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Sex and age dependent effects of gut microbiota manipulation in App^{SAA} mouse model of Alzheimer disease

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Abstract

Background: Population based studies indicate that women are at significantly greater risk of developing Alzheimer's disease (AD) than men. Gut microbiome is involved in the pathogenesis of AD however sex specific (/differential) effect of gut microbiome manipulation is not well understood.

Method: To determine the effect of sex and age on the impact of gut microbiota manipulation on cognitive outcomes, 3-4 months old male and females App^{SAA} mice (AD) were treated with probiotics (for 8 weeks) and antibiotics for (10-days) along with C57BL/6J and hApp as controls. Based on our previous studies, probiotic had beneficial effects on younger AD females and had no effect on males. To understand if gut bacteria are directly involved in eliciting these differential effects, we collected the stool samples from AD females treated with probiotic (VSL#3) and did fecal microbiota transplantation (FMT) in younger and older male and female AD mice. Neurobehavioral testing was performed including Open field task (OFT), Y-Maze, Contextual fear conditioning (CFC) and Novel object recognition. Brain and intestine samples were collected for biochemical and molecular characterization.

Result: In OFT, App^{SAA} mice travelled more distance as compared to C57BL/6J, and treating App^{SAA} mice with probiotic or antibiotic resulted in increased distance traveled. Antibiotic mice also showed less freezing in CFC task when compared to controls. Overall, FMT mice had a trend towards lower mean speed and distance travelled on Y-maze with no significant change in memory functions. That said, the App^{SAA} mice at 5-6 months of age showed no significant memory deficits as assessed using CFC and Y-maze, and will need to be aged further to assess the effect of antibiotics and FMT on cognitive deficits.

Conclusion: Treating App^{SAA} mice with probiotic or FMT (samples from probiotic treated females to AD young and old animals) had effects on motor behavior, but no effects in terms of memory functions. This lack of change is not surprising, as AD mice at early age did not demonstrate a behavioral phenotype compared to controls. Currently, we are doing biochemical analysis to elucidate if FMT influenced brain pathology (inflammation or Aβ) in AD mice.

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