Protein restriction improves metabolic health independent of dietary sugar content

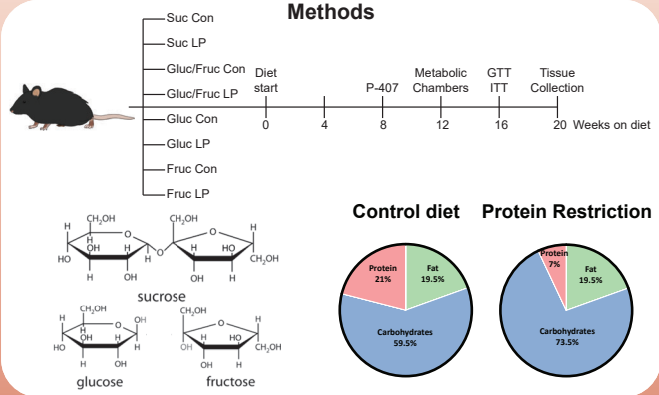
Michelle M Sonsalla[1,2,3], Madeline Johnson[1,2], Samuel Cai[1,2], Reji Babygirija[1,2], Isaac Grunow[1,2], Yang Liu[1,2], Bailey Knopf[1,2], Julia Illiano[1,2], Chung-Yang Yeh[1,2], Mari Cole[1,2], David Harris[1,2], Dudley Lamming[1,2,3]

[1] University of Wisconsin-Madison, Madison, WI, USA, [2] William S. Middleton Memorial Veterans Hospital, Madison, WI, USA, and [3] Comparative Biomedical Science Graduate Program, University of Wisconsin-Madison, Madison, WI, USA

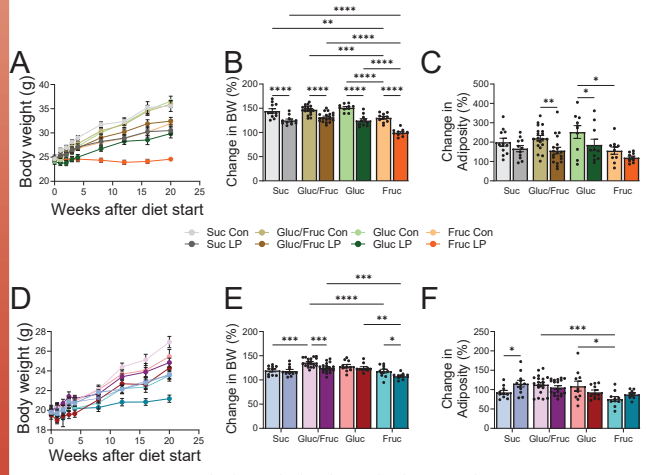
Introduction

- In recent decades, the consumption of highly processed foods and beverages, particularly using high-fructose corn syrup, has hit an all-time high, which is associated with a multitude of negative health consequences.
- Fructose has been implicated in the development of several diseases, including obesity, type 2 diabetes, and non-alcoholic fatty liver disease.
- Due to the high prevalence of these diseases, it is important to identify interventions that are effective at combatting these diseases.
- Protein restriction (PR) has been shown to have beneficial effects on metabolic health and longevity in a variety of model organisms as well as in humans.
- When adopting a PR diet, caloric content remains consistent, and the decrease in calories from protein is compensated for by increased carbohydrates, suggesting that if sugar type alters health, it may be able to alter response to PR even more strongly.

Methods



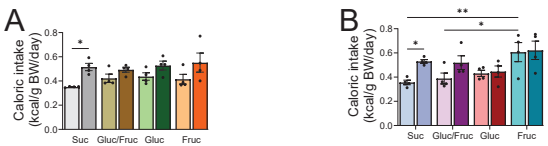
Protein restriction improves body weight in all diets but fructose-only diets have the lowest body weight and adiposity.



A-B) In male mice, protein restriction (PR) reduced body weight regardless of carbohydrate type. Fructose-only diets resulted in lower body weight, even at 21% protein.
C) Overall, PR was effective at reducing adiposity, with the most dramatic changes occuring in the Gluc/Fruc and Gluc diets. Again, fructose-only diets had decreased adiposity compared to the other carbohydrate compositions
D-E) In female mice, PR reduced body weight in only Gluc/Fruc an Fruc conditions, but as in males, females fed fructose only had decreased body weight.
F) Fructose-only diets had decreased adiposity. PR had minimal impact on adiposity in female mice.

* = p < 0.05, ** = p < 0.01, *** = p < 0.001, **** = p < 0.0001; n =10-19

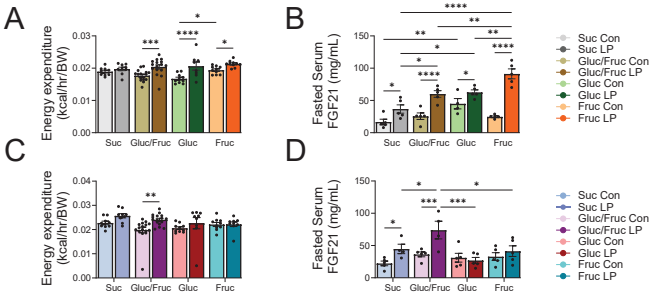
PR and fructose both increase caloric intake.



Food consumption was measure in the home cages of male (A) and female (B) mice.
A) In male mice, PR increased caloric intake overall, but most strongly in the sucrose-fed groups.
B) In female mice, PR increased caloric intake in groups with both glucose and fructose present, but not in gluctose- or fructose-only groups. Fructose-fed females had increased food consumption compared to the other control groups.

* = p < 0.05, ** = p < 0.01; n = 4

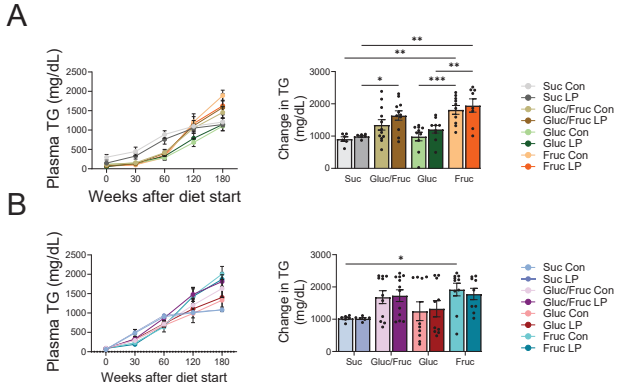
PR increases energy expenditure and induces FGF21 production in all males, but only in females consuming both glucose and fructose.



A) PR increased energy expenditure in all groups except sucrose-fed males.
B) PR induced FGF21 production in all groups, however Fruc LP mice had the most dramatic increase.
C) PR only increases energy expenditure in Gluc/Fruc-fed mice.
D) Only diets with both glucose and fructose exhibit a PR-induced increase in FGF21.

* = p < 0.05, ** = p < 0.01, *** = p < 0.001; n = 8-16 for energy expenditure, 4-5 for FGF21

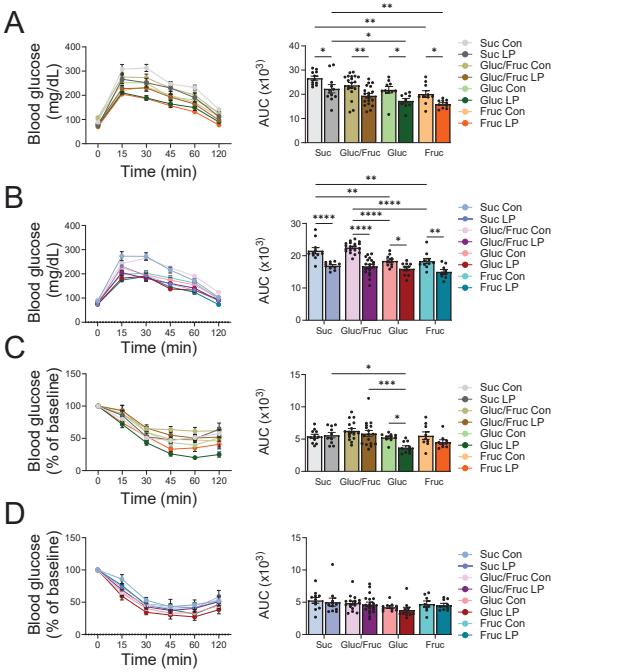
Gluc/Fruc and Fruc diets had increased triglyceride production.



A P-407 assay was performed to determine triglyceride production.
A) In male mice, both Gluc/Fruc and Fruc diets had increased triglyceride production.
B) In female mice, only Fruc diets had increased triglyceride production.

* = p < 0.05, ** = p < 0.01, *** = p < 0.001, **** = p < 0.0001; n =10-19

PR improves glucose tolerance in male and female mice regardless of carbohydrate source.



A-B) Glucose tolerance tests were performed in male (A) and female (B) mice. PR improved glucose tolerance in both males and females. Surprisingly, fructose-only diets had the best glucose tolerance, particularly compared to diets containing both glucose and fructose.
C-D) Insulin tolerance tests were performed in male (C) and female (D) mice. PR only improved insulin sensitivity in male mice fed the glucose-only diet.

* = p < 0.05, ** = p < 0.01, *** = p < 0.001, **** = p < 0.0001; n =10-19

Conclusions

Protein Restriction improves:
- Body Weight
- Adiposity (in males)
- Glucose tolerance
- Insulin sensitivity (in males)

Fructose-only diets resulted in decreased body mass and adiposity and improved glucose tolerance.

Fructose-containing diets contributed to increased triglyceride production.

Protein restriction is an effective dietary intervention that can improve health regardless of carbohydrate type. However, fructose and glucose result in different metabolic phenotypes that may result in different health outcomes overall. As such, further research is needed to determine the role of carbohydrates in metabolic health and longevity.

Acknowledgements

We would like to thank all the members of the Lamming lab for their assistance and insight, and the Merrins, Kimple, and Davis labs for their support. The Lamming lab is supported in part by the NIA (AG056771, AG062328, AG081482, and AG084156), the NIDDK (DK125859), by a grant from the Alzheimer's Association (23AARG-1029665), and by startup funds from UW-Madison. RB was supported in part by F31AG081115. MMS was supported in part by a Supplement to Promote Diversity in Health-Related Research RF1AG056771-06S1. The Lamming lab was supported in part by the U.S. Department of Veterans Affairs (I01-BX004031 and IS1-BX005524), and this work was supported using facilities and resources from the William S. Middleton Memorial Veterans Hospital. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. This work does not represent the views of the Department of Veterans Affairs or the United States Government.

LAMMING LAB
for the Molecular Physiology of Aging