Decreased Excitability of Prelimbic Pyramidal Neurons Induced by Extended Cocaine Self-administration Contributes towards Compulsive Drug Seeking

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The role of prelimbic pyramidal neurons in compulsive cocaine seeking

NIDA Mini-Convention
Frontiers in Addiction Research

Billy T. Chen
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Addiction

- Drugs of abuse are thought to usurp normal learning and memory processes.

- Addiction is a series of transition starting from initial use, where drugs have hedonic effects, and evolving into habitual and ultimately compulsive behavior.

- This is hypothesized to result from loss of inhibitory control over drug-seeking behaviors.
Different brain regions are implicated in the development of addiction.

Koob and Volkow, 2010
Drug-induced hypofrontality

Reduced basal activity in prelimbic cortex (rat)

Sun and Rebec 2006
Aims of study

1. Does long-term (compulsive) cocaine self-administration induce hypofrontality in the PFC?

2. How do changes in neuronal activity in the PFC contribute towards compulsive drug use?
Can we model compulsive drug use in rodents?

Compulsion: Drug use is continued despite incurring negative consequence.

Pelloux et al. 2007, Psychopharm.
Modified self-administration paradigm

1. Rats are trained to self-administer cocaine on a seek-take chain schedule
2. Rats are trained to self-administer cocaine on a seeking-taking chain schedule with progressively longer Random Interval schedule.
### Behavior paradigm (cont.)

<table>
<thead>
<tr>
<th>2 months</th>
<th>Seek-take task</th>
<th>Extended (80 inf)</th>
<th>Seek-take baseline</th>
<th>ChR2</th>
<th>Punishment (Shock)</th>
<th>ChR2</th>
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<tbody>
<tr>
<td></td>
<td>Seek-take</td>
<td>With seek-take interspersed</td>
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**Seek-take task**
- **RI 60sec**
- **Seek**
  - 30%
- **Take**
- **Cocaine**
Cocaine seek-take
Addicted rat
Non-compulsive and compulsive groups

**Punishment sensitive**

- **Seek lever presses**
  - Decrease in lever presses over sessions.
  - Error bars indicate variability.

- **Reinforcers earned**
  - Decrease in reinforcers over sessions.
  - Error bars indicate variability.

**Punishment-resistant**

- **Seek lever presses**
  - Decrease in lever presses over sessions.
  - Error bars indicate variability.

- **Reinforcers earned**
  - Decrease in reinforcers over sessions.
  - Error bars indicate variability.
Hypofrontality in prelimbic neurons after long-access cocaine self-administration

*In vivo* whole-cell recording in anesthetized rat, targeting prelimbic region
Long-access to cocaine decreases excitability of deep-layer cortical neurons
Resistant rats have lower Input resistant
More current is needed to evoke action potential in mPFC neurons from Resistant rats.
Augmenting activity in the prelimbic area
Channelrhodopsin-expressing mPFC neurons exhibit robust photo-excitation
In vivo photo-stimulation

Optrode recording

-1.0 mm
-3.5 mm
1 Hz stimulation during Seek chain
Activation of prelimbic neurons prior to punishment has no effect on the rat’s drug-seeking behavior.
Photostimulation of mPFC decreases compulsive cocaine seeking
What happens after the rats learned that they might be shocked?

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![Bar chart](chart.png)

- **Latency to seek**
  - No ChR2: 50
  - ChR2: 200

- **Avg. Lever presses / trial**
  - No ChR2: 7.5
  - ChR2: 2.5
Conclusion

- Rats with a history of long-term cocaine use exhibit hypofrontality in the prelimbic region of the PFC.
Conclusion

- *Rats with a history of long-term cocaine use exhibit hypofrontality in the prelimbic region of the PFC.*

- Introducing negative consequence (cost) reveals the role of mPFC in mediating inhibitory control over unwanted behaviors.
Conclusion

- Rats with a history of long-term cocaine use exhibit hypofrontality in the prelimbic region of the PFC.

- Introducing negative consequence (cost) reveals the role of mPFC in mediating inhibitory control over unwanted behaviors.

- Photo-stimulation of prelimbic region decreases compulsive cocaine-seeking behavior.
Addiction: loss of willpower to resist drugs

Impulsive
- VTA
- Amygdala
- Striatum/Accumbens

Reflective
- mPFC
- Orbital cortex
- Insula
Addiction: loss of willpower to resist drugs

Prolong drug use

Impulsive
VTA
Amygdala
Striatum/Accumbens

Reflective
mPFC
Orbital cortex
Insula
Addiction: loss of willpower to resist drugs

Therapeutic approach

Impulsive
VTA
Amygdala
Striatum/Accumbens

Reflective
mPFC
Orbital cortex
Insula
Addiction: loss of willpower to resist drugs

Impulsive
- VTA
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