ORGINAL ARTICLE

The Effect of Endurance Exercise Training on the Expression of Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) Genes of the Cerebellum in Diabetic Rat

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Abstract

Objective: Few studies have been conducted on variations of the central nervous system of diabetic patients and much fewer investigations done on the cerebellum of diabetes patients. The current research aims to investigate the effect of endurance training on neurotrophic factors affecting the cerebellum in the diabetic rat.

Materials and Methods: This study is experimental.Twenty Wistar rat were randomly allocated in four groups including: (1) control (n=5), (2) diabetic exercise (n=5), (3) healthy-control (n=5), (4) and exercise-healthy (n=5). Diabetes were induced by intraperitoneal Streptozotocin injection. The endurance exercise training was performed at moderate intensity for six weeks. Expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) genes were measured using the Real-Time PCR method in the cerebellum of the rat. Two-way ANOVA test was used for comparing the means of expression of genes between groups. All statistical analyses were done using SPSS 22 software.

Results: A significant increase was observed in the expression of NGF (from 1.03±0.11 to 1.61±0.24; *P*-value≤ 0.05) and BDNF (from 1.59±0.06 to 3.24±0.46; *P*-value≤ 0.05) genes in male rats with experimental diabetes and healthy subjects after six weeks endurance training.

Conclusion: Endurance training may be helpful for diabetic patients by increasing the neurotrophic factors and thereby preventing diabetes-related neural complications.

Keywords: Diabetes, Cerebellum, Neurotrophic genes, Endurance Training

Introduction

Diabetes mellitus is a type of disease that is created due to an increase in blood glucose and is associated by disorder in the metabolism of carbohydrate, lipid, and protein (1). Hyperglycemia is one of the factors that plays an effective role in the progress of diabetic neuropathy alongside other influential factors such as deficiency of vascular system, rising free radicals and axon transport degeneration (2). Diabetes causes

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cerebellar atrophy and reduces gray matter and causes abnormalities in the white matter of the brain that is led to perceptual disorders and disruption in the structure of cerebellum (3). Diabetes in the child, also, may cause hypoplasia or not forming of the cerebellum in babies (4). The mass of gray matter and white matter is reduced in some cerebellar areas in diabetic patients versus healthy subjects (4). Given the brain tissue is weak in the context of the antioxidant system compared to other tissues it may be exposed to the impairment because of high oxygen consumption. Rising production of types of free radicals that followed by activation of cellular planned apoptosis signals is led to apoptosis of neurons in brain tissue (5). Cellular apoptosis is common in diabetes and degenerative disorders relating to the central nervous system (nervous degeneration) (6). Exercise training may affect various aspects of function in nerve cells including brain plasticity, antioxidant system, rise of neurotrophins, and it prevents from planned apoptosis in nerve cells (7). Exercise on a treadmill has therapeutic potential to inhibit apoptosis paths of neurons and is useful for the prevention and treatment of degenerative disorders of neurons (8). Regular training improves some brain functions such as perception (9). Similarly, they reduce the symptoms of neuropathic pain in human and rodents because of their anti-inflammatory effects and have helpful effects on neural degenerative diseases (10). Diabetes damages all the layers of cerebellum including myelin sheath and cerebellar vessels. Diabetes disrupts blood circulation in the brain and this is led to vascular diseases in the brain (11). Neurotrophins are the known foremost trophic agents in the nervous system where they are considered as the important and prominent family of polypeptide growth factors and affect replication, survival and death of nerve cells and non-nervous cells (12). The family of secreted polypeptide neurotrophins includes Nerve Growth Factor (NGF), Brain- Derived Neurotropic Factor (BDNF), neurotrophin-3, and neurotrophin-4 (13). Physical activity and exercise enhance brain health because of the rising function of nutrient factors in the brain (14). BDNF is one of the most important factors of this group. BNDF is involved in some processes including neurogenesis, neuroprotection, and synaptogenesis (15). Similarly, BDNF improves cell survival by anti-apoptosis protein induction and inhibition of pre-apoptotic factors (16). It has been shown that BDNF is low in patients with Alzheimer's disease and in many animal models of Alzheimer's diseases and exerts neuroprotective effects when performing neural degenerative of animal models (17). It has been shown that the endurance exercise may temporarily increase BDNF concentration in blood and brain about two to three times (14,18). According to best of our knowledge, there is little evidence has examined the effect of exercise on BDNF and NGF genes in cerebellar tissue of diabetic rats. So, the aim of this study was to assess the effect of endurance training on the expression of BDNF and NGF genes in the cerebellum of STZ-induced diabetic male rats.

Materials and Methods

Study design

In this experimental study, 20 matured male Wistar rats (240-250 g), (age= 10 weeks) were obtained from the experimental animal holding of Shahid Chamran University of Ahavz, Ahvaz, Iran. All rats were placed under controlled condition and temperature of 22±3 °C and 12:12h light: dark cycle (awaking cycle started at 16:00). All rats were housed in conventional conditions and fed standard diet and water ad libitum at the animal facility for 1 week before experiments began. For familiarization animals walked on a rodent treadmill 10-15 min at 10 m/min speed 5 sessions/week. 20 rats were randomly divided equally into 4 groups as follows: 1) Diabetic Trained group (DT; n= 5): they did endurance exercise 5 sessions per week for 6 weeks. 2) Diabetic Control (DC; n= 5) group: They were diabetic and excluded from any exercise training. 3) Healthy Trained (HT; n= 5) group:

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They were involved in the endurance exercise similar to the DT group. 4) Health Control (HC; n= 5) group: They were not involved in any exercise. Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ, 40 mg/kg) and diabetes were confirmed as the blood glucose level higher than 240 mg/dl (19). Body weight was measured weekly.

Endurance exercise training conducted at the moderate intensity (50- 55% VO2max) according to Chae et al (20). The protocol included running on a rodent treadmill 5 sessions/week for 6 weeks as follows: Table 1. Exercise stayed constant as same as week 5 for last week to obtain the given adaptations under steady state condition.

Rats were anesthetized by intraperitoneal injection of the mixture of ketamine (75 mg/kg) and xylazine (5 mg/kg) 12 hours after the last exercise session. They were killed by cutting their heads using a guillotine and the cerebellum tissue was excised under a sterilized condition and put in the 10% formalin solution.

Real time-PCR

At the end of experiment, all animals were sacrificed under ether anesthesia. They were decapitated; their cerebellums were removed with dissection and tissues were frozen in -70ºC for subsequent analysis. Cerebellum tissues (100 mg) were immediately added to 1 mL of RNX^{TM} reagent (SinaClon Bioscience, Iran) and homogenised using a homogeniser (Tissue Ruptor, Qiagen GmbH, Germany). One milliliter of the tissue homogenate was transferred to a microfuge tube and total RNA was extracted by the addition of 0.2 mL chloroform. Next, the samples were vigorously vortexed for 15 sec and incubated at room temperature for 3 min. After centrifugation (12,000 g, 15 min) at 4°C, the aqueous phase containing RNA was transferred to new tubes. RNA was precipitated by mixing the aqueous phase with 0.5 mL isopropyl alcohol and incubated at room temperature for 10 min. After centrifugation at 12,000 g for 10 min at 4°C, RNA pellets were washed by mixing and vortexing with 1 mL of 75% ethanol. After centrifugation (7,500 g, 5 min) at 4°C, RNA pellets were resuspended in nuclease-free water (Sina Clon Bioscience, Iran). The purity of RNA at 260/280 OD ratio and the RNA integrity were evaluated using a Multi-Mode Microplate reader (Eppndorf, Germany). Only high purity samples (OD260/280> 1.8) were subjected to further manipulation. cDNA was synthesized from RNA samples using a YTA cDNA synthesis kit (Yekta tajhiz, Iran) and Eppendorf Thermal Cycler (Germany). Briefly, total RNA was activated at 70°C for 10 min and 20 µ L reaction mixtures were prepared with 4 µ L of reverse transcription 5 x buffers, 1 µ L of dNTP mixture (10 mM), 2 µ L of random primers (10 mM), 1 µ L of M-MLV reverse transcriptase enzyme, 1 ul of RNAsein, 1 ug RNA and nuclease-free water to a final volume of 20 µ L. Next, the reaction was incubated at 42°C for 60 min, followed by incubation at 94°C for 5 min. The cDNA was diluted up to 100 µ L with nuclease-free water for PCR amplification.

The Real-time RT-PCR was performed using Roche Light-Cycler detection system (Basel, Switzerland) by the qPCR^{TM} Green Master Kit for SYBR Green I® (Yektatajhiz, Iran). The 12.5 µ L reaction for each examined gene was prepared from 6.25 µ L of 2X master mix, 0.25 µ L of each forward primer (10 uM), 3 µ L cDNA of the sample and 2.25 µ L of nuclease-free water. The cycling parameters were 95°C for 4 min, 40 cycles of 95°C for 15 sec, followed by 60°C for 30 sec. Two separate reactions without cDNA or with RNA were performed in parallel as controls. The relative gene expression levels were determined using the comparative threshold cycle ($2^{-\Delta\Delta CT}$) method and Lightcycler 96® software. The GAPDH mRNA fragment was used as a housekeeping gene to normalize the expression data. The primer sequences are described in Table 2 (21).

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Table 1. Numeric display of protocols in different weeks

Variable	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Duration exercise training(min)	10	20	20	30	30	30
Speed exercise training(m/min)	10	10	15	15	17-18	17-18

Table 2. Characteristics of primers used in the present study

Gene name	Sequence
BDNF-mice-F	CGCAAAGAAGTTCCACCAG
BDNF-mice-R	TAGGCCAAGTTGCCTTGT
NGF-mice-F	CTTCACAGAGTTTTGGCCTG
NGF-mice-R C	ATTACGCTATGCACCTCAGA
GAPDH-mice-F	CTGGAGAAACCTGCCAAGTA
GAPDH-mice-R	GAAGAGTGGGAGTTGCTGTT

All qPCR analysis was performed according to The Minimum Information for Publication of Quantitative Real-Time PCR Experiments (MIQE) guideline (22).

Statistical method

All data expressed as mean ± standard deviation. Normality and homogeneity were assessed by Kolmogorov-Smirnov and Leven's test, respectively. Two-way ANOVA test was used for comparing the means of expression of genes between groups. The significance level was set at *P*-value≤ 0.05. All statistical analyses were done using SPSS 22 software.

Ethical considerations

All experimental protocols were approved by an ethics committee of Shahid Chamran University of Ahvaz for animal and human experiments (EE/97.24.3.69971/scu.ac.ir).

Results

Body weight of all groups is shown in Table 3. Endurance exercise and diabetes, both, had significant effects on BDNF gene expression (*P*-value≤ 0.05). As shown in Figure 1.A, by changing training status from untrained to trained, BDNF gene expression significantly increased in , both, diabetic and healthy rat, with more increase in the diabetic group (*P*-value≤ 0.05).

In the other hand, by changing health status from healthy to diabetic, BDNF gene expression, again, increased in, both, trained and untrained rat (Figure 1.B, *P*-value≤ 0.05). Trained group showed more increase than untrained group.

We found similar results for NGF, in spite of decreasing by diabetes. NGF gene expression were significantly increased by changing training status from untrained to trained (*P*-value≤ 0.05) in diabetic as relatively same as healthy rat (Figure 2.A). However, NGF gene expression were decreased by changing health status from healthy to diabetic in, both, trained and untrained rat (Figure 2.B, *P*-value≤ 0.05).

Discussion

In the present study, a STZ rat model of diabetes was used to investigate the potential protective effects of endurance training on regulates the expression of neurotrophic genes in the cerebellum of, both, experimental diabetic and healthy rats.

The results of the present study demonstrated that diabetic rats showed up-regulated of BDNF and GNF genes. Although the main reason for diabetic neuropathy is not completely known, the disorder in vascular function oxidative stress and change in neurotrophic support are important factors of this disease (23). In accordance with our findings several studies on diabetic rats have shown that lack and deficiency of neurotrophic factors are involved in diabetes progress. Also, by a study on human, Pederson et al. have shown that BDNF cerebral output stops under hyperglycemic status. Thus, low levels of BDNF in diabetic people could be justified and low levels of BDNF of also related to excessive insulin resistance (24).

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Table 3. Body weight (g) of rat before exercise training

Group	Mean (±SD)
Health Control	249.0 (± 8.0)
Healthy Trained	249.8 (± 11.6)
Diabetic Control	259.1 (± 8.0)
Diabetic Trained	256.1 (± 10.8)

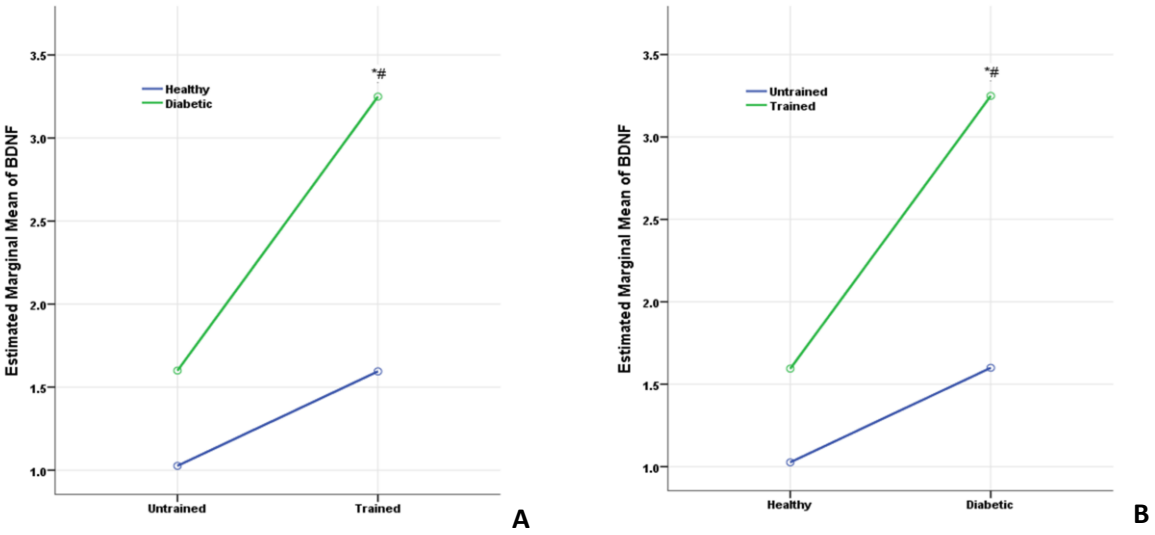


Figure 1. Estimated marginal mean of BDNF gene expression and its change by A) Training, and B) Diabetes.

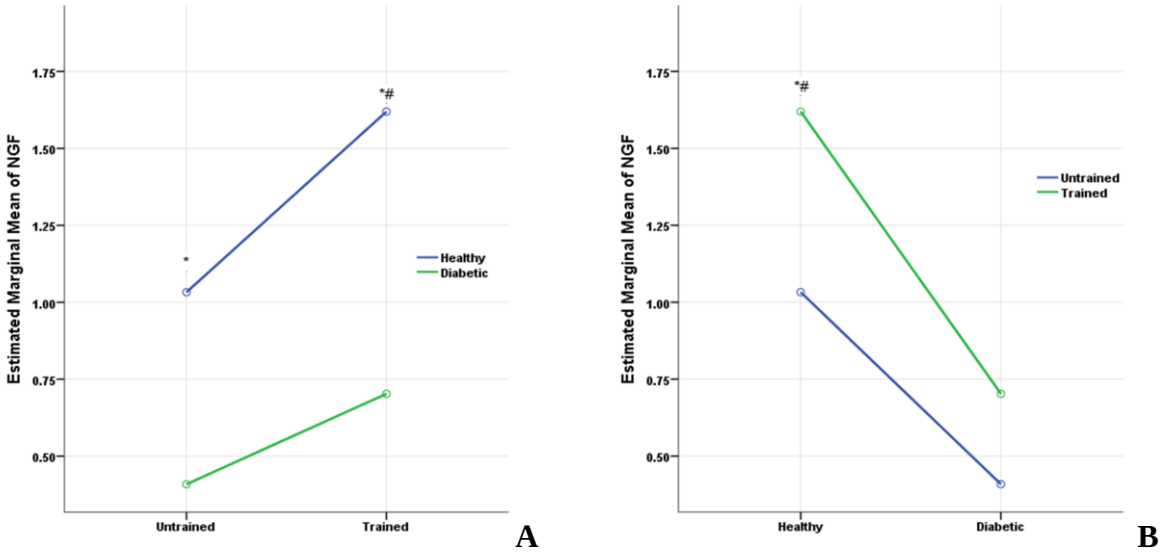


Figure 2. Estimated marginal mean of NGF gene expression and its change by A) Training, and B) Diabetes.

Some changes may occur in the levels of expression of neurotrophic factors in diabetes condition as a result of damage to neurons and Schwann cells (25). Anderson et al. indicated that the expression of neurotrophic factors decreases in the distal muscles in comparison to the proximal muscles (26). Kim and sang (2017) showed that regular training has had a positive impact in BDNF level of the hippocampus (27). In addition to neuroprotective effects, neurotrophins also have antioxidant activity. In the mitochondrial

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electron transport chain, reactive oxygen species (ROS) are produced as a natural product, but they can lead to apoptosis when their levels are higher than the antioxidant capacity of the cell. Exercise-induced increasing in the antioxidant capacity protects the neurons in diabetes due to neurotrophins upregulation (28). Recently, it is demonstrated that secretion of PGC1α , a key exercise factor in muscle, is associated with neurotrophins gene expression in the brain. PGC1α is activated in skeletal muscle through exercise and bind to an ERRE element that can activate the expression of FNDC5 gene; as a result, upregulates BDNF in the brain (29). BDNF cerebral secretion in the diabetic patients is suppressed because of hyperglycemia. In addition, there is an inverse relationship between BDNF and blood glucose and it is regulated by plasma glucose levels (30).

The role of regular exercise activity in the improvement of cerebral functions such as perception has been proved and, also, enhances brain plasticity, antioxidant system, and neurotrophins upregulation. It prevents nerve cells from apoptosis. Enhances biosynthesis of acetylcholine and its axoplasmic transport, and neurogenesis (31). Unlike, Lee et al. reported that BDNF level in serum of diabetic subjects decreased after 12 weeks endurance training at 50-60% VO2max and no significant changes in inflammatory parameter and NGF have been reported (32). However, the results of another research indicated that running on a treadmill and/or swimming increased NGF levels significantly after four weeks of training and stimulated neurogenesis (33). Deficiency of NGF synthesis in diabetic patients can be due to hyperglycemia or hypoinsulinemia; as a result, polyol accumulation and change in corticosterone concentration can occur. Corticosterone decreases NGF synthesis and regular exercise suppresses the glucocorticoids secretion and, hereby, decreases NGF synthesis (34). Exercise-induced changes in expression of neurotrophins such as NGF and BDNF in the nerve-degenerating conditions and diabetes is, generally, proved (35), although, there are some contradictions between the results of previous studies and our findings that it seems to be due to different experimental techniques and different training protocols. Further study are necessary to determine the molecular mechanism of endurance training on attenuation of release or expression of neurotrophic factors in cerebellum in diabetes condition.

Conclusions

It seems that the change in neurotrophic factors is one of the potential factors involved in nerve degeneration in diabetic patients that endurance exercise training as a non-medical strategy can attenuate these changes. Thus, it can be suggested that diabetic patients engage in exercise training along with other treatments to prevent more effectively from neural side-effects of diabetes.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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