Neuroprotective effects of treadmill exercise on BDNF and PI3-K/Akt signaling pathway in the cortex of transgenic mice model of Alzheimer’s disease

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ABSTRACT

Many epidemiological studies have shown that brain insulin dysfunction significantly increases the risk of Alzheimer’s disease (AD). Although physical exercise and AD have received attention in the scientific literature, the mechanism through which treadmill exercise may impact the brain insulin signaling of AD has not been elucidated. This study aimed to evaluate the neuroprotective effects of treadmill exercise on apoptotic factors (Bcl-2/Bax ratio, caspase-3), HSP70, COX-2, BDNF and PI3-K/Akt signaling pathway in the cortex of NSE/hPS2m transgenic mice model of AD. Treadmill exercise ameliorated cognitive function in water maze test and significantly increased the level of Bcl-2/Bax ratio and HSP-70 in Tg-exe group compared to Tg-con group; on the other hand, it significantly decreased the expression of caspase-3 and COX-2 in Tg-exe group compared to Tg-con group. In addition, treadmill exercise significantly increased the expression of BDNF and PI3K/Akt in Tg-exe group compared to Tg-con group. Consequently, treadmill exercise improves cognitive function possibly via activating neurotrophic factor, BDNF and PI3k/Akt signaling pathway, and Aβ-induced neuronal cell death in the cortex of Tg mice was markedly suppressed following treadmill exercise. These results suggest that treadmill exercise may be beneficial in preventing or treating Alzheimer’s disease.

Keywords: Alzheimer’s disease, neuronal cell death, Bcl-2/Bax ratio, COX-2, BDNF, PI3k/Akt

INTRODUCTION

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder clinically characterized by the loss of memory and multiple cognitive dysfunctions [1,2]. Recently, AD is increasing rapidly as life expectancy is prolonged, and the number of patients is expected to increase to 80 million by 2040, as the ailment/disease is predicted to become a major social problem and a major health care issue all over the world [3].

The two major pathological hallmarks of AD are the extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) in the brain, yet the correct pathogenetic mechanisms remain unclear. However, many recent reports and reviews have suggested that the accumulation of amyloid-β (Aβ) peptide is widely accepted as having an important role in the pathogenesis of AD. Aβ protein first deposits always develop in the neocortex, only to be followed by accumulation from hippocampus to cerebellum, leading to neuronal loss, synapses destruction, and ultimately, neuronal cell death [4,5]. Furthermore, the accumulation of Aβ protein is closely linked to a state of relative mitochondria dysfunction, hyperphosphorylation of tau, inclusion-body myositis (IBMs) and insulin resistance such as type 2 diabetes mellitus (T2D) [6-9].

More recently, clinical, experimental and epidemiological evidences have indicated that brain insulin dysfunction may significantly contribute to AD, even being referred to as “type 3 diabetes” [7,9]. Insulin is produced in the within the β-cell of the and is emerging as a major mediator of energy
metabolism, especially glucose metabolism, protein synthesis and gene expression [10]. Also, insulin is abundantly distributed in the brain tissue and can be partially formed by regulating neuronal growth, synapse formation and plasticity [11,12]. However, excessive accumulation of Aβ protein in the AD brain may disrupt insulin signaling pathway by hindering the combination of insulin and insulin receptors [13], leading to a decrease in the levels of phosphatidylinositol-3 kinase (PI3-k) and protein kinase B (Akt) activity [14,15].

The PI3-K/Akt signaling pathway is responsive to metabolic signals and environmental stress and regulates cell survival, growth, differentiation, and other homeostatic functions [16]. In particular, Akt, the serine/threonine protein kinase B, is a signaling downstream of PI3-kinase which is highly expressed in the brain and has an important role in cell survival by decreasing GSK3 (glycogen synthase kinase-3) activity, which in turn may favor the condition that induces hyperphosphorylation of tau and neuronal cell death [17-19]. In addition, Aβ protein has been shown to induce neuronal cyclooxygenase-2 (COX-2) in AD, leading to neuronal cell death and cognitive dysfunction [20]. Kotilinek et al. [21] showed that COX-2 expression is induced by Aβ protein, indicating that inhibition of COX-2 may protect Aβ-mediated suppression of memory function in AD. Therefore, reducing Aβ protein is the main target for prevention and treatment of AD by activating insulin signaling pathways and inhibiting COX-2 protein.

As mentioned above, inhibiting Aβ protein production or delaying its accumulation are of great focus, but most therapies have depended primarily on drugs so far. Pharmacological treatments could improve cognitive function for AD; however, its effect is only temporary and limited, and may produce unexpected side effects for AD. On the other hand, new integrated non-pharmacological approaches concerning/involving physical exercise can help the brain function more than approaches through medicine [22, 23]. Among the positive effects of physical exercise are the enhancement of cognition function and up-regulation of neurotrophic factors such as insulin signaling pathway (PI3-k/Akt) and brain derived neurotrophic factor (BDNF) [24-26]. However, despite the positive physiologic change observed with treadmill exercise by previous studies, treadmill exercise effects on the brain insulin signaling pathway and the neurotrophic factor have not been examined in the cortex of AD.

More interestingly, we found that NSE/hPS2m transgenic mice of AD model markedly increased the level of serum insulin, glucose and total cholesterol, suggesting that this model may have insulin resistance problem [27]. However, the mechanism linking the effect of treadmill exercise on insulin resistance is not unclear in NSE/hPS2m transgenic mice. In the present study, we used NSE/hPS2m transgenic mice model of AD to investigate whether treadmill exercise could improve cognitive function in the Morris water maze task and suppresses Aβ-induced apoptotic factor (Bel-2/Bax ratio, caspase-3, COX-2). Moreover, we examined the neuroprotective effects of treadmill exercise on BDNF, HSP70, and PI3-K/Akt signaling in the cortex of NSE/hPS2m transgenic mice model of AD. Therefore, our data are helpful for better understanding the neuroprotective effects of treadmill exercise in the pathogenesis of AD.

METHODS AND MATERIALS

Transgenic mice

All animal experiments in this study were approved by the Institutional Animal Care and Use Committee at Korea National Sport University and by the Korea FDA. Transgenic mice, Tg-NSE/hPS2m, expressing human PS2 mutant under the control of neuron-specific enolase (NSE) were maintained in the genetic background of C57BL/6 × DBA/2 mice. The mice were maintained under controlled light and environmental condition (12 : 12 hour dark-light cycle, housed at 23 ± 1°C with 50 % relative humidity) with food and water (Purina Mills, Seoul, Korea) made available ad libitum. Mice were carried out in an accredited Korea FDA animal facility in accordance with the AAALAC International Animal Care Policies (Accredited Unit-Korea Food and Drug Administration: Unit Number-000996).

Treadmill exercise

Tg-NSE/hPS2m mice and their control non-Tg mice at 24 months of age were divided into four groups: non-Tg-control mice (non-Tg-CON, n = 8), non-Tg- treadmill-exercised mice (non-Tg-EXE, n = 8), Tg-control-mice (Tg-CON, n = 8) and Tg- treadmill-exercised mice (Tg-EXE, n = 8). To perform the treadmill exercise, all mice were conducted at 5 m/min, 10 min/day for 5 days so that the mice became familiar with the treadmill-exercise environment. After this period, the treadmill exercise training was performed at 12 m/min, 60 min/day, 5 days/week for 3 months. However, the control group (CON) remained in their home cage throughout the course of the experiment.