

Brain-derived neurotrophic factor, insulin-like growth factor 1 and its binding protein responses to a session of endurance exercises in healthy elderly men

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ABSTRACT

Purpose: This study investigated the effect of endurance activity on brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1) and its binding protein 3 (IGFBP-3) in elderly healthy individuals.

Materials and Methods: Eleven healthy old males (mean age of 68 ± 2.31 years old, height of 177 ± 3.1 cm and weight of 79 ± 1.5 kg) were studied. Seventy two hours after maximal oxygen consumption (VO_2 max) evaluation, the participants performed an endurance activity at the intensity of 70% of their VO_2 max. Three blood samples were collected from the antecubital vein before, immediately and 30 minutes after the activity. The data were analyzed by repeated measures ($P \leq .05$).

Results: There was a significant increase in serum BDNF and IGF-1 immediately after the endurance activity ($P = .040$ and $P = .047$, respectively). However, 30 minutes after the activity, there were no significant changes in serum BDNF and IGF-1 compared to the serums before the activity. There was also no significant change in IGFBP-3 immediately and 30 minutes after the research protocol relative to serums before activity ($P = .067$ and $P = .154$, respectively).

Conclusion: The findings showed that BDNF and IGF-1 increase significantly in response to endurance activity, but no significant change was observed in IGFBP-3. Endurance activities might contribute to an increase in neurotrophical factors involved in memory and cognitive function which in turn decrease the incidence of neurological diseases such as Alzheimer, depression and many other related neurophysiological ones in elderly adults.

Keywords: brain-derived neurotrophic factor (BDNF); insulin-like growth factor 1 (IGF-1); insulin-like growth factor binding protein 3 (IGFBP-3); endurance exercise; elderly men.

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INTRODUCTION

Healthy aging is any human beings' natural right. This reflects the importance of ageing and preventing its related problems. Among the aging-related physiological changes in older adults is the gradual increase in limbs' function impairment that threatens the elderly with different diseases, cancer and even death. Impaired memory

formation, retention and recall,¹ and cognitive function² in old age results in many diseases, such as Alzheimer, depression³ and dementia.⁴ It is assumed that this impairment is due to the decrease in the volume of some brainregions, especially the hippocampus.⁵ Regarding the brain regions neurotrophic factor (BDNF), which is one of the most important factors in the hippocampus,⁶

researches have shown a direct relationship between the decrease in hippocampus volume (hippocampal atrophy) and the decrease in BDNF.^{7,8}

BDNF is a member of the neurotrophin protein that helps the neurogenesis, neuroprotection and neurodegeneration, survival of existing neurons, synapses formation and memory retention and recall.⁹ It seems that doing exercises can increase the secretion of BDNF at the mRNA and protein levels.¹⁰

One of the mechanisms mediating the effect of exercise on BDNF is the growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis. Physical activity enhances the growth hormone secretion in blood circulation which in turn stimulates the production of IGF-1. While the IGF-1 in blood circulation is mainly secreted by the liver, it can also be produced by other tissues such as the brain.¹¹ The increase in blood IGF-1 intake by brain cells after the physical activity has an apparent effect on brain function. Given the physiological role of blood IGF-1 (as well as its neural mechanism that involves IGF-1 passing from brain blood barrier), the interaction of this factor with special neuron groups leads to neural stimulation. This process results in the expression of c-Fos, BDNF and subsequently long-term change in nervous system function.¹²

In blood circulation, insulin-like growth factor binding protein 3 (IGFBP-3) is the main IGFs carrier protein that is not able to pass the capillaries wall; therefore it remains in the blood circulation. Of all IGFs, 80% bind to this receptor.¹³ This protein has a great tendency to form a complex with IGF-1. In addition to its mitogenic and antiapoptotic actions, it also has an IGF-1 independent inhibitory effect on cell growth.¹⁴

Although recent evidences show that physical activity enhances neuroplasticity, related to the increase in neurotrophic factors like BDNF induced by physical activity, its underlying mechanism is not clear yet. Since BDNF has a prominent role in neuroplasticity in adults nervous system,¹⁵ and age-related decrease in neurotrophic factors is reported in the researches,¹⁶ therefore BDNF decrement must be considered as an important issue in aging. It seems that the increase in BDNF induced by physical activity, as well as other factors involved in BDNF secretion like IGF-1 and IGFBP-3, help protecting the brain against age-related neural degeneration and destruction. According to the previous researches and the inconsistency of the findings on the effect of endurance and resistance exercises, this study set out to investigate the effect of endurance exercises on BDNF levels, their related factors on the health of elder peoples' brains.

MATERIALS AND METHODS

Eleven healthy old males (mean age of 68 ± 2.31 years old, height of 177 ± 3.1 cm and weight of 79 ± 1.5 kg) participated voluntarily in this study. The participants with diseases such as cardiovascular, high blood pressure, diabetes mellitus, cognitive dysfunctions, osteoarthritis and any other conditions, such as drug use, smoking, hormone therapy, etc, which might have affected the participants ability in performing the protocol were excluded from the study. All subjects were aware of the aims of the study, provided informed written consent and completed a medical information questionnaire.

All participants visited Shahid Beheshti University's physiology laboratory twice in order to complete the two experimental procedures. In the first visit, the participants' body composition was determined. Their height was measured using height rods (Seca, 0.01 precision, Hamburg, Germany) and other body composition factors were determined using body composition analyzer (X-SCAN plus II, Jeongeup, South Korea). For more precision and error prevention, the participants were asked to refrain from eating and drinking two hours before the measurement, participating in a high intensity physical exercise 12 hours prior to the measurement and avoid taking diuretic drugs seven days before the measurement. The subjects were also asked not to have any metal object with them. In case of necessity, the participants could urinate 30 minutes before the measurement. One day after body composition evaluation, the participants returned to the laboratory to determine maximum oxygen consumption (VO_{2max}).

VO_{2max} Measurement

Subjects' VO_{2max} was measured using Monark cycle ergometers (839 E, Monark AB, Varberg, Sweden) and a gas analyzer (CORTEX Technology, Niederlassung, Germany) through an incremental test. In the first two minutes after the warm up (5 minutes of pedaling without load), the intensity was 50 w, followed by a 25 w increase in every two minutes until the participants reached exhaustion. The burnout criteria were:

1. Respiratory exchange ratio (RER) ≥ 1.15
2. Reaching a plateau in oxygen uptake (in spite of the increase in intensity)
3. Reaching beyond level 17 in Borg scale [The Borg Scale is a simple method of rating perceived exertion (RPE) and can be used by coaches to gauge an athlete's level of intensity in training and competition. Perceived exertion is an individual's

rating of exercise intensity, formed by assessing their body's physical signs such as heart rate, breathing rate and perspiration/sweating].

4. When the subjects were not able to continue the activity

The test procedure was stopped if the subjects reached 3 of the 4 mentioned criteria.¹⁷ Using a gas analyzer during the test, oxygen uptake, carbon dioxide output, respiratory exchange ratio, heart rate, energy expenditure, and cardiac output were recorded.

Main Protocol

Three days after VO_{2max} measurement, the participants returned to the laboratory for the main protocol. They were asked to refrain from high intensity exercise 48 hours after the protocol and avoid taking caffeine 12 hours before the research protocol. The basal serums of BDNF, IGF-1 and IGFBP-3 were collected while the subject was seated quietly for 30 minutes. The subjects immediately underwent the main protocol that was 30 minutes pedaling on Monark cycleergometer in 70% VO_{2max} .¹⁸

The second and third blood samples were collected from an antecubital vein immediately and 30 minutes after the exercise. Five mL blood was taken in each blood sample. Blood serum was separated by centrifuge at 3,000 rpm at 4°C for 10 minutes (Boeco U-320R centrifuge, Boeckel, Germany) and then stored at -80°C until assay. BDNF levels were measured by the ELISA kit (Human BDNF, ELISA, Mediagnost, Wuhan, China, Sensitivity: 2 pg/mL), IGF-1 levels were measured by the ELISA kit (Human IGF-1, ELISA, Mediagnost, Reutlingen, Germany, Sensitivity: 6 pg/mL) and IGFBP-3 levels were also measured by the ELISA kit (Human IGFBP-3, ELISA, Mediagnost, Wuhan, China, Sensitivity: 10 pg/mL).

Statistical Analysis

Data analysis was conducted by the statistical package for the social science (SPSS Inc, Chicago, Illinois, USA) version 16. Since Kolmogorov–Smirnov test showed the normality of the data distribution, Repeated Measure (1×3) and Bonferroni post hoc test were used to investigate BDNF, IGF-1 and IGFBP-3 responses to the endurance exercises immediately and 30 minutes after the activity. *P* value of less than .05 was considered as significant.

RESULTS

Eleven healthy old males (mean age = 68 ± 2.31 years, height = 177 ± 3.1 cm and weight = 79 ± 1.5 kg,

fat mass = 18.1 ± 0.6 kg, fat-free mass = 63.9 ± 2.3 kg, body mass index = 25 ± 1.7 kg/m² and VO_{2max} = 33 ± 2.9 mL/(Kg.min)) were investigated in this study. While there was a significant increase in serum BDNF and IGF-1 in response to the endurance activity ($P \leq .05$), no significant increase was observed in serum IGFBP-3 ($P \geq .05$).

Bonferroni post hoc test showed a 46.8% significant increase in serum BDNF (330.72 ± 91.93 pg/mL) immediately after the endurance activity ($P = .040$). There was also a 0.08% increase in serum BDNF 30 minutes after the activity compared to immediately after the activity, though this increase was not significant ($P = .104$). Serum BDNF changes in response to the endurance activity in the older adults is indicated in Figure 1.

Serum IGF-1 also had a 33.6% significant increase

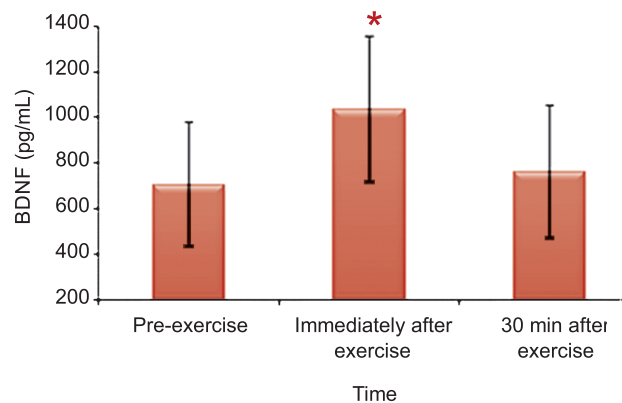


Figure 1. Elderly serum brain-derived neurotrophic factor changes immediately (1036.09 ± 318.71 pg/mL) and 30 minutes (763.09 ± 291.24 pg/mL) after the endurance exercise compared to pre-exercise (705.39 ± 272.5 pg/mL) which was significantly different than pre-exercise ($P \leq .05$).

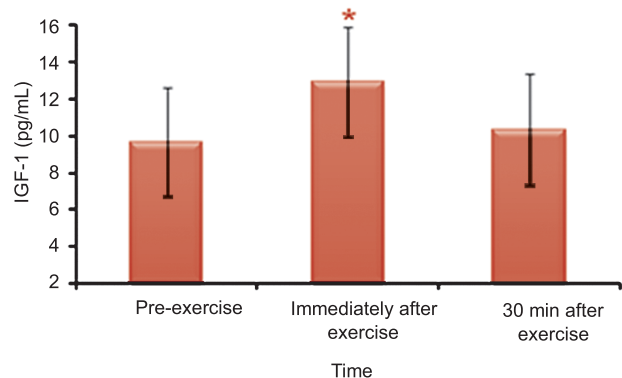


Figure 2. Elderly serum insulin like growth factor 1 changes immediately (12.92 ± 2.97 pg/mL) and 30 minutes (10.33 ± 3.03 pg/mL) after the endurance exercise compared to pre-exercise (9.66 ± 2.93) which was significantly different than pre-exercise ($P \leq .05$).

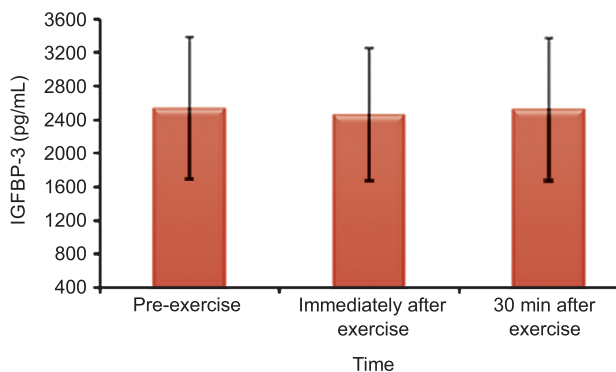


Figure 3. Elderly serum insulin like growth factor binding protein 3 changes immediately (2458.36 ± 793.1 pg/mL) and 30 minutes (2520.55 ± 849.74 pg/mL) after the endurance exercise compared to pre-exercise (2536.73 ± 850.49 pg/mL) which was significantly different than pre-exercise ($P \leq .05$).

(3.25 ± 1.42 pg/mL) immediately after the exercise ($P = .047$). However, the amount of this factor decreased to its basic level 30 minutes after the activity and no significant increase was observed in the serum level compared to its pre-protocol level ($P = .149$). Figure 2 illustrates the serum IGF-1 changes in response to the endurance exercise in the older adults. There was no significant change in serum IGFBP-3 immediately and 30 minutes after the endurance activity ($P = .067$ and $P = .154$, respectively) (Figure 3).

DISCUSSION

The purpose of this study was to investigate BDNF, IGF-1 and IGFBP-3 responses to a session of endurance exercise in elder men. The findings showed that serum BDNF increased significantly immediately after the endurance exercise in older adults. This finding is consistent with the findings of Ferris and colleagues,¹⁹ Winter and colleagues,²⁰ Geokint and colleagues,²¹ Tang and colleagues,²² and Rasmussen and colleagues.²³ However, it is inconsistent with the results of Rojas Vega and colleagues²⁴ who reported no significant change in serum BDNF in response to endurance activity. This inconsistency might be due to the lower intensity of endurance exercise protocol. It seems that only high intensity endurance activity results in BDNF expression in the brain.

Several researches have shown that endurance activity leads to prominent changes in neurotrophical factors' expression and secretion through changes in signal pathways.²⁵ By increasing the mitogen-activated protein kinase (an important intracellular signal pathway involved in BDNF production and secretion), phosphorylation in hippocampus and brain cortex, endurance exercise

can increase BDNF. On the other hand, Sartori and colleagues²⁶ have shown that endurance exercise increases mature BDNF (mBDNF) through changing some signal pathways [i.e. Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) and Synapsin I; increasing the expression and activation of tissue plasminogen activator (tPA) and p11; and increasing proteolytic mRNA of mBDNF]. Therefore, it seems that the observed increase in BDNF immediately after the endurance activity in the present research might be because of the mentioned mechanism.

Cellular-molecular studies have shown that endurance exercises increases the activity of some signal pathways [i.e. pCaMKII, protein kinase B pathway (pAkt)] and extracellular signal-regulated kinase pathway (pERK) and the amount of proteins [i.e. growth associated protein-43 (GAP-43) and Synapsin I] involved in BDNF expression and secretion.^{27,28} These, in turn, increase tPA density and activation and subsequently the serum BDNF level as well as binding to its receptor [tropomyosin related kinase B (TrkB)].²⁹ This issue is likely another reason for increased serum BDNF immediately after the activity.

Since a few researches have been done on this matter, the underlying reason of decreased serum BDNF during the recovery period is unknown. This is probably due to the decrease in BDNF expression, translation and secretion from the main resources of this protein (i.e. hippocampus, vascular endothelial cells and platelets). Studies have indicated that serum BDNF in hippocampus,²⁷ vascular endothelial cells³⁰ and platelets³¹ decrease after an endurance exercise. Thus, the serum BDNF decrement from the mentioned organelles might cause the decreased serum BDNF after the endurance exercise.

Since IGF-1 easily passes the blood-brain barrier³² and participates in the transformation of proBDNF to mBDNF in central nervous system, its changes were investigated in this study alongside the BDNF changes. IGF-1 increased significantly immediately after the endurance activity. This is consistent with the finding of Rojas Vega and colleagues,^{24,33} Tissandier and colleagues,³⁴ and Mejri and colleagues.³⁵ Still, most of the previous studies have not reported any changes in IGF-1 during and immediately after a short-term session of exercises.^{36,37}

IGF-1 production and secretion are controlled by expressed genes in cerebellum granule cells. c-Fos is one of these important genes. However, it has been indicated that this gene expression in cerebellum granule cells would increase in response to physical activity.³⁸ Although the physiological relationship between c-Fos expression and IGF-1 production and secretion is still

unknown, the increase in c-Fos expression is associated with increase in IGF-1. Hence, another probable cause of the increased IGF-1 immediately after the exercise could be related to the increase in c-Fos expression. Nevertheless for more accuracy, it would have been better to measure this gene expression by polymerase chain reaction.

Since there was no change in IGFBP-3, another possible reason for increased serum IGF-1 in this study might be the decrease in IGF-1 binding to IGFBP-3. In binding to its most important receptor, that is IGFBP-3, IGF-1 binds to specific molecular receptors in nerve cell membrane.³⁹ In addition, the increase in IGF-1 and lack of change in IGFBP-3 in response to endurance activity can result in an increase in serum IGF-1.³⁹

The reason behind IGF-1 decrease in the recovery period is unknown. Still, it is likely that the increased IGF-1 serum intake due to the shift of blood flow toward some tissues (in order to provide physiological demands), such as the brain and muscles, might be the reason.^{40,41}

IGFBP-3 level decreased slightly compared to its basal levels. This factor did not change significantly in response to endurance activity immediately and 30 minutes after it. This is consistent with Mejri and colleagues,³⁵ but is inconsistent with the findings of Schwarz and colleagues,⁴² who reported an increase in IGFBP-3 levels after the endurance activity. Probably this inconsistency is due to the more amount of protocol used in their study.

The changes in IGFBP-3, as a protein with a long half-life, are associated with the changes in metabolite pathways.⁴³ So it appears that this protein would change only by intervening factors like long-term endurance exercises. Nindl and colleagues⁴⁴ demonstrated that long-term exercise intervention increases IGFBP-3 production and secretion immediately and during the recovery period after the activity by changing the metabolite pathways. The lack of change in IGFBP-3 in this study might be the result of short-term duration of endurance protocol. However, this is need of further investigations.

CONCLUSION

BDNF and IGF-1 serum increases significantly immediately after endurance exercises in healthy elder men, but IGFBP-3 serum does not change significantly. According to these findings, it is likely that prescribing endurance exercises can increase neurotrophic factors like BDNF and other factors involved in BDNF production and secretion such as IGF-1. Thus, it might be possible to understand the ways for preventing or decreasing the

incidence of diseases such as depression, Alzheimer and dementia by preserving the brain's health in old ages.

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CONFLICT OF INTEREST

None Declared.

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