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Treadnill exercise ameliorated stress-induced neuron impairment and dopamine loss in rat hippocampus and improved working memory

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Abstract

Stress-related memory deficit is correlated with neurotransmitter system impairment. Exercise improves memory function and neurotransmitter. However, no studies have been performed to directly observe exercise-related effects on neurotransmitter in stress model, in association with memory function and hippocampal neuron. This study aimed to investigate the effect of exercise on hippocampal neuron and dopamine in stress model, followed by working memory in a passive avoid test. Our study found that stress rat had significantly neuron impairment and dopamine loss in hippocampus plus working memory deficit, which can be rescued by exercise. In summary, this study demonstrated that the neuroprotective effect of stress-associated working memory by treadmill exercise via ameliorated neuron impairment and dopamine loss.

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Abstract

Stress-related memory deficit is correlated with neurotransmitter system impairment. Exercise improves memory function and neurotransmitter. However, no studies have been performed to directly observe exercise-related effects on neurotransmitter in stress model, in association with memory function and hippocampal neuron. This study aimed to investigate the effect of exercise on hippocampal neuron and dopamine

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Keywords: Treadmill exercise; Stress; Working memory; Neuron; Dopamine.

Introduction

As an important psychiatric disease, stress is one of the most common triggers of clinical depression, causing lasting anxiety, depressed mood and memory deficit[1]. Extensive studies at different molecular levels aimed at understanding the mechanisms underlying stress-induced memory deficit. Synaptic pathway[2], inflammation[3]and neurotransmitter[4] all can be regard as an important partner to induced memory deficit. Importantly, long-term memory, working memory, and self-reported memory all can be affected by stress[5]. As the basic structure of cognitive formation, stress disrupts the structural and functional integrity of neuronal networks in the brain of rats[6]. Neuron injury may further contribute to stress induced memory deficit[7]. Therefore, how to improve memory by rescue neuron injury have been a hot topic in the field of stress research.

Accumulating evidence demonstrates that exercise plays a key role in stress model and it has become an interesting target for therapeutic intervention[8-9]. Various clinical studies have revealed that exercise improve cognition and mental health[10-11]. Loprinzi PD et al. demonstrated that exercise at 70%–85% of estimated maximum heart rate are effective in enhancing long-term memory function[12]. And abundant animal model further elucidated beneficial effects of exercise on memory function possibly via facilitating local neurogenesis, neurons activity, the excitability of neurons, and so on[13-15]. These molecular studies have elucidated neuron that may be important in the neuroprotective effect of exercise. In addition, as an important material for transmitting information between neurons, neurotransmitter is necessary for the beneficial effect of running on motor skill learning[16]. exercise improve memory by increase dopamine level, in addition to functional recovery in AD and other diseases of the central nervous system[17-18]. No direct study, however, has been elucidated the molecular mechanism connecting exercise and hippocampal neuron on working memory in stress model. The molecular mechanism connecting exercise and dopamine in hippocampus is also lacking.

To determine the regulatory of exercise-related effects on neurotransmitter in stress model, in association with working memory function and hippocampal neuron. We used passive avoid test to evaluate working memory after exercise in stress rat model. Immunofluorescence, ELISA to label NeuN cells and dopamine in the hippocampus, respectively.

Materials and methods

Experimental animals and grouping

Adult male Sprague–Dawley rats (Experimental Animal Center of Peking University, Peaking, China), weighing 200-250 g at the onset of the experiment, were housed in groups of 3 per cage. All experimental protocols have been pre-approved by the Laboratory Animal Ethics Committee in accordance with National Guidance for Animal Experiment. The animal room was maintained on a 12 hour reversed light-dark cycle a with a temperature of 23 ± 2°C, and 30 to 70% humidity.

Rats were allowed one week to habituate to the animal facility. Following 1 week of habituation, rats (n = 24) were enrolled in this study and randomly divided into following 4 groups: control group (Con group, n = 6), stress group (n = 6), exercise and stress group (Exe-stress group, n = 6), exercise group(Exe group, n = 6). The rats in Exe-stress and Exe groups were received 4 weeks treadmill exercise interventions, respectively. Then, the rats in stress group and Exe-stress group were received repeated restraint stress to establish stress model. Next, all rats received behavior test, including open file test and passive avoidance test. Last, hippocampal dopamine level were detected by ELISA. Immunofluorescence was performed to observe the number of the neural cells in hippocampus. Timeline in our study is shown in Fig. 1.

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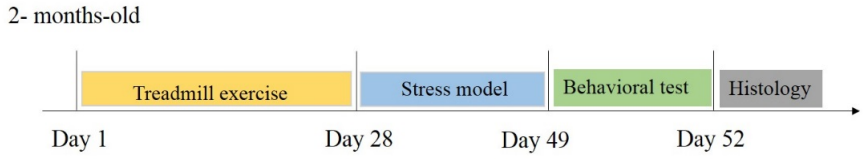

Fig. 1 Timeline in this experiment.

Treadmill exercise

Treadmill exercise was performed according to previous literature[19]. Briefly, a treadmill exercise apparatus for rat as used for chronic physical exercise. During the test session, the rat were allocated in the test room for 30 min acclimation, followed by normal exercise intervention. The speed of the treadmill exercise was 15 m/min, and the animal performed exercise 30 min daily for 4 weeks (5 days/week).

Repeated restraint stress protocol

Repeated restraint stress model was generated by physical restrain as previous described[20]. The rat was restrained for 6 h daily (15:00–21:00) in a wire mesh restrainer for 21 days. After restrain treatment, the rat were returned to their own cages. All the procedures were performed after physical exercise.

Behavioral procedures

On the test day, rats were transferred to the testing room and acclimated to the room conditions for at least 1 h. After each individual test session, the apparatus was thoroughly cleaned with 70% alcohol to eliminate the previously tested rat's odor and trace.

Open field test was to evaluated anxiety-like behavior[21]. Open field experiment box (100 cm × 100 cm ×50 cm) were made out of plexiglass. Each animal was placed in the open field box for freely exploring the arena during a single 5 min session. During the test session, movement paths in open field experiment box were measured automatically by digital camera.

Passive avoidance test is a common measure of learning memory[22]. The apparatus consisted of a light compartment and a dark compartment. In acquisition trial, rats we placed them in the light compartment and allowed them to freely explore it. As expected, due to their natural aversion to the light and preference for the dark, rats very quickly entered the dark chamber. The time of rat from the light chamber to enter the dark compartment was noted. Upon entry into the dark chamber, the guillotine door was closed. Then, rats received a single mild electric footshock (0.5mA; 1s) for 30s and then were returned to their homecage. 24 h later, we subjected rats to an retention trial. The procedure was similar to the acquisition trial except this time rats did not receive the electrical foot shock, and we recorded the time to enter the dark compartment (up to 300 s).

Immunofluorescence

Animals were sacrificed and perfused with ice-cold PBS, followed by perfusion with 4% paraformaldehyde. The brain were removed rapidly, immersed in a tube containing 4% paraformaldehyde for 12 hours at 4 and cryoprotected in PBS containing 20% and 30% sucrose, respectively. They were then frozen on powdered dry ice and stored at - 80 until they were processed. Serial coronal sections (40 μm) were cut through the hippocampus on a cryostat. Brain sections were incubated at 37@C for 30 min and rinsed in PBS for 10 min, incubated in 0.3% Triton X-100 for 10 min and 10% normal donkey serum for 2 hour. Then subsequently incubated overnight at 4 with primary antibody, including rabbit monoclonal to NeuN- neuronal marker. Next day, they were incubated in second antibody (Goat Anti-Rabbit IgG) for 2 hour after washed by PBS. After rinsing three times with PBS, the brain slices were attached to coated slide glasses and evaluated for confocal fluorescence microscopy[23].

Golgi staining

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For the quantification of hippocampal morphological changes, Golgi staining kit (FD Rapid Golgi Stain Kit PK-401, USA)was used to analyze neuronal spine density following the manufacturer's protocols. Briefly, the whole brains were extracted and placed in in EP tube with Golgi-Cox solution for 17 days in the dark. Then the brains were subsequently frozen and coronal sections (60 μm) were obtained using a cryostat (Leica, Nussloch, Germany). And the sections were incubated in the staining solution for 15 min, dehydrated in ethanol solution (30%, 50%, 80%, and 100%). Finally, slides were cover-slipped with Permount. Images of hippocampal pyramidal cells were obtained by panoramic multi-layer scanning with digital slice scanner at a magnification. To calculate the number of spine, a length of dendrite (at least [?]10 μm long, 2nd-oder dendrites) was traced (at 1000×).

ELISA

The hippocampal brain tissue was lysed in RIPA buffer (Beyotime, Shanghai, China) and processed in ultrasonication and was centrifuged for 10 min to collect the supernatant. Hippocampal dopamine were detected after purification using ELISA kits (Nanjingjiancheng, China). Briefly, the wells of a 48-well flat-bottom high-affinity ELISA plates were coated overnight and add prepared sample and standards. Subsequently, the plate was washed five times in each well, and the plate was incubated for 20 min in the dark at room temperature. Finally, the reaction was stopped and measure the OD values within 10 minutes.

Statistics

All data in this experiment are presented as the mean ± SEM. Data analysis was performed by GraphPad Prism software. Data analysis was performed by GraphPad Prism software. Student's t-test was used to compare means between two groups. A statistical significant level was defined when $P < 0.05$.

Results

Stress-induced anxiety behavior can be rescued by treadmill exercise

The open-field test showed that stress rat displayed decreased central exploration time and central distance relative to the control group (Fig. 2 A-B; $p < 0.01$, $p < 0.001$). Locomotor activity, measured by total distance traveled, did not differ between the stress and control groups (Fig. 2 C; $p > 0.05$). Then we tested whether treadmill exercise could ameliorate stress related behavior abnormality. The results demonstrated that significantly elevated central exploration time and central distance in Exe-stress group when compared with stress group (Fig. 2 A-B; $p < 0.01$, $p < 0.001$). and there were no significantly different in total distance between the stress and control groups (Fig. 2 C; $p > 0.05$). These data demonstrate that stress rat develop an anxiety-like phenotype after repeated restraint stress exposure, which can be rescued by treadmill exercise.

Fig. 2. Treadmill exercise alleviated stress-induced anxiety behavior.$^{###}$p<0.001 vs. control;***p<0.001 vs. stress.

Stress-induced working memory impairment was ameliorated by treadmill exercise

Fig. 3 shows that the latency time of passive avoidance test in each group. In the acquisition trail, there are no significant difference for the four groups (Fig. 3, $p > 0.05$). In the retention trail: when compare to C group, the time in stress group was significantly shorter (Fig. 3, $p < 0.001$). As compare to stress group, the time in Exe-stress groups were significantly longer (Fig. 3, $p < 0.001$). The results indicated that stress-induced working memory impairment was ameliorated by treadmill exercise.

Fig. 3. Treadmill exercise alleviated stress-induced working memory impairment. $^{###}$p<0.001 vs. control;***p<0.001 vs. stress.

Treadmill exercise prevented stress-induced neuron loss

In order to examine the effect of exercise on hippocampal neuron in stress rat, staining with NeuN was used to detect hippocampal neuronal viability in each group (Fig. 4A). The number of NeuN cells in the stress group was significantly increased compared with that observed in the control group (Fig. 4B, $p < 0.01$). But

a greater NeuN-positive cells was observed in the hippocampus after treadmill exercise intervention (Fig. 4B, p <0.05). These results suggest that stress-induced hippocampal neuron loss can be rescued by treadmill exercise.

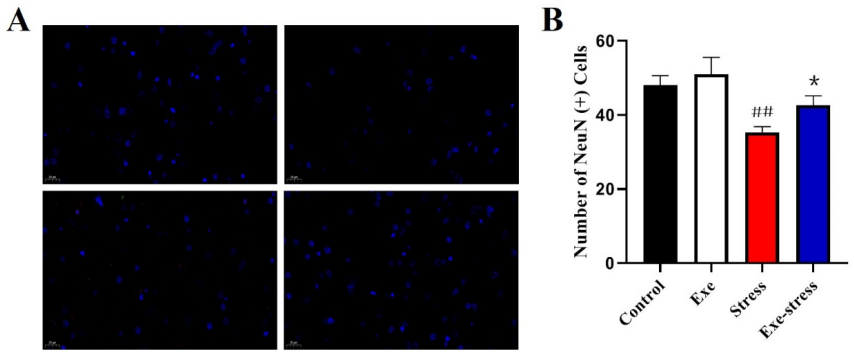

Fig. 4. Effect of treadmill exercise on hippocampal neuron in stress model. (A) Representative photomicrograph of NeuN immunostaining showing neuron cells in each group. (B) NeuN cells were counted in the hippocampal brain sections. $^{\#\#}p<0.01$ vs. control; $^{*}p<0.05$ vs. stress.

Treadmill exercise prevented stress-induced the decrease of spine density

Dendritic spines are small, thin, hair-like protrusions located on the neurons. Previous studies have shown that the dynamics of dendritic spine's morphology and structure is associated with learning and memory[24]. We further analyzed the dendritic spine numbers of the secondary dendrites in the hippocampus by Golgi staining (Fig. 5A). Our results demonstrated that hippocampal spine density significantly decreased in stress group when compared with C group, (Fig. 5B, p¡0.05), but the neuron from Exe-Stress group rat exhibited a more density than those from VD rat (Fig. 5B, p¡0.05). Thus, we concluded that stress-induced the decrease of hippocampal spine density can be rescued by treadmill exercise.

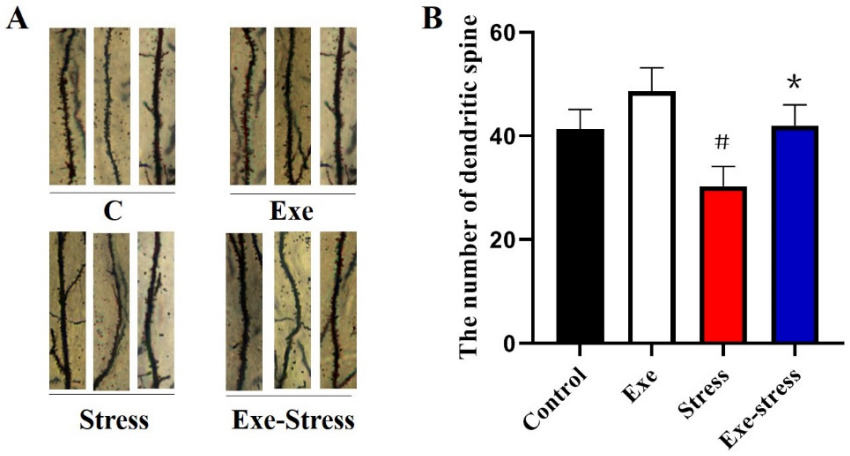

Fig. 5. Effect of treadmill exercise on hippocampal spine density in stress model. (A) Representative Golgi staining images of the secondary dendrites in the hippocampus. (B) The spines numbers of hippocampus in each group. $^{\#}p<0.05$ vs. control;$^{*}p<0.05$ vs. stress.

Treadmill exercise prevented stress-induced dopamine loss

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To further investigate the changes of dopamine in each group, ELISA method was used to detected dopamine. In stress rats, the hippocampal concentrations of dopamine significantly decreased when compared with control rats (Fig. 6, $p < 0.05$). But in Exe-stress group, the level of dopamine was significantly higher than that in stress group (Fig. 6, $p < 0.05$). Thus, we concluded that stress-induced hippocampal dopamine loss can be rescued by treadmill exercise.

Fig. 6. Effect of treadmill exercise on hippocampal dopamine in stress model. $^{\#\#}p<0.01$ vs. control;$^{**}p<0.01$ vs. stress.

Discussion

In this study, we found stress-induced working memory deficit and anxiety-like behavior, which is associated with hippocampal neuron impairment and dopamine loss. Furthermore, we also found healthier neuronal and dendritic spine as well as increased

dopamine of hippocampus after treadmill exercise in stress rat, in addition to improved working memory.

Repeated stress may lead to the development of various somatic, cognitive and mental disorders[25]. And those phenomenon was observed in human studies. A follow-up study in clinical subjects demonstrated that even very low levels of stress exposure can have negative effects on cognition[26]. And chronic stress early in life can influence working memory in adulthood[27]. Alternatively, stress-induced memory deficit and was also observed in vivo studies, such as spatial memory, recognition memory[28-29]. Passive avoid test were used to evaluated working memory in this study, which revealed that significantly working memory deficit in stress rat. In addition, consist with previous study, we also demonstrated that repeated restraint stress rats also exposed anxiety-like behavior in open filed test[30]. but the mechanism of stress-induced memory deficit need to be further studies.

The hippocampus has long been considered critical for encoding memories[31]. Furthermore, the hippocampus is implicated in disease states that result in cognitive dysfunction and synaptic function. Chronic stress has frequently been shown to impair the structure and function of the hippocampus, in associated with memory deficit[32-33]. Our research showed that stress rats exhibit fewer neurons in the hippocampus. Previous finding revealed that stress triggers divergent dendritic alterations in immature neurons of the adult hippocampus[34]. Golgi staining in our study also found that the dendritic spine numbers of the secondary dendrites in the hippocampus significantly decreased after stress. This results are consist with previous study[35]. In addition, neuromodulator and intracellular signaling events that underlie memory retrieval mediated by the hippocampus[36]. As an important neuromodulator, dopamine is involved in memory formation through information transmission between neurons[37]. In our study, significantly decreased of hippocampal dopamine were observed in stress rats. A review by Holly EN et al. reported that extracellular dopamine and its metabolites have found a robust variation during stress. This review further revealed that the nature and degree of the dopaminergic change vary according to stressor and intensity[38]. Thus, we concluded that stress-induced working memory deficit is associated with the loss of neuron and dopamine in the hippocampus.

Exercise has beneficiary effects on both memory and mental functions. Exercise effective in enhancing logical memory and motor learning in humans[39-40]. And animal studies also found that exercise improves motor skill learning and spatial memory, especially in stress model[41-43]. In this study, we revealed that working memory was significantly improved after treadmill exercise interventions in stress rat. As further evidence, we also revealed that stress-induced anxiety behavior can be rescued by treadmill exercise. This results are consist with previous study[44]. Alternatively, a follow-up molecular study demonstrated that increased in mTOR signaling could contribute to the beneficial effects of exercise on cognitive function and mental health[45]. The transmission of neurotransmitter between neurons is the necessary structure of memory formation, and changes in any of these factors can lead to memory dysfunction. Thus, we hypothesized that treadmill exercise improved working memory and mental health via modulating neurotransmitter and neuron in stress model. The subsequent results in our study proved that stress-induced hippocampal neuron

impairment and dopamine loss, which can be rescued by treadmill exercise. First, Immunofluorescence results revealed that a greater NeuN-positive cells was observed in the hippocampus in stress rat model after treadmill exercise intervention. Those results suggest that stress-induced hippocampal neuron loss can be rescued by treadmill exercise. It is related to exercise followed by stress enhanced the new cells with mature neuron phenotype[46]. Second, our study confirmed that there were more spines on the apical dendrites of pyramidal cells from Exe-Stress rat than on those from stress rat. Chen's study directly confirmed that chronic exercise facilitates new spine formation in the brain[47]. Last, our study also demonstrated that stress-induced hippocampal dopamine loss can be rescued by exercise. Similar recent studies showed that moderate exercise can induce the released of dopamine under normal or disease status[48-49].

In summary, this study demonstrated that treadmill exercise improved working memory via ameliorating hippocampal neuron and dopamine loss in stress rat. This study provided evidences for stress-related memory deficit, and potential treatment of stress-induced memory deficit by treadmill exercise, although further studies are required to elucidate underlying neural circuits and molecular mechanisms.

Conclusion

Treadmill exercise ameliorated stress-induced neuron impairment and dopamine loss in rat hippocampus and improved working memory.

Acknowledgement

The author declare that there are no any conflict.

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