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Effect of treadmill exercise on miR-191-5p expression in the hippocampus of sleep-deprived rats

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ABSTRACT

The positive and protective effects of regular exercise on the learning and memory impairments induced by sleep deprivation (SD) have been demonstrated in previous studies, and recently, it was found that miR-191-5p by targeting BDNF as an essential factor in cognitive function causes memory and learning impairments in sleep deprivation conditions. This study aims to investigate the effects of regular treadmill exercise on the expression of miR-191-5p in sleep-deprived rats. Ovariectomized (OVX) rats are more vulnerable to the effects of sleep deprivation than intact rats. In this study, we performed our experiments on OVX female rats. MiRNAs are vital regulators of many biological functions, mainly brain functions such as learning and memory. The effect of 72 hours of sleep deprivation and four weeks of treadmill exercise on the expression of miR-191-5p and BDNF was investigated. Seventy-two hours of sleep deprivation was performed using the multiple platform method, and the exercise protocol was four weeks of regular treadmill exercise. Expression of miR-191-5p and BDNF was done using the Real-time PCR method. Sleep deprivation down-regulated the level of miR-191-5p and BDNF, all of which were ameliorated by four weeks of treadmill exercise. Despite increased BDNF expression in exercised rats, miR-191-5p did not show significant changes. The mechanism of the possible effect of exercise on the expression of BDNF was independent of its effect on the expression of miR-191-5p.

Introduction

Today, exercise is considered an essential factor in improving the quality of life through epigenetic changes such as various microRNAs (miRNAs), which alter the expression levels of different genes (Ntanasis-Stathopoulos, Tzanninis, et al. 2013). Exercise is one of the most potent non-

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pharmacological interventions to improve cognitive function, especially in postmenopausal women (Shangold and Gynecology 1990). Numerous studies have shown that sleep deprivation negatively affects memory and learning processes and reduces BDNF expression in the hippocampus (Hajali, Sheibani et al. 2012, Zagaar, Alhaider et al. 2012, Saadati, Sheibani et al. 2014, Adams, Arem et al. 2018).

Analysis and investigation of miRNA microarray in three brain regions showed changes in the expression of fifty miRNAs, such as an increase in hsa-miR-191 expression in the hippocampus region Davis, 2007 #86). Several studies, both in vitro and in vivo, have shown that miR-191-5p reduces the expression of internal BDNF by binding to it.

Conversely, decreasing miR-191-5p is associated with increased expression of BDNF (Varendi, Kumar et al. 2014, Mohammadipoor-Ghasemabad, Sangtarash et al. 2019).

MiR-191-5p is a microRNA extensively studied in various biological processes and diseases. Several studies have also investigated the functional role of miR-191-5p in different contexts, such as cancer, Neurodegenerative, and cardiovascular diseases. MiR-191-5p has been shown to act as an oncogene and a tumour suppressor based on the specific cancer type. MiR-191-5p functions as an oncogene or onco-miR by targeting multiple genes involved in the growth arrest of cancer cell lines such as breast (female), prostate, colon, lung, colorectal cancer, and gastric cancer, etc. (Ferretti, De Smaele et al. 2009, Fulci, Colombo et al. 2009, Shen, DiCioccio et al. 2010, Gombos, Horváth et al. 2013, Nagpal and Kulshreshtha 2014, Zhang, Li et al. 2015, Li, Zhou et al. 2017). However, in some cancer types, such as retinoblastoma, severe medulloblastomas, etc., it acts as a tumour suppressor (Shi, Su et al. 2011, Nagpal and Kulshreshtha 2014, Chen, Pan et al. 2018). It has been linked to neurodegenerative disorders like Alzheimer's disease. In Alzheimer's disease, dysregulation of miR-191-5p plays a role in the development of the disease by targeting genes involved in amyloid-beta production and tau hyperphosphorylation (Wang, Shui et al. 2022). MiR-191-5p, by modulating gene expression involved in lipid metabolism and inflammation, has also been linked to cardiovascular diseases such as heart failure and atherosclerosis (Pordzik, Pisarz et al. 2018, Wakabayashi, Eguchi et al. 2020, Yu, Zhou et al. 2022). Based on the current understanding of miR-191 biology, it is a potential biomarker for cancer/disease diagnosis, prognosis, and therapy. Several miR-191 targets have been functionally validated and characterized, including chromatin remodelers, transcription factors, and cell cycle regulators (Nagpal and Kulshreshtha 2014). However, its role has been unknown in SD and exercise conditions.

In this study, we aim to investigate the effects of regular treadmill exercise on the expression of miR-191-5p and BDNF in the hippocampus of OVX female rats after 72 hours of SD, considering the proven effects of exercise on miRNAs and the relation between miR-191-5p and BDNF in SD condition.

Materials and methods:

Animals

In the present study, a total of 42 female Wistar desert rats (n = 7 per group) (weighing 200-250 g, 3–4 months old) were housed in groups of four and maintained under standard conditions (12/12 h light/dark cycle and at temperature: 23 ± 1 °C with free access to food and water). Groups used in this study included Control (rats were ovariectomized) (C), Sleep deprivation (rats were ovariectomized (OVX) and deprived of sleep for 72 hours) (Logsdon), Exercise (OVX rats exercised for one month) (E), Sham exercise (OVX rats were placed on a treadmill for a month) (Sham E), and Exercise/ Sleep deprivation (OVX experienced treadmill exercise for a month and sleep deprivation for 72 hours) (E/SD). All stages were carried out under the guidelines of the National Council for Care and Use of Laboratory Animals, supervised by the Ethics

Committee of Kerman Neuroscience Research Center (Ethics Code: KNRC-94-46).

Ovariectomy surgery

Ovariectomy surgery was performed under general anesthesia (a mixture of ketamine (60 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.)) on both ovaries (Mohammadipoor-Ghasemabad, Sangtarash et al. 2019). All rats were placed in a controlled animal room for one month following ovariectomy.

Regular treadmill exercise protocol

The rats were subjected to exercise five days a week, from Saturday to Wednesday, with a 0° inclination. This exercise occurred during the light cycle, specifically between 9:00 and 14:30. To ensure compliance, the rats received a mild shock of 0.25 mA if they stopped running. Before starting the exercise protocol, the rats were given 30 minutes on two consecutive days to become accustomed to the treadmill environment. This habituation was done to minimize any unrelated stress responses. The animals exercised for 30 minutes at a 10 m/min speed for the first two weeks. In the third week, the exercise duration increased to 45 minutes at a 10 m/min speed. Finally, the animals exercised for 60 minutes at a 15 m/min speed in the fourth week. During each session, the animals took a five-minute rest break every 15 minutes (Saadati, Sheibani et al. 2014).

Sleep deprivation

Sleep deprivation was induced continuously for 72 hours using a multiple-platform method. The column-in-water method (multi-platform method) was used to reach SD. This device (90 cm x 50 cm x 50 cm) contained ten columns (10 cm high and 7 cm in diameter) placed 2 cm above the water) arranged in two rows 10 cm apart (edge). The device allows rats to move from platform to platform. The animal was placed on a small platform. Therefore, SD was reached when the animal began to sleep with rapid eye movements (REM), muscle tone loss caused by rats' exposure to water, and waking up (Hajali, Sheibani et al. 2012).

Real-time PCR procedure

Animals were anesthetized with CO2 after completion of the tests, and both hippocampi were separated from the brain. Total RNA was extracted using RNX-plus reagent purchased from Sinaclon (Iran). Real-time PCR was used to measure the expression of BDNF and beta-actin (reference gene), while miR-191-5p and U6 (reference genes) were measured using poly (T) adaptor RT-PCR (Shi, Sun et al. 2012). The primers of U6 and miR-191 were designed by Parsgenom (Iran). The primer sequences of BDNF and β-actin are listed in Table 1.

Table 1- The primers sequences of BDNF and β-actin.

Genes name	Forward primer 5′⟶3′	Reverse primer 5′⟶3′
BDNF	GACGACGACGTCCCTGGCTGA	ACGACTGGGTAGTTCGGCCTGG
β-actin	CCCAGAGCAAGAGAGGCA TC	GCCTTAGGGTTCAGAGGGGC

Statistical analysis

Statistical analysis was done by the SPSS statistical package, version 24 (SPSS, Inc., Chicago, Illinois, USA). All data are given as mean ± standard error of the mean (SEM). Differences in the mean gene expression (miR-191-5p and BDNF) between the experimental groups were analyzed using One-way ANOVA.

Tukey's multiple comparison tests were performed to clarify significant differences where statistical significance was found between groups. $P < 0.05$ was considered a significant level.

Results:

The quality of extracted RNA was by 1.5% agarose gel electrophoresis (Fig. 1A). To optimize the annealing temperature of qPCR of BDNF mRNA, we used gradient PCR and determined the annealing temperature at 60.5 °C (Fig. 1B).

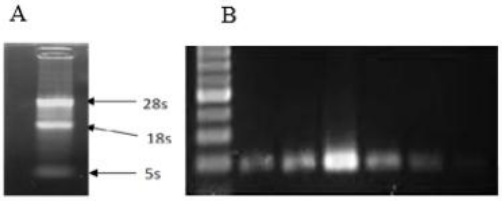

Fig.1 - Agarose gel electrophoresis: A. RNA. B. qPCR products of BDNF mRNA.

The relative expression of miR-191-5p in the hippocampus of female OVX rats showed a significant increase after sleep deprivation ($P < 0.001$, 74.4 ± 8.1), which was improved by exercise to the extent that there was no significant difference between the E/SD group and the C group (Fig. 2). Other groups did not show significant changes in the expression of this gene.

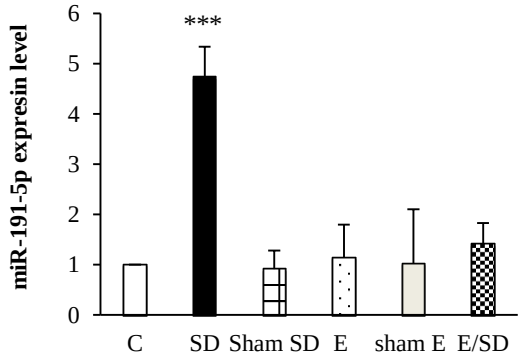

Fig.2 - The relative expression changes of miR-191-5p in the hippocampus of rats. *** P<.0001 in comparison to the control group.

Furthermore, real-time PCR results showed that four weeks of treadmill exercise increased the relative expression of BDNF, which had significantly decreased in the sleep-deprived group ($P < 0.01$, 2.0 ± 0.4) to the extent that there was no significant difference between the E/SD group and the C group. The level of BDNF also significantly increased in the E group ($P < 0.05$, 89.1 ± 49.0) (Fig. 3).

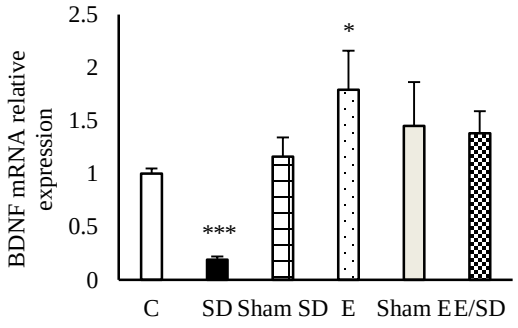

Fig.3 - The relative expression changes of BDNF in the hippocampus of rats. *** P<.0001 in comparison to the control group. *P<.05 in comparison to the control group.

Discussion:

This study showed that one month of regular treadmill exercise improved the effects of reduced miR-191-5p expression in the hippocampus of OVX rats under SD conditions. We report for the first time about the interaction between regular treadmill exercise and the expression level of miR-191-5p in the hippocampus of sleep-deprived female rats. In the previous study, we demonstrated that miR-191-5p upregulated to decrease the level of BDNF protein (Mohammadipoor-Ghasemabad, Sangtarash et al. 2019). So, we measured the level of miR-191-5p and BDNF. The results of real-time PCR showed that BDNF level was increased after a month of treadmill exercise, but the level of miR-191-5p did not show changes after exercise.

Several mechanisms, such as calcium/calmodulin-dependent protein kinase type II messenger system (Vaynman, Ying et al. 2004), cAMP-binding factor (CREB), CpG methylation, and histone H3 acetylation in the BDNF gene promoter regarding the effects of exercise on increased expression of BDNF has been reported (Vaynman, Ying et al. 2004, Gomez- Pinilla, Zhuang et al. 2011). On the other hand, regular exercise has also been revealed to protect hippocampus-related functions and sleep deprivation-induced impairments, potentially by increasing BDNF expression (Saadati, Sheibani et al. 2014). However, the mechanism of these effects was not clearly understood.

Our previous study demonstrated that SD leads to increased levels of miR-191-5p in both OVX and intact female rats. Notably, changes in miR-191a levels were more pronounced in OVX female rats compared to intact female rats, indicating a higher susceptibility to the negative effects of SD on miR-191a levels. We focused on the OVX female rats. We also showed that BDNF is a direct target of miR-191-5p in the SD condition (Mohammadipoor-Ghasemabad, Sangtarash et al. 2019). In addition, it has been found that the memory impairment was more pronounced in the female rats than the male rats. Surprisingly, the stress caused by SD in

the female was not responsible for these impairments, as there was no significant change in plasma corticosterone levels (Hajali, Sheibani et al. 2012).

Several studies have shown that exercise can regulate the expression level of miR-191-5p (Paim, Schreiber et al. 2019, Di, Amdanee et al. 2020, Siqueira, Batabyal et al. 2023).

Endurance exercise in humans causes a significant decrease in the expression of miR-10b in the fat tissues of the thigh and pelvis (Tsiloulis, Pike et al. 2017). Nevertheless, regular exercise with a treadmill had no significant effect on the expression of this gene in the hippocampus (Mohammadipoor-ghasemabad, Sangtarash et al. 2018). In another study, it was proved that treadmill exercise could increase the expression of miR-1b, and the changes of miR-1b showed a positive correlation with the increase in the expression of BDNF (Mohammadipoor-Ghasemabad, Sangtarash et al. 2019). Exercise affects the expression of BDNF, and it also confirms that the effect of exercise on the expression of miR-191-5p is probably done with targets other than BDNF.

A study has reported that mice who exercised for an extended period showed higher calorie consumption, weight maintenance, and more excellent resistance to obesity than mice who did not exercise. Additionally, this study identified the mechanism of prolonged exercise effectiveness as a decrease in miR-191 expression and, ultimately, an increase in PRDM16 gene expression, which is one of the targets of miR-191 (Di, Amdanee et al. 2020). It has been proven that low levels of miR-191-5p in the blood are associated with a high body mass index, and conversely, high levels of miR-191-5p are associated with a low body mass index (Adams, Arem et al. 2018). In our study, treadmill exercise modulated miR-191-5p expression by targeting another pathway, which will be evaluated in future experiments.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

All stages were carried out under the guidelines of the National Council for Care and Use of Laboratory Animals, supervised by the Ethics Committee of Kerman Neuroscience Research Center (Ethics Code: KNRC-94-46).

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