Substance Use Disorders: Neurobiology

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Addiction is a Brain-Based Disorder

Photo courtesy of the NIDA Web site. From A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana.
Neurobiologic Advances from the Brain Disease Model of Addiction

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This article reviews scientific advances in the prevention and treatment of substance-use disorder and related developments in public policy. In the past two decades, research has increasingly supported the view that addiction is a disease of the brain. Although the brain disease model of addiction has yielded effective preventive measures, treatment interventions, and public health policies to address substance-use disorders, the underlying concept of substance abuse as a brain disease continues to be questioned, perhaps because the aberrant, impulsive, and compulsive behaviors that are characteristic of addiction have not been clearly tied to neurobiology. Here we review recent advances in the neurobiology of addiction to clarify the link between addiction and brain function and to broaden the understanding of addiction as a brain disease. We review findings on the desensitization of reward circuits, which dampens the ability to feel pleasure and the motivation to pursue everyday activities; the increasing strength of conditioned responses and stress reactivity, which results in increased cravings for alcohol and other drugs and negative emotions when these cravings are not sated; and the weakening of the brain regions involved in executive functions such as decision making, inhibitory control, and self-regulation that leads to repeated relapse. We also review the ways in which social environments, developmental stages, and genetics are intimately linked to and influence vulnerability and recovery. We conclude that neuroscience continues to support the brain disease model of addiction. Neuroscience research in this area not only offers new opportunities for the prevention and treatment of substance addictions and related behavioral addictions (e.g., to food, sex, and gambling) but may also improve our understanding of the fundamental biologic processes involved in voluntary behavioral control.

In the United States, 8 to 10% of people 12 years of age or older, or 20 to 22 million people, are addicted to alcohol or other drugs. The abuse of tobacco, alcohol, and illicit drugs in the United States exacts more than $700 billion annually in costs related to crime, lost work productivity, and health care. After centuries of efforts to reduce addiction and its related costs by punishing addictive behaviors failed to produce adequate results, recent basic and clinical research has provided clear evidence that addiction might be better considered and treated as an acquired disease of the brain (see Box 1 for definitions of substance-use disorder and addiction). Research guided by the brain disease model of addiction has led to the development of more effective methods of prevention and treatment and to more informed public health policies. Notable examples include the Mental Health Parity and Addiction Equity Act of 2008, which requires medical insurance plans to provide the same coverage for substance-use disorders and other mental illnesses that is provided for other illnesses, and the proposed bipartisan Senate legislation that
<table>
<thead>
<tr>
<th>Substance</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Alcohol</td>
<td>GABA, opioid agonist; NMDA antagonist</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Blocks re-uptake of dopamine</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Stimulate dopamine release</td>
</tr>
<tr>
<td>PCP, ketamine</td>
<td>NMDA antagonist</td>
</tr>
<tr>
<td>Opioids</td>
<td>Mu, delta, and kappa agonism</td>
</tr>
<tr>
<td>Cannabis</td>
<td>CB1 agonist</td>
</tr>
<tr>
<td>MDMA</td>
<td>5HT release and re-uptake inhibition; mild DA and NE reuptake inhibition</td>
</tr>
<tr>
<td>LSD</td>
<td>5HT2a agonism leading to increased glutamate?</td>
</tr>
</tbody>
</table>
GABA Receptor

Schematic representation of the NMDA (N-Methyl D-Aspartate) receptor complex

- Polyamine site
- Zn$^{2+}$ site
- K$^{+}$ site
- Glycine site
- Mg$^{2+}$ site
- Na$^{+}$
- Ca$^{2+}$

**Extracellular side**

**Cytoplasmic side**

PCP site
Catecholamine Neurotransmission

Normal

Dopamine
Norepinephrine

Nerve Impulse

Transporter

Synapse

Receptors
Dopamine Mesolimbic Pathway

- Nucleus accumbens
- Ventral tegmental area
- Behavior

- pleasure
- reward
- reinforcing behavior
- substance misuse
**Neurochemistry of Reinforcement**

- **Endorphin or Dynorphin Inhibitory Neuron**
- **Glutamate Excitatory Input**
- **Dopamine Neuron**
  - **GABA-A Receptors**
  - **GABA Inhibitory Feedback**
- **GABA Inhibitory Neuron**
  - **μ Opioid Receptors**
  - **κ Opioid Receptors**
- **Presynaptic Opioid Receptors (μ, δ?)**
- **Ventral Tegmental Area (VTA)**
- **Nucleus Accumbens (NAc)**
- **REWARD**
The Ventral Tegmental Area (VTA)-nucleus accumbens pathway is activated by all drugs of dependence including alcohol.

This pathway is important not only in drug dependence, but also in essential physiological behaviors such as eating, drinking, sleeping, and sex.
Major Brain Circuits Involved in Addiction

Photo courtesy of the NIDA Web site. From A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana.
The Story of Marijuana

Photo courtesy of the NIDA Web site.
From A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana.
Significant brain growth and development occurs during adolescence, and continues into the twenties. Some studies show that this growth and development extends to the age of 30!

(Sowell et al., 1999; Sowell et al., 2001)
Does dyssymmetry in prefrontal control of limbic regions drive TAY behavior?

Dysregulated Mood
(e.g. frustration, Irritability, temper tantrums)

Exaggerated with certain disorders such as Mood, Substance Abuse, ADHD?


Courtesy N Strang
The Memory of Drugs

Photo courtesy of Anna Rose Childress, Ph.D.
Smokers who quit and then relapse have greater brain reactivity than those who maintain abstinence.

Gianelli et al, Biol Psych 2010
Positron Emission Tomography (PET) And Brain Recovery from SUD
Your Brain After Drugs

Drugs Have Long-term Consequences

Photo courtesy of NIDA from research conducted by Melega WP, Raleigh MJ, Stout DB, Lacan C, Huang SC, Phelps ME.
NEUROBIOLOGY OF ALCOHOL

EFFECTS OF ALCOHOL WITHDRAWAL:

• **CNS HYPERACTIVITY- NO OPPOSITION TO ALCOHOL INDUCED EXCITATORY STATE (NMDA HYPERACTIVITY)**

• **RELEASE OF CRF**

• **DELAYED RECOVERY OF D 2 RECEPTOR SENSITIVITY AFTER DETOX IS ASSOCIATED WITH HIGH RISK FOR RELAPSE**
NEUROBIOLOGY OF OPIOID WITHDRAWAL

• HYPERACTIVITY OF NOR-ADRENERGIC NEURONS IN THE LOCUS COERULEUS
  – INCREASE BP, HR, RESPIRATIONS
  – INCREASE SWEATING, DIARRHEA
  – CLONIDINE & OPIATES REVERSE THESE EFFECTS

• INCREASED GABA EFFECTS: REDUCED DOPAMINE IN NUCLEUS ACCUMBENS
  – CAUSES DYSPHORIA, DEPRESSION, CRAVING
  – ONLY OPIATES REVERSE THESE EFFECTS
Neurobiology of SUD: Summary

• Competing neurocircuitry may result in, and/or be secondary to, SUD
• Adaptations occur at molecular and macro levels with SUD
• Brain recovery may link with clinical recovery—brain health recovery may take months with certain substances
• Therapeutics associated with brain biomarkers of SUD
Questions?