

Review

The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review

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The purpose of this study was to summarize the effects of physical activity and exercise on peripheral brain-derived neurotrophic factor (BDNF) in healthy humans. Experimental and observational studies were identified from PubMed, Web of Knowledge, Scopus, and SPORT Discus. A total of 32 articles met the inclusion criteria. Evidence from experimental studies suggested that peripheral BDNF concentrations were elevated by acute

and chronic aerobic exercise. The majority of the studies suggested that strength training had no influence on peripheral BDNF. The results from most observational studies suggested an inverse relationship between the peripheral BDNF level and habitual physical activity or cardiorespiratory fitness. More research is needed to confirm the findings from the observational studies.

Evidence has demonstrated positive effects of physical activity and exercise on brain structure and cognitive function in humans (Aberg et al., 2009; Centers for Disease Control and Prevention, 2010; Erickson et al., 2011). Animal research has identified brain-derived neurotrophic factor (BDNF) as a crucial mediator of the benefits of exercise for brain health (Cotman & Berchtold, 2002). Voluntary exercise increased levels of BDNF mRNA and protein in the hippocampus and other brain regions (Neeper et al., 1995; Cotman & Berchtold, 2002), whereas the beneficial effect of exercise on cognitive function was inhibited when blocking BDNF action in the hippocampus (Vaynman et al., 2004). BDNF is a member of the neurotrophin family, which includes nerve growth factor, neurotrophin-3, neurotrophin-4/5, and neurotrophin-6 (Poo, 2001). BDNF is broadly expressed in the developing and adult mammalian brain (Poo, 2001), as well as in several peripheral tissues, such as the muscle (Cassiman et al., 2001) and adipose tissue (Sornelli et al., 2009). By activating its major tropomyosin receptor kinase B, BDNF plays an important role in various aspects of developmental and adult brain plasticity, including proliferation, differentiation, and survival of neurons, neurogenesis, synaptic plasticity, and cognitive function (Hofer & Barde, 1988; Poo, 2001; Monteggia et al., 2004).

Findings also indicate that BDNF is involved in both central metabolic pathways (Wisse & Schwartz, 2003) and mediation of energy metabolism in peripheral

organs (Pedersen et al., 2009). Recent evidence has shown that BDNF signaling pathway in the hypothalamus had a potential to regulate energy homeostasis, body weight control, and feeding behavior (Noble et al., 2011). Besides, BDNF has been identified as a contraction-induced muscle cell-derived protein that can increase fat oxidation in skeletal muscle in an AMP-activated protein kinase-dependent signaling pathway (Matthews et al., 2009). Moreover, BDNF has been linked to metabolic disorders, mainly including obesity and diabetes (Hristova & Aloe, 2006; Suwa et al., 2006; Krabbe et al., 2007; Fujinami et al., 2008). For example, elevated BDNF levels have been found in newly diagnosed type 2 diabetes patients (Suwa et al., 2006); and low levels have been presented as the disease progresses (Hristova & Aloe, 2006).

It has been demonstrated that factors, such as age, gender, and weight status, have an influence on stored and circulating BDNF levels in humans (Lommatzsch et al., 2005). Recently, there has been a growing body of research that focused on the relationship between physical activity and BDNF levels in peripheral blood. Two review articles in this area have been published. The first one presented a systematic review of experimental studies on the effects of exercise on peripheral BDNF in healthy subjects and persons with a disease or disability, including the methodological issues (Knaepen et al., 2010). More recently, Coelho et al. (2013) provided a review of six studies that examined the effect of exercise

on BDNF in elderly individuals. From a perspective of public health, the elucidation of the relationship between habitual physical activity and peripheral BDNF levels is of importance. The two existing reviews did not investigate the effects of habitual physical activity on peripheral BDNF. In the present review, we provide an update on the topic and include both experimental and observational studies. The inclusion of observational studies enables the investigation of the association between habitual physical activity and peripheral BDNF.

Methods

Literature search

We searched the following electronic databases: PubMed, Web of Knowledge, Scopus, and SPORT Discus. The search terms used to find the studies were variants of (a) physical activity (e.g., physical activity, physical education, training, physical fitness, and exercise) and (b) BDNF. They were specifically adjusted to each database to search as free text words and categorized subject terms (e.g., MeSH in PubMed). Language was limited to English. The search covered the period from January 1995 to July 2012 since the first evidence for the presence of BDNF in human blood emerged in 1995 (Rosenfeld et al., 1995). Additionally, we searched the references of published studies manually. The searching and the first screening on the basis of title and abstract were conducted independently by two authors (T. H and K. T. L.) using the same protocol. The full search strategy can be obtained on request.

Inclusion criteria

Studies retrieved from the initial searches were screened using the following inclusion criteria: (a) studies had to investigate the effects of exercise on peripheral BDNF levels in humans, or assess the relationship between habitual physical activity or cardiorespiratory fitness (CRF) and peripheral BDNF levels in humans; (b) the population studied had to be subjects without known diseases; (c) studies had to be published in English; (d) full texts had to be available; and (e) data used in more than one study were only included once to avoid replication. A flow diagram of literature search and selection is shown in Fig. 1.

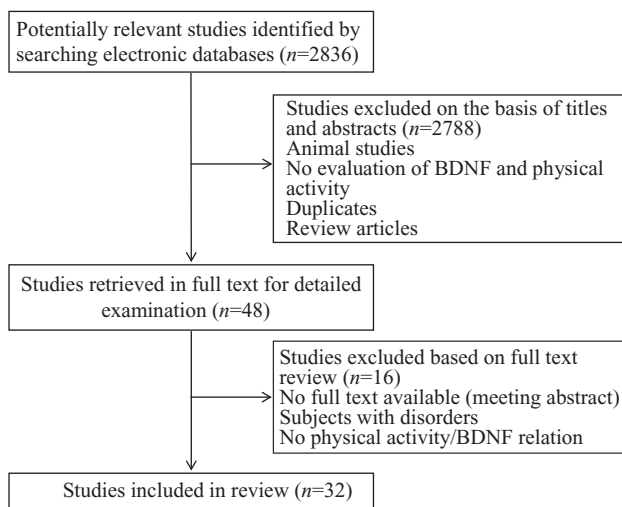


Fig. 1. Flowchart of literature search.

Results

Results from experimental studies

Effects of acute aerobic exercise on BDNF

The literature search yielded 32 relevant publications in total. The experimental studies examined the effects of different types of exercise on peripheral BDNF, including acute aerobic exercise, chronic aerobic exercise, and strength training. Fifteen studies investigating the effects of acute aerobic exercise on BDNF were summarized in Table 1. The exercise protocols (type, intensity, and duration) were heterogeneous. Nevertheless, the results were relatively consistent. Fourteen of the 15 studies demonstrated that peripheral BDNF concentrations were elevated significantly in response to acute aerobic exercise (Rojas Vega et al., 2006, 2012; Ferris et al., 2007; Winter et al., 2007; Goekint et al., 2008, 2011; Tang et al., 2008; Rasmussen et al., 2009; Bos et al., 2011; Griffin et al., 2011; Vega et al., 2011; Cho et al., 2012; Heyman et al., 2012; Nofuji et al., 2012), although the effect was not long-lasting. Two studies suggested that the magnitude of increase in BDNF might be exercise intensity-dependent (Rojas Vega et al., 2006; Ferris et al., 2007). Only one study reported no effects of a single bout of maximal cycling on plasma BDNF in young adults (Zoladz et al., 2008).

Effects of strength training on BDNF

Seven studies have examined the effects of strength training on peripheral BDNF concentrations (Table 2). Except for two uncontrolled studies (Yarrow et al., 2010; Coelho et al., 2012), five investigations failed to show a significant change in BDNF in response to a single bout of strength training or a prolonged period of strength training (Levinger et al., 2008; Schiffer et al., 2009; Correia et al., 2010; Goekint et al., 2010; Rojas Vega et al., 2010).

Effects of chronic aerobic exercise on BDNF

Table 3 summarizes the six studies investigating the effects of chronic aerobic exercise on BDNF. Both the resting levels of BDNF and its response to acute exercise following a prolonged period of aerobic exercise have been investigated. The durations of exercise intervention ranged from several weeks to 1 year. Four out of six studies reported that resting BDNF levels were increased to some extent after a period of endurance training (Zoladz et al., 2008; Seifert et al., 2010; Erickson et al., 2011; Ruscheweyh et al., 2011), while one study found that a period of aerobic exercise did not significantly influence BDNF concentrations (Schiffer et al., 2009). Additionally, two studies showed that the response of BDNF to a single bout of exercise was augmented after a prolonged period of aerobic exercise (Zoladz et al., 2008; Griffin et al., 2011).

Table 1. Summary of studies on effects of acute aerobic exercise on BDNF

| Study (first author, year) | Subjects | Exercise protocol | Main outcomes | Main results |
|----------------------------|---|--|---|--|
| Cho et al., 2012 | 18 college male students Age: 19 ± 1 years | Maximal treadmill test using the walking and/or running modification in the Bruce protocol | Serum, plasma and platelet BDNF | Post-exercise: Significant increase in BDNF concentration ($P < 0.05$). |
| Heyman et al., 2012 | 11 trained male cyclists Age: 23.3 ± 5.1 years | 60 min of pedaling at 55% W_{max} followed by 30 min at 75% W_{max} | Serum BDNF | Post-exercise: BDNF levels rose significantly ($P < 0.001$). Recovery: return. |
| Nofuji et al., 2012 | 8 physically active females and 8 sedentary females Age: 21.6 ± 3.0 years and 22.8 ± 1.9 years, respectively | Trial 1: maximal graded cycling to determine VO_{2max} Trial 2: cycling at 60% of VO_{2max} for 30 min Trial 3: cycling at 40% of VO_{2max} for 30 min | Serum and plasma BDNF | Post-exercise: Serum BDNF increased significantly ($P < 0.05$) after trials 1 and 2 in both groups. No group differences were observed in the pattern of plasma BDNF change for all exercise trials. Recovery: The serum BDNF returned to the baseline level in sedentary group, whereas serum BDNF decreased below the baseline level in the active group after the maximal exercise test. |
| Rojas Vega et al., 2012 | 11 healthy males Age: 24.8 ± 1.6 years | 10 min of low-intensity (LIE) and following high-intensity cycling exercise to exhaustion (HIE) in two separate trials (received either a placebo infusion or an isotonic sodium bicarbonate infusion) | Serum BDNF | Post-exercise: BDNF increased significantly at the end of HIE ($P < 0.01$) and remained elevated until 3 min post-exercise in both trials. Recovery: return. |
| Bos et al., 2011 | 38 healthy males and females Age: 43 years | 20 min of cycling either near a major traffic road or in an air-filtered laboratory Intensity: $74.0 \pm 8.6\%$ and $74.1 \pm 8.8\%$ of maximal HR | Serum BDNF | Post-exercise: BDNF increased significantly when cycling in the air-filtered laboratory ($P = 0.02$), but not near the major traffic road ($P = 0.42$). |
| Goekint et al., 2011 | 11 well-trained males Age: 23.3 ± 5.1 years | Four trials of cycling with citalopram or placebo treatment in an environmental temperature of 18 °C or 30 °C Exercise: 60 min of cycling at 55% W_{max} followed by a time trial at 75% W_{max} | Serum BDNF | Post-exercise: BDNF levels rose significantly in all trials ($P < 0.001$). Recovery: return. |
| Griffin et al., 2011 | 47 healthy male students Age: 22 ± 2 years | Graded cycling to determine VO_{2max} | Serum BDNF, IGF-1, and cognitive function | Post-exercise: Exercise increased BDNF concentration ($P < 0.05$) and improved memory ($P < 0.05$). |
| Vega et al., 2011 | 20 pregnant women Age: 35.2 ± 3.6 years | Two trials of graded cycling with initial load of 25 W performed during pregnancy and postpartum. Exercise stopped when HR reached 150 bpm | Serum BDNF, IGF-1, VEGF, and hormones | Post-exercise: BDNF increased significantly at HR150 in both trials ($P < 0.05$). Recovery: return. |
| Rasmussen et al., 2009 | 8 healthy trained males Age: 22–40 years | Type: rowing Duration: 4 h Intensity: 10–15% below the lactate threshold | Plasma BDNF | During-exercise: Release of BDNF from the brain increased significantly ($P < 0.05$). Post-exercise: Internal jugular venous BDNF increased significantly ($P < 0.05$). Recovery: return. |
| Goekint et al., 2008 | 11 well-trained male cyclists Age: 22.9 ± 4.3 years | Two separate exercise sessions with either SNRI or placebo treatment Exercise: 60 min of cycling at 55% W_{max} followed by a time trial at 75% W_{max} | Serum BDNF and cognitive function | Post-exercise: BDNF increased significantly ($P < 0.0001$) without any effects of drug administration. Short-term memory was not affected significantly, but midterm memory decreased ($P = 0.02$). Recovery: return. |
| Tang et al., 2008 | 16 healthy men and women Age: 19–30 years | Type: step-exercise Duration: 15 min | Serum BDNF | Post-exercise: Significant increases in BDNF concentrations ($P = 0.014$). Recovery: return. |
| Zoladz et al., 2008 | 13 young, healthy and physically active men Age: 22.7 ± 0.5 years | Maximal incremental cycling test up to VO_{2max} | Plasma BDNF | No significant effect on plasma BDNF. |
| Ferris et al., 2007 | 15 healthy male and female subjects Age: 25.4 ± 1.01 years | GXT: graded cycling test to volitional fatigue Trial 1: 30-min cycling at 10% above ventilatory threshold ($V_{Th} + 10\%$) Trial 2: 30-min cycling at 20% below ventilatory threshold ($V_{Th} - 20\%$) | Serum BDNF and cognitive function | Post-exercise: BDNF increased significantly ($P < 0.05$) after trial 1 (13%) and the GXT (30%). There was no significant change in BDNF after trial 2. Cognitive function scores improved after all exercise conditions. |
| Winter et al., 2007 | 27 healthy male sports students Age: 22.2 ± 1.7 years | “Relaxed” condition: 15 min of being sedentary “Moderate” condition: 40 min of low impact running “Intense” condition: two sprints of 3 min at increased speed | Serum BDNF and cognitive function | Post-exercise: “Intense” condition elicited strongest increase in BDNF concentrations. Vocabulary learning was 20% faster after intense running as compared to other two conditions. |
| Rojas Vega et al., 2006 | 8 male athletes Age: 24.6 ± 1.3 years | Type: cycling Exercise: 10 min warm-up and following incremental cycling to exhaustion | Serum BDNF | Post-exercise: Significant increase in BDNF concentration ($P < 0.05$). Recovery: return. |

BDNF, brain-derived neurotrophic factor; GXT, graded exercise test; HR, heart rate; IGF-1, insulin-like growth factor 1; SNRI, selective noradrenaline reuptake inhibitor; VEGF, vascular endothelial growth factor; VO_{2max} , maximal oxygen uptake; W_{max} , maximal power output.

Table 2. Summary of studies on effects of strength training on BDNF

| Study (first author, year) | Design | Subjects | Exercise protocol | Main outcomes | Main results |
|----------------------------|-----------------------------|--|--|---|---|
| Coelho et al., 2012 | Uncontrolled trial | 20 older women Age: 71.0 years | Training: resistance training of knee extensors and flexors Frequency: three times per week Duration: 10 weeks | Plasma BDNF | Plasma BDNF significantly increased ($P < 0.001$) after training program. |
| Goekint et al., 2010 | Controlled trial | Training group: 15 healthy subjects Age: 20.1 ± 0.4 years Control group: 8 healthy subjects Age: 21.5 ± 0.8 years | Training: resistance training, 50–80% 1 RM Frequency: three times per week Duration: 10 weeks | Serum BDNF, IGF-1, IGF-1, IGF-1, and cognitive function | Both a single bout of training and 10 weeks of training did not significantly affect BDNF. No effects of training on cognitive function. |
| Rojas Vega et al., 2010 | Uncontrolled trial | 8 healthy males Age: 23.4 ± 1.8 years | Two separate test sessions, intensity set at 110% or 40% of the averaged individual maximal effort curve | Serum BDNF, IGF-1, and VEGF | Both exercise sessions increased IGF-1 ($P < 0.05$), but not BDNF and VEGF. |
| Yarrow et al., 2010 | Uncontrolled trial | 20 healthy male individuals Age: 21.9 ± 0.8 years | Traditional resistance group: 52.5–75% 1 RM Eccentric-enhanced training group: 40–120% 1 RM Frequency: three times per week Duration: 5 weeks | Serum BDNF | Baseline: BDNF increased 32% ($P < 0.05$) after a single bout of resistance exercise. Post-intervention: There was no change in resting BDNF levels. BDNF increased 77% ($P < 0.01$) in response to a single bout of resistance exercise. |
| Correia et al., 2010 | Uncontrolled trial | 16 healthy male subjects Age: 26.4 ± 3.7 years | Strength exercise of knee and elbow muscles on separate days, 5 series of 10 repetitions, at 60 deg/s | Plasma BDNF | Plasma BDNF did not significantly change after both arm and leg strength exercise. |
| Schiffer et al., 2009 | Randomized controlled trial | Training group: 10 sports students Age: 22 ± 1.6 years Control group: 9 sports students Age: 22 ± 2.3 years | Intensity: 70–80% 1 RM and strength exercise until exhaustion Frequency: three times per week Duration: 12 weeks | Plasma BDNF and IGF-1 | No significant change in basal plasma BDNF. |
| Levinger et al., 2008 | Randomized controlled trial | 49 untrained men and women Age: 50.9 ± 6.2 years | Intensity: 40–50% 1 RM (week 1), 50–85% 1 RM (weeks 2–10) Frequency: three times per week Duration: 10 weeks | Plasma BDNF and metabolic risk factors | Resistance training had no effect on resting BDNF ($P > 0.28$). |

BDNF, brain-derived neurotrophic factor; IGF-1, insulin-like growth factor 1; IGF-1, insulin-like growth factor binding protein-3; RM, repetition maximum; VEGF, vascular endothelial growth factor.

Results from observational studies

Table 4 summarizes the observational studies investigating the relationship between peripheral BDNF concentrations and habitual physical activity or CRF. Seven studies have looked into the association between physical activity and BDNF (Chan et al., 2008; Nofuji et al., 2008; Zoladz et al., 2008; Currie et al., 2009; Floel et al., 2010; Winker et al., 2010; Correia et al., 2011). Only one study used objective measure of physical activity (Nofuji et al., 2008). Three studies compared the groups on the basis of their participation in sports instead of measuring actual levels of physical activity (Zoladz et al., 2008; Winker et al., 2010; Correia et al., 2011). Three studies have investigated the correlation between BDNF and CRF estimated by maximal oxygen uptake (VO_{2max} ; Currie et al., 2009; Jung et al., 2011; Cho et al., 2012). The results of the studies are inconsistent; but five of the nine studies showed a negative relationship between the levels of physical activity or CRF and BDNF (Chan

et al., 2008; Nofuji et al., 2008; Currie et al., 2009; Jung et al., 2011; Cho et al., 2012).

Implication of BDNF in exercise-induced cognitive enhancement

In order to understand the potential role of BDNF in exercise-induced improvement in brain function, seven reviewed studies examined the effects of exercise on cognitive function in addition to BDNF concentrations (Ferris et al., 2007; Winter et al., 2007; Goekint et al., 2008, 2010; Erickson et al., 2011; Griffin et al., 2011; Ruscheweyh et al., 2011). Despite using different cognitive measurements, most of the studies showed that cognitive function was improved after acute exercise (Ferris et al., 2007; Winter et al., 2007; Griffin et al., 2011) and chronic aerobic exercise (Erickson et al., 2011; Griffin et al., 2011; Ruscheweyh et al., 2011). Those studies provided some evidence that peripheral BDNF was

Table 3. Summary of studies on effects of chronic aerobic exercise on BDNF

| Study (first author, year) | Design | Subjects | Exercise protocol | Main outcomes | Main results |
|----------------------------|-----------------------------|---|--|---|--|
| Erickson et al., 2011 | Randomized controlled trial | Aerobic group: 60 older adults Age: 67.6 ± 5.81 years Control group: 60 older adults Age: 65.5 ± 5.44 years | Aerobic group: walking, 50–60% of HRR (1–7 weeks), 60–75% of HRR (remainder of the program), 40 min Control group: stretching and toning exercise Frequency: three times per week Duration: 12 months | Serum BDNF, MRI, and cognitive function | BDNF increased and memory improved in both groups. Increased hippocampal volume was associated with greater levels of BDNF. |
| Griffin et al., 2011 | Controlled trial | 47 healthy male students Age: 22 ± 2 years | Aerobic training: cycle training, gradually increased workload and duration until 60% VO_{2max} for 60 min Frequency: three times per week Duration: 3 weeks or 5 weeks | Serum BDNF, IGF-1, and cognitive function | No effects of exercise on basal serum BDNF concentrations. The response of BDNF to acute exercise improved ($P < 0.05$) after aerobic training. Memory improved after 5 weeks of aerobic training. |
| Ruscheweyh et al., 2011 | Randomized controlled trial | Nordic walking group: 20 older adults Age: 60.1 ± 6.2 years Gymnastics group: 21 older adults Age: 62.5 ± 6.4 years Control group: 21 older adults Age: 58.1 ± 6.7 years | Nordic walking: 50–60% of maximal exertion, 50 min Gymnastics: 30–40% of maximal exertion, 50 min Frequency: five times per week Duration: 6 months | Serum BDNF, MRI, and cognitive function | There was a trend for increase in BDNF with increasing physical activity over 6 months. Cognitive function improved in intervention groups. |
| Seifert et al., 2010 | Randomized controlled trial | Exercise group: 7 healthy males Age: 29 ± 6 years Control group: 5 healthy males Age: 31 ± 7 years | Exercise group: aerobic exercise, energy expenditure of 600 kcal Control group: on a diet to create a negative energy balance of 600 kcal each day Frequency: seven times per week Duration: 3 months | Plasma BDNF | Resting release of BDNF enhanced ($P < 0.05$). There was no training-induced increase in the release of BDNF during exercise. |
| Schiffer et al., 2009 | Randomized controlled trial | Exercise group: 8 sports students Age: 23 ± 1.7 years Control group: 9 sports students Age: 22 ± 2.3 years | Training: running, 80% HR of aerobic-anaerobic threshold, 45 min Frequency: three times per week Duration: 12 weeks | Plasma BDNF and IGF-1 | No significant change in basal plasma BDNF. |
| Zoladz et al., 2008 | Uncontrolled trial | 13 young, healthy and physically active men Age: 22.7 ± 0.5 years | Training: continuous aerobic cycling (90% VO_2 at lactate threshold, 40 min) or intermittent aerobic cycling Frequency: four times per week Duration: 5 weeks | Plasma BDNF, HOMA2-IR | Resting BDNF was significantly ($P = 0.01$) elevated and its response to acute exercise was augmented ($P = 0.003$). |

BDNF, brain-derived neurotrophic factor; HOMA2-IR, homeostasis model assessment of insulin resistance version 2; HR, heart rate; HRR, heart rate reserve; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; VO_{2max} , maximal oxygen uptake.

associated with exercise-induced enhancement in brain function.

Discussion

Effects of physical exercise on BDNF

In the present review, we provide an update on the effects of physical activity and exercise on peripheral BDNF and include both experimental and observational studies. The experimental studies demonstrated that peripheral BDNF concentrations were elevated significantly in response to acute aerobic exercise, and the increase returned during the exercise recovery period (Rojas Vega

et al., 2006, 2012; Ferris et al., 2007; Winter et al., 2007; Goekint et al., 2008, 2011; Tang et al., 2008; Rasmussen et al., 2009; Bos et al., 2011; Griffin et al., 2011; Vega et al., 2011; Cho et al., 2012; Heyman et al., 2012; Nofuji et al., 2012). The dose-response of BDNF is not clear. Nevertheless, there is some evidence showing that the magnitude of increase in BDNF might be exercise intensity-dependent. Specifically, it has been shown that serum BDNF concentrations did not significantly change during 10 min of moderate exercise in the warm-up period in healthy male athletes; however, the serum BDNF concentrations significantly increased after the following ramp test to exhaustion (Rojas Vega et al.,

Table 4. Summary of observational studies on the correlation between physical activity and BDNF

| Study (first author, year) | Sample specifics | Measures of physical activity and CRF | Main results |
|----------------------------|--|--|--|
| Cho et al., 2012 | Subjects: 18 college male students Age: 19 ± 1 years | CRF: VO_{2max} | VO_{2max} showed a significant negative correlation with serum, plasma, and platelet BDNF ($P < 0.05$). |
| Correia et al., 2011 | Subjects: international sprinters ($n = 14$), domestic sprinters ($n = 8$) and sedentary individuals ($n = 15$) Age: 25.6 ± 5.8 , 24.2 ± 4.1 , and 26.2 ± 3.8 years, respectively | None (comparison of groups) | Plasma BDNF levels in both the international and domestic sprinters were significantly higher than those in sedentary subjects ($P < 0.05$). |
| Jung et al., 2011 | Subjects: 955 healthy men Age: 20–76 years | CRF: VO_{2max} | Serum BDNF significantly negatively correlated with relative VO_{2max} ($P < 0.0001$). |
| Winker et al., 2010 | Subjects: elderly athletes ($n = 56$) and inactive controls ($n = 58$) Age: 66.0 ± 4.7 and 65.9 ± 4.1 years, respectively | None (comparison of groups) | Athletes and controls did not differ significantly in serum BDNF. |
| Floel et al., 2010 | Subjects: 75 older males and females Age: 60.5 ± 6.9 years | Physical activity: physical activity questionnaire | Physical activity was not significantly associated with serum BDNF. |
| Currie et al., 2009 | Subjects: 44 healthy men and women Age: 34.3 ± 10.9 years | Physical activity: modified Baecke questionnaire CRF: VO_{2max} | Serum BDNF was negatively associated with estimated VO_{2max} ($P < 0.05$) and habitual physical activity ($P < 0.05$). |
| Chan et al., 2008 | Subjects: 85 healthy males and females Age: 36.05 ± 7.8 years | Physical activity: lifestyle questionnaire | Subjects with moderate frequency of exercise (1–30 times of 30 min exercise per month) showed higher resting serum BDNF levels than the subjects with more than 30 times ($P < 0.05$). Serum BDNF showed a significant negative correlation with the total physical activity per month ($P < 0.05$). |
| Nofuji et al., 2008 | Subjects: trained males ($n = 12$) and sedentary males ($n = 14$) Age: 21.8 ± 0.9 and 22.4 ± 1.2 years, respectively | Physical activity: energy expenditure evaluated by Lifecorder | Serum BDNF levels in the trained men were significantly lower than that in the sedentary group ($P < 0.01$). Serum BDNF negatively correlated with daily total energy expenditure ($P < 0.05$). |
| Zoladz et al., 2008 | Subjects: 16 athletes and 13 untrained subjects Age: 22.8 ± 0.7 years and 22.7 ± 0.5 years, respectively | None (comparison of groups) | Plasma BDNF levels in the trained men were significantly higher than those in the sedentary group ($P = 0.013$). |

BDNF, brain-derived neurotrophic factor; CRF, cardiorespiratory fitness; VO_{2max} , maximal oxygen uptake.

2006). A following study by Ferris et al. (2007) further supports this finding. They showed that 30 min of cycling at the intensity of 10% above the ventilatory threshold resulted in a significant increase in serum BDNF concentrations compared to baseline, whereas cycling at 20% below ventilatory threshold did not yield a significant post-exercise increase in serum BDNF concentrations (Ferris et al., 2007). Although the sources and regulation of the acute exercise-induced response of BDNF remain to be determined, several possibilities were suggested by the literature. Firstly, since most of the peripheral BDNF is stored in the platelets, it was proposed that platelets might contribute to the serum BDNF concentrations increased in response to exercise (Tang et al., 2008). Secondly, the brain might be another source since the cerebral output of BDNF has been shown in resting healthy humans (Krabbe et al., 2007). Indeed, Rasmussen et al. (2009) have provided preliminary evidence indicating that the brain was a major source (70–80%) for increased plasma BDNF during exercise through the measurement of arterial-to-internal jugular venous difference in BDNF in healthy subjects. Additionally, evidence showed that BDNF was synthesized by skeletal muscle cells in response to contraction,

but it was not released into the circulation (Matthews et al., 2009).

We identified seven studies that examined the effects of strength training on peripheral BDNF. Most of these studies failed to observe a significant change in BDNF in response to a single bout of strength training or a prolonged period of strength training (Levinger et al., 2008; Schiffer et al., 2009; Correia et al., 2010; Goekint et al., 2010; Rojas Vega et al., 2010). In contrast, Yarrow et al. (2010) reported a transient increase in serum BDNF after a single bout of resistance training. The study showed that 5 weeks of resistant training augmented the transient increase of BDNF as well. Recently, Coelho et al. (2012) showed that plasma BDNF increased significantly after 3 months of strength training in elderly women. Nevertheless, those two investigations are prone to the limitations of the study design of uncontrolled trial.

Five out of six reviewed studies showed that peripheral BDNF levels were elevated to some extent after a prolonged period of aerobic exercise in healthy adults (Zoladz et al., 2008; Seifert et al., 2010; Erickson et al., 2011; Griffin et al., 2011; Ruscheweyh et al., 2011). Zoladz et al. (2008) found that a 5-week moderate intensity aerobic training program resulted in a significant

increase in the resting plasma BDNF concentrations in young healthy men. Erickson et al. (2011) reported that 1 year of aerobic exercise increased serum BDNF in the elderly. There is also some evidence that the acute exercise-induced elevation of BDNF was augmented after prolonged aerobic exercise training periods (Zoladz et al., 2008; Griffin et al., 2011). Importantly, a more thorough study has shown that 3 months of endurance training enhanced the resting release of BDNF from the brain by arterial and internal jugular venous catheterization in healthy males, although there was no training-induced increase in the release of BDNF during exercise (Seifert et al., 2010). Those results are in agreement with the findings from animal studies, which have clearly shown that a period of aerobic exercise elevates levels of BDNF mRNA and protein in the hippocampus and other brain regions (Neeper et al., 1995; Cotman & Berchtold, 2002). In contrast, one study did not find significant effects of chronic aerobic training on resting BDNF levels in healthy sports students (Schiffer et al., 2009). However, the study suffered from the limitations in terms of the small sample size (less than 10 subjects in each group) and the specific study population. The sports students remained their own exercise training during the intervention period, which might be the reason for the lacking of additional effects of exercise intervention on BDNF. More studies are warranted to determine the adaptation of peripheral BDNF in response to long-term exercise training.

The association between physical activity and BDNF

The inclusion of observational studies in the present review enabled the examination of the association between habitual physical activity or CRF and peripheral BDNF. Daily physical activity is suggested to be positively related to CRF in adults and adolescents (Dencker & Andersen, 2011). CRF is frequently used as a proxy of recent physical activity pattern, although it is partly determined by genetics (Bouchard et al., 1986). As shown in Table 4, sample sizes of these studies ranged from 18 to 955 and the results were inconsistent. All these articles were published within the last 5 years, suggesting that this is an emerging area of interest. Two studies reported that BDNF was higher in active sportsmen compared with sedentary individuals (Zoladz et al., 2008; Correia et al., 2011), whereas Nofuji et al. (2008) showed the opposite results. Two studies failed to observe the significant association (Floel et al., 2010; Winker et al., 2010). Two studies demonstrated an inverse correlation between BDNF and physical activity measured by questionnaires (Chan et al., 2008; Currie et al., 2009). Similarly, evidence indicated that CRF was negatively correlated with peripheral BDNF in healthy humans (Currie et al., 2009; Jung et al., 2011; Cho et al., 2012). For example, one of those investigations with a relatively large sample (955 subjects) demonstrated that

serum BDNF was negatively correlated with VO_{2max} when adjusting for age, body mass index (BMI), triglyceride (TG), and total cholesterol (TC)/high-density lipoprotein cholesterol (Jung et al., 2011). The majority of the findings suggested an inverse association between BDNF and habitual physical activity or CRF, which seems to be conflicted with the results from experimental studies. The biological mechanism underlying the inverse relationship between peripheral BDNF and habitual physical activity is still unclear, but several potential explanations are suggested. BDNF could transport across the blood-brain barrier in both directions (Pan et al., 1998). Thus, the observed inverse relationship may reflect a more efficient uptake mechanism of circulating BDNF into the brain in physically active individuals (Currie et al., 2009). The possibility remains to be elucidated in future research. Besides, high levels of physical activity and CRF are associated with a favorable cardiovascular risk profile in adults and youth (Steele et al., 2008). Recent evidence showed that peripheral BDNF was positively related to cardiovascular risk factors, such as BMI, abdominal fat, TG, TC, and fasting plasma glucose (Levinger et al., 2008; Golden et al., 2010; Jung et al., 2011). Recent findings also suggested that BDNF levels may be increased as a compensatory mechanism in the pathogenesis of metabolic disorders (Suwa et al., 2006; Levinger et al., 2008). It is therefore likely that the decreased peripheral BDNF may be in parallel with improved cardiovascular risk profile in physically active individuals. It is worth noting that the current observational studies did not adjust for potential lifestyle confounders, such as nutrition and smoking (Chan et al., 2008; Bus et al., 2011). Therefore, it is possible that the associations are explained by unknown and residual confounding. It is too early to draw a clear conclusion of the relationship between BDNF and habitual physical activity due to the limitations, such as selected study populations, subjective measures of physical activity, and uncontrolled confounding factors. Additionally, the functional importance of the alterations in BDNF in metabolic disorders remains to be elucidated. It is of great interest to further examine the effects of physical activity and exercise on metabotropic action of BDNF.

Physical exercise, BDNF, and cognitive function

Results from available animal studies have strongly demonstrated that BDNF is a crucial mediator of exercise-induced neuroplasticity (Cotman & Berchtold, 2002). The beneficial effects of exercise on cognitive function were inhibited when blocking the action of BDNF signaling in the hippocampus (Vaynman et al., 2004). Feeding a high-saturated fat diet for 2 months led to impaired cognitive function in rats, and this harmful effect was associated with decreased levels of BDNF and markers of synaptic function (Molteni et al., 2002).

Furthermore, the authors reported that exercise reversed the decrease in BDNF and its downstream effectors on plasticity (Molteni et al., 2004). It has been reported that hippocampal BDNF expression and dendritic spine density were reduced in diabetic mice (*db/db* mice), an animal model of insulin-resistant diabetes. Exercise and caloric restriction increased hippocampal dendritic spine density and BDNF in *db/db* mice, which suggested that the detrimental effect of diabetes on brain could be attenuated by exercise (Stranahan et al., 2009). Nevertheless, research is required to elucidate the extent to which findings from those animal models translate to human studies. Indeed, some studies included in the current review linked exercise-induced improvement of cognitive function with the measures of peripheral BDNF (Ferris et al., 2007; Winter et al., 2007; Erickson et al., 2011; Griffin et al., 2011; Ruscheweyh et al., 2011). It was reported that an acute bout of aerobic exercise resulted in improved performance in cognitive tasks, and was associated with increases in serum BDNF levels (Ferris et al., 2007; Winter et al., 2007; Griffin et al., 2011). Obviously, the prospective correlation between changes in BDNF and brain function is of great interest. In a well-designed randomized controlled trial (RCT) of 1 year duration of exercise training in 120 healthy elderly adults, Erickson et al. (2011) reported that aerobic exercise increased serum BDNF and spatial memory. Meanwhile, they showed that the increases in BDNF were positively related with the exercise-induced changes in anterior hippocampal volume. Another RCT also demonstrated an increase in resting BDNF levels (a trend) after 6 months of aerobic exercise, and the cognitive function improved significantly in healthy elderly subjects (Ruscheweyh et al., 2011). More well-designed experimental studies are needed to understand the effects

of physical activity and exercise on neuroplasticity and cognitive development.

Perspectives

In this review, we presented an update on the relationship between physical activity and exercise and BDNF in healthy subjects. The majority of reviewed studies support the notion that peripheral BDNF concentrations can be elevated by acute and chronic aerobic exercise. However, more well-designed experimental studies are needed to clarify the dose-response of BDNF. Conversely, strength training seems not efficient to affect peripheral BDNF. The findings from the experimental studies are in agreement with the previous reviews. We also investigated the associations between habitual physical activity and peripheral BDNF levels, and the results are relatively conflicting. However, most of included studies suggested that peripheral BDNF levels were inversely correlated with habitual physical activity and CRF in healthy individuals. The biological mechanism behind the observed associations is still unclear. Future studies should use objectively measured physical activity to better understand the relationship between habitual physical activity and peripheral BDNF in larger sample sizes. Potential interactions between physical activity, metabolic risk factors, and BDNF will be an interesting topic for future research. Furthermore, the associations between exercise-induced change in BDNF and brain function in human subjects should be elucidated.

Key words: physical activity, exercise, brain-derived neurotrophic factor, cardiorespiratory fitness, cognitive function.

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