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Exercise Delays Alzheimer's Disease Through Enhancing Lysosomal Function

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Objective Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by aggregation of amyloid-β (Aβ) peptides. Reduction of progressive accumulation of Aβ will delay the progression of AD. As a main digestive organelles in cells, lysosome is crucial to clear the harmful proteins from extracellular and intracellular. Recent evidences have shown that exercise improves cognitive function of AD, but the reason is not very clear. This manuscript is to study the effect of long-term running exercise training on lysosomal function in mouse brain and explore its relationship with the progress of Alzheimer's disease.
Methods the APP/PSEN1 transgenic mice were used as the AD model to examine the relationship between AD, exercise and lysosomes. The mice were trained on a treadmill from the 5 months old, 60 min/day and 5 days/week for 5 months. The Lashley water maze and the novel object recognition test were used to estimate the cognitive ability of the mice; the balance beam and the rotating rod experiment were used to estimate motor coordination. The Aβ accumulation was measured with brain section and immunochemistry. The effects of long-term exercise on lysosomal function of cerebral cortex, striatum and hippocampus were measured. Among them, the autophagy/lysosome associated proteins level was determined by Western blot and the autophagy vacuoles and lysosome were observed through electron microscope. TFEB nuclear translocation was determined by Western blot and Immunofluorescence. The transcription of the TFEB-regulating genes were determined by quantitative PCR (qPCR).
Results Long-term exercise improved the cognitive ability and physical coordination of AD transgenic mice. Exercise reduced Aβ accumulation through increase the clearance of Aβ and affected little on the production of Aβ. Exercise, not only increased the colocalization of lysosomes with Aβ, but also increased the mature type of lysosomal protease cathepsin D and cathepsin L. In the meanwhile, exercise promoted the nuclear translocation of TFEB, a master transcriptional regulator of lysosomal biogenesis and autophagy, and increased the transcription of genes associated with the biogenesis of lysosome.
Conclusions Long-term exercise training delays the progress of Alzheimer's disease through activating function of lysosome and enhancing the biogenesis of lysosome. Exercise may be a therapeutic approach for the treatment of Alzheimer's disease.