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"A Double Burden: Age- and Sex-Dependent Phenotype of Alzheimer's Disease in 5xFAD Mice"

BACKGROUND: Alzheimer's Disease (AD) is the leading cause of dementia worldwide. It affects approximately 7 million people in the U.S., with nearly two-thirds of cases occurring in women. AD is characterized by progressive memory loss, neuronal degradation, and accumulation of beta-amyloid plaques (Aβ), tau pathology, and neurofibrillary tangles (NFTs). Although these pathological features of AD are well characterized, effective treatments or preventive therapies remain limited. In addition, relatively little research has focused on sex-dependent mechanisms that might contribute to disease progression. Animals are therefore essential for studying these mechanisms, particularly those that closely mimic AD in humans. While several transgenic mouse models have advanced our understanding of the pathology, many do not fully recapitulate the disease in both males and females.

OBJECTIVES: The 5xFAD mouse model reproduces key pathological features, including robust Aβ pathology and neuronal loss, making it well suited for examining sex-dependent differences in the behavioral and cognitive manifestations of AD.

METHODS: In this preliminary study, we used young adult (4 months of age) and one-year-old male and female 5xFAD mice to characterize age- and sex-dependent differences in behavioral phenotypes. Groups were subjected to three different behavioral testing including the Novel Arm Y-maze, Open Field (OF), and Novel Object Recognition (NOR) tests. At the end, mice were single housed in Metabolic Cages for 5 days to assess physiological parameters and locomotor activity.

RESULTS: We observed distinct age- and sex-dependent differences in the AD phenotype. Compared with younger females, older female 5xFAD mice displayed increased anxiety-like behavior in the OF, altered novel arm entry ratios in the Y-Maze, and reduced performance in the NOR test. Additionally, metabolic cage assessments revealed genotype-dependent divergences in locomotor activity and energy balance in both males and females.

CONCLUSIONS: Together, these findings demonstrate that both sex and age significantly affect AD progression and behavior outcomes, supporting the use of the 5xFAD mouse model to investigate sex-dependent mechanisms in AD pathogenesis. Further research is needed to determine the translational relevance of these findings to human AD.