Central Mechanisms Underlying the Efficacy of GLP-1 Receptor Agonists to Reduce Cocaine-Seeking Behavior

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No conflicts to declare

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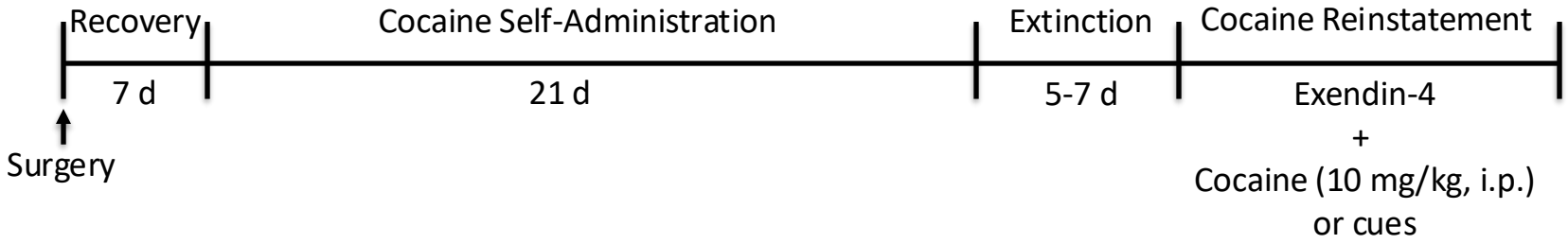
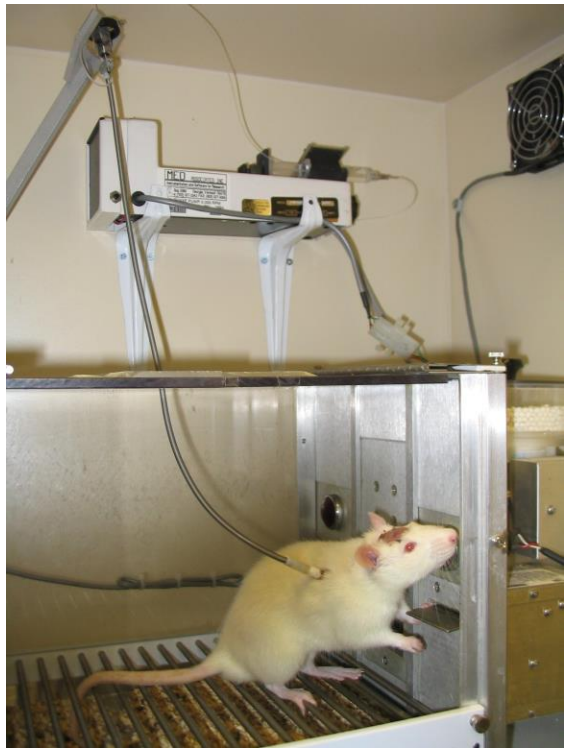
University of Pennsylvania

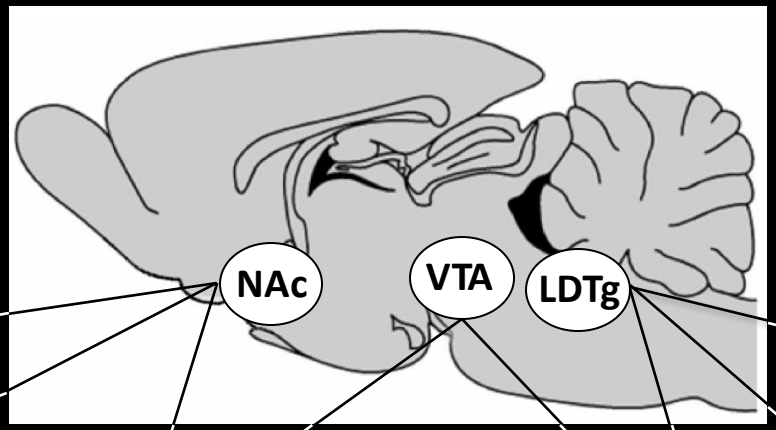
Systemic Infusions of the GLP-1 Receptor Agonist Exendin-4 Attenuate Cocaine Seeking in Rats

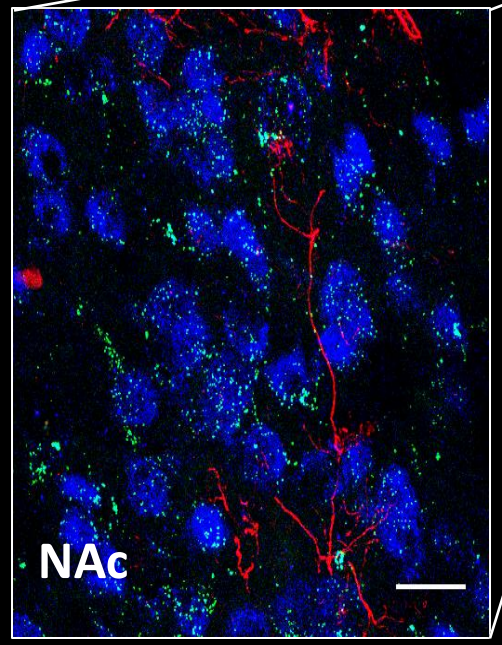


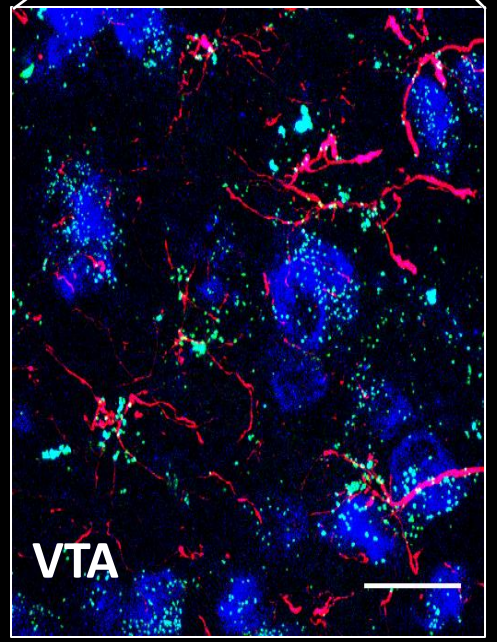


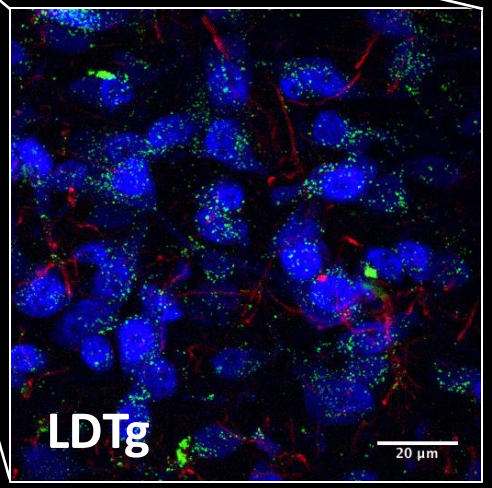
Hernandez *et al.* 2018

Systemic Exendin-4 Crosses the Blood Brain Barrier and Distributes to Nuclei Known to Regulate Drug Seeking





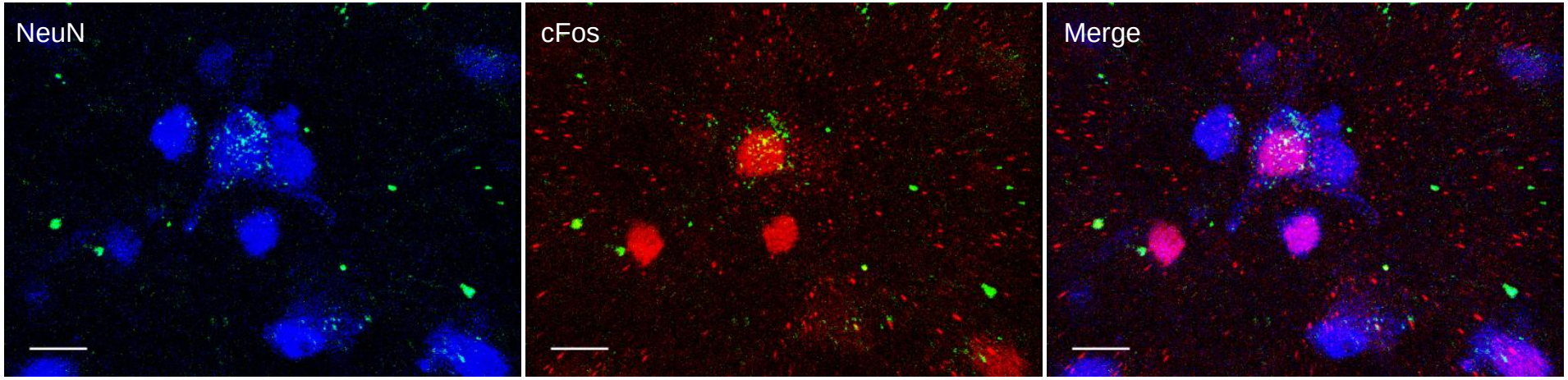




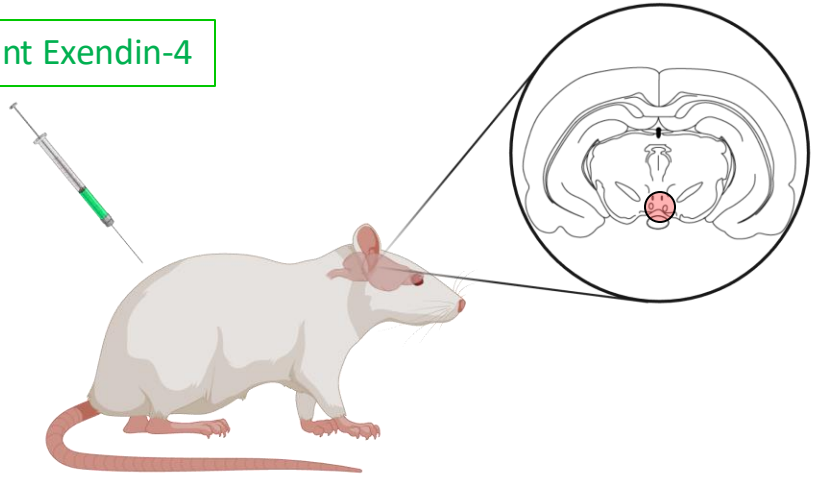
Exendin-4 (GLP-1 receptor agonist)
NeuN (Neurons)
GFAP (Astrocytes)

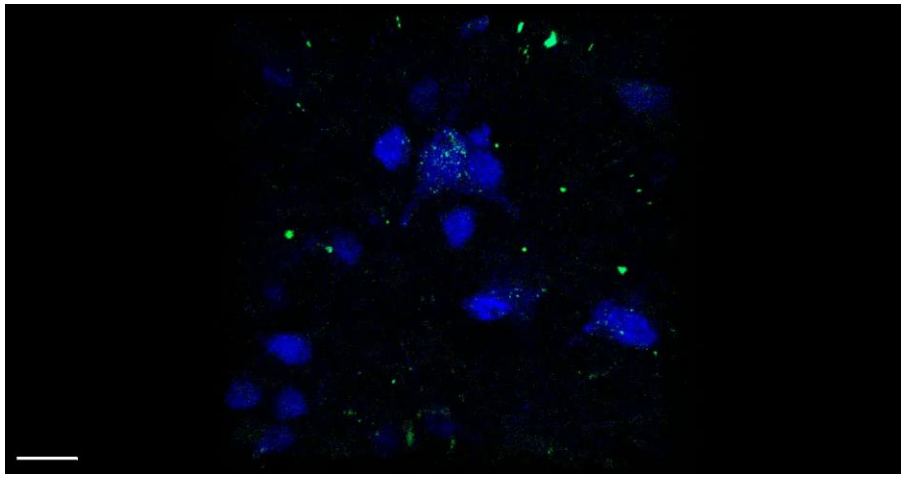
Hernandez *et al.* 2018, 2019, 2021

Systemic Exendin-4 Crosses the Blood Brain Barrier and Induces c-Fos Expression in VTA Cells



Fluorescent Exendin-4

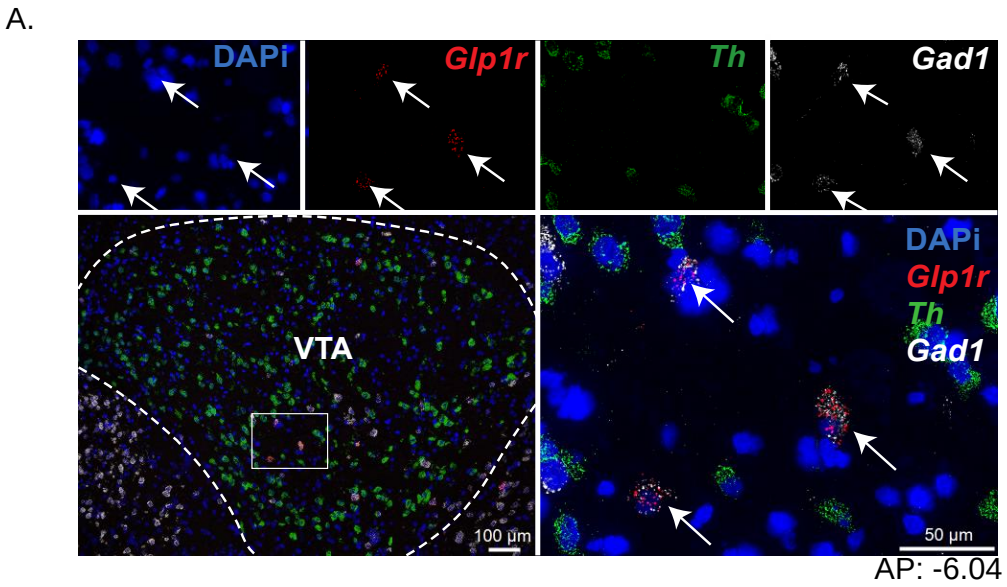


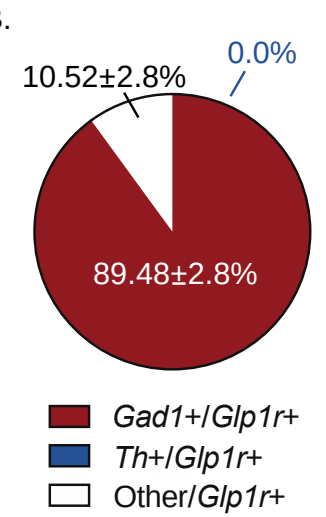


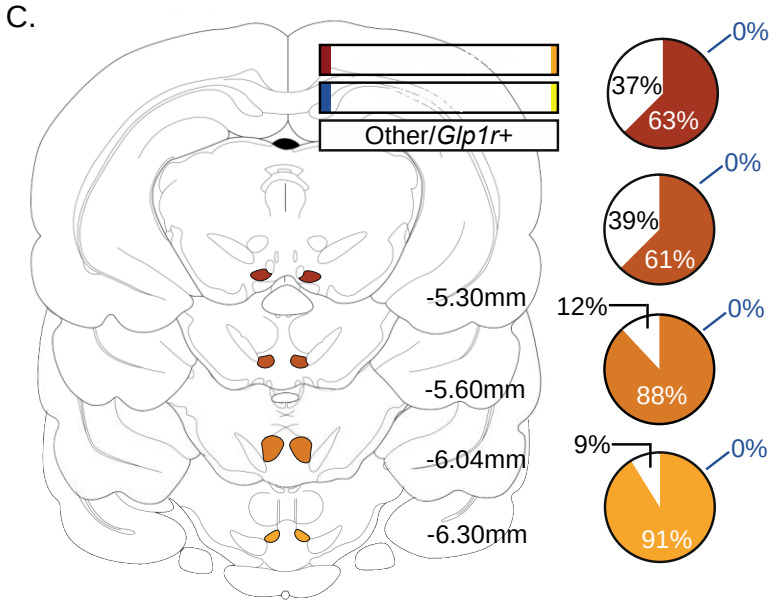
Exendin-4
NeuN (Neurons)
c-Fos

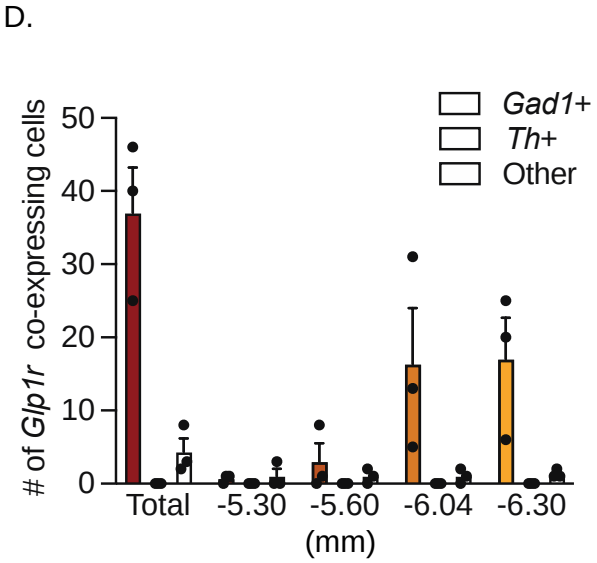
Unpublished data

What are the mechanisms in the midbrain underlying the efficacy of exendin-4 on cocaine seeking?



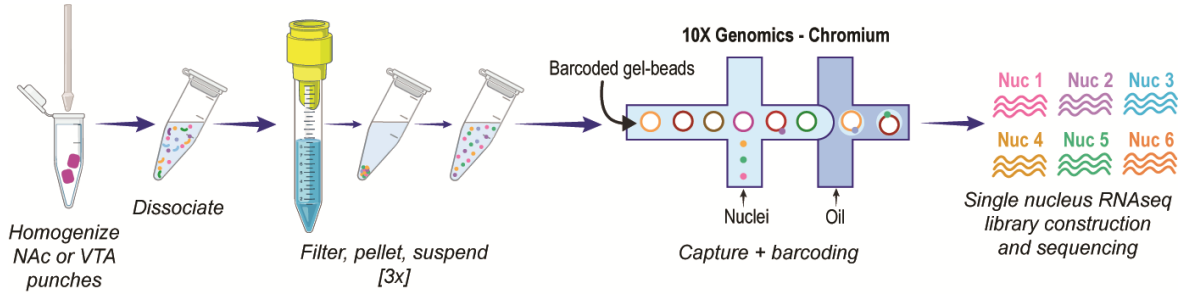


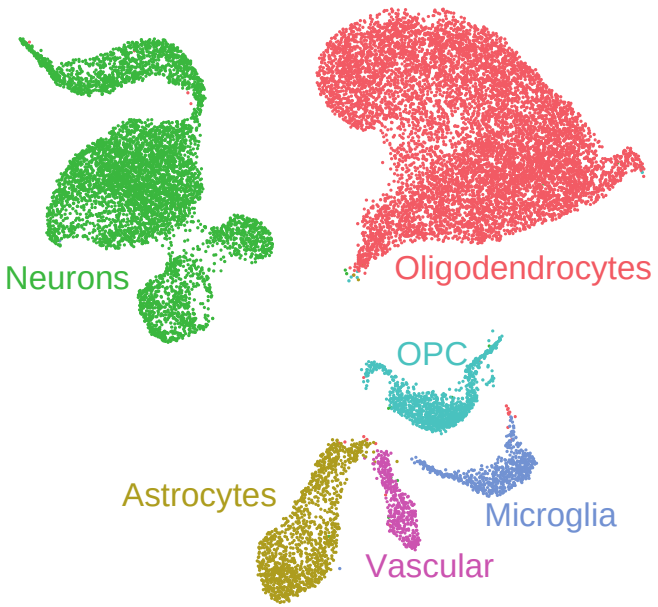


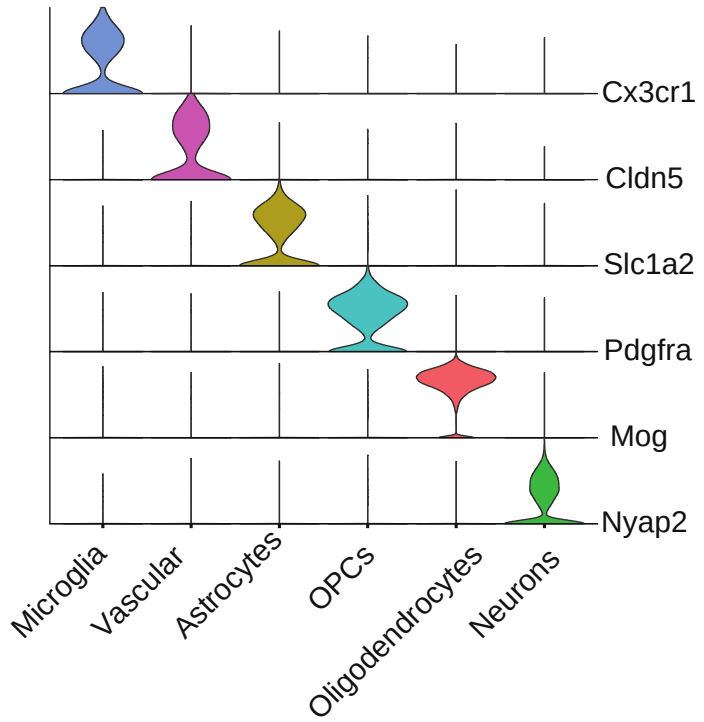


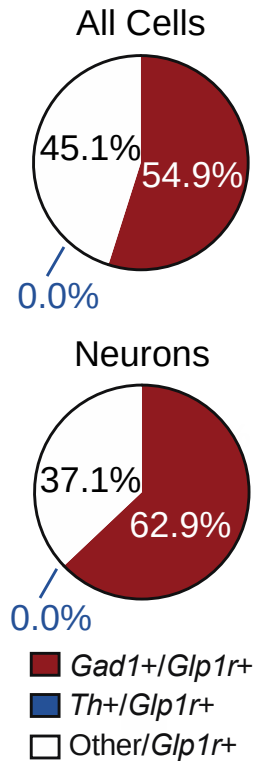
Unpublished data

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





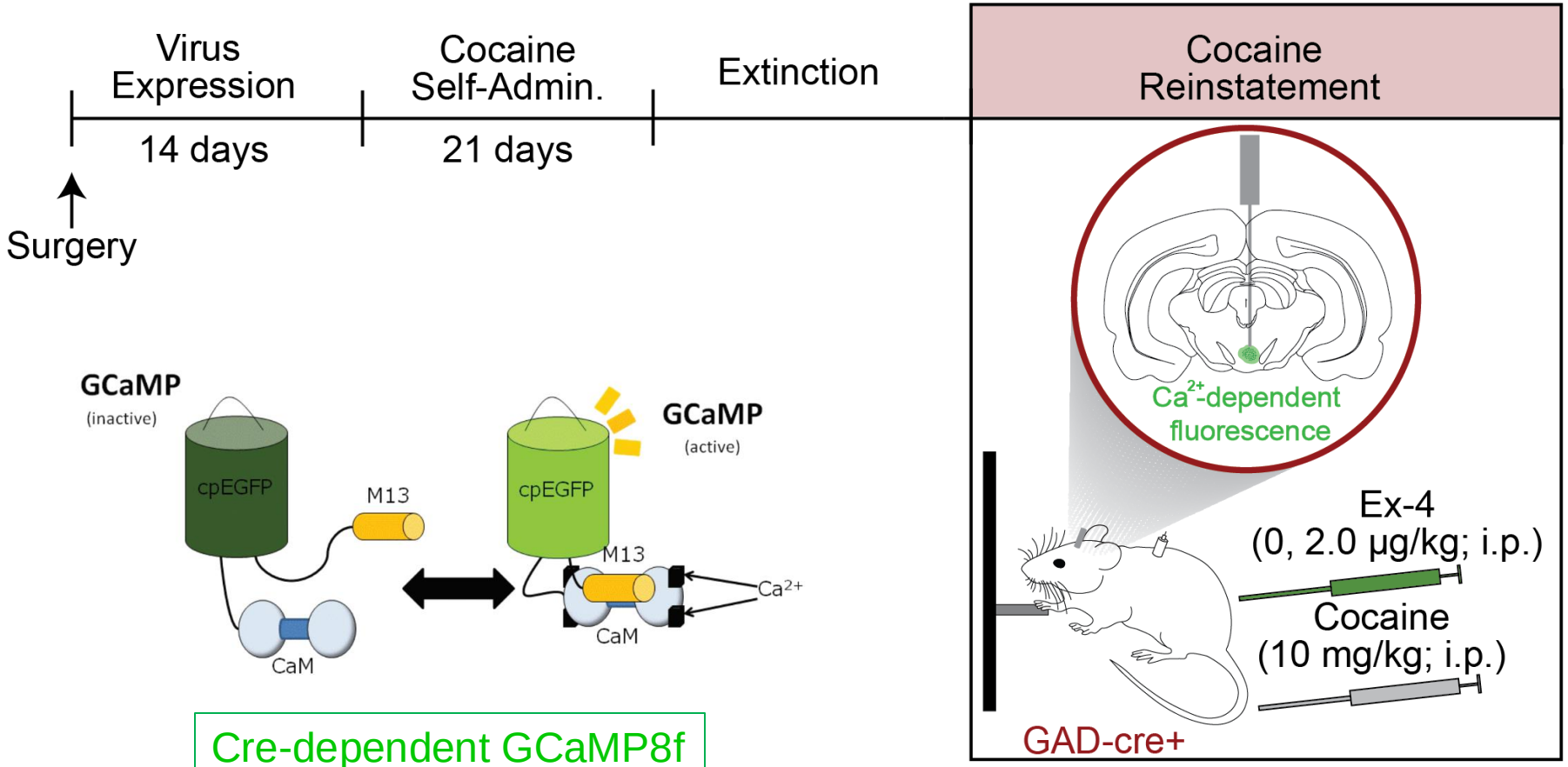




Unpublished data

GLP-1R pharmacotherapy increases activity of VTA GABA neurons and attenuates cocaine seeking

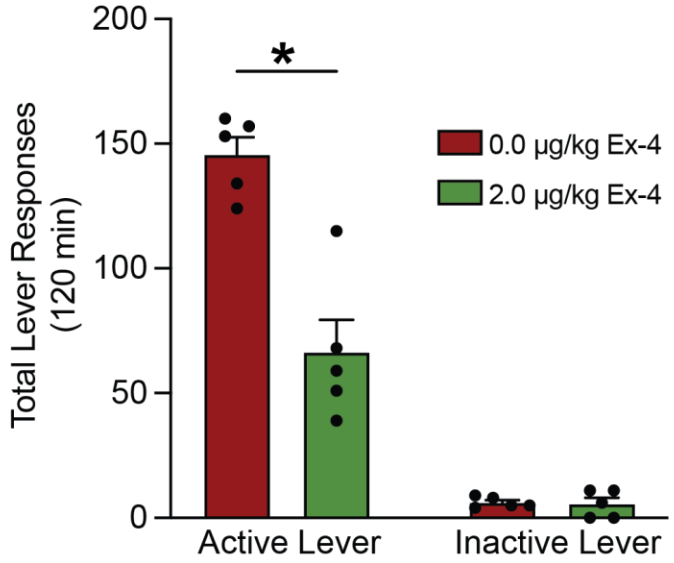
LE-Tg(Gad1-iCre)3Ottc

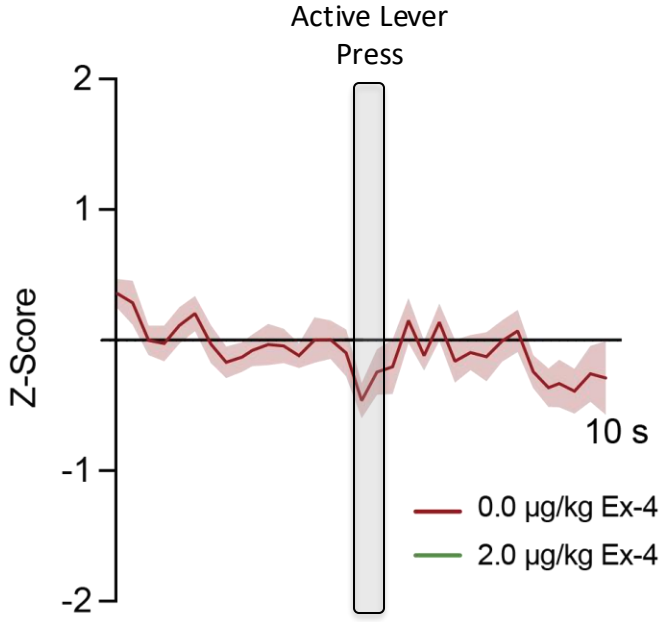


Cre-dependent GCaMP8f

Unpublished data

GLP-1R pharmacotherapy increases activity of VTA GABA neurons and attenuates cocaine seeking





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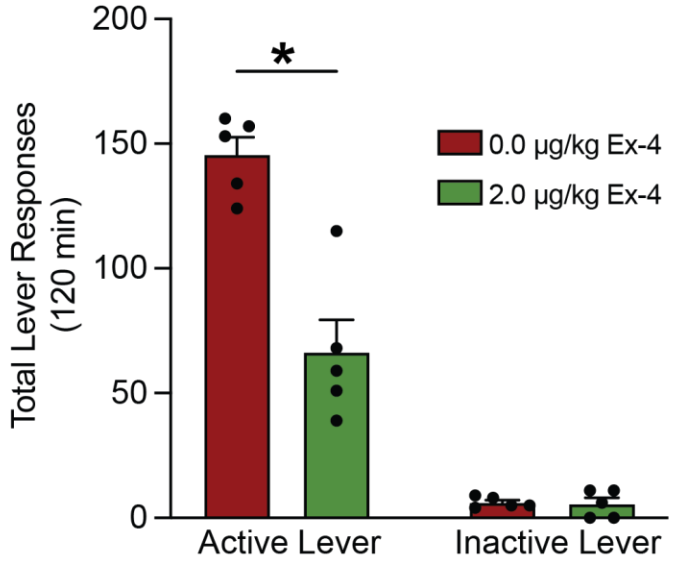
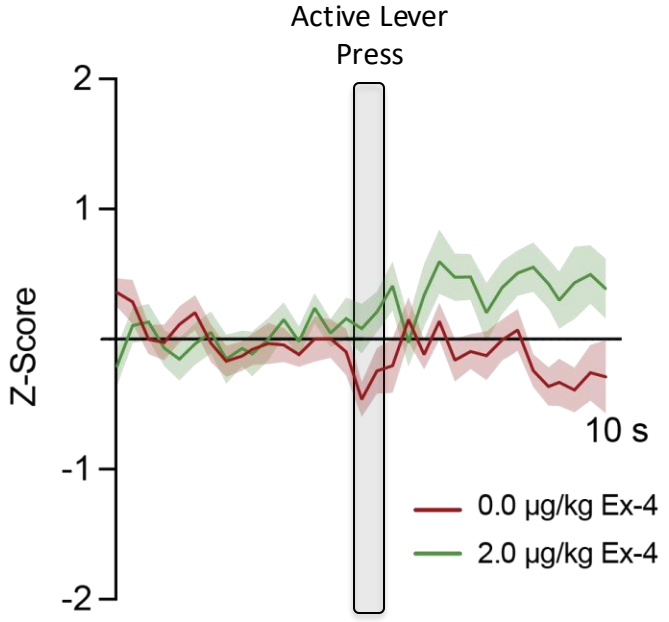
GLP-1R pharmacotherapy increases activity of VTA GABA neurons and attenuates cocaine seeking





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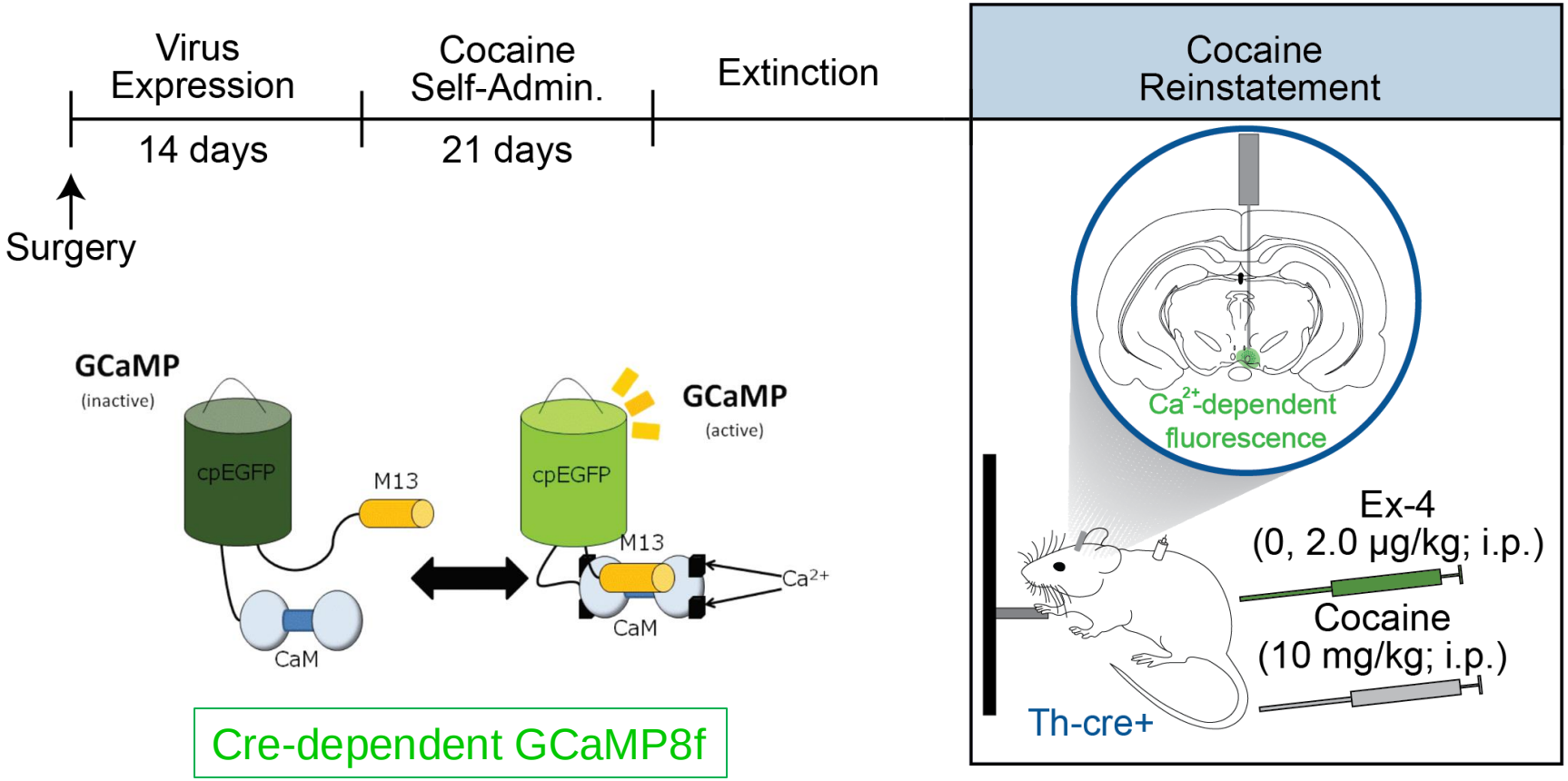
GLP-1R pharmacotherapy decreases activity of VTA dopamine neurons and attenuates cocaine seeking

HsdSage:SD-*TH*$^{em1(IRES\text{-}Cre)Sage}$



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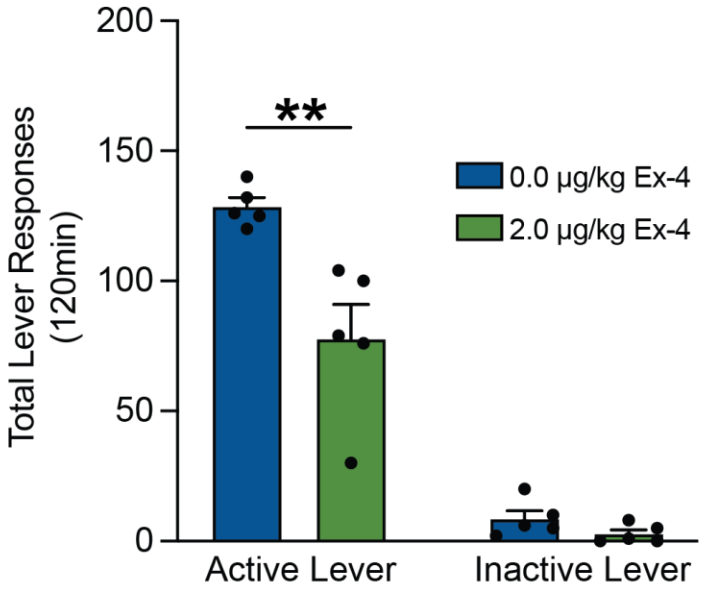
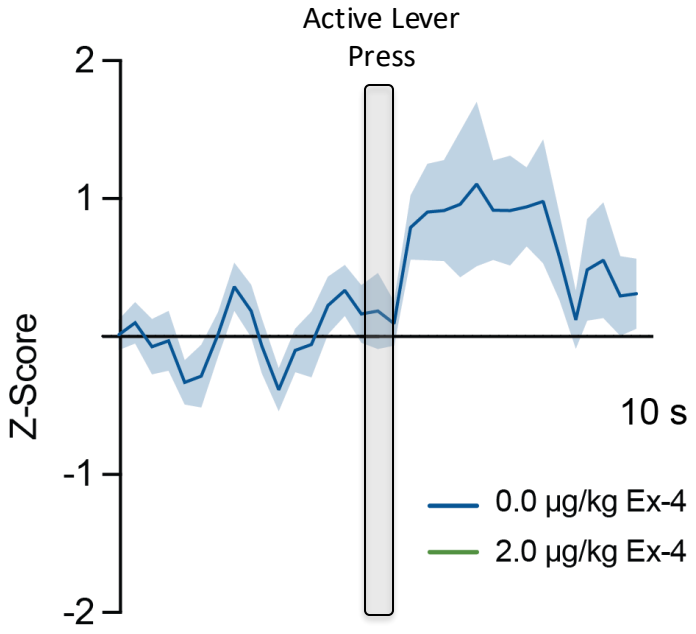
GLP-1R pharmacotherapy decreases activity of VTA dopamine neurons and attenuates cocaine seeking





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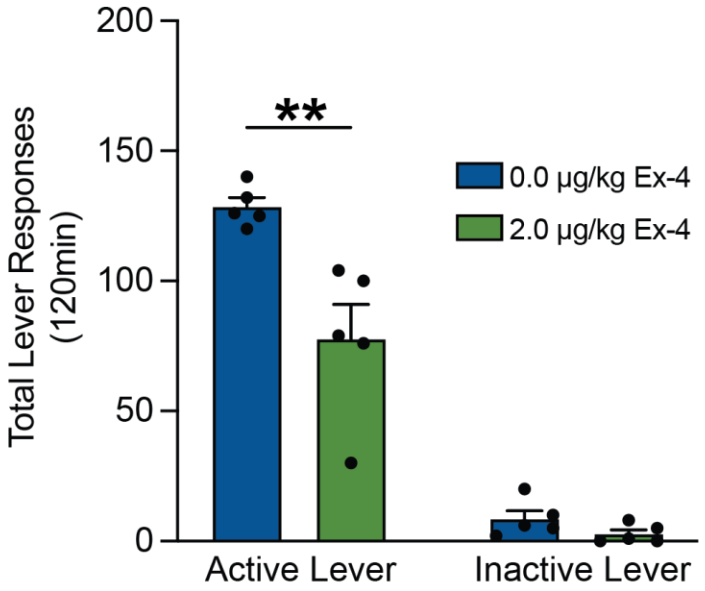
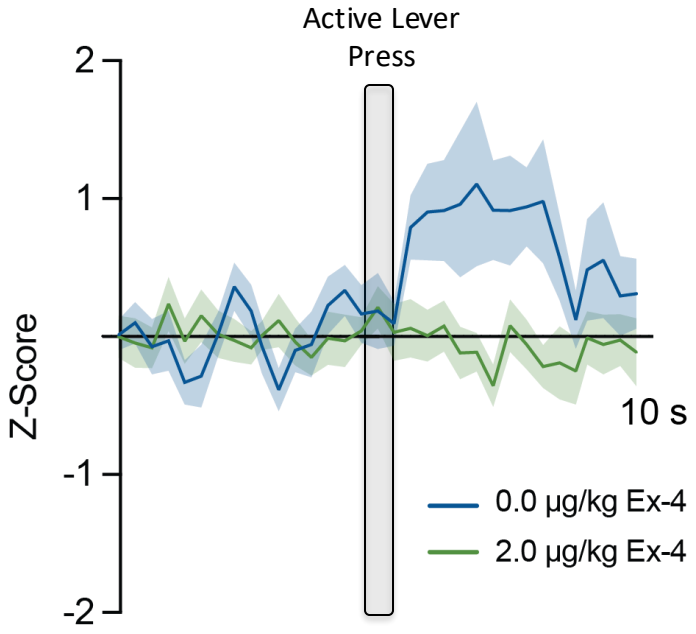
GLP-1R pharmacotherapy decreases activity of VTA dopamine neurons and attenuates cocaine seeking





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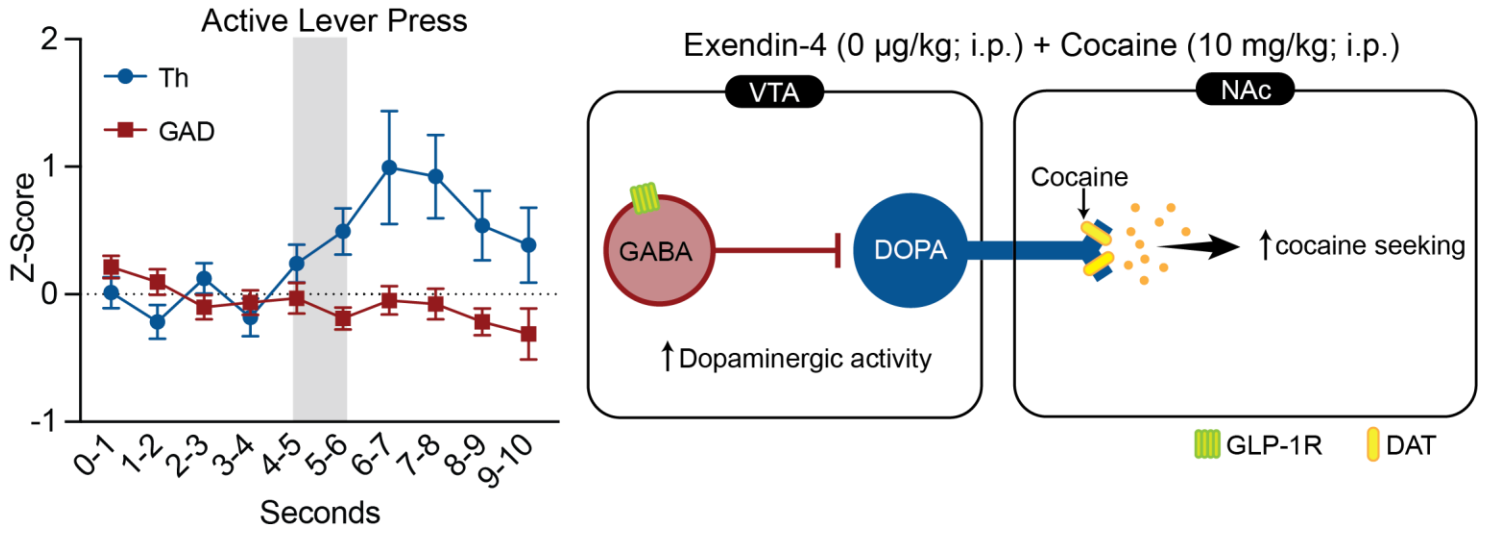
GLP-1R pharmacotherapy engages VTA GABA neurons to regulate mesolimbic dopamine neurons and attenuate cocaine seeking



Summary & Conclusions

- Systemic administration of a GLP-1 receptor agonist attenuates drug-seeking behavior at doses that are well-tolerated in cocaine-experienced rats. These findings suggest that GLP-1R agonists could be re-purposed for treating cocaine use disorder.

- The efficacy of systemic exendin-4 to reduce cocaine seeking is associated with increased activity of VTA GABA neurons and decreased activity of VTA dopamine neurons.

Outstanding Questions & Future Directions

- What are the downstream molecular and cellular mechanisms underlying the efficacy of GLP-1R agonists on voluntary drug-taking and -seeking behaviors?
- Define post-synaptic versus pre-synaptic mechanisms of action.
- Can we target central GLP-1-producing circuits to selectively reduce drug-mediated behaviors?
- Are next-generation GLP-1R agonists more efficacious?
- What are the adverse effects of GLP-1R agonists in humans with SUDs?
- Will approaches that target GLP-1Rs and additional neuropeptide systems with overlapping functional activity be more efficacious and/or better tolerated than GLP-1R agonist monotherapy alone?

Acknowledgments

Schmidt Lab

- Antonia Caffery
- Camille Carthy
- Victoria Chinaka
- Micah Ford
- Rae Herman
- Nicole Hernandez, Ph.D.
- Kelsey Ige
- Enzo LaVecchia
- Riley Merkel
- Suraj Neelamagam
- Austin Pothikamjorn
- Kael Ragnini
- Vanessa Weir
- Yafang Zhang, Ph.D.

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