Glucagon-Like Peptide-1 Receptor (GLP-1R) Agonism in the Interpeduncular Nucleus Decreases Opioid Reinstatement

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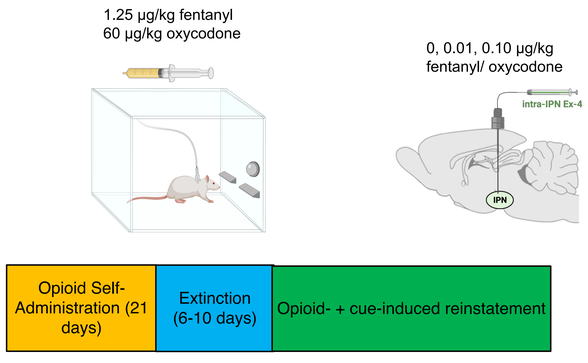
INTRODUCTION

Opioid overdose is currently a leading cause of preventable death in the US, and one half of these deaths are associated with synthetic opioids like fentanyl[1]. Previous studies from our lab showed that systemic administration of the glucagon-like peptide-1 (GLP-1) receptor agonist exendin-4 (Ex-4) reduced reinstatement of opioid-seeking behavior, an animal model of opioid relapse[2,3]. However, the neural mechanisms underlying this effect are still unknown. In order to characterize these mechanisms, we studied the contribution of GLP-1 receptors in the interpeduncular nucleus (IPN) in opioid-seeking behavior during abstinence. GLP-1 is an incretin hormone and neuropeptide that mediates both food and drug reward[4]. Given that the IPN contains GLP-1 receptors and is known to mediate the mesolimbic dopamine system, we hypothesized that central administration of the GLP-1 analogue Ex-4 into the IPN will attenuate reinstatement of opioid seeking behavior[5,6,7]. We used both male and female rats to investigate potential sex differences in the effect of Ex-4 on opioid reinstatement and measured body weight change and feeding behaviors to determine whether Ex-4 has non drug-specific effects on behavior.

METHODS



RESULTS

GLP-1R activation in the IPN attenuates the reinstatement of fentanyl-seeking behaviors in both male and female rats

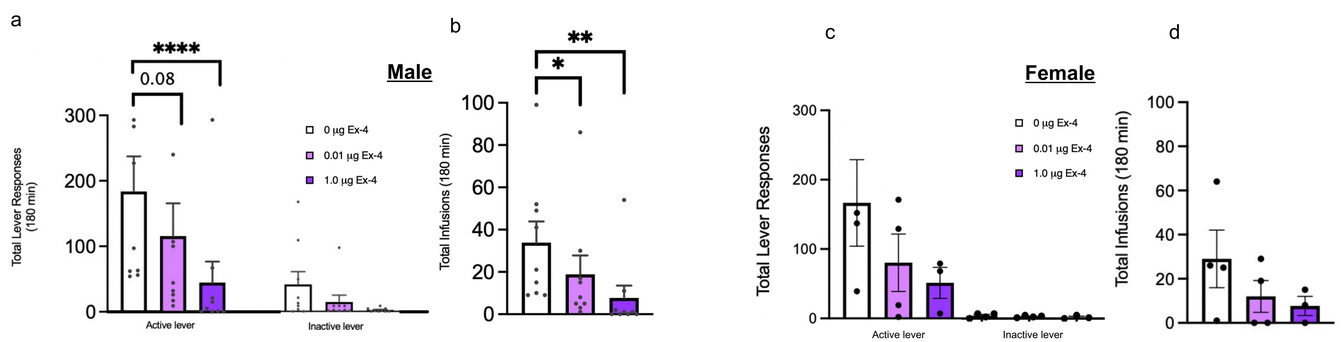


Figure 1: Intra-IPN administration of a GLP-1R agonist reduces fentanyl seeking during reinstatement test sessions in male rats. (a) Intra-IPN Ex-4 dose-dependently decreases lever responses during reinstatement to fentanyl seeking in male rats. There was no effect on inactive lever presses. (n= 11) (**b**) Intra-IPN Ex-4 dose-dependently decreases infusions during reinstatement to fentanyl seeking. (n=11) (**c**)There was a non-significant trend of decreased infusions during reinstatement to fentanyl seeking There was no effect on inactive lever presses. (n=4) (**d**)There was a non-significant trend of decreased infusions during reinstatement to fentanyl seeking after intra-IPN Ex-4. (n=4) Statistical analysis was performed using a Two-way ANOVA test. * p < 0.05; ** p<0.01; **** p < 0.0001 compared to vehicle (Bonferroni)

IPN Ex-4 doesn't affect 24-hour body weight, food Intake, or water intake in opioid-experienced male rats

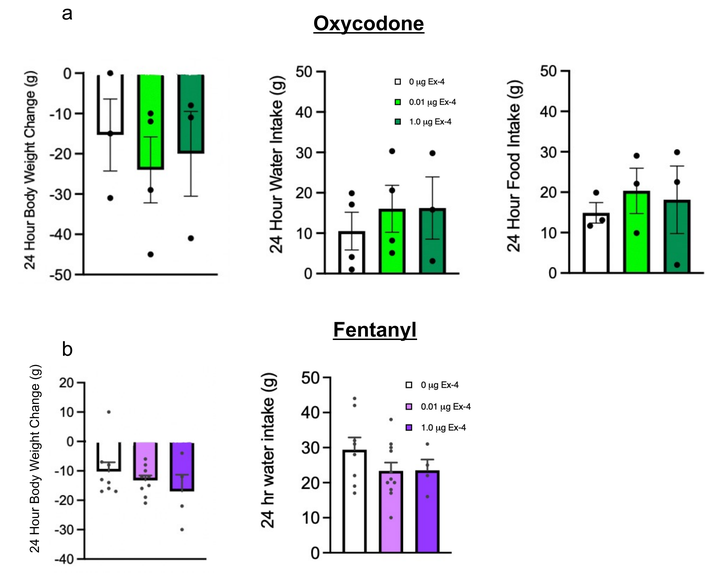


Figure 2: Intra-IPN administration of a GLP-1R agonist does not affect body weight, water intake, or food intake (a) Intra-IPN Ex-4 during oxycodone reinstatement does not affect 24-hour change in body weight, water intake, or food intake. (Ex-4 0, 0.01, 0.1; n= 8, 9, 4) **(b)** Intra-IPN Ex-4 during fentanyl reinstatement does not affect 24-hour body weight or water intake. (Ex-4 0, 0.01, 0.1; n= 8, 11, 4) Statistical analysis was performed using mixed-effects analysis.

GLP-1R activation in the IPN attenuates the reinstatement of oxycodone-seeking behaviors in male rats

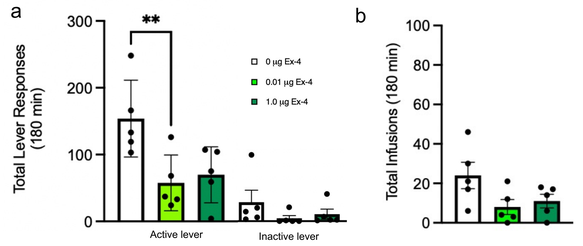


Figure 3: a) Intra-IPN Ex-4 decreases lever responses during reinstatement to oxycodone seeking. There was no effect on inactive lever presses (n=3) **(b)** There was a non-significant trend of decreased infusions during reinstatement to oxycodone seeking after intra-IPN Ex-4. (n=3) Statistical analysis was performed using a Two-way ANOVA test. * p < 0.05; ** p<0.01; **** p < 0.0001 compared to vehicle (Bonferroni)

GLP-1Rs are expressed on GABAergic neurons in the IPN

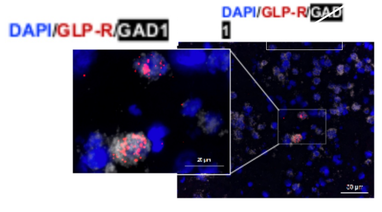
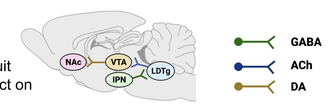


Figure 4: GLP-1Rs are expressed on GABAergic IPN neurons. Fluorescent in situ hybridization (FISH) was performed on IPN slices.

Summary and Conclusion

- Administration of Ex-4 directly into the IPN dose-dependently attenuates opioid seeking in male rats
- There is a non-significant trend of decreased fentanyl seeking behaviors in female rats following administration of Ex-4
- There is no effect of treatment on 24-hour body weight change, food intake, or water intake
- GLP-1 receptors are expressed on GABAergic IPN neurons
- These data are the first to identify a functional role of the IPN and IPN GLP-1Rs in opioid-seeking behaviors



Future Directions

•Examine the effect of IPN GLP-1R agonism on measures of anxiety and aversion

•Use fiber photometry to measure population-level calcium responses of IPN neurons during fentanyl reinstatement and the unique effects of Ex-4 on these responses.

•Specifically activate IPN circuits using DREADDs to determine the role of endogenous IPN signaling in fentanyl seeking

References

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