# Cell Type-Specific Effects of Amylin Receptors in the Nucleus Accumbens Shell on Oxycodone Reinforcement

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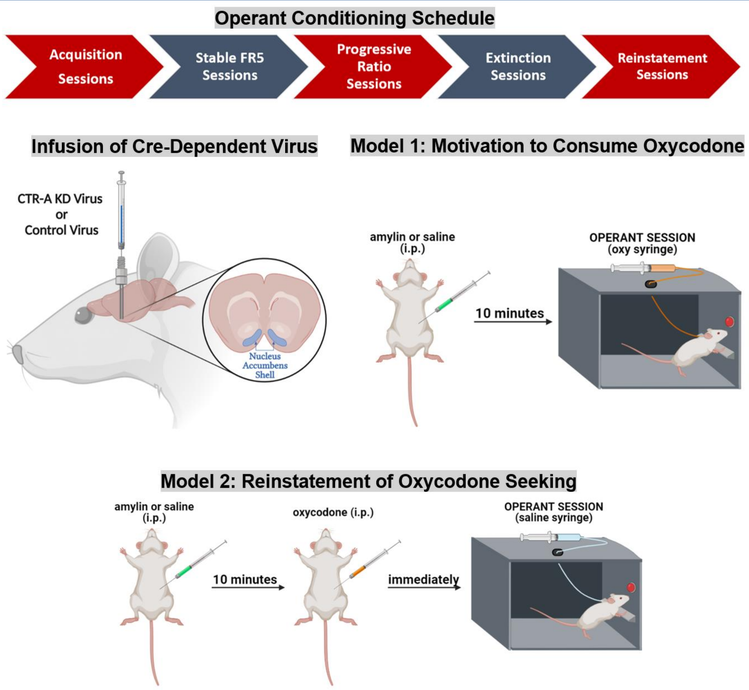
## Introduction

Current pharmacotherapies used to treat opioid use disorder have modest efficacy in promoting long-term abstinence[1,2]. Thus, there is a critical need for the development of novel medications that reduce opioid abuse liability. Emerging studies from our lab suggest that amylin, a neuropeptide and metabolic factor, reduces oxycodone taking and seeking in rats. However, the circuit- and cell type-specific mechanisms that mediate amylin's suppressive effects are still unknown.

The mesolimbic dopamine system plays a critical role in the reinforcing effects of natural rewards and drugs of abuse. Specifically, the nucleus accumbens (NAc) is involved in decoding rewarding and aversive stimuli[3,4]. The two main cell populations involved are dopamine D1 receptor-expressing medium spiny neurons (D1R-MSNs) and dopamine D2 receptor-expressing medium spiny neurons (D2R-MSNs). Recent studies from our lab show that amylin administration directly into the nucleus accumbens (NAc) shell reduces oxycodone taking- and seeking-behaviors in rats.

The present study sought to characterize the relative contribution of D1R- and D2R-MSNs to these suppressive effects of amylin on opioid-mediated behaviors. Using a Cre-dependent knock-down (KD) virus in transgenic rats, we reduced amylin receptor expression selectively in D1R- and D2R-MSNs in the NAc shell. We hypothesized that reduced amylin receptor expression in D1R- and D2R-MSNs would respectively potentiate and attenuate oxycodone reinforcement..

## Methods

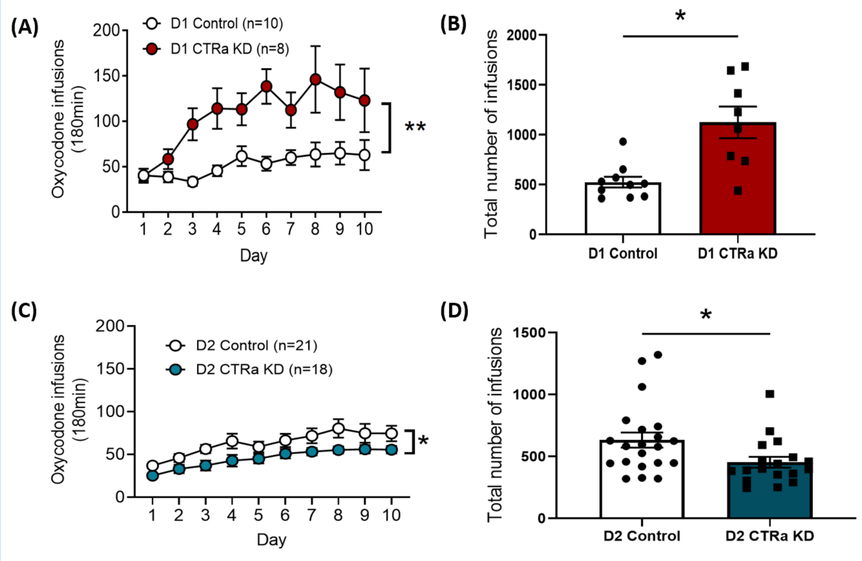



## Acknowledgements

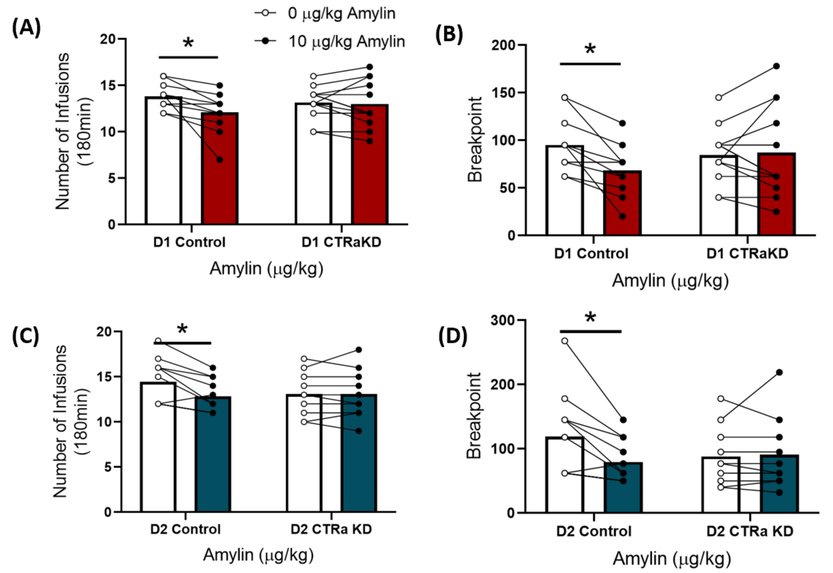
I would like to thank my mentor Dr. Heath D. Schmidt and all members of the Schmidt lab at the University of Pennsylvania for their support on this project. This project was funded by a CURF College Alumni Society Undergraduate Research grant.

## Results

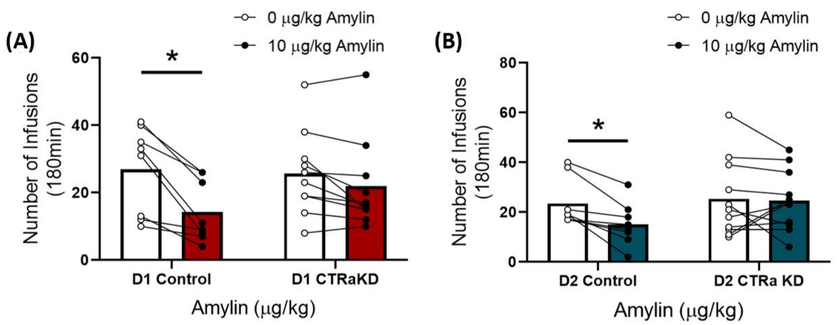
### Fig 1: D1-CTRa-KD potentiates, while D2-CTRa-KD attenuates, the acquisition of oxycodone self-administration.



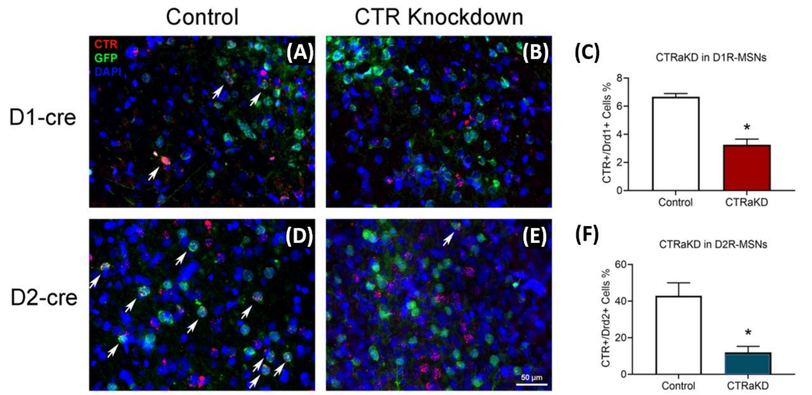

### Fig 2: CTRa-KD in D1R- and D2R-MSNs attenuates the suppressive effects of amylin on the motivation to consume oxycodone.




### Fig 3: Systemic amylin attenuates the reinstatement of oxycodone seeking in D1- and D2-Control but not D1- and D2-CTRa-KD rats.




### Fig 4: CTRa-KD virus reduces CTRa expression in D1R- and D2R-MSNs




## Summary & Conclusions

- Amylin receptor activation in the NAc shell reduces opioid reinforcement in rodent models of drug addiction.
- Endogenous amylin signaling through D1R-MSNs and D2R-MSNs regulates the acquisition of oxycodone taking in rats.
- Exogenous amylin signaling through D1R-MSNs and D2R-MSNs attenuates the motivation to consume oxycodone and oxycodone seeking.
- Collectively, these findings suggest that central amylin receptors may serve as molecular targets to reduce opioid abuse liability..

## References

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