Long-term treadmill exercise improves spatial memory of male APPswe/PS1dE9 mice by regulation of BDNF expression and microglia activation

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ABSTRACT: Increasing evidence suggests that physical activity could delay or attenuate the symptoms of Alzheimer's disease (AD). But the underlying mechanisms are still not fully understood. To investigate the effect of long-term treadmill exercise on the spatial memory of AD mice and the possible role of β-amyloid, brain-derived neurotrophic factor (BDNF) and microglia in the effect, male APPswe/PS1dE9 AD mice aged 4 months were subjected to treadmill exercise for 5 months with 6 sessions per week and gradually increased load. A Morris water maze was used to evaluate the spatial memory. Expression levels of β-amyloid, BDNF and Iba-1 (a microglia marker) in brain tissue were detected by immunohistochemistry. Sedentary AD mice and wildtype C57BL/6J mice served as controls. The results showed that 5-month treadmill exercise significantly decreased the escape latencies ($P<0.01$ on the 4th day) and improved the spatial memory of the AD mice in the water maze test. Meanwhile, treadmill exercise significantly increased the number of BDNF-positive cells and decreased the ratios of activated microglia in both the cerebral cortex and the hippocampus. However, treadmill exercise did not significantly alleviate the accumulation of β-amyloid in either the cerebral cortex or the hippocampus of the AD mice ($P>0.05$). The study suggested that long-term treadmill exercise could improve the spatial memory of the male APPswe/PS1dE9 AD mice. The increase in BDNF-positive cells and decrease in activated microglia might underpin the beneficial effect.

CITATION: Xiong JY, Li SC, Sun YX, Zhang XS, Dong ZZ, Zhong P, Sun XR. Long-term treadmill exercise improves spatial memory of male APPswe/PS1dE9 mice by regulation of BDNF expression and microglia activation. Biol Sport. 2015;32(4):295–300.

Received: 2014-06-19; Reviewed: 2015-01-30; Re-submitted: 2015-05-22; Accepted: 2015-05-22; Published: 2015-08-04.

Key words:
Alzheimer's disease
exercise
mice
brain-derived neurotrophic factor
microglia

INTRODUCTION

Alzheimer's disease (AD) is the most commonly occurring form of dementia [1]. It is predicted that AD will affect 1 in 85 people globally by 2050 [2]. At present, drug treatment of AD is expensive and time-consuming. Furthermore, the effect is unsatisfactory. As an alternative or complementary choice, physical activity is simple, cheap, and fairly effective in delaying or attenuating the symptoms of AD [3-8]. However, the mechanisms by which physical activity exerts the beneficial effect are still not fully understood and even controversial in some reports [3, 9].

Many AD mice models have been created to facilitate research on AD. However, none of them completely mimics the pathology and pathogenesis of AD. Therefore, it is necessary to investigate the effect and mechanisms of physical activity in different AD mice models. Among the AD models, APPswe/PS1dE9 transgenic mouse is a frequently used one. The APPswe/PS1dE9 mice express a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1dE9) [10]. Mice carrying these double transgenes develop beta-amyloid deposits in the brain as early as 4 months of age, and display a progressive increase in Aβ (β-amyloid) plaque up to 12 months [11]. Furthermore, APPswe/PS1dE9 mice showed obvious memory deficits in several kinds of tests [12, 13]. Therefore, APPswe/PS1dE9 mice are a valuable model in AD research.

It has been reported that treadmill exercise improved the spatial learning and memory of APPswe/PS1dE9 mice [8]. But the detailed mechanisms underpinning the beneficial effect have not been investigated. The aim of this study was to analyse the effect of long-term treadmill exercise on spatial memory of APPswe/PS1dE9 mice, and further explore the possible mechanisms, including β-amyloid accumulation, BDNF expression and microglia activation, involved in the effect.

MATERIALS AND METHODS

Animal preparation. B6C3-Tg(APPswe,PSEN1dE9)85Dbo/J transgenic AD mice were obtained from the Model Animal Research Center of Nanjing University, China. Nine wildtype C57BL/6J mice were obtained from the Center of Experimental Animals, Sun Yat-sen University, China. All experimental protocols abided by the Guide for the Care and Use of Medical Laboratory Animals (Ministry of Health, People's Republic of China, 1998) and followed the laboratory animal ethical standards of Lingnan Normal University, China. The mice were maintained in a controlled environment at 24±2°C and 55±5% relative humidity with a 12-hour dark/light cycle, and were allowed access to food and water ad libitum.

Mice grouping and treadmill exercise

Eighteen male transgenic AD mice were randomly divided into the control (AD-control) or exercise group (AD-exercise), each containing 9 mice. The control mice were relatively sedentary, while the mice in the exercise group were allowed to run on a levelled, motor-driven treadmill (DST7202, Hangzhou Yatai Science and Technology Ltd, China). The exercise began at the age of 4 months and lasted for 5 months, with 6-day training per week. The exercise began with a distance of 70 m per day at a speed of 5-8 $m \cdot min^{-1}$, and gradually increased up to 300 m per day with a speed of 10-15 $m \cdot min^{-1}$ in one month. Then the running distance was maintained constant until the end of the experiment. To minimize the stress otherwise associated with treadmill exercise, only gentle tail touching was used to induce the mice to run, and no electric or voice stimulant was used in the exercise paradigm. According to a previous study, the running speed in this study was approximately the exercise intensity of 30-40% VO_2max [14]. To eliminate the interference factor of environment, control transgenic mice were placed on the treadmill every day to stay for the same time as the exercise mice did, but with no running.

The Morris water maze test and immunohistochemical detection were performed after the 5-month treadmill exercise. The age-matched wildtype C57BL/6J male mice (WT mice) receiving no special treatment served as a normal control in these detections.

Morris water maze test

The Morris water maze test was performed in a circular pool with a diameter of 120 cm and a depth of 50 cm (ZH0065, Zhenghua Biological Instrument and Equipment Ltd of Anhui Province, China). Four different cards were fixed onto the interior wall of the pool to serve as the spatial cues as well as the water-entering points. Mice were trained to locate a platform (9 cm diameter, 0.8 cm below the water surface) in the pool.

The test procedures were as in the previous reports with minimal modification [15]. On the first day, the platform was indicated by a visible flag (5×7 cm). The mice were allowed to find the platform within 60 s and then stay there for 5 s. If the mice failed to discover the platform, they were placed on the platform by the experimenter and stayed there for 20 s. Five repeated trials were applied for each mouse. The platform position changed in each trial on the first day. The following 2-5 days were acquisition trials with the flag removed and the platform fixed in a constant quadrant. Five repeated trials were performed every day. The latencies of platform escape were recorded with a digital camera. On the sixth day, a probe trial was performed with the platform removed from the pool. The time the mice spent in each quadrant of the pool was recorded. The time in the quadrant where the platform was previously placed and in the opposite quadrant were analysed as reported [16].

Brain section and immunohistochemical detection

To make a paraffin section of the brain tissue, the mice was sacrificed by cervical vertebra dislocation, and perfused with phosphate-buffered saline and 4% paraformaldehyde solution sequentially from the left ventricle. The paraffin-embedded brain tissue was horizontally sliced and then detected with hematoxylin eosin (HE) staining or immunohistochemical staining.

The primary antibodies used in immunohistochemical staining included rabbit polyclonal anti-BDNF (sc-20981, SANTA CRUZ), rabbit polyclonal anti-IBA1 (CP290A, Biocare, Concord, CA) and mouse monoclonal anti-β-Amyloid (CM333AK, Biocare Medical, CA, USA). The staining procedures followed the instructions of the DAB detection kit (Kit-0017, Maixin, China), which includes the endogenous hydrogen peroxide blocker, biotin-labelling secondary antibodies, and DAB substrate, etc. The staining was observed under an upright microscope (DM2500, Leica) and counted manually or using Image-Pro Plus 6.0 software.

Statistics

Data are expressed as mean ± standard error (number of observations). SPSS 19.0 software was used to analyse the results. The repeated measurement data of latency and the data of BDNF and microglia were analysed by ANOVA, followed by LSD post-hoc test for pairwise comparison. The data of time in the quadrant and of β-amyloid plaque were analysed by t-test. Effect size (d value) was calculated according to the previous reports [17]. $P<0.05$ was taken to be significant.

RESULTS

Treadmill exercise improves spatial memory of transgenic AD mice

The hippocampus-dependent Morris water maze test is a classic method to examine the spatial learning and memory. At the first day of the 4-day spatial acquisition trials, the latencies among wildtype, AD control and AD exercise mice were similar ($P>0.05$, $n=9$). However, with the development of the trials, AD control mice gradually displayed longer escape latency than wildtype mice, which became significant as early as the 2nd day ($P<0.01$, $d=3.6$). The results suggested an impaired spatial learning ability in the AD control mice (Fig. 1A). 5-month treadmill exercise obviously decreased the escape latency of AD mice, and the effect became significant at the 4th day of acquisition trials ($P<0.01$, $d=3.2$, Fig. 1A).

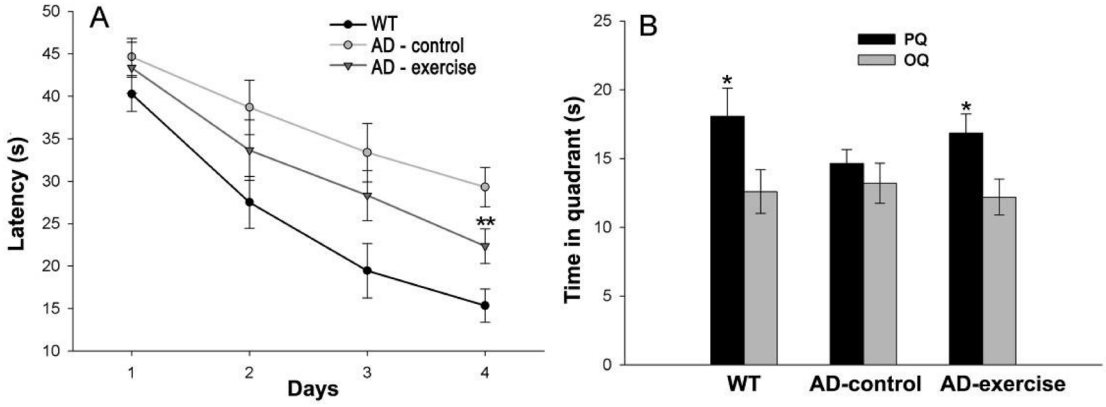

FIG. 1. Treadmill exercise improved the spatial learning and memory of transgenic ad mice in Morris water maze test.
A, the escape latencies of wildtype mice (WT), sedentary AD mice (AD-control) and trained AD mice (AD-exercise) in the 4-day platform acquisition training. B, the time mice spent in the platform quadrant (PQ) and the opposite quadrant (OQ) in the no-platform probe trial stage. ** represents $P<0.01$ vs. AD-control. * represents $P<0.05$ vs. OQ. Data are mean ± standard deviation (n=9).

Likewise, in the probe trial stage, AD control mice spent similar time in the platform quadrant (PQ) versus the opposite quadrant (OQ) of the pool (14.6±1.0 s vs. 13.2±1.5 s, $P>0.05$, n=9), while wildtype mice spent significantly more time in PQ than OQ (18.1±2.1 s vs. 12.6±1.6 s, $P<0.05$, d=2.9). The difference suggested a deficient memory in transgenic AD mice. As expected, treadmill exercise enhanced the time AD mice spent in the platform quadrant and decreased the time in the opposite quadrant. Consequently, AD exercise mice spent evidently more time in PQ than in OQ (16.8±1.4s vs. 12.2±1.3 s, $P<0.05$, d=3.4, in Fig. 1B).

These results altogether suggested that 5-month treadmill exercise could significantly enhance the spatial learning and memory of the APPswe/PS1dE9 mice.

Treadmill exercise did not significantly reduce β-amyloid plaque

To explore the mechanisms by which treadmill exercise improved the spatial learning and memory, brain tissue of 4 mice in each group were fixed, sliced and then detected by HE staining or immunohistochemistry.

HE staining showed that the tissue morphology of the cerebral cortex and hippocampus, 2 key sites involved in memory, did not display any obvious difference among wildtype, AD control and AD exercise mice (data no shown).

β-amyloid accumulation in the brain is a key pathological characteristic in AD development. This study showed that, compared with the AD-control group, 5-month treadmill exercise only slightly reduced the accumulation of β-amyloid plaque in both the cerebral cortex (13.1±2.1/field vs. 12.5±1.6/field, respectively, n=4) and the hippocampus (10.7±1.6/field vs. 8.6±2.2/field, n=4), but the differences were not significant (Fig. 2, $P>0.05$).

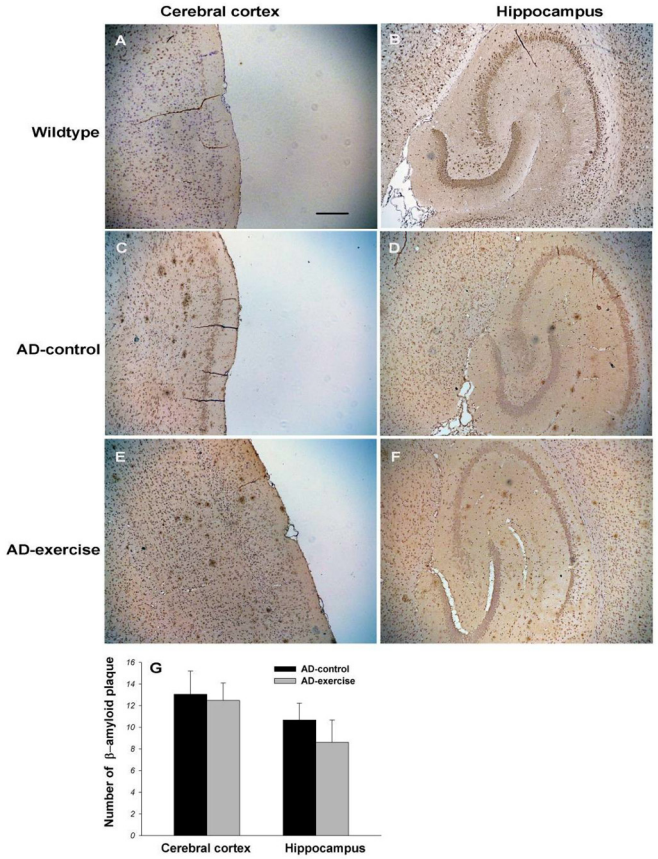

FIG. 2. Treadmill exercise did not obviously attenuate β-amyloid plaque accumulation.
The sections were stained with β-amyloid antibody and the plaque number per field was counted under a microscope. Compared with that of AD-control mice (C, D), the accumulation of amyloid plaque in AD-exercise mice (E, F) slightly decreased, but the difference was not significant in either the cerebral cortex or the hippocampus (G, $P<0.05$). Note that there was no β-amyloid plaque accumulation in the brain tissue of wildtype mice (A, B). The bar in A is 200 μm. Data are mean ± standard deviation (n=4).

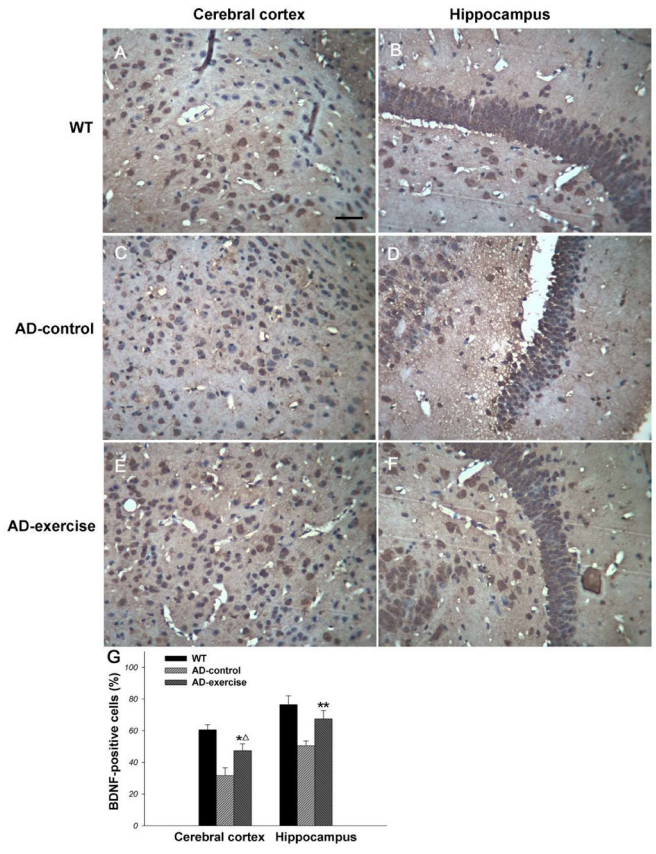

FIG. 3. Treadmill exercise enhanced BDNF-positive cells in transgenic AD mice.
Compared with wildtype mice, control AD mice possessed fewer BDNF-positive cells in the cerebral cortex and hippocampus (A-D, G). Five-month treadmill exercise significantly increased BDNF-positive cells in the AD mice (C-G). The bar in A is 20 μm. Data are mean ± standard deviation (n=4). * and ** respectively represent P<0.05 and P<0.01 vs. AD-control. Δ represents P<0.05 vs. WT.

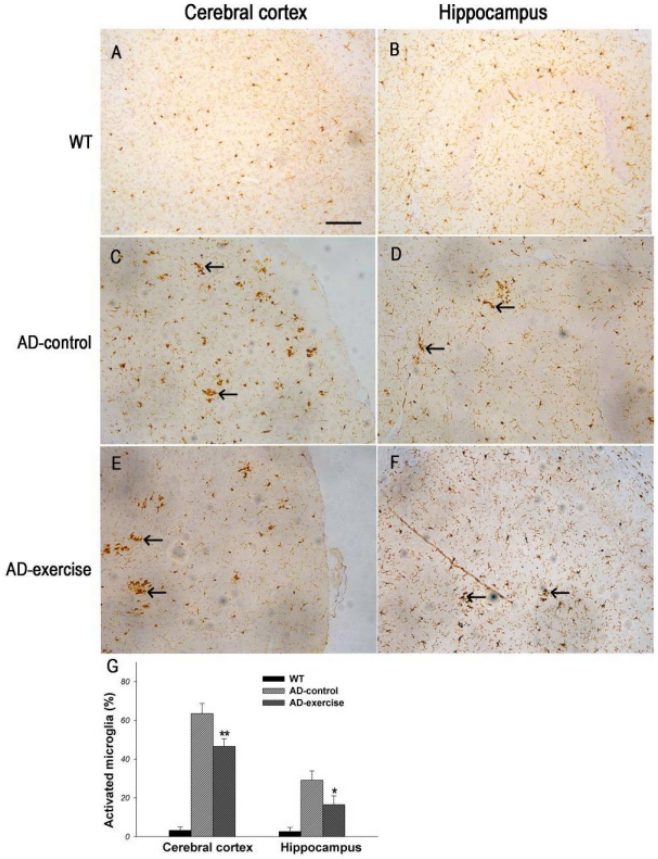

FIG. 4. Treadmill exercise inhibited excessively activated microglia in transgenic AD mice.
Activated microglia, indicated by an arrow, showed enlarged cell bodies and thickened/retracted branches (C-F), compared with the quiescent microglia (A-B). Exercise significantly reduced the excessive activation of microglia in both the cerebral cortex and the hippocampus of the AD mice (C-G). The bar in A is 100 μm. Data are mean±standard deviation (n=4). * and ** represent P<0.05 and P<0.01 vs. AD-control, respectively.

Treadmill exercise increased BDNF-positive cells

BDNF is an endogenous growth factor involved in neurogenesis, synaptic plasticity, and inhibitory neurotransmission, etc [9]. Compared with the age-matched wildtype mice, sedentary AD mice had obviously fewer BDNF-positive cells in both the cerebral cortex (P<0.01, d=7.0) and the hippocampus (P<0.01, d=5.7). However, 5-month treadmill exercise significantly enhanced the ratios of BDNF-positive cells in both the cerebral cortex (P<0.05, d=3.4) and the hippocampus (P<0.01, d=3.9) of the AD mice (Fig. 3).

Treadmill exercise inhibited activated microglia

Microglia were detected by immunohistochemistry based on Iba-1 protein, a specific marker for microglia. The results showed that sedentary AD mice possessed excessively activated microglia in both the cerebral cortex (63.5±5.2%, n=4) and the hippocampus (29.1±4.8%, n=4), while the corresponding regions in wildtype mice had few activated microglia. Five-month treadmill exercise significantly reduced the ratio of activated microglia in both cerebral cortex (P<0.01, d=3.6) and hippocampus tissue (P<0.05, d=2.7) of AD mice (Fig. 4).

DISCUSSION

Increasing evidence shows that physical activity exerts a beneficial effect on the cognition function of AD patients [18, 19]. The molecular mechanisms underpinning the beneficial effects of physical activity are currently under intensive investigation. The revealed mechanisms include enhanced expression of neurotrophic factors, reduced amyloid deposition, reduced accumulation of phosphorylated tau, and decreased inflammatory reaction in the central nervous system, etc. [9, 20]. Different mechanisms are involved in different conditions, which depend on the experimental object, exercise pattern, the time point of intervention, and the duration of exercise, etc. It has been reported that treadmill exercise could reduce Aβ-42 deposition and repress the cerebral inflammation in aged presenilin 2 mutant mice [21]. But it is unknown whether the same mechanisms are adopted in APPswe/PS1dE9 transgenic mice.

Treadmill exercise is an involuntary activity for mice, but very close to the running exercise of humans. To investigate whether treadmill running can delay the progression of AD, the training was undertaken in mice from 4 to 9 months of age, when accumulation of Aβ plaque continuously increases in APPswe/PS1dE9 mice [11]. The results showed that treadmill exercise could significantly improve the deficiency in spatial learning and memory of the AD mice. Our results are similar to the previous reports which began the treadmill exercise before the accumulation of Aβ plaque in APPswe/PS1dE9 mice [8]. Together with the effectiveness of treadmill exercise in other AD mice models [22-25], the results suggest that treadmill exercise or running is an effective exercise pattern for AD prevention and therapy.

β-amyloid (Aβ) deposition plays a key role in AD pathogenesis. Previous investigations have shown that physical activity can reduce Aβ plaque loading in some but not all studies [3, 9, 23]. In this study, we found that long-term treadmill running exerted no significant effect on Aβ plaque loading in both the hippocampus and the cerebral cortex, implying that enhancement of spatial learning and memory should not be attributed to ameliorated Aβ plaque.

Induction of BDNF expression has been suggested to play an important role in the beneficial effect of exercise [9, 26, 27]. The current study shows that treadmill exercise could significantly increase BDNF-positive cells in both the hippocampus and the cerebral cortex. Furthermore, the BDNF-positive cells usually have thin processes, implying new neurogenesis in these locations.

Activated microglia play a complex role in AD pathogenesis, as they may be helpful or harmful, either alternately or even simultaneously [28-30]. Microglia can be activated through engulfing Aβ when the Aβ deposit surpasses a certain size. The Aβ-activated microglia usually adopt an inflammatory phenotype and aggravate neuronal dysfunction [30, 31]. In our study as well as those of others [11, 32], APPswe/PS1dE9 mice at 9 months have an abundant Aβ deposit and excessively activated microglia in the brain, implying a harmful role of the activated microglia. In this study, treadmill exercise significantly reduced the activated microglia. Therefore, inhibition of activated microglia and the concomitant inflammatory reaction might be an important mechanism underlying the beneficial effect of treadmill exercise. The activated microglia can also express and secrete BDNF [33, 34]. The increase of BDNF-positive cells and inhibition of activated microglia by treadmill exercise suggest that the newly emerged BDNF-positive cells may not be microglia, but possibly are neurons.

From the epidemiological data, females have a much higher incidence of AD than males, indicating the correlation of AD with sex steroid hormones [35, 36]. It has been suggested that female animals or humans might benefit more from exercise than males do in improving AD symptoms [9]. In this study, the results showed that treadmill running could significantly improve the cognitive function of male AD mice, suggesting that treadmill exercise or running is an appropriate exercise pattern for male animals or humans.

It has been suggested that physical exercise would be more effective in improving cognitive performance when combined with mental activity [37, 38]. While exercise increases the proliferation of hippocampal neurons, mental activity is required to keep these cells alive [37]. Thus, the combination of treadmill exercise and mental activity such as listening to music might be a better choice in AD prevention.

CONCLUSIONS

The current study shows that 5-month, 6 sessions/week treadmill exercise training could improve the spatial memory of male APPswe/PS1dE9 AD mice. The enhanced BDNF expression and inhibited microglia activation, which imply increased neurogenesis and decreased inflammation respectively, might underpin the beneficial effect of treadmill exercise. Treadmill exercise does not exert an obvious influence on Aβ deposition. The study also emphasizes the important role of BDNF and microglia in AD development.

Acknowledgements

We appreciated the undergraduates Zeping Liu, Junming Li, Jianchao Shen, Zhejun Gong and Guangyu Wang in Zhanjiang Normal College for their efforts in training the mice. This work was supported by the Medical Scientific Research Foundation of Guangdong Province (A2012420), the Doctoral Initial Funding of Guangdong Medical College (B2011005) and the Science & Technology Innovation Fund of Guangdong Medical College (STIF201102).

Conflict of interests: the authors declared no conflict of interests regarding the publication of this manuscript.

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