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Research paper

Swimming exercise reverses CUMS-induced changes in depression-like behaviors and hippocampal plasticity-related proteins

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ABSTRACT

Background: Stress-induced failed resilience of brain plasticity can contribute to the onset and recurrence of depression. Chronic stress has been reported to open windows of epigenetic plasticity in hippocampus. However, how hippocampal plasticity underlies depression-like behaviors and how it adapts in response to stress has not been addressed. The present study aimed to investigate the signaling mechanisms of CUMS affecting hippocampal plasticity-related proteins expression and the regulation of swimming exercise in mice.

Methods: Male C57BL/6 mice were subjected to chronic unpredictable mild stress (CUMS) for 7 weeks. From the 4th week, CUMS mice were trained in a moderate swimming program for a total of 4 weeks. A videocomputerized tracking system was used to record behaviors of animals for a 5-min session. Real-time PCR and Western Blotting were used to examine gene expression in mouse hippocampus.

Results: Our results demonstrated that CUMS induced depression-like behaviors, which were reversed by swimming exercise. Moreover, the behavioral changes induced by CUMS and exercise were correlated with hippocampal plasticity-related proteins expression of growth-associated protein-43 (GAP-43) and synaptophysin (SYN). The molecular mechanisms regulating this plasticity may include SIRT1/mircoRNA, CREB/BDNF, and AKT/GSK-3β signaling pathways.

Limitations: We did not establish a correlation between depression-like behaviors induced by chronic stress and epigenetic changes of hippocampal plasticity, either a causal molecular signaling underling this plasticity.

Conclusions: Our findings have identified swimming exercise effects on CUMS-induced changes in depression-like behaviors and hippocampal plasticity-related proteins, which provide a framework for developing new strategies to treat stress-induced depression.

1. Introduction

The brain possesses remarkable structural and functional plasticity in response to stress (McEwen, 2007), whereas stress-induced failed resilience of brain plasticity can contribute to the onset and recurrence of depression (Southwick and Charney, 2012). Chronic stress associated with the development of depression (Ferrarelli, 2017), has been reported to open windows of epigenetic plasticity in hippocampus (Nasca et al., 2015). Chronic unpredictable mild stress (CUMS) in rodents, a classical animal model of depression, has been linked to hippocampal plasticity (Wu et al., 2007). Most literature on structural and functional plasticity induced by stress in rodents has focused on the hippocampus and prefrontal cortex (Russo and Nestler, 2013). The hippocampus is an especially plastic and vulnerable region of brain and is a target of stress response (McEwen, 1999). However, how hippocampal plasticity underlies depression-like behaviors and how it adapts in response to stress has not been addressed.

Both clinical and animal studies on stress-induced hippocampal plasticity have paid more attention to structural plasticity, including atrophy of dendrites in CA3 region and suppressed neurogenesis of dentate gyrus granule neurons (McEwen, 1999). It has been suggested that molecular mechanisms underlying this plasticity are possible to

Abbreviations: AKT, protein kinase B; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; CUMS, chronic unpredictable mild stress; FST, forced swim test; GAP-43, growth-associated protein-43; GSK-3β, glycogen synthase kinase-3β; OFT, open field test; SIRT1, sirtuin 1; SPT, sucrose preference test; SYN, synaptophysin; TST, tail suspension test

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become 'overwhelmed' in response to stress and consequently promote pathological behaviors (Russo and Nestler, 2013). Hippocampal sirtuin 1 (SIRT1), identified as one of two genome-wide significant loci contributing to depression (Anon, 2015), has been reported to mediate chronic stress-elicited depression-like phenotype and aberrant dendritic atrophy (Abe-Higuchi et al., 2016). The promotion of hippocampal memory and synaptic plasticity has been found to be correlated with significant activation of SIRT1/mircoRNA signaling (Chen et al., 2016). MircoRNA has been reported to regulate SIRT1/cAMP response element-binding protein (CREB) signaling (Zhang et al., 2017). Activating CREB/brain-derived neurotrophic factor (BDNF) pathway in hippocampus can contribute to ameliorative effects of alpha-linolenic acid supplement on cognitive deficits (Gao et al., 2016). In schizophrenia, mircoRNA has also been reported to regulate neuronal level of glycogen synthase kinase-3β (GSK-3β), which acts downstream of BDNF signaling (Thomas et al., 2017). Inhibition of protein kinase B (AKT)/GSK-3β signaling can mediate depression-like behaviors and synaptic plasticity of hippocampal neuron in CUMS rats (Mao et al., 2017). GSK-3β deletion in dentate gyrus has been found to inhibit hippocampal synaptic transmission and reduce protein level of synaptophysin (SYN, a presynaptic marker) (Liu et al., 2017a). Besides SYN, growth-associated protein-43 (GAP-43, a marker of neuronal structural plasticity) may also play a role in pathophysiology of depression and mechanisms of antidepressants (Iwata et al., 2006).

However, side effects of antidepressants attenuate their efficacy and safety as reliable strategies for anti-depression treatment in clinical practice (Varela and Adan-Manes, 2017). As a non-pharmacological coping strategy, physical exercise as a regular life-style prevents depression relapse much better than antidepressant medication in clinical reports (Strawbridge et al., 2002). Adult hippocampal neurogenesis has been suggested as an important target associated with antidepressant effects of exercise (Sun et al., 2017). It has been reviewed that aerobic exercise contributes to hippocampal plasticity-related proteins expression (Gomes et al., 2013). Treadmill running has been found to activate hippocampal plasticity-related proteins expression of BDNF and SYN in obese rats (Cai et al., 2016). Co-treatment of 7,8-Dihydroxyflavone and voluntary running wheel exercise can ameliorate the reductions in hippocampal levels of SYN and GAP-43 (Krishna et al., 2017). Therefore, the aim of the present study was to investigate the signaling mechanisms of CUMS affecting hippocampal plasticity-related proteins expression and the regulation of swimming exercise in mice.

2. Materials and methods

2.1. Animals and groups

Male C57BL/6 mice (5-week old, 15–20 g) obtained from Shanghai SLAC Experimental Animal Center (Shanghai, China) were housed with a 12-h light:dark cycle under controlled temperature (22 ± 2 °C) and humidity (50 ± 10%), and were given standard diet and water ad libitum. All mice were divided into three groups: control (Con), CUMS, CUMS + Swim; n = 8 per group. All procedures were in accordance with the guidelines for the use of laboratory animals published by the People's Republic of China Ministry of Health (No. 55 order, January 25, 1998) and were approved by the Experimental Animal Care and Use Committee at East China Normal University (ECNU 2006-05).

2.2. Chronic unpredictable mild stress procedure

The CUMS procedure was performed as described (Surget et al., 2009) with a slight modification. Mice in CUMS group were subjected to different stressors: cage tilting for 24 h (45°), wet bedding for 24 h (200 ml of water per cage), cold swimming for 5 min (at 10 °C), swimming in hot water for 5 min (at 40 °C), fasting for 48 h, water deprivation for 24 h, level shaking for 10 min, tail nip for 1 min (1 cm from the end of the tail), and inversion of the light/dark cycle for 24 h. It should be pointed out that cold water and hot water stressors are used broadly in CUMS regimen (Hu et al., 2017). In view of the innate ability to swim in rodents, cold water and hot water stressors in CUMS should be considered as temperature stress rather than water stress. These stressors were applied for 49 days, during which each stressor was applied 5–6 times. Mice received one of these stressors at different time every day and the same stressor was not applied consecutively over two days so that animals could not predict the occurrence of stimulation. Control group was undisturbed except for necessary procedures such as routine cage cleaning.

2.3. Exercise protocol

As an innate ability of rodents, swimming exercise presents advantages over treadmill running; moreover, swimming requires an unelaborate device relative to treadmill running and spontaneous wheel exercise (Seo et al., 2014). Moreover, studies using this model revealed similarities in the adaptations to the exercise in relation to those observed in humans (Gobatto et al., 2001; Voltarelli et al., 2002). Thus, swimming is the most used in exercise physiology studies and induces various changes in the functions of the brain (Ra et al., 2002). Mice were trained in a moderate swimming program with no weight loading in free style, the antidepressant effects of which have been validated by our previous study (Liu et al., 2017c) and other report (Jiang et al., 2014). Daily swimming exercise was performed in a large glass water tank (100 cm(L) × 60 cm(W) × 80 cm(H)) at 32 ± 1 °C, a thermostat being used to maintain water temperature and an aquarium thermometer being stuck on the glass to present real-time temperature. The water depth was 60 cm so that the mice could not support themselves by touching the bottom with their feet; additionally, liquid soap was added to reduce surface tension and to abolish floating behavior (Mazzardo-Martins et al., 2010). The swimming was continuously supervised. The animals were swum as a group of six to eight mice, because it has been demonstrated that the intensity of swimming exercise was significantly raised by interaction among the animals (Iemitsu et al., 2004). The swimming program included two phases: adaptation and training. During the first week for adaptation, the training was graded beginning with 15 min on the first day until 60 min on the last day. The adaptation was aimed at reducing the water-induced stress without promoting physiological alterations in relation to the physical training (Contarteze et al., 2008). Then, the training period began from the 4th week during CUMS exposure, with intensity of 60 min/day, 5d/week, for a total of 4 weeks. Generally, swimming 1 h a day for 5 days a week is considered as moderate exercise, while swimming more than that is classified as strenuous exercise (Seo et al., 2014). Damghani et al. have suggested that only 14 days of swimming exercise (45 min/day, five days per week) is sufficient to reduce depression in rats (Damghani et al., 2016). Exercise was performed at the same time every day (between 9:00 and 11:00 a.m.). After swimming, mice were toweled dry and kept warm by electric heater.

2.4. Behavioral testing

Except sucrose preference, a videocomputerized tracking system (DigBehav, Jiliang Co. Ltd., Shanghai, China) was used to record the behaviors of the animals. All testing equipment was thoroughly cleaned between each session.

2.4.1. Sucrose preference test (SPT)

The procedure was performed as described previously (Willner et al., 1987). Briefly, 72 h before the test mice were trained to adapt 1% sucrose solution (w/v): two bottles of 1% sucrose solution were placed in each cage, and 24 h later 1% sucrose in one bottle was replaced with tap water for 24 h. After adaptation, mice were deprived of water and food for 24 h, followed by the sucrose preference test, in which mice housed in individual cages had free access to two bottles containing