The Role of Physical Activity in Inflammation and Neurogenesis in 5xFAD Mice

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Objective/Hypothesis The apoliprotein E epsilon 4 (APOE4) variant is the strongest genetic risk factor for late-onset Alzheimer's disease (AD) and is associated with accelerated clinical disease. Increasing evidence suggests that the immune system plays a direct role in AD pathogenesis, and several studies show that APOE genotype alter inflammatory pathways. However, the mechanism by which APOE4 influences the immune system is unknown. Physical activity (PA) is thought to play a neuroprotective role in late-onset AD and represents a possible strategy to attenuate cognitive decline and amyloid beta deposition in APOE4 carriers. We hypothesize that PA counteracts the negative inflammatory effects mediated by APOE4 by promoting a protective microglial response.

Methods Mice with humanized APOE3 and APOE4 were crossed to 5xFAD transgenic mice, which carry mutant human APP and presenilin genes to drive amyloid pathology and neurodegeneration. The resultant transgenic mice (5xFAD;APOE4/4 and 5xFAD;APOE3/3) were subjected to a voluntary wheel running paradigm or stationary wheels for 4 months. We used immunohistochemical and ELISA-based techniques to evaluate microglia and neurons. The microglia disease-associated phenotype was assessed by Clec7a staining while homeostatic microglia markers were evaluated by P2ry12 staining. Neuronal numbers in cortical lamina V were evaluated by NeuN staining. Neurogenesis was evaluated by doublecortin staining.

Results We expect to see an increase in Clec7a and a decrease in P2ry12 staining on microglia surrounding beta amyloid plaques in 5xFAD;APOE4/4 mice subjected to running compared to mice housed with stationary wheels. In addition, we anticipate PA will ameliorate neuronal loss and promote neurogenesis in the subgranular zone of the dentate gyrus in the hippocampus.

Conclusion/Potential Impact The study will support the benefit of PA in attenuating the progression of late-onset AD in individuals with the APOE4 risk allele. The study will also elucidate the relationship between microglial responses, APOE genotype, and PA in AD.