Neuroscience 298 (2015) 357–366

TREADMILL EXERCISE ENHANCES SYNAPTIC PLASTICITY, BUT DOES NOT ALTER β-AMYLOID DEPOSITION IN HIPPOCAMPI OF AGED APP/PS1 TRANSGENIC MICE

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Abstract—Several studies reveal that the beneficial effects of exercise interventions are dependent on the progression of Alzheimer's disease (AD). We have previously shown that long-term treadmill exercise begun before the onset of β-amyloid (Aβ) pathology prevents the deficits of cognition and long-term potentiation (LTP) in amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mice (8 months of age) paralleled by the reduction of soluble Aβ levels and Aβ deposition in the hippocampus. In the present study, treadmill exercise was initiated at a developed Aβ deposition stage in order to further investigate whether or not treadmill exercise in this phase can delay the progression of AD in aged APP/PS1 mice (17 months of age). Our results show that 5-month treadmill exercise ameliorates the impairment of spatial learning and memory with age paralleled by synaptic plasticity enhancement in aged APP/PS1 mice. In addition, exercise-induced enhancement of synaptic plasticity was accompanied by a significant reduction of soluble Aβ levels rather than Aβ plaque deposition. Therefore, the investigation demonstrates that long-term treadmill exercise has beneficial effects on cognition and synaptic plasticity even when the brain has developed Aβ deposition, and changes in soluble Aβ levels rather than Aβ plaque deposition may contribute to exercise-induced benefits.

Key words: Alzheimer's disease, APP/PS1 transgenic mice, treadmill exercise, learning and memory, synaptic plasticity, β-amyloid.

INTRODUCTION

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, clinically characterized by progressive declines in learning and memory. The prevalence of AD increases with age, rising from just 3% between ages 65–74 to almost 50% in people over the age of 85 (Ferrer, 2012), and is projected to reach over 100 million people by 2050 (Barnes and Yaffe, 2011). Because of the growing AD prevalence and escalating health care costs, more attention is being paid to the accessible and potent therapeutic strategy for the prevention and treatment of AD. A number of epidemiological studies suggest that physical exercise may reduce the risk of AD and be sufficient to slow the onset and progression of AD (Friedland et al., 2001; Laurin et al., 2001; Rovio et al., 2005; Lautenschlager et al., 2008; Akbaraly et al., 2009; Scarmeas et al., 2009, 2011). In support of existing epidemiological studies, extensive evidence in animal models suggests that exercise is one of the best candidates for amelioration of the pathological phenotypes of AD (Cho et al., 2003; Adlard et al., 2005; Um et al., 2008; Tapia-Rojas et al., 2015). Therefore, physical exercise is a potential intervention to delay and rescue cognitive deficits associated with AD. However, the effect of exercise on cognitive function and pathology in AD remains controversial. Moreover, the cellular and molecular mechanisms for such benefits have not yet been identified.

Although the aggregated β-amyloid (Aβ) peptide has been shown to play a critical role in the pathogenesis of AD, several studies have demonstrated that impairment of synaptic function is a key characteristic of AD (Pozueta et al., 2013). It has been widely accepted that the severity of dementia in AD patients correlates better with the extent of synaptic dysfunction rather than the loss of neurons and the plaque burden (Delaere et al., 1989; Terry et al., 1991). Hippocampal long-term potentiation (LTP) is a form of synaptic plasticity accepted as an electrophysiological model of learning and memory that has emerged as a cellular model for studying mechanisms involved in cognitive deficits related to AD (Klyuvin et al., 2004). For these reasons, researchers often focus on LTP changes in the hippocampus as a measure of synaptic dysfunction in AD transgenic mouse models, and synaptic plasticity can be considered as a possible target for therapeutic intervention in the disease process. More importantly, the results of many studies confirm that

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Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; Aβ, β-amyloid; DG, dentate gyrus; ELISA, enzyme-linked immune sorbent assay; f-EPSP, field-excitatory postsynaptic potential; HFS, high-frequency stimulation; IHC, immunohistochemical; LTD, long-term depression; LTP, long-term potentiation; PS, population spike; PS1, presenilin 1.

http://dx.doi.org/10.1016/j.neuroscience.2015.04.038
0306-4522/

improved synaptic plasticity occurs in response to exercise in both rats and mice (Van Praag et al., 1999; Farmer et al., 2004; Titterness et al., 2011; Patten et al., 2013).

Many studies have shown that the beneficial effects of exercise interventions in patients are dependent on the progression of AD. Accumulating evidence suggests that exercise before the onset of AD-like neuropathology can slow AD progression in varieties of transgenic models of AD (Adlard et al., 2005; García-Mesa et al., 2011; Maesako et al., 2012). These findings support the view that the therapeutic effect of exercise on AD is critically dependent on the timing of the treatment (Richter et al., 2008). Most AD patients have accrued Aβ pathology prior to diagnosis (Becker et al., 2011); thus it is debatable that whether treadmill exercise, if initiated after the onset of AD-like neuropathology, can delay progression of AD.

In our previous studies, amyloid precursor protein (APP) and presenilin 1(PS1) double-transgenic mice started treadmill exercise at 3 months of age, before the beginning of pathology. Our results demonstrated that 5-month treadmill exercise attenuated behavioral deficits in AD transgenic mouse models paralleled by LTP enhancement (Liu et al., 2011). Furthermore, the beneficial effect of treadmill exercise is likely attributable to decreased Aβ deposition (Liu et al., 2013).

APP/PS1 double-transgenic mice express a chimeric mouse/human APP (Mo/HuAPP695swe) and a mutant human PS1 (PS1-ΔE9) in which mutations cause autosomal dominant AD. Its symptoms and pathology have pronounced similarities with sporadic AD. APP/PS1 transgenic mice developed an age-dependent progressive neuropathology and associated behavioral disturbances of AD (Trinchese et al., 2004). A previous study showed Aβ deposition at 4 months with a progressive increase in plaque number up to 12 months and a similar increase of Aβ levels in APP/PS1 mice (Garcia-Alloza et al., 2006). It has also been suggested that increased formation and aggregation of Aβ with aging is responsible for impaired LTP with aging in this AD model (Gengler et al., 2010). Therefore, APP/PS1 transgenic mouse model appears to be a valuable model for the preclinical and clinical intervention studies of Aβ-related dysfunctions in synaptic activity and cognitive performance.

In the present study, we used aged APP/PS1 transgenic mice to investigate the effect of treadmill exercise, which began at a developed neuropathology stage, on cognitive function and hippocampal LTP. Moreover, we sought to elucidate whether or not Aβ pathology contributes to the beneficial effects of treadmill exercise in this phase.

EXPERIMENTAL PROCEDURES

Animals

APP/PS1 mice were obtained from the laboratory animal center of the China Medical University. Twenty-four young (3 months of age) and 24 old mice (12 months of age) were divided into sedentary [young sedentary mice (YS), $n = 12$; old sedentary mice (OS), $n = 12$] or exercise [young exercise mice (YE), $n = 12$; old exercise mice (OE), $n = 12$] group. All animals were housed in standard plastic cages (four mice per cage) with free access to food and water *ad libitum*. They were maintained at a constant temperature of 22–24 °C, humidity at 40–60% and under a standard 12-h light/dark cycle.

All animal procedures were conducted in accordance with the care and use of medical laboratory animals (Ministry of Health, Peoples Republic of China, 1998) and were approved by the laboratory animal ethical standards of the China Medical University.

Treadmill exercise protocol

Transgenic mice in the YE group were subjected to treadmill exercise treatment from 3 months of age, while OE group mice started exercise training at 12 months of age. The treadmill exercise protocol was performed as described previously (Liu et al., 2011). Before the exercise training commenced, all the exercise mice were familiarized with treadmill running for 10 min on two consecutive days (first day at 5 m/min; second day at 8 m/min). After acclimatization, exercise groups were subjected to treadmill exercise for 30 min each day, 5 days per week, for 5 months. During each training session, running time and speed were started at 5 m/min for 5 min, increased to 8 m/min for 5 min, and then reached a maximum of 11 m/min for 20 min. Sedentary groups were left on the treadmill without running for the same duration as the exercise groups. No animal was excluded from the experiment.

According to a previous study, this training protocol maintains exercise intensity from 45% to 55% of VO2 max (Baker and Gleeson, 1999). At this intensity, the mice accomplished training without the electric stimulant. Only gentle tail touching was used to prompt the mice the run to minimize the stress associated with treadmill exercise once they stopped.

Morris water maze tests

After treadmill exercise for 5 months, the spatial learning and memory were evaluated by the Morris water maze tests (Van Praag et al., 1999; Wolf et al., 2006). Briefly, the animals were subjected to 1 day of visible platform tests (4 trials/day), followed by 6 days of hidden platform tests (4 trials/day) and a probe trial 24 h later. The task was conducted in a circular pool (120 cm in diameter) filled with water (23 ± 1 °C) made opaque using non-toxic white paint. An 8-cm-diameter platform was placed in one of the four maze quadrants and kept at the same position. The mice were gently released into the water, always facing the tank wall. A different starting position was used on each trial every day. They were given 60 s to find and climb onto the platform. If they did not find the platform in 60 s, the experimenter gently guides the mice to the platform with the hand and lets them sit on the platform for 10 s. Escape latency (s), and path length (cm) to reach the platform were recorded by a video-tracking system in visible platform tests and hidden platform tests.