Exercise Biochemistry Review

Proceedings of IBEC 2018, Beijing, China, October 23-25
PL-028

Aerobic exercise inhibits tau hyperphosphorylation through activation of the PI3K/Akt pathway in the hippocampus of APP/PS1 mice

Guoliang Fang,Jiexiu Zhao,Li Zhang,Pengfei Li
China Institute of Sport Science

Objective Many *studies* suggest that regular physical exercise can reduce the risk of Alzheimer's disease and slow its onset and progression. However, the exact mechanism is still unclear. Clinically, Alzheimer's disease is characterized by the presence of extracellular amyloid plaques and intraneuronal neurofibrillary tangles, which are associated with amyloid-β and tau hyperphosphorylation respectively. The PI3K/Akt signaling pathway regulates tau phosphorylation and plays a pivotal role in the development of pathology in Alzheimer's disease. Here we investigated the effects of aerobic exercise on tau phosphorylation and examined whether these effects were mediated by the PI3K/Akt pathway in the hippocampus of APP/PS1 transgenic mice.
Methods 40 male APP/PS1 transgenic mice were randomly divided into four groups: sedentary group (T-SE; n=10), exercise group (T-EX; n=10), sedentary with GNE-317 treatment group (T-SEG; n=10) and exercise with GNE-317 treatment group (T-EXG; n=10). GNE-317 is a potent and selective PI3K/Akt pathway inhibitor that can cross the blood-brain barrier and show effective suppression of Akt phosphorylation in the mice brain. The mice in the T-EX and T-EXG groups were given exercise training on a treadmill for 5 days/week for 8 weeks with 0% grade, and progressively ran from 30 min/day at 12 m/min, up to 60 min/day at 15 m/min. The mice in the T-SE and T-SEG groups were placed individually on another treadmill at 0 m/min for the same duration. 48 hours after the last exercise bout, all mice were intraperitoneally injected an anesthetic for inducing anesthesia, and the hippocampus were rapidly extracted. The protein and phosphorylation levels of tau, PI3K, Akt and GSK3β were assayed by Western blot and *immunohistochemistry*. The cognitive function were tested by morris water maze.
Results We found out that 8 weeks of aerobic exercise reduced tau phosphorylation at multiple sites including Ser202, Thr231 and Ser396, and increased phosphorylation of Akt at Thr308 and Ser473 and of GSK3β at Ser9. Furthermore, in the morris water maze test, the exercise group showed a reduced escape time and distance compared with those of the sedentary group, suggesting that aerobic exercise improved learning and cognitive ability. While the above-mentioned results were attenuated in the PI3K/Akt inhibitor GNE-317 treatment groups.
Conclusions Our study demonstrated that aerobic exercise could inhibit tau hyperphosphorylation and improve cognitive funtion through activation of the PI3K/Akt pathway in the hippocampus of APP/PS1 mice.