Extended access to cocaine self-administration results in reduced glutamate function within the medial prefrontal cortex


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Research heavily interested in cocaine abuse, and the transition from recreational to compulsive cocaine user.
Has published numerous papers studying the neurochemical changes in the brain

Authors

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Dr. Kevin Lominac
Was a graduate student at the time of the research, but is currently a post-doctoral fellow at the University of Texas.
He constructed the probes and helped with the microdialysis samples.

Dr. Ami Cohen
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Played role in animal data collection and critical revisions

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Lab Assistants and Technicians

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Undergraduates

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Addiction Biology
Produced by the Society for the study of Addiction
Impact factor 4.833
Number 1 ranking for substance abuse Journals
produced quarterly
Question

In your opinion what is addiction?

Cocaine Addiction

Addiction is a relapsing disorder which is characterized by compulsive drug seeking behavior that occurs due to a loss of control over drug intake. (Kasanetz et al., 2012)

DSM IV-TR has two classifications for substances of abuse: Abuse and Dependence.

Estimated about 21 million people use cocaine

Cocaine abuse is a consistent health problem that has no approved pharmacological treatment.

Cocaine Addiction and the Brain

• The brain regions involved: Hippocampus, amygdala, striatum, Nucleus accumbens, basal ganglia, medial prefrontal cortex, VTA
• Play a role in both memory, and reward functions
• vmPFC deterioration and role in loss of control.

Cocaine’s Action on Dopamine

Location: Nucleus accumbens = Reward

Dopamine (DA)

Two Major families of DA receptors:
D₁-like family (D₁ and D₅)
D₂-like family (D₂-D₄)
This paper focuses on D₂ receptors

Mesolimbic DA pathway

Glutameric: Blue
Dopaminergic: Red
GABAergic: Orange
Orexinergic: green
Glutamate Plays a major role in learning and memory.
Known to play a role in the behavioral changes
NMDA is a very important receptor, and there are many different changes that occur in both
the Nac and VTA.
Cocaine does not directly act on glutamate receptors or its transporters.

How can you determine if someone is a recreational user or a chronic user?

Purpose
To monitor extracellular glutamate and dopamine content within the mPFC at different conditions.

Methods
Albino Sprague Dawley rats
Food Training
Surgery and recovery
Cocaine Self-Administration
Microdialysis

Surgery
Catheter implantation
Stereotaxic
1.2.3- show NT, modulators, neural peptides
3,4- nueroglial interaction (occurs with Glu, GABA IL)
5- second messengers (cAMP..)
6- Blood capillary molecules (glucose, drugs..)
7- neurovasuclar
8- CSF transport

Experiment 1 - Glutamate and Dopamine concentration in the mPFC during Self-administration

Cocaine-induced changes in glutamate content in mPIC

- Significant change due the drug, and not random chance

Glu is shown to decrease in the naive rats, and not in the brief access group or the extended access group.
Cocaine induced rise in Dopamine content within the mPFC

DA levels are increased in last brief access group, and all other levels we not significantly different.

Cocaine induced changes in Dopamine content in mPFC

No significant difference between sessions

Based on a t-test there was a significant difference in DA levels for first 6hr, but not for last 6hr.

10 sessions of extended access to cocaine diminished the ability of cocaine to increase DA levels over the entire 6hr session.

Experiment 2- Basal glutamate and dopamine concentration in the mPFC following various exposures

Basal Concentrations of Glutamate within the mPFC

A history of excessive cocaine intake reduces basal extracellular mPFC glutamate concentration

Basal Concentrations of Dopamine within the mPFC

The data shows that while a history of cocaine intake under brief access conditions reduces basal mPFC DA concentration, this effect normalizes with excessive cocaine intake.

Discussion- Experiment 1

Brief access animals that had 17 days of coc. SA demonstrated increased DA levels.

Extended access animals displayed the increase in DA in the first extended access session but not the last.

10 days of extended access to cocaine lowered both baseline DA and Glu levels compared to all other conditions.
Discussion- Experiment 2

Glu but not DA displayed significant changes compared to baseline levels 24 hrs after the 10th extended access day. DA displayed significant decreases in all other conditions 24 hours after.

Conclusions

Cocaine SA altered both Glu and DA within the mPFC. The nature of the alterations were dependent on the length of access to cocaine and the amount of intake. It was hypothesized that the decrease in basal Glu levels could be the result of an increase in DA levels in the extended access group which would inhibit the release of Glu.

Relation to Humans

The inability of cocaine to elucidate the release of DA in the extended access group after 10 days indicates why it is difficult for humans to reach the same level of reward. The loss in baseline Glu in mPFC leads to the impulsivity and the loss of control which results in addiction. This loss of control or loss of ability to learn can play a role in relapse, and is likely the cause of no pharmacological agent.

Brain Pathways

Glutameric- Blue
Dopaminergic- Red
GABAergic- orange
Orexinergic- green

Thought questions

How do you define Addiction in your own words? And how does this definition differ from the authors view?
What model did the authors use as their basis for drug addiction?
When comparing repeated extended- and brief- access to cocaine self-administration what effects did it have on dopamine release when animals self-administered cocaine. What are the potential comparisons to humans with cocaine use?
What effects did cocaine have on the glutamate and dopamine levels within the mPFC?
Thank you
Any Questions?