Different circulating brain-derived neurotrophic factor responses to acute exercise between physically active and sedentary subjects

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Running Head: Circulating BDNF and acute exercise

Abstract

Although circulating brain-derived neurotrophic factor (BDNF) level is affected by both acute and chronic physical activity, the interaction of acute and chronic physical activity was still unclear. In this study, we compared the serum and plasma BDNF responses to maximal and submaximal acute exercises between physically active and sedentary subjects. Eight active and 8 sedentary female subjects participated in the present study. Both groups performed 3 exercise tests with different intensities, i.e. 100% (maximal), 60% (moderate) and 40% (low) of their peak oxygen uptake. In each exercise test, blood samples were taken at the baseline and immediately, 30 and 60 min after the test. The serum BDNF concentration was found to significantly increase immediately after maximal and moderate exercise tests in both groups. In maximal exercise test, the pattern of change in the serum BDNF concentration was different between the groups. While the serum BDNF level for the sedentary group returned to the baseline level during the recovery phase, the BDNF levels for the active group decreased below the baseline level after the maximal exercise test. No group differences were observed in the pattern of plasma BDNF change for all exercise tests. These findings suggest that regular exercise facilitates the utilization of circulating BDNF during and/or after acute exercise with maximal intensity.

Key words: Serum BDNF, plasma BDNF, acute exercise.

Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors. In addition to its neurotrophic and synaptotrophic actions, such as the promotion of growth and survival of neurons (Aloe and Calza, 2004; Thoenen, 1995) and learning and memory (Ma et al., 1998), BDNF may play important metabotrophic roles such as the regulation of food intake (Xu et al., 2003), glucose and lipid metabolism, and energy homeostasis (Chaldakov, 2011; Nakagawa et al., 2000; Noble et al., 2011; Tsuchida et al., 2002). BDNF is present in the nervous system and peripheral tissues, and is also found in blood (Fujimura et al., 2002; Radka et al., 1996; Rosenfeld et al., 1995). Chronic treatment with subcutaneous BDNF administration significantly decreased food intake and improved the glucose uptake in skeletal muscle (Yamanaka et al., 2007) in diabetic mice, and increased glucose transporter 4 expression in normal mice (Suwa et al., 2010). In humans, the level of circulating BDNF is associated with depression (Duman, 2004), Alzheimer's

disease (Tapia-Arancibia et al., 2008), obesity (Suwa et al., 2006), glucose and lipid metabolism (Levinger et al., 2008; Suwa et al., 2006), type 2 diabetes mellitus (Suwa et al., 2006) and metabolic syndrome (Chaldakov et al., 2004). Although it has been generally accepted that the neurotrophins act by paracrine or autocrine mechanisms (Davies, 1996), evidence also indicates that circulating BDNF may exert endocrine action to reveal or execute physiologic functioning.

BDNF is present in human serum and plasma, and is much more concentrated in the serum (Radka et al., 1996). Because more than 90% of blood BDNF is stored in the platelets and is released during the clotting process (Fujimura et al., 2002), serum BDNF seems to reflect both the platelet-stored BDNF and the freely-circulating BDNF in the blood, while plasma BDNF seems to reflect only the freely-circulating *BDNF* (Lommatzsch et al., 2005).

Regular exercise is well known to have many health benefits, including the prevention and improvement of obesity (Wing and Hill, 2001), type 2 diabetes mellitus (Orozco et al., 2008) and Alzheimer's disease (Heyn et al., 2004). Several animal studies have shown that mRNA[BDNF] and BDNF protein levels increase with acute and chronic voluntary wheel running in the hippocampus (Neeper et al., 1996; Gomez-Pinilla et al., 2011), and improved learning and memory (Vaynman et al., 2004). In addition, the mRNA[BDNF] and BDNF protein expression levels in skeletal muscle have been shown to be enhanced in response to muscle contraction, which is associated with enhanced lipid oxidation (Matthews et al., 2009). Collectively, these results raise the possibility that BDNF mediates, at least in part, the adaptation to exercise.

There have been several studies examining circulating BDNF responses to acute endurance exercise (Ferris et al., 2007; Gold et al., 2003; Gustafsson et al., 2009; Matthews et al., 2009; Rasmussen et al., 2009; Rojas Vega et al., 2006; Zoladz et al., 2008). In the majority of these studies, serum (Ferris et al., 2007; Gold et al., 2003; Matthews et al., 2009; Rojas Vega et al., 2006) and plasma (Gustafsson et al., 2009; Rasmussen et al., 2009) BDNF levels increased following acute exercise. On the other hand, we (Nofuji et al., 2008) and Chan et al. (2008) showed that regular physical activity affected the resting serum BDNF level. Therefore, it appears that the circulating BDNF level is affected by both acute and chronic

physical activity. However, the interaction of acute and chronic physical activity was still unclear.

Therefore, the aim of this study was to clarify the effect of chronic physical activity on the circulating BDNF responses to acute exercise. In the present study, we simultaneously measured the serum and plasma BDNF concentrations before and after three exercise tests with different intensities for the physically active and sedentary subjects.

Methods

Subjects

Eight physically active and 8 sedentary female Japanese subjects participated in this study. "Active" was defined as performing regular sports activities more than 3 times per week for more than 3 years. The active group included distance runners (n = 3), basketball players (n = 3), and badminton players (n = 2). The sedentary subjects had not performed any regular exercise for at least 1 year. All participants were non-smokers, free from any diseases, and not taking any medications. This study was conducted in accordance with the Declaration of Helsinki, and approved by the ethics committee of the Institute of Health Science, Kyushu University, Fukuoka, Japan. Written informed consent was obtained from all participants prior to their participation.

Exercise tests

All subjects performed 3 different exercise tests in 3 separate days. At Day1, they performed the graded exercise test (maximal) to determine their volume of peak oxygen uptake (VO_2peak). After 15 min of seated rest, the subjects started pedaling at 0 W (for the sedentary group) or 30 W (for the active group). The workload was increased by 30 W in every 4 min until a 4.0 mmol·L^{-1} of blood lactate level was obtained. After that, the workload was increased by 15 W in every 1 min until exhaustion. "The blood for measuring the lactate concentration was obtained from an ear lobe and blood lactate level was measured using the Lactate Pro instrument (Lactate Pro LT-1710, ARKRAY, Kyoto, Japan) in every 3 min and immediately after exercise test." The heart rate (HR) was monitored using an electrocardiogram telemetry system (DS-3140, Fukuda Denshi, Tokyo, Japan). The VO_2 peak was defined as the highest VO_2 obtained during a maximal exercise test.

Two submaximal exercise tests were conducted at Day2 or 3 in random order. Trials consisted of a 30-min cycle ergometry (Monark 828E) at a constant load of 60% (moderate) or 40% (low) of the subject's VO_2peak, preceded by a 15 min of seated rest. The HR and VO_2 were recorded during each exercise test.

The subjects were instructed to refrain from heavy exercise the day before each exercise test. All exercise tests were conducted at 9:00-10:30 to diminish the effect of circadian changes in circulating BDNF levels (Piccinni et al., 2008).

Physical activity level

The daily physical activity level was evaluated with an accelerometer (Lifecorder, Suzuken Co., Nagoya, Japan).

This device comprises an acceleration sensor, an amplifier, a microprocessor and memory, and was employed to ensure different physical activity levels between the two groups. All participants attached the accelerometer for 1 week just before the Day1.

Anthropometric measurements

Anthropometric measurements were conducted at Day1. The percentage of body fat was measured by bioelectrical impedance analysis device (Tanita, Tokyo, Japan).

Blood collection and biochemical analysis

In each exercise test, blood samples were taken from an antecubital vein in a sitting position at the baseline time, and immediately, 30 min and 60 min after the exercise. The blood samples were drawn into additive-free containers (serum) or heparinized containers (plasma). After kept at room temperature for 1 hour, the serum samples were centrifuged at 2000 × g for 10 min at 4°C. Plasma samples were immediately centrifuged. Supernatants were stored at -80°C until the analyses were performed. The serum and plasma BDNF concentrations were measured using an enzyme-linked immunoassay (ELISA) kit (Promega, Madison, WI).

Statistical analysis

The anthropometric measurements and physiological responses to maximal exercise tests between the active and sedentary groups were compared using Student's unpaired t-test. The comparisons of physical responses during moderate and low exercise tests in each group and serum BDNF level at rest between the groups were performed using the paired t-test. The changes in BDNF responses were assessed by two-way (4 time point × 2 groups) repeated measures analysis of variance (ANOVA). If an interaction was significant, one-way ANOVA was performed. A Dunnett's test was employed for all post-hoc tests. The alpha-level was set at 0.05.

Results

Characteristics of the subjects

The subject characteristics are summarized in Table 1. There were no significant differences in any anthropometric variables between the two groups. The daily physical activity level was significantly higher in the active group compared to the sedentary group (p < 0.05).

Table 1. Characteristics of the subjects. The data are expressed as the means (± SD).

	Sedentary	Active
Age (years)	22.8 (1.9)	21.6 (3.0)
Height (m)	1.59 (.06)	162.9 (6.8)
Weight (kg)	50.8 (6.7)	54.5 (7.5)
Body mass index (kg·m^{-2})	20.0 (2.0)	20.5 (1.9)
Body fat (%)	23.6 (5.9)	21.8 (2.0)
Total energy expenditure (kJ·day^{-1})	7451 (793)	8749 (842)**
Moving-related energy expenditure (kJ·day^{-1})	1115 (379)	1970 (640)**
Step count (steps·day^{-1})	10890 (2950)	14961 (4188)*

* p < 0.05, ** p < 0.01

Table 2. Physical parameters at the end of the low and moderate exercise tests. The data are expressed as the means (± SD).

	Low exercise		Moderate exercise	
	Sedentary	**Active**	**Sedentary**	**Active**
VO_2 (ml·kg^{-1}·min^{-1})	10.8 (2.6)*	14.7 (2.4)*	20.0 (4.4)	22.9 (2.7)
%VO_2 (%)	30.8 (5.6)*	35.2 (8.0)*	58.4 (8.9)	54.8 (5.1)
Heart rate (bpm)	99 (12)*	100 (13)*	141 (16)	130 (14)
Workload (W)	39 (11)*	66 (8)*	77 (16)	107 (12)

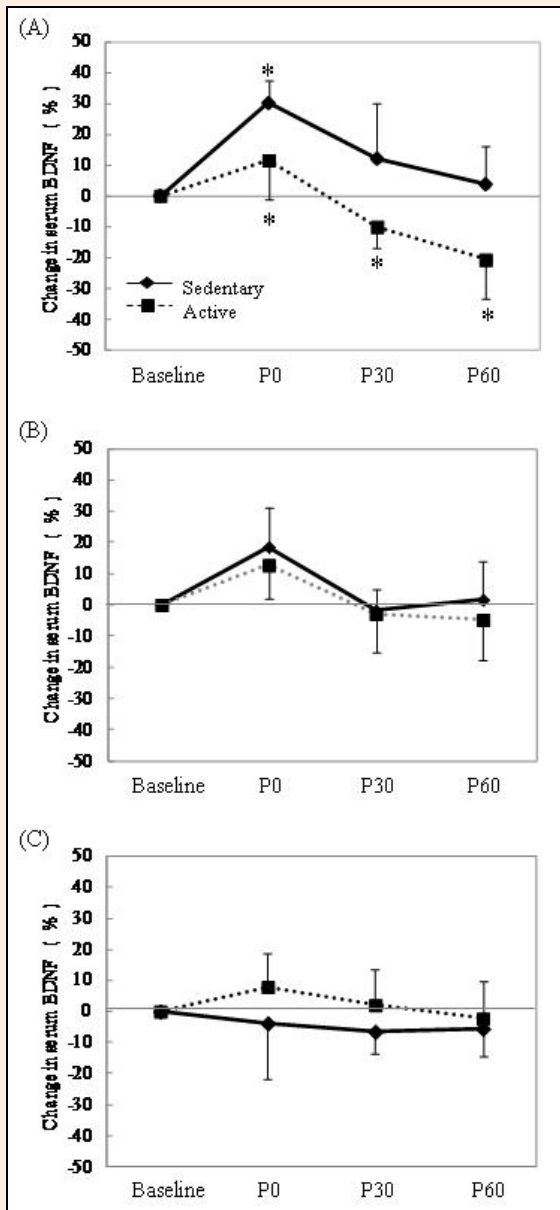* Significantly different from the moderate exercise (p < 0.05)

Figure1. Level of serum BDNF concentrations before maximal (A), moderate (B), or low (C) exercise tests (baseline), immediately after (P0), 30 min after (P30), and 60 min after (P60) the exercise session. The data are expressed as the means ± SD. * p < 0.05 vs. baseline. The changes in BDNF responses for the groups were assessed by two-way repeated ANOVA. As an interaction and main effect of time were significant, one-way ANOVA followed by a Dunnett's post-hoc test was performed.

Physical parameters in the exercise test

The VO_2peak and workload at the end of maximal exercise in the active group (42.3 ± 4.5 ml·kg^{-1}·min^{-1}, 199 ± 16 W, respectively) was significantly higher than that in the sedentary group (34.7 ± 4.0 ml·kg^{-1}·min^{-1}, 147 ± 16 W, respectively, < 0.01). There were no significant differences in the HR (Sedentary 183 ± 5 bpm, Active 179 ± 12 bpm, p = 0.45) and blood lactate level (Sedentary 9.6 ± 0.8 mmol·L^{-1}, Active 8.6 ± 1.4 mmol·L^{-1}, p = 0.14) between the groups at the end of the maximal exercise test. Table 2 shows the physical parameters for two submaximal exercise tests. All parameters were significantly higher at the moderate exercise test than at the low exercise test. There was no group difference in the average BDNF level at rest (Sedentary; 11.9 ng·ml^{-1}, Active; 12.5 ng·ml^{-1}, p = 0.49).

Change in the serum BDNF concentration

For the maximal exercise test, a two-way ANOVA for repeated measures on serum BDNF levels revealed significant interactions of the factors (F(3, 42) =7 .01, p < 0.01). A subsequent one-way ANOVA for repeated measures revealed a significant effect of time (F(3, 45) = 24.8, p < 0.01). The serum BDNF concentrations significantly increased immediately after the maximal exercise test in both groups (Sedentary; +30% p < 0.01, Active; +11% p < 0.01 vs. baseline, Figure 1A). While BDNF levels in the sedentary group returned to the baseline level during the recovery phase (30 min; +12% p = 0.06, 60 min; +4% p = 0.80, Figure 1A), the BDNF levels in the active group decreased below the baseline level (30 min; -15% p < 0.01, 60 min; -25% p < 0.01 vs. baseline, Figure 1A).

For the moderate exercise, neither interactions (F(3, 42) = 0.68, p = 0.57) nor the effect of groups (F(1, 14) = 0.86, p = 0.37) on the BDNF response was observed, although the effect of time was significant (F(3, 42)=18.7, p < 0.01). The serum BDNF concentrations in both groups increased immediately after the exercise tests (+16%, p < 0.01 vs. baseline, Figure 1B) and returned to the baseline level during the recovery phase (30 min; -2% p = 0.84, 60 min; -2% p = 0.94 vs. baseline, Figure 1B).

The low exercise did not affect the BDNF concentration in either group (time × group; F(3, 42) = 1.19, p = 0.33, time; F(3, 42) = 1.17 p = 0.33, group; F(1, 14) = 4.06 p = 0.06, Figure 1C).

Change in the plasma BDNF concentration

For the maximal and moderate exercise test, interactions (F(3, 42) = 1.85, p = 0.15, F(3, 42) = 1.19, p = 0.33, respectively) nor the effect of groups (F(1, 14) = 1.40, p = 0.26, F(1, 14) = 0.67, p = 0.43, respectively) on the plasma BDNF response were detected. Although the effect of time were significant (F(3, 42) = 4.24, p = 0.01, F(3, 42) = 5.40, p < 0.01, respectively), a subsequent Dunnett's post-hoc test showed no significant difference in plasma BDNF between baseline and each time point

(maximal; 0min +33% p = 0.10, 30min +10% p = 0.87, 60min -9% p = 0.89 vs. baseline, Figure 2A, moderate; 0min +11% p = 0.58, 30min -11% p = 0.59, 60min -19% p = 0.17 vs. baseline, Figure 2B).

No interaction ($F_{(3, 42)}$ = 0.65, p = 0.59) or main effects (time; $F_{(3, 42)}$ = 0.77, p = 0.52, group; $F_{(1, 14)}$ = 0.03, p = 0.86, Figure 2C) were found in the low exercise.
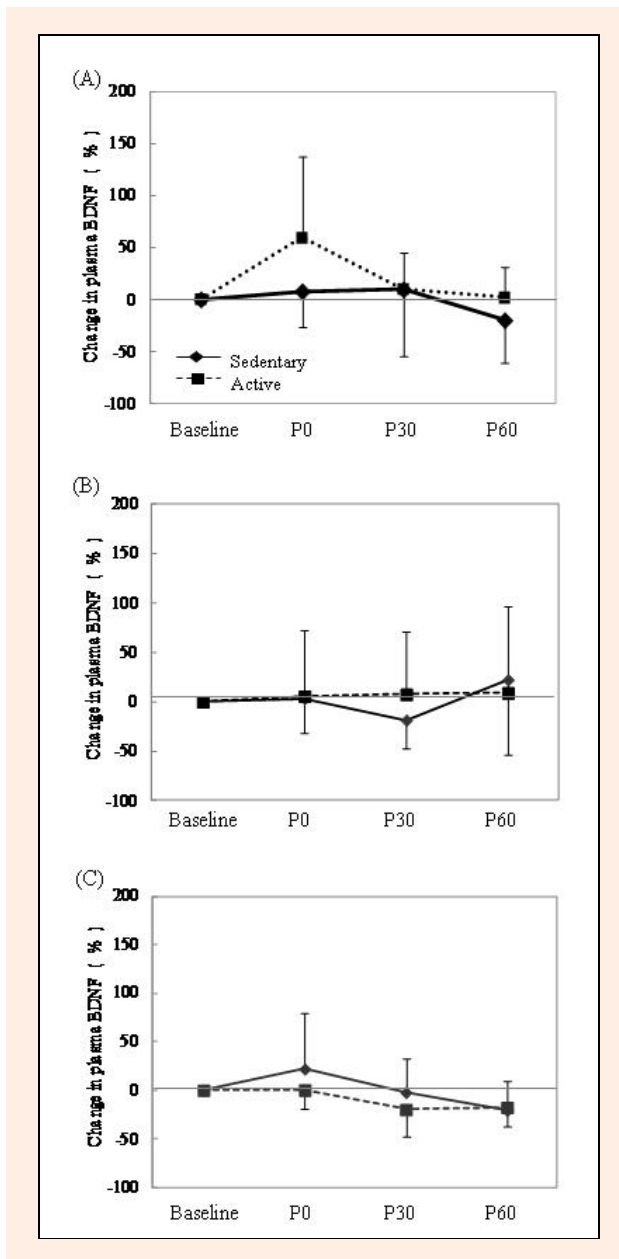

Figure 2. Level of plasma BDNF concentrations before maximal (A), moderate (B), or low (C) exercise tests (baseline), immediately after (P0), 30 min after (P30), and 60 min after (P60) the exercise session. The data are expressed as the means ± SD.

Discussion

We investigated the differences in the serum and plasma BDNF responses to acute maximal and submaximal exercises between the active and sedentary subjects. One of the novel findings of the present study was that the serum BDNF responses to maximal exercise were different be-

tween active and sedentary subjects. Especially, serum BDNF levels in the active group decreased below the baseline level during the recovery phase, while it was not the case in the sedentary group. A possible mechanism for this excessive reduction of serum BDNF in the active group is an enhanced utilization mediated by the upregulation of BDNF TrkB (tyrosine protein kinase) receptor in the peripheral tissues. Previous studies demonstrated that physical training increased the expression of TrkB in the spinal cord (Skup et al., 2000), brain (Widenfalk et al., 1999) and soleus muscle (Gómez-Pinilla et al., 2002) in rats. Although the physiological significance of the decreases in BDNF after exercise remains unknown, one of the possible roles of BDNF utilization is the repair of exercise-induced muscle damage. Ninety percent of circulating BDNF is stored in the platelets, where are also epidermal growth factor (EGF) (Oka and Orth, 1983), vascular endothelial growth factor (VEGF) (Tischer et al., 1989), and platelet-derived growth factor (PDGF) (Antoniades et al. 1979), all of which play a role in wound healing. In the current and previous studies (Ferris et al., 2007; Rojas Vega et al., 2006), serum BDNF increased with moderate- to high-intensity exercise, which has been shown to induce muscle damage (Kuipers, 1994). Therefore, it is possible that the increased BDNF during exercise contributes to the repair of skeletal muscle damaged. Although there are no direct reports demonstrating that circulating BDNF acts in the repair of exercise-induced muscle damage, BDNF treatment suppressed the release of creatine kinase and prostaglandin E2, which are common indicators of muscle cell damage in the rat muscle exposed to oxidative stress *in vivo* (Lian et al., 1998). Furthermore, the delayed regeneration of muscle fibers after injury was observed in muscle-specific BDNF knockout mice, suggesting that BDNF plays an important role in the regeneration of muscle fibers (Clow and Jasmin, 2010). Based on the potential wound-healing functions of BDNF, it is proposed that the utilization of serum BDNF during exercise may help muscle regeneration following exercise-induced damage and that the active group may have adapted to utilize circulating BDNF for the promotion of muscle repair.

Conclusion

In conclusion, the circulating BDNF responses to acute maximal exercise were different between active and sedentary groups. While serum BDNF levels in the sedentary group returned to the baseline level during the recovery phase, the BDNF levels in the active group decreased below the baseline level after high-intensity exercise. These results raise the possibility that regular exercise facilitates the utilization of circulating BDNF after acute exercise with maximal intensity. Limitations of this study were the small sample size. Additional studies with large sample size are called for. Likewise, further studies should clarify the mechanisms and physiological significance of the exercise-induced responses to circulating BDNF.

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Key points

- In maximal exercise test, the pattern of change in the serum BDNF concentration was different between the groups.
- While the serum BDNF level for the sedentary group returned to the baseline level during the recovery phase, the BDNF levels for the active group decreased below the baseline level after the maximal exercise test.
- No group differences were observed in the pattern of serum BDNF change for moderate or low exercise tests.
- No group differences were observed in the pattern of plasma BDNF change for all exercise tests.

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