



Dietary restriction of individual BCAAs improves metabolic health and cognition in a mouse model of Alzheimer's disease

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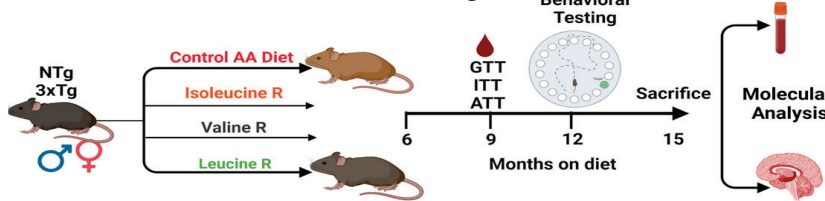
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Introduction

- The benefits of low-protein diets are recapitulated by diets with reduced levels of the three branched-chain amino acids (BCAAs), leucine, isoleucine, and valine.
- Elevated plasma levels of BCAAs are associated with an increased risk of multiple age-associated diseases including diabetes and Alzheimer's disease (AD).
- Dietary protein restriction (PR) slows the progression of AD at both the molecular and pathological levels in the 3xTg mouse.
- Objective: we aim to investigate the contribution of each dietary BCAA to the beneficial effects of PR on the development of AD.

Research Design



Restricting any of the BCAAs improved short-term memory in males but not females

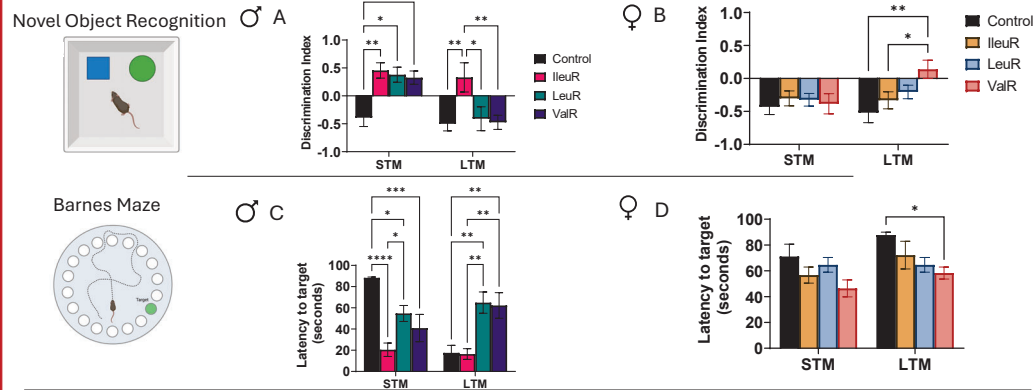


Figure 3: Novel Object Recognition and Barnes Maze assays on 12-month-old 3xTg AD mice following 6 months of individual BCAA restriction. (A-B) Discrimination index of the amount of time interacting with the novel object compared to familiar object in both male and female 3xTg mice after short term memory test (STM) and long-term memory test (LTM). (C-D) Latency to target hole following Barnes maze spatial memory assessment in both males and female 3xTg AD mice.

Restriction of Isoleucine and Valine decreased body weight in both males and females

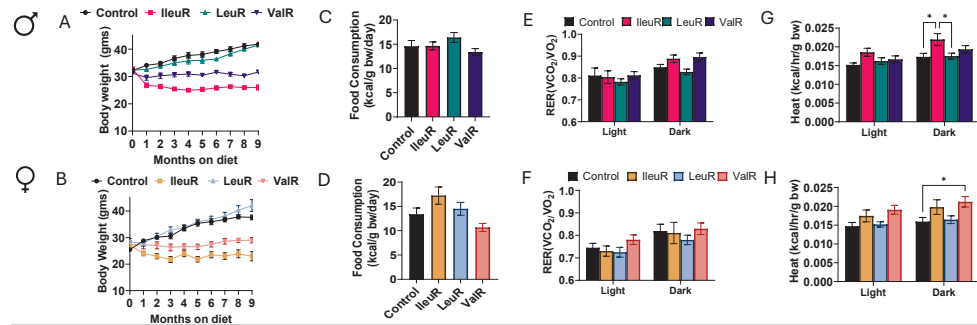


Figure 1: Bodyweight and fuel utilization patterns in 3xTg AD mice following individual BCAA restriction. (A-B) Bodyweight over the course of 9 months in males and females. (C-D) Food consumption in males and females. Metabolic chambers were utilized for fuel utilization. (E-F) Respiratory exchange ratio (RER) in males and (G-H) Energy Expenditure in males and females.

Isoleucine restriction reduced AD pathology: suppressing Tau phosphorylation and mTORC1 activity in males

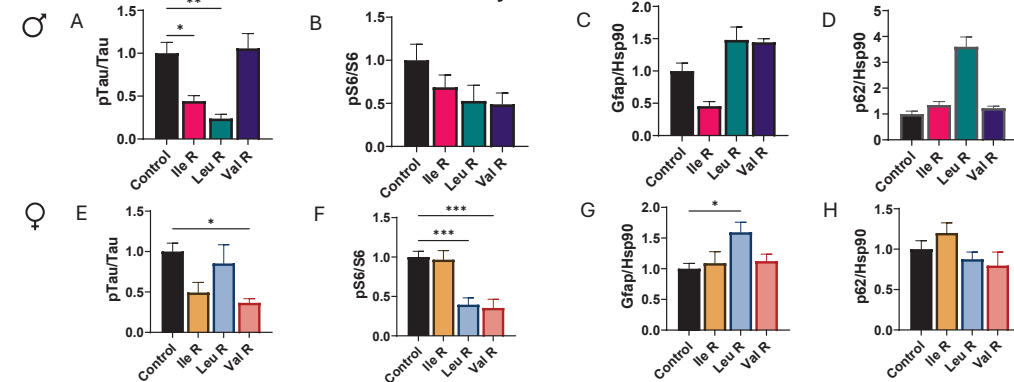


Figure 4: Western blot analysis of p-Tau/Tau, pS6/S6, Gfap, p62 expression in 3xTg mice, n=6 biologically independent mice per group. (A-D) Male brains. (E-H) Female brains.

Restriction of Isoleucine improved glycemic control in both males and females

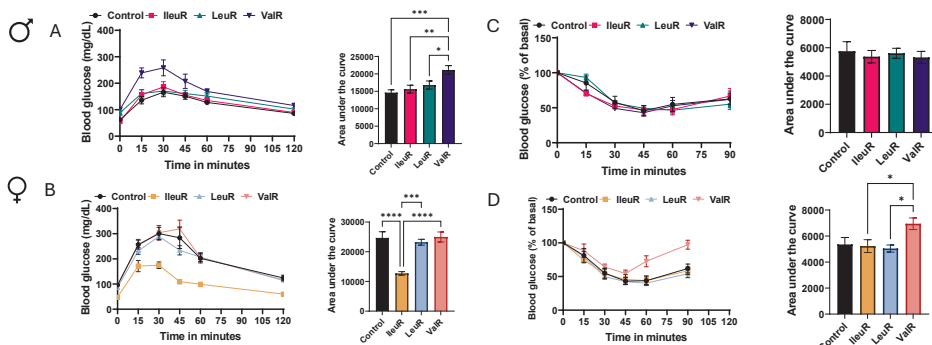


Figure 2: Isoleucine restriction improves glucose tolerance in both males and females. (A-B) Glucose tolerance test (GTT) was performed in mice after 3 months on diet in both males and females. (C-D) An insulin tolerance test (ITT) was performed in 3xTg mice after one week following GTT in both males and females. Restriction of individual BCAAs didn't affect insulin sensitivity in neither of the sexes.

Conclusion

BCAA restriction improved metabolic health and cognition in the 3xTg mouse model of AD in a sex dependent manner. Specifically: Isoleucine and valine have better effects in regulating metabolism than valine. All three BCAAs have a more significant influence on cognition in male mice than in females. Isoleucine restriction exhibited reduced AD pathology compared to the other two amino acids.

Future direction: Reducing dietary isoleucine could serve as a novel approach to prevent or delay the progression of AD.

Acknowledgements

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