The endogenous role of hindbrain ghrelin receptors in regulating feeding behavior

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Background

- Obesity is an epidemic in the U.S. and a leading cause of multiple major health problems; therefore, an effective treatment is needed.
- Obesity is caused by increased food intake, which is controlled by various circuits and signals in the central nervous system, so understanding the neuroendocrine control of food intake will be important in treatment development.
- One such signal is ghrelin which is released from the stomach. Circulating ghrelin levels are elevated before a meal and increase food intake. Ghrelin's intake stimulatory effects are attributable to its actions on its receptor, growth hormone secretagogue receptor 1a (GHSR1a) in the brain, where it is widely expressed, including in the hindbrain.
- Ghrelin increases food intake when injected into the hindbrain ventricle and into specific hindbrain nuclei including the nucleus tractus solitarius (NTS), but the endogenous role of GHSR1a in the hindbrain is not well understood. Also not known is the hindbrain role of the recently identified endogenous antagonist to GHSR1a, LEAP-2.
- This project tested the hypothesis that hindbrain GHSR1a plays a physiological role in the hindbrain to increase food intake and tested this hypothesis by [1] chronically knocking down GHSR1a in the NTS using an AAV shRNA and [2] acutely injecting the endogenous GHSR1a antagonist LEAP-2 into the fourth (hindbrain) ventricle.

Methods

Experiment 1:

Subjects: Male Sprague-Dawley rats
Surgery: Bilateral NTS injection of an AAV shRNA to knock down the GHSR1a and implantation of an injection cannula in the fourth ventricle
Surgical verification: In progress
Behavior:

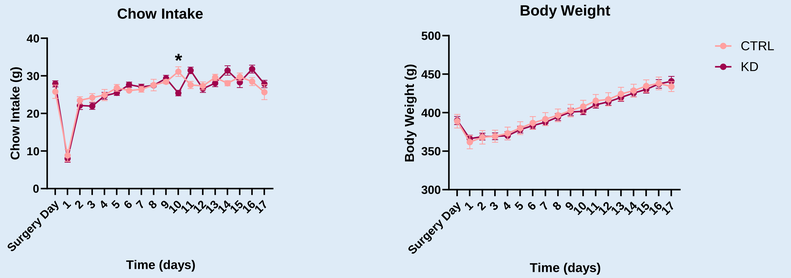
- Measured baseline 24h food intake and body weight
- Injected 0 or 150pmol ghrelin into the fourth ventricle and measured chow intake.
- Measured baseline chow intake in light and dark cycles.
- Injected 0 or 0.5ug of the intake inhibitory GI satiation signal Cholecystokinin (CCK) subcutaneously and measured short-term chow intake.

Experiment 2:

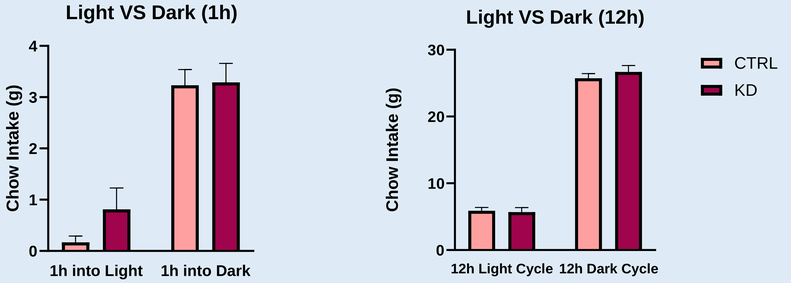
Subjects: separate group of Male Sprague-Dawley rats
Surgery: Implantation of an injection cannula into the fourth ventricle
Surgical verification: Placement verified by 4V injection of 5TG and 100% increase in blood glucose
Behavior:

- Injected 0, 150 or 1500pmol LEAP2 and measured chow intake and body weight.

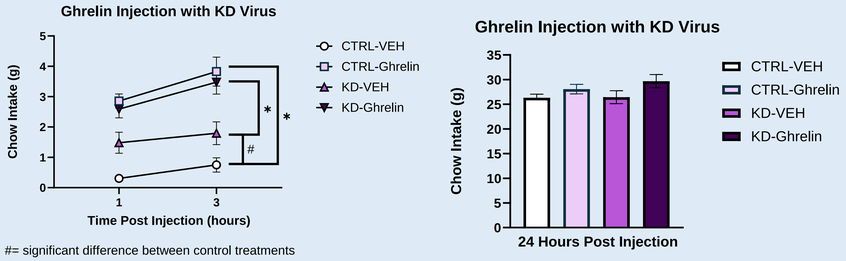
GHSR1a KD did not impact baseline chow intake and body weight



GHSR1a KD did not impact light vs dark cycle chow intake



GHSR1a KD attenuated ghrelin stimulated chow intake

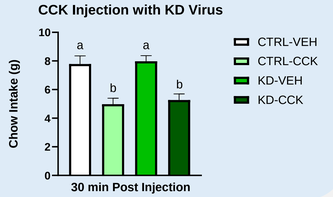


#= significant difference between control treatments

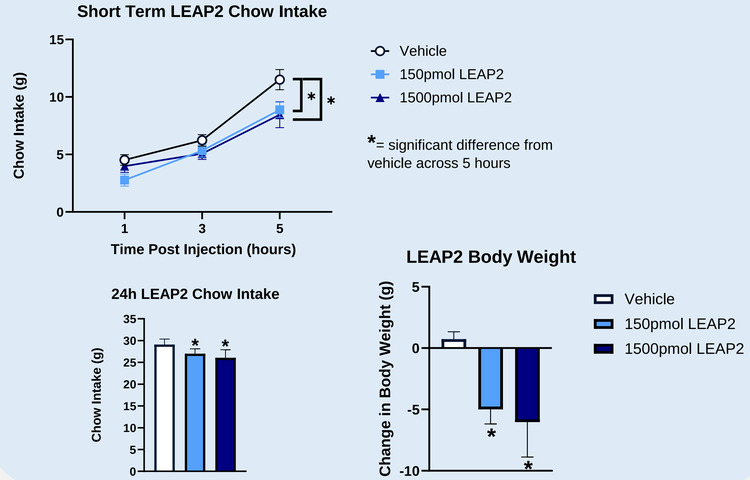
*= significant difference between ghrelin treatment and control treatment

GHSR1a KD did not impact CCK induced intake inhibition

- Hindbrain ghrelin blocks CCK induced intake inhibition.
- This experiment tested the hypothesis that KD would increase CCK sensitivity.



LEAP2 decreases chow intake and body weight



Conclusions

- Results show that while the chronic NTS knockdown of the GHSR1a did not result in baseline differences in chow intake or body weight and only mildly attenuated the intake stimulatory effects of ghrelin, acute hindbrain injections of LEAP-2, the endogenous GHSR1a antagonist, significantly reduced chow intake and body weight.
- Together, results suggest a role for hindbrain GHSR1a in the endogenous control of food intake.