

# Exercise Benefits on Alzheimer's Disease

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## Abstract

Alzheimer's disease (AD) is a major threat to the health of the elderly, and there are few drugs that can completely cure AD. Here we find that long-term exercise improves cognitive impairment and motor coordination in AD mice, maintains lysosomal Golgi morphology, promotes lysosomal maturation to enhance lysosomal function, stimulates enhanced effects of TFEB and AMPK mediated acetyl-CoA synthetase2 (ACSS2) for lysosomal biogenesis thereby increasing amyloid degradation and reducing its accumulation in the hippocampus and cortex.

**Keywords:** Exercise, Lysosome function, Alzheimer's disease

## Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder [1] and the most common cause of human dementia, accounting for approximately 60%–80% of cases. It is estimated that more than 30 million AD patients, and the number likely to increase to over 100 million by 2050 because of the increase of the elderly population [2]. Its main clinical manifestations are memory disorder, personality abnormality, apraxia, visual space abnormality, executive dysfunction and neuropsychiatric symptoms [3,4]. Alzheimer's disease is characterized by accumulation of abnormal protein aggregates including amyloid plaques (composed of beta-amyloid (A $\beta$ ) peptides) and neurofibrillary tangles (formed by hyper-phosphorylated tau protein) [5,6]. Fibrillar aggregates of the amyloid- $\beta$  protein (A $\beta$ ) are the main components of the senile plaques found in brains of Alzheimer's disease patients [7]. Synaptic plasticity [8], neuroinflammation [9], calcium signaling etc. also show dysfunction in AD patients [2]. Lysosome is the degradation center and signaling hubs in cells and play important roles in cellular homeostasis, development, and aging [10,11]. In neurons, A $\beta$  accumulates in endo-lysosomal vesicles at low pH [12]. It is important to maintain the normal function of lysosome for A $\beta$  degradation.

It is well known that exercise is beneficial to physical and mental health and can relieve the occurrence and

development of neurodegenerative diseases to a certain extent. Therefore, in this commentary, we conducted regular running on 5-month-old APP/PS1 mice at 18r/min per day for 5 months and found that exercise can relieve Alzheimer's disease by activating lysosome function.

## Exercise Alleviates Cognitive Impairment through Different Brain Regions

Exercise has been shown to benefit brain structure and function, especially in aging populations. Various modes, frequencies, intensities, and durations of exercise might elicit different pathways and thus have differing effects on brain health outcomes [13]. Studies have shown that moderate exercise improves cognition including processing speed, memory, and executive function [14]. Regular physical exercise has proven to be beneficial for traditional cardiovascular risk factors (e.g., reduced vascular flow, diabetes) involved in the pathogenesis of Alzheimer's disease, which exerts anti-inflammatory effects and improves the brain redox status. Otherwise, exercise-induced metabolic factors, ketone bodies and lactate, and muscle-derived myokines, such as cathepsin-B and irisin, can stimulate the secretion of brain-derived neurotrophic factor and promote neurogenesis [15]. In summary, physical activity has a relation to areas of the brain that support complex cognitive processes during laboratory tasks [16].

Hippocampus plays an important role in learning and higher order cognition [17]. Together with its medial temporal lobe and subcortical circuits, the hippocampus is compromised early in ageing and neurodegenerative conditions, most notably in Alzheimer's disease and frontotemporal dementias [18]. Hippocampus comprises three main subfields: the dentate gyrus (DG), area CA3, and area CA1. The DG is unique in its ability to generate new neurons in mammals, which can be doubled or tripled by exercise in rodents [19-21]. Facilitated plasticity is most evident in the dentate gyrus (DG), where exercise enhances both short-term potentiation and long-term potentiation (LTP) [22].

While the hippocampus is critical for spatial memory formation, it does not store long-term memories, and studies have shown that the prefrontal and anterior cingulate cortex are critical for storage and retrieval of remote spatial memories. Consolidation of spatial memory requires a time-dependent hippocampal-cortical dialogue, ultimately enabling widespread cortical networks to mediate effortful recall and use of cortically stored remote memories independently [23,24]. The prefrontal cortex is one of the most vulnerable brain regions during aging, and previous studies have linked PFC atrophy to AD [25].

### Long Term Exercise Activates Lysosomal Function

In our study, we tested cognition-related behavioral, water mazes and new object recognition, and found that 40 minutes of exercise per day from 5 months to 10 months of age, enhanced learning ability in APP/PS1 mice. Behavioral studies related to balance including rotarod and balance beam showed that exercise saved coordination in AD mice. Long term exercise also reduced amyloid deposition and phosphorylation of Tau in the hippocampal cortex. We also found that the decrease of A $\beta$  was not because exercise affected A $\beta$  production but increased degradation.

Lysosomes are cytoplasmic membrane-enclosed organelles that degrade macromolecules and cell components [26], which are found in all eukaryotic cell types, except for erythrocytes. Lysosomes are acidic organelles with an internal pH of 4.5-5.5 [27], maintained by the presence of the vacuolar-type H<sup>+</sup> ATPase(V-ATPase) on the lysosomal membrane [28]. Lysosomes are involved in catabolism (autophagy, heterophagy), cell signaling (calcium storage, mTOR function, amino acid release) and cell death(cancer therapy, antibacterial infection) [29].

#### Exercise improve the maturation of lysosomal enzymes

Lysosomes contain more than 70 hydrolases and more than 200 membrane proteins [30] that control the distribution, number, size and activity of lysosomes, and the specificity of cargo flux and degradation time (initiation and termination) [31]. In our study, we found that the lysosome morphology in the CA1 region of APP/PS1 mice was abnormally enlarged

and contained the undegraded contents, while the lysosome morphology in AD mice after long-term wheel running was normal. In addition, lysosomal membrane LAMP1, was significantly increased in the hippocampus and cortex of AD mice by western blot, which consisted of enlarged lysosomes in AD mice, and it was reversed after exercise. With long-term exercise, Cathepsin L and Cathepsin D levels increased in the hippocampus and cortex, and autophagy flow was smooth. The result of immunofluorescence showed that A $\beta$  was transported to the lysosome for degradation. These results indicate that lysosome function is enhanced in AD mice with long-term exercise.

Lysosomal enzymes are synthesized in the endoplasmic reticulum and transported to the endosomal system via Golgi complexes [32]. On the one hand, the morphology and function of Golgi in CA1 region were impaired in AD mice, on the other hand, the lysosomal modification of Golgi was damaged when transported to the lysosome through vesicles, which both caused the accumulation of unmaturing cathepsins in AD mice. Rab7 located in late endosomal lysosomes can promote the maturation of autophagosomes [33,34]. Although the fusion of autophagosomes with early endosomes and multivesicular bodies can still occur in Rab7 knockdown cells, but fusion with lysosomes is blocked [35,36].

#### Exercise enhance the lysosomal biogenesis

Transcription factor EB (TFEB) is a master regulator of autophagy and lysosomal biogenesis [37,38]. Autophagy is promoted by AMP activated protein kinase (AMPK), which is a key energy sensor and regulates cellular metabolism to maintain energy homeostasis [39]. In our study, we found that exercise enhanced phosphorylation of AMPK. AMPK is involved in ULK1(Unc-51 like autophagy activating kinase 1) [40] activation and lysosomal biogenesis [41]. AMPK phosphorylates ACSS2, resulting in nuclear translocation. In nuclear ACSS2 forms a complex with TFEB, which up-regulates lysosomal and autophagosomal genes by locally producing acetyl-CoA for histone H3 acetylation in the promoter regions of these genes by utilizing acetate generated from the turnover of histone acetylation [42,43]. In our study, exercise enhances nucleation of ACSS2. Finally, the enhanced action of ACSS2 and TFEB ultimately promotes lysosomal biogenesis.

### Lysosome in Glia

Microglia are the resident phagocytotic immune cells of the CNS [44] and have highly dynamic processes. It plays important roles in investigating brain pathogens, contacting neurons, shaping synaptic connections, etc. The lysosome contributes to these functions, playing a role in the exocytosis of extracellular matrix proteases, endocytosis and phagocytosis of myelin debris, extracellular aggregates, and pathogens [45]. Sphingolipids are mainly degraded in lysosomes, and the disruption of the sphingolipid degradation pathway

in neurosphingolipid storage diseases affects the normal homeostasis of microglia. The abnormal lysosomal function causes the formation of destructive pro-inflammatory phenotypes in microglia and exacerbates the disease process [46]. When microglia overexpress deacetylated TFEB, which accelerates the degradation of intracellular fibrillar A $\beta$  by stimulating lysosome biogenesis and greatly reduced the deposited amyloid plaques in the brain slices of APP/PS1 transgenic mice [47].

*In vitro*, overexpression of exogenous TFEB in primary astrocytes enhances Tau fiber absorption and lysosomal activity; *In vivo*, the induced TFEB expression in astrocytes reduces pathology in the hippocampus of PS19 tauopathy mice, as well as prominently attenuates tau spreading from the ipsilateral to the contralateral hippocampus in a mouse model of tau spreading [48]. Proteins related to Parkinson's disease genes and genetic risk factors of Parkinson's disease are highly expressed in glial cells. Damage of endo-lysosome causes in glial cells causes the phagocytic substances are unable to be degraded. The undigested substances in cells in turn interfere with the homeostasis of glial cells and affects neurological health [49].

## Conclusions

Physical exercise can increase metabolic activity in skeletal muscles, enhance antioxidant systems, and reduce inflammation [50]. At the meanwhile, we also found that long-term regular exercise can affect different brain regions and delay the process of the cognitive dysfunction in the APP/PS1 mice by promoting the lysosomal biogenesis and lysosomal enzyme maturation, which subsequently enhance the degradation of amyloid protein and keep the cell homeostasis both in neurons and glia. Therefore, it is necessary for Alzheimer's patients and healthy adults to maintain regular exercise.

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