Reducing Astrocyte Calcium Signaling in the Nucleus Accumbens Increases Cocaine Self-administration behavior

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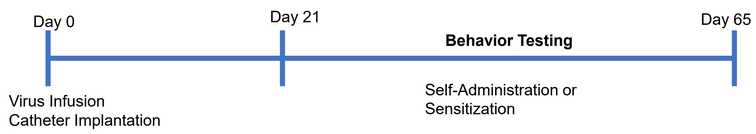
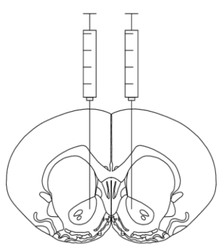
Introduction:

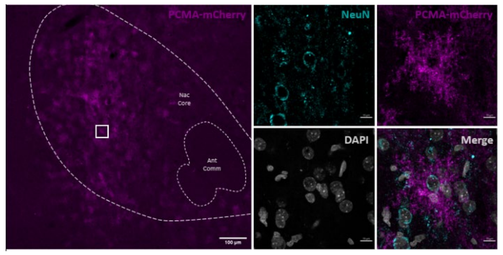
- Accumulating evidence demonstrates that astrocytes are affected by drugs of abuse and may underlie pathology of substance use disorders.
- Under normal conditions, astrocytes sense neural transmission and modulate neural signaling via their intracellular calcium signaling cascades.
- The nucleus accumbens (NAc), a critical node in the brain's reward circuitry, is particularly susceptible to drug induced astrocyte pathology. Previously, our lab has found rat cocaine self-administration is associated with long-lasting changes in astrocyte structure and activity (Kim et al., 2022).
- However, exactly how astrocyte signaling dynamics influence active drug taking and drug seeking behavior are still unknown. Moreover, little is known about how astrocyte signaling may impact other drug related behaviors.

Thus, aim of this study is to determine the effects of NAc astrocyte calcium depletion on behavioral responses to cocaine, using both sensitization and self-administration models

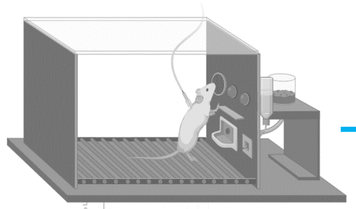
Methods:



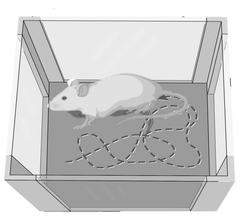




Infused directly into the NAc core:
AAV-GfaABC1D-mCherry-hPMCA2w/b ("**CalEx**") or
AAV-GfaABC1D-Lck-mCherry ("**Lck**")



Self-Administration:
Male rats were placed in an operant box and food trained to lever press. After food training, rats underwent 10 days of long access (6h/d) cocaine self-administration (.75 mg/kg/infusion)



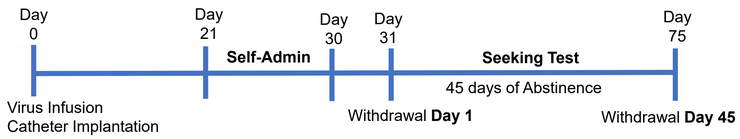
Behavioral Sensitization

Test Day 1 & 7: Male rats were placed in locomotor chambers and activity was monitored. After 30 minutes, rats received an IP injection of cocaine (15 mg/kg) and activity was monitored for 2 hours.

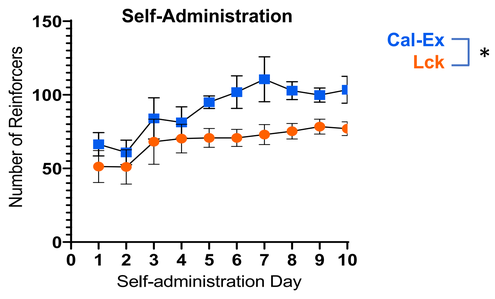
Days 2-6: Male rats received IP injections daily in their home cages (20mg/kg).

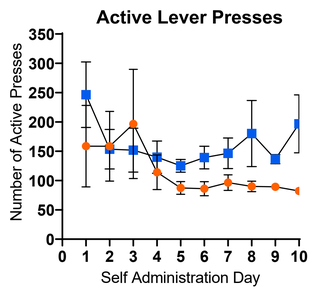
Results:

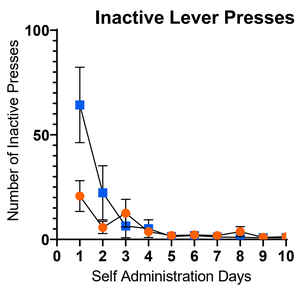
A. Cal-Ex increases drug taking but not seeking behavior



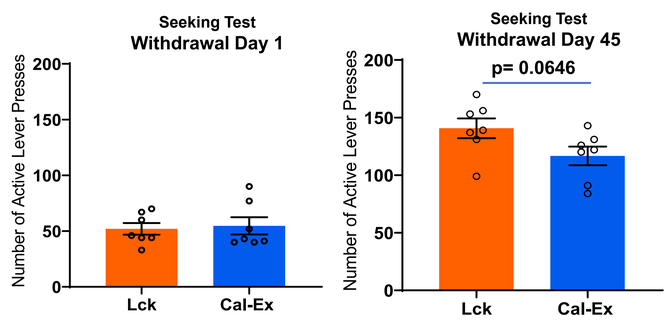
Drug-Taking Behavior



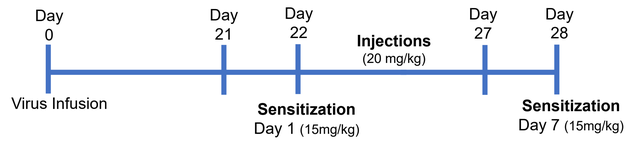




Drug-Seeking Behavior

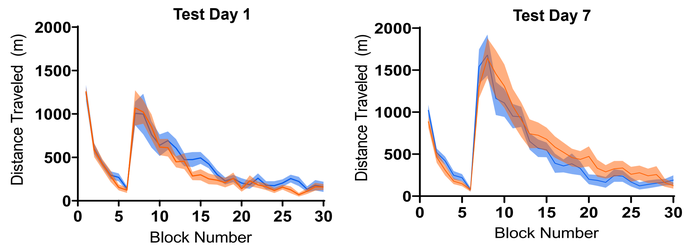


B. Cal-Ex does not change cocaine induced behavioral sensitization

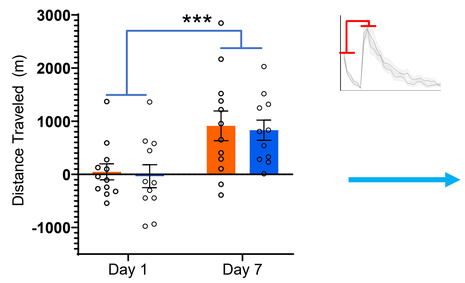


Cocaine Induced Behavioral Sensitization

Changes in locomotor activity

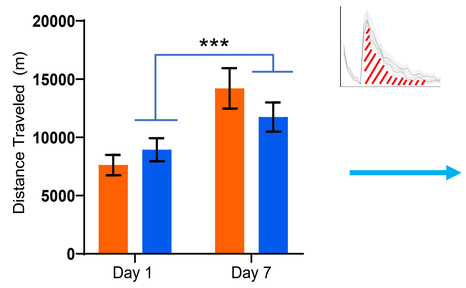


Magnitude of Sensitization:



Quantification of peak locomotor response to cocaine minus peak baseline activity

Area Under the Curve After Cocaine:



Quantification for total locomotor response to cocaine

Conclusions & Future Directions:

A. **Silencing astrocytes in the NAc alters drug-taking, but not seeking, behavior.** *This data suggests that astrocytes are critical to the on-demand neural signaling during drug use.*

B. **We found no difference in behavioral sensitization in Cal-Ex treated rats.** *This indicates that the actions of astrocytes may be specific to drug related behaviors*

Our data highlights the divergent roles of astrocytes during drug taking and seeking behaviors. Future experiments will investigate how astrocytes contribute to each of these processes.

We still don't know how astrocyte Ca2+ signaling alters reward processing in the NAc. Do astrocytes regulate behavior differently in contingent vs. non-contingent drug use paradigms? Are astrocytes critical for reward valuation of drugs of abuse?

Acknowledgements:

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