GLP-1 receptor agonism reverses the effects of cocaine on neural dynamics of VTA dopamine neurons

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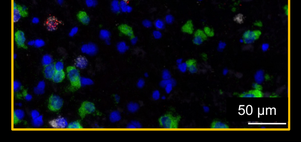
INTRODUCTION

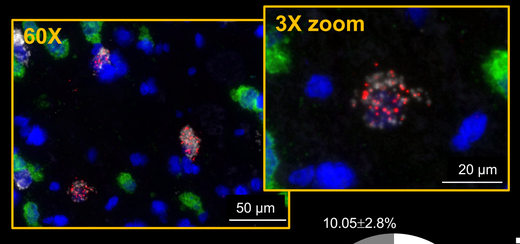
- Despite significant morbidity and mortality burdens, there are still no medications available to treat cocaine use disorder. The development of effective pharmacotherapies requires an improved understanding of the neurobiological mechanisms underlying cocaine use and relapse.
- Our lab has identified a novel role for glucagon-like peptide-1 receptors (GLP-1Rs) in the ventral tegmental area (VTA) in reducing cocaine taking and seeking in rats.
- Here, we investigated the cell-type specific effects of GLP-1R activation on cocaine-induced changes in Ca^{2+} transients.

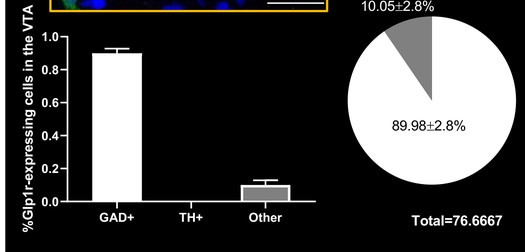
BACKGROUND



Fluorescence in situ hybridization (FISH)

- GLP-1Rs are primarily expressed in GABA neurons in the VTA.

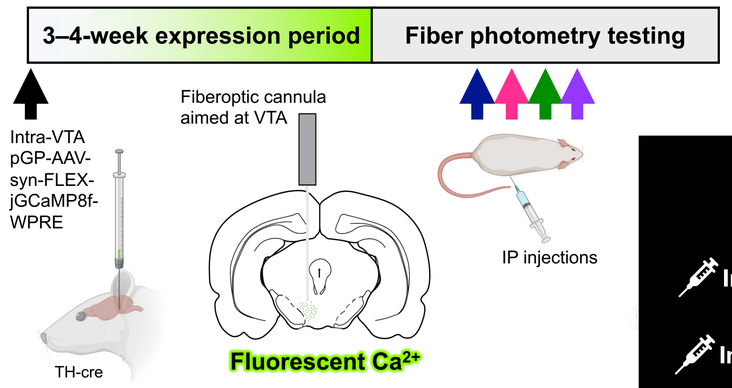


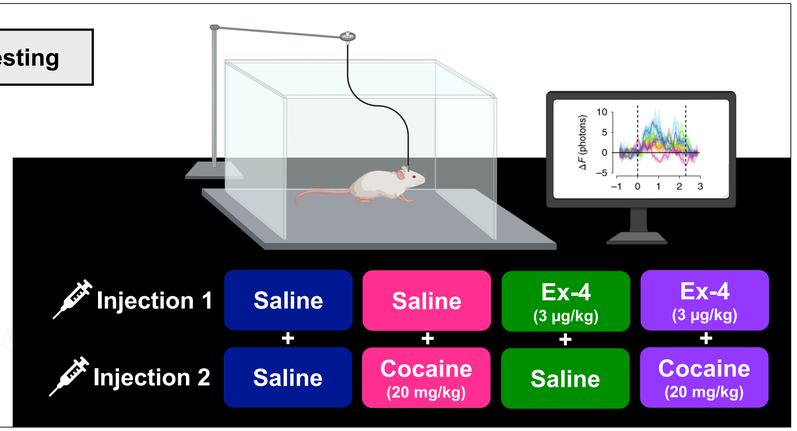


Hypothesis: GLP-1R activation enhances GABA release on VTA dopamine neurons, which subsequently attenuates dopamine release. This action may reverse the effects of cocaine on these neurons.

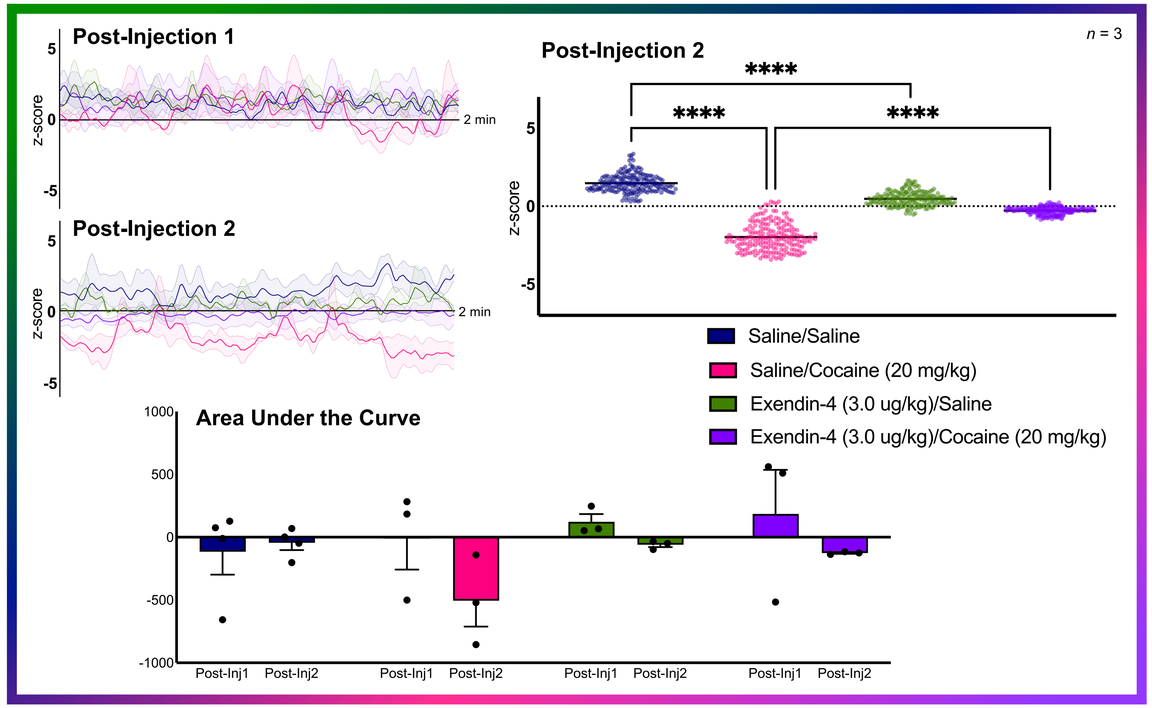
METHODS

- Used fiber photometry techniques to record population-level signals from fluorescent Ca^{2+} sensors selectively expressed in VTA TH-cre neurons.
- Explored the effects of systemic cocaine and pretreatment with GLP-1R agonist Exendin-4 on changes in fluorescent Ca^{2+} in these neurons.





RESULTS



SUMMARY

- Acute systemic cocaine attenuated Ca^{2+} transients in VTA dopamine neurons.
- Pretreatment with Ex-4 blocked the effects of acute cocaine on Ca^{2+} dynamics.
- These findings suggest that GLP-1R activation modulates the effects of cocaine on the neuronal dynamics of VTA dopamine neurons.

Future Directions

- Assess the effects of systemic cocaine and Ex-4 pretreatment on changes in fluorescent Ca^{2+} in VTA GABA neurons.
- Explore the effects of Ex-4 on VTA dopamine neurons following a cocaine prime in rats re-exposed to cocaine during withdrawal.

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Reference for data analysis: Bruno CA, O'Brien C, Bryant S, Mejaes JI, Estrin DJ, Pizzano C, Barker DJ. pMAT: An open-source software suite for the analysis of fiber photometry data. Pharmacol Biochem Behav. 2021;201:173093. doi:10.1016/j.pbb.2020.173093.