for us, but at least the path seems clear."

Role(s) of the crucial Nucleus Accumbens dopaminergic reward-related neurons

1) Encoding of receipt of reward
2) Encoding of degree of reward
3) Encoding of reward-anticipation
4) Encoding of disconfirmation of reward expectancy
5) Encoding errors of reward prediction

- Lee et al, *Synapse* 33:49-58, 1999
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).

- Experimental evidence for this.
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-induced locomotor activity
• High novelty-seeking
• High impulsivity

• Laboratoire de Psychobiologie des Comportements Adaptatifs INSERM Unité 259, Université de Bordeaux II, France
• Behavioral and Clinical Neuroscience Institute, Department of Experimental Psychology, University of Cambridge, UK
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”
FIGURE 1. Distribution Volume Images of $[^{11}\text{C}]$Raclopride at the Levels of the Striatum (left) and Cerebellum (right) in a Healthy Male Subject Who Reported the Effects of Methylphenidate as Pleasant and in a Healthy Male Subject Who Reported Them as Unpleasant$^{a}$
FIGURE 2. D$_2$ Receptor Levels ($B_{\text{max}}/K_d$) in 23 Healthy Male Subjects Who Reported the Effects of Methylphenidate as Pleasant, Unpleasant, or Neutral$^a$

$^a$ $B_{\text{max}}/K_d$ values were lower in subjects who reported the effects of methylphenidate as pleasant than in those who reported them as unpleasant. The horizontal lines represent the means for the $B_{\text{max}}/K_d$ estimates for the different groups.
Fig. 3. $[^{18}\text{F}]$FCP binding potential increases in dominant monkeys. Normalized, co-registered PET images (percent injected dose per ml) of $[^{18}\text{F}]$FCP binding in the basal ganglia of a dominant and a subordinate monkey, while individually housed and socially housed.
PET Images of [18F]Fluoroclebopride 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 the Disease of Addiction

- Recreational occasional use
- Recreational steady use
- Reward-driven use → Habit-driven use
  - No longer rewarding or only with first use of day
  - Transition from ventral striatum to dorsal striatum
- Habit-driven use use → Compulsive use
- Denial, the “Crash,” “Bottoming Out”
- Treatment and achievement of abstinence
- Persistent vulnerability to craving and relapse
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

“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
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
Animal Models of Relapse

• Reinstatement (Self-administration)
  – Drug-triggered
  – Stress-triggered
  – Cue-triggered

• Reactivation (Conditioned Place Preference)
  – Drug-triggered
  – Stress-triggered
  – Cue-triggered
Cocaine + Cues
Saline
No Cues
Cocaine

Responses (Mean + SEM)

Session
Acc   VTA

FCX

AMYG

VP

HYPOTHAL

LAT-TEG

BNST

ICSS

HIPP

CRF

GLU

GABA

ENK

DYN

5HT

DA

GABA

NE

LC

NE

END

Opiates

Amphetamine

Cocaine

Opiates

Cannabinoids

Phencyclidine

Ketamine

Opiates

Ethanol

Barbiturates

Benzodiazepines

Nicotine

Cannabinoids

To dorsal horn
A

'THETA BURST' ELECTRICAL STIMULATION (VSUB)

lever press

active

inactive

time (min)

B

VENTRAL SUBICULUM

number of lever presses

SHAM

2Hz

THETA

*
RELAPSE (number of drug-seeking lever presses)

VSUB = VENTRAL SUBICULUM (HIPPOCAMPUS)
VTA = VENTRAL TEGMENTAL AREA

VSUB: E  
VTA: VEH

VSUB: E  
VTA: KYN  
(glutamate antagonist at NMDA receptor)

VTA: NMDA  
(glutamate agonist)

VTA: VEH

*Statistically significant difference
Incubation of Relapse Propensity Over Time

![Graph showing the incubation of relapse propensity over time with bars for 1, 2, 4, 7, 15, 29, and 60 days. The graph compares responses over 6 hours and 1 hour, with error bars indicating variability.](image-url)
B. Accumbens

BDNF

NGF

% of control rats

1 30 90

1 30 90

* #
C. Amygdala

![Bar chart showing the percentage of control rats for BDNF and NGF on withdrawal days 1, 30, and 90. The chart indicates significant differences marked by asterisks (*) and hash marks (#).]
Why is this important?

Long-term potentiation (LTP) and long-term depression (LTD) – considered by many to be mechanistic substrates of synaptic remodeling and learning – have been shown to be produced by addictive drugs in:

1) Nucleus accumbens
2) Amygdala
3) Hippocampus
Why is this important?

BDNF may be involved in – indeed, may be a mechanism for – the synaptic remodeling in the:

1) Nucleus accumbens
2) Amygdala
3) Hippocampus (?)

That could possibly underlie the “incubation of craving” phenomenon
Why is this important?

If this is true, this could open up a whole new strategy for anti-addiction, anti-craving, anti-relapse medication development:

Medications that target BDNF-mediated synaptic remodeling in the:

1) Nucleus accumbens
2) Amygdala
3) Hippocampus (?)
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
  – Locus Coeruleus and Dorsal Mesencephalon
• Analgesia
  – Periaqueductal Gray Matter and Raphé Nuclei
Can one produce addiction by long-term treatment of pain with opiates?
Chronic pain inhibits opioid-seeking behavior in animal models

- Oe et al, *Psychopharmacology* 177:55-60, 2004
Chronic pain inhibits opioid-enhanced dopamine in the VTA-MFB-NAc reward/relapse circuitry

Chronic pain inhibits electrical brain-stimulation reward in animal models

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

World Health Organization Guidelines on Treatment of Chronic Pain

“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.”

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
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ABBREVIATIONS

ABN – Anterior bed nuclei of the medial forebrain bundle  VP – Ventral pallidum
Acc – Nucleus accumbens  VTA – Ventral tegmental area
ANYG – Amygdala
BNST – Bed nucleus of stria terminalis
CRF – Corticotrophin releasing factor
DA – Dopamine
DYN – Dynorphin
END – Endorphin
ENK – Enkephalin
FCX – Frontal cortex
GABA – Gamma aminobutyric acid
GLU – Glutamate
HIPP – Hippocampus
5HT – 5-Hydroxytryptamine (serotonin)
HYPOTHAL – Hypothalamus
LAT-TEG – Lateral tegmental nuclei
LC – Locus coeruleus
NE – Norepinephrine
OFT – Olfactory tubercle
OPIOID – Endogenous opioid neurotransmitter
PAG – Periaqueductal grey matter
Raphé – Raphé nuclei of brain stem
RETIC – Reticular activating system