

## Neuroprotective Effects of Voluntary Exercise Against Amyloid Beta1-42-Induced Neurotoxicity, Endoplasmic Reticulum Stress, and Apoptosis in the Hippocampus of Aged Male Rats

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## ABSTRACT

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\*Corresponding Author: Neurophysiology Research Center, Cellular and Molecular Medicine Research Institute, Urmia University of Medical Sciences, Urmia, Iran **Introduction:** Amyloid beta-protein (A $\beta$ ) is a significant component of senile plaques that appear in the cortex during aging and are abundant in Alzheimer's disease. Accumulated A $\beta$  deposition triggers a cellular stress response called the unfolded protein response (UPR). The UPR signaling pathway can be a cellular defense system for dealing with the accumulation of misfolded proteins. However, the switch to apoptosis occurs when endoplasmic reticulum (ER) stress is prolonged. ER stress is involved in neurodegenerative diseases, including Alzheimer's disease (AD), but the molecular mechanisms of neuronal apoptosis by A $\beta$ -induced ER stress to voluntary exercise are not fully understood. Here, we demonstrated that voluntary exercise reduced A $\beta$ 1-42 deposition in the hippocampus of aged male rats.

**Methods and Materials:** Young male Wistar rats were randomly divided into three groups: young, old, and old exercise groups (six rats in each group). Rats were housed individually in a cage containing a wheel and equipped with a digital magnetic counter activated by wheel rotation. Each exercising rat had a separate running wheel in its cage, allowing it to run voluntarily during the 8 weeks of the study. Rats with running distances lower than ~2000 m per day were eliminated before statistical analysis. Hippocampi samples from the right hemisphere of the brain were obtained. Also, coronal sections from the brain's left hemisphere were obtained for Cresyl Violet and immunohistochemical staining. A $\beta$ 1-42 level of the hippocampus was measured using a rat ELISA Kit. ATF6, CHOP, PERK, p-PERK, ProCaspase8, CleavedCaspase8, ProCaspase12, and CleavedCaspase12 protein levels in the hippocampus tissue were determined by Western immunoblotting assay.

**Results:** Our results showed that voluntary exercise improved the expression levels of A $\beta$ 1-42 in the old exercise group more than in the old group. We also found that voluntary exercise down-regulated the expression of ATF6, CHOP, PERK, and p-PERK proteins and inhibited activation of caspase-8 and caspase-12. Moreover, voluntary exercise increased the number of positive cells of Bcl-2 and decreased the number of positive cells of Bcl-2 and decreased the number of positive cells of Bax in the hippocampus of aged male rats. Voluntary exercise also improved the expression levels of CleavedCaspase8 and CleavedCaspase12 in the old exercise group compared to the old group. A significant difference was observed in comparing the expression levels of CleavedCaspase8 and CleavedCaspase12 between the young and old exercised group.

**Conclusion and Discussion:** These results showed that voluntary exercise suppressed the activation of UPR signaling pathways and inhibited the apoptotic pathways of the UPR following A $\beta$ -induced ER stress. Thus, therapeutic strategies that modulate A $\beta$  induced ER stress through voluntary exercise represent a promising approach to the prevention of AD.

Keywords: Apoptosis, Exercise, Endoplasmic reticulum stress

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