A Paradoxical Role of Amygdalar GLP-1 Signaling on Drug-Seeking Behavior

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INTRODUCTION

Cocaine is a widely abused illicit drug and recent epidemiological data indicate that the prevalence of cocaine use is increasing. Despite cocaine use disorder being a major public heath concern and years of research, there currently exists no FDA-approved pharmacotherapies to reduce the rate of cocaine relapse in individuals suffering from the disorder. Thus, further exploration of the neurobiological mechanisms underlying relapse is imperative.

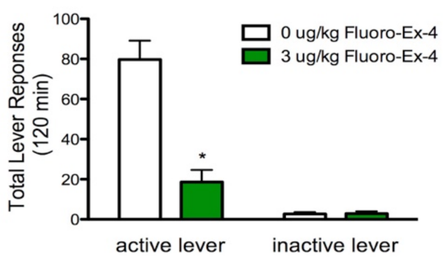
Glucagon–like peptide-1 (GLP-1), an endogenous modulator of the mesolimbic reward system, plays an important role in regulating food intake in both human and animal models. Growing preclinical evidence suggests that activation of GLP-1 receptors (GLP-1Rs) may serve as potential molecular targets for novel pharmaceutical interventions aimed at preventing cocaine craving induced-relapse. Specifically, previous work from our lab showed that systemic administration of the GLP-1R agonist exendin-4 (Ex-4) attenuated the reinstatement of cocaine-seeking behavior, an animal model of relapse. This indicates that activation of GLP-1Rs reduces the rewarding effects of drugs of abuse and attenuates drug-seeking behavior during abstinence.

In contrast, our preliminary data show that acute activation of GLP-1Rs in the central nucleus of the amygdala (CeA) augments the ability of a priming injection of cocaine to reinstate drug-seeking behavior during abstinence.

The overarching goal of this study is to further examine the role of CeA GLP-1 signaling in cocaine-mediated behaviors. That is, we plan to verify our preliminary data, determine if inhibition of endogenous GLP-1 signaling in the CeA is sufficient to reduce cocaine seeking, and identify potential downstream targets of the CeA GLP-1 pathway.

PRELIMINARY DATA

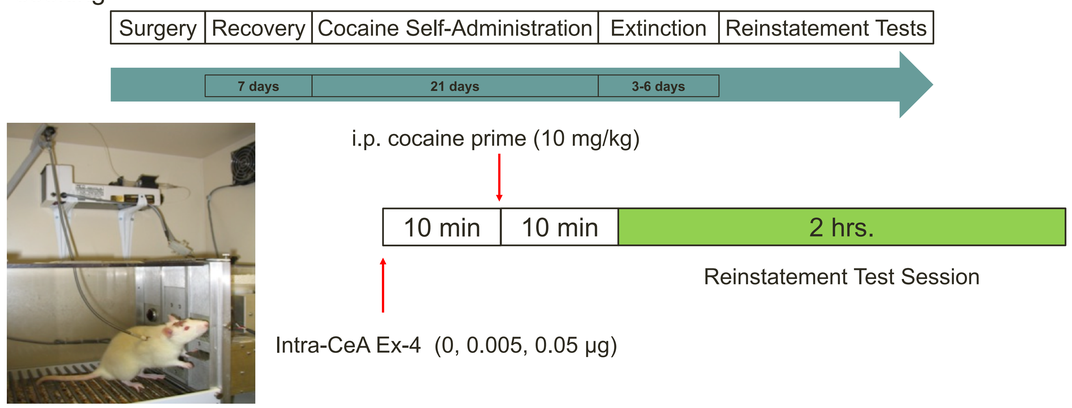
Systemic administration of GLP-1 receptor agonist Exendin-4 attenuates cocaine-seeking behavior



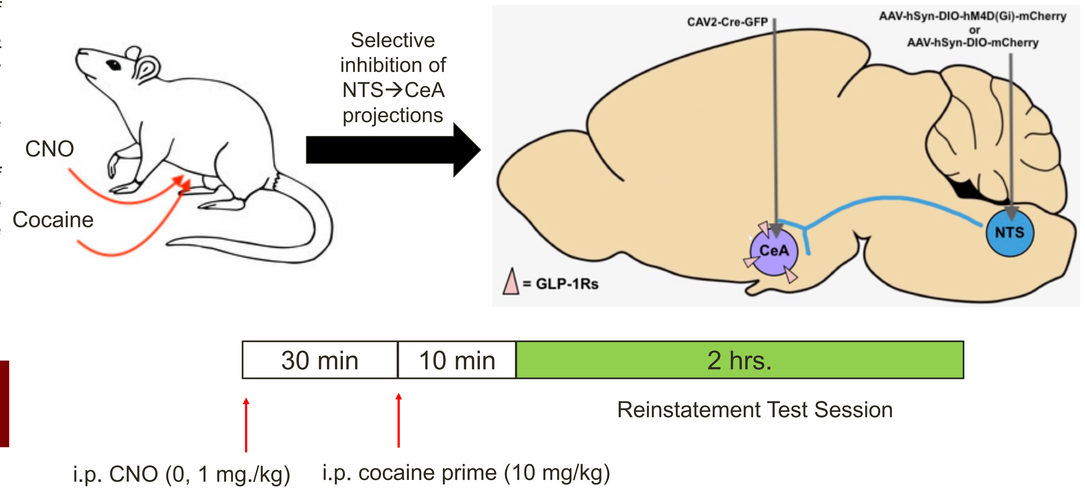
Hernandez et al., unpublished

METHODS AND MATERIALS

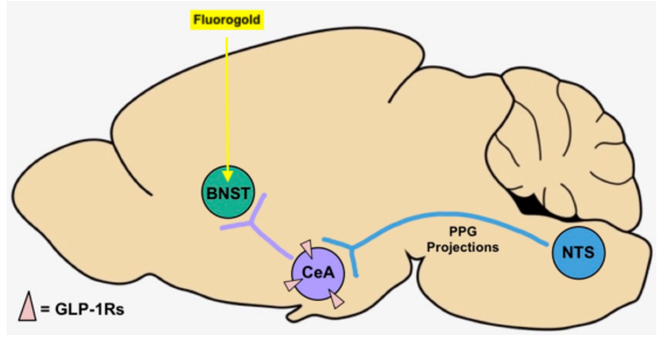
Experiment 1: Examine the behavioral pharmacology of Exendin-4 in the CeA on cocaine seeking



Experiment 2: Determine if inhibiting endogenous NTS→CeA GLP-1 circuits is sufficient to attenuate cocaine seeking

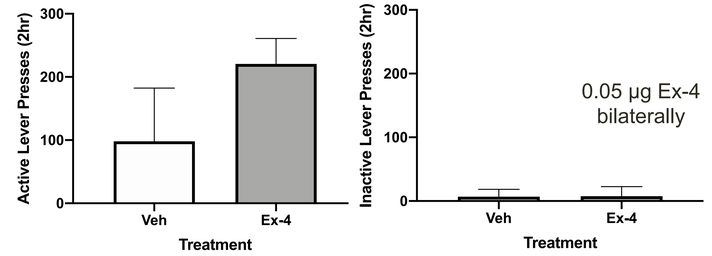


Experiment 3: Identify downstream targets of GLP-1R-expressing CeA neurons



RESULTS

Intra-CeA Exendin-4 microinjections potentiate cocaine-seeking behavior during abstinence induced by re-exposure to cocaine and conditioned cues



SUMMARY AND CONCLUSION

- Activation of GLP-1Rs in the CeA potentiates cocaine seeking during abstinence.
- These unexpected findings suggest that central GLP-1 signaling has *differential* roles in motivated behaviors depending on the circuits studied and thus opens a vast new area of research in addiction neuroscience.
- **Perhaps there exists one mechanism by which cocaine promotes *both* drug-seeking behavior and anxiety through increased GLP-1 signaling in the CeA.**
- Further exploration of this paradoxical circuitry is critical toward developing a therapeutic intervention that targets central GLP-1 circuits to reduce cocaine craving-induced relapse.

FUTURE DIRECTIONS

- **GLP-1 and cocaine are *both* anxiogenic and anxiety promotes cocaine-seeking behavior. Furthermore, CeA GLP-1 signaling promotes anxiety and these preliminary data suggest CeA GLP-1 signaling promote cocaine-seeking behaviors as well. Thus, it is possible that CeA GLP-1 signaling mediates stress-induced cocaine seeking.**
- Verify the role of GLP-1 is the NTS→CeA pathway by selectively activating the projections via an excitatory DREADD and intra-CeA microinjections of Exendin-9.
- Further investigation of the proposed CeA→BNST pathway. Perhaps inhibition of this pathway can attenuate the negative anxiogenic effects of cocaine that potentiate cocaine seeking.
- Explore the role of stress in this system. Do other stressors potentiate cocaine-seeking behavior through CeA GLP-1 signaling?
- Explore other structures implicated in both anxiety and drug circuitry, such as the BLA.

ACKNOWLEDGEMENTS

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