International Journal of EXERCISE SCIENCE

Original Research

A New, Simple and Practical Approach to Increase the Effects of Aerobic Exercise on Serum Levels of Neurotrophic Factors in Adult Males

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ABSTRACT

International Journal of Exercise Science 16(2): 932-941, 2023. Environmental enrichment (EE) is defined as a combination of complex inanimate and social stimulation. Physical activity and EE may augment the beneficial effects of each other. This study aimed to assess the effects of running in an enriched environment on neurotrophic factors in adult males. Twelve volunteer adult males (age 26.75 ± 5.34 yrs, body mass 70.72 ± 8.61 kg, height 172.50 ± 5.68 cm, VO_{2max} 56.8 ± 2.93) completed two sessions, each consisted of one hour of running at an intensity of 12-13 on the Borg Scale. One session was completed in a normal environment, while the other was performed in an enriched environment (running track with several obstacles). Participants completed this randomized cross-over study interspersed by two weeks. Ten minutes before and after each session, blood samples were collected from all participants. Serum levels of BDNF, IGF-1, and VEGF were measured by ELISA. There was a statistically significant interaction of condition and exercise on BDNF, F (1, 11) = 43.71, $p < 0.001$, $\eta_P^2 = 0.799$; IGF-1, F (1, 11) = 83.58, $p < 0.001$, $\eta_P^2 = 0.884$; and VEGF, F (1, 11) = 31.86, $p < 0.001$, $\eta_P^2 = 0.743$. There was also a significant effect of condition on BDNF F (1, 11) = 21.08, $p = 0.001$, $\eta_P^2 = 0.657$; IGF-1, F (1, 11) = 32.35, $p < 0.001$, $\eta_P^2 = 0.746$; and VEGF, F (1, 11) = 116.29, $p < 0.001$, $\eta_P^2 = 0.914$. In addition, there was a significant effect of Exercise on BDNF F (1, 11) = 52.86, $p < 0.001$, $\eta_P^2 = 0.828$; IGF-1, F (1, 11) = 39.14, $p < 0.001$, $\eta_P^2 = 0.781$; and VEGF, F (1, 11) = 171.21, $p < 0.001$, $\eta_P^2 = 0.940$. One hour of moderate-intensity running in adult males significantly increased serum levels of BDNF, IGF-1, and VEGF. But, exercising in an enriched environment may have a significantly greater effect. Therefore, if enhancing neurotrophic factors are desired outcomes of training sessions, then including obstacles may enhance the likelihood of achieving this goal.

KEY WORDS: Environmental enrichment, learning, memory, neurotrophic factors, running

INTRODUCTION

Environmental enrichment (EE) is defined as a combination of complex inanimate and social stimulation (32). In animal studies, several mazes, running wheels, and tubes have been used as means of environmental enrichment. EE has been reported to positively impact the brain function, including increasing the number of dendritic branches, developing synapses, and improving cognitive functions (25). Furthermore, human and animal studies have indicated the

beneficial effects of exercise on cognitive functions, learning, and memory (1, 5, 13, 45). Physical activity enhances neural plasticity in a healthy brain and can also improve brain function following nerve damages (41). Regular physical activity is also associated with a better cognitive function, a reduced risk of cognitive conditions, as well as lowering the relative risk of dementia to 28% (15).

The proposed mechanisms for the cognitive benefits of physical activity include direct effects on the brain, such as increased cerebral blood flow, angiogenesis (37), the production of neurotrophic factors, and the expression of neurotrophins (9, 14). Neurotrophic factors are defined as proteins regulating survival, growth, morphological plasticity, or the synthesis of proteins for differentiated functions of neurons. The family of neurotrophic factors include classic neuroprotective neurotrophins such as brain-derived neurotrophic factor (BDNF), factors linked to more than merely neural cells, such as insulin-like growth factor-1 (IGF-1), and growth factors involved in vasculogenesis, such as vascular endothelial growth factor (VEGF) (11, 21). These proteins can cross the blood-brain barrier (BBB) (6) and may improve neural repairs, growth, and neural plasticity. There is a large body of studies suggesting that exercise and environmental enrichment could enhance BDNF levels and improve the survival of new neurons in the hippocampus (18, 26, 33, 34, 36). Further, the levels of BDNF in the bloodstream increase in response to exercise (4). Animal studies have revealed that IGF-1 mediates exercise-induced angiogenesis, boosts the production of the central source of VEGF and BDNF, and is necessary for exercise-induced neurogenesis (7, 21). It has also been suggested that aging induces the cognitive decline (44), which may be associated with the reduced availability of BDNF, IGF-1, and VEGF (8, 12, 35).

Notably, when exercise and cognitive stimuli are combined, their synergistic positive effects on the cognitive function and brain health are elevated (28, 29). However, each component seems to present different mechanisms of action. For example, environmental enrichment enhances neural plasticity as well as the odds of the survival of new neurons and their linkage to the neural network (38), while exercise usually improves cell proliferation (17).

In this study, for the first time, we evaluated the effect of aerobic exercise performed in an enriched environment. This design, simultaneously integrated aerobic and cognitive training, and as an interesting aspect of it, this mental stimulation was achieved with a minimum physiological stress, no more than the aerobic exercise alone. To evaluate the effect of this alteration, we measured the serum levels of BDNF, IGF-1, and VEGF in active men before and after each training condition. We hypothesized that enriched exercise results in a greater elevation in the serum levels of BDNF, IGF-1, and VEGF.

METHODS

Participants

Twelve physically active healthy males (age 26.75 ± 5.34 yrs, body mass 70.72 ± 8.61 kg, height 1.72 ± 0.06 m, VO_{2max} 56.8 ± 2.93) volunteered to participate in this randomized cross-over study.

Healthy participants, aged between 24 and 30 years, with no history of medications for chronic conditions were eligible to participate in this study. Participants were physically active and they performed high-intensity aerobic training (30 to 50 minutes) on average three times a week and recreational futsal game approximately once a week. The exclusion criteria were any acute condition that would limit the ability to exercise. Before the start of the intervention, participants were informed about the benefits and risks involved with this study, read plain language statements, and signed informed consent forms. This research project was approved by the relevant Human Ethics Committee (code: IR.LUMS.REC.1398.183) and was performed under the declaration of Helsinki along with ethical guidelines in exercise science (27).

Data for this study were collected in three sessions including the familiarization, normal environment training (NET) (45), and enriched environment training (EET). The first one served as the familiarization session in which participants visited the Exercise Science laboratory and were given adequate time to experience both training environments. Additionally, the anthropometric and maximum aerobic capacity assessments were performed during this session, whereby they were familiarized with the Borg scale to adjust the intensity of training. At the end of this session, participants were randomly assigned to either NET or EET, then they completed the third session under a different condition (NET or EET).

Assessment of the maximum aerobic capacity**:** The Bruce treadmill test was used to measure the maximum aerobic capacity of the subjects. Briefly, the subjects started at a low intensity walking and with the increase in speed and slope, they ran on the treadmill to exhaustion. During the test, the speed (km/hr) and grade of slope (%) of the treadmill were increased according to the protocol. When the subject was unable to continue the test, the total time was recorded in minutes and seconds. Then, using the following formula, the maximum aerobic capacity was calculated.

$$VO_{2max} = 14.8 - (1.379 \times T) + (0.451 \times T^2) - (0.012 \times T^3)$$

In the above formula, 'T' is the total time of the test in minutes and fractions of a minute (23).

Protocol

At the beginning of each training session, participants performed a warm-up including jogging at a low to moderate intensity for 10 minutes followed by a 5-minute active stretching of major muscle groups in the lower and upper body. Following this warm-up, they completed 60 minutes of running at an intensity equal to 12-13 on the Borg scale. At the end of each 400m lap, participants specified the intensity of exercise using the Borg scale between 6 and 20 and verbal cues were provided to increase, decrease, or maintain the speed of running. This was to ensure the intensity of training was maintained at ~12-13 on the Borg scale. Upon the completion of a 60-min running exercise, in the cool-down stage, the subjects performed a 5-minute walking. In the normal training environment (NET), there was a 400-m outdoor track. However, in the enriched training environment (EET), several obstacles were placed on the track [Figure 1]. Participants of this study were asked to overpass and underpass the obstacles, and zigzag

through the cones which were placed along the 400-m outdoor track. Since there was no published similar study, researchers self-developed this training protocol.

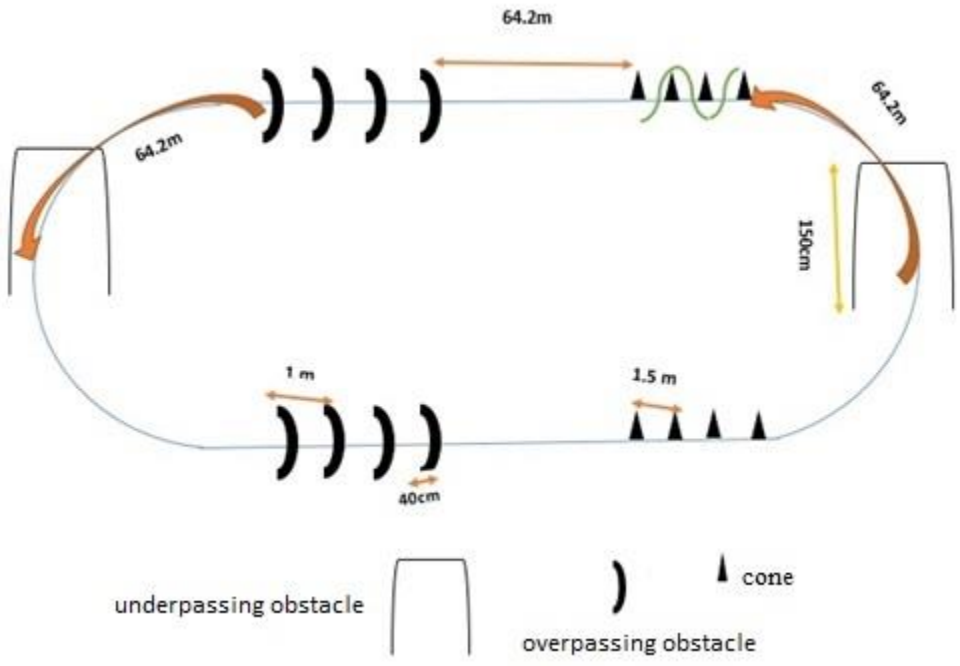

Figure 1. Enriched environment plan

Both sessions were performed 3 hours after the lunchtime at 15:00. To minimize the effect of diet on the dependent variables, participants were asked to replicate their diets for 24 hours before the start of each session. There was a two-week interval between the training sessions.

Blood Sampling and Analysis: Ten minutes before and after each training session, blood samples were collected from the median antecubital vein. Blood serum was separated by spinning the blood at 3000rpm for 15 minutes in a refrigerated centrifuge and stored at -80°c for later analyses. Serum BDNF, IGF-1, and VEGF concentrations were measured using ELISA kits (BDNF: sensitivity: 0.063 ng/ml, detection range: 0.325-20 ng/ml; IGF-1: sensitivity: 1.95 ng/ml, detection range: 7.80-500 ng/ml and VEGF: sensitivity: 0.063 ng/ml, detection range: 0.20-325 ng/ml, Cusabio, Japan). Each sample was measured in duplicate and the mean values were used in the subsequent analyses.

Statistical Analysis

Data were analysed using SPSS 24.0 (SPSS Inc, Chicago, IL) and the results are presented in mean and standard deviation (SD). Normality of the data was assessed with the Shapiro–Wilk test. A 2 (Time) x 2 (Group) mixed-model of repeated measures ANOVA test was conducted, since in this kind of experimental design, subjects were served as their own control and two different time points (pre and post-test) were assumed, while two groups (NET and EET) were compared. Also, the level of significance was set at 0.05 for all analyses.

RESULTS

Series of exercise by Group condition repeated measure ANOVA tests compared the effect of training and condition on dependent variables. There was a statistically significant exercise and condition interaction on BDNF, F (1, 11) = 43.71, $p < 0.001$, $\eta_P^2 = 0.799$; IGF-1, F (1, 11) = 83.58, $p < 0.001$, $\eta_P^2 = 0.884$; and VEGF F (1, 11) = 31.86, $p < 0.001$, $\eta_P^2 = 0.743$.

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The mean values of BDNF, IGF-1, and VEGF are illustrated in Table 1.

Table 1. Mean and SD of study variables in pre and post-time for normal and enriched environments.

	Normal			Enriched		
	Before 95% CI	After 95% CI	ES	Before 95% CI	After 95% CI	ES
BDNF (ng/ml)	8.33 ± 0.71 [7.87-8.78]	8.85 ± 0.71* [8.29-9.20]	0.59	8.39 ± 0.64 [7.98-8.79]	9.46 ± 0.71*¥ [9.01-9.91]	1.60
IGF-1 (ng/ml)	333.06 ± 45.81 [303.95-362.16]	338.82 ± 40.96* [312.79-364.84]	0.13	341.30 ± 37.95 [317.19-365.41	379 ± 31.96*¥ [359.25-399.86]	1.09
VEGF (ng/ml)	121.91 ± 25.97 [105.41-138.41]	131.41 ± 25.81* [115.01-147.80]	0.37	130.91 ± 28.48 [112.81-149.00]	168.03 ± 29.31*¥ [149.41-186.65]	1.28

* Significantly different from pre-intervention ($p \leq 0.001$).
¥s Significantly different from normal environment ($p \leq 0.001$).

DISCUSSION

The present study examined the effects of aerobic exercise in an enriched environment on the serum levels of neurotrophic factors, including BDNF, IGF-1, and VEGF. Within-group comparison results indicated that aerobic exercise could significantly elevate the levels of BDNF, IGF-1, and VEGF, compared to pre-exercise levels. Furthermore, a remarkable and valuable result of our study was that aerobic exercise in the enriched environment, compared to aerobic exercise in the normal environment, significantly raised the serum levels of BDNF, IGF-1, and VEGF.

Studies have reported that skeletal muscles produce BDNF in response to exercise (24), and as such BDNF can be considered a contraction-induced protein that contributes to the beneficial effects of exercise on neurons and synapses. Additionally, BDNF is among the most essential molecular mediators that have been studied in the context of complex and supported relationships between exercise and memory (42). Exercise improves the expression of this

protein and is critical for neuroplasticity (4). BDNF mediates the beneficial effects of exercise on cognition, mood, cardiovascular function, and metabolism (16). This study in line with extensive research in this regard, demonstrated an increase in the serum levels of BDNF following aerobic exercise, highlighting the important role of BDNF in mediating the beneficial effects of exercise on individuals. It has been suggested that BDNF can cross the BBB and seems to have beneficial effects on neurogenesis (20, 22).

Further, animal studies have reported that IGF-1 mediates exercise-induced angiogenesis, triggering an increase in the production of central VEGF and BDNF, which is necessary for exercise-induced neurogenesis (7, 21). Previous studies have suggested that exercise improves the temporal lobe functional connectivity through increased levels of growth factors (BDNF & IGF-1) and may be associated with elevated levels of VEGF (43). It has been documented that IGF-1 facilitates BDNF signaling in response to exercise (3). In addition, IGF-1 passes through the BBB and is superior to BDNF in this case. As a result, the IGF-1 concentration of peripheral and central blood flow may help facilitate the BDNF function in the hippocampus; this, in turn, can lead to neurogenesis of the hippocampus (6). Thus, measuring the blood flow IGF-1 to examine the effects of exercise on neurogenesis is more reasonable. Additionally, previous studies have reported that VEGF is necessary for the exercise-induced neurogenesis of the adult hippocampus (8), and VEGF values increase after exercise in adults (19, 43). Furthermore, exercise boosts the uptake of circulating IGF-1 by the brain (2, 39). In this regard, previous studies have indicated that aerobic exercise can elevate the serum levels of BDNF, IGF-1, and VEGF. Accordingly, increased levels of these neurotrophic factors may be related to the beneficial effects of exercise.

However, the effect of exercise training on serum BDNF levels is dose-dependent and they will quickly return to the baseline levels after the end of the exercise. Therefore, it is important to develop other methods that enhance the expression of neurotrophic factors in combination with exercise. Likewise, previous studies have revealed that in addition to exercise activities, environmental enrichment can also increase the expression of these proteins. Environmental enrichment enhances BDNF levels and improves the survival of new neurons in the hippocampus (33, 36). Environmental enrichment is associated with an increase in the number of dendritic branches, the development of synapses, and the improvement of cognitive function (25). Thus, it seems that combined exercise activity and cognitive stimuli can present synergistic effects on the cognitive function and brain health (28, 29). Accordingly, the current research results highlighted that, compared to the normal environment, when aerobic exercise was performed in an enriched environment, it could enhance the serum levels of BDNF, IGF-1, and VEGF more considerably.

The simultaneous use of exercise and environmental enrichment provide additional effects on neurogenesis over exercise alone (10). However, each has distinct effects and mechanisms (30). Environmental enrichment has been suggested to modulate the expression of BDNF in the hippocampus (33). Environmental enrichment in mice with BDNF knockout failed to produce hippocampal neurogenesis (33). It has been determined that exposure to enriched environments,

especially physical activity in an enriched environment, enhances the expression of VEGF in the hippocampus (31, 40). VEGF modifies the environmental enrichment effects on adult hippocampal neurogenesis. Unlike BDNF and VEGF, which increase in response to physical activity and environmental enrichment, increased expression of IGF-1 is attributed to physical activity rather than environmental enrichment (2, 3, 13). IGF-1 regulates exercise-induced angiogenesis (21), with an interaction effect with BDNF and has proven its role in exercise-induced neuroplasticity. Thus, each of these neurotrophic factors may play different roles following the exposure to environmental enrichment and exercise activity.

Nevertheless, there were some limitations in our study which may have affected the outcome. One limitation was the neurotrophic factors measurement in blood serum. Their levels in cerebrospinal fluid (CSF) would provide more precise data. Another limitation was the sample size; a larger sample size could have generated more generalizable results.

Overall, the present study showed that performing aerobic exercise in an enriched environment could greatly elevate the serum levels of neurotrophic factors, including BDNF, IGF-1, and VEGF, compared with exercise in a normal environment. This suggests that running in different environments has different effects on the serum levels of some neurotrophic factors.

ACKNOWLEDGEMENTS

We would like to thank all participants for their aid with this project.

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