Influence of Isolation Stress on Aβ Production and Cognitive Function in 5xFAD mice

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Alzheimer's Disease (AD) is a devastating neurodegenerative disease that affects nearly 44 million people worldwide, and is increasing exponentially in prevalence. Thus, research into its causes and prevention is crucial. Mouse models of Alzheimer's disease are often used to better study AD pathology. These mice have human genes that cause AD and this results in heightened production of a protein called amyloid beta (Aβ). This protein is a pathological marker of AD. It has been well established that stress can influence AD pathology. This study investigates how isolation stress influences the production of amyloid beta in an AD mouse model. In addition, we investigated whether isolation stress causes cognitive deficits. The mice were group-housed or isolated for both 2 and 3 months, followed by cognitive testing and tissue collection. We found that isolated AD mice had significantly more amyloid beta plaques than group-housed animals. AD mice isolated for 3 months also displayed impaired cognition. All together, our results support the research that isolation stress increases Aβ production and impacts cognition in a mouse model of Alzheimer's disease.

Introduction

- Alzheimer's disease (AD) is a neurodegenerative disorder that affects nearly 5.5 million Americans, and there is currently no cure (1).
- The two main pathological hallmarks of AD are Aβ plaques and neurofibrillary tangles.
- We hypothesized that 5xFAD+ mice housed in isolation for 2 or 3 months would produce significantly more Aβ than 5xFAD- mice.
- We also hypothesized that 5xFAD+ isolated mice would experience greater cognitive deficits in CFC compared to group housed 5xFAD+ or 5xFAD- animals, and that the performance will get worse as the time of isolation increases.

Methods

- 5xFAD mice were isolated or group housed for 2 or 3 months, followed by CFC.
- Animals were perfused one day after testing. A hemisphere of the brain was collected for immunohistochemistry and the hippocampus was removed from the other hemisphere and Aβ was quantified by an Aβx-42 ELISA.
- Sagittal sections of the brain were stained for Aβ plaques with thioflavin. Confocal microscopy was used to image the sections, and ImageJ software was used to count plaques.
- Student's T-test were used to examine how extended isolation stress affected plaque counts in the hippocampus of 5xFAD+ animals.
- A 2x2 ANOVA was used to examine the effects of isolation and genotype on freezing in a CFC paradigm and soluble Aβ levels.

Histochemistry

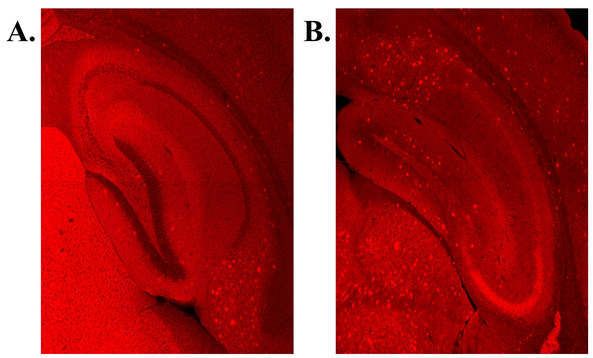


Figure 1. Representative images of plaques in the hippocampus of 5xFAD+ animals group housed (A) and isolated for 3 months (B).

Two months of isolation

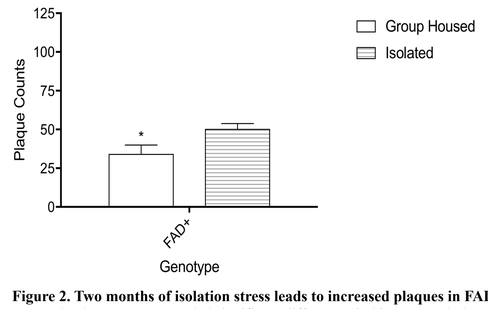


Figure 2. Two months of isolation stress leads to increased plaques in FAD+ mice. Student's t-tests revealed significant differences in hippocampal plaque counts between isolated and group housed animals.

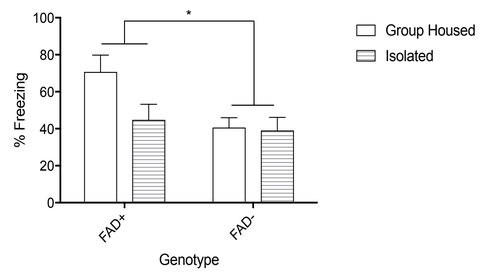
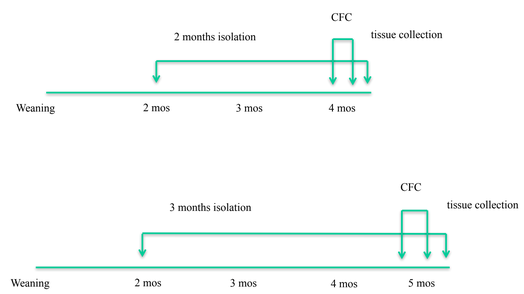


Figure 3. Two months of isolation stress did not impact freezing behavior in CFC. A 2x2 ANOVA revealed a main effect of genotype such that FAD+ animals froze significantly more than FAD- animals regardless of condition.

Timeline



Three months of isolation

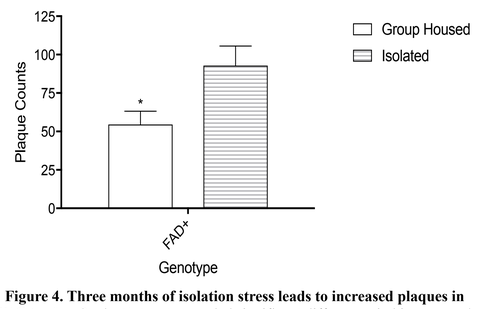


Figure 4. Three months of isolation stress leads to increased plaques in FAD+ mice. Student's t-tests revealed significant differences in hippocampal plaque counts between isolated and group housed animals.

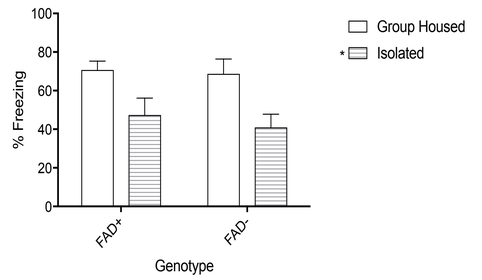


Figure 5. Three months of isolation stress leads to decreased freezing in CFC. A 2x2 ANOVA revealed a main effect of condition such that isolated animals froze significantly less than group housed animals regardless of genotype.

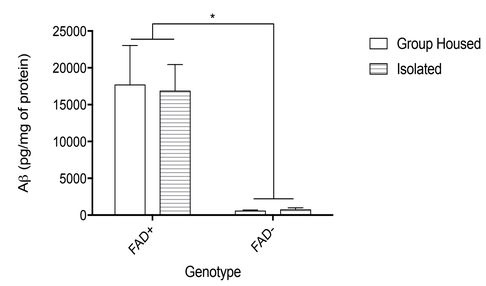


Figure 6. Three months of isolation stress did not significantly impact soluble Aβ levels. A 2x2 ANOVA revealed a main effect of genotype such that FAD+ animals had significantly more hippocampal Aβ than FAD- animals regardless of condition.

Conclusion

•Isolated 5xFAD+ mice produced significantly more plaques after 2 and 3 months of isolation
•CFC performance was not significantly different after 2 months of isolation
•CFC performance significantly worsened after 3 months of isolation
•Soluble Aβ levels were not significantly different after 3 months of isolation

The objective of this study was to examine how a social stressor, isolation stress, contributes to Alzheimer's disease. We have demonstrated that extended isolation can amplify Alzheimer's pathology in 5xFAD transgenic mice. In addition, we have also demonstrated that 3 months of isolation stress results in cognitive deficits regardless of genotype.

Future directions

- Identifying the pathways that cause our observed results is imperative. Future research will examine the mechanism behind the cognitive deficits observed in contextual fear conditioning and the increase in hippocampal plaques, which appears to be independent of soluble amyloid beta production.
- We also plan to explore methods of rescuing these isolation induced deficits. Studies have demonstrated enriched environment and exercise can reduce Aβ and we plan to explore if these can prevent the stress induced deficits.

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