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Original Article

Effect of eight weeks of aerobic Exercise on some neurotrophic and growth factors of hippocampal tissue of parkinsonian rats induced by 6-hydroxydopamine

Nariman Safaeian [1], Hossein Abednatanzi [2]*, Khosrow Ebrahim [3], Mandana Gholami [4]

[1]Ms. Student, Department of physical education, Faculty of literature, humanity and social science, Science and research branch, Islamic Azad University, Tehran, Iran. [2]Assistant Professor, Department of physical education, Faculty of literature, humanity and social science, Science and research branch, Islamic Azad University, Tehran, Iran. [3] Professor of Department of Exercise physiology, Faculty of physical education,shahid Beheshti University, Tehran,Iran [4] Assistant Professor, Department of physical education, Faculty of literature, humanity and social science, Science and research branch, Islamic Azad University, Tehran, Iran.

Correspondence: Hossein Abednatanzi; Assistant Professor, Department of physical education, Faculty of literature, humanity and social science, Science and research branch, Islamic Azad University, Tehran, Iran. E-Mail: abednazari@gmail.com

ABSTRACT

Parkinson's disease is caused by the loss of dopamine-secreting cells. The neuropathological characteristic of this disease is the destruction of dopaminergic neurons in the midbrain black substance. The aim of this study was to investigate the effect of eight weeks of aerobic training on some of the neurotrophic and growth factors of hippocampal tissue of mice with Parkinson's disease induced by 6-hydroxydopamine. Methodology: we purchased thirty male Wistar rats from the Pasteur Institute of Tehran and transferred to the Research Center. Animals will be randomly divided into two groups of Parkinson's and Exercise after entering the research environment and two weeks of acquaintance with the new environment and mode of activity. Results: The results of this research showed that eight weeks of aerobic training significantly increased BDNF levels (P = 0.0000) and significantly increased GH (P = 0.0000) in Parkinson's rat. Discussion: The results of this research showed that eight weeks of aerobic training increased the levels of neurotrophic factors and growth hormone in the brains of Parkinson's rats.

Keywords: Parkinson's, Aerobic Exercise, BDNF, GH

Introduction

Parkinson's disease is caused by the loss of dopamine secreting cells [1]. The neuropathological characteristic of this disease is the destruction of dopaminergic neurons in the midbrain black substance. The clinical symptoms of this disease occur after the destruction of approximately 80% of the dopaminergic neurons of the black substance. This cell secretes a substance called dopamine. Dopamine delivers the nerve message from the middle brain to another part of the brain called the corpus striatum. The transmission of these messages balances body movements. As the dopamine-secreting cells in the midbrain are destroyed, other centers of control of the body's movements also become irregular. This disorder at the body's control centers causes symptoms of Parkinson's. Vibration at rest is a special sign (PD) that is one of the most common symptoms of Parkinson's disease [2, 3]. Factors such as oxidative stress and increased lipid peroxidation, decreased glutathione level, DNA degradation, and iron accumulation are the most important causes of dopaminergic neuron degeneration [4]. Free radicals are continuously produced by dopamine metabolism in dopaminergic neurons of the black substance [5]. It is well known today that regular physical activity produces numerous adaptations, including metabolic, neuromuscular, and cardiovascular adaptations. Recently, the effects of exercise on the brain and its function have been the focus of much research, as new researches have shown that numerous anatomical and

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cellular changes occur with exercise in the central and peripheral nervous system [6]. These neurobiological adaptations can ultimately lead to improved central and peripheral nervous system function, memory, learning, and cognitive and motor functions. Therefore, exercise enhances neurogenesis. These changes may occur due to neurochemical changes or changes in brain-derived growth factors and neurons. Recent researches have shown that these neurotransmitters and growth factors respond to exercise. Neurotrophins are a family of growth factors whose identification primarily is possible by their ability to protect neuronal survival. In addition to protecting neuronal survival, neurotrophins regulate neuronal plasticity, maintenance, and differentiation of neurons, as well as the fate of divisions and neuronal cell death. These growth factors mainly shape the activity of the nervous system and affect peripheral and central nervous systems [1]. BDNF is a brain-derived growth factor. One component of the family of neurotrophins that are found throughout the brain abundantly and most of its gene expression occurs in the hippocampus, brain cortex, cerebellum, thalamus, hypothalamus, and striatum. Given that BDNF is able to cross the brain-blood barrier in both directions, we assume that BDNF present in peripheral blood flow is transmitted into the brain and plays a role in the formation of neurons. Due to the high expression of BDNF in brain regions and its bilateral transfer from the blood-brain barrier, BDNF blood flow may be a reflection of its changes in the brain. BDNF plays a central role in metabolismby altering skeletal muscle and fat burning in an Ampk-dependent manner [3]. IGF-1 is expressed in many tissues including the brain and is important for nerve cell growth, differentiation, synthesis, and release of neurotransmitters. Acute exercise stimulates the expression and release of IGF-1 from the liver. Thus, it appears that it is essential for hippocampal neurogenesis resulting from the acute activity and recovery of function after brain injury, expression and secretion of IGF-1. Recently, evidence has shown that sport activity promotes brain neuronal plasticity [7]. It is associated with increased neurotrophic factors such as BDNF induced by sport activity, but its mechanism of action is not fully known. Given that in the adult nervous system, BDNF has a prominent role in neuronal plasticity. As has been shown in researches, decreasing levels of neurotrophic factors occur with increasing age. So the aim of this study was to investigate the effect of eight weeks of aerobic training on some of the neurotrophic and growth factors of hippocampal tissue of rats with Parkinson's disease induced by 6-hydroxydopamine.

Research Methodology

We purchased thirty male Wistar rats from the Pasteur Institute of Tehran and transferred to the Research Center. After entering the research environment and two-week acquaintance with the new environment and mode of activity, animals are randomly divided into two groups: Parkinson's control group and Parkinson's and Exercise group. - To become afflicted with Parkinson's disease, the stereotaxic 6-hydroxydopamine solution is injected into the ventricle of the brain to destroy the rat's corpus striatum to create a Parkinson's model. Animals in this research are housed in Razi Company's transparent polycarbonate cages for a two-week familiarization with the new environment in 5-rat groups; they are maintained at an ambient temperature of 22±2 ° C and the lighting cycle at 12:12 hour darkness and 50±5% of air humidity. Because rats are highly susceptible to respiratory diseases, appropriate ventilation is placed at the site to prevent ammonia accumulation in the animals' urine. The rat cage is cleaned once every four days. The Parkinson's group and the intense periodic exercise perform eight training sessions for eight weeks and one each week three sessions.

Research environment

Animals in this research are housed in Razi Company's transparent polycarbonate cages for a two-week familiarization with the new environment in 5-rat groups; they are maintained at an ambient temperature of 22±2 ° C and the lighting cycle at 12:12 hour darkness and 50±5% of air humidity. Because rats are highly susceptible to respiratory diseases, appropriate ventilation is placed at the site to prevent ammonia accumulation in the animals' urine. The rat cage is cleaned once every four days.

Rats' Nutrition

Rats are usually fed by a pellet of animal feed production centers. Rats require 10 grams of pellets per 100 g body weight. But in this research, rats were given free access to food. Their food was the production of Karaj Animal Feed Company Behparvar. Rats also need 10 to 12 ml of water per 100 g of body weight. In this research, each animal was given free water in a 500 ml bottle specific for laboratory animals.

Preparing the animal for surgery

We transported the animal to the operating room and weighed by a scale. After caressing and handling, we injected rats intraperitoneally by a 60% ratio of ketamine and xylazine (5 ml ketamine x 3 ml xylazine). Then we shaved completely animal's hair and placed in a towel to maintain body heat during surgery. Up to this point, the rat was prepared for surgery and implanted in the stereotaxic device.

The way the animal is placed in a stereotaxic device is that one ear bar is fixed and the other movable. Ear bars should be placed in the ear of the animal so as not to damage the ear and the number of the two ear bars be equal to each other. The animal's head was then fixed in the device as described previously

Fixing the head of the rat

To prevent injury to the animal's eyes, during surgery cotton was soaked in distilled water and placed on the eyes of rats. Sterilization tips were followed throughout the surgical procedure. Surgical instruments were sterilized and surgery sites were disinfected and closed. We used a study light to provide

appropriate light for the surgical area. At first, 0.1cc adrenaline lidocaine 3% was injected subcutaneously into the surgical area. Then, the scalp and the connective tissue were removed to allow the skull to be clearly visible. The Bregma and Lambda points were determined on the skull (the lambda is a point in the middle of the triangle created by the location of the intersection of the two hemispheres along the midline with the hypothetical interaural line).

Cannulation method and injection of 6-OHDA

According to the data obtained from Atlas Paxinus, the best place to inject into the ventricle is a depth of 10.5 mm down. For this purpose, a canal was implanted using a 27-gauge syringe with 9 mm length (7 mm plastic trunk and 2 mm injectable iron part) and a remaining 1.5 mm for a 30-gauge dental syringe that was attached to the Hamilton syringe. The coordinates obtained for perforation and injection based on Atlas Paxinus are as follows: 1 mm lateral, 0.5 mm anterior-posterior and 1.5 mm deep.

The volume and dose of injection of the toxic 6-hydroxy dopamine solution based on available sources were 250 µg in a volume of 5 µl per mouse. To prepare this solution, 20 µg of 6-hydroxy dopamine was combined with 0.4 cc saline. Then, a 10-microgram syringe was used to inject the solution into the ventricle of the rats' brains. The arrangement of the material inside the outer tube of the syringe is as follows: first one-third of the trunk of the syringe was filled with saline, its second one-third with air (bubble) and its final one-third with 6-hydroxy dopamine solution. For injection into the brain nuclei, it is necessary to inject every 0.5 µL for 30 seconds, but less time is needed for intraventricular injection. After injection, the rats were kept constant for 1 min.

Rotational Test

After stereotaxis, one of the most commonly used tests, the rotational test, was used to assess the extent of damage to the brain of rats and the possibility of developing a Parkinson's model. The way to do this test is to take the rats off the tail and keep them suspended in space. If the stereotaxis surgery and the brain injection are effective, the rats start to rotate, so that if the rat's tail is not left will be removed. The test was performed three times at 24, 48 and 72 hours after stereotaxis and intraventricular injection. In the present study, in the first test 24 hours after stereotaxis, the rats showed severe muscle tension associated with seizure and tremor. In the second phase of testing, more than 60% of rats that received stereotaxis rotated. Finally, at the last stage of the rotational test, more than 85% of the rats developed a severe rotational state known as Parkinson's.

Biopsy

The brain tissue was quickly removed from the skull immediately after killing the animal. By removing the upper cerebral cortex, the corpus striatum was removed with the help of Paxinus atlas, and frozen in a nitrogen capsule at -80° C. For measuring the BDNF level, it was kept in the refrigerator with temperature below 80 ° C.

Homogenization, preparation of tissue extract and measurement of dependent variables

The frozen tissues in the refrigerator were placed in a nitrogen-filled mortar; they were crushed while floating in the liquid. Before the powder was lost its state, 100 mg of it were rapidly placed in a microtube and 1 cc of saline phosphate buffer was added to it. Then it was placed on the American IKA MS 3D digital shaker for 1 minute. The kits were centrifuged at 15,000 rpm for 20 minutes at a rotation speed of 3000 Revolutions per Minute, using a Centrifuge Model (FEF 1401). The centrifuged extract was frozen again and maintained in the refrigerator for the measurement of the research variables. Measurement of IGF-1, BDNF was done by using enzyme-linked immunoassay and kit for rat samples according to the manufacturer's instructions (CUSABIO, China) with scaling and sensitivity coefficients of the method by 0.039 ng/ml and 8%, respectively. The ELISA steps were performed to measure the dependent variable of BDNF, IGF-1 as the following. First, dilution of standard solution was prepared according to the kit leaflet, then 40 L of tissue sample was combined with 10 L of antibody, and after half an hour it was washed with automatic washer and maintained at 37 ° C. The mixture of substrate A and B was added to it in equal proportions and incubated at 37 ° C without any light. Next, 50 Landau of the stop solution was added to and the color changed from blue to yellow.

Statistical analysis of data: we used Independent and dependent T-test to investigate differences between experimental and control groups. In these studies, P≤0.05 was considered as a rejection of the null hypothesis.

Results

This section examines the research hypotheses. Since the Kolmogorov-Smirnov test showed that the distribution of data was normal (Table 1), parametric tests were used to test the hypotheses. Therefore, we used a dependent t-test to investigate within-group differences and independent t-test for examining inter-group differences. A significance level of tests was set at P≤0.05.

Table 1: Test of Sample Distribution Normality (Kolmogorov-Smirnov Test)

Control group		Experimental group		Kolmogrov-Smirnov	
Post-test	Pre-test	Post-test	Pre-test		
59.0	78.0	92.0	63.0	Z	BDNF
97.0	92.0	687.0	555.0	Sig.	
85.0	73.0	54.0	66.0	Z	IGF-1
83.0	96.0	88.0	92.0	Sig.	

Testing the first hypothesis

Hypothesis Zero: Eight weeks of aerobic training did not significantly affect BDNF in the cerebral cortex of parkinsonian rats induced by 6-hydroxydopamine (6-OHDA).

Table 2: Comparison of BDNF changes in the control and experimental groups

BDNF	Pre-test	Post-test	Change (%)	dependent t value	Significance level
Experimental	98.88±0.3	1.+223	1.+223	12.2	000.0
control group	47.11± 0.4	011.- 0	011.- 0	15.2	09.0
Independent t value	4.12				
significance level	0.000				

According to the data in Table 1, for the experimental group, comparison of pre-test and post-test means showed that the BDNF level of the subjects increased significantly after the training; with respect to the t value of 4.12 and the significance level of 0.000, this change is significant. Therefore, the null hypothesis of the research cannot be confirmed.

In the control group, the results of the pre-test and post-test comparison of the control group (t-value of 2.15 and a significance level of 0.09) indicated no significant difference between the two stages.

A comparison of pre-test and post-test changes of BDNF showed a significant difference between the control and experimental groups (P = 0.000).

A comparison of pre-test and post-test of BDNF between experimental and control groups has been shown in Figure 1-4.

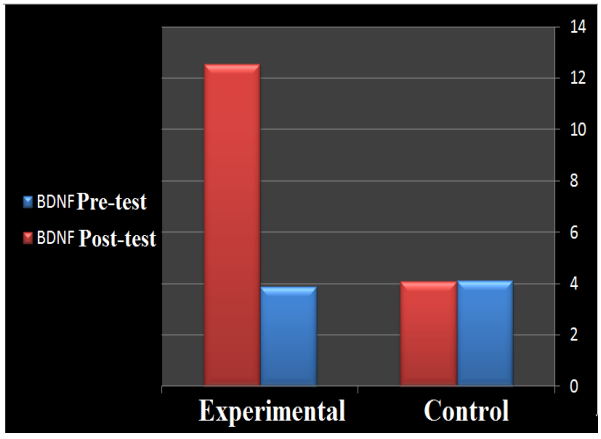

Diagram 1: Comparison of BDNF pre-test and post-test changes in the two groups understudy

Second Hypothesis

Hypothesis Zero: Eight weeks of aerobic exercise did not significantly affect IGF-1 in the cerebral cortex of parkinsonian rats induced by 6-hydroxydopamine (6-OHDA).

The results of the second hypothesis analysis using dependent and independent t-tests have been shown in Table 3.

Table 3: Comparison of IGF-1N changes in control and experimental groups

Homocysteine	Pre-test	Post-test	dependent t value	Significance level
Experimental	52.12 ± 0.4	15.2 ± 0.8	2.15	0.000
control group	77.65 ± 0.4	65.51 ± 0.4	1.47	0.725
Independent t value	1.74			
significance level	0.000			

According to the data in Table 3, for the experimental group, comparison of pre-test and post-test means showed that the IGF-1 level of the subjects increased significantly after the training; with respect to the t value of 2.15 and the significance level of 0.000, this change is significant. Therefore, the null hypothesis of the research is confirmed.

In the control group, the results of the pre-test and post-test comparison of the control group (t-value of 1.478 and significance level of 0.725) indicated no significant difference between the two stages.

A comparison of pre-test and post-test changes of IGF-1 showed a significant difference between the control and experimental groups (P = 0.000).

A comparison of pre-test and post-test of IGF-1 between experimental and control groups has been shown in Diagram 2.

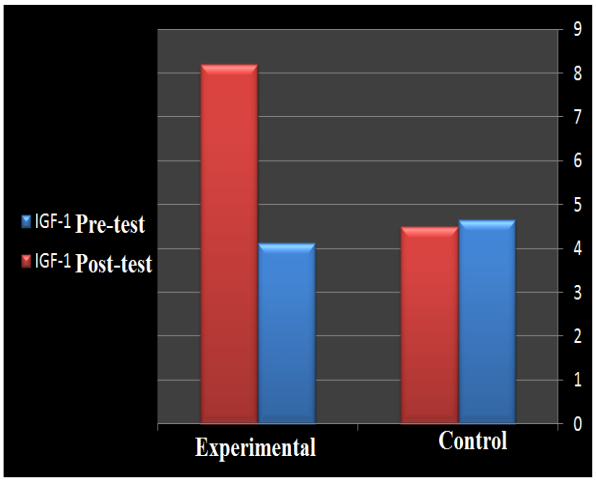

Diagram 2: Comparison of pre-test and post-test IGF-1 changes in the two groups understudy

Discussion and Conclusion

The results of the present research showed that intra-group and within-group values of BDNF in the aerobic group were statistically significant (P≤ 0.05). The findings of the present research are in line with those of Gomes et al. (2008), Ferris et al. (2007) and Tange et al., (2008). On the other hand, it is not in line with the results of Nofuji's (2008) and Curia's (2009) researches. Perhaps this inconsistency was due to the

implementation of the training program and its duration, the gender of the subjects, the physiological adaptations in the long-term exercises. Results of a research conducted by Frris et al. (2007) do not change 10 minutes of moderate exercise or 20% exercise under the aerobic threshold do not alter the serum concentration of BDNF. Ramp-to-fatigue test of 15 to 30 minutes of moderate exercise or 10% exercise above the aerobic threshold increases BDNF serum concentrations and BDNF endurance training week increases plasma BDNF concentration in healthy young men. But Andress et al. (2008) reported that short-term, moderate-intensity (10-min) periods increase instability in BDNF serum levels of a progressive test until fatigue in human subjects. Contrary to the results of the present research, Nofuji et al. (2008) suggested that physical activity decreases BDNF serum levels and there may be an inverse relationship between BDNF serum concentration and daily activity. BDNF is known to be the second neurotrophic factor that is produced in various tissues, especially in the brain; due to its bilateral crossing of the blood-brain barrier, its circulating levels may reflect its amount produced in the brain. Also, given that this factor is also produced by platelets, its plasma level can also reflect its amount stored in platelets. The serum level of this factor was measured in order to evaluate the amounts produced in the nervous system and muscles. Some previous researches have shown that regular exercise can increase tissue expression and BDNF levels in blood circulation. The intensity of exercise activity to influence BDNF changes is an important factor, so that low-intensity exercise may not significantly alter this factor, but moderate-intensity exercise increases BDNF levels in blood circulation. In the present research, in line with some previous researches, elevated BDNF serum levels were observed following endurance training, which may indicate the appropriate intensity of sport protocols to influence this factor. This finding is in line with the results of Zoladz et al. (2008) and Yarrow et al (2010). Zoladz et al. (2008) investigated the effect of five weeks of endurance exercise on plasma BDNF concentration in healthy young active men and found that after training the plasma BDNF was in resting significantly higher than its values before exercise. Yarrow et al (2010), in research, showed that resistance training increased BDNF of blood circulation in healthy male students; despite a significant increase in BDNF levels in endurance and resistance training groups, no significant differences were found between training groups; there was a significant difference between endurance and resistance training groups. Various researches have shown that regular physical activity increases levels of neurotrophic factors, which may contribute to improved learning and memory. Seifert et al (2010) observed that endurance training increased BDNF at rest and suggested that increased BDNF in the hippocampus and increased release into the human brain indicate that endurance training improved brain health. Recently reported, BDNF of resistance exercise activity may affect the central nervous system by increasing the expression of this factor in the active muscles. Exercise can improve the function of neurons in the central and peripheral nervous system and prevent them from responding to aging or diseases of the nervous system. These effects of exercise on the central nervous system may be due to changes in expression and levels of neurotrophic factors. Varghese (2013) stated that neuroscientific research provided credible evidence that exercise stimulates greater production of BDNF, generating more recipients and nerves in the brain, thereby enhancing learning and affecting memory. Goekint et al (2010) investigated the effect of 10 weeks of increased resistance exercise on serum levels of IGF-BDNF. The researchers reported that there was no significant difference between IGF-1 and BDNF during the training period between the control and experimental groups. This difference in results may depend on several factors, including the intensity of exercise activity so that the intensity of sports activities is an important factor in changes in this factor. Serum BDNF Levels have a direct relation to its brain levels. In addition to the main source of production, which is the brain, BDNFs are widely derived from platelets, which in turn separate BDNF from circulation. Platelets are separated from megakaryocytes following exercise and their count in blood rises. Since they remain in circulation for 11 days, they can have significant BDNF storage; on the other hand, after exercise, they release their contents due to adhesion and coagulation. There was a significant relationship between p-selectin and BDNF of a platelet coagulation factor in cardiac patients. Little is known about the source and how BDNF is secreted. Studies have shown that the midbrain septum of the source of cholinergic and gambargic afferents to the hippocampus plays a role in the up-regulation of BDNF following exercise. The degradation of these afferents led to a decrease in BDNF after exercise. Septal-hippocampus pathway neurons are activated by physical activity and regulate the activity of the cholinergic system of BDNF gene expression in the hippocampus. In addition, acetylcholine is one of the neurotransmitters of the brain that plays an important role in learning and memory. A new study has shown that exercise induces a protein called FNDC5 from skeletal muscle and this induces BDNF release from hippocampus. Increasing LTP in the hippocampus and inducing synaptic plasticity can ultimately increase synapsin I and increase memory. The 2004 research conducted by Farmer et al., after 10 days of activity chariot, reported increased BDNF mRNA only in brain dentate protuberances. At the end of a 2009 research, it was found that 6 weeks of activity increased BDNF mRNA activity in dentate protuberances. The emergence of the BDNF gene and protein in response to exercise rapidly, within a few days after exercise, is rapidly regulated by the most apparent strong and sustained increase in the hippocampus. The results of the present research show the effect of aerobic training as well as resistance training on increasing BDNF levels. The importance of BDNF signaling in exercise-dependent improvements in cognitive performance has been demonstrated by blocking antibody to TrKB, the BDNF receptor. In particular, intra-hippocampal injection of anti-TrKB antibody to prevent BDNF signaling decreases the useful effects of exercise on the hippocampal-dependent learning and blocks the improvements in acquisition and retention of 3D learning process. In addition, blocking BDNF signaling with anti-TrKB

reduces the creation of synaptic proteins in the hippocampus in response to exercise. Vainan et al. (2006) show that BDNF signaling probably initiates a cascade. They are important as mediating the effects of exercise on cognitive function. Berchold et al. (2005) have proven that in rats at the end of the exercise period, BDNF protein shows a strong up-regulation, then partly it declines, but it remains on sedentary levels for several weeks, eventually returning to baseline levels 4-3 weeks after exercise is completed. These data are consistent with our previous findings on rats: BDNF protein remains elevated after exercise is completed. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that has some widespread effects through the central nervous system. It acts to support neuronal survival, dissociation and connectivity: it also plays a role in activity-related synaptic plasticity and is involved in learning, memory, and neurodegenerative processes. BDNF protein and mRNA levels can increase after forced and voluntary physical activity. Increased flow will oxygenate and nourish the brain's neurons better and prevent narrowing of the brain vessels. These effects in turn prevent the forgetfulness and deterioration of mental abilities in old age. Exercise also releases a type of growth factor called B.D.N.F that can protect neurons against injury and extensively prevent Alzheimer's and Parkinson's disease. This factor, on the one hand, works by enhancing synaptic effects on "presynaptic" cell receptors, and on the other hand, by activating factors on "postsynaptic" cell receptors, it prepares transcripts for the formation of new synapses. These specialized structures establish communication between neurons and the point of contact between neurons where neurotransmitters exchange occurs between presynaptic and postsynaptic neurons .According to the results of our research, 8 weeks of aerobic training resulted in a significant increase in BDNF, confirming the probability of above points.

Our results showed that aerobic exercise increased insulin-like growth hormone (IGF-1) levels 48 hours after the end of exercise compared to pre-exercise ($p < 0.05$). The findings of the present research are consistent with the findings of Jennifer et al. (2000), Maria et al. (2005), Smilius et al. (2006), and Sebastio et al. (2011) based on which growth hormone is followed by aerobic exercise. It is not consistent with the researches of Hakin et al (1995, 2000). This inconsistency may be related to the type of training period or sampling time. In this research, a significant increase in IGF-1 was observed after eight weeks of aerobic training. Jennifer et al. 2015 examined the hormonal response to endurance and resistance exercise in 19- to 69-year-old women. The subjects were divided into three groups of resistance, aerobic and control exercises. Resistance training consisted of 3 sets of 10 repetitions, three times a week for 4 months. The growth hormone showed a significant increase. In 2006, Smilius et al. studied the response of IGF-1, cortisol, and lactate to 8 aged male and 9 male young following an endurance and resistance protocol (with 6 exercises). The mean age of the subjects was 69 and 23 years, respectively, who did recreational strength training. Both groups participated in control or non-exercise session. The exercise consisted of 3 sets and 15 repetitions in 60% of 1RM and 1.5 minutes rest between sets. Blood samples were taken before, immediately and 15 minutes after exercise. Another explanation for the increase in insulin-like growth hormone after exercise may be related to hypoglycemia, the stimulatory effect of the motor cortex, and sympathetic nervous system activity (neuro-adrenaline) due to exercise activity on GHRH-producing nuclei in the hypothalamus. Resulting from aerobic exercise, it can be attributed to an increase in nitric oxide (NO). Nitric oxide is one of the most important intracellular and intercellular transporters that play an important role in controlling hormone release from the hypothalamic-pituitary axis.

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