Gcg-Knockdown Rats Overconsume a Palatable Western Diet

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ABSTRACT

The peptide product of the gene encoding glucagon (*Gcg)* is processed to form Glucagon-like peptide-1 (GLP-1) in the intestine and in hindbrain neurons. GLP-1 acts in the brain to reduce intake of palatable, rewarding foods. We developed a homozygous Gcg-Cre knock-in Sprague-Dawley rat model, and discovered that these rats have markedly reduced expression of *Gcg* and very low levels of GLP-1 (Zheng et al., 2022). The purpose of this experiment was to determine if homozygous Gcg-Cre rats (here, called Gcg-KD rats) display altered food intake compared to wild type (WT) control rats. We hypothesized that Gcg-KD rats will eat more of a palatable "Western Diet" (WD; high in fat and sugar) than WT rats, since Gcg-KD rats have reduced levels of GLP-1 in the body and brain. Home-cage intake of regular chow and WD was assessed every day for 8 weeks, and rats were weighed three times a week. EchoMRI scans were performed before and after the experiment to measure body composition (lean and fat mass). Gcg-KD rats consumed more WD compared to wild type controls, and displayed greater preference for WD vs. chow. This effect was larger in female vs. male rats. Gcg-KD rats also gained more weight and had higher fat mass at the end of the study compared to WT controls. Thus, lower levels of GLP-1 in Gcg-KD rats may lead them to overconsume palatable WD.

INTRODUCTION & BACKGROUND

Gcg-KD rats (i.e., homozygous for Gcg-Cre) have reduced levels of GLP-1 in the brain and body (Zheng et al., 2022). Since drugs that increase GLP-1 receptor signaling (e.g., Semaglutide, Ozempic) have been shown to reduce intake and preference for palatable foods in humans and in animal models, **we hypothesized that Gcg-KD rats (with reduced GLP-1 signaling) will display increased preference for a palatable Western Diet (WD)** compared to wild type (WT) controls.

Background:

- Homozygous Gcg-Cre rats have reduced levels of GLP-1 in the blood and brain (Zheng et al., 2022)
- GLP-1 receptor agonists, which can be used to treat obesity, also aid in in reducing food intake and motivation for palatable foods (Drucker, 2022)
- GLP-1 receptor agonists include medications such as Semaglutide and Ozempic, which have anti-obesity effects (Bettadapura et al., 2024)

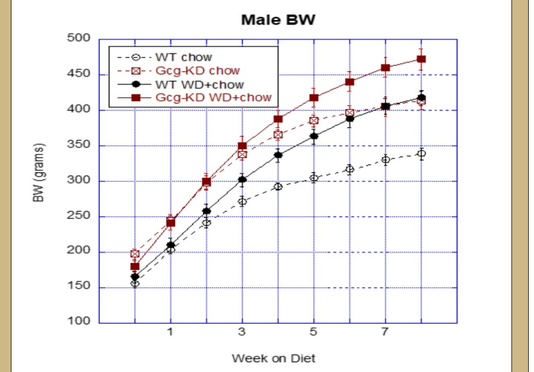
Research Goal

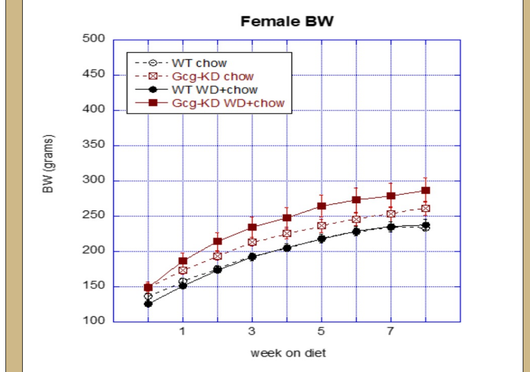
We set out to test the hypothesis that male and female Gcg-KD rats will overconsume palatable WD and display greater preference for WD vs. chow, compared to WT control rats.

METHODS

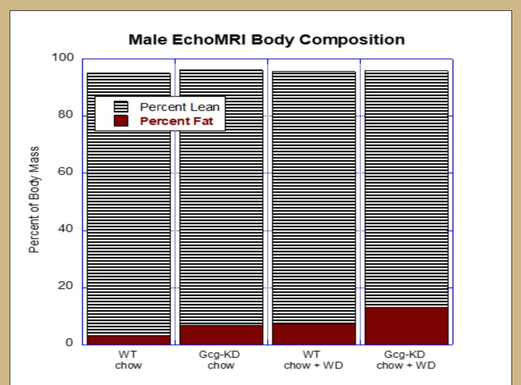
- A total of 42 age-matched Sprague Dawley rats were used (N=10-12 per genotype, per sex)
- Rats were assigned to either a chow-only group, or were given a choice between chow vs. WD. Rats were housed 2-3 per cage (same sex, genotype, and diet within each cage)
- EchoMRI scans were conducted at the beginning of the experiment (before diet assignment) and again after 8 weeks of diet maintenance
- Daily intake of chow and WD by rats in each cage (i.e., combined intake of 2-3 rats, averaged per rat) was measured for 8 weeks
- Rats were individually weighed 3 times/week

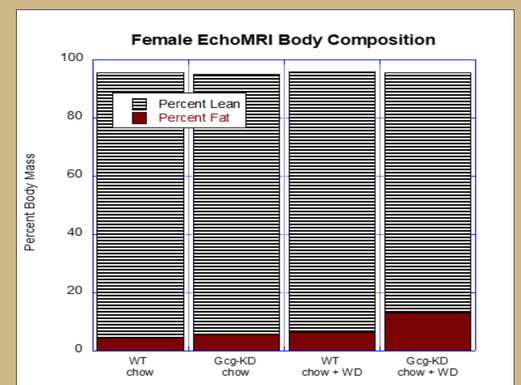
RESULTS



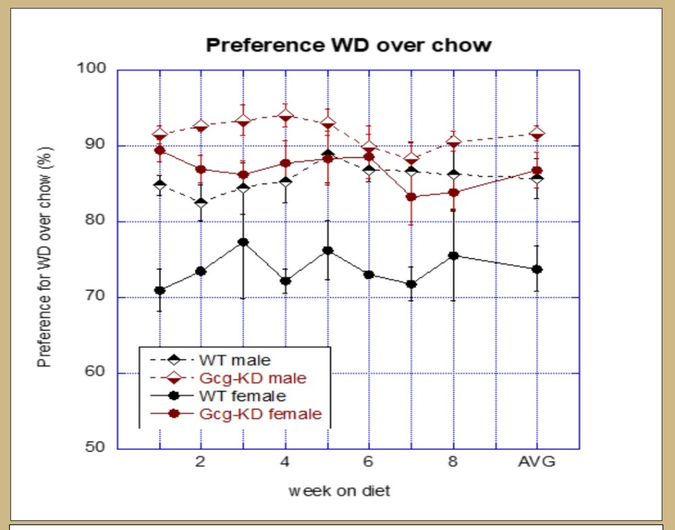


There was a significant effect of genotype on body weight (BW), but not on BW gain. There was a significant effect of diet on BW gain. There was no interaction between genotype and diet on BW or BW gain in males or females.





Both Sexes: WD adds more fat to males and females. There are significant effects of genotype and diet on body composition.
Males: There is no significant interaction between genotype and diet. WD increases body fat similarly in male Gcg-KD and WT rats.
Females: There is a significant interaction between genotype and diet. WD adds more body fat in female Gcg-KD vs. WT rats.



- Compared to male WT rats, male Gcg-KD male display a trend towards a higher preference for WD vs. chow (p=0.08).
- Gcg-KD female rats display a significantly higher preference for WD vs. chow, compared to WT females (p=0.04).

SUMMARY & DISCUSSION

- The Rinaman Lab developed a novel Gcg-Cre rat model that is useful for anatomical and functional studies.
- Homozygous Gcg-Cre rats are a novel animal model for studying the behavioral effects of *Gcg* knockdown, accompanied by reduced levels of GLP-1 (and other products of the *Gcg* gene) in the body and brain.
- Our results support the view that *Gcg* knockdown is associated with increased preference for palatable WD, leading to increased BW gain and accumulation of body fat.
- While there currently is no evidence that humans with obesity have reduced levels of endogenous GLP-1, GLP-1 agonist drugs such as Semaglutide and Ozempic are effective in reducing BW by reducing the motivation to consume palatable foods.
- Our Gcg-KD rat model may be useful for research to understand how GLP-1 signaling modulates food intake and preference for highly palatable, obesogenic foods.

REFERENCES

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- Zheng et al., (2022). https://doi.org/10.1016/j.molmet.2022.101631