Neurobiology of Addiction

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University of Wisconsin – La Crosses
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Financial Disclaimers
• Dr. Hall-Flavin has no financial interests to disclose
• Dr. Hall-Flavin will address off-label use of some medications to treat addictive illness.

Learning Objectives
• To cite the three major developmental stages of addiction.
• To understand the basic neurobiological hierarchy of phenotypic expression in these stages
• To understand
• To understand the targets of treatment
• To understand how the environment impacts the biological underpinnings of addiction

Question 1
Emotional regulatory structures include:
 a) Amygdala
 b) Anterior cingulate cortex
 c) Prefrontal cortex
 d) B and C
 e) All of the above

Question 2
Allostasis in the context of substance use disorders:
 a) Occurs in binge drinking cycle before the onset of negative reinforcement.
 b) Occurs once addiction is established.
 c) Is characterized by overactivity of GABA and serotonin.
 d) Occurs with activation of the insula.
 e) B and D
**Question 3**

True or false:

Activation of the emotions processing areas (amygdala and insula) are not consistently observed.

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**Question 4**

The concept of neuroplasticity includes all of the following, except:

- a) Dendritic sprouting
- b) Long term potentiation
- c) An increase in metabotropic glutamate receptors post-synaptically
- d) B and C
- e) Decreased responsivity to glutamate in the presence of drug cues.

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**Substance Use Disorder – DSM 5**

- Recurrent use of alcohol and/or other psychoactive substance that causes clinically and functionally significant impairment in health, disability, and failure to meet major responsibilities at work, school, or home.
- Classified as mild, moderate, or severe. The latter is considered to be synonymous with addiction (substantial evidence of impaired control over use).
- 11 criteria that may be summarized by evidence of impaired control, continued use despite adverse consequence, preoccupation, and evidence of physiologic dependence.

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**Epidemiology**

- 8-10% of people 12 years of age or older (20 to 22 million people) are addicted to alcohol and other drugs.
- Economic cost 700 billion dollars annually.
What factors determine if a person will become addicted?

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Domain</th>
<th>Protective Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Aggressive Behavior</td>
<td>Individual</td>
<td>Self-Control</td>
</tr>
<tr>
<td>Poor Social Skills</td>
<td>Individual</td>
<td>Positive Relationships</td>
</tr>
<tr>
<td>Lack of Parental Supervision</td>
<td>Family</td>
<td>Parental Monitoring and Support</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>Peer</td>
<td>Academic Competence</td>
</tr>
<tr>
<td>Drug Availability</td>
<td>School</td>
<td>Anti-Drug Use Policies</td>
</tr>
<tr>
<td>Poverty</td>
<td>Community</td>
<td>Neighborhood Attachment</td>
</tr>
</tbody>
</table>

The brain continues to develop into adulthood and undergoes dramatic changes during adolescence.

The Addiction Cycle

Development of Addiction

Withdrawal
Stress
Negative reinforcement

Compulsion to seek alcohol and drugs
Loss of control in limiting intake

Intoxication
Reward
Positive reinforcement

Compulsion to seek alcohol and drugs
Loss of control in limiting intake
Development of Addiction


Withdrawal
Stress
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Positive reinforcement

The Antireward System

Some of the neural substrates implicated in motivation to use during withdrawal and protracted abstinence

Dopamine
Serotonin
Opioid peptides
GABA
Corticotropin-releasing factor (CRF)
Norepinephrine
Dynorphin
Neurokinin (Substance P)
Neuropeptide Y (NPY)

Negative reinforcement
Down-regulation of Reward System
Disruption of natural rewards
Recruitment of Extra-Hypothalamic Stress System
Negative emotional state

The Addiction Cycle

Source: Volkow, NEJM, 2016

MAYO CLINIC
Emotional Regulation

- Affective Intensity/Reactivity of Affect (magnitude and degree of changeability)
- Affective Modulation
- Cognitive Modulation
- Behavioral Control

Impaired Emotional Regulation

Functional Categories and Regions

Connectivity

Controls vs. SUD Individuals

Novel Treatment Targets I

Augment Activity PFC
Improve WM/resting state
Conductivity CBT
Change default network activation
Circuits to Cells

Cells and their Receptors

Neuroplasticity

Neuroplasticity in Brain Circuits associated with the Development of Addiction


MAYO CLINIC

Cortical Spheroids

Lower Dopamine D2 Receptor Neurons
Opioid Dependent Individuals

Targets for Drugs of Abuse are Known and Can be Investigated

Possible Families of Risk Factors
- Alcohol Metabolizing Enzymes
- Level of Response (LR)
- Impulsivity
- Psychiatric Disorders

Alcohol Metabolism

Associated Studies Candidates

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABRA6</td>
<td>COMT</td>
<td>5HTT</td>
</tr>
<tr>
<td>GABRG2</td>
<td>DRD2/ANKK1</td>
<td>ADORA</td>
</tr>
<tr>
<td>GABRA5</td>
<td>DRD4</td>
<td>NPY</td>
</tr>
<tr>
<td>GABRA1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCNMA1</td>
<td>DGKZ</td>
<td>ADHIB</td>
</tr>
<tr>
<td>GNAS</td>
<td>ADHIC</td>
<td>CYP2E</td>
</tr>
<tr>
<td>PK</td>
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</tr>
</tbody>
</table>
BDNF and Alcohol Use Disorders

Gene Expression

Epigenetics and Drugs of Abuse

Epigenetics and Drugs of Abuse

The brain continues to develop into adulthood and undergoes dramatic changes during adolescence.

Neurobiology and Treatment
These images of the dopamine transporter show the brain’s remarkable potential to recover, at least partially, after a long abstinence from drugs—in this case, methamphetamine.


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**Antidipsotropic Medications Currently on the Market**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Addiction</th>
<th>Year of release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>Nicotine</td>
<td>2006</td>
</tr>
<tr>
<td>Naltrexone extended</td>
<td>Alcohol</td>
<td>2005</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Alcohol</td>
<td>2004</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Opiate</td>
<td>2002</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Nicotine</td>
<td>1997</td>
</tr>
<tr>
<td>Naltrexone*</td>
<td>Alcohol</td>
<td>1994</td>
</tr>
<tr>
<td>Methadone</td>
<td>Opiate</td>
<td>1954</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Alcohol</td>
<td>1972</td>
</tr>
<tr>
<td>Nicotine replace Tx</td>
<td>Nicotine</td>
<td></td>
</tr>
</tbody>
</table>

Based on Koob et al: Nature Reviews Drug Discovery, June 2009

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**Varenicline: How Does It Work?**

- Varenicline activates the nicoбавe receptors in the brain, which reduces the reward from nicotine.
- Partial the reward of nicotine.

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**Comorbidity: Targets and Treatment**

**Antidipsotropic Medications & Their Targets Conceptual Framework – Novel Drugs II**

- Behavioral (clinical) phenotypes
- Intermediate phenotypes (endophenotypes)
- Brain function (circuits)
- Cellular function (pathways)
- Gene expression & protein modification
- Epigenetic effects
- Gene variations (genotypes)

Summary

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**Cocaine Vaccine**

Source: DEA

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Thank You, and Enjoy the Conference!