The Relationship Between the Reward and Stress Systems and How They are Perturbed in Addiction

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Learning Objectives

1. Understand a conceptual framework of addiction that goes beyond the acute rewarding effects of drugs

2. Understand the neuroplasticity in the brain reward, stress systems and executive function systems associated with the transition to addiction

3. Understand how such knowledge may predict vulnerability and novel treatments for addiction
Stress and Reward: The Two Faces of Janus

Bottom lines

1. Addiction is an incentive salience disorder
2. Addiction is a reward deficit disorder
3. Addiction is a stress surfeit disorder
4. Addiction is a self-regulation disorder
Addiction — can be defined as a chronically relapsing disorder that is characterized by a compulsion to seek and take drug or stimulus, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) when access to the drug or stimulus is prevented (here, defined as the “dark side” of addiction)

Positive and Negative Reinforcement - Definitions

**Positive Reinforcement** — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (non dependent drug taking paradigms).

**Negative Reinforcement** — defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking).

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**Stages of the Addiction Cycle**

- **Preoccupation with obtaining**
  - Persistent physical/psychological problems

- **Anticipation**

- **Addiction**
  - Persistent desire
  - Larger amounts taken than expected

- **Withdrawal**
  - Negative Affect

- **Tolerance**
  - Compromised social, occupational or recreational activities

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Non Drug “Process” Addiction Cycles

Drug Addiction
- Possessive, intrusive
- Urging
- Supernatural
- Persuasive
- Mind-wiped
- Compromised social, occupational

Compulsive Exercise
- Thought about parts, wanting you were there
- Stuffed
- Overspent
- In the "zone"

Compulsive Shopping
- Rubbery
- Plunging
- Sesseous
- Frighten, shiver, shudder

Compulsive Gambling
- Killing, excitement
- Caleum - Playful
- Relief of problems
- Addressed
- Depressed, low self-esteem

Compulsive Eating
- Choosing
- Unhealthy
- Losing, depression
- Poisoned
- Poisoned

Compulsive Sex
- Excited
- Rice
- Excited
- Excited
- Excited

Neurobiology of Addiction

Binge-Intoxication Stage


Effects of Cocaine and Amphetamine on Dopamine Synaptic Function

Mesolimbic Dopamine System

Mesolimbic dopamine system
1. Ventral tegmental area
2. Nucleus accumbens

Nucleus Accumbens

Ventral Tegmental Area (VTA)
Cocaine Self-Administration

Unit Dose (mg/kg/injection)  Total / 3 h

- 0.75 mg/kg/inj. Cocaine
  60  120  180
  31

- 0.375 mg/kg/inj. Cocaine
  59

- 1.0 mg/kg/inj. Cocaine
  18

- 0.75 mg/kg/inj. Cocaine + prtreat w/ 20 μg/kg SCH23390 (Dopamine D-1 Receptor Antagonist)
  67


![Pieter Bruegel](image-url)
Opioid Peptide Reward System

Enkephalin and endorphin reward system

1. Ventral tegmental area
2. Nucleus accumbens
3. Amygdala

Alcohol Consumption Induces Endogenous Opioid Release in the Human Nucleus Accumbens

Converging Acute Actions of Drugs of Abuse on the Ventral Tegmental Area and Nucleus Accumbens


The Ventral to Dorsal Striatal Shift: Ascending Spirals of VTA/Nigra-Striatal pathways

Haber et al. 2000
Ikemoto 2007
similar organization in rat brain

Neurocircuitry of Incentive Salience

The Ventral to Dorsal Striatal Shift: Ascending Spirals of VTA/Nigra-Striatal pathways

Everitt & Robbins 2005
Ikemoto 2007 - similar organization in rat brain

goal-directed drug seeking & taking pavlovian conditioning
drug seeking & taking habits
vulnerability
abstinence/relapse
compulsive drug seeking

Haber et al. 2000
"Absinthe Drinker"
Pablo Picasso (1910)

Withdrawal-Negative Affect Stage


Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

Positive Hedonic Effects
- ↑ Dopamine
- ↑ Opioid peptides
- ↑ Serotonin
- ↑ GABA

Negative Hedonic Effects of Withdrawal
- ↓ Dopamine … “dysphoria”
- ↓ Opioid peptides … pain
- ↓ Serotonin … “dysphoria”
- ↓ GABA … anxiety, panic attacks

Decreased Dopamine D$_2$ Receptor Activity in a Cocaine Abuser


CNS Actions of Corticotropin-Releasing Factor (CRF)

<table>
<thead>
<tr>
<th>CRF</th>
<th>Pituitary Gland</th>
<th>Amygdala</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>β-Endorphin</td>
<td>Medulla Oblongata</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Sympathetic Activation</td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Stroke volume</td>
<td>Peripheral vascular resistance</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Heart rate</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Adrenal Medulla</td>
<td>Epinephrine</td>
<td>Gastric acid secretion</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Behavioral response to stressors</td>
<td>Behavioral activation</td>
</tr>
</tbody>
</table>
**Rodent Model of Excessive Drinking During Withdrawal**

**Self-administration training**
- Sweetened solution fading used to train animals to lever press for: 10%w/v EtOH vs Water

**Dependence induction**
- Chronic intermittent alcohol vapors (4+ wks)
- Target blood alcohol levels (BALs): 0.125-0.250 g%

**Withdrawal from alcohol vapors**
- Negative emotional state:
  - Anxiety-like behavior
  - Reward threshold deficits
  - Increased CRF release in the extended amygdala
- Excessive drinking:
  - 2-3 fold higher alcohol intake
  - Increased progressive ratio breakpoints
  - Relapse following prolonged abstinence

**Methods**

**Summary of Drugs of Abuse Interactions with Corticotropin-Releasing Factor Systems**

**CRF Antagonist Effects**

<table>
<thead>
<tr>
<th>Withdrawal-induced changes in extracellular CRF in CeA</th>
<th>Withdrawal-induced anxiety-like or aversive responses</th>
<th>Baseline self-administration or place preference</th>
<th>Dependence-induced increases in self-administration</th>
<th>Stress-induced reinstatement</th>
</tr>
</thead>
</table>

Anti-Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

- Dynorphin … “dysphoria”
- CRF … stress
- Norepinephrine … stress

[Diagram showing positive and negative reinforcement pathways involving neurotransmitters such as DA, GABA, NE, CRF, and their roles in reward systems.]
Neurobiology of Addiction: Preoccupation-Anticipation ("Craving") Stage


Loss of Control Over Intake — Self-medication

Medications Development - A Rosetta Stone Approach

Future Targets for Medications Development Derived from Preclinical Basic Research

<table>
<thead>
<tr>
<th>Class</th>
<th>Target</th>
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<tbody>
<tr>
<td>Dopamine receptor partial agonists</td>
<td>D₂ receptor partial agonist (aripiprazole)</td>
</tr>
<tr>
<td></td>
<td>D₃ receptor partial agonist</td>
</tr>
<tr>
<td>Modulators of γ-aminobutyric acid</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Modulators of brain stress systems</td>
<td>CRF₁ receptor antagonist</td>
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<tr>
<td></td>
<td>Dynorphin antagonist</td>
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<tr>
<td></td>
<td>Neurokinin-1 receptor antagonist</td>
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<tr>
<td>Modulators of glutamate</td>
<td>AMPA receptor antagonist</td>
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<tr>
<td></td>
<td>NMDA receptor antagonist</td>
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<tr>
<td></td>
<td>Metabotropic glutamate receptor agonist</td>
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<tr>
<td></td>
<td>Glutamate-5 receptor antagonist</td>
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<td></td>
<td>Topiramate</td>
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</tbody>
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Bottom lines

1. Addiction is a facilitation of incentive salience - compulsive drug taking is associated with engagement of associative (stimulus response) mechanisms involving cortico-striatal-pallidal-thalamic loops that converge in the basal ganglia

2. Addiction is a reward deficit disorder - all drugs of abuse compromise reward function and decrease dopamine activity

3. Addiction is a stress surfeit disorder - all drugs of abuse sensitize brain stress systems such as CRF

4. Addiction is an executive system disorder - all drugs of abuse compromise frontal cortical executive function which disinhibits impulsivity and disinhibits the brain stress systems

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# Neurobiology of Drug Addiction

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- Prefrontal Cortex, c-Fos, CRF, and executive function

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