Parallel Hindbrain Circuits Mediate GLP1-Induced Food Suppression

Nicholas Hanchak[1,2], Kuei-Pin Huang[2], Aaron McKnight[2], Amber Alhadeff[1,2]
[1]University of Pennsylvania, Department of Neuroscience; [2]Monell Chemical Sense Center

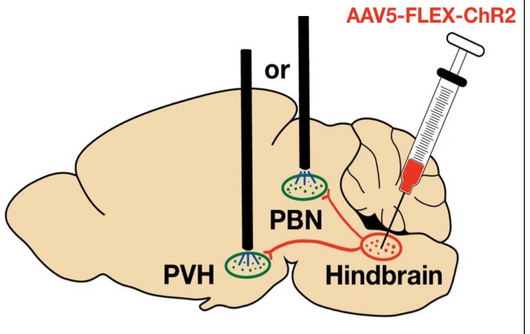
Introduction

Glucagon-like peptide 1 (GLP1) is an anorexigenic gut hormone released upon the ingestion of food. The Alhadeff Lab has shown that activity in GLP1R^{DVC} neurons robustly reduces food intake and body weight in mice. The DVC is composed of the area postrema (AP) which mediates nausea-like behaviors and project to the parabrachial nucleus (PBN), and the nucleus of the solitary tract (NTS) which may play a role in satiation and projects to the paraventricular nucleus of the hypothalamus (PVH).

GLP1 agonists (such as exendin-4 and semaglutide) are common therapeutic drugs used for weight loss; however, common side effects include nausea, vomiting, and diarrhea. Future obesity therapeutics aim to suppress food intake without causing these side effects. This study will aim to elucidate the differences that PBN- and PVH-projecting GLP1R^{DVC} neurons have on of food intake inhibition using feeding and real-time place-preference assays.

Methods

GLP1R Cre-dependent mice were injected in the hindbrain with AAV5-FLEX-ChR2. An optic fiber was inserted into either the PVH or PBN to optogenetically activate the inputs to these neurons.



Feeding: PVH- and PBN- projecting neurons were stimulated and the amount of chow consumed was measured over a 1-hour period.

Real-time Place-Preference (RTPP): Testing included a a 10-minute NO STIM period followed by a 20-minute optogenetic STIM trial in an RTPP Chamber with two zones.

Acknowledgements

- Research funded by NIH R00DK119574 and the CURF College Alumni Society Undergraduate Research Grant

Axon Stimulation Inhibits Food Intake

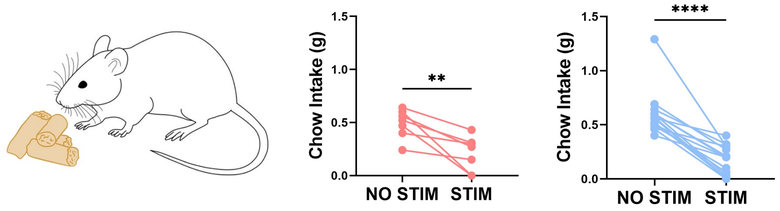


Figure 1. Stimulation of PVH- (left) and PBN- (right) projecting axons inhibited food intake, with a greater difference shown with the PBN.

PVH Circuit Does not Cause a Place Preference

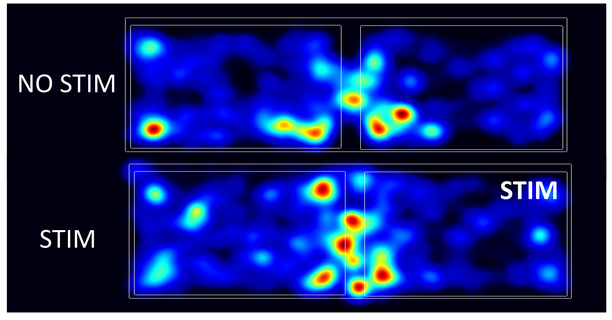


Figure 2. The PVH mice show uniform activity on both sides of the chamber in the NO STIM and STIM trials.

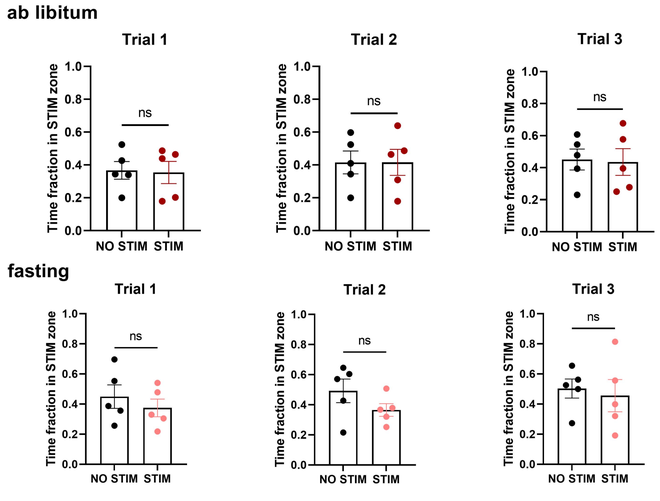


Figure 3. There was no significant difference between the time spent in the STIM zone between the NO STIM and STIM trials.

PBN Circuit Cause a Place Preference

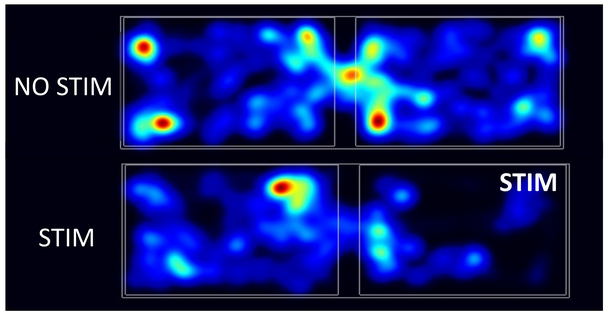


Figure 4. The PVH mice show uniform activity on both sides of the chamber in the 10-min NO STIM and 20-min STIM trials.

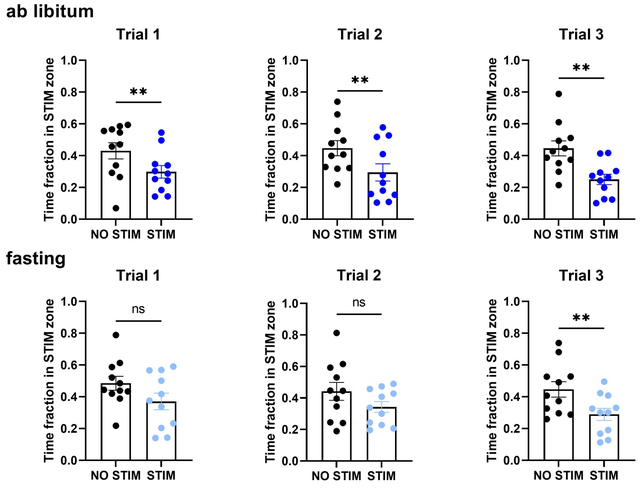


Figure 5. There was a significant difference between the time spent in the STIM zone between the NO STIM and STIM trials.

Conclusions

- Independent stimulation of PBN- and PVH-projecting neurons are sufficient to reduce food intake.
- A place preference was not observed when PVH-projecting neurons were stimulated, but mice exhibited a place preference when PBN-projecting neurons were stimulated ab libitum and when fasted.
- This may indicate that the PVH-projecting DVC neurons may be a key target of future obesity therapeutics as its projections do not cause aversive symptoms.