Addiction: Reward, motivation and stress

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Addiction: Reward, Motivation and Stress

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The Scripps Research Institute
La Jolla, California
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

Withdrawal Negative Affect:
- Compromised social, occupational or recreational activities

Binge Intoxication:

Tolerance 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

<table>
<thead>
<tr>
<th>Unit Dose (mg/kg/injection)</th>
<th>Total / 3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75 mg/kg/inj. Cocaine</td>
<td>31</td>
</tr>
<tr>
<td>0.375 mg/kg/inj. Cocaine</td>
<td>59</td>
</tr>
<tr>
<td>1.5 mg/kg/inj. Cocaine</td>
<td>18</td>
</tr>
<tr>
<td>0.75 mg/kg/inj. Cocaine + pretreat w/ 20 μg/kg SCH23390 (Dopamine D-1 Receptor Antagonist)</td>
<td>67</td>
</tr>
</tbody>
</table>

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

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

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 shows % of baseline threshold over days post amphetamine.
   - Data from: Paterson et al., Psychopharmacology 2000, 152:440

B. Ethanol Withdrawal
   - Graph shows % of baseline threshold over hours post ethanol.
   - Data from: Schulteis et al., Proc Natl Acad Sci USA 1995, 92:5980

C. Cocaine Withdrawal
   - Graph shows % of baseline threshold over hours post cocaine.
   - Data from: Markou & Koob, Neuropsychopharmacology 1991, 4:17

D. Morphine Withdrawal
   - Graph shows % of baseline threshold over naltrexone dose (mg/kg).
   - Data from: Schulteis et al., J Pharmacol Exp Ther 1994, 271:1391

E. Nicotine Withdrawal
   - Graph shows % of baseline threshold over hours post nicotine.
   - Data from: Epping-Jordan et al., Nature 1998, 393:76

F. THC Withdrawal
   - Graph shows rewards/30 sec over frequency (Hz).
   - Data from: Gardner & Vorel, Neurobiol Dis 1998, 5:502
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
CNS Actions of Corticotropin-Releasing Factor (CRF)

- Pituitary Gland
  - ACTH
  - β-Endorphin

- Amygdala

- Medulla Oblongata
  - Sympathetic Activation
    - ACh
    - NE

- Adrenal Medulla
  - Epinephrine

- Cardiac output
- Stroke volume
- Peripheral vascular resistance
- Blood glucose
- Heart rate
- Blood pressure

- Gastric acid secretion
- Gastric emptying

Behavioral response to stressors
Behavioral activation
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\textsubscript{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 the changes in Extracellular CRF (% baseline) over time during Basal, Cocaine SA Session, and Cocaine Withdrawal Session. The graph compares Control group (○) and Cocaine group (●) with significant differences indicated by asterisks (*) and double asterisks (**) at specific time points.](image-url)
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$_1$ 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

Initiation of the free-choice operant task: ethanol (10%) 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.
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 $\text{d-Phe-CRF}_{12-41}$ – Central Nucleus of the Amygdala –

**Ethanol Responses**

- **Dependent**
- **Nondependent**

<table>
<thead>
<tr>
<th>$\text{d-Phe-CRF}_{12-41}$ (μg/μl)</th>
<th>Dependence</th>
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<tbody>
<tr>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>0.25</td>
<td>60</td>
</tr>
<tr>
<td>0.50</td>
<td>40</td>
</tr>
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</table>

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

**Water Responses**

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 –

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

![Graph showing Ethanol Responses](image)

- Ethanol Responses
- D-Phe-CRF$_{12-41}$ (µg/µl) vs. Number Ethanol Presses
- * p < 0.001 vs. same-dose, nondependent group

![Diagram showing brain regions](image)

- Water Responses
- D-Phe-CRF$_{12-41}$ (µg/µl) vs. Number Water Presses
Effect of CRF Antagonist D-Phe-CRF$_{12-41}$ – Nucleus Accumbens Shell –

Ethanol Responses

<table>
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<tr>
<th>D-Phe-CRF$_{12-41}$ (µg/µl)</th>
<th>Number Ethanol Presses</th>
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<tbody>
<tr>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>0.125</td>
<td>60</td>
</tr>
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From: Funk C, O’Dell LE and Koob GF, unpublished results.
CRF$_1$ Specific Antagonists

- **Antalarmin**
  - $K_i = 1.0$ nM
  - $c\text{LogP} = 7$

- **R121919 NBI-30775**
  - $K_i = 3.5$ nM
  - $c\text{LogP} = 4.8$

- **MJL-1-109-2**
  - $K_i = 1.9$ nM
  - $c\text{LogP} = 3$

- **DMP904 Analog**
  - $K_i = 10$ nM
  - $c\text{LogP} = 3.85$
CRF₁ Specific Antagonists
R121919

Ethanol Responses

<table>
<thead>
<tr>
<th>R121919 (mg/kg, s.c.)</th>
<th>Number Ethanol Presses</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
</tr>
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<td>60</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
</tr>
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- Dependent
- Nondependent

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

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<tr>
<th>R121919 (mg/kg, s.c.)</th>
<th>Number Water Presses</th>
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<tbody>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Kᵢ = 3.5 nM
cLogP = 4.8
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. CRF$_1$ 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

Koob Laboratory

## Post-Doctoral Fellows
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- Nick Gilpin
- Chitra Mandyam
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- Elena Crawford
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- Tess Kimber
- Yanabel Grant
- Ron Smith

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---

Special thanks to:
- Mike Arends  
  (Senior Research Assistant)
- Janet Hightower  
  (Biomedical Graphics Dept)
Neurobiology of Drug Addiction
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Floyd Bloom        Jean Rivier
Barbara Mason      Catherine Rivier
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Luis Stinus        George Siggins
Friedbert Weiss    Marisa Roberto
Athina Markou      Kenner Rice
Amanda Roberts     Kim Janda
Larry Parsons      Laura O’Dell
Pietro Sanna       Robert Purdy
Luigi Pulvirenti   Walter Francesconi
Eric Zorrilla      Sheila Specio
Wylie Vale         Marc Azar

Support from:
National Institute on Alcohol Abuse and Alcoholism
National Institute on Drug Abuse
National Institute of Diabetes and Digestive and Kidney Diseases
Pearson Center for Alcoholism and Addiction Research