Dietary protein restriction mitigates the development and progression of Alzheimer's disease

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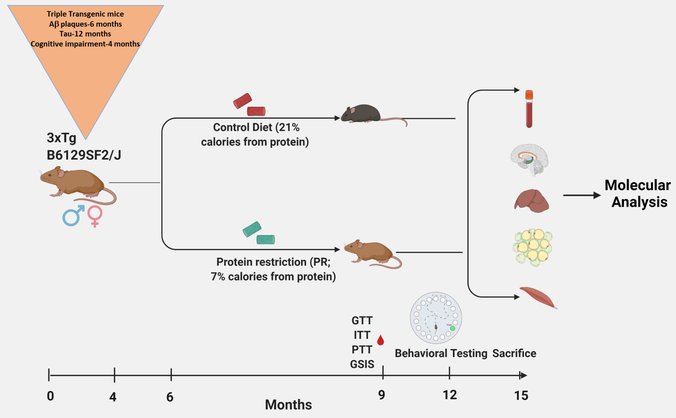
Introduction

- Alzheimer's disease (AD) is the most common form of dementia, and it is estimated that by the year 2050 the number of people aged 65 and older with AD may grow to a projected 13.5 million leading to a huge public health crisis in the United States.
- Aging is one of the biggest risk factor for AD and dietary interventions have been proven to delay the onset of age related diseases.
- Dietary protein restriction has been shown to be beneficial in improving overall health span in both humans and mice. However, the effect of dietary protein restriction in delaying the symptom progression of AD is largely unknown
- In this study we sought to determine the effects of a low protein diet in improving metabolic dysfunction, cognitive deficits as well as AD pathology using an early onset model of AD.

Study Design



Results

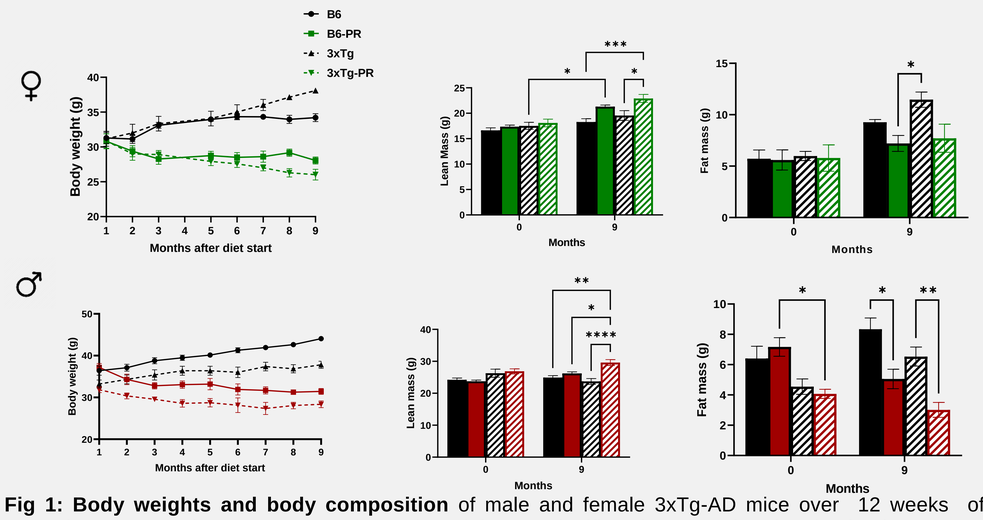


Fig 1: Body weights and body composition of male and female 3xTg-AD mice over 12 weeks of feeding. Control = 21% protein, LP = 7% protein. Body weight was significantly reduced and maintained on a PR diet (n=8-10 mice/group*p<0.05,**p<0.01 (genotype vs diet), Sidak's multiple comparison test)

Protein restriction improves glucose homeostasis

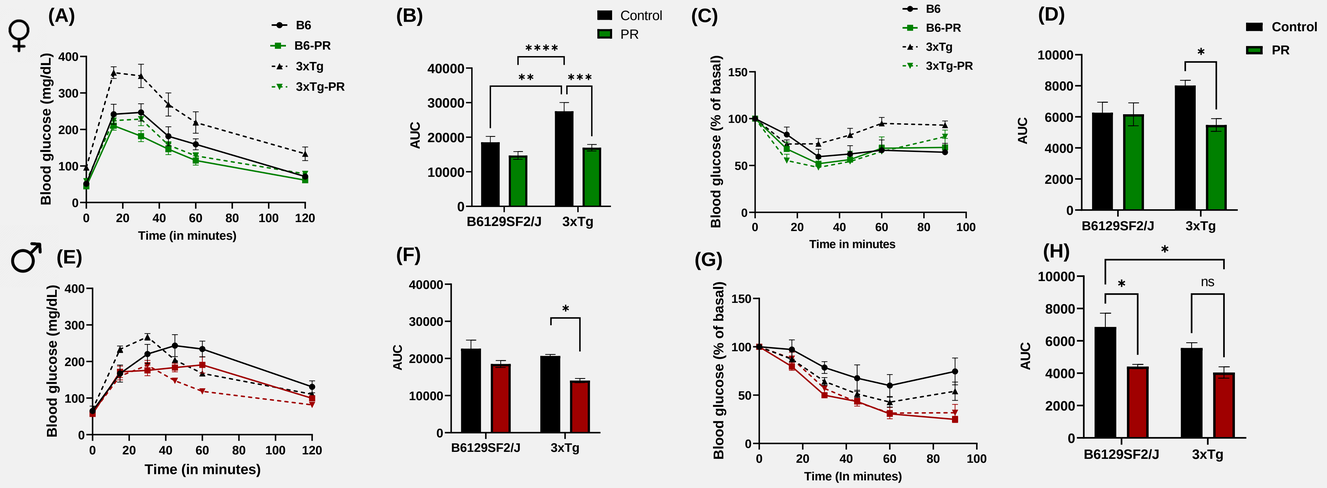


Fig 2: **A Low protein diet improves glucose homeostasis.** A glucose tolerance test (GTT) and an insulin tolerance test (ITT) on female mice (A- D) and male mice mice (E-H) fed on a low protein diet (PR) or control diet in both 3xTg as well as B6129SF2/J strains following 3 months. (n=10- 12 mice/group, **=p<0.05 vs LP, *=p<0.01 vs LP, Tukey-Kramer test following ANOVA). Improved glucose tolerance and insulin sensitivity was observed in mice fed on a low protein diet.

Protein restriction improves cognition

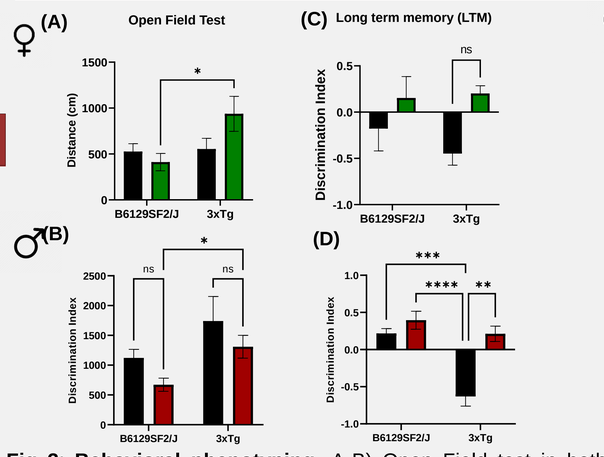


Fig 3: **Behavioral phenotyping**. A-B) Open Field test in both male and female 3xTg mice fed on a low protein diet or control diet. C-D) Spatial learning and Long term memory performance**.** In both the males and females, low protein diet fed animals exhibited better spatial memory in a barnes maze compared with the ones that were on control diet (n=8-10 mice/group*p<0.05,**p<0.01 (genotype vs diet), Sidak's multiple comparison test)

Male 3xTg-AD mice have lower survival probability than PR fed mice.

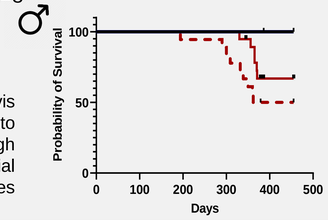


Fig 5. PR increased survival probability in males. Survival curves of 15 month old male 3xTg-AD mice and B6 control mice following PR. Kaplan-Meyer Test

Low protein diet decreases tau-phosphorylation and mTORC1 signaling in the brain

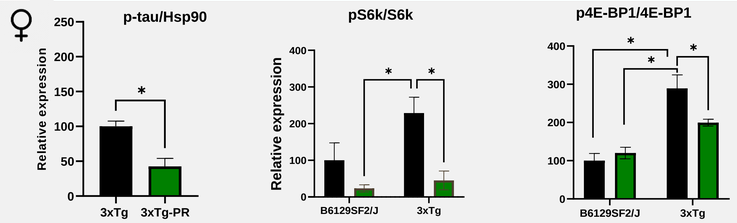


Fig 4: **A low protein diet decreases tau phosphorylation and mTORC1 signaling in the brain**. Female mice on a low protein diet had decreased tau phosphorylation, a trend towards decreased S6k phosphorylation and p-62 levels.(n=6 mice/group, **=p<0.05 vs control, *=p<0.01 vs LP, Tukey-Kramer test following ANOVA)

Protein restriction reduces amyloid β plaques

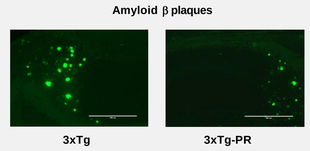
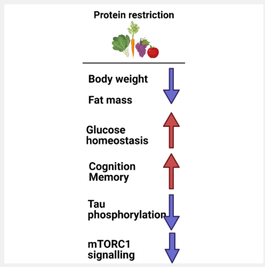


Fig 5. PR reduced amyloid β-plaques. Thioflavin-S (ThS) staining of 5 m paraffin embedded brain slices. Increased ThS positive aggregates in the **hippocampus of female 3xTg mice** was reduced following PR. Scale bar-400 m

Conclusions and Future Directions



- **Protein restriction improved glucose homeostasis in both males and females with a stronger effect seen on females.**
- **Restricting protein improved cognition in a long term memory test in females**
- **In females, a low protein diet decreased tau phosphorylation and mTORC1 signaling along with a decrease in p-62 autophagy marker.**
- **These results are promising and suggests that a low protein diet is beneficial in mitigating the symptom progression of AD.**

Acknowledgments

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