Neurobiology of Addiction

Essentials of Addiction Medicine Program
AOAAM
Pittsburgh, PA
March 2, 2019

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No Disclosures
What is addiction?

- Compulsion to seek and take the drug
- Loss of control in limiting intake
- Emergence of negative emotional state when access to drug is prevented (dependence)
- Relapsing disorder with roots in impulsivity and compulsivity and neurobiological mechanisms that change as an individual moves from one domain to another
The definition of addiction (ASAM)

• A primary chronic disease of brain **reward, motivation, memory** and related circuitry
• Impairment in behavioral **control, craving, diminished recognition** of significant problems with one’s behaviors and interpersonal relationships, and a **dysfunctional emotional response**
• Dysfunction in these neural circuits leads to characteristic **biological, psychological, social** and **spiritual** manifestations
What causes addiction?

• ½ Genetic
• ½ Environmental:
  • Impaired resiliency through parenting or life experiences
  • Culture of how addiction is actualized
Reflective Reward System ("Top Down")

- Prefrontal cortex → NA
- Regulates impulses, emotions, analyzing situations
- Controls what reactive reward system is triggering
## Neural Mechanisms

### Mesolimbic/Mesocortical Pathways

<table>
<thead>
<tr>
<th>Feature</th>
<th>Neural substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reward</td>
<td>Mesocorticolimbic dopamine pathway</td>
</tr>
<tr>
<td>Inhibition of behavior</td>
<td>Prefrontal cortex (PFC)- lateral</td>
</tr>
<tr>
<td>Associative learning</td>
<td>Amygdala (medial temporal lobe)</td>
</tr>
</tbody>
</table>

![Brain Diagram]
Mesolimbic Pathway

• Naturally triggered by events that cause dopamine release
• Inputs from brain’s own morphine (endorphins), anandamide (marijuana), nicotine (Ach), cocaine & amphetamine (dopamine) → DA release
• Drugs of abuse (DOA) bypass brain’s NTs to directly stimulate receptors
Stimulation of the Reward Circuit
Neurochemical substrate for acute rewarding effects

<table>
<thead>
<tr>
<th>Drug of abuse</th>
<th>Neurotransmitter</th>
<th>Site</th>
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</thead>
<tbody>
<tr>
<td>Cocaine and amphetamines</td>
<td>Dopamine</td>
<td>Nucleus accumbens</td>
</tr>
<tr>
<td></td>
<td>- Aminobutyric acid</td>
<td>Amygdala</td>
</tr>
<tr>
<td>Opioids</td>
<td>Opioid peptides</td>
<td>Nucleus accumbens</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>Ventral tegmental area</td>
</tr>
<tr>
<td></td>
<td>Endocannabinoids</td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>Dopamine</td>
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</tr>
<tr>
<td></td>
<td>Opioid peptides</td>
<td>Amygdala</td>
</tr>
<tr>
<td>9-Tetrahydrocannabinol</td>
<td>Endocannabinoids</td>
<td>Nucleus accumbens</td>
</tr>
<tr>
<td></td>
<td>Opioid peptides</td>
<td>Ventral tegmental area</td>
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<td>Alcohol</td>
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<td></td>
<td>Glutamate</td>
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<td></td>
<td>Endocannabinoids</td>
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</tbody>
</table>
What role does will power play?
Reactive Reward System ("Bottom Up")

- Motivation/drive to achieve pleasure or avoid pain
- VTA is site of DA cell bodies
- NA is where DA neurons project
- Amygdala is connected to VTA and NA
- Rewarding input → phasic DA firing in NA → “fun” → conditioned reward
- NA → amygdala → reward learning
- Amygdala → VTA = relevance detection to previous pleasure
- Amygdala → NA = emotional response, impulsivity, automatic
Drugs and Natural Rewards ACTIVATE Dopamine in Reward Regions

Drugs of abuse increase DA in the Nucleus Accumbens, which is believed to trigger the neuroadaptions that result in addiction.
Effects of Drugs on Dopamine Release

Amphetamine

Cocaine

Nicotine

Morphine

Di Chiara and Imperato, PNAS, 1988
• In short...Dopamine release in Nac mediates “goodness” effects of drugs (reward) while hijacking the PFC (cognitive control) and the OFC (motivation).
• Opioidergic System ("hedonic"): mediates reinforcing effects of EtOH by indirectly modulating DA release.
Dopamine D2 Receptors are Lower in Addiction

Cocaine
Meth
Alcohol
Heroin

Volkow et al., Neuro Learn Mem 2002.
ADDICTION IS A DISEASE OF THE BRAIN
as other diseases it affects the tissue function

Decreased Brain Metabolism in **Drug Abuse Patient**

Decreased Heart Metabolism in **Heart Disease Patient**

Sources: From the laboratories of Drs. N. Volkow and H. Schelbert
Repeated Drug Use Changes the Brain
Weakens the Brain Dopamine System

Control

Cocaine Abuser

REPEATED USE OF COCAINE OR OTHER DRUGS REDUCES LEVELS OF DOPAMINE D2 RECEPTORS
Mechanism of Action - \( \text{GABA}_A \) Receptor

- The \( \text{GABA}_A \) receptor
  - An ionotropic receptor and ligand-gated ion channel.
  - Activation, selectively conducts \( \text{Cl}^- \) through its pore, resulting in hyperpolarization (stabilization), of the neuron.
  - Resulting in an inhibitory effect on neurotransmission by diminishing the chance of a successful action potential occurring.
GABA<sub>A</sub> receptor is the binding site for GABA

- Different allosteric binding sites modulate the activity
  - Direct agonists
  - Enhanced GABA binding
- The allosteric sites are the targets of various drugs,

- benzodiazepines, ethanol
- non-benzodiazepines, neuroactive steroids,
- barbiturates, inhaled anaesthetics
ADDICTION IS A DEVELOPMENTAL DISEASE
starts in adolescence and childhood

Brain areas where volumes are smaller in adolescents than young adults


% in each age group who develop first-time cannabis use disorder

Age at cannabis use disorder as per DSM IV

NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003
Low Levels of Striatal D2 Receptors Are Associated with Impaired Activity in Frontal Regions

Volkow et al., PNAS 2011 108(37): 15037-42
Non-Addicted Brain

Medications for Opioid Addiction

- An agonist drug has an active site of similar shape to the endogenous ligand, so it binds to the receptor and produces the same effect.

- An antagonist drug is close enough in shape to bind to the receptor but not close enough to produce an effect. It also takes up receptor space and prevents the endogenous ligand from binding.

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**Opioid Effect**

- **Full Agonist** (Methadone)
- **Partial Agonist** (Buprenorphine)
- **Antagonist** (Naloxone)

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Other secondary factors

- Underlying biologic deficit of enhanced reward function
- **Neuroadaptation** in motivational circuitry secondary to repeated use
- Cognitive and affective disorders
- Disruption of healthy supports and relationships
- Exposure to trauma (coping abilities overwhelmed)
- Distortion in meaning, purpose, and values that guide behavior
- Distortion in a person’s connection with self, others, and the transcendent
Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence

Some Resources

- www.pcssnow.org
  - Provider clinical support system for medication assisted treatments
- www.aoaam.org
  - Amer. Osteo. Acad. of Addiction Medicine
- www.asam.org
  - Amer. Soc. Of Addiction Medicine
- www.drugabuse.gov/ NIDA
- www.NIAAA.nih.gov/ NIAAA
- www.scopeofpain.com/ Scope of Pain