

RESEARCH ARTICLE

Effects of Resistance Exercise on mRNA Expression of Brain Neuroplasticity Related Factors in Hippocampus and Cognitive Function in Ovariectomized Rats

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저항성 운동이 난소절제 쥐 해마의 신경가소성 관련인자 및 인지기능에 미치는 영향

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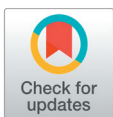
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ABSTRACT

This study aimed to investigate the impact of brain neuroplasticity-related factors' mRNA expression patterns in the hippocampus and cognitive function in ovariectomized rats following resistance exercise. Twenty-week-old female SD rats (n=30) were randomly divided into normal control (NC, n=10), ovariectomy (OVX, n=10), and ovariectomy + resistance exercise (OVX+REX, n=10) groups. A ladder-climbing exercise, in which rats climbed to the top of ladder with a weight applied to their tails 8 times a day, 3 days a week for 12 weeks, was used for resistance training. After 12 weeks, rats from the OVX group had higher body weights and were significantly lower in the OVX-REX group than in the OVX group. The mRNA expression levels of the brain neuroplasticity-related genes, BDNF, IGF-1 and VEGF were significantly decreased by ovariectomy. However, they were significantly increased in the OVX+REX group compared to that in the OVX group. In addition, the learning and memory function of rats in the OVX group was significantly improved by resistance exercise. These results suggest that resistance exercise contributing to improved learning and memory function may be in part due to increased mRNA expression of brain neuroplasticity-related factors in ovariectomized rats.

Key words: Resistance exercise, ovariectomy, BDNF, IGF-1, VEGF, cognitive function, learning, memory



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Introduction

Postmenopausal women are at a higher risk than premenopausal women for various diseases, such as obesity, osteoporosis, and cognitive impairment. Because estrogens play an important role in the control of body functions in females, estrogen deficiency in menopausal status is associated with cognitive dysfunction, calcium deficiency, and oxidative stress (Hampson, 2018; Imtiaz et al., 2017). Several studies have shown that estrogens influence brain functions, such as behavior, sexual orientation and cognition (Gillies & McArthur, 2010). In particular, estrogens prevent the onset of the cerebrovascular event-induced decline in neuronal function, enhance neuronal connectivity and cognition, and delay senile dementia in animal experiments (Gibbs, 2010). In addition, estrogen has a significant impact on diverse brain regions involved in memory-related processes. Specifically, estrogens control memory and cognitive functions in the temporal cortex, and the limbic system, which also controls high-level mental functions in the cerebral cortex. It is also associated with the hippocampus, which plays an important role in memory and cognition (Goveas et al., 2011; Henderson, 2008).

Therefore, the last few decades, hormone replacement therapy has been used for postmenopausal women, but in recent years, many studies have focused on physical exercise to control the memory impairment associated with postmenopausal women. Exercise improves the maintenance and promotion of cognitive function in experimental animals. Treadmill exercise enhances the learning speed and memory retention ability (Fordyce & Wehner, 1993). In addition, spatial perception improved following three weeks of swimming training in brain hemorrhagic rats (Zheng et al., 2019), and aging rats undergoing six weeks of treadmill exercise experienced improved spatial perception (Tsai et al., 2018).

Although the mechanism and effects of exercise on cognitive function remain poorly understood, the increase in synaptic proteins by exercise may reportedly increase neuronal plasticity through neuronal signaling and neuronal activity (Bettio et al., 2019). Brain plasticity plays a critical role in the recovery of cerebral functions, such as learning and memory, after brain lesions (Krakauer, 2006). In particular, brain plasticity-related genes, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) were considered key proteins that were upregulated after exercise and that could promote cell proliferation and growth or neuronal development and function, including learning and memory (Maass et al., 2016). BDNF is a member of the neurotrophin family that supports neural survival, growth, and synaptic plasticity and is expressed in the hippocampus and cortex (Cowansage et al., 2010). IGF-1 is mainly known for its role in energy metabolism and homeostasis, alongside its modulation of synaptic plasticity (Trejo et al., 2007). Furthermore, VEGF is expressed in multiple cells and tissues, including muscle cells, endothelial cells, and glial cells (Tang et al., 2010). It is a hypoxia-inducible protein that is associated with cognitive deficit (During & Cao, 2006).

Many studies have sought to demonstrate the mechanism and positive effects of exercise on cognitive function. However, these studies have mostly focused on aerobic exercise. The mechanisms and effects of resistance exercise remains unclear. Therefore, in this study, we investigated the expression of brain neuroplastic factors in the hippocampus in relation to cognitive function after resistance exercise in ovariectomized rats.

Materials and Methods

Animals

Twenty-week-old female Sprague-Dawley rats were purchased from Damul Science (Daejeon, Korea). They were housed in an environmentally controlled room with constant temperature ($22 \pm 2^\circ\text{C}$), relative humidity ($60 \pm 5\%$), and a 12-h light/dark cycle. All rats were housed in pairs and were fed standard rodent chow (protein, 22.5%; fat, 3.5%; low fiber 7.5%, ash 9.0%, phosphorus 0.5%, calcium 0.7%) and purified water ad libitum. All experimental procedures were approved and carried out in accordance with the Institutional Animal Care and Use Committee of Hannam University, Korea (Approval #: HNU 2018-1).

Following acclimation to the laboratory environment for one week, the rats were randomly assigned to the following groups: normal group (NC; n=10), OVX group (OVX; n=10), and OVX resistance exercise group (OVX-REX; n=10).

Ovariectomy

At the beginning of the protocol, twenty one-week-old rats underwent a bilateral ovariectomy, as described hereafter. Systemic anesthesia was performed with ketamine (100 mg/kg) and 2% xylazine (0.15 mL/kg), and sterile treatment (10% povidone-iodine scrub followed by 70% alcohol wipe) was performed prior to hair removal and treatment. After performing an incision of approximately 1 cm in the center of the dorsal side of the experimental animal, the ovaries were ligated with suture threads, and an ovarian resection was performed on both sides. To this end, antibiotics (cafazolin 50 mg/kg) were injected into the muscles. The experiment was then conducted following a 2-week recovery period.

Resistance Exercise

For resistance exercise, a ladder climbing exercise was used. This involved climbing a 1.35-m-high ladder with 2.5-cm grid steps and an 80° gradient. The resistance exercise was performed by modifying a previously described method (An et al., 2016). Two weeks after ovariectomy, the rats were familiarized with the process of climbing to the top of the ladder with a weight load (plastic bolt) attached to their tail, representing 50% of their body weight during 1 week. The exercise took place on three alternating days (one day with training and one day without training). Following adaptation, the one-rep maximum (1RM) of the exercised rats was calculated. Resistance exercise was performed 8 times a day, 3 days a week, for 12 weeks, and training was performed with intensities of 50%, 75%, 90%, and 100% of each rat's 1RM. If, during these 12 weeks, a rat was able to complete eight climbs each with an increasing weight load, the resistance exercise was considered to have been performed from the bottom to the top, and 20 g of extra weight was added to the next trial period from 9 to 12 weeks. Once a rat had climbed from the bottom to the top of the ladder, it was allowed to rest for 2 min prior to the next trial.

Morris Water Maze Procedures

Pre-training for cognitive functions was carried out once prior to the experiment and 12 weeks after exercising for 24 h. The hydrographic lab was filled with water ($25 \pm 2^\circ\text{C}$) with circular pools (60 cm high and 120 cm in diameter) and 35 cm deep. Subsequently, the underwater maze was divided into four identical quadrants, and a circular platform (30 cm high and 10 cm diameter) was installed in the center of the southwest quadrant; the water was opaque with squid ink powder such that the experimental animals could not see the platform with their naked eyes. The surface of the platform was treated roughly such that the experimental animals could climb easily. On the first day of the experiment, experimental animals were allowed to swim freely in the tank for 60s without a platform, and cognitive adaptation training was carried out twice a day, with different quadrants obtained daily for four days. Experimental animals were allowed to stay on the platform for 10 s when they reached the platform; and if they could not find the platform within 120 s, they were allowed to stay on the platform for 10 s to become familiar with visual cues and remember the platform location. The experiment was repeated every 20 minutes. The final test conducted a 60-second free swim test 12 weeks before sacrificing the experimental animals to assess cognitive function using a video tracking program (Panlab, S.L.U., Spain) (Cassilhas et al., 2010).

Passive Avoidance Test

Passive avoidance performance was assessed using a shuttle box ($50 \times 15 \times 40$ cm, electric grid floor, Ugo, Italy); and the box was divided in half by a partition door to form a room (5×15 cm), after which each room is illuminated with a 20 W bulb. Noise was generated at 20 dB or less. First, a rat was placed in one of the two rooms divided into partitions, and the 1,500 Lux lights were turned on to open the partitions; when the rats roamed the room and entered another room without lighting, the partitions were automatically closed. The lighting was turned on to measure the period of time from the opening of the partition to the closing of the partition. When the learning experiment was repeated five times, an electric shock was applied by passing a current of 3 mA for 3 s when the rat passed from the first room to another dark room; and the rat was remembered by recognizing the relationship between the dark room and the electric shock. Even after the door was opened after 24 h, the time the rat stayed in a bright room, that is, the time to reach the shock chamber, was measured for up to 300 s.

Reverse Transcription Real-time PCR

Rats were sacrificed 24 h after the last bout of exercise. Tissues from the hippocampus were immediately frozen in liquid nitrogen and stored at -80°C until analyses. Total RNA was isolated from the hippocampus using TRIzol Reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. Four micrograms of total RNA was utilized for reverse transcription to generate cDNA using a high-capacity cDNA Reverse Transcription kit (Applied Biosystems, Foster City, CA, USA), and the generated cDNA was used as a template for subsequent PCR reactions. Quantitative real-time PCR reactions were conducted using the Power SYBR Green PCR Master Mix (Agilent technology, Santa Clara, CA, USA). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal

standard to normalize the expression of target transcripts. Primer sets were used to amplify brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF) (Table 1). Reactions were carried out in a AriaMx Real-Time PCR system (Agilent technology). Triplicate data were analyzed by three independent assays using the comparative Ct method (Yon et al., 2018).

Table 1. Sequences of the primers used in the current study

Gene Name	Accession No.	Rat primer	
		Forward (5' – 3')	Reverse (5' – 3')
BDNF	XM_032903861	ATAATGTCTGACCCAGTGCC	CTGAGGGAACCCGGTCTCAT
IGF-1	XM_032910837	GCTTTTACTTCAACAAGCCCACA	TCAGCGGAGCACAGTACATC
VEGF	XM_032900654	AACGAAAGCGCAAGAAATCC	GCTCACAGTGAACGCTCCAG
GAPDH	XM_039103226	GTCGGTGTGAACGGATTGG	CCACTTTGTCACAAGAGAAGGCA

Statistical Analysis

Statistical comparisons between the groups were performed using a one-way analysis of variance followed by a Tukey's multiple comparison test. All analyses were conducted using the Statistical Package for Social Sciences for Windows software version 22.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set to $P < 0.05$. All data are expressed as mean $\pm$ SD.

Results and Discussion

In this study, we demonstrated that resistance exercise improved cognitive function by enhancing the mRNA expression of brain neuroplasticity-related genes in ovariectomized rats.

Changes in Body Weight of Ovariectomized Rats over the Course of 12 Weeks of Resistance Exercise

Generally, the body weight of ovariectomized rats was increased by upregulation of the obesity-related mRNA expression levels, such as leptin, alongside an increase in food intake (Kimura et al., 2002). The increase in body weight following ovariectomy can be suppressed by estrogen supplementation (Wade, 1975). Resistance exercise is also associated with decreased body weight due to increased lipolysis metabolism and energy expenditure (An et al., 2016). Therefore, we used body weight as a marker for animal modeling and an adequate resistance exercise regimen in this study. Fig. 1 represents the changes in body weight observed in rats during the weeks of resistance exercise. Analyses showed that there was an interaction among the NC, OVX and OVX-REX groups ($P < 0.05$). At baseline (0 weeks), the body weights of rats in the NC (301.52 ± 2.59), OVX (301.73 ± 2.62), and OVX-REX (301.54 ± 2.27) groups were similar. There was a significant difference in body weight observed among the three groups at 12 weeks, with body weight significantly higher in the OVX group (345.91 ± 2.60) ($P < 0.05$) than the NC group (326.77 ± 2.97), and body weight significantly lower in the OVX-REX group (331.29 ± 2.09) ($P < 0.05$) than the OVX group. Therefore, the animal modeling and intensity of exercise were considered adequate.

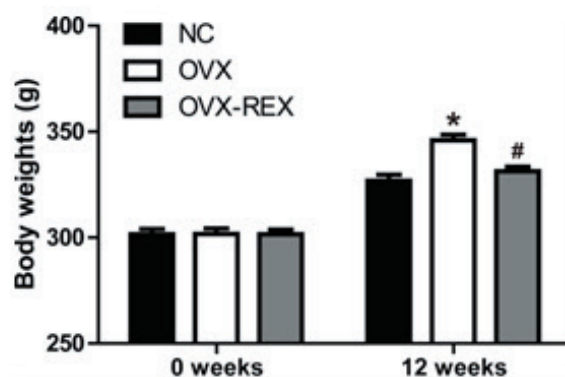


Fig. 1. Changes in the body weight of rats during 12 weeks of resistance exercise. NC; normal group, OVX; ovariectomized group, OVX-REX; ovariectomized resistance exercise group. The data was expressed as the mean $\pm$ SD. * Significantly different from NC ($p < 0.05$). # Significantly different from OVX ($p < 0.05$)

Learning and Memory Function in Ovariectomized Rats over the Course of 12 Weeks of Resistance Exercise

It is well known that estrogen is associated with learning and memory functions. Estrogen deficiency induces hippocampal apoptosis, neuronal loss, and cognitive dysfunction (Kim et al., 2016; Sales et al., 2010). Likewise, in this study, rats in OVX group showed memory deficits. To investigate learning and memory function, the Morris water maze and passive avoidance test were carried out (Fig. 2). In the Morris water maze test, the escape latency time was significantly increased in the OVX group (38.70 ± 2.54) compared with the NC group (27.70 ± 1.76 , $P < 0.05$) (Fig. 2A). Resistance exercise significantly improved learning and memory functions in ovariectomized rats. As shown in Fig 2A, it was significantly improved in the OVX-REX group (31.10 ± 1.44) as compared with the OVX group ($P < 0.05$). Similarly, in the passive avoidance test, the retention time was significantly decreased in the OVX group (265.12 ± 4.76) as compared with the NC group (286.80 ± 4.90 , $P < 0.05$) (Fig. 2B). Moreover, it was significantly improved in the OVX-REX group (276.80 ± 3.71) as compared with the OVX group ($P < 0.05$).

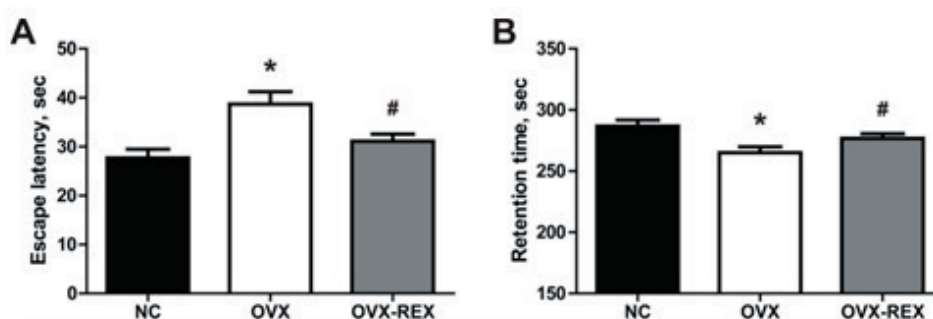


Fig. 2. Learning and memory function of rats after 12 weeks of resistance exercise. (A) Morris water maze performance and (B) passive avoidance test. NC; normal group, OVX; ovariectomized group, OVX-REX; ovariectomized resistance exercise group. The data was expressed as the mean $\pm$ SD. * Significantly different from NC ($p < 0.05$). # Significantly different from OVX ($p < 0.05$)

mRNA Expression of BDNF, IGF-1 and VEGF in Rat Hippocampal Tissue

Another study reported that BDNF, IGF-1, and VEGF were considered as key proteins that were upregulated after exercise and that may promote cell proliferation and growth or neuronal development and function including learning and memory (Maass et al., 2016). Based on this, we analyzed mRNA expression in the hippocampal tissue after resistance exercise. Following ovariectomy, the mRNA expression level of synaptic plasticity-related genes, BDNF (83.75 ± 2.56), IGF-1 (83.97 ± 2.55), and VEGF (85.55 ± 2.93) observed in hippocampal tissue were significantly decreased in the OVX group as compared to those observed in the NC group ($P < 0.05$) (Fig. 3). However, after resistance exercise in ovariectomized rats, the mRNA levels of these genes were significantly increased in the OVX-REX group (92.36 ± 2.34 , 93.02 ± 1.72 and 91.72 ± 2.07 , respectively) as compared with the OVX group ($P < 0.05$). Plastic changes mainly occur in synapses, which are widely distributed in the cerebrum, resulting in a new network in the brain (Cooke & Bliss, 2006). Although the underlying mechanisms are not yet fully understood, brain neuroplasticity factors and neurotransmitters are increased during exercise. Many studies have assessed the relationship between growth factors and exercise. Physical exercise increases synapsin I expression in brain tissue and improves neuroplasticity (Chae & Kim, 2009). BDNF has been shown to increase expression during exercise and is known to promote neuronal production (Russo-Neustadt et al., 2001). It has been reported that high-intensity interval training modulates hippocampal oxidative stress and inflammatory mediators, alongside increasing hippocampal BDNF levels (Freitas et al., 2018). IGF-1 also contributes to the growth, differentiation and survival of neurons and shows increased expression in the brain and peripherals by exercise (Arsenijevic & Weiss, 1998). Moderate resistance exercise increases IGF-1 (Mannerkorpi et al., 2017). Moreover, VEGF exhibits increased expression during running exercise (Ding et al., 2004; Schobersberger et al., 2000). It was upregulated after a single bout of exercise (Breen et al., 1996). Acute resistance exercise has been reported to increase VEGF mRNA, protein, and plasma proteins (Gavin et al., 2007). In addition, VEGF is known to be necessary for the production of neurons in the hippocampus (Fabel et al., 2003), and new neurons produced by exercise are mainly observed around blood vessels (Palmer et al., 2000). It was also reported that the level of BDNF in the high-intensity resistance group was higher than that in the low-intensity resistance group in adult men (Dominguez-Sanchez et al., 2018). Therefore, the intensity of resistance is may constitute a factor associated with the expression of neurotrophic factors. Similarly, IGF-1 levels significantly increased after resistance training in an intensity-dependent manner (Taylor et al., 2012).

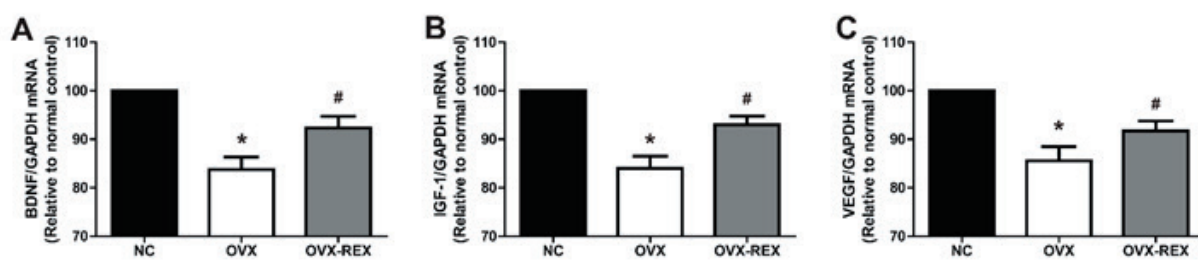


Fig. 3. Activity level of synaptic plasticity-related genes, (A) BDNF, (B) IGF-1, (C) VEGF, measured as mRNA expression, in the hippocampal tissue of rats following 12 weeks of resistance exercise. Value are normalized to GAPDH and expressed as the mean $\pm$ SD. NC; normal group, OVX; ovariectomized group, OVX-REX; ovariectomized resistance exercise group. * Significantly different from NC ($p < 0.05$). # Significantly different from OVX ($p < 0.05$)

The role of the BDNF, IGF-1 and VEGF in exercise-related changes of human brain function remains unclear, although much research has been invested into understanding the underlying mechanisms of the beneficial effect of exercise on cognitive function. Moreover, studies have still mostly focused on aerobic exercise. Although the mechanism and effect of resistance exercise remain unclear, in this study, we demonstrated that the expression of brain neuroplastic factors such as BDNF, IGF-1, and VEGF in the hippocampus region related to cognitive function was upregulated following resistance exercise in ovariectomized rats.

Conclusion

Taken together, the present study found that resistance exercise during 12 weeks increased the expression of neuroplasticity-related factors such as BDNF, IGF-1 and VEGF in the hippocampus in ovariectomized rats and it had an influence on improvement of cognitive function. It was thought that neuroplasticity-related factors upregulated by resistance exercise protect neuronal cells and induce maturation and generation of neuronal cells, so it improved cognitive function by regulating synaptic plasticity. Therefore, these results suggest that resistance exercise contributing to improved learning and memory function may partially result from the protection of brain damage and regulation of synaptic plasticity by increased mRNA expression of brain neuroplasticity-related factors BDNF, IGF-1, and VEGF in menopausal women.

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