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

• Sana Zeb1,2, R.J. Herman1,2,3, K. Ragnini1,2, Y. Zhang1,2, and H.D. Schmidt1,2

1 Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
2 Biobehavioral Health Sciences, School of Nursing, University of Pennsylvania, Philadelphia, PA
3 Neurosciences Graduate Group, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

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. 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. 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 like Peptide-1 (GLP) and is involved in feeding behaviors to determine whether Ex-4 affects opioid-seeking behaviors in both male and female rats. 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

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

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

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

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

iciente

RESULTS

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 intact male rats. **p < 0.01 compared to vehicle. (b) There was no trend of decreased infusions during reinstatement to fentanyl seeking after intra-IPN Ex-4. (n=11) Statistical analysis was performed using a two-way ANOVA test. *p < 0.05; **p < 0.01; ****p < 0.0001 compared to vehicle (Bonferroni).

Figure 2: intra-IPN administration of a GLP-1R agonist does not affect body weight, water intake, or food intake in opioid-experienced male rats. (a) Intra-IPN Ex-4 during equilibration period does not affect 24-hour body weight change in body weight, water intake, or food intake. (Ex-4: 0.01, 0.05, 0.1, n= 11, p > 0.05). **(b) Intra-IPN Ex-4 during reinstatement does not affect 24-hour body weight or water intake. (Ex-4: 0.01, 0.05, 0.1, n= 11, p > 0.05). Statistical analysis was performed using two-way ANOVA test.

Figure 3: (a) Intra-IPN Ex-4 decreases lever responses during reinstatement to oxycodone-seeking. **p < 0.01 compared to vehicle. (b) There was no significant trend of decreased infusions during reinstatement to oxycodone-seeking after intra-IPN Ex-4. (n=11) Statistical analysis was performed using a two-way ANOVA test. *p < 0.05; **p < 0.01; ****p < 0.0001 compared to vehicle (Bonferroni).

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

• Administration of Ex-4 directly into the IPN dose-dependently attenuates oxycodone-seeking in male rats.
• There is no significant trend of decreased oxycodone-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 within GABAergic IPN neurons.
• These data are the first to identify a functional role of the IPN and GLP-1Rs in opioid-seeking behaviors.

FUTURE DIRECTIONS

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.

Acknowledgments

I would like to thank my advisors John Schuh and Rachel Herman and everyone in the Schmidt Lab. I would also like to acknowledge CURT (CIA) for funding my research.

REFERENCES