Novel, cell type-specific roles for nucleus accumbens amylin receptors in oxycodone taking in rats

Jennifer Ben Nathan[1], Amanda Moreno[1], Yafang Zhang[2,3], Heath D. Schmidt[2,3]

[1]Department of Biological Basis of Behavior, College of Arts and Sciences (2023, 2021), University of Pennsylvania, Philadelphia, PA

[2]Department of Biobehavioral Health Sciences, School of Nursing, University of Pennsylvania, Philadelphia, PA [3]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

INTRODUCTION

The widespread abuse of opioids necessitates therapies that mitigate the compulsive behaviors that characterize opioid use disorder (OUD). Research must elucidate the underlying mechanisms of OUD and identify molecular targets for pharmacotherapies. Amylin, a glucoregulatory hormone, reduces oxycodone taking in rats when administered into the nucleus accumbens (NAc) shell, a brain region critical to opioid reinforcement. Amylin crosses the blood brain barrier and activates its cognate receptors, which comprise a CTR and RAMP. Dopamine D1 receptor- and D2 receptor-expressing GABAergic medium spiny neurons (D1R/D2R-MSNs) are the main cell populations in the NAc shell. Evidence suggests that D1R-MSNs encode reward while D2R-MSNs encode aversion. The current study hypothesized that reduced CTR expression in D1R- and D2R-MSNs would potentiate and attenuate oxycodone taking, respectively.

METHODS

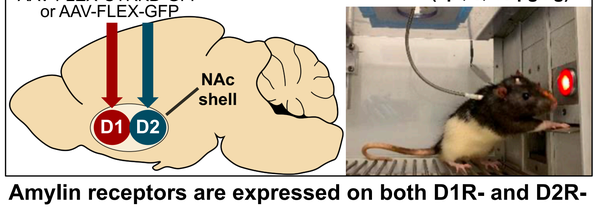
Effects of CTR-A knockdown in D1R- and D2R-MSNs on:

1. Acquisition of oxycodone self-administration
2. Motivation to self-administer oxycodone

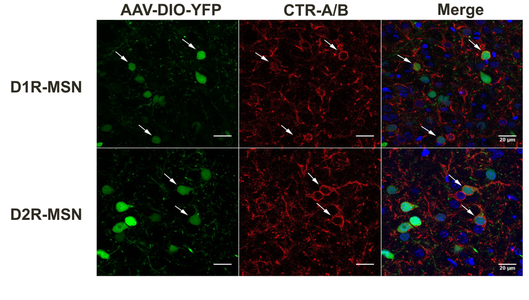
Oxycodone SA (i.v., 0.06 mg/kg)

FR1 → FR3 → FR5 → PR

Amylin pretreatment (i.p., 0, 10 µg/kg)



Amylin receptors are expressed on both D1R- and D2R-MSNs in the NAc shell.



RESULTS

Figure 1: CTR-A knockdown in D1R-MSNs, but not D2R-MSNs, increases acquisition of oxycodone self-administration

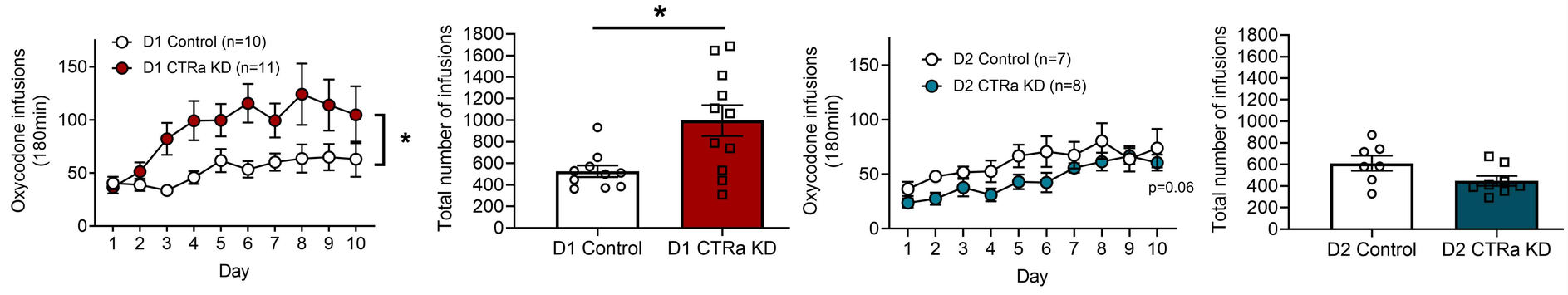
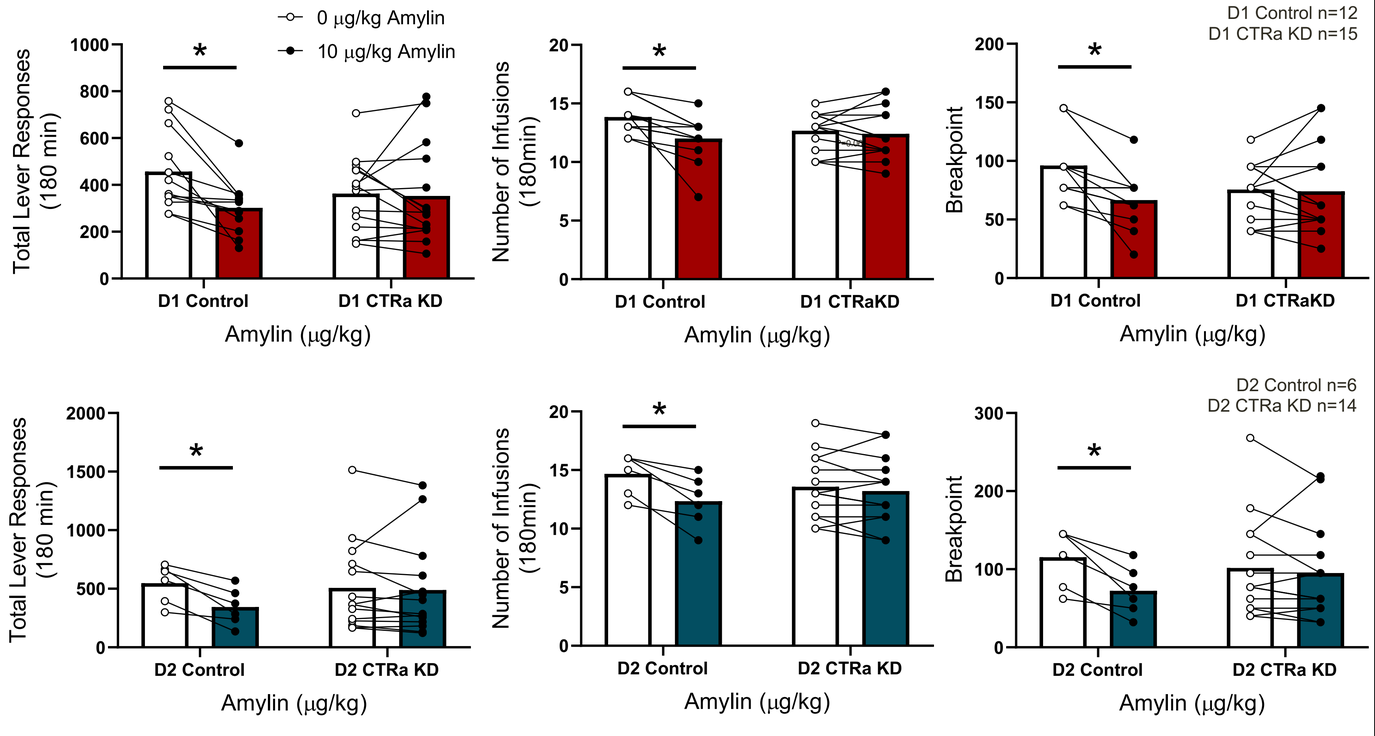


Figure 2: CTR-A knockdown in D1R- and D2R-MSNs inhibits amylin suppression of oxycodone self-administration



SUMMARY & CONCLUSION

- Reduced CTR expression in D1R-MSNs, but not D2R-MSNs, facilitated the acquisition of oxycodone taking.
- However, reduced CTR expression in D2R-MSNs demonstrated a trend toward decreased oxycodone taking.
- Therefore, D1R- and D2R-MSNs may have different roles in the development of oxycodone taking in which endogenous amylin works against the acquisition of oxycodone taking via D1R-MSNs.
- Reduced CTR expression in D1R- and D2R-MSNs attenuated amylin's suppressive effects on oxycodone taking; thus, exogenous amylin reduces oxycodone taking via both cell types.

Future Directions:

- Determine the effects of a CTR-A knockdown in D1R- and D2R-MSNs on oxycodone reinstatement to identify the neuron types by which amylin attenuates oxycodone seeking.

ACKNOWLEDGEMENTS

I would like to thank CURF's PURM Program for funding my research. I would also like to thank Dr. Heath D. Schmidt and everyone in the Schmidt lab for sharing their meaningful research and invaluable insights.