N-Acetylcysteine Prevents Nicotine Relapse Associated Synaptic Plasticity

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Addiction treatment strategies

Pharmacotherapeutic Interventions

Psychosocial interventions

Replacement Therapies

Restoring control (NAC, Ceftriaxone, Etc.)
Preclinical Model of Relapse
Cues

• Individuals become sensitive to environmental stimuli that acquire motivational salience through repeated associations with self-administered drugs, including cocaine and nicotine

• In preclinical models, these cues enhance drug self-administration and can trigger motivation to seek drugs

How do drug-paired cues influence the neurobiology of addiction?

O’Brien (2003); Gipson & Beckmann (in press), Current Beh Neurosci Reports
Circuitry Involved in Relapse

- Glutamatergic projection
- Dopaminergic projection

Diagram showing connections between PFC, NAcc, AMG, and VTA.
Nicotine Self-Administration and Cue-Induced Reinstatement

A

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Food</th>
<th>Recovery</th>
<th>Nicotine Self-administration</th>
<th>Yoked Saline</th>
<th>Extinction</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>-9</td>
<td>-8</td>
<td>-7 to 0</td>
<td>1-14</td>
<td></td>
<td>15-28</td>
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<tr>
<td></td>
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<td>Day</td>
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B

- Inactive
- Active

C

Lever Presses (2 hr)

- Inactive
- Active

Nicotine Self-Administration
0.02 mg/kg/infusion

Day

Extinction
Cue

*
Cue-Induced Reinstatement: A within-session extinction curve
Nucleus Accumbens Core Glutamate Overflow During Cue-Induced Nicotine Seeking

**A**
Cue-Induced Reinstatement

- **Active**
- **Inactive**
- **Ext**
- **Yoked**
- **Saline**
- **Nicotine**
- **SA**

**B**
Active Lever Presses

- Time (min)

**C**
Glutamate (% change)

- Nicotine
- Saline

Gipson et al., 2013; *PNAS*
Nucleus Accumbens Core: Relapse Vulnerability

Gipson et al., 2013; Neuropharmacology
Long term potentiation (LTP) and long term depression (LTD) provide measures of changes in synaptic strength.

Scofield*, Gipson*, et al., in preparation, Pharmacological Reviews
Spine Morphology: Dil and 3-D reconstruction

Haowei Shen
Conclusion: Cue-induced cocaine relapse induces rapid, transient increases in spine diameter in accumbens core

Gipson et al. 2013, Neuron
Rapid Spine Head Enlargement in NAcore in Cue-Induced Nicotine Seeking

Conclusion: Cue-induced nicotine relapse induces rapid, transient increases in spine diameter in accumbens core

Gipson et al. 2013, PNAS
AMP A/NMDA Ratio

- The ratio of AMPA receptor- to NMDA receptor-mediated excitatory postsynaptic currents (EPSCs)

- Surrogate measure of synaptic strength
Rapid NAcote Synaptic Potentiation During Cue-induced Nicotine-Seeking

Gipson et al. (2013), PNAS
Alterations in AMPA and NMDA receptor subunits and GLT1 in nicotine withdrawal

Gipson et al., 2013, PNAS
Withdrawal from nicotine reduces sodium dependent glial glutamate transport (GLT1)
Nucleus Accumbens Core: Relapse Vulnerability

Gipson et al., 2013; *Neuropharmacology*
N-Acetylcysteine (NAC)

- NAC is an FDA-approved antioxidant that upregulates GLT-1 and increases activity of the cystine-glutamate exchanger.

- Potential uses of NAC
  - Obsessive-compulsive disorders, Schizophrenia, Bipolar, Addiction, etc. (Berk et al., 2013; McClure, Gipson et al., 2014)

- High safety/tolerability profile, shown some clinical efficacy in treatment of cocaine, cannabis, and nicotine dependence
NAC Attenuates Nicotine Cue-Dependent NAc core Rapid Synaptic Plasticity

Gipson et al., in preparation

Michael Scofield
Nic Allen
Neringa Stankeviciute
NAC Attenuates Nicotine Cue-Dependent NAc core Rapid Synaptic Plasticity

Gipson et al., in preparation
NAC Restores Na+-Dependent Glial Glutamate Uptake After Nicotine

Gipson et al., in preparation
Summary: NAC and GLT1

- N-Acetylcysteine (NAC) increases GLT1 expression.
- GLT1 blocks extrasynaptic GluN2B receptors.
- This leads to an increase in N-Acetylcysteine (NAC) levels in glial cells.
- NAC and GLT1 work together to regulate glutamate transport and function in synapses.
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