Neurobiology of Addiction: Springboard to New Treatments

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“When people talk about drugs, they assume people take drugs because they enjoy it,” Williams told the Toronto Star. “But really, it's no different from overeating or watching too much television or drinking too much. You take drugs to make yourself feel better, to fill a hole.”

- Ricky Williams

-Byline Damien Cox, Toronto Star, May 29, 2006
Positive and Negative Reinforcement
—Definitions—

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

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

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

- ADDICTION
  - Persistent desire Larger amounts taken than expected
  - Tolerance Withdrawal Compromised social, occupational or recreational activities
  - Binge Intoxication
  - Negative Affect Withdrawal

Preoccupation Anticipation

- Preoccupation with obtaining Persistent physical/psychological problems

- ADDICTION
  - Persistent desire Larger amounts taken than expected
  - Tolerance Withdrawal Compromised social, occupational or recreational activities
  - Binge Intoxication
  - Negative Affect Withdrawal
Neurocircuitry of Addiction

Key Common Neuroanatomical Structures in Addiction

**Nucleus Accumbens**
Central Nucleus of the Amygdala — Forebrain structures involved in the **rewarding** effects of drugs of abuse and drives the binge intoxication stage of addiction. Contains key reward neurotransmitters: **dopamine and opioid peptides**

**Extended Amygdala** — Composed of central nucleus of the amygdala, bed nucleus of the stria terminalis, and a transition zone in the medial part of the nucleus accumbens. Contains “brain stress” neurotransmitter, **corticotropin releasing factor** that controls hormonal, sympathetic, and behavioral responses to stressors, and is involved in the **anti-reward** effects of drug dependence

**Medial Prefrontal Cortex** — neurobiological substrate for “**executive function**” that is compromised in drug dependence and plays a key role in facilitating relapse. Contains major **glutamatergic** projection to nucleus accumbens and amygdala
Existing and Future Medications for Addiction: Binge/Intoxication Stage

**Existing medications**
- disulfiram
- naltrexone
- methadone
- buprenorphine

**Future targets**
- partial agonists
- drug vaccines
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

Existing and Future Medications for Addiction: Binge/Intoxication Stage

Existing medications
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Future targets
- partial agonists
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Existing and Future Medications for Addiction: Withdrawal/Negative Affect Stage

**Existing medications**
- methadone
- buprenorphine
- varenicline

**Future targets**
- GABA modulators
- CRF₁ receptors
- κ opioid antagonists
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.

Protocol for Drug Escalation

1) Initial Training Phase
   - All Rats
   - 1-hr SA session
   - Fixed Ratio 1
   - 0.25 mg cocaine/injection

2) Escalation Phase
   - Short Access
     - 22 x 1-hr SA session
   - Long Access
     - 22 x 6-hr SA session

3) Testing Phase
   - Neuropharmacological probes

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

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
Extracellular DA and 5-HT in the Nucleus Accumbens During Cocaine Self-Administration and Withdrawal

Effect of $\alpha$-flupenthixol on Cocaine Self-Administration in Escalated and Non-Escalated Animals

Dopamine Partial Agonists

Aripiprazole

CAS# 129722-12-9

Lisuride

SDZ 208-911

Terguride

CAS# 18016-80-3

CAS# 120478-64-0

CAS# 37686-84-3
Partial Agonists:
Hypothesized Mechanism of Action

- Normal Conditions
- Exposure to Drug
- Drug Withdrawal

○ = reward neurotransmitter
△ = partial agonist

With Partial Agonist

- "Normalized" Response
- "Normalized" Response

- Stimulated Response
- Reduced Response
Dopamine Partial Agonist Terguride in Reverses Motivational Withdrawal following Chronic Amphetamine

Escalation of Methamphetamine Self-administration in Rats

Effects of Aripiprazole on Methamphetamine Self-administration (0.05 mg/kg/inf progressive-ratio)

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

Effect of Partial Opioid Agonist Buprenorphine on Heroin Self-Administration in Rats

Existing and Future Medications for Addiction: Withdrawal/Negative Affect Stage

**Existing medications**
- methadone
- buprenorphine
- varenicline

**Future targets**
- GABA modulators
- CRF₁ receptors
- κ opioid antagonists
Anti-Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

↑ Dynorphin … “dysphoria”

↑ CRF … stress

↑ Norepinephrine … stress

↓ NPY … anti-stress
CNS Actions of Corticotropin-Releasing Factor (CRF)
Major CRF-Immunoreactive Cell Groups and Fiber Systems in the Rat Brain

<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>
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
Withdrawal-induced Increases in Extracellular Levels of CRF

Ethanol Withdrawal
- Basal
- 2-4 h
- 6-8 h
- 10-12 h
- Ethanol withdrawal group
- Control group

Cannabinoid Withdrawal
- Injection
- HU-210
- HU-210 + SR 141716A

Cocaine Withdrawal
- Basal
- 12 h Cocaine SA Session
- 12 h Cocaine Withdrawal Session
- Control group
- Cocaine group

Opiate Withdrawal
- Morphine
- Morphine + Naltrexone
- NTX

Nicotine Withdrawal
- Non-dependent
- Nicotine dependent
- Vehicle
- Mesamycinamine

Rodent model of excessive drinking during withdrawal

*(Roberts et al 1996, 2000; O’Dell et al 2004)*

**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
Enhanced Ethanol Self-Administration During Withdrawal in Dependent Animals

From: Funk C and Koob GF, unpublished results.

Pre-vapor Responding

Post-vapor Responding

From: Funk C and Koob GF, unpublished results.
CRF₁ Specific Antagonists

MPZP

Ethanol Responses

![Bar graph showing ethanol presses vs. MPZP dosage.]

- Dependent
- Nondependent

MPZP (mg/kg, s.c.)

0 5 10 20

Number Ethanol Presses

* p < 0.001 vs. same-dose, nondependent group
# p = 0.002 vs. dependent, vehicle group

Water Responses

![Bar graph showing water presses vs. MPZP dosage.]

MPZP (mg/kg, s.c.)

0 5 10 20

Number Water Presses

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

**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>80 (*)</td>
</tr>
<tr>
<td>0.25</td>
<td>60 (*)</td>
</tr>
<tr>
<td>0.50</td>
<td>40 (#)</td>
</tr>
</tbody>
</table>

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

**Water Responses**

## Role of Corticotropin-releasing Factor in Dependence

<table>
<thead>
<tr>
<th>Drug</th>
<th>CRF antagonist effects on withdrawal-induced anxiety-like responses</th>
<th>Withdrawal-induced changes in extracellular CRF in CeA</th>
<th>CRF antagonist effects on dependence-induced increases in self-administration</th>
<th>CRF antagonist reversal of stress-induced reinstatement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Opioids</td>
<td>↓*</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ethanol</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Nicotine</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Δ⁹-tetrahydrocannabinol</td>
<td>↓</td>
<td>↑</td>
<td>nt</td>
<td>nt</td>
</tr>
</tbody>
</table>

* = aversive effects with place conditioning. nt = not tested. CeA = central nucleus of the amygdala.
Positive Reinforcement

Negative Reinforcement

Dependent
Existing and Future Medications for Addiction: Withdrawal/Negative Affect Stage

Existing medications
• methadone
• buprenorphine
• varenicline

Future targets
• GABA modulators
• CRF₁ receptors
• κ opioid antagonists
Existing and Future Medications for Addiction: Preoccupation/Anticipation “Craving” Stage

Existing medications
- acamprosate
- bupropion

Future targets
- homeostatic resetters (GABA modulators)
- stress reducers (CRF₁ antagonists)
- habit reducers (glutamate modulators)
Craving-Type 1

• “Craving”- induced by stimuli that have been paired with ethanol self-administration such as environmental cues

• An animal model of craving- type 1 is cue induced reinstatement where a cue previously paired with access to ethanol reinstates responding for a lever that has been extinguished.

• Neurobiological substrates include glutamatergic projections from medial prefrontal cortex and basolateral amygdala to nucleus accumbens
Craving-Type 2

• State of protracted abstinence in alcoholics weeks after acute withdrawal.

• Conceptualized as a state change characterized by anxiety and dysphoria or a residual negative affective state that combines with Craving-Type 1 situations to produce relapse to excessive drinking.

• Animal models of Craving-Type 2 include stress-induced reinstatement, or increased drinking in animals after a prolonged deprivation (Alcohol Deprivation Effect).

• Neurobiological substrates include residual activation of brain stress systems including corticotropin releasing factor and norepinephrine in the extended amygdala.
Neurobiological Effects of Exposure to Drug-Associated Contextual Stimuli

Daily Sessions of Self-Administration

Reinstatement

<table>
<thead>
<tr>
<th></th>
<th>SA</th>
<th>EXT</th>
<th>S⁻</th>
<th>S⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Responses 30 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effects of mGlu$_{2/3}$ Agonist LY379268 on Stress- and Cue-induced Reinstatement of Ethanol-seeking Behavior in Rats

Effects of D-Phe-CRF$_{12-41}$ and Naltrexone on Stress- and Cue-Induced Reinstatement of Ethanol-Seeking

Existing and Future Medications for Addiction: Preoccupation/Anticipation “Craving” Stage

Existing medications
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• homeostatic resetters (GABA modulators)
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Key Findings and Conclusions

Addiction — loss of control over drug intake and compulsive drug taking driven by elements of impulsivity and compulsivity that are mediated by separate but overlapping neurocircuitry

Acute rewarding effects of drugs of abuse — are mediated by neurochemical elements such as dopamine and opioid peptides in the nucleus accumbens and amygdala

Acute withdrawal from all major drugs of abuse — produces increases in reward thresholds, increases in anxiety-like responses and increases in CRF in the amygdala that are of motivational significance

Compulsive drug use associated with dependence — is mediated by not only loss of function of reward systems but recruitment of brain stress systems such as corticotropin releasing factor, norepinephrine and dynorphin in the extended amygdala

Brain-arousal stress systems in the extended amygdala — may be key components of not only for the negative emotional states that drive dependence on drugs of abuse but also may overlap with the negative emotional components of other psychopathologies
Allostatic View of Neurotransmitter Adaptation During the Transition from Drug Use to Addiction

# Neurobiology of Drug Addiction

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