The Neuroscience of Addiction: Implications for Health Professionals

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Definitions

- Addiction
- Craving
- Dysphoria
- Drug-induced neuroplasticity
- Euphoria
- Negative reinforcement
- Positive reinforcement
- Substance-use disorder
DSM-5 Criteria

- Hazardous use
- Social/interpersonal problems related to use
- Neglected major roles to use

  - Withdrawal
  - Tolerance

  - Used larger amounts/longer
  - Repeated attempts to quit/control use
  - Much time spent using
  - Physical/psychological problems related to use
  - Activities given up to use
  - Craving

Substance-use disorder

1. Mild (2-3)
2. Moderate (4 to 6)
3. Severe (>6)
Major Characteristics

• Compulsivity
• Impulsivity
• Impairment in health
• Impairment in social function

Difficulty arises when attempting to draw the lines between legitimate drug use and loss of control, and by extension, the molecular and cellular mechanisms that lead to addiction.

The Balance Between Happy Chemicals & Stress Hormone

• Dopamine: seek reward and joy of finding reward
• Endorphin: mask pain
• Oxytocin: safety and social bonds
• Serotonin: get respect from others
• Cortisol: stress

Craving

Behavioral Mechanisms

Dopamine Neuropeptides

Euphoria

Anxiety Relief

Functional Enhancement

Positive Reinforcement

Neuronal Mechanisms

Modulating Variables

Social Context

Genetics

Modified from Koob 1992
Dopamine Receptors

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Signal Transduction</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 and D5</td>
<td>Gs</td>
<td>Stimulation</td>
</tr>
<tr>
<td>D2, D3, D4</td>
<td>Gi</td>
<td>Inhibition</td>
</tr>
</tbody>
</table>
D. Biosynthesis of Dopamine

Step 1

Tyrosine → DOPA (tyrosine hydroxylase)

Step 2

DOPA → Dopamine (DOPA decarboxylase)

Comments on GABA:
Most abundant inhibitory amino acid
Monocarboxylic acids are inhibitory
regulate Cl- influx resulting in cell
hyperpolarization
GABA

Endogenous Opioids

• Enkephalins
• Dynorphins
• β-endorphins

Opioid: Pharmacological Targets

• Pharmacological targets
  • Opioid receptors
    • Members of the GPCR family
      • Mu, delta, and kappa
        • Go and Gαo
      • Inhibition AC, voltage-gated Ca^{2+} channels
      • Activation of MAPK, inwardly rectifying K⁺ (GIRK) channels
    • Results in decreased neurotransmitter release and inhibition of neuronal firing
Opioids:

μ-receptors:
- G protein coupled
- Decrease release of glutamate and substance P

Glutamate

- Most abundant excitatory amino acid
- Dicarboxylic acids are excitatory
- Glutamate excitotoxicity

Long-Term Potentiation (LTP)
- Prolonged increase in the size of a post synaptic response to a pre-synaptic stimulus.
- NMDA receptors
- Major role in memory acquisition
Ionotropic Glutamate Receptors

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<th>Signal Transduction</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>NMDA</td>
<td>Na+/K+/Ca++ influx</td>
<td>Excitation (N-methyl-D-aspartate)</td>
</tr>
<tr>
<td>AMPA</td>
<td>Na+/K+/Ca++ influx</td>
<td>Excitation (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)</td>
</tr>
<tr>
<td>Kainate</td>
<td>Na+/K+/Ca++ influx</td>
<td>Excitation</td>
</tr>
</tbody>
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Metabotropic Glutamate Receptors

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<tbody>
<tr>
<td>mGluR1 &amp; mGluR5</td>
<td>Gs and Gq</td>
<td>Stimulation</td>
</tr>
<tr>
<td>mGluR2-4 &amp; mGluR6-8</td>
<td>Gi</td>
<td>Inhibition</td>
</tr>
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Pharmacological Targets of Drugs of Abuse

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Target</th>
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<tbody>
<tr>
<td>a. Opiates</td>
<td>Agonists at mainly the $\mu_1$ receptor</td>
</tr>
<tr>
<td>b. Cocaine</td>
<td>Increase DA levels by blocking DAT</td>
</tr>
<tr>
<td>c. Amphetamine</td>
<td>Stimulate DA release</td>
</tr>
<tr>
<td>d. Ethanol</td>
<td>Facilitates GABA$_\alpha$ receptor function</td>
</tr>
<tr>
<td>e. Nicotine</td>
<td>Agonist at NACHr</td>
</tr>
<tr>
<td>f. Cannabinoids</td>
<td>Agonists at CB$_1$ receptors</td>
</tr>
<tr>
<td>g. Hallucinogens</td>
<td>Agonists at 5-HT$_{2A}$ receptors</td>
</tr>
</tbody>
</table>

Common Cellular & Molecular Adaptation

Translational Changes
Epigenetic Changes
1. Increases in histone deactylase in the NAc & VTA
2. Decreases in histone methyltransferase in the NAc

Genetic Changes
1. D2 receptors (D2R)
2. D4 receptors (D4R)
3. Catechol-O-methyltransferase (COMT)
Positive Reinforcement
Activation of DA and Opioid Systems

Incentive salience

Memory

Negative Reinforcement
Inactivation of DA & Opioid Systems & Increase CRF
Binge Intoxication

- Dopamine: increase
- Opioid peptides: increase
- Serotonin: increase
- GABA: increase
- Acetylcholine: increase

Withdrawal/negative effects

- Dopamine: decrease
- Opioid peptides: decrease
- Serotonin: decrease
- Corticotropin-release factor: increase
- Dynorphin: increase
- Norepinephrine: increase

Preoccupation/anticipation

- Dopamine: increase
- Opioid peptides: increase
- Serotonin: increase
- Glutamate: increase
- CRF: increase
Pharmacogenomic Application of the Neurobiology to the Opioid Crisis

Definitions

Molecular Level
- Pharmacogenomics: The study of variations of DNA and RNA characteristics as related to drug response.¹
- Pharmacogenetics: The study of variations in DNA sequence as related to drug response.¹

Clinical Level
- Pharmacogenomics: The study of many genes, in some cases the entire genome, involved in response to a drug.²
- Pharmacogenetics: The study of a gene involved in response to a drug.²


DNA to Protein Drug Targets: Pharmacogenes

Receptors or Transporters or Enzymes

Examples:
- Histamine
- β-adrenergic
- Estrogen

Examples:
- OATP1B1 (influx)
- P-glycoprotein (efflux)

PGx: Drug Efficacy • Adverse Drug Events


Ineffective Medication


Adverse Drug Events

Adverse Drug Events: Example

Rani Jamieson
- Son Tariq was born April 18, 2005;
- Episiotomy:
  - Received acetaminophen with codeine;
- 12 days later Tariq died.

Adverse Drug Events: Example

- Cause: morphine overdose
- Tariq not receiving morphine
- Brain/nervous system depression
- Slow breathing
- Inactivity/inaction
- Skin color
- Poor feeding/failure to thrive

Gene Form | Drug (Dos. Dose) | Response | Outcome
--- | --- | --- | ---
CYP2D6*1/*1 | Codeine | Morphine overdose | Adverse Drug Reaction: Death


CPIC: CYP2D6-Codeine

Table 1: Assignment of Risk of Codeine Overdose in Babies with CYP2D6*1/*1 Genotype

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CPIC: CYP2D6 - Codeine

The Ohio Opioid PGx Study

• Supported by the Ohio Attorney General's Office
• Collaboration with the Emergency Departments at the University of Cincinnati and The Ohio State University
• Sample size: 1200 patients
• PGx screening of 180 genes associated with opioid metabolism and pharmacodynamic response of the reward pathway

The Ohio Opioid PGx Study: Specific Aims

• Aim 1: Determine which genes are associated with development of opioid use disorder.

• Aim 2: Develop a Genomic Opioid Addiction Risk Score (G-OARs).

Sample Gene Targets

Pharmacokinetic
ABCB1
CYP2D6
CYP2B6
UGT2B7

Pharmacodynamic
TH
COMT
OPRM1
DRD2
References


References