Examination of GPR160 Activity in the Regulation of Food Intake

Michael K. Hagan[1], Lauren M. Stein[2], Matthew R. Hayes[2]
[1]College of Arts and Sciences, University of Pennsylvania
[2]Translation Research Laboratory, Perelman School of Medicine

Introduction

- Nearly 72% of Americans are considered overweight or obese (1).
- Despite numerous therapies for obesity (lifestyle modifications, pharmacological and surgical interventions), long-term weight management is largely unsuccessful.
- Investigation into how the brain regulates food intake can lead to the identification of novel therapeutic targets.
- CART is an endogenous neuropeptide produced in the CNS that exerts anorectic effects
- Recent discovery of the CART receptor Gpr160 (2) provides an avenue to investigate the role of CART in energy balance.
- Preliminary evidence revealed abundant Gpr160 is expressed in the brainstem. CART is known to act in the brainstem to suppress food intake and body weight (3).

We hypothesized that brainstem GPR160 is required for the anorectic actions of CART.

Methods

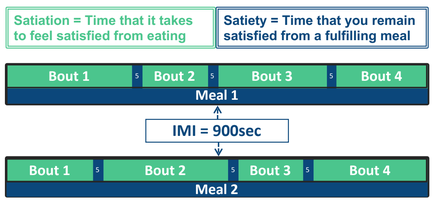
Aim 1: Investigate the effect of GPR160 knockdown in the brainstem on food intake and body weight.

- Male Sprague Dawley rats with ad libitum access to either chow (n=10) or 60% high fat diet (HFD; n=12)were housed in food monitoring cages (BioDaq)
- Rats received bilateral nucleus tractus solitarius infusion of either AAV-GFP (Control) or an AAV-shRNA-Gpr160 (GPR160-KD)
- Continuous food intake monitoring and 48hr body weights were recorded

Aim 2: Examine whether Gpr160 is required for the anorectic effects of Exendin-4 (Ex4)

- Prior to lights out, body weights were recorded. Rats received intraperitoneal injections of either saline (1ml/kg) or Ex4 (3µg/ml/kg).
- Chow intake monitored continuously for 24hrs and body weight recorded 24hrs post-drug administration
- Within-subjects, counter-balanced designed. Injections separated by 72h

BioDaq Meal-Pattern Analysis



Aim 1: Examine effects of Gpr160-KD on feeding behavior

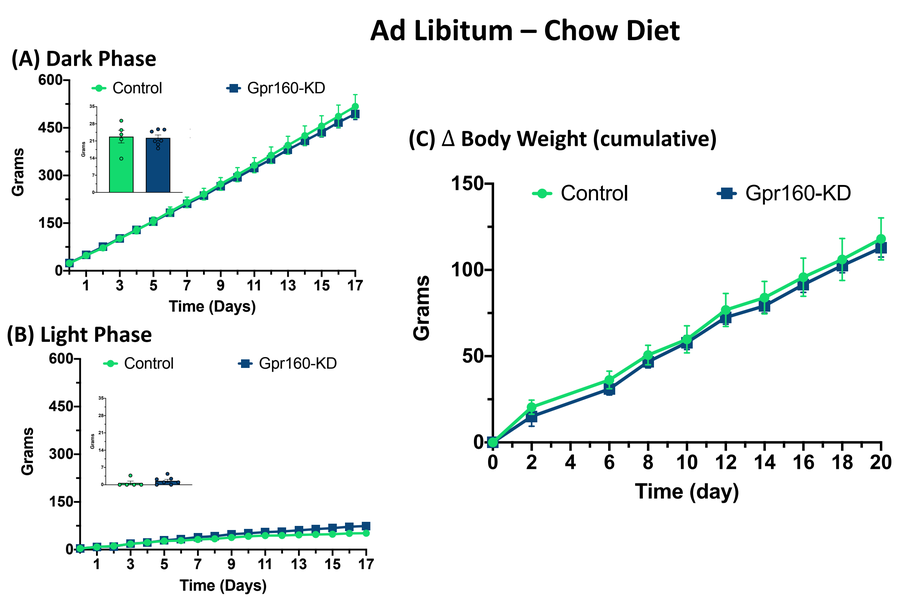


Figure 1 Effects of Gpr160-KD in the brainstem on ad libitum chow intake. Food intake was monitored continuously for 18 days. Feeding behavior during the (A) dark phase and (B) light phase was no significantly different between the AAV-control group (n=6) and the AAV-GPR160-KD (n=7) group. (C) Cumulative change in body weight was not impacted by GPR160-KD. All data represented as Mean ± SEM. Data analyzed with an unpaired multiple t-test.

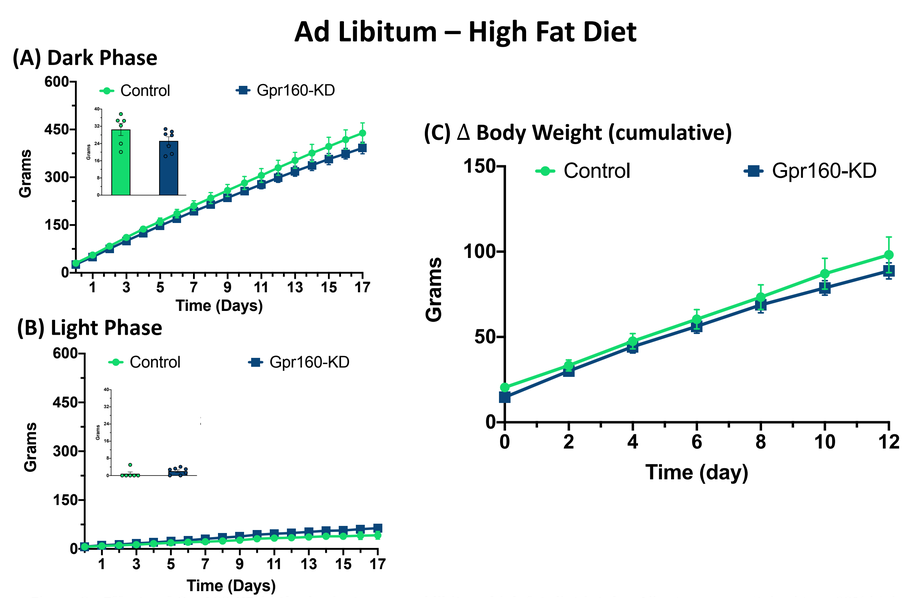


Figure 2: Effects of Gpr160-KD in the brainstem on ad libitum high fat diet intake. All rats were switched to a 60% high fat diet for continuous continuous food intake and 48hr body weight was recorded for an additional 18 days. No significant difference between control (n=6) and Gpr160-KD (n=7) rats in food intake during the dark phase (A), light phase (B), or cumulative change in body weight body weights (C). All data represented as Mean ± SEM. Data analyzed with an unpaired multiple t-test.

Aim 2: Examine the role of Gpr160 in Ex4-mediated satiety

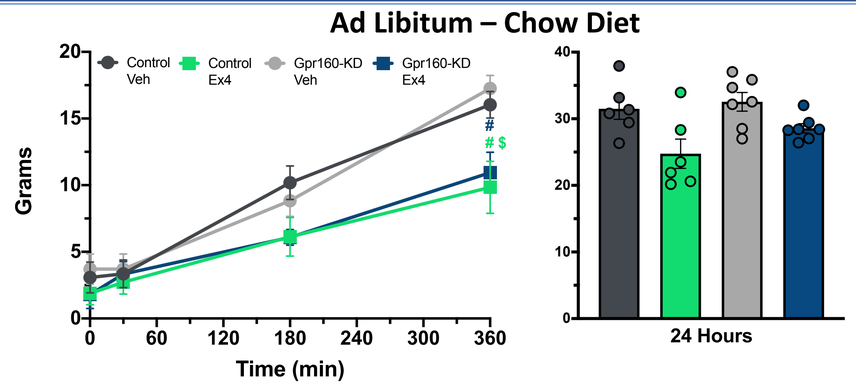


Figure 3: Effects of Gpr-160-KD on anorectic effects of Exendin-4 with ad libitum chow intake Prior to dark phase, control (n=6) and Gpr160-KD (n=7) rats received i.p. injections of either 1ml/kg saline (Veh) or 3ug/mg/ml Exendin-4 (Ex4). Food intake and body weight was recorded over a 24h period. In both viral cohorts, Ex4 significantly suppressed cumulative food intake at 180, 360, and 1440min post-ip. Knockdown of Gpr160 did not attenuate the intake suppressive effects of Ex4. Experiment carried out in a within-subjects, counter-balanced design. Data analyzed with repeated measure two-way ANOVA and tukey's post hoc test. All data expressed as mean ± SEM. $^{\#}p < 0.05$ *versus* Gpr160-KD Vehicle and $^{\$}p < 0.05$ *versus* Control Vehicle rats.

Summary

- While not significant, GPR160-KD may be shifting the diurnal feeding patterns in which Gpr160-KD rats exhibited a slight increase in light phase feeding (**Fig 2A**) and corresponding slight decrease in dark phase feeding (**Fig 2B**) compared to the control.
- Despite evidence to suggest an interaction between CART and Glp1 to regulate energy balance, compromise of brainstem Gpr160 did not impact the anorectic effects of Ex4 (Glp1 agonist).
- Lack of an effect could be due to an insufficient degree Gpr160KD, the studies were underpowered, or the brainstem may not be a primary site of action for CART-induced satiety
- Future studies can examine other regions of the brain as well as other neuropeptide's known to be involved or contribute to CART-mediated energy balance.

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References

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