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Changes in serum BDNF levels associated with moderate-intensity exercise in healthy young Japanese men

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Abstract

Purpose: The purpose of this study was to examine the influence of acute moderate-intensity exercise on serum brain-derived neurotrophic factor (BDNF) levels in healthy young Japanese men. BDNF is one of a family of neurotrophic factors involved in neuronal transmission, modulation and plasticity. Previous human-based studies have demonstrated that acute exercise leads to increases in BDNF; however, to date there has been no study conducted among Japanese male subjects.

Methods: Forty young adult Japanese men (aged 24.1 ± 2.9 years) – reduced to a total of thirty three following subjection to exclusion criteria – performed 30 minutes of exercise at 60% of VO_{2max} on a stationary bicycle. Serum BDNF was analyzed both before and after exercise.

Results: Eighteen of the total thirty three subjects demonstrated an increase in serum BDNF after exercise. However, on aggregate, the change in serum BDNF associated with exercise was not significant ($p = .17$).

Conclusions: This is the first study to demonstrate that serum BDNF levels are not consistently increased by acute moderate-intensity exercise in Japanese men. It is likely that something in the lifestyle and/or environment of male Japanese subjects underlies the difference between our findings and studies conducted in other countries.

Keywords: Brain-derived neurotrophic factor; Japanese; Human; Physical activity; Aerobic exercise

Background

Approximately 35.6 million people worldwide were living with dementia in 2010, with the prevalence expected to increase to 65.7 million in 2030 and 115.4 million in 2050 (Prince et al. 2013). Japan is considered to be one of the most rapidly aging nations in the world. It is estimated that the number of Japanese people with dementia will increase from 1.56 million in 2000 to over 3 million by 2025 (Cabinet Office, Government of Japan 2012).

Numerous studies suggest that regular physical activity could reduce the incidence of cognitive impairment and dementia in older people at risk for these disorders. For example, Laurin et al. (2001) demonstrated significantly lower odds of developing cognitive impairment and Alzheimer's disease (AD) in subjects with higher levels of

physical activity suggesting that regular physical activity could represent an important and potent protective factor against cognitive decline and dementia in elderly persons. A recent meta-analysis of 29 studies involving aerobic exercise interventions reported modest but significant improvements in attention and processing speed, executive function and memory in exercise-trained subjects (Smith et al. 2010). Also, both cross-sectional (Erickson et al. 2009) and prospective (Erickson et al. 2011) human investigations suggest that higher aerobic fitness level is associated with larger hippocampal volume and improved neuronal health. These reports further suggest that the improvements in cognitive function associated with aerobic activity may be mediated by neurophysiological and structural changes in the brain (Erickson et al. 2009); however, the physiological mechanisms underlying these effects remain unclear.

One possible mechanism involves changes in brain derived neurotrophic factor (BDNF) levels associated with aerobic exercise. This relationship was first observed in

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animal studies which demonstrated that physical activity increases the expression of BDNF in the rat brain (Neeper et al. 1995). Since this discovery, a number of studies have sought to establish the link between the neurotrophin BDNF and post-exercise enhancement of mood and cognitive functions in humans (Zoladz and Pilc 2010). BDNF is an important molecular mediator of structural and functional plasticity in the brain and plays many important roles in nervous system function, including neuroplasticity, neuronal growth, repair and differentiation. Altered BDNF levels have been described in several neurological and psychiatric disorders including AD (Schindowski et al. 2008), Huntington's disease (Ciammola et al. 2007), major depression (Laske et al. 2007) and schizophrenia (Reis et al. 2008). Furthermore, higher BDNF serum levels are associated with a slower rate of cognitive decline in AD patients (Laske et al. 2011).

Several studies in human subjects have demonstrated that acute aerobic exercise induced increased BDNF in peripheral blood (Nofuji et al. 2012; Schmolesky et al. 2013; Gustafsson et al. 2009; Rasmussen et al. 2009; Ferris et al. 2007; Gold et al. 2003; Rojas Vega et al. 2006; Tang et al. 2008). The acute effect of exercise on human serum BDNF levels is characterized as a transient, moderate (approximately 20 to 40%) increase (Gold et al. 2003; Rojas Vega et al. 2006; Tang et al. 2008). Serum BDNF levels rise during aerobic exercise, and quickly return to baseline levels upon exercise cessation, approximately 10–15 minutes after exercise termination (Rojas Vega et al. 2006; Tang et al. 2008). Ferris et al. (2007) suggested that low intensity exercise was insufficient to elevate BDNF levels relative to baseline, while high intensity exercise for a comparable duration significantly elevated serum BDNF levels.

While many studies in this field have been done in Western subject, there was a single study in Japanese subject (Nofuji et al. 2012). Nofuji et al. (2012) demonstrated an effect of acute aerobic exercise on peripheral blood BDNF levels in Japanese women. However, there has been no study to date that has investigated the effects of acute aerobic exercise on peripheral blood BDNF levels in Japanese men. Therefore, the aim of this study was to clarify the effect of acute physical activity on the circulating BDNF responses in Japanese men. In the present study, we measured the serum BDNF concentrations before and after aerobic exercise healthy young Japanese men subjects.

Results

GXT

The mean peak values of work rate (190.43 ± 29.06 W), VO_{2max} (37.19 ± 6.47 mL/min/kg), HR (173.73 ± 13.45 bpm), RER (1.29 ± 0.14), and Borg Scale (17.85 ± 1.78), during graded exercise test are presented in Table 1. These data are consistent with the ACSM criteria for estimating VO_{2max} .

Table 1 Physiological maximal values during graded exercise test (GXT)

	Peak value
VO_{2max} (mL/min/kg)	37.2 (6.5)
Work rate (W)	190.4 (29.1)
HR (bpm)	173.7 (13.5)
RER	1.29 (0.14)
Borg Scale	17.9 (1.8)

Values shown are means (\pm SD). [N = 40].

VO_{2max} maximal oxygen consumption, HR heart rate, RER respiratory exchange ratio.

Endurance ride measures

On the basis of the exclusion criteria, 7 subjects were excluded from the analysis (2 subjects with an over-load and 5 subjects with an under-load). An analysis was performed on 33 remaining subjects. The average of the physiological values collected during exercise (3 minutes rest, 3 minutes warm-up, and each 5 minutes average during 30 minutes of endurance ride) are shown in Table 2. These results suggest that exercise intensity was maintained at a moderate level during the endurance ride.

Serum BDNF responses

Basal BDNF values, post-exercise BDNF values, pre-post change in serum BDNF (Δ BDNF) and pre-post percentage change in serum BDNF ($\% \Delta$ BDNF) are presented in Table 3. 18 of 33 subjects demonstrated increased serum BDNF after exercise compared with their personal baseline. However, on average for the entire group, post-exercise serum BDNF values did not increase relative to the baseline average ($p = 0.168$). There is a positive correlation between basal BDNF value and post-exercise BDNF value ($r = .475$, $p < 0.01$). There are no significant differences between the group with increased BDNF and the one with decreased BDNF in baseline values (Table 4). Equally, there are no significant correlations between exercise-induced BDNF change and basal baseline values (Table 5).

Discussion

This is the first study to examine changes in serum BDNF levels associated with a single bout of aerobic exercise in healthy young Japanese men. Based upon previous research in non-Japanese populations, we hypothesized that moderate aerobic exercise would lead to significantly increased serum BDNF levels in Japanese male subjects. However, serum BDNF increase due to exercise was evident in only half of the subjects, and group mean values of serum BDNF were not significantly increased by exercise compared with the pre-exercise group mean. The study found that serum BDNF did not increase consistently in healthy young Japanese men exposed to 30 minutes of moderate exercise.

Table 2 Change physiological values during the endurance rides

	Rest	Warm-up	Ex1-5	Ex6-10	Ex11-15	Ex16-20	Ex21-25	Ex26-30
VO ₂ (mL/min/kg)	7.1 (2.4)	12.9 (2.1)	18.3 (2.7)	21.4 (3.2)	21.8 (3.5)	21.8 (3.5)	21.8 (3.6)	21.8 (3.5)
%VO ₂ max (%)	20.4 (7.0)	36.0 (4.9)	51.3 (6.0)	59.5 (4.1)	60.6 (3.5)	60.5 (3.5)	60.4 (3.2)	60.4 (3.4)
W/kg	-	0.99 (0.17)	1.4 (0.21)	1.53 (0.27)	1.51 (0.28)	1.47 (0.29)	1.45 (0.28)	1.43 (0.27)
HR (bpm)	75.4 (11.3)	111.0 (12.3)	132.7 (15.1)	145.9 (13.8)	151.5 (14.1)	154.2 (13.4)	156.1 (13.8)	157.8 (12.8)
%HRR (%) ^a	-	32.3 (8.2)	52.1 (11.4)	64.0 (10.9)	69.1 (11.5)	71.6 (10.8)	73.3 (11.1)	74.8 (10.3)
RER	0.8 (0.07)	0.88 (0.08)	1.06 (0.11)	1.05 (0.1)	1.03 (0.11)	1.01 (0.11)	1.0 (0.09)	0.99 (0.09)
Borg scale	-	8.1 (1.8)	11.4 (2.5)	13.2 (2.2)	14.1 (2.1)	14.8 (2.1)	15.2 (2.0)	15.5 (2.2)

Values shown are means (±SD). [N = 33].
 VO₂ oxygen consumption, VO₂max maximal oxygen consumption, HR heart rate, HRR heart rate reserve, RER respiratory exchange ratio.
^a(HR - rest HR)/(220 - age - rest HR) *100.

Several studies on non-Japanese populations have demonstrated that brief periods of moderate aerobic exercise are associated with transient increases of serum BDNF concentrations (Goekint et al. 2008; Gold et al. 2003; Gustafsson et al. 2009); however, a study by Castellano and White (2008) suggested a negative relationship between moderate aerobic exercise and serum BDNF. Nofuji et al. (2012) reported that healthy young Japanese women subjects did not display increased serum BDNF levels after moderate exercise. The results of the present study prove that healthy young Japanese male subjects did not exhibit increased serum BDNF levels. Moderate aerobic exercise therefore does not seem to affect serum BDNF levels in healthy young Japanese populations as a whole.

Basal BDNF values from other studies have been reported as 24.95 ± 7.28 ng/ml (Schmolesky et al. 2013) and 22.94 ± 9.12 ng/mL (Cho et al. 2012) in healthy young men. Nofuji et al. (2008) demonstrated basal BDNF levels of 23.63 ± 2.94 ng/ml in sedentary young Japanese men. Among participants in this study, baseline BDNF was 14.9 ± 5.0 ng/ml. Although slightly lower than the values reported in prior studies, this level can be considered to be within the normal range (1.5 to 30.9 ng/mL) for basal BDNF in healthy subjects (Knaepen et al. 2010).

One factor that might be associated with our findings is the possible effect of stress hormones. Schmolesky et al. (2013) showed that BDNF levels may actually decrease in sedentary control subjects (by approximately 13% on average), and suggested this may be due to stress related to the laboratory environment and/or blood collection. Thus, it

Table 3 BDNF values and change

	Mean (SD)	Max value	Minimal value
Basal BDNF	14.9 (5.0)	26.1	3.2
Post-exercise BDNF	15.9 (5.6)	25.7	4.8
ΔBDNF ^a	1.0 (4.2)	10.57	-6
%ΔBDNF ^b	15 (59.9)	295.3	-45.6

[N = 33].

^apost BDNF value - basal BDNF value.

^b(post BDNF value - basal BDNF value)/basal BDNF value.

is possible that an exercise induced increase in BDNF may be offset by a stress-induced decrease associated with the blood collection process. Other studies have shown that elevated stress, exogenous cortisol application, or glucocorticoid receptor agonism can lead to reduced BDNF levels (Pluchino et al. 2013). If stress levels are particularly high or individual stress reactions are particularly strong, they could obscure the impact of exercise on the BDNF level.

One other possible explanation for our findings is the effect of human BDNF gene polymorphism (Val66Met), which is more common among Japanese individuals than those of Western heritage. Shimizu et al. (2004) showed that there are significant differences between individuals from Japan (50.3%), Italy (43.2%) and the USA (27.1%) in genotype frequencies of BDNF 196G/A (Val66Met) polymorphism, with the prevalence being significantly higher in the Japanese population (p < 0.0001). Val66Met is known to impair intracellular trafficking and neuronal activity-dependent secretion of BDNF (Egan et al. 2003). It is thought that Val66Met polymorphism carriers demonstrate lower BDNF production during exercise compared with

Table 4 Results of t-test on basal values by group

	Increased BDNF group [N = 18]	Decreased BDNF group [N = 15]	p value
Basal BDNF (ng/ml)	14.2 (4.7)	15.8 (5.4)	0.40
Age (years)	23.2 (1.7)	24.8 (3.1)	0.11
Height (cm)	171.5 (6.4)	168.5 (7.8)	0.25
Weight (kg)	64.6 (10.8)	61.6 (8.6)	0.40
BMI	21.9 (2.8)	21.6 (2.1)	0.78
VO ₂ max (ml/min/kg)	35.1 (5.6)	37.5 (7.6)	0.30
Peak value of GXT (W/kg)	2.9 (0.3)	3.16 (0.7)	0.20
Resting HR (bpm)	74.5 (9.9)	76.6 (13.2)	0.61
HR during endurance exercise (bpm)	150.6 (15.3)	148.4 (10.2)	0.65

Values shown are mean (±SD). [N = 33].

VO₂max maximal oxygen consumption, BMI body mass index, HR heart rate.

Table 5 The results of a correlation analysis between basal characteristics and BDNF change

	ΔBDNF		%ΔBDNF	
	r	p value	r	p value
Age (years)	-0.25	0.15	-0.15	0.40
Height (cm)	-0.11	0.54	-0.14	0.41
Weight (kg)	0.00	0.99	-0.18	0.30
BMI	-0.05	0.77	-0.19	0.28
VO _{2max} (ml/min/kg)	-0.06	0.72	0.06	0.74
Peak value of work rate (W/kg)	-0.02	0.92	0.08	0.65
Resting HR (bpm)	-0.13	0.45	-0.18	0.30

[N = 33].

VO_{2max} maximal oxygen consumption, BMI body mass index, Resting HR resting heart rate.

individuals who do not carry this polymorphism. Within the Japanese population, the prevalence of BDNF polymorphism is reported to be approximately 50% (Itoh et al. 2004; Itoh et al. 2005). Interestingly, this prevalence is approximately equal to the proportion of subjects demonstrating increased serum BDNF after exercise in the present study.

Although serum levels of BDNF can be affected by BDNF production in peripheral cells or endocrine organs, including vascular endothelial cells (Nakahashi et al. 2000), immune cells (e.g. T and B lymphocytes) (Besser and Wank 1999; Kerschensteiner et al. 1999) and submandibular glands (Tsukinoki et al. 2007; Tsukinoki et al. 2006), the brain is considered to be the major contributor to exercise-related increases in circulating BDNF. Rasmussen et al. (2009) reported that the brain contributes almost 75% of all BDNF in circulation under normal circumstances, and that the brain generally demonstrates a significant increase in BDNF production during prolonged exercise (a 2- to 3-fold increase of the production at rest). The BDNF polymorphism found in half of the Japanese population affects intracellular trafficking of BDNF, reducing neuronal activity-dependent BDNF release by approximately 25% (Chen et al. 2008; Egan et al. 2003). While we were unable to directly measure the BDNF polymorphism for each individual participant, we believe there is a possibility that the prevalence of BDNF polymorphism among Japanese individuals might account for our finding that, on average, BDNF levels do not increase after exercise.

Limitations of this study include the absence of control groups (both a rest control group and one consisting of subjects of Western heritage) or a vigorous exercise subgroup to explore possible dose-response relationships between exertion-level and BDNF levels, as well as the lack of measurements of gene polymorphism (Val66Met) among our Japanese male subjects. Further studies are needed to explain changes in serum BDNF levels

associated with exercise, as well as to elucidate the effect of BDNF polymorphism on exercise-induced BDNF secretion in Japanese subjects. Future studies should ascertain BDNF polymorphism status for each study participant, and included in analyses of the relationship between exercise and serum BDNF levels. Also, the influence of different levels of exercise intensity, its duration and type should be compared across sexes, age groups, health conditions, and fitness levels in order for exercise-induced BDNF secretion among Japanese individuals to be fully understood.

In conclusion, an exposure to 30 minutes of moderate aerobic exercise was not found to be associated with a consistent increase in serum BDNF concentrations in healthy young Japanese men. It is likely that something in the lifestyle and/or environment of male Japanese subjects underlies the difference between our findings and studies conducted in other countries.

Methods

Subjects and study design

The study population consisted of 40 healthy young Japanese men (mean age 24.1 ± 2.9 year; mean height 170.6 ± 6.7 cm; mean weight 64.8 ± 9.4 kg; mean BMI 22.2 ± 2.4 kg/m²; mean ± SE) with a sedentary lifestyle, which was defined as not having engaged in 30 minutes or more of purposeful physical activity per day at least three times a week over the previous 6 months. All subjects denied the presence of cardiopulmonary, metabolic, and musculoskeletal disease. All experiments were conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Seirei Christopher University, Japan. Written informed consent was also obtained from all participants.

Study protocol

The study was conducted in two phases. In the first phase, each subject performed a graded exercise test (GXT) on a stationary bicycle to determine the work load that corresponded to 60% maximal oxygen consumption (VO_{2max}) for that individual. This level of exertion was chosen because previous studies on subjects from Western populations used this intensity (Castellano and White 2008; Gold et al. 2003; Schulz et al. 2004). During the second phase, blood samples were collected from the subjects immediately before and after 30 minute endurance rides with a fixed exercise intensity level of 60% VO_{2max}. There was a rest period of 48 hours between the GXT and the endurance ride. Participants were instructed to forgo strenuous exercise for 24 hours prior to both the baseline VO_{2max} measurement and the 30 minute endurance ride. Similarly, food, caffeine, alcohol intake and smoking were prohibited during the 3 hours prior to each phase.

Graded exercise test

Baseline VO_{2max} was evaluated using a cycle ergometer on which participants exercised to volitional fatigue. Cardio-pulmonary and metabolic parameters, maximal work rate, VO_{2max} , and respiratory exchange ratio (RER) were determined on a breath-by-breath basis with samples averaged for 5-second intervals using the Aero Monitor AE-310 s (Minato Ika, Japan). Heart rate (HR) and rhythm were monitored during the GXT via electrocardiography (Bedside monitor scope 1; Nihon Kohden, Japan). We used the American College of Sports Medicine (ACSM) criteria for reaching VO_{2max} , in which a participant meets at least two of the following criteria: (1) a leveling off of the VO_2 ; (2) a rate of perceived exertion >17 , using Borg's scale; (3) volitional exhaustion; and (4) achievement of the participant's age-predicted maximal heart rate [calculated from $(220 - \text{age})$]. We defined the VO_{2max} plateau as a VO_2 change $< 2 \text{ mL kg}^{-1} \text{ min}^{-1}$ over the last 60 seconds of the test.

Endurance ride

After a 3 minutes' warm-up period at a power of 50 w, each subject performed 30 minutes of exercise at a power output that corresponded to 60% of his VO_{2max} , as determined using the GXT. The power output was adjusted in increments of 2 w to reach 60% of $VO_{2max} \pm 100 \text{ mL/min/kg}$, as needed. Metabolic, ventilator, and heart rate parameters were collected at 1-minute intervals during the rides.

Blood sampling and analysis

Basal and post-exercise BDNF levels were examined by drawing a 5-mL blood sample from the antecubital vein, with the subject in a sitting position, into a vacuum blood collection tube containing blood separating agent (NP-SP1029, NIPRO, Osaka, Japan), and using 21 gauge needles. The blood was sampled within 5 minutes before exercise initiation and 3 minutes post-exercise. It was clotted at room temperature for one hour and then centrifuged (Tabletop Centrifuge 2040, Kubota, Tokyo, Japan) at 3000 g for 15 minutes and the supernatant was decanted and stored in a -20°C freezer until analysis (approximately 2 to 3 months). Serum BDNF levels were determined using a commercially available quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kit, in accordance with protocols provided by the test manufacturer (R& D Systems, USA). Each sample was tested twice with a sensitivity threshold of 20 pg/mL, producing an intra-assay variance under 6.2%, which was within the range specified by the manufacturer.

Exclusion criteria

An analysis was conducted excluding subjects with a longer than 5 minutes' period of deviation from the appropriate load strength (outside the range of 50-70% of VO_{2max}

at average value for each minute) during the 30 minutes endurance ride.

Statistical analysis

Paired t-tests were used to compare serum BDNF levels measured prior to exercise onset, with BDNF levels measured after completion of the endurance rides. The statistical significance level was set at $p < 0.05$, and data were presented as mean \pm standard deviation (SD). All statistical analyses were conducted using the software package (IBM SPSS Statistics 19 for Windows, Chicago, IL).

Abbreviations

AD: Alzheimer's disease; BDNF: Brain-derived neurotrophic factor; BMI: Body mass index; VO_2 : Oxygen consumption; VO_{2max} : Maximal oxygen consumption; GXT: Graded exercise tests; HR: Heart rate; HRR: Heart rate reserve; RER: Respiratory exchange ratio; SNP: Single nucleotide polymorphism; Val: Valine allele; Met: Methionine allele.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AG contributed to conception and design, conducted experiments, participated in data analysis and drafting the manuscript. SO contributed to conception and design, data analysis and drafting the manuscript. KK contributed to conception and design, conducted experiments. KS contributed to conception and design, drafting the manuscript. KF contributed substantially to conception and design, conducted experiments. EBS contributed to drafting the manuscript. All authors read and approved the final manuscript.

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