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Addiction: Reward, motivation and stress

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The Neurocircuitry of Drug Addiction: Neuroadaptive Mechanisms from the “Dark Side”

• What is Addiction?
  1. Conceptual framework
  2. The ‘dark side’ of compulsivity

• Animal Models for the Motivational Effects of Dependence
  1. Brain stimulation reward
  2. Place aversion
  3. Anxiogenic-like responses in the plus maze and defensive burying tests
  4. Escalation in drug self-administration with prolonged access

• A Role for Corticotropin-Releasing Factor in Drug Addiction
  1. Cocaine
  2. Nicotine
  3. Heroin
  4. Alcohol

• Future Directions
  1. Development of CRF₁ antagonists for treatment of addiction
  2. The neurocircuitry of emotional behavior
"Absinthe Drinker"
Pablo Picasso (1910)
Key Definitions

**Drug Addiction** — Chronically relapsing disorder that is characterized by a compulsion to seek and take drug, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) when access to the drug is prevented (here, defined as the “dark side” of addiction)

**Extended Amygdala** — Forebrain macrostructure composed of central medial amygdala, bed nucleus of the stria terminalis, and a transition zone in the medial part of the nucleus accumbens

**Corticotropin-Releasing Factor** — 41 amino acid polypeptide “brain stress” neurotransmitter that controls hormonal, sympathetic, and behavioral responses to stressors
Drug addiction is conceptualized as a chronic relapsing syndrome that moves from an impulse control disorder involving positive reinforcement to a compulsive disorder involving negative reinforcement.
Stages of the Addiction Cycle

Preoccupation Anticipation

Preoccupation with obtaining Persistent physical/ psychological problems

Persistent desire Larger amounts taken than expected

ADDICTION

Binge Intoxication

Tolerance Withdrawal
Compromised social, occupational or recreational activities

Negative Affect

Withdrawal
Animal Models for the Motivational Components of Dependence

Animal Models for the Withdrawal/Negative Affect Stage
1. Brain stimulation reward
2. Place aversion
3. Anxiogenic-like responses in elevated plus maze and defensive burying

Animal Models for the Transition to Addiction
1. Drug taking in selected lines of drug preferring animals
2. Withdrawal-induced drug taking
3. Escalation in drug self-administration with prolonged access
4. Drug taking despite aversive consequences
Cocaine Self-Administration

Unit Dose (mg/kg/injection) | Total / 3 h
---|---
0.75 mg/kg/inj. Cocaine | 31
0.375 mg/kg/inj. Cocaine | 59
1.5 mg/kg/inj. Cocaine | 18
0.75 mg/kg/inj. Cocaine + pretreat w/ 20 μg/kg SCH23390 (Dopamine D-1 Receptor Antagonist) | 67

Neurochemical Circuitry in Drug Reward
Potential Substrates in the Extended Amygdala for the Motivational Effects of Drug Dependence

Equilibrium State for a Homeostatic Regulatory System in a Nondependent and Dependent Organism

Standard Pattern of Affective Dynamics Produced by Novel and Repeated Unconditioned Stimulus

Nondependent

Peak of A
Adaptation
Steady Level of A
Decay of B

Dependent

Peak of A'
Steady Level of A
Peak of B'

Mood Changes Associated with Plasma Levels of Cocaine During Coca Paste Smoking

Dysphoric Feelings followed the initial euphoria in experimental subjects who smoked cocaine paste, even though the concentration of cocaine in the plasma of the blood remained relatively high. The dysphoria is characterized by anxiety, depression, fatigue and a desire for more cocaine.

Sampling of Interstitial Neurochemicals by *in vivo* Microdialysis

- Allows sampling of neurochemicals in conscious animals (correlate brain chemistry with behavior).
- Implanted so that semi-permeable probe tip is in specific brain region of interest.
- Substances below the membrane MW cutoff diffuse across membrane based on concentration gradient.
- Both neurochemical sampling and localized drug delivery are possible.

Collaborators: Dr. Friedbert Weiss, Dr. Larry Parsons, Dr. Emilio Merlo-Pich, Dr. Regina Richter
Extracellular DA and 5-HT in the Nucleus Accumbens During Cocaine Self-Administration and Withdrawal

Drug Withdrawal

Withdrawal from chronic drugs of abuse produces a reward (motivational) dysregulation as measured by thresholds for intracranial self-stimulation.
Intracranial Self-Stimulation (ICSS) Threshold Procedure

Elevations in ICSS Reward Thresholds During Withdrawal

A. Amphetamine Withdrawal

- Graph showing % of Baseline Threshold over Days Post Amphetamine withdrawal.
- Data from Paterson et al., Psychopharmacology 2000, 152:440.

B. Ethanol Withdrawal

- Graph showing % of Baseline Threshold over Hours Post Ethanol withdrawal.
- Data from Schulteis et al., Proc Natl Acad Sci USA 1995, 92:5880.

C. Cocaine Withdrawal

- Graph showing % of Baseline Threshold over Hours Post Cocaine withdrawal.
- Data from Markou & Koob, Neuropsychopharmacology 1991, 4:17.

D. Morphine Withdrawal

- Graph showing % of Baseline Threshold over Naloxone Dose (mg/kg).
- Data from Schulteis et al., J Pharmacol Exp Ther 1994, 271:1391.

E. Nicotine Withdrawal

- Graph showing % of Baseline Threshold over Hours Post Nicotine withdrawal.
- Data from Epping-Jordan et al., Nature 1998, 393:76.

F. THC Withdrawal

- Graph showing % of Baseline Rewards over Frequency (Hz) Post-THC.
Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

Positive Hedonic Effects

- \( \uparrow \) Dopamine
- \( \uparrow \) Opioid peptides
- \( \uparrow \) Serotonin
- \( \uparrow \) GABA

Negative Hedonic Effects of Withdrawal

- \( \downarrow \) Dopamine ... “dysphoria”
- \( \downarrow \) Opioid peptides ... pain
- \( \downarrow \) Serotonin ... “dysphoria”
- \( \downarrow \) GABA ... anxiety, panic attacks
CNS Actions of Corticotropin-Releasing Factor (CRF)
Major CRF-Immunoreactive Cell Groups and Fiber Systems in the Rat Brain

CRF Produces Arousal, Stress-like Responses, and a Dysphoric, Aversive State

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>CRF Agonist</th>
<th>CRF Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acoustic startle</td>
<td>Facilitates startle</td>
<td>Blocks fear-potentiated startle</td>
</tr>
<tr>
<td>Elevated plus maze</td>
<td>Suppresses exploration</td>
<td>Reverses suppression of exploration</td>
</tr>
<tr>
<td>Defensive burying</td>
<td>Enhances burying</td>
<td>Reduces burying</td>
</tr>
<tr>
<td>Fear conditioning</td>
<td>Induces conditioned fear</td>
<td>Blocks acquisition of conditioned fear</td>
</tr>
<tr>
<td>Cued electric shock</td>
<td>Enhances freezing</td>
<td>Attenuates freezing</td>
</tr>
<tr>
<td>Taste / Place Conditioning</td>
<td>Produces place aversion</td>
<td>Weakens drug-induced place aversion</td>
</tr>
</tbody>
</table>
Chronic cocaine administration produces a dependence syndrome that is reversed by blockade of CRF function.
Defensive Burying: Active Anxiety-Like Behavior

Habituation
- Two 45-min sessions in test cage
- No shock probe present

Testing
- Electrified shock probe present
- Probe delivers a single, < 1 sec, 1.5 mA shock on contact
- Probe is shut off after shock
- Defensive burying scored for 10 min

Endpoints
- Latency to bury
- Duration of burying
- Duration of other active behaviors
Effect of CRF Antagonist D-Phe-CRF$_{12-41}$ Administered ICV on Anxiogenic-Like Effect Following Chronic Cocaine Administration

Extracellular CRF Levels in the Central Nucleus of the Amygdala During Cocaine Self-administration and Subsequent Withdrawal


Graph showing Extracellular CRF (% baseline) over Fractions (20 min) during basal, cocaine self-administration (SA) session, and cocaine withdrawal session.
Protocol for Drug Escalation

1) Initial Training Phase
   All Rats (n=24):
   2-hr SA session
   Fixed Ratio 1
   0.25 mg cocaine/injection

2) Escalation Phase
   Short Access (n=12)
   22 x 1-hr SA session
   Long Access (n=12)
   22 x 6-hr SA session

3) Testing Phase
   Dose-response for neuropharmacological probes

Change in Brain Stimulation Reward Thresholds in Long-Access (Escalation) vs. Short-Access (Non-Escalation) Rats

Dose-Dependent Decrease of Cocaine Intake with Administration of a CRF<sub>1</sub> Antagonist

Chronic alcohol exposure produces a dependence syndrome that is reversed by blockade of CRF function.
Elevated Plus Maze

- Unconditioned approach/avoidance behavior
- 3 underlying factors: anxiety, activity, assessment of risk
- Predictive validity for anxiolytic and anxiogenic drugs
Competitive CRF Antagonist $\alpha$-Helical CRF$_{9-41}$ Injected into Central Nucleus of the Amygdala Blocks the Anxiogenic Effects of Alcohol Withdrawal

Extracellular CRF Levels in the Central Amygdala During Ethanol Withdrawal

Protocol for Initiation of Lever Pressing for Oral Ethanol Self-Administration in the Rat

<table>
<thead>
<tr>
<th>Training</th>
<th>Saccharin (w/v)</th>
<th>EtOH (w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-3</td>
<td>0.2%</td>
<td>0% *</td>
</tr>
<tr>
<td>Days 4-9</td>
<td>0.2%</td>
<td>5% *</td>
</tr>
<tr>
<td>Day 10</td>
<td>-</td>
<td>5% *</td>
</tr>
<tr>
<td>Days 11-12</td>
<td>0.2%</td>
<td>5%</td>
</tr>
<tr>
<td>Day 13</td>
<td>-</td>
<td>5%</td>
</tr>
<tr>
<td>Day 14</td>
<td>0.2%</td>
<td>8%</td>
</tr>
<tr>
<td>Days 15-16</td>
<td>-</td>
<td>8%</td>
</tr>
<tr>
<td>Day 7</td>
<td>0.2%</td>
<td>10%</td>
</tr>
<tr>
<td>Day 18+</td>
<td>-</td>
<td>10% *</td>
</tr>
</tbody>
</table>

Rats trained to lever press on a FR-1 schedule
Ethanol added to the saccharin solution
Access to ethanol and water or ethanol + saccharin and water

Ethanol Dependence Induction

Ethanol Vapor Chambers

- Ethanol vapor concentrations range from 22-27 mg/liter
- BAL's are determined every 3 days and ethanol flow is adjusted to maintain BAL's of 150-200 mg%
- Dependence is reliably induced following 2 weeks of exposure
- Control rats are placed in identical chambers into which only air is pumped


Ethanol Liquid Diet

- 8.7% (w/v) ethanol with 35% ethanol-derived calories
- Consists of ethyl alcohol, chocolate flavored sustacal, vitamin and mineral diet fortification
- With unlimited access, maintains BALs over 140 mg%
- Dependence is reliably induced following 2 week exposure
- Control rats are fed liquid diet substituting sucrose for ethanol

Enhanced Ethanol Self-Administration During Withdrawal in Dependent Animals

From: Funk C and Koob GF, unpublished results.

Pre-vapor Responding

Post-vapor Responding

# Lever Presses

Dependent-EtOH
Dependent-Water
Nondependent-EtOH
Nondependent-Water
Effects of a Competitive CRF Antagonist Injected ICV on Ethanol Self-Administration During Withdrawal in Dependent Rats
(60 min session 2 h into withdrawal)

Effect of CRF Antagonist d-Phe-CRF$_{12-41}$ – Central Nucleus of the Amygdala –

Ethanol Responses

Water Responses

* $p < 0.001$ vs. same-dose, nondependent group
# $p < 0.001$ vs. dependent, vehicle group

From: Funk C, O’Dell LE and Koob GF, unpublished results.
Effect of CRF Antagonist D-Phe-CRF$_{12-41}$ – Lateral Bed Nucleus of the Stria Terminalis –

**Ethanol Responses**

<table>
<thead>
<tr>
<th>D-Phe-CRF$_{12-41}$ (µg/µl)</th>
<th>Number Ethanol Presses</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>0.125</td>
<td>80</td>
</tr>
<tr>
<td>0.25</td>
<td>60</td>
</tr>
<tr>
<td>0.50</td>
<td>80</td>
</tr>
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</table>

* Dependent

* Nondependent

* $p < 0.001$ vs. same-dose, nondependent group

**Water Responses**

<table>
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<th>D-Phe-CRF$_{12-41}$ (µg/µl)</th>
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From: Funk C, O’Dell LE and Koob GF, unpublished results.
Effect of CRF Antagonist D-Phe-CRF<sub>12-41</sub> – Nucleus Accumbens Shell –

From: Funk C, O’Dell LE and Koob GF, unpublished results.

* $p < 0.001$ vs. same-dose, nondependent group
CRF₁ Specific Antagonists

**Antalarmin**
- Structure
- $K_i = 1.0 \text{ nM}$
- cLogP = 7

**R121919**
- Structure
- $K_i = 3.5 \text{ nM}$
- cLogP = 4.8

**NBI-30775**
- Structure
- $K_i = 1.9 \text{ nM}$
- cLogP = 3

**MJL-1-109-2**
- Structure
- $K_i = 10 \text{ nM}$
- cLogP = 3.85

**DMP904 Analog**
- Structure
CRF\textsubscript{1} Specific Antagonists

**R121919**

**Ethanol Responses**

- * administered s.c.
- **60 min pre-incubation**
- *n* = 9
- **HBC (20% w/v)**

```
Number Ethanol Presses

<table>
<thead>
<tr>
<th>R121919 (mg/kg, s.c.)</th>
<th>Dependent</th>
<th>Nondependent</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>10</td>
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- * $p < 0.001$ vs. same-dose, nondependent group
- # $p < 0.001$ vs. dependent, vehicle group

**Water Responses**

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Number Water Presses

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<td>0</td>
<td>0</td>
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<td>5</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
</tr>
</tbody>
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Interaction of CRF Antagonists in Animal Models of Protracted Abstinence

1. CRF antagonists injected into the extended amygdala block stress-induced reinstatement of drug seeking
   Erb S, Salmaso N, Rodaros D and Stewart J, Psychopharmacology, 2001, 158:360-365
   Funk D, Li Z, Shaham Y and Le AD, Neuroscience, 2003, 122:1-4

2. CRF antagonists injected i.c.v. block stress-induced anxiogenic-like responses and excessive drinking during protracted abstinence

3. CRF₁ knockout mice show a blunted anxiogenic-like response to alcohol withdrawal and a blockade of excessive drinking during protracted abstinence
The extended amygdala is a rich substrate for neurochemical and neurocircuitry interactions that produce the “dark side” of motivation.
Neurochemical Changes in the Extended Amygdala during the Development of Dependence: Implications for Emotional Processing
Neurochemical Changes Associated with the Transition from Drug Use to Dependence

Conclusions

CRF in the extended amygdala is recruited during the development of dependence and has motivational significance for drug seeking.

Compulsive drug taking associated with addiction derives both from decreases in reward neurotransmission and from recruitment of anti-reward systems ("dark side" of addiction).

Other neurochemical elements in the extended amygdala—such as norepinephrine, NPY and galanin—may have a role in motivational neuroadaptation associated with drug dependence.

The common interface in the extended amygdala of the neurochemistry of addiction and pain and fear conditioning pathways provides a heuristic framework for exploring the neural basis of negative emotional states.
# Neurobiology of Drug Addiction

## Current Collaborators

<table>
<thead>
<tr>
<th>Floyd Bloom</th>
<th>Jean Rivier</th>
</tr>
</thead>
<tbody>
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<td>Barbara Mason</td>
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<td>Marisa Roberto</td>
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<td>Kenner Rice</td>
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<tr>
<td>Wylie Vale</td>
<td>Marc Azar</td>
</tr>
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- National Institute of Diabetes and Digestive and Kidney Diseases
- Pearson Center for Alcoholism and Addiction Research