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Journal of Basic and Clinical
PATHOPHYSIOLOGY

Volume 5, Number 2, Spring-Summer 2017

Preconditioning effect of aerobic exercise with vitamin D3 intake on VEGF levels in 6-OHDA-lesioned rat model of Parkinson's disease

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Article info
Received: 15 Jul 2017
Revised: 27 Aug 2017
Accepted: 03 Sep 2017

p-ISSN:2322-1895
e-ISSN: 2345-4334

Key Words:
Aerobic exercise
Vitamin D3
VEGF
6-hydroxydopamine
Parkinson's disease

ABSTRACT

Background and Objective: The purpose of this study was to investigate the preconditioning effect of aerobic exercise with vitamin D3 consumption on vascular endothelial growth factor (VEGF) level in the 6-hydroxydopamine (6-OHDA)-lesioned rat model of Parkinson's disease.

Materials and Methods: Forty-eight male rats weighing 250-300 g were randomly assigned to 6 groups: healthy control, Parkinson's control, sham, exercise-Parkinson's, vitamin-Parkinson's, and vitamin+exercise-Parkinson's groups. The exercise groups exercised for 4 weeks, 5 days per week for 30 minutes on a treadmill at the speed of 15 m/min and with the slope of zero. The vitamin groups received vitamin D3 for 4 weeks, 2 days per week and at a dose of 1 mg/kg of body weight. After 4 weeks of exercising and taking the vitamin, an experimental model of Parkinson's disease was developed using stereotactic surgery and injection of 6-OHDA into the striatum. Three weeks later, apomorphine-induced rotational test was conducted in order to verify the parkinsonian condition in rats and then VEGF levels in the striatum were measured by ELISA method after the isolation and extraction of the striatum of the rats' brain.

Results: The results showed that four weeks of treadmill aerobic exercise in combination with vitamin D3 intake before 6-hydroxydopamine injection could significantly increase VEGF levels in the striatum ($p<0.005$).

Conclusion: The results of this study demonstrated that preconditioning with aerobic exercise combined with D3 intake can increase the protection of dopaminergic neurons against 6-hydroxydopamine-induced damage by increasing the levels of VEGF and thus play a protective role against Parkinson's disease.

1. Introduction

One of the diseases mostly occurring in people over 50 years old is Parkinson's disease (PD) which is an incurable neurodegenerative disorder that causes mobility, emotional, and cognitive problems (1). This disease produces symptoms like bradykinesia, rigidity, tremor, balance disorder, and progressive functional decline (2). The cause of this disease has not been fully known yet, but genetic factors (to a lesser extent) and various environmental factors such as agricultural jobs, well water consumption, rural life, and exposure to herbicides are mentioned for the etiology of the disease (3). Although loss of neurons causes mobility and cognitive impairment, the beginning of movement disorders is not obvious until 80% of the dopamine in striatum is destroyed (4). The decrease in the level of dopamine and the consequent disruption in acetylcholine-dopamine balance, which are both important neurotransmitters, are the main reason of this disease and entail various mobility disorders (5). Dopamine transmits nerve signals from midbrain to striatum. Transmission of these signals maintains the body balance. When dopamine-secreting cells in the midbrain are destroyed, other centers that are in charge of controlling body movements get disordered (6).

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Although there have been drugs that can control the development of the disease symptoms for a decade, there is no treatment which can stop its development or reverse its damage.

There is a growing body of evidence suggesting that exercising can decrease physical and cognitive weakness of the patients suffering from central nervous system disorders including PD, stroke, and spinal cord injury (8-10). Studies have revealed that exercising could have a protective effect on the nervous system and prevent nervous system diseases through neurotrophins and angiogenesis (11, 12). Angiogenesis is the formation of new blood vessels which is not induced without stimulation. Amongst angiogenesis factors, vascular endothelial growth factor (VEGF) is known as the strongest endothelial cell-specific mitogen (13). It is reported that in PD, VEGF noticeably protects the nerve cells by increasing dopaminergic cells. Therefore, increasing VEGF level in the regions of brain which are more influenced by PD has a potential therapeutic effect (14). In addition to the protective role, according to Yasuhara et al, VEGF may have an important role in creating nerve cells (11). They tested the protective role of VEGF using rat models of PD and found that the rats receiving VEGF injection in their brain exhibited a significant decrease in their amphetamine-induced rotational behaviors (11). Moreover, in the studies carried out on the rat models of PD, increased angiogenesis in the striatum of exercising parkinsonian rats was observed compared with the non-exercising parkinsonian rats (15). These results showed that VEGF indirectly plays its protective role through increasing angiogenesis (14).

On the other hand, some studies have demonstrated the positive effect of D3 intake on the prevention and treatment of PD (16). Over the last 10 to 15 years, studies on diet and vitamin D (VD) in laboratory animals have revealed compelling evidence indicating that vitamin D is required for the brain's natural homeostasis and growth. This hormone has a major role in the nervous system including differentiation, calcium regulation, homeostasis, modulation, neurotrophin release, activity of brain-related genes, and neurotransmitter metabolic enzymes (17). It has recently been discovered that vitamin D insufficiency leads to the pathogenesis and development of PD. It seems that the distributions of VD receptors are significantly affected in PD. Moreover, this vitamin is involved in regulating tyrosine hydroxylase (TH) gene expression and, consequently, dopamine biosynthesis. There are various forms of vitamin D. However, vitamin D3 is the naturally occurring form in animals and the form referred to in endocrinology. It has shown that the brains of the newly born rats with vitamin D3 insufficiency has larger lateral ventricles and thinner cortex. These findings suggest a protective role for vitamin D in the brain (19).

The prevalence of PD increases with age. Thus, finding new therapeutic approaches to prevent the development of the disease and stop the damage caused by PD is of particular importance (20). Regarding the available evidence, vitamin D3 as an effective hormone for the reduction of PD affects striatum and brain and physical exercise and it can be an appropriate measure to prevent PD, which is due to its effect on the increase of growth factors such as VEGF. Concerning the reported side effects of the medicines used for the control and treatment of PD (21, 22) and the reported positive effects of physical exercise and vitamin D3 intake, this study aimed to find whether 4 weeks of aerobic exercise of treadmill running and vitamin D3 intake can affect the VEGF level in striatum of parkinsonian rats and plays a preconditioning and protective role against PD.

2. Materials and Methods

2.1. Experimental groups

In the present experimental study which was approved by Ethics Committee of Mazandaran University of Medical Sciences, 48 seven-week old male Wistar rats weighing 250-300 g were used. The animals were transferred to the laboratory and maintained in groups of four rats in transparent polycarbonate cages at 20-24°C and 45-55% humidity with 12:12-h light-dark cycles in order to adapt to the new environment. The food was in the form of pellets and they had free access to water through special bottles. After one week of getting familiar with the treadmill, they were randomly assigned to 6 groups including sham, healthy control, Parkinson's control, exercise-Parkinson's, vitamin+

Parkinson's and vitamin + exercise-Parkinson's groups.

2.2. Exercise program

After being assigned into 6 groups, the exercising groups were trained on the treadmill for 4 weeks. The exercise program involved forced running on the treadmill at the speed of 15 m/min for 4 weeks, 5 days a week and twice a day, each session lasting for 15 min with the minimum interval of 1 h (20). This exercise program was modeled from a study carried out by Landers et al.

2.3. Vitamin D3 injection

Vitamin D3 was purchased from Sigma chemical company. Then, 1 ml of vitamin D3 was dissolved in 100 ml of normal saline and the rats in the vitamin groups received an intraperitoneal injection of vitamin D3 (at a dose of 1 µg per kg of body weight) twice a day for 4 weeks by an insulin syringe (19, 23).

2.4. Stereotactic surgery and 6-hydroxydopamine injection to develop a PD rat model

After 4 weeks of treadmill exercise and D3 vitamin injection, in order to develop a PD rat model, striatum of the rats, except for the healthy control and sham groups, was destroyed by injecting 6-hydroxydopamine (6-OHDA) stereotaxically into the right striatum (Figure 1). The appropriate point for stereotactic surgery was located according to Paxinos and Watson atlas, with the coordinates of 0.5 mm anterior-posterior, 1.0 mm lateral, and 1.5 mm ventral and a 27 gauge cannula was placed inside the rats' skull. Then, using a Hamilton syringe and through this hole, 5 µg of 6-OHDA (at a flow rate of 1 µl per 30 min) was injected into the rats' brain in Parkinson's groups. The Sham group only received saline through stereotactic surgery. To examine the effect of 6-OHDA injection and confirm that the rats were parkinsonian, 3 weeks after the injection, apomorphine-induced rotational test was performed.

2.5. Apomorphine-induced rotational test

First, every rat was placed in a cylinder (22 cm in diameter and 26 cm in height) for habituation. Then, 0.5 mg/kg of apomorphine hydrochloride was subcutaneously injected and the rats were placed in the cylinder again. The total number of ipsilateral and contralateral full rotations was recorded for 30 min and counted by the researcher later. The number of ipsilateral rotations to the lesioned side was subtracted from the number of contralateral rotations to get the net number of contralateral rotations. Higher rotations indicated the severity of lesion in terms of dopaminergic cell loss (24, 25).

2.6. Tissue processing

After following the protocol, the rats were decapitated under deep anesthesia and their brains were removed from the skull. Then, the striatum was separated from the rest of the brain and placed in a microtube. In order to freeze the tissue, the microtube was placed in the liquid nitrogen and then kept in the refrigerator at -70°C to measure the intended index. To measure the VEGF levels of striatum, ELISA kit (Cusabio, China) with a sensitivity of 0.39 pg/ml was used.

2.7. Data Analysis

After testing the normality of data distribution by Kolmogorov-Smirnov test, parametric tests were carried out. To examine the difference between the groups, one-way analysis of variance (ANOVA) and Tukey's tests were used. The level of significance for all of the tests was considered $p<0.05$.

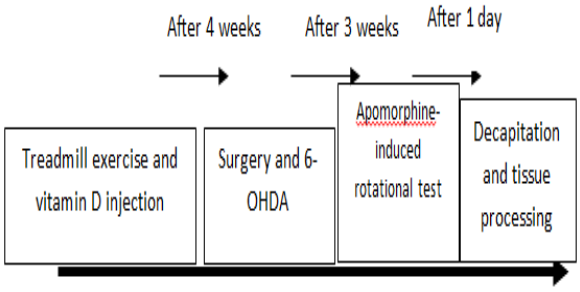

Figure 1. Schematic illustration of the experimental design

3. Results

Table 1 shows the mean and standard deviation of the results of apomorphine-induced rotational test and VEGF levels of striatum of the groups after 4 weeks of treadmill exercising and vitamin D3 intake. The results of one-way analysis of variance demonstrated a significant difference in various groups in terms of the number of rotations (P= 0.000). Tukey's test results showed that the difference was between the exercise, vitamin and exercise + vitamin, control healthy and Parkinson's, and Sham groups. In fact, 4 weeks of treadmill exercising (P=0.000) and vitamin intake (P=0.004), especially the combination of these two (P=0.000), caused a significant difference in the number of rotations after apomorphine injection compared with the Parkinson's control group, which indicated the positive effect of exercise and vitamin D3 pretreatment on Parkinson's disease (Table 1). Furthermore, the results showed a significant difference between VEGF levels of the groups (P=0.000) which was between the experimental and sham groups. In other words, exercising (P=0.000) and vitamin D3 (P=0.002), separately and in combination, increased VEGF levels of striatum of the rats compared with Parkinson's control group (P=0.000), which implies that the effect of exercise and vitamin D3 pretreatment on PD was caused by 6-OHDA injection. However, as illustrated in Table 1 and Figure 1, exercising had a greater effect than vitamin intake on the VEGF levels of rat striatum, which was also true about the number of rotations in apomorphine test (Figure 2), as the number of rotations in the exercise group was less than that of the vitamin group.

Table 1. Results of apomorphine-induced rotational test and VEGF levels after exercise and vitamin intake (mean ± standard deviation)

Group	Number	Apomorphine-induced rotational test number of rotations	VEGF (pg/ml)
Healthy control	8	9.57±3.59	13.79±1.82
Parkinson's control	8	218.00±26.97	7.95±1.82
Sham	8	11.57±2.22	12.13±5.63
Exercise	8	169.16±11.49*	72.93±12.53*
Vitamin	8	185.85±8.15*	23.91±8.65*
Exercise+ Vitamin	8	148.14±21.25*	81.94±9.43*

(*) indicates a significant difference compared with control and sham groups.

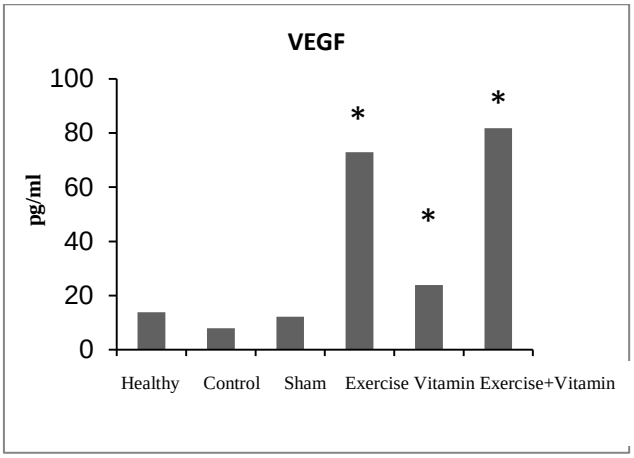

Figure 1. VEGF levels of the studied groups

(*) indicates a significant difference compared with the control and sham groups.

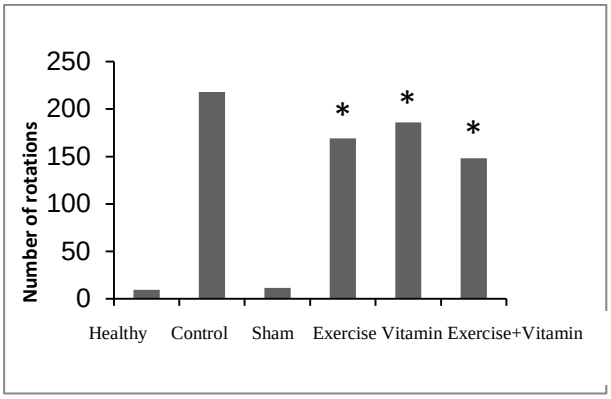

Figure 2. Number of rotations of the studied groups in apomorphine-induced rotational test

(*) indicates a significant difference compared with the control and sham groups.

4. Discussion

Parkinson's disease is a prevalent neurodegenerative disorder which generally occurs in the fifth or sixth decades of life (26). There are various medications/treatments that slow down the development of the disease, the most common of which is pharmacotherapy. However, these medicines can delay the symptoms of the disease just for one decade. Thus, it is better to take preventive measures. Hypothesizing that 4 weeks of treadmill exercise with vitamin D3 intake can induce protective effects against PD, this study was carried out using animal models.

The results demonstrated that 4 weeks of physical exercise on the treadmill with vitamin D3 intake can have protective effects against PD and exercising has a greater effect on the results compared with vitamin intake. The results were consistent with the findings of many researchers concerning the positive effect of exercise (7-10) and vitamin D3 intake (16, 18). Al-Jarrah et al (2010) investigated the effect of endurance exercise training on angiogenesis in the brain of rat models with Parkinson's disease. The exercise groups were run on the treadmill at the speed of 18 m/min and slope of 0 for 40 min, 5 days per week and 4 weeks. They found that 4 weeks of exercising significantly increased VEGF level and, consequently, increased angiogenesis in the striatum (25). The results obtained by Tajiri et al (2010) were consistent with the findings of this study. They pointed out that exercising through enhancing muscle strength and improving response speed can lead to protective effects and neural development in PD patients (24). In this regard, Murray et al showed that exercising is a sensible approach toward developing neuroprotective treatments for PD. It increases energy, stimulates antioxidant defense system, reduces inflammation, and increases angiogenesis as well as synaptic plasticity, which can lead to noticeable physical adaptation and movement disorders treatment in PD patients (28). Researchers broadly agree about the effects of exercising against 6-OHDA. The relevant findings indicate that exercising, whether on the treadmill or rotating wheels is effective for reducing dopaminergic cell loss. These results are consistent with the findings of other studies carried out in this field (4).

Different factors cause angiogenesis in skeletal and cardiac muscles during physical exercises. The most important factors include hypoxia, hemodynamic forces, metabolites, blood vessel dilators, muscle contraction, some cytokines, and a variety of tensions (29, 30). Noorshahi et al in 2012 suggested that during physical exercises, various factors come together and lead to angiogenesis in skeletal muscle: Ischemic and hypoxic conditions of skeletal muscle, increase in blood flow or shear stress, blood vessel dilation caused by shear stress, mechanical tension in tissue, skeletal muscle contraction, and metabolites (30). Although extensive studies have been carried out, the extent to which each factor is effective is still unclear. According to the existing evidence, it is probable that VEGF increase, through increasing dopaminergic cells, has created the considerable protection of neurons. Consistent with this mechanism, Cadet et al in 1991 also reported that VEGF levels had a potential therapeutic effect in the areas of brain affected by PD. Wang et al in 2001 studied the effects of vitamin D3 on 6-hydroxydopamine-induced neurotoxicity. They reported that taking vitamin D3 for 8 consecutive days at a dose of 1 mg/kg in 6-hydroxydopamine-lesioned group could noticeably improve mobility of the rats. Furthermore, tyrosine hydroxylase level in vitamin group showed less decrease than the saline group (31) According to the findings by Sanchez et al in 2009, vitamin D3 can prevent dopaminergic neurons damage (19).

The present study found that exercising compared with vitamin D3 intake had greater effect on VEGF levels of striatum and consequently on angiogenesis and behavior improvement of parkinsonian rats. However, the most important finding of this research was that pretreatment effect of the combination of exercising and vitamin intake which could distinguish this study from others. The results of Tukey's test revealed that VEGF levels of combination group had a significant difference from that of the vitamin group (P=0.000). Taking the theoretical principles into account, it seems that exercising and vitamin D intake can have a neuroprotective effect against PD through increasing angiogenesis and neurotrophic factors (10, 16). When neurotrophic factors increases, tyrosine hydroxylase activity increases too, its direct consequence is the increase in the conversion of tyrosine into dopamine (32, 33). As a result, it can prevent PD.

Regarding the introduced mechanisms, the improvement yielded by apomorphine in rotational test and the increase in VEGF levels as the most important growth factor involved in angiogenesis process (30), the consequent protective effect of exercising and vitamin D3 might be due to the increased number of mitochondria and angiogenesis and neurotrophic factors in the brain after physical activity and enhancement of muscle strength and speed resulted from exercise and role of vitamin D3 in releasing neurotrophins and brain-related gene activities and neurotransmitter metabolic enzymes.

In conclusion, the results of this study showed that 4 weeks of aerobic exercises on the treadmill and vitamin D3 intake can play a pretreatment and preventive role against 6-hydroxydopamine-induced model of Parkinson's disease in male rats. Thus, it seems to help take an important step toward preventing PD in the coming years and can be used as a non-pharmaceutical protective method.

Acknowledgements

We would like to thank Vice Chancellorship for Research, Sari Islamic Azad University, for financial support.

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