Impact of Aerobic Exercise on Tau, Amyloid, Iron Accumulation, Oligodendrocyte Ferroptosis, and Inflammaging in the Hippocampal Formation of Aged Rats

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline, with neuropathological changes—such as amyloid-beta plaques, tau tangles, demyelination, and iron accumulation—preceding symptoms by decades. This underscores the urgent need for preventive strategies. Physical exercise has emerged as a promising non-pharmacological intervention with potential to counteract key AD hallmarks. In this study, we quantified amyloid-beta, tau aggregates, iron deposits, and markers of ferroptosis in oligodendrocytes within the hippocampal formation of aged rats subjected to an aerobic exercise protocol. We also analyzed cell-cell interactions, including neuron–neuron, neuron–glia, and glia–glia crosstalk, and evaluated the impact of exercise on these relationships. Our findings demonstrate that iron overload in oligodendrocytes triggers ferroptosis, while aerobic exercise mitigates inflammaging, enhances axon–myelin integrity, and modulates pathological protein accumulation. Furthermore, statistical correlations among tau, amyloid, iron levels, and hippocampal cellular interactions support a systems-level perspective of hippocampal vulnerability and resilience. These results provide strong evidence for the neuroprotective role of aerobic exercise in aging and AD and introduce a quantifiable model of hippocampal cell interplay that may inform translational research in both preclinical and clinical settings.

Keywords: Stereology, Alzheimer's disease, Hippocampus, Aerobic exercise, Neurodegeneration