Long term habitual exercise is associated with lower resting level of serum BDNF

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**Highlights**

- Association of basal level of BDNF with long lasting habitual exercise was studied.
- Serum BDNF level was lower in trained subjects than sedentary men.
- Aerobic and anaerobic exercise increased serum BDNF level.
- Memory performance was better in trained than sedentary.
- BDNF inversely correlated with VO2max.

**Abstract**

This experiment has been designed to evaluate the basal serum BDNF level and memory performance, and also the change in BDNF in response to acute aerobic and anaerobic training in athletes and sedentary groups. Nineteen middle aged elite athletes (45–65 years) who used to be competing at domestic championship for more than 10 years and 20 sedentary subjects participated in this study. Blood samples and cognitive function were assessed at rest and also after performing a single bout of acute aerobic and anaerobic exercise. Basal serum BDNF significantly was lower in the athletes group compared to the control one (475.18 ± 45.32, 1089.30 ± 94.92, P = 0.001). Serum BDNF was inversely correlated with VO2max (r = -0.5, P = 0.013), but positively with BMI (r = 0.2, p = 0.4). Pictures recall memory was better in the athlete group (9.25 ± 1.61) compared with the control ones (8 ± 1.15, p = 0.04). Basal platelets did not show any significant differences between athletes and controls (p > 0.05). Both acute aerobic and anaerobic activity elevated serum BDNF and platelets in athletes and sedentary groups compared with rest (P < 0.001). This study suggests that long-term habitual exercise is associated with lower peripheral BDNF and better intermediate memory, however acute form of intensive activity either aerobic or anaerobic are capable to elevate serum BDNF level in both sedentary and athletes.

1. Introduction

Increasing longevity multiplies the number of individuals with cognitive impairment. Considering the devastating effects of cognition deficit on the quality of life, maintaining brain health is an important public health goal. Exercise intervention could be one of the best non pharmacologic preventive tools from cognitive deficit.
Previous studies suggest that physical activity improve memory and attention [6,7,29], delays the decline in cognitive functions [15,17] and diminishes the risk of dementia [17]. Physical exercise has also shown to increase neurotrophins secretion [21], and more notably, brain derived neurotrophic factor (BDNF) [1,12,20].

Brain derived neurotrophic factor, is a member of the neurotrophins family which promote neuronal survival and synaptic plasticity [1]. It has been known that BDNF is mostly produced by the central nervous system (CNS) and also a range of peripheral tissues [9]. Since BDNF crosses the blood brain barrier [23], the peripheral levels of BDNF may represent a biomarker of mental health. For example its expression is reduced in several neurodegenerative diseases and depression [16]. On the other hand, it has been assumed that the beneficial effects of physical activity on brain function could be mediated by BDNF, however the existing literatures reflect wide controversies. For example, increase in BDNF level and memory performance after physical activity have been reported in some studies [4,10,27]. However an inverse relationship between physical activity and serum BDNF level has been reported too [8,14]. In addition to the inconsistency in the existing literatures, almost no study to our knowledge has specifically focused on the impact of long term training on cognitive health, and serum BDNF level in well-trained athletes. This experiment has been designed to evaluate the basal BDNF level and memory performance, also responsiveness of BDNF regulation system to acute aerobic and anaerobic training in athletes and sedentary groups.

2. Materials and methods

This study was designed in two parts: In Experiment 1 the basal serum BDNF level, platelets and memory performance were evaluated. Experiment 2 compared the changes in these parameters to a single bout of aerobic and anaerobic exercise.

2.1. Experiment 1

Twenty five elite athletes (age 45–65 years) who used to be compete at domestic soccer championship for more than 10 years and continued their regular training (3 times/week), after retirement, and 22 sedentary subjects without any regular physical activities were informed about the study. Then they were controlled for age and education level, and those who signed the consent document participated in the study. Exclusion criteria based on the clinical and physical examinations were cardiovascular, neurological, musculoskeletal disturbances, smoking, and alcohol drinking. The study was approved by the local ethics committee of Guilan University of Medical Sciences and performed according to the principles of the Declaration of Helsinki. Six athletes and two sedentary subjects left the study because of dyslipidemia, hypertension and mistake in performing the Rast test.

Cognitive function: Since working memory and attention are more affected than others with aging [24], we used picture recall memory tests for assessing the intermediate term memory. Subjects were shown 12 emotionally neutral pictures, and then 30 min after the last picture, they asked to recall the pictures. Score was the total number of remembered pictures. Subject was defined to have impaired intermediate memory if he was in the lowest quartile of the corresponding cognitive domain.

Blood sampling: Fasting blood samples were divided into two distinct falcon tubes: one pre-cooled tube for BDNF analysis (BD Vacutainer® SST II Advance), and the other for CBC. Blood was left to clot at room temperature and was centrifuged (12 min, 3000 rpm), and the resulting serum was decanted and stored at −80 °C until analysis. Serum BDNF was assayed in duplicate according to the manufacturer’s instructions (R&D BDNF ELISA kit, USA). The BDNF ELISA kit has a detection range from 7.8 to 500 pg/ml. The intra-assay and inter-assay variations were ±4.66% and ±9%, respectively.

Cardiorespiratory fitness was assessed as Vo2 max by a respiratory gas analysis in symptom-limited maximal maximal exercise stress test on the Astrand-rhynge treadmill ergometry.

2.2. Experiment 2

Nineteen athletes and 20 controls were randomly divided into two groups: aerobic exercise (Shuttle Run test, n = 10 athletes, n = 10 control) and anaerobic exercise (Rast test, n = 9 athletes, n = 10 control).

Shuttle Run involved continuous running between two lines 20 m apart in time to recorded beeps. For this reason subjects stand behind one of the lines and begin running with slow speed (8.5 km/h), but was increased by 0.5 km/h each minute. The subject continued running between the two lines, turning when signaled by the recorded beeps. After one minute, a sound indicated an increase in speed, and the beeps became closer together. This continued each minute. If the line was not reached in time for each beep, the subject must run to the line turn and try to catch up with the pace within two more beeps. The test was stopped if the subject failed to reach the line for two consecutive ends.

For Rast test, the subjects undertook six 35 m sprints after 10 min warm up with 10 s recovery between each sprint with maximum speed and power till exhaustion.

Blood sampling was done before and after exercise. Also intermediate-term memory function was evaluated according to the experiment 1.

Statistical analysis: Normality of data was checked using Kolmogorov–Smirnov Goodness of Fit test. The data were analyzed by correlated T-test and independent T-test and P<0.05 was considered statistically significant. Pearson correlation was used to assess correlations between parameters.

Table 1
Subjects characteristics and description of variables at baseline. Values are presented as mean ± SD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>GROUP</th>
<th>Athletes</th>
<th>Control</th>
<th>Sig level</th>
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<tr>
<td></td>
<td></td>
<td>Aerobic</td>
<td>Anaerobic</td>
<td>Aerobic</td>
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<td>Age (years)</td>
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<td>Weight (kg)</td>
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<td>Height (cm)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<td>27.04 ± 2.88</td>
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<tr>
<td>Education level</td>
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<td>12.80 ± 1.3</td>
<td>12.88 ± 2.02</td>
<td>12.60 ± 1.64</td>
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<tr>
<td>Vo2 max (ml/min)</td>
<td></td>
<td>45 ± 5.8</td>
<td>43 ± 4.4</td>
<td>32 ± 4.5</td>
</tr>
</tbody>
</table>

* Significant difference between athletes and control groups.
3. Results

The clinical characteristics of the participants are presented in Table 1.

Baseline characteristics of athletes and sedentary were similar ($P>0.05$) according to assignments, except BMI ($p=0.03$) and $V_{O2\text{max}}$ ($p=0.02$).

As Fig. 1 shows, serum BDNF unexpectedly was lower in the athletes group compared to the control one (475.18 ± 45.32, 1089.30 ± 94.92, $P=0.001$). However the athletes showed better intermediate memory (9.25 ± 1.61) compared with control ones (8 ± 1.15, $p=0.04$, Fig. 2).

There was significant inverse relationship between serum BDNF and $V_{O2\text{max}}$ ($r=-0.559$, $P=0.013$) (Fig. 3), and positive insignificant correlation with body mass index ($r=0.201$, $P=0.410$, Fig. 4). Serum BDNF level did not show significant correlation with platelet number ($r=-0.06$, $P=0.805$).

Results from the Experiment 2 showed that BDNF level was elevated after both anaerobic ($P=0.001$, Fig. 5) and aerobic activity ($P=0.04$, Fig. 6) compared with pre exercise values. Also platelets number increased 22% after anaerobic ($P=0.001$) and 12% after aerobic activity ($p=0.009$). Intermediate memory score of two exercise protocols did not show any significant difference compared to rest state ($P>0.05$).

![Graph 1](image1.png)

**Fig. 1.** Baseline serum brain-derived neurotrophic factor (BDNF) in athletes and controls. Significant difference was observed between two groups. ***$P<0.001$.

![Graph 2](image2.png)

**Fig. 2.** Intermediate-term memory score in athletes and controls. Significant difference was observed between two groups. *$P<0.05$.

![Graph 3](image3.png)

**Fig. 3.** Correlation (a solid line) between serum BDNF and $V_{O2\text{max}}$ ml/kg/min ($n=19$, $r=-0.559$, $p=0.013$) with a Pearson correlation. Significant correlation was observed between baseline BDNF and maximal oxygen consumption.

![Graph 4](image4.png)

**Fig. 4.** Results of correlation between basal serum BDNF and body mass index. A correlation (solid line) between serum BDNF and body mass index kg/m$^2$ ($n=19$, $r=0.201$, $p=0.410$) with a Pearson correlation. No significant correlation was found between baseline BDNF and body mass index.

4. Discussion

The present study showed a significant lower basal serum BDNF, but better picture recall memory test in athletes group. This finding is in agreement with other studies [8,14] showing lower resting levels of serum BDNF in subjects with long sporting activities. However the results of present study investigations are in contrast with
Zoladz et al. [29] and Correia et al. [6] reports indicating higher BDNF levels in athletes. Discrepancy in the results may be partly due to the duration and form of sport activities, or the age of participants. It should be noticed that in Zoladz et al. study [29], samples were not matched for mode or volume of training and they were young age from different sport events, i.e. sprinters, jumpers and distance runners. Correia and colleagues [6] did not consider sex effect on BDNF and their subjects were both female and male sprinters with 4 years activity engagement. Considering few studies about the relationship between BDNF and sporting activity, it should be mentioned that the long duration (at least 30 years) of sport engagement in one specific aerobic activity (soccer) is the strong point of the present study.

Interestingly, the athletes group showed better picture recall memory, which is in line with previous studies [12,24]. Reduced level of serum BDNF parallel with better cognitive performance in more physically active individuals might reflect a more efficient uptake mechanism of serum BDNF into the central nervous system and promoting neural plasticity. We cannot exclude the other possible mechanisms, distinct from BDNF that exercise might induce cognitive enhancement such as: increase in brain–blood flow [17], and brain volume [4,11].

It is not clear why lower resting level of serum BDNF has been found in more active individuals. Tang and colleagues [25] related the reduction in BDNF to the higher level of blood cortisol at rest in athletes. This assumption needs more investigation, because chronic stress is expected to impair memory [5], whereas our well-trained participants together with the previous studies [12,24] showed better intermediate memory. Whether reduction in serum BDNF reflects a kind of adaptation or down regulation of BDNF synthesis or releasing mechanisms [22], or more consumption by CNS needs more investigation. The findings that both forms of acute intense activity increased BDNF in athletes and controls suggest that not only the system of BDNF release keep enough sensitivity to elevate whenever encounter to the different forms of physical training, but also less likely is inhibited by glucocorticoids induced by exercise. It is more likely that the novelty of the sport activity, independently of the nature of exercise is important for inducing BDNF cascade. Because aerobic metabolism, coordination, speed, reaction time and power which were more relevant to Shuttle Run test than Rast, did not significantly influence on BDNF enhancement in our experiment.

The source and mechanisms of BDNF release after exercise have not been understood yet. Recently an interesting study carried out by Wann and colleague reported that a protein FNDCS5 is released during exercise from skeletal muscle induces BDNF from the hippocampus [26]. Platelets as a peripheral source of BDNF storage could elevate serum levels of this protein following aggregation [18,28]. In our study, platelets numbers were increased after aerobic and anaerobic exercises, however anaerobic caused more elevation, which is in line with Husmi et al. study [13]. Lack of correlation between BDNF and platelets indicates that serum BDNF is not influenced by BDNF stored in these cells.

Our finding of an inverse correlation between BDNF and VO2max confirms previous studies [3,16,21] indicating that BDNF can be affected by cardiovascular fitness.

On the other hand, positive relationship between BDNF and BMI which has been reported before [2,16,19] reflects compensatory metabotropic role for peripheral BDNF rather than a neurotrophic one. For future studies we suggest to measure CNS and peripheral BDNF changes in athletes and sedentary individuals.

Taken together, professional athletes with long sporting activity having low BMI, better cardiovascular fitness showed lower peripheral BDNF, but better intermediate memory compared with sedentary counterparts.

**References**


