Impact of cocaine sensitization on GLT1 protein levels in the medial Prefrontal Cortex and Nucleus Accumbens Core

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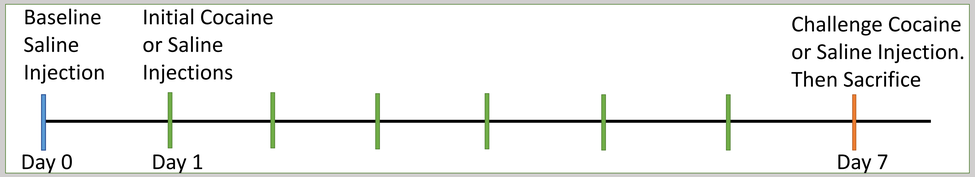
Background

- Deaths due to overdoses on cocaine, an addictive stimulant, have doubled between 2011 and 2016.[1]
- Cocaine targets reward circuit components like the medial prefrontal cortex (mPFC) and nucleus accumbens core (NAcC).
- The mPFC communicates with the NAcC via glutamatergic projections, which regulates reward-seeking behavior.[2]
- Cocaine self administration downregulates glutamate transporter 1 (GLT1) gene expression, causing a decrease in the regulation of reward seeking behaviors like cocaine seeking.[3]
- This study's goal is to assess GLT1 protein levels following cocaine sensitization in the mPFC and NAcC

Methods



- Above is a timeline for sensitization and tissue collection
- On day 0 all rats were given a saline injection (blue). On day 1- 6 rats were given injections of 15 mg/kg cocaine or saline (black). On day 7, rats received a challenge injection of saline or cocaine (orange).
- Rats were divided into groups based on the initial and challenge injections they received: cocaine & cocaine (c-c), cocaine & saline (c-s), saline & cocaine (s-c), saline & saline (s-s).
- Locomotion of rats was tracked for forty-five minutes following daily injections. On the 7th day, brain tissue from the mPFC and NAc core was extracted, and western blots were run
- Protein levels in the P2 synaptosome fraction were quantified
- We hypothesize that group c-c will have the lowest GLT1 protein levels and group s-s will have the highest GLT1 levels

Results

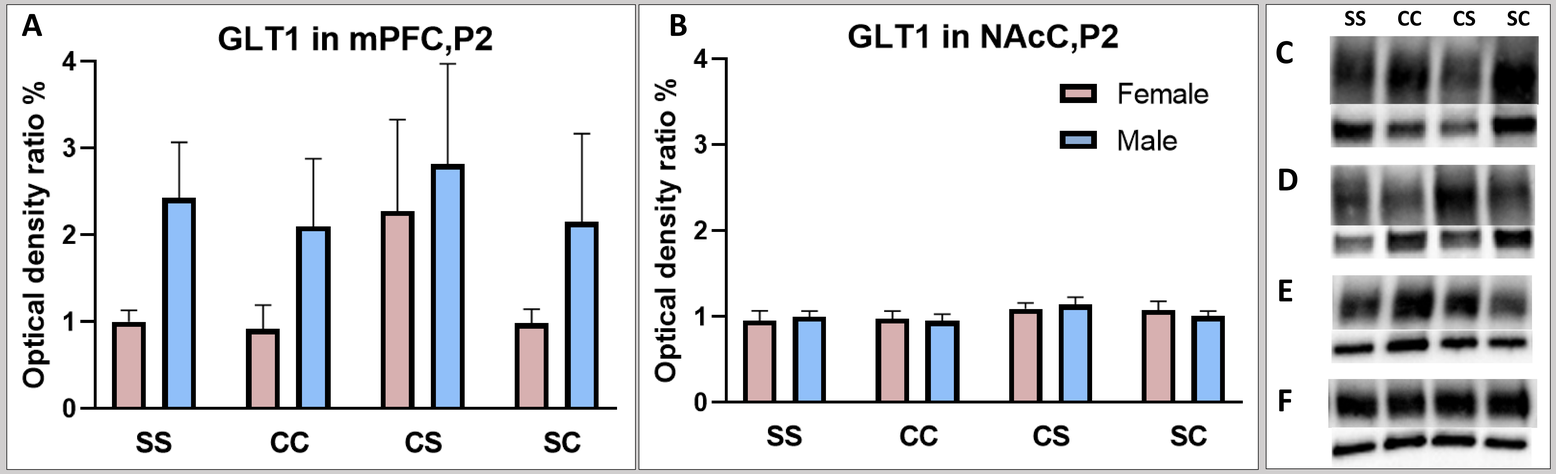


Figure 1: GLT1 protein levels in P2 fraction of the (A) mPFC and (B) NAcC in male and female rats where n=5-6 per sex per group. (C) GLT1 (top) & control N-Cadherin (bottom) western blot bands from mPFC of male rats and (D) female rats. (E) GLT1 (top) and N-Cadherin (bottom) bands from NAcC of male rats and (F) female rats.

Discussion

- Two-way ANOVAs revealed there was no significant difference in GLT-1 levels between the treatment groups in mPFC and NAcC.
- Self administration and experimental administration (sensitization) could have different effects on GLT1.
- The difference in length of administration for self administration and cocaine sensitization could account for the different impacts on GLT1 levels.
- The data suggests there could be a sex difference between mPFC GLT1 levels. We will repeat this experiment with a higher sample number to see if that yields significant results.
- We will also look into the outlying samples to see if there is a reason for their especially high or low GLT1 levels.

References:

1) Hedegaard H, Bastian B, Trinidad J, Spencer M, Warner M (2018) Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011–2016. National Vital Statistics reports Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_09-508.pdf [Accessed April 9, 2022].
2) Schmidt HD, Pierce RC (2010) Cocaine-induced neuroadaptations in glutamate transmission: Potential therapeutic targets for craving and addiction. Annals of the New York Academy of Sciences Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5413205/ [Accessed May 27, 2022].
3) Kim R, Sepulveda-Orengo MT, Healey KL, Williams EA, Reissner KJ (2018) Regulation of glutamate transporter 1 (GLT-1) gene expression by cocaine self-administration and withdrawal. Neuropharmacology Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5714670/ [Accessed March 16, 2022].