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Neuroplasticity – Exercise-Induced Response of Peripheral Brain-Derived Neurotrophic Factor

A Systematic Review of Experimental Studies in Human Subjects

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Abstract

Exercise is known to induce a cascade of molecular and cellular processes that support brain plasticity. Brain-derived neurotrophic factor (BDNF) is an essential neurotrophin that is also intimately connected with central and peripheral molecular processes of energy metabolism and homeostasis, and could play a crucial role in these induced mechanisms.

This review provides an overview of the current knowledge on the effects of acute exercise and/or training on BDNF in healthy subjects and in persons with a chronic disease or disability. A systematic and critical literature search was conducted. Articles were considered for inclusion in the review if they were human studies, assessed peripheral (serum and/or plasma) BDNF and evaluated an acute exercise or training intervention. Nine RCTs, one randomized trial, five non-randomized controlled trials, five non-randomized non-controlled trials and four retrospective observational studies were analysed. Sixty-nine percent of the studies in healthy subjects and 86% of the studies in persons with a chronic disease or disability, showed a 'mostly transient' increase in serum or plasma BDNF concentration following an acute aerobic exercise. The two studies regarding a single acute strength exercise session could not show a significant influence on basal BDNF concentration. In studies regarding the effects of strength or aerobic training on BDNF, a difference should be made between effects on basal BDNF concentration and training-induced effects on the BDNF response following an acute exercise. Only three out of ten studies on aerobic or strength training (i.e. 30%) found a training-induced increase in basal BDNF concentration. Two out of six studies (i.e. 33%) reported a significantly higher BDNF response to acute exercise following an aerobic or strength training programme (i.e. compared with the BDNF response to an acute exercise at baseline). A few studies of low quality (i.e. retrospective observational studies) show that untrained or moderately trained healthy subjects have higher basal BDNF concentrations than highly trained subjects. Yet, strong evidence still has to come from good methodological studies.

Available results suggest that acute aerobic, but not strength exercise increases basal peripheral BDNF concentrations, although the effect is transient.

From a few studies we learn that circulating BDNF originates both from central and peripheral sources. We can only speculate which central regions and peripheral sources in particular circulating BDNF originates from, where it is transported to and to what purpose it is used and/or stored at its final destination. No study could show a long-lasting BDNF response to acute exercise or training (i.e. permanently increased basal peripheral BDNF concentration) in healthy subjects or persons with a chronic disease or disability. It seems that exercise and/or training temporarily elevate basal BDNF and possibly upregulate cellular processing of BDNF (i.e. synthesis, release, absorption and degradation). From that point of view, exercise and/or training would result in a higher BDNF synthesis following an acute exercise bout (i.e. compared with untrained subjects). Subsequently, more BDNF could be released into the blood circulation which may, in turn, be absorbed more efficiently by central and/or peripheral tissues where it could induce a cascade of neurotrophic and neuroprotective effects.

Neuroplasticity refers to the ability of the brain and CNS to adapt to environmental change, respond to injury and to acquire novel information by modifying neural connectivity and function. Neurotrophins support (activity-dependent) neuroplasticity; in particular, they are capable of signalling neurons to survive, differentiate or grow.[1-5] Therefore, neurotrophins gain increasing attention in research for the treatment and prevention of neurodegenerative and, more recently, metabolic diseases.[5-10] Neurotrophic factors not only play a role in neurobiology, but also in central and peripheral energy metabolism.[11] Their effect on synaptic plasticity in the CNS involves elements of cellular energy metabolism[12] and in the periphery they take part in metabolic processes such as enhancing lipid oxidation in the skeletal muscle via activation of AMPK (i.e. adenosine monophosphate-activated protein kinase).[10]

Physical activity and, in particular, acute exercise and training seem to be key interventions to trigger the processes through which neurotrophins mediate energy metabolism and in turn neural plasticity.[1-3,13-17] Of all neurotrophins, brain-derived neurotrophic factor[18] (BDNF) seems to be the most susceptible to regulation by exercise and physical activity.[2,3,5] BDNF is a basic protein of 252 amino acids that is coded by the *BDNF* gene. This gene extends over 70 kb, is located on chromosome 11, band p13 and contains 11 exons and 9 functional promoters.[19-21] As in all other neurotrophins, BDNF has a single coding exon; the 3′ exon that encodes for most of the protein.[21] Recently, a variant in the human *BDNF* gene has been identified,[22] Val66Met, a single nucleotide polymorphism (SNP) at nucleotide 196 (G/A) that encodes an amino acid substitution (i.e. a valine [Val] to methionine allele [Met]) at codon 66 in the prodomain of the *BDNF* gene.[22,23] This gene mutation occurs in 20–30% of the human population[24,25] and results in a decreased activity-induced response of BDNF.[23] Casey et al.[25] predict that carriers of the variant $BDNF_{Met}$ allele will have less neurotrophic support for plasticity at a certain moment in their development, whereas carriers of the $BDNF_{Val}$ allele will experience the inverse.[25,26]

It is generally accepted that BDNF has a wide repertoire of neurotrophic and neuroprotective properties in the CNS and the periphery; namely, neuronal protection and survival, neurite expression, axonal and dendritic growth and remodelling, neuronal differentiation and synaptic plasticity such as synaptogenesis in arborizing axon terminals, and synaptic transmission efficacy.[27-31] Animal studies also revealed a neuroendocrine and/or metabotrophic capacity of BDNF in the periphery, which (i) reduces food intake; (ii) increases oxidation of glucose; (iii) lowers blood glucose levels; and (iv) increases insulin sensitivity.[32-36] In addition, Molteni et al.[37] found that, in animals, a high-fat diet reduces hippocampal levels of

BDNF, but exercise is able to reverse this dietary decrease. Komori et al.[38] showed a central interaction between the adipocyte-derived hormone leptin that plays a key role in regulating appetite and energy metabolism and BDNF expression in the hypothalamus of mice. A human case study revealed a clinical phenotype of impaired cognitive function, hyperactivity and severe obesity associated with a chromosomal inversion of a region encompassing the *BDNF* gene and a reduction of serum BDNF.[39] Additionally, Araya et al.[40] found that serum BDNF was increased in insulin-resistant, overweight and obese subjects after a reduced-calorie diet. These findings confirm that BDNF is not only essential in the neuronal system, but is also intimately connected with central and peripheral molecular processes of energy metabolism and homeostasis.[11,41]

In search of mechanisms underlying plasticity and brain health, exercise is known to induce a cascade of molecular and cellular processes that support (brain) plasticity. BDNF could play a crucial role in these induced mechanisms. Therefore, since the early 1990s, studies started to investigate the effects of physical activity, acute exercise and/or training on BDNF concentration, first in animals[42-46] and then, since 2003, in humans.[47] The first human study examined the effect of acute exercise on peripheral BDNF in subjects with a neurodegenerative disease (i.e. multiple sclerosis [MS]) in order to explore the restorative potential of exercise.[47] Since then, two dozen other studies on the effects of acute exercise and/or training on BDNF have been conducted of which most concern healthy subjects. The purpose of the current review is to provide an insight in the overall effect of physical activity on peripheral concentration of BDNF.

1. Literature Search Methodology

1.1 Search Strategy

A comprehensive literature search was conducted in 2009–10. The following seven databases were consulted: PubMed, Web of Science, SportDiscus®, Cochrane Library, PEDro, Darenet and Narcis. Databases were screened on relevant literature from the beginning of each database up to July 2010. The search combined the following keywords: 'BDNF', 'exercise', 'training', 'physical activity', 'neuroplasticity', 'neuroplasticity proteins', 'neurotrophins', 'activity-dependent plasticity' and 'neurogenesis'. Eligibility of the studies based on titles, abstracts and full-text articles was initially determined by the first author (figure 1). The second author independently came to the same selection of studies after screening the literature.

1.2 Criteria for Consideration

Studies were selected using predetermined inclusion and exclusion criteria. An initial raw screening resulted in a selection of 860 articles. A more profound screening of titles, abstracts and full-text articles, based on specific criteria, resulted in a final selection of 24 studies. Figure 1 shows the progress of the literature screening and the reasons for inclusion or exclusion.

Inclusion criteria were as follows: healthy subjects; persons with a chronic disability or disease; acute aerobic and strength exercise protocols (low to high intensity); endurance/aerobic, strength/resistance training protocols (low to high intensity); randomized controlled trials; controlled trials; clinical trials; comparative and evaluation studies; assessment of peripheral (serum and plasma) BDNF concentrations; and articles written in English, French, Dutch or German. Studies were excluded when they concerned animals, no exercise/training intervention, no physical activity, behavioural studies, reviews, studies on cognitive learning, no assessment of peripheral BDNF and general studies on neuroplasticity/neurogenesis. Inclusion and exclusion criteria were selected to be able to give an answer to the question whether acute exercise or training has an effect on peripheral BDNF, in particular, in humans. This question is of interest as acute exercise and training could be a viable treatment of neurodegenerative and metabolic diseases through their possible effect on neurotrophins and, thus, neuroplasticity. Four studies with no acute exercise or training intervention were nevertheless included in this review because of their possible relevant contribution. The four studies research the relation

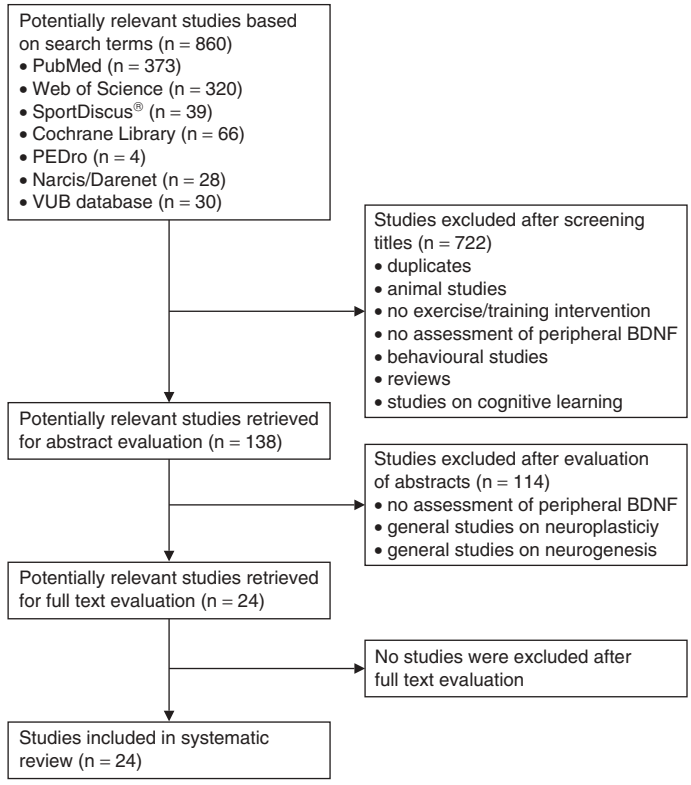

Fig. 1. Flow diagram of the systematic literature research.[48,49] **BDNF** = brain-derived neurotrophic factor.

between the level of physical fitness and basal peripheral BDNF concentration.

1.3 Data Extraction

The 24 included studies were reviewed for relevant information by the first author. Data on study design, sample size, study population, intervention, outcome measures and results were collected and are summarized in table I.

2. Exercise and Peripheral Brain-Derived Neurotrophic Factor (BDNF)

The main purpose of this literature review is to provide an insight in the effects of exercise and/or training on peripheral concentration of BDNF. The second purpose is to review the materials and methods that were used to research the effects of exercise and/or training on BDNF. The following sections summarize the study populations, exercise protocols, biochemical analysis, basal BDNF concentrations and the effects of exercise or training on peripheral BDNF in all included studies.

2.1 Number and Type of Studies

Twenty-four studies were included; nine studies were randomized controlled trials,[50,54,56,60,66-69,71] one was a randomized non-controlled trial,[72] five were non-randomized controlled trials,[47,51,57-59] five were non-randomized, non-controlled comparative trials (the study of Rojas Vega et al.[63] has a corrigendum that was published a year later;[64] we always refer to this study and the corrigendum)[62-65,70,75] and four studies were retrospective observational studies.[52,53,55,61]

Table I. Data extraction from 24 included studies

Study (year)	Study design	Sample size; sex; age (mean ± SD)	Intervention; Groups	Outcome measures	Results
Baker et al.[50] (2010)	RCT	33 patients with mild cognitive impairment; 48% M; 70.0 ± 8.3 y	24-wk aerobic training, pre-/post-training GXT; Aerobic training and stretching control group	$\dot{V}O_{2peak}$, $[BDNF]_p$, $[insulin]_p$, $[COR]_p$, $[IGF\text{-}1]_p$, $[\beta\text{-amyloids } 40\text{-}42]_p$, cognitive tests	$[BDNF]_p$ in F with MCI > $[BDNF]_p$ in M with MCI ($p = 0.09$) Wk 24 at rest: ↓ in $[BDNF]_p$ in F and ↑ in $[BDNF]_p$ in M vs controls[a]; $[BDNF]_p$ ~ $[cortisol]_p$ in aerobic training group
Castellano and White[51] 2008)	CT	22 subjects (11 MS patients, 11 healthy controls); 27.3% M; 40.0 ± 10.0 y	8-wk aerobic training, pre-training: GXT, pre-/mid-/post-training: LMI; Persons with MS and healthy control group	$\dot{V}O_{2peak}$, $[BDNF]_s$, $[IGF\text{-}1]_s$	Wk 0 at rest: $[BDNF]_s$ in MS < $[BDNF]_s$ in controls Wk 0 after LMI: $[BDNF]_s$ ↓ in MS and controls Wk 4 at rest: $[BDNF]_s$ ↑ in MS; $[BDNF]_s$ → in controls Wk 4 after LMI: $[BDNF]_s$ ↓ in MS and controls Wk 8 at rest: $[BDNF]_s$ → in MS and controls Wk 8 after LMI: $[BDNF]_s$ ↓ in MS and controls BDNF was measured 30 min, 2 h and 3 h post-LMI
Chan et al.[52] (2008)	ROS	85 healthy subjects; 48.2% M; 36.1 ± 7.8 y	No intervention; Highly and moderately trained	$[BDNF]_s$, questionnaire on lifestyle	$[BDNF]_s$ highly trained < $[BDNF]_s$ moderately trained $[BDNF]_s$ ~ watching television at younger age
Currie et al.[53] (2009)	ROS	44 healthy subjects; 63.6% M; 34.3 ± 10.9 y	No intervention; High cardio-respiratory and low cardio-respiratory fit group	$\dot{V}O_{2max}$ (estimated), HR, $[BDNF]_s$, HPA index	$[BDNF]_s$ in high cardio-respiratory fit subjects < $[BDNF]_s$ in low cardio-respiratory fit subjects
Ferris et al.[54] (2007)	RCT (crossover)	15 healthy subjects; 73.3% M; 25.4 ± 1.0 y	Acute aerobic exercise: LMI and HI, pre exercise: GXT; LMI and HI (crossover) group	HR, $[BDNF]_s$, lactate, cognitive assessment	GXT: ↑ in $[BDNF]_s$; $[BDNF]_s$ ~ [lactate] LMI: → in $[BDNF]_s$ HI: ↑ in $[BDNF]_s$ Cognitive function ↑ after LMI and HI
Floël et al.[55] (2010)	ROS	75 healthy subjects; 32.9% M; 60.5 ± 6.9 y	No intervention	$[BDNF]_s$, $[G\text{-}CSF]_s$, MRI, test and questionnaire on physical activity and memory encoding	No correlation between $[BDNF]_s$ and level physical activity $[G\text{-}CSF]_s$ ↑ ~ level physical activity ↑ Memory encoding ↑ ~ level physical activity ↑ Gray matter volume ↑ ~ level physical activity ↑
Goekint et al.[56] (2008)	RCT (double-blind, placebo, crossover)	11 healthy trained subjects; all M; 22.9 ± 4.3 y	Acute aerobic exercise: LMI and HI, acute drug administration (reboxetine), pre-exercise: GXT; No drug and drug group	HR, $[BDNF]_s$, $[COR]_s$, RPE[b], cognitive assessment	LMI and HI: ↑ in $[BDNF]_s$ HI ↑ > LMI ↑ No influence of drug on $[BDNF]_s$, but ↑ in $[COR]_s$, HR and memory

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Table I. Contd

Study (year)	Study design	Sample size; sex; age (mean ± SD)	Intervention; Groups	Outcome measures	Results
Goekint et al.[57] (2010)	CT	23 healthy subjects; 78.3% M; 20.8 ± 0.6 y	Acute strength exercise, 10-wk strength training; Strength training and control group	$[BDNF]_s$, $[IGF\text{-}1]_s$, $[IGFBP\text{-}3]_s$, cognitive assessment	Acute strength exercise, after sixth session: $[BDNF]_s \rightarrow$, $[IGF1]_s \rightarrow$, $[IGFBP3]_s \rightarrow$ After thirtieth session: $[BDNF]_s \rightarrow$, $[IGF1]_s \rightarrow$, $[IGFBP3]_s \rightarrow$ Strength training, wk 10 at rest: $[BDNF]_s \rightarrow$, $[IGF1]_s \rightarrow$, $[IGFBP3]_s \rightarrow$ in strength training group and controls; short-term memory ↑ in both groups (no differences between strength training group and controls); wk 10 after strength exercise: $[BDNF]_s \rightarrow$, $[IGF1]_s \rightarrow$, $[IGFBP3]_s \rightarrow$ in strength training group and controls
Gold et al.[47] (2003)	CT	45 subjects (25 MS patients, 20 healthy controls); 33.3% M; 39.9 ± 1.9 y	Acute aerobic exercise: LMI, pre-exercise: GXT; Persons with MS and healthy control group	$\dot{V}O_{2max}$, HR, $[BDNF]_s$, $[NGF]_p$, lactate	At rest: $[NGF]_p$ in MS > $[NGF]_p$ in controls; $[BDNF]_s$ in MS = $[BDNF]_s$ in controls LMI: $[BDNF]_s$ ↑ in MS and controls (no differences between MS and controls)
Gustafsson et al.[58] (2009)	CT	36 subjects (18 patients with MDD, 18 healthy controls); 50% M; 34.0 y	Acute aerobic exercise: LMI and HI; Patients with moderate MDD and healthy control group	HR, RPE[b], $[BDNF]_p$, [COR], MADRS-score	At rest: $[BDNF]_p$ in MDD = $[BDNF]_p$ in controls LMI: $[BDNF]_p$ ↑ in M MDD; $[BDNF]_p \rightarrow$ in M controls, F MDD and F controls HI: $[BDNF]_p$ ↑ in M MDD at 0 min and 60 min post-HI exercise; $[BDNF]_p$ ↑ in F MDD and M controls at 0 min post-HI; $[BDNF]_p \rightarrow$ in F controls at 0 min post-HI; $[BDNF]_p \rightarrow$ in F MDD and F and M controls at 60 min post-HI; $[BDNF]_p \rightarrow$ in M and F MDD and controls at 30 min post-HI No correlation between: $[BDNF]_p$ and cortisol; $[BDNF]_p$ and MADRS scores
Laske et al.[59] (2010)	CT	55 subjects (35 patients with remitted MDD, 20 healthy controls); 0% M; 60.0 ± 6.9 y	Acute aerobic exercise: HI; Patients with remitted MDD and healthy control group	$\dot{V}O_{2peak}$, ECG, RPE[b], lactate, $[BDNF]_s$, HAMD-scale, MMSE and DemTect score, HPA index	At rest: $[BDNF]_s$ in MDD < $[BDNF]_s$ in healthy controls; BMI in MDD > BMI in healthy controls; physical fitness in MDD < physical fitness in healthy controls; $[BDNF]_s$ ~ HAMD-score in MDD HI: $[BDNF]_s$ ↑ in MDD, $[BDNF]_s \rightarrow$ in healthy controls at 0 min post-HI; $[BDNF]_s$ ↓ in MDD, $[BDNF]_s$ ↓ 30 min post-HI

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Table I. Contd

Study (year)	Study design	Sample size; sex; age (mean ± SD)	Intervention; Groups	Outcome measures	Results
Levinger et al.[60] (2008)	RCT	49 healthy untrained subjects; 51.0% M; 50.9 ± 6.2 y	10-wk strength training; HiMF and LoMF group	$[BDNF]_p$, $[TG]_p$, $[HDL]_p$, $[glucose]_p$, $[insulin]_p$, $[HbA1_c]_p$, anthropometry, muscle strength, MetS, blood pressure	Wk 0 at rest: $[BDNF]_p$ in HiMF > $[BDNF]_p$ in LoMF Wk 10 at rest: $[BDNF]_p \rightarrow$, muscle strength ↑, lean body mass ↑ $[BDNF]_p \sim$ risk factors for MetS ($[TG]_p$, $[glucose]_p$, $[HbA1_c]_p$, insulin resistance)
Nofuji et al.[61] (2008)	ROS	26 healthy subjects; all M; 22.1 ± 1.1 y	No intervention; Sedentary and trained group	$[BDNF]_s$, $[BDNF]_p$, $HbA1_c$, FBG, TC, HDL-C, TG, BMI, body fat (%), WHR, psychological assessment, physical activity	$[BDNF]_s$ in sedentary > $[BDNF]_s$ in trained subjects $[BDNF]_p$ in sedentary = $[BDNF]_p$ in trained subjects $[BDNF]_s$ negative ~ TEE, MEE and WC No differences in age, anthropometric and psychological parameters between sedentary and trained subjects
Rasmussen et al.[62] (2009)	T	8 healthy subjects; all M; 22–40 y	Acute aerobic exercise: HI, pre-exercise: GXT; No groups	HR, $[BDNF]_p$, lactate, glucose, S_aO_2, $S_{jv}O_2$, P_aCO_2	At rest: $[BDNF]_{p\ arterial} < [BDNF]_{p\ a\text{-}v\ diff} < [BDNF]_{p\ vena\ jug}$; $f_{BDNF} = 72 \pm 32\%$ HI: $[BDNF]_{p\ arterial} \uparrow$, $[BDNF]_{p\ vena\ jug} \uparrow$, $[BDNF]_{p\ a\text{-}v\ diff} \uparrow$; $[BDNF]_{p\ arterial} < [BDNF]_{p\ a\text{-}v\ diff} < [BDNF]_{p\ vena\ jug}$; $f_{BDNF} = 84 \pm 8\%$
Rojas Vega et al.[63,64] (2006, 2007)	T	8 healthy athletes; all M; 24.6 ± 1.3 y	Acute aerobic exercise: LMI and HI, pre-exercise: GXT; No groups	$\dot{V}O_{2max}$, HR, $[BDNF]_s$, $[COR]_s$, lactate, RPE[b]	LMI: $[BDNF]_s \rightarrow$, $[COR]_s \rightarrow$, lactate $\rightarrow$ HI: $[BDNF]_s \uparrow$, lactate ↑; $[COR]_s \uparrow$ during recovery (10 min and 15 min post-HI)
Rojas Vega et al.[65] (2008)	T	11 SCI athletes; all M; 40.6 ± 6.3 y	Acute aerobic exercise: LMI and HI, pre-exercise: GXT; No groups	$\dot{V}O_{2max}$, HR, $[BDNF]_s$, $[IGF\text{-}1]_s$, $[PRL]_s$, $[COR]_s$, lactate	At rest[c]: $[BDNF]_s \uparrow$; $[IGF\text{-}1]_s$, $[PRL]_s$, $[COR]_s$ normal LMI: $[BDNF]_s \uparrow$, $[IGF\text{-}1]_s \uparrow$, $[PRL]_s \rightarrow$, $[COR]_s \rightarrow$ HI: $[BDNF]_s \rightarrow$, $[IGF\text{-}1]_s \uparrow$; $[PRL]_s \uparrow$, $[COR]_s \uparrow$
Schiffer et al.[66] (2009)	RCT	27 healthy subjects; NS; 22.2 ± 1.8 y	12-wk strength training, 12-wk aerobic training, pre-/post-training: GXT; Aerobic, strength training and control group	$\dot{V}O_{2max}$, HR, $[BDNF]_p$, $[IGF\text{-}1]_p$, lactate	Wk 12 at rest, strength training: $[BDNF]_p \rightarrow$, strength ↑, $[IGF\text{-}1]_p \downarrow$; aerobic training: $[BDNF]_p \rightarrow$, aerobic performance ↑, $[IGF\text{-}1]_p \downarrow$ – controls: $[BDNF]_p \rightarrow$, $[IGF\text{-}1]_p \downarrow$

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Table I. Contd

Study (year)	Study design	Sample size; sex; age (mean ± SD)	Intervention; Groups	Outcome measures	Results
Schulz et al.[67] (2004)	RCT	28 MS patients; 32.1% M; 39.5 ± 10 y	8-wk aerobic training, pre-/post-training: GXT and LMI; Persons with MS and MS control (no intervention) group	$\dot{V}O_{2max}$, HR, $[BDNF]_s$, $[NGF]_s$, $[IL\text{-}6]_p$, $[sIL\text{-}6R]_p$, $[ACTH]_p$, $[COR]_p$, $[NE]_p$, $[E]_p$, $[lactate]_s$, assessment of coordinative function, psychological assessment	Wk 0 after LMI: $[BDNF]_s$ ↑ [d] Wk 8 after LMI (vs rest at wk 8): lactate ↓, $[BDNF]_s$ ↑ [d] Wk 8 at rest and after LMI vs wk 0: $[BDNF]_s$ →, $[NGF]_s$ →, $[IL\text{-}6]_p$ →, $[sIL\text{-}6R]_p$ →, $[ACTH]_p$ →, $[COR]_p$ →, $[NE]_p$ →, $[E]_p$ →; disease-specific quality of life ↑ <–> wk 8 at rest and after LMI: $[BDNF]_s$ ↑ in MS, but difference with MS control group and assessment at wk 0 was not significant
Seifert et al.[68] (2010)	RCT	12 obese subjects; all M; 30.0 ± 6.5 y	12-wk aerobic training, pre-training: GXT, pre-/post-training: LMI and HI; Aerobic training and control group	$\dot{V}O_{2max}$, HR, $[BDNF]_{p\ arterial}$ and $[BDNF]_{p\ vena\ jug}$, MCA V_{mean}, CBF	Wk 0 after HI: $[BDNF]_{p\ arterial}$ ↑, $[BDNF]_{p\ vena\ jug}$ →; $[BDNF]_{p\ vena\ jug}$ in trained > $[BDNF]_{p\ vena\ jug}$ in control; $[BDNF]_{p\ a\text{-}v\ diff}$ in trained $[BDNF]_{p\ a\text{-}v\ diff}$ in control Wk 12 at rest: $[BDNF]_{p\ arterial}$ →, $[BDNF]_{p\ vena\ jug}$ ↑, $[BDNF]_{p\ a\text{-}v\ diff}$ ↑; $[BDNF]_{p\ vena\ jug}$ in trained > $[BDNF]_{p\ vena\ jug}$ in control; $[BDNF]_{p\ a\text{-}v\ diff}$ in trained $[BDNF]_{p\ a\text{-}v\ diff}$ in control Wk 12 after HI: $[BDNF]_{p\ arterial}$ → compared with pre-training after HI; $[BDNF]_{p\ arterial}$ ↑ compared with post-training at rest; $[BDNF]_{p\ vena\ jug}$ → compared with pre-training after HI and to post-training at rest; $[BDNF]_{p\ vena\ jug}$ in trained > $[BDNF]_{p\ vena\ jug}$ in control; $[BDNF]_{p\ a\text{-}v\ diff}$ in trained $[BDNF]_{p\ a\text{-}v\ diff}$ in control
Ströhle et al.[69] (2010)	RCT (crossover)	24 subjects (12 patients with panic disorder, 12 healthy controls); 25% M; 31.4 ± 2.4 y	Acute aerobic exercise: LMI; LMI, quiet rest and healthy control group	$VAS_{arousal/anxiety}$, $[BDNF]_s$	At rest: $[BDNF]_s$ ↓ in subjects with panic disorder LMI: $[BDNF]_s$ ↑ in subjects with panic disorder, $[BDNF]_s$ in healthy controls; $[BDNF]_s$ ~ $VAS_{arousal/anxiety}$
Tang et al.[70] (2008)	T	16 healthy subjects; 50% M; 19–30 y	Acute aerobic exercise: LMI; No groups	HR, $[BDNF]_s$	At rest: large inter-individual differences in $[BDNF]_s$; LMI: $[BDNF]_s$ ↑
Winter et al.[71] (2007)	RCT (crossover)	27 healthy subjects; all M; 22.2 ± 1.7 y	Acute aerobic exercise: LMI and HI, pre-exercise: GXT; LMI, HI and control group	HR, $[BDNF]_s$, $[DA]_p$, $[NE]_p$, $[E]_p$, lactate, RPE[b], cognitive assessment, mood rating	LMI: $[BDNF]_s$ ↑, $[DA]_p$ ↑, $[NE]_p$ ↑, $[E]_p$ ↑ HI: $[BDNF]_s$ ↑, $[DA]_p$ ↑, $[NE]_p$ ↑, $[E]_p$ ↑ $[BDNF]_s$: HI ↑ > controls ↑

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Table I. Contd

Study (year)	Study design	Sample size; sex; age (mean ± SD)	Intervention; Groups	Outcome measures	Results
					$[DA]_p$: HI ↑ = LMI ↑ = controls ↑ $[NE]_p$: HI ↑ > LMI ↑ > controls ↑ $[E]_p$: HI ↑ > controls ↑ Cognitive assessment: 20% better after HI compared with LMI and controls
Yarrow et al.[72] (2010)	RT	20 healthy subjects; all M; 21.9 ± 0.8 y	Acute strength exercise: 5-wk strength training; TRAD and ECC+ group	$[BDNF]_s$, $[testosterone]_s$, [growth hormone]$_s$, $[lactate]_s$[73,74]	Acute strength exercise (wk 0): $[BDNF]_s$ → in TRAD and ECC+ Strength training, wk 5 at rest: $[BDNF]_s$ → in TRAD and ECC+; wk 5 after strength exercise: $[BDNF]_s$ ↑ in TRAD and ECC+ ↑ $[BDNF]_s$ from rest to post-strength exercise is 98% greater in post-strength training compared with baseline ↑ $[BDNF]_s$ is load dependent
Zoladz et al.[75] (2008)	T	13 healthy subjects; all M; 22.7 ± 0.5 y	5-wk aerobic training, pre-/post-training: GXT; No groups	$\dot{V}O_{2max}$, HR, $[BDNF]_p$, $[insulin]_p$, $[glucose]_p$, $[lactate]_p$	Wk 0 after GXT: $[BDNF]_p$ → Wk 5 at rest: $[BDNF]_p$ ↑ Wk 5 after GXT: $[BDNF]_p$ ↑ Wk 5: $[BDNF]_p$ ↑ after GXT > $[BDNF]_p$ ↑ at rest

a This is a sex-specific effect of aerobic training versus stretching on $[BDNF]_p$ (i.e. group X sex ANOVA, $F_{1,23} = 4.68$; $p = 0.04$).[50]

b See Borg[76] for the RPE = rating of perceived exertion.

c Rojas Vega et al.[65] did not include a control group of healthy subjects in their study. Consequently, the finding that baseline $[BDNF]_s$ is increased compared with able-bodied subjects cannot be verified.

d Schulz et al.[67] found no statistically significant differences at wks 0 and 8 of aerobic training at rest or after LMI between the MS group and the MS control group. The differences that are mentioned in this table are not significant.

ACTH = adrenocorticotropic hormone; **BDNF** = brain-derived neurotrophic factor; **$[BDNF]_{p\ arterial}$** = [BDNF] measured in arterial plasma; **$[BDNF]_{p\ vena\ jug}$** = [BDNF] measured in jugular venous plasma; **$[BDNF]_{p\ a\text{-}v\ diff}$** = difference between arterial and jugular venous plasma BDNF concentration; **BMI** = body mass index; **CBF** = cerebral blood flow; **COR** = cortisol; **CT** = non-randomized controlled trial; **DA** = dopamine; **DemTect** = cognitive screening for diagnosis of mild cognitive impairment and dementia ; **E** = epinephrine; **ECC+** = eccentric-enhanced resistance exercise/training; **ECG** = electrocardiogram; **F** = female; **FBG** = fasting blood glucose; **f_{BDNF}** = cerebral fractional release of BDNF; **G-CSF** = granulocyte colony stimulating factor; **GXT** = graded exercise test; **HAMD-scale** = Hamilton rating scale for depression; **HbA_{1c}** = glycated hemoglobin A_{1c}; **HDL** = high density lipoprotein; **HI** = high-intensity exercise; **HiMF** = high metabolic risk group; **HPA-index** = Baecke habitual physical activity index; **HR** = heart rate; **IGF-1** = insulin-like growth factor-1; **IGFBP-3** = insulin-like growth factor binding protein 3; **IL** = interleukin; **LMI** = low to moderate intensity exercise; **LoMF** = low metabolic risk group; **M** = male; **MADRS-score** = Montgomery-Asberg depression rating scale; **MCA V_{mean}** = mean flow velocity of middle cerebral artery; **MCI** = mild cognitive impairment; **MDD** = major depressive disorder; **MEE** = movement-related energy expenditure; **MetS** = metabolic risk factor; **MMSE** = mini-mental status examination; **MRI** = magnetic resonance imaging; **MS** = multiple sclerosis; **NE** = norepinephrine; **NGF** = neuronal growth factor; **NS** = not specified; **P_aCO_2** = arterial carbon dioxide tension; **PRL** = prolactin; **RCT** = randomized controlled trial; **ROS** = retrospective observational study; **RPE** = rating of perceived exertion; **RT** = randomized non-controlled trial; **S_aO_2** = arterial haemoglobin oxygen saturation; **SCI** = spinal cord injured; **$S_{jv}O_2$** = jugular venous haemoglobin oxygen saturation; **T** = non-randomized non-controlled trial; **TC** = cholesterol; **TEE** = total daily energy expenditure; **TG** = triglycerides; **TH** = threshold; **TRAD** = traditional resistance exercise/training; **$VAS_{arousal/anxiety}$** = visual analogue scale for arousal and anxiety; **V_{th}** = ventilator threshold; **$\dot{V}O_{2max}$** = maximal oxygen uptake; **$\dot{V}O_{2peak}$** = peak oxygen uptake; **WC** = walking count; **WHR** = waist-to-hip ratio; $[]_s$ indicates serum concentration; $[]_p$ indicates plasma concentration; ~ indicates correlation; ↑ indicates significant increase; ↓ indicates significant decrease; → indicates no significant difference.

2.2 Study Populations

The sample size of trials that were included in this review varied from 8[62-64] to 55[59] subjects with a mean sample size of 24 subjects. For the four retrospective observational studies, sample sizes were larger, ranging from 26[61] and over 44[53] and 75[55] to 85[52] subjects. Proof of evidence would become more solid if all studies included an *a priori* power analysis to determine the appropriate sample size.

Study populations were drawn from several sources; for example, general population,[47,54,57,60,66] students,[66] athletes,[56,63,64] spinal cord injured (SCI) athletes,[65] persons with major depression,[58,59] cognitive impairment[50] or MS.[47,51,67] Thirteen studies examined both males and females,[47,50-55,57-58,60,67,69-70] while nine studies examined only males[56,61-65,68,71-72,75] and one study only females.[59] The mean age of participants in all the included studies ranged from 20.8 ± 0.6 years[57] to 70.0 ± 8.3 years.[50] Three studies examined a population of the elderly (i.e. mean age ≥55.0 years)[50,55,59] and no study that included children or adolescents (i.e. mean age ≤18.0 years). Lommatzsch et al.[77] showed that basal concentrations of BDNF significantly changes with increasing age. Katoh-Semba et al.[78] stated that children and adolescents could be prone to changes in neurotrophines due to maturation and growth. Therefore, it might be interesting to study possible differences in effects of acute exercise and training on peripheral concentration of BDNF between young and old healthy subjects or in young and old persons with a chronic disease or disability.

In most of the included studies, it is not always clear whether it concerns untrained, moderately trained or well trained subjects. Studies should report on the level of fitness, expressed in maximal oxygen uptake ($\dot{V}O_{2max}$) or maximal power output, of their study population. It is likely that the effects of acute exercise and training on peripheral BDNF depend on the physical fitness of the subjects, as BDNF could be involved in processes of energy metabolism.[37,40,79]

2.3 Exercise Protocols

Twenty out of 24 studies applied an exercise intervention. In general, four different interventions can be distinguished as follows: an acute aerobic or strength exercise; and an aerobic or strength training programme.

2.3.1 Acute Exercise Protocols

Predominantly, the effect of an acute aerobic exercise on peripheral BDNF has been investigated in human subjects. However, there is a large variation in the protocols used to apply to an acute aerobic exercise intervention (tables II and III).

Graded exercise tests (GXTs) should be distinguished from acute aerobic exercise protocols of long or short duration. Sixteen of 20 interventional studies carried out a GXT until exhaustion a few days prior to the intervention or as an intervention on its own. In these studies, GXTs are mainly performed to determine the intensity of an acute aerobic exercise or training protocol. In three studies, a GXT was used as an isolated intervention to study its effect on circulating concentrations of BDNF.[54,59,75] In these cases, a GXT is evaluated as a short acute exercise of high intensity (table III). In two studies a GXT was part of a prolonged acute exercise protocol of high intensity[1].[55,62,63] Protocols of all GXTs can be found in table II.

Fifteen of 20 studies applied an acute aerobic exercise intervention (table III). Seven of those studies (table III) investigated the effect of both low to moderate and high-intensity aerobic exercises,[54,56,58,63-65,68,71] five studies focused only on exercises of low to moderate intensity[47,51,67,69,70] and three on the effects of an isolated high-intensity exercise[59,62,75] on concentration of BDNF. The protocols of the acute exercise interventions differ in each study, which makes it difficult to

1 It should be noted that in the studies of Rojas Vega et al.[63,64] and Gustafsson et al.,[58] an acute exercise of low to moderate intensity preceded the GXT. This could influence the effect of a GXT on peripheral BDNF levels. The preceding exercise of low to moderate intensity, together with the GXT, has also been evaluated as a prolonged acute exercise protocol of high intensity and will be discussed in section 2.6.1.

Table II. Protocols for graded exercise tests (GXTs) until volitional fatigue prior to or following an acute exercise or training protocol

Study (year)	GXT	Exercise	GXT protocol	GXT until exhaustion (mean maximal exercise values at baseline)	BDNF measured pre- and post-GXT
Acute aerobic exercise protocols					
Castellano and White[51] (2008)	Yes	Cycling	NS + 5–20 W every 2 min	Yes (NS: symptom-limited maximum or 85% of estimated HR_{max})	No
Ferris et al.[54] (2007)	Yes	Cycling	NS	WR_{max} (293.47 ± 17.65 W); $\dot{V}O_{2max}$ (2805.80 ± 164.31 mL/min); HR_{max} (175.67 ± 3.19 bpm), % pred HR_{max} (90.31 ± 1.75 %); RER (1.27 ± 0.02); lactate (10.67 ± 0.66 mmol/L)	Yes ↑
Goekint et al.[56] (2008)	Yes	Cycling	80 W + 40 W every 3 min	Yes (NS)	No
Gold et al.[47] (2003)	Yes	Cycling	25 W + 25 W every 2 min	Yes (NS)	No
Gustafsson et al.[58] (2009)	Yes	Cycling	50 W (30 W F) + 5 W every 20 s (30 s F)	Yes (NS)	Yes ↑ [a,b]
Laske et al.[59] (2010)	Yes	Treadmill	3 km/h at 0% inclination + simultaneous ↑ in speed and inclination every 3 min[c]	$\dot{V}O_{2max}$ (1.9 ± 0.3 mol/L/min); W_{max}/kg (1.3 ± 0.4 W/kg)	Yes ↑ [d]
Rasmussen et al.[62] (2009)	Yes	Rowing	NS	Yes (NS)	No
Rojas Vega et al.[63,64] (2006, 2007)	Yes	Cycling	NS + 40 W every 5 min	Time test (7.3 ± 1.1 min); W_{peak} (431.3 ± 57.9 W); relative W_{peak} (5.9 ± 0.7 W/kg); $\dot{V}O_{2max}$ (56.6 ± 8.6 mL/kg/min); HR_{max} (189.3 ± 10.3 bpm)	Yes ↑ [a]
Rojas Vega et al.[65] (2008)	Yes	Handcycling	20 W + 20 W every 5 min	W_{max} (158.2 ± 28.9 W); HR_{max} (183 ± 11.8 bpm); $\dot{V}O_{2max}$ (34.5 ± 9.2 mL/kg/min); RPE_{max} (19.5 ± 1.2)	No
Ströhle et al.[69] (2010)	No	NS	NS	NS	NS
Tang et al.[70] (2008)	No	NS	NS	NS	NS
Winter et al.[71] (2007)	Yes	Running (field)	8 km/h + 2 km/h every 3 min	Yes (NS)	No
Acute strength exercise protocols					
Goekint et al.[57] (2010)	No	NS	NS	NS	NS
Yarrow et al.[72] (2010)	No	NS	NS	NS	NS
Aerobic training protocols					
Baker et al.[50] (2010)	Pre/post	Treadmill walking	2 km/h + NS[e]	$\dot{V}O_{2peak}$ (22.95 ± 4.35 mol/L/kg)	No
Castellano and White[51] (2008)	Pre	Cycling	NS + 5–20 W every 2 min	Yes (NS: symptom-limited maximum or 85% of estimated maximum heart rate)	No
Schiffer et al.[66] (2009)	Pre/post	Running	7 km/h + 1.5 km/h; NS	Yes (NS: RER >1.1; HR >190; lactate > 8)	No
Schulz et al.[67] (2004)	Pre/post	Cycling	25 W + 25 W every 2 min	W_{max} (168.8 ± 40.5 W); $\dot{V}O_{2max}$ (31.0 ± 7.45 mL/kg/min)	No
Seifert et al.[68] (2010)	Pre	Cycling	75 W + 25 W every 1 min	$\dot{V}O_{2max}$ (3.45 ± 0.3 L/min); RER >1.14	No
Zoladz et al.[75] (2008)	Pre/post	Cycling	30 W + 30 W every 3 min	$\dot{V}O_{2max}$ (3472 ± 94 ml/min [or 45.29 ± 0.93 mL/kg/min]); W_{max} (255 ± 7 W)	Yes →

Continued next page

Table II. Contd

Study (year)	GXT	Exercise	GXT protocol	GXT until exhaustion (mean maximal exercise values at baseline)	BDNF measured pre- and post-GXT
Strength training protocols					
Goekint et al.[57] (2010)	No	NS	NS	NS	NS
Levinger et al.[60] (2008)	No	NS	NS	NS	NS
Schiffer et al.[66] (2009)	Pre/post	Running	7 km/h+1.5 km/h every NS	Yes (NS: RER >1.1; HR >190; lactate >8)	No
Yarrow et al.[72] (2010)	No	NS	NS	NS	NS

a In the studies of Gustaffson et al.[58] and Rojas Vega et al.,[63,64] the GXT was preceded by an acute aerobic exercise of moderate intensity, so the increase in BDNF may not be exclusively contributed to the effect of a GXT on its own. Protocols of both studies will be considered as a prolonged acute aerobic exercise protocol of high-intensity exercise and will be described in table III.

b Significant increase in $[BDNF]_p$ in M and F MDD patients and healthy M control subjects following a GXT but not in healthy F control subjects (Gustaffson et al.[58]).

c Laske et al.[59] used the same protocol as Porszasz et al.[80] for the acute aerobic exercise protocol.

d Significant increase in $[BDNF]_s$ in MDD patients following a GXT but not in healthy control subjects (Laske et al.[59]).

e Baker et al.[50] used the modified Balke test[81] for their aerobic training protocol.

% pred HR_{max} = percentage of predicted maximal heart rate; **BDNF** = brain-derived neurotrophic factor; **bpm** = beats per minute; **F** = female; **HI** = exercise of high-intensity; **HR** = heart rate; HR_{max} = maximal heart rate; **M** = male; **NS** = not specified; **RER** = respiratory exchange ratio; RPE_{max} = maximal rating of perceived exertion[82]; $\dot{V}O_{2max}$ = maximal oxygen uptake; $\dot{V}O_{2peak}$ = peak oxygen uptake; W_{max} = maximal power output; WR_{max} = maximal work rate; ↑ indicates significant increase; → indicates no significant difference.

compare between studies. Nevertheless, all studies could be categorized according to their exercise intensity (i.e. based on exercise load and duration) [table III]. In four studies the acute exercise intervention was part of the test protocol before and after an aerobic training programme. The effect of an aerobic training programme on the BDNF response from rest to the end of a standardized acute exercise of low, moderate or high intensity was studied.[51,67,68,75]

Recently, the relation between an acute strength exercise session and concentration of BDNF was researched in two studies.[57,72] Goekint et al.[57] and Yarrow et al.[72] used an acute strength exercise session to analyse the change in BDNF from rest to immediately post-exercise and this was repeated at the end of a strength training programme.

Table III shows that the moments of blood acquisition for analysis of BDNF are similar in most of the 16 studies on acute exercise: (i) at baseline; (ii) immediately following a low-, moderate- or high-intensity strength or aerobic exercise; and (iii) 15-60 minutes following the acute exercise. In two cases blood was not collected immediately following the acute exercise[51,70] and only Castellano and White[51] collected blood more than 60 minutes following the acute exercise.

2.3.2 Exercise Training Protocols

Six studies implemented an aerobic training programme ranging from 5 to 24 weeks, two to seven sessions a week of different loads, mode and duration.[50,51,66-68,75] Except for Baker et al.[50] and Schiffer et al.,[66] all studies on aerobic training investigated the effects of training on basal concentration of BDNF and on BDNF concentration following an acute exercise. Details on the aerobic training programme can be found in table IV. A strength training programme was conducted in four studies during 5, 10 or 12 weeks, respectively, three sessions a week of different intensity and repetitions.[57,60,66,72,83] Goekint et al.[57] and Yarrow et al.[72] studied the effects of strength training on basal concentration of BDNF and on BDNF concentration following an acute strength exercise session. A complete body workout with strength training devices was

Table III. Protocols for acute aerobic and strength exercise interventions in 17 studies (i.e. acute exercise protocols, not graded exercise tests [GXTs])

Study (year)	Setting	Exercise	Protocol	Moment of BDNF collection before, during and after the acute exercise
Acute aerobic exercise protocols				
LMI				
Castellano and White[51] (2008)	Laboratory	Cycling	30 min at 60% $\dot{V}O_{2peak}$	T0 // T30, T120, T180 post-LMI
Gold et al.[47] (2003)	Laboratory	Cycling	30 min at 60% $\dot{V}O_{2max}$	T0 // T0, T30 post-LMI
Schulz et al.[67] (2004)	Laboratory	Cycling	30 min at 60% $\dot{V}O_{2max}$	T0 // T0, T30 post-LMI
Ströhle et al.[69] (2010)	Laboratory	Walking	30 min at 70% $\dot{V}O_{2max}$	T0 // T0 post-LMI
Tang et al.[70] (2008)	Laboratory	Stepping	15 min	T0 // T10, T35 post-LMI
LMI and HI				
Ferris et al.[54] (2007)	Laboratory	Cycling	LMI: 30 min at V_{th} – 20% HI: 30 min at V_{th} + 10% GXT (see table II)	T0 // T0 post-LMI and -HI
Goekint et al.[56] (2008)	Climatic chamber	Cycling	LMI: 60 min at 55% W_{max} HI: LMI + TT equal to 30 min at 75% W_{max}	T0, T60 // T0, T15 post-HI
Gustafsson et al.[58] (2009)	Laboratory	Cycling	LMI in F: (30 W + 5 W every 30 s) + 6 min at $W_{constant}$ HI in F: LMI + GXT until exhaustion LMI in M/HI in M: *idem* as in F but with different intensity: 50 W + 5 W every 20 s	T0 // T0 post-LMI; T0, T30, T60 post-HI
Rojas Vega et al.[63,64] (2006, 2007)	Laboratory	Cycling	LMI: 10 min at 2 W/kg + 2 min at 2 W/kg HI: LMI + GXT with 25 W every 30 s until exhaustion + 15 min active recovery	T0, T10 // T0, T3, T6, T10, T15 post-HI
Rojas Vega et al.[65] (2008)	Laboratory	Handcycling	LMI: 10 min warm up at 54% HR_{max} HI: LMI + TT over 42 km at 89% HR_{max}	T0, T10 // T0 post-HI
Seifert et al.[68] (2010)	Laboratory	Cycling	LMI: 15 min at 70% $\dot{V}O_{2max}$ HI: 60% $\dot{V}O_{2max}$ with 10% $\dot{V}O_{2max}$ every 4 min (6 min rest between workloads until 100% $\dot{V}O_{2max}$)	T0, T5, T10, T15 // and at the end of each workload during incremental cycling
Winter et al.[71] (2007)	Laboratory	Running	LMI: 40 min at fixed individual HR and lactate <2 mM/L HI: 3 min sprint – 2 min rest – 3 min sprint at 8 km/h and every 10 s + 2 km/h until exhaustion and lactate >10 mmol/L	T0 // T0 post-HI // T0 post-learning task
HI				
Laske et al.[59] (2010)			See table II (GXT)	
Rasmussen et al.[62] (2009)	Laboratory	Rowing	240 at 10–15% below LT	T0, T120 // T0, T60 post-HI
Zoladz et al.[75] (2008)			See table II (GXT)	
Acute strength exercise protocols				
Goekint et al.[57] (2010)	Fitness centre	6 strength exercises	Warm up: 20 repetitions at 30% 1RM Exercise: 3 × 10 repetitions at 80% 1RM	T0 // T0 post-strength training session both in UC and TC

Continued next page

Table III. Contd

Study (year)	Setting	Exercise	Protocol	Moment of BDNF collection before, during and after the acute exercise
Yarrow et al.[72] (2010)	Laboratory (NS)	2 strength exercises per group	TRAD group: 4×6 repetitions at 52.5% 1RM concentrically and eccentrically ECC+ group: 3×6 repetitions at 40% 1RM concentrically and 100% 1RM eccentrically	T0 // T1, T30 and T60 post-strength exercise

1RM = one repetition maximum; **BDNF** = brain-derived neurotrophic factor; **ECC+** = eccentric-enhanced resistance exercise/training; **F** = female; **HI** = exercise of high-intensity; **HR** = heart rate; $\mathbf{HR_{max}}$ = maximal HR; **LMI** = exercise of low to moderate intensity; **LT** = lactate threshold; **M** = male; **NS** = not specified; **T** = moment of BDNF collection e.g. T120 = at 120 minutes following the start of the acute exercise or T60 post HI = 60 minutes following the end of the high-intensity exercise; **TC** = trained condition (at 30th strength training session); **TT** = time trial; **TRAD** = traditional resistance exercise/training; **UC** = untrained condition (at sixth strength training session); $\mathbf{V_{th}}$ = ventilatory threshold; $\mathbf{\dot{V}O_{2max}}$ = maximal oxygen uptake; $\mathbf{\dot{V}O_{2peak}}$ = peak oxygen uptake; $\mathbf{W_{constant}}$ = constant power output; $\mathbf{W_{max}}$ = maximal power output; [] indicates concentration; // separates moments of BDNF collection in time e.g. T0 // T0 post HI = T0 is at the start of the high intensity exercise, T0 post HI is the first BDNF collection immediately at the end of the high intensity exercise; so '//' separates moments of BDNF collection *during* and *following* an acute exercise.

accomplished in three out of four strength training studies.[57,60,66] Only Yarrow et al.[72] used just two strength exercises for the workout. In all studies circulating BDNF was analysed pre-/post-training and in two cases also halfway through the training programme.[50,51] Overall, training protocols differed in all studies (table IV).

2.4 Blood Sampling and Biochemical Analysis

For the analysis of free circulating peripheral BDNF, blood serum (16 studies) is preferred to that of blood plasma (eight studies). This could be due to the fact that blood serum has been the conventional standard for most biochemical analysis although, generally, the choice between blood serum and plasma is determined by the requirements of the individual laboratory. In some studies, preference is given to blood serum because the addition of anticoagulants (e.g. heparin or EDTA) in blood plasma can activate blood platelets and change the concentration of the constituents to be measured.[84,85] Concentrations of serum BDNF are approximately 200-fold higher relative to those of plasma BDNF, indicating that low concentrations of BDNF are circulating free in the blood and higher amounts of BDNF are stored in platelets or in immune cells.[86,87] Moreover, platelets circulate for up to 11 days in peripheral blood, whereas BDNF protein circulates in plasma for <1 hour, indicating that platelets could be a storage compartment and its BDNF could represent a long-term marker of varying plasma BDNF concentrations.[87,88] To finally unravel the link between plasma and serum BDNF, measurement of both plasma and serum BDNF could be interesting in future studies.

Table V provides an overview of the biochemical analysis of BDNF throughout the 24 studies. Methods for biochemical analysis of BDNF in venous blood samples were very heterogeneous and poorly described in most of the studies. Details of the blood sample collection and the preparation and storage of serum or plasma are generally not clarified enough in the materials and methods of the given studies. Yet, it is important to report accurately on the methodology used in order to interpret the given results because methodological factors could strongly influence measured BDNF values. When serum is being used, time to clot and temperature of clotting is often not mentioned. However, Katoh-Semba et al.[78] showed that BDNF in serum is gradually released from platelets at 4°C, while at room temperature of 26°C it immediately degrades. Moreover, a maximum concentration of BDNF could be found 24 hours after blood collection and remained stable until 42 hours.[78] This indicates the importance of the time the blood is left to clot prior to serum extraction and the temperature at which clotting occurs. A study of Trajkovska et al.[89] showed a decreased BDNF concentration in whole blood stored at 4°C but not at −20°C, whereas storage at −20°C of blood serum was associated with a significant decrease in BDNF concentration over time (i.e. after 6–10

Table IV. Protocols for aerobic and strength training interventions in nine studies

Study (year)	Exercise mode	Duration	Protocol	GXT	Standardized acute exercise	Moment of BDNF collection during the training period
Aerobic training protocols						
Baker et al.[50] (2010)	Treadmill, cycling ergometer, elliptical trainer	4 ×/wk for 24 wk	45–60 min at 75–85% $HR_{reserve}$	Pre- and post-training	NS	At 0, 12 and 24 wk at rest
Castellano and White[51] (2008)	Cycling	3 ×/wk for 8 wk	30 min at 60% $\dot{V}O_{2peak}$	Pre-training	Pre-, mid- and post-training	At 0, 4 and 8 wk at rest and T30, T120 and T180 post-LMI
Schiffer et al.[66] (2009)	Running	3 ×/wk for 12 wk	45 min at 80% HR of aerobic-anaerobic threshold	Pre- and post-training	NS	At 0 and 12 wk at rest
Schulz et al.[67] (2004)	Cycling	2 ×/wk for 8 wk	30 min interval training at maximum 75% W_{max} and 60% $\dot{V}O_{2max}$	Pre- and post-training	Pre- and post-training	At 0 and 8 wk at rest and T0 and T30 post-LMI
Seifert et al.[68] (2010)	Cycling, swimming, running or rowing	7 ×/wk for 12 wk	60 min at 70% of HR_{max} or 65% of $\dot{V}O_{2max}$	Pre-training	Pre- and post-training	At 0 and 12 wk at rest and post-HI
Zoladz et al.[75] (2008)	Cycling	4 ×/wk for 5 wk	2 ×/wk 40 min at PO of 90% $\dot{V}O_2$ at LT; 2 ×/wk 4 × 6 min unloaded + 3 min loaded at 50% Δ (= PO at LT + 0.5 [PO_{max} + PO_{LT}])	Pre- and post-training	NS	At 0 and 5 wk at rest and post-GXT
Strength training protocols						
Goekint et al.[57] (2010)	Complete body workout with strength training devices	3 ×/wk for 10 wk	0–2 wk: warm-up 20 repetitions at 30% 1RM; 3 × 10 repetitions at 50–70% 1RM; 2–10 wk: warm-up 20 repetitions at 30% 1RM; 3 × 10 repetitions at 80% 1RM	NS	Pre-[a] and post-training	At 0 and 10 wk at rest and T0 post-strength exercise
Levinger et al.[60] (2008)	Complete body workout with strength training devices	3 ×/wk for 10 wk	0–2 wk: 2 × 15–20 repetitions at 40–50% 1RM; 2–10 wk: 3 × 8–20 repetitions at 50–85% 1RM	NS	NS	At 0 and 10 wk at rest
Schiffer et al.[66] (2009)	Complete body workout with strength training devices	3 ×/wk for 12 wk	3 × 8–10 repetitions at 70–80% 1RM	Pre- and post-training	NS	At 0 and 12 wk at rest
Yarrow et al.[72] (2010)	2 strength exercises with strength training devices	3 ×/wk for 5 wk	TRAD group: 4 × 6 repetitions at 52.5–75% 1RM concentrically and eccentrically; ECC+: 3 × 6 repetitions at 40–50% 1RM concentrically and 100–120% 1RM eccentrically	NS	NS	At 0 and 5 wk at rest and T1, T30 and T60 post-strength exercise

a The first assessment of BDNF following a standardized acute strength exercise took place on the sixth session of the strength training programme instead of the first session. Goekint et al.[57] considered the sixth training session as the 'untrained condition' so that subjects were capable of completing the training session.

1RM = 1 repetition maximum; **BDNF** = brain-derived neurotrophic factor; **ECC+** = eccentric-enhanced resistance exercise/training; **GXT** = graded exercise test; **HR** = heart rate; $\mathbf{HR_{max}}$ = maximal HR; $\mathbf{HR_{reserve}}$ = heart rate reserve; **LT** = lactate threshold; **NS** = not specified; **PO** = power output; $\mathbf{PO_{LT}}$ = power output at lactate threshold; $\mathbf{PO_{max}}$ = maximal power output; **T** = moment of BDNF collection e.g. T60 post HI = 60 minutes following the end of the high-intensity exercise; **TRAD** = traditional resistance exercise/training; $\mathbf{\dot{V}O_2}$ = oxygen uptake; $\mathbf{\dot{V}O_{2max}}$ = maximal $\dot{V}O_2$; $\mathbf{\dot{V}O_{2peak}}$ = peak $\dot{V}O_2$; $\mathbf{W_{max}}$ = maximal power output; ×/**wk** = sessions per week; [] indicates concentration; Δ indicates PO at LT + 0.5 (PO_{max} + PO_{LT}).

months). These results suggest that when BDNF is stored in platelets, it is protected from degradation.[89]

When plasma is being used, the type of anticoagulant that is added to the collection tubes is not clarified and only one study corrected plasma BDNF for platelet reactivity.[50] However, Schneider et al.[85] pointed out that some anticoagulants (i.e. EDTA) may activate blood platelets and thus influence the concentration of plasma BDNF *ex vivo*. Rasmussen et al.[62] and Seifert et al.[68] centrifuged blood plasma a second time to ensure that platelets were spun down and thus removed from the surfactant. Nevertheless, to ascertain plasma BDNF is not influenced by BDNF stored in platelets, a correction for platelet reactivity is recommended. For both plasma as well as serum, details of centrifugation are lacking in 12 studies and details of storage temperature after centrifugation are missing in eight studies. In the studies of Gold et al.[47] and Schulz et al.,[67] blood serum was analysed for BDNF; nevertheless, they report on the use of heparinized tubes for the collection of blood samples. As a result, it is not clear whether they analysed serum or plasma BDNF. Additionally, only two of the 24 studies[71,72] reported on corrections of BDNF concentrations for changes in serum or plasma volume following acute exercise or training. BDNF values could change due to haemoconcentration following acute exercise or pseudo anemia following training.[90,91] Kargotich et al.[92,93] pointed out that moderate to intense exercise results in a decrease of blood volume or also haemoconcentration. As a result, changes in blood solutes after exercise or training could represent an inherent change in haemoconcentration due to shifts in blood volume instead of a real exercise-induced change in BDNF concentration.[92,93] Future studies should present corrected serum and plasma BDNF concentrations (i.e. corrected for the shift in plasma volume by the formula of Van Beaumont and colleagues[94]).

In all studies, the diagnostic biochemical technique used to detect BDNF in blood serum or plasma is the ELISA. Trajkovska et al.[89] showed that ELISA-kits (ChemiKine™; Millipore, Billerica, MA, USA) are an accurate, valid and reproducible analysis tool for peripheral BDNF. ELISA-kits of different manufacturers were used and details on the sensitivity of the assay or intra- and interassay variations were not always given (table V). Guidelines on how to handle the samples from collection until analysis or on storage conditions are not provided in the manuals of any of the kits. With regard to the biochemical analysis of BDNF, laboratories and/or manufacturers of analysis kits should reach a uniform consensus on the peripheral assessment of BDNF from the collection of blood until the analysis with ELISA. Meanwhile, researchers should repeatedly use uniform collection and analysing techniques within their own laboratories.

2.5 Basal Concentrations of BDNF

2.5.1 Healthy Subjects

For serum, basal BDNF concentrations in healthy subjects range from 1.5[55] to 30.9 ng/mL throughout the 24 studies.[70] Literature confirms that basal values of serum BDNF in healthy subjects (non-athletes) vary extremely.[77,86,95-99] Values could be influenced by different factors such as diurnal fluctuations, physical fitness, age, sex, bodyweight, nutrition and possible neurological, immunological or metabolic disorders.[77,100] A remarkable finding is that basal serum BDNF values in the studies of Floël et al.[55] 1.5 ± 0.5 ng/mL, Currie et al.[53] (7.2 ± 2.7 ng/mL), Gold et al.[47] (4.7 ± 0.5 ng/mL) and Rojas Vega et al.[63,64] (5.8 ± 1.9 ng/mL), were low compared with values in all other studies. The study of Rojas Vega et al.[63,64] concerned recreational athletes and the study of Currie et al.[53] included predominantly subjects engaged in some level of recreational and sport-based activity. Two other studies confirm that basal BDNF concentrations in athletes could be lower than in untrained subjects,[52,61] while the studies of Zoladz et al.[75] and Seifert et al.[68] disagree with this. A lower level of BDNF in trained subjects and athletes could indicate that BDNF clearance in trained subjects or athletes is more effective (i.e. a higher disappearance rate), with less stored or circulating BDNF in the periphery as a result. Alternatively, plasma volume increases by 10–20% following regular physical training,

Table V. Biochemical analysis of blood samples for determination of plasma and/or serum brain-derived neurotrophic factor (BDNF)

Study (year)	Analysis kit (manufacturer)	Sample	Time to clot (min)	Clotting temp.	Centrifugation	Storage temp. after centrifugation (°C)	Sensitivity of assay	Intra-assay; inter-assay variations (%)[a]	Corrected for change in plasma volume	[BDNF]; mean ± SD (mean ± SE)
Acute aerobic exercise protocols										
Ferris et al.[54] (2007)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Serum	NS	NS	1300 g for 12 min	–80	7.8–500 pg/mL	3.7 [1.7][b]; 8.5	NS	Pre-exercise: 18.17 (± 1.19 ng/mL)
Goekint et al.[56] (2008)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Serum	60	Room temp.	NS	–80	7.8-500 pg/mL	NS	NS	Pre-exercise in placebo controls: 17.12 (± 3.45 ng/mL) Pre-exercise in reboxetine group: 18.36 (± 3.20 ng/mL)
Gold et al.[47] (2003)	ELISA (Promega, Madison, WI, USA)	Serum (NS)	NS	NS	NS	NS	1 pg/mL	NS	NS	Pre-exercise in healthy controls: 4.72 ± 0.49 ng/mL Pre-exercise in MS: 4.44 ± 0.53 ng/mL
Gustafsson et al.[58] (2009)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Plasma	NS	Ice cooled	3000 rpm for 10 min at 4°C	–70	NS	<15; <15	NS	Pre-exercise in healthy controls: 299 pg/mL Pre-exercise in MDD: 427 pg/mL T0 post-LMI exercise in healthy controls: 664 pg/mL T0 post-LMI exercise in MDD: 602 pg/mL T0 post-HI exercise in healthy controls: 1239 pg/mL T0 post-HI exercise in MDD: 1135 pg/mL T60 post-HI exercise in healthy controls: 457 pg/mL T60 post-HI exercise in MDD: 790 pg/mL

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Table V. Contd

Study (year)	Analysis kit (manufacturer)	Sample	Time to clot (min)	Clotting temp.	Centrifugation	Storage temp. after centrifugation (°C)	Sensitivity of assay	Intra-assay; inter-assay variations (%)[a]	Corrected for change in plasma volume	[BDNF]; mean ± SD (mean ± SE)
Laske et al.[59] (2010)	ELISA (R&D Systems, Minneapolis, MN, USA)	Serum	<30	Ice cooled	2500 g for 30 min at 4°C	–20	NS	NS; <10	NS	Pre-exercise in healthy controls: 30.5 ± 6.9 ng/mL Pre-exercise in MDD: 24.4 ± 6.1 ng/mL T0 post-exercise in healthy controls: 31.0 ± 8.1 ng/mL T0 post-exercise in MDD: 28.5 ± 7.3 ng/mL T30 post-exercise in healthy controls: 26.7 ± 7.2 ng/mL T30 post-exercise in MDD: 21.4 ± 7.1 ng/mL
Rasmussen et al.[62] (2009)	ELISA (R&D Systems, Minneapolis, MN, USA)	Plasma	NS	NS	2600 g for 15 min at 4°C; 10 000 g for 10 min at 4°C[c]	–80	NS	NS	NS	Pre-exercise ($[BDNF]_{vena\ jug}$): 442 ± 272 pg/mL Pre-exercise ($[BDNF]_{p\ a\text{-}v\ diff}$): –347 ± 316 pg/mL T0 post-exercise ($[BDNF]_{vena\ jug}$): 1172 ± 968 pg/mL T0 post-exercise ($[BDNF]_{p\ a\text{-}v\ diff}$): –902 ± 876 pg/mL
Rojas Vega et al.[63,64] (2006, 2007)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Serum	NS	NS	3000 rpm for 10 min at 4°C	–70	7.8–500 pg/mL	3.7; 8.5	NS	Pre-exercise: 5.79 ± 1.9 ng/mL
Rojas Vega et al.[65] (2008)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Serum	NS	NS	4000 rpm for 10 min at 4°C	–70	7.8–500 pg/mL	3.7; 8.5	NS	Pre-exercise in SCI: 37.2 ± 19.8 ng/mL
Ströhle et al.[69] (2010)	ELISA (Promega, Madison, WI, USA)	Serum	NS	NS	NS	NS	1 pg/mL	± 6.7; ± 34.1	NS	NS

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Table V. Contd

Study (year)	Analysis kit (manufacturer)	Sample	Time to clot (min)	Clotting temp.	Centrifugation	Storage temp. after centrifugation (°C)	Sensitivity of assay	Intra-assay; inter-assay variations (%)[a]	Corrected for change in plasma volume	[BDNF]; mean ± SD (mean ± SE)
Tang et al.[70] (2008)	ELISA (Promega, Madison, WI, USA)	Serum	NS	NS	NS	NS	NS	NS	NS	Pre-exercise: 30.9 ng/mL T25 post-exercise: 34.5 ng/mL T50 post-exercise: 31.0 ng/mL
Winter et al.[71] (2007)	ELISA (R&D Systems, Minneapolis, MN, USA)	Serum	NS	NS	NS	NS	NS	NS	Yes	NS
Acute strength exercise protocols										
Goekint et al.[57] (2010)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Serum	60	Room temp.	1300 g for 12 min at 4°C	−80	7.8–500 pg/mL	± 3.5; ± 8.5	NS	Pre-exercise in UC: 15.2 ± 0.8 ng/mL Pre-exercise in TC: 15.7 ± 0.6 ng/mL Post-exercise in UC: 15.7 ± 1.0 ng/mL Post-exercise in TC: 15.5 ± 1.0 ng/mL
Yarrow et al.[72] (2010)	ELISA (R&D Systems, Minneapolis, MN, USA)	Serum	NS	NS	3000 g for 12 min	−80	20 pg/mL	<6.2; NS	Yes	Pre-exercise: 23.3 ± 1.8 ng/mL Post-exercise: 30.8 ng/mL[d]
Aerobic training protocols										
Baker et al.[50] (2010)	ELISA (Promega, Madison, WI, USA)	Plasma	NS	NS	NS	NS	NS	NS	NS	NS
Castellano and White[51] (2008)	ELISA (R&D Systems, Minneapolis, MN, USA)	Serum	NS	NS	3000 g for 15 min at 4°C	−80	<20 pg/mL	8; 5	NS	Healthy controls at rest: 20.15 ng/mL; MS at rest: 10.05 ng/mL

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Table V. Contd

Study (year)	Analysis kit (manufacturer)	Sample	Time to clot (min)	Clotting temp.	Centrifugation	Storage temp. after centrifugation (°C)	Sensitivity of assay	Intra-assay; inter-assay variations (%)[a]	Corrected for change in plasma volume	[BDNF]; mean ± SD (mean ± SE)
Schiffer et al.[66] (2009)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Plasma	NS	NS	3000 rpm for 10 min at 4°C	–70	NS	NS	NS	Pre-training at rest: 128.4 ± 90.2 pg/mL Post-training at rest: 102.6 ± 66.2 pg/mL Pre-training controls at rest: 102.2 ± 108.7 pg/mL Post-training controls at rest: 98.9 ± 78.6 pg/mL
Schulz et al.[67] (2004)	ELISA (Promega, Madison, WI, USA)	Serum	NS	NS	NS	NS	1 pg/mL	NS	NS	Pre-training in MS at rest: 4.35 ± 3.22 ng/mL Post-training in MS at rest: 5.93 ± 5.18 ng/mL Pre-training in control MS at rest: 5.08 ± 2.31 ng/mL Post-training in control MS at rest: 4.20 ± 2.07 ng/mL
Seifert et al.[68] (2010)	ELISA (R&D Systems, Minneapolis, MN, USA)	Plasma	NS	NS	2600 g for 15 min at 4°C; 7500 g for 10 min at 4°C[c]	–80	NS	NS	NS	$[BDNF]_{arterial}$: Pre-training at rest: 1.2 ± 0.6 ng/mL; post-training at rest: 1.0 ± 0.3 ng/mL; pre-training after HI: 2.4 ± 1.3 ng/mL; post-training after HI: 2.0 ± 0.9 ng/mL $[BDNF]_{vena\ jug}$: Pre-training at rest: 2.5 ± 2.4 ng/mL; post-training at rest: 5.5 ± 2.3 ng/mL; pre-training after HI: 4.4 ± 2.4 ng/mL; post-training after HI: 5.9 ± 3.9 ng/mL

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Table V. Contd

Study (year)	Analysis kit (manufacturer)	Sample	Time to clot (min)	Clotting temp.	Centrifugation	Storage temp. after centrifugation (°C)	Sensitivity of assay	Intra-assay; inter-assay variations (%)[a]	Corrected for change in plasma volume	[BDNF]; mean ± SD (mean ± SE)
Zoladz et al.[75] (2008)	ELISA (Phoenix Pharmaceuticals Inc., Burlingame, CA, USA)	Plasma	NS	NS	NS	NS	7.8–500 pg/mL	<10; <12	NS	Pre-training at rest: 10.3 (± 1.4 pg/mL) Post-training at rest: 16.8 (± 2.1 pg/mL) Pre-training after GXT: 10.9 (± 2.3 pg/mL) Post-training after GXT: 68.4 (± 16.0 pg/mL) in untrained at rest: 10.3 (± 1.4 pg/mL) in athletes at rest: 29.5 (± 9.5 pg/mL)
Strength training protocols										
Goekint et al.[57] (2010)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Serum	60	Room temp.	1300 g for 12 min at 4°C	–80	7.8–500 pg/mL	± 3.5; ± 8.5	NS	Pre-training at rest: 13.6 ± 0.8 ng/mL Post-training at rest: 14.6 ± 0.5 ng/mL Pre-training controls at rest: 14.9 ± 1.4 ng/mL Post-training controls at rest: 15.4 ± 0.7 ng/mL
Levinger et al.[60] (2008)	ELISA (R&D Systems, Minneapolis, MN, USA)	Plasma	NS	NS	NS	–20	NS	NS	NS	Pre-training in LoMF at rest: 709.6 ± 243.0 pg/mL Pre-training in HiMF at rest: 898.2 ± 240.1 pg/mL
Schiffer et al.[66] (2009)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Plasma	NS	NS	3000 rpm for 10 min at 4°C	–80	NS	NS	NS	Pre-training at rest: 136 ± 109 pg/mL Post-training at rest: 117.2 ± 94.9 pg/mL Pre-training controls at rest: 102.2 ± 108.7 pg/mL Post-training controls at rest: 98.9 ± 78.6 pg/mL
Yarrow et al.[72] (2010)	ELISA (R&D Systems,	Serum	NS	NS	3000 g for 12 min	–80	20 pg/mL	<6.2; NS	Yes	Pre-training at rest: 23.3 ± 1.8 ng/mL

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Table V. Contd

Study (year)	Analysis kit (manufacturer)	Sample	Time to clot (min)	Clotting temp.	Centrifugation	Storage temp. after centrifugation (°C)	Sensitivity of assay	Intra-assay; inter-assay variations (%)[a]	Corrected for change in plasma volume	[BDNF]; mean ± SD (mean ± SE)
	Minneapolis, MN, USA)									Pre-training after strength exercise: 30.8 ng/mL[d]; Post-training at rest: 19.4 ± 1.9 ng/mL Post-training after strength exercise : 34.4 ng/mL[d]
Trained vs untrained; no intervention										
Chan et al.[52] (2008)	ELISA (Promega, Madison, WI, USA)	Serum	30	Room temp.	1000 g	−70	NS	NS	NS	At rest: 28.9 ± 6.6 ng/mL
Currie et al.[53] (2009)	ELISA (ChemiKine™, Millipore, Temecula, CA, USA)	Serum	NS	NS	NS	NS	NS	NS	NS	At rest: 7.17 ± 2.68 ng/mL
Floël et al.[55] (2010)	ELISA (R&D Systems, Minneapolis, MN, USA)	Serum	NS	NS	NS	−80	NS	NS	NS	At rest: 1.473 ± 0.51 ng/mL
Nofuji et al.[61] (2008)	ELISA (Promega, Madison, WI, USA)	Serum/plasma	NS	NS	NS	−80	NS	NS	NS	$[BDNF]_s$ in trained at rest: 19.5 ± 4.5 ng/mL $[BDNF]_s$ in untrained at rest: 23.6 ± 2.9 ng/mL $[BDNF]_p$ in trained at rest: 1143.6 ± 600.5 pg/mL $[BDNF]_p$ in untrained at rest: 1440.6 ± 1090.3 pg/mL

a Predicted intra-assay and inter-assay variations as given in the manual of the ELISA kit.

b 1.7 % = intra-assay variation between duplicates as measured in the applied assay kit.

c Blood samples were immediately spun at 2600 g for 15 min at 4°C. Plasma was isolated and re-spun at 7500 g[62] and 10 000 g[68] for 10 min at 4°C.

d Point values for $[BDNF]_s$ post strength exercise at baseline and after strength training were not given. To complete this table we calculated these values from the baseline point values and the percentage of increase of $[BDNF]_s$[72]

$[BDNF]_{arterial}$ = arterial concentration of BDNF; **$[BDNF]_{p\ a\text{-}v\ diff}$** = difference between arterial and jugular venous plasma BDNF concentration; **$[BDNF]_{vena\ jug}$** = vena jugular concentration of BDNF; **ELISA** = Enzyme-linked ImmunoSorbent Assay; **GXT** = graded exercise test; **HI** = high-intensity exercise, **HiMF** = group with two or more metabolic risk factors for MetS; **LoMF** = group with one or no metabolic risk factors for MetS; **MDD** = major depression disorder; **MetS** = metabolic syndrome; **MS** = multiple sclerosis; **NS** = not specified; **rpm** = rounds per minute; **SCI** = spinal cord injury; **SD** = standard deviation; **SE** = standard error; **T** = moment of BDNF collection e.g. T60 post-HI-exercise = 60 minutes following the end of the high-intensity exercise; **TC** = trained condition (at thirtieth strength training session); **temp.** = temperature; **UC** = untrained condition (at sixth strength training session); [] indicates concentration.

thus lower levels of BDNF could merely represent the shift in blood volume instead of a true increase in BDNF.[90,91] The study of Floël et al.[50] indicates no correlation between the level of physical activity and basal BDNF, and five out of seven studies on strength or aerobic training in healthy subjects showed no short term effect on basal concentration of BDNF.[56,57,60-61,72] Nevertheless, it should be noted that more studies with a longer duration of the training period and in different populations (i.e. trained versus untrained, healthy versus diseased) are necessary to elucidate whether basal plasma and serum BDNF concentrations are influenced by the level of physical fitness/activity.

Not only physical fitness, but also factors such as sex, age, bodyweight and nutrition could influence basal concentration of BDNF. For instance, the low basal serum BDNF value in the studies of Gold et al.[47] and Floël et al.[55] could be due to sex effects. (i.e. 6/14,[49] 28/47[50] male/female, respectively). According to Lommatzsch et al.,[77] women display significantly lower concentrations of platelet BDNF levels than men (i.e. groups matched for bodyweight) because of the sex-specific differences in BDNF expression of resident cells or organs and thus experience an altered uptake of BDNF into platelets. However, Gustaffson et al.,[58] Katoh-Semba et al.[78] and Ziegenhorn et al.[88] found no sex-related differences regarding serum and plasma BDNF, while Trajkovska et al.[89] and Baker et al.[50] reported higher concentrations of whole blood and plasma BDNF, respectively, in women. The mean basal serum BDNF level (i.e. 30.5 ± 6.9 ng/mL) measured in healthy control women in the study of Laske et al.[59] is the second highest value reported in 13 of the included studies. Basal values of serum BDNF could also be influenced by age and/or bodyweight. Katoh-Semba et al.[78] found an increase of serum BDNF over the first several years in healthy individuals and then a slight decrease after reaching adult age (i.e. mean level in 30- to 39-year-old age group). Also, Ziegenhorn et al.[88] observed a decreasing concentration of serum BDNF with increasing age, while Lommatzsch et al.[77] reported the same in plasma concentration of BDNF but, on the other hand, no age-related influence on platelet concentration of BDNF. Floël et al.[55] measured basal BDNF concentration in 75 healthy older individuals (i.e. mean age 60.5 ± 6.9 years) and reported the lowest serum BDNF concentration of all 24 included studies (i.e. 1.5 ± 0.5 ng/mL). On the other hand, Laske et al.[59] reported very high concentrations of serum BDNF in healthy older female controls (mean age 58.9 ± 6.6 years; $[BDNF]_{serum}$ 30.5 ± 6.9 ng/mL). Monteleone et al.[101] suggest that serum BDNF concentration is also increased with increasing bodyweight. The studies of Floël et al.[55] and Castellano and White[51] both studied healthy (control) subjects with a mean BMI > 27, yet found very different basal concentrations of serum BDNF (i.e. 1.5 vs 20.2 ng/mL). It is likely that, next to age or sex, alternations in energy balance and nutritional variables also influence peripheral BDNF concentrations,[101] yet it is still unclear in which direction.

In plasma, basal BDNF concentrations in the 24 included studies range from 10.3[75] pg/mL to 2.5 ng/mL[61] in healthy subjects. Thus, basal plasma values of BDNF vary even greater than in serum values. Three other studies in the literature also report strongly varying resting BDNF values, ranging from 77.0 over 92.5 to 1700.0 pg/mL.[77,86,96] Overall, the large variations in plasma BDNF concentration confirm the hypothesis of Lommatzsch et al.[77] and Ziegenhorn et al.[88] that peripheral BDNF is stored, for most of the time, in the blood platelets and varying concentrations of BDNF are released from the platelets upon agonist stimulation and circulate free in the blood plasma, depending on the specific need of BDNF in certain tissues.[96] Moreover, not only between studies, but also within a study, large variations in basal plasma BDNF concentrations can be observed, as pointed out by the large standard deviations of plasma BDNF concentrations in five studies.[60,61,66,75,96] This clearly indicates that basal plasma BDNF concentrations are extremely fluctuating. In the six studies on plasma BDNF concentration, it is not clear which type of anticoagulant was used. Only in the studies of Rasmussen et al.[62] and Seifert et al.[68] was it specified that tubes containing EDTA were used. It is possible that the type of anticoagulant influences platelet activation

in vitro and, thus, plasma BDNF concentration.[85] Only Baker et al.[50] adjusted plasma BDNF levels for the contribution of activated platelets to ensure only plasma BDNF is measured.

Peripheral BDNF is also subject to sex-related diurnal variations.[102-104] In men, plasma BDNF peaks in the morning and decreases substantial during the day similar to the cortisol circadian rhythm.[102,103] This rhythmic circadian variation and correlation with cortisol levels is less explicit in plasma BDNF of women.[103,104] In women, hormonal fluctuations blunt the diurnal rhythm related to cortisol.[104] Researchers should take these circadian hormonal fluctuations into account when measuring plasma BDNF.

2.5.2 Persons with a Chronic Disease or Disability

Only one study investigated SCI athletes and recorded a basal serum BDNF concentration of 37.2 ng/mL. Yet, the sample size of the study was small (n = 8), it concerned athletes and there was no control group to verify this result.[65] In persons with MS, basal serum BDNF values range from 4.4[47,67] to 10.0 ng/mL.[51] This means that in MS, basal serum BDNF concentrations were significantly lower (i.e. ≤10.0 ng/mL) compared with the pool of BDNF data we found in the literature for healthy subjects. Nevertheless, Gold et al.[47] found equal concentrations of BDNF in MS and healthy controls in their study. Gold et al.[47] used stable persons with MS (i.e. persons with an acute relapse were excluded from their study).[47] Castellano and White,[51] on the other hand, reported significantly lower values of basal BDNF in MS versus healthy controls. According to Azoulay et al.,[105] lower concentrations of serum BDNF in MS could suggest that there is a reduction in tissue protection by BDNF or that there is an increase in the consumption of BDNF by the CNS due to damaged tissue. In the elderly and in persons with MS, the low level of BDNF at rest could also be due to a reduced production of BDNF as a result of lower levels of messenger RNA (mRNA);[106] this can be confirmed by animal studies.[107-109]

Gustafsson et al.[58] and Laske et al.[59] both studied the effects of exercise on BDNF in subjects with major depressive disorder (MDD). Only Laske et al.[59] found decreased basal serum BDNF concentrations in female patients with MDD. Gustafsson et al.[58] included only moderately depressed patients. According to Ströhle et al.[69] basal BDNF concentration in patients with panic disorder is also decreased. Thus, most studies on persons with a chronic disease or disability found deviating concentrations of serum BDNF compared with levels in young, healthy, untrained subjects. This is in agreement with other studies on neurodegenerative and metabolic diseases. Altered peripheral BDNF concentrations could be observed in persons with depression,[97] anorexia nervosa[101] (serum BDNF is decreased), and in persons with allergic asthma[95] and obesity[101] (serum BDNF is increased). All point values on basal BDNF concentration can be found in table V.

2.6 Exercise-Induced Response of BDNF

2.6.1 Effect of an Acute Aerobic Exercise

Fifteen studies investigated the effect of an acute aerobic exercise protocol on circulating concentrations of BDNF (tables III and VI). Thirteen studies reported on the effects in healthy (control) subjects[54,56,58,59,62-64,68-71] and seven on the effects in persons with a chronic disease or disability.[47,51,58,59,65,67,69] Sixty-nine percent of the studies[47,54,56,58,62-65,67-68,70-71] in healthy subjects and 86% of the studies in persons with a chronic disease or disability,[47,51,58,59,65,67,69] found a 'mostly transient' increase in peripheral BDNF (ranging from 11.7% to 410.0%) following an acute exercise protocol, with the tendency of acute high-intensity exercise protocols and GXTs having larger increases in BDNF concentrations than acute low-intensity exercise protocols. Except for the studies of Zoladz et al.,[75] Rojas Vega et al.[65] and Laske et al.,[2] [59] an acute aerobic exercise of high intensity or a GXT increases basal BDNF concentrations in healthy

2 In the study of Laske et al.,[59] BDNF concentration in healthy control subjects did not increase following an acute exercise of high intensity.

Table VI. Significant ($p < 0.05$) acute exercise- and training-induced effects on brain-derived neurotrophic factor (BDNF)

Study (year)	Subjects	Result ($p < 0.05$)	[BDNF] increase or decrease (%)[a]
Acute aerobic exercise			
Castellano and White[51] (2008)	H	LMI: ↓ in $[BDNF]_s$ at wk 0, 4 and 8 of aerobic training[b]	LMI at wk 0: −13.2[a,c]
Ferris et al.[54] (2007)	H	GXT: ↑ in $[BDNF]_s$ HI: ↑ in $[BDNF]_s$ LMI: → in $[BDNF]_s$	GXT: 30.0 HI: 13.0 LMI: 10.0
Goekint et al.[56] (2008)	H	HI and LMI: ↑ in $[BDNF]_s$ (HI > LMI)	HI: 42.7[d] LMI: 25.4[d]
Gold et al.[47] (2003)	H	LMI: ↑ in $[BDNF]_s$	LMI: 43.1[a]
Gustafsson et al.[58] (2009)	H	LMI: → in $[BDNF]_p$ in M → in $[BDNF]_p$ in F HI: ↑ in $[BDNF]_p$ in M, (→ LMI + GXT = HI) → in $[BDNF]_p$ in F	LMI in M: 87.9 LMI in F: 142.8 HI in M: 398.2 HI in F: 265.5
Laske et al.[59] (2010)	H	GXT: → in $[BDNF]_s$ 0 min after acute exercise ↓ in $[BDNF]_s$ 30 min after acute exercise	GXT at T0 after exercise: 1.6 GXT at T30 after exercise: −12.5
Rasmussen et al.[62] (2009)	H	HI: ↑ in $[BDNF]_{p\ arterial}$, $[BDNF]_{p\ vena\ jug}$ and $[BDNF]_{p\ a\text{-}v\ diff}$	HI: $[BDNF]_{p\ vena\ jug}$ 165.2 $[BDNF]_{p\ a\text{-}v\ diff}$ 159.9
Rojas Vega et al.[63,64] (2006, 2007)	H	LMI: → in $[BDNF]_s$ HI: ↑ in $[BDNF]_s$ (LMI + GXT = HI)	LMI: 1.3[a] HI: 38.7[a]
Seifert et al.[68] (2010)	H	LMI: no results given HI: ↑ in $[BDNF]_{p\ arterial}$ at wk 0 and 12 of aerobic training → in $[BDNF]_{p\ vena\ jug}$ at wk 0 and 12 of aerobic training	LMI: NS HI at wk 0, $[BDNF]_{p\ arterial}$: 100.0 $[BDNF]_{p\ vena\ jug}$: 76.0
Ströhle et al.[69] (2010)	H	LMI: → in $[BDNF]_s$	LMI: −9.1[a]
Tang et al.[70] (2008)	H	LMI: ↑ in $[BDNF]_s$	LMI: 11.7
Winter et al.[71] (2007)	H	HI and LMI: ↑ in $[BDNF]_s$	HI: 12.0[a] LMI: 15.6[a]
Zoladz et al.[75] (2008)	H	GXT: → in $[BDNF]_p$ at wk 0	GXT at wk 0: 5.8
Castellano and White[51] (2008)	D	Baseline at rest: $[BDNF]_s$ in MS < $[BDNF]_s$ healthy controls at wk 0 LMI: ↓ in $[BDNF]_s$ at wk 0, 4 and 8 of aerobic training[b]	LMI at wk 0: −42.1[a,c,e]
Gold et al.[47] (2003)	D	Baseline at rest: $[BDNF]_s$ in MS = $[BDNF]_s$ in healthy controls at wk 0 LMI: ↑ in $[BDNF]_s$	LMI: 35.3[a]
Gustafsson et al.[58] (2009)	D	Baseline at rest: $[BDNF]_p$ in MDD = $[BDNF]_p$ in healthy controls LMI: ↑ in $[BDNF]_p$ in M → in $[BDNF]_p$ in F HI: ↑ in $[BDNF]_p$ in M, (LMI + GXT = HI), ↑ in $[BDNF]_p$ in F	LMI in M: 66.3 LMI in F: 7.4 HI in M: 234.1 HI in F: 74.9
Laske et al.[59] (2010)	D	Baseline at rest: $[BDNF]_s$ in F with MDD < $[BDNF]_s$ healthy F controls GXT: ↑ in $[BDNF]_s$ 0 min after acute exercise ↓ in $[BDNF]_s$ 30 min after acute exercise	GXT at T0 after exercise: 16.8 GXT at T30 after exercise: −11.1

Continued next page

Table VI. Contd

Study (year)	Subjects	Result ($p < 0.05$)	[BDNF] increase or decrease (%)[a]
Rojas Vega et al.[65] (2008)	D	Baseline at rest: $[BDNF]_s$ ↑ in SCI athletes[f] LMI: ↑ in $[BDNF]_s$ HI: → in $[BDNF]_s$	LMI: 44.6[a] HI: 16.1[a]
Schulz et al.[67] (2004)	D	LMI: ↑ in $[BDNF]_s$ at 0 and 8 wk of aerobic training[g]	LMI at wk 0: 410.0
Ströhle et al.[69] (2010)	D	Baseline at rest: $[BDNF]_s$ in persons with panic disorder < $[BDNF]_s$ in healthy controls LMI: ↑ in $[BDNF]_s$	LMI: 86.2[a]
Acute strength exercise[h]			
Goekint et al.[57] (2010)	H	→ in $[BDNF]_s$	3.6[i]
Yarrow et al.[72] (2010)	H	↑ in $[BDNF]_s$	32[i]
Strength training[j]			
Goekint et al.[57] (2010)	H	At rest: → in $[BDNF]_s$ at 10 wk After strength exercise: → in $[BDNF]_s$ at 10 wk	At rest: 10.2[k] After strength exercise: −2.1[i]
Levinger et al.[60] (2008)	H	Baseline at rest: $[BDNF]_p$ in HiMF > $[BDNF]_p$ in LoMF At rest: → in $[BDNF]_p$ at 10 wk	At rest HiMF: −0.5[a] At rest LoMF: −8.7[a]
Schiffer et al.[66] (2009)	H	At rest: → in $[BDNF]_p$ at 12 wk	At rest: −13.8
Yarrow et al.[72] (2010)	H	At rest: → in $[BDNF]_s$ at 5 wk After strength exercise: TRAD: ↑ in $[BDNF]_s$ at wk 5; ECC+: ↑ in $[BDNF]_s$ at wk 5	At rest: −16.6[i] after strength exercise: TRAD: 79[i]; ECC+: 74[i]
Aerobic training			
Castellano and White[51] (2008)	H	At rest: → in $[BDNF]_s$ at 4 and 8 wk After LMI: ↓ in $[BDNF]_s$ at 0, 4 and 8 wk vs rest at 0, 4 and 8 wk → in $[BDNF]_s$ at wk 8 vs LMI at wk 0 and 4	NS NS NS
Schiffer et al.[66] (2009)	H	At rest: → in $[BDNF]_p$ at 12 wk	At rest: −20.1
Seifert et al.[68] (2010)	H	At rest: $[BDNF]_{p\ arterial}$ → $[BDNF]_{p\ vena\ jug}$ ↑ $[BDNF]_{p\ a\text{-}v\ diff}$ ↑ at wk 12 After LMI: no results given After HI: $[BDNF]_{p\ arterial}$ ↑, $[BDNF]_{p\ vena\ jug}$ → at wk 0 $[BDNF]_{p\ arterial}$ → vs HI at wk 0 $[BDNF]_{p\ arterial}$ ↑ vs rest at wk 12 $[BDNF]_{p\ vena\ jug}$ → vs HI at wk 0 and rest at wk 12	At rest $[BDNF]_{p\ arterial}$: −16.7 $[BDNF]_{p\ vena\ jug}$:120.0 LMI: NS HI at wk 12 vs HI at wk 0: $[BDNF]_{p\ arterial}$: −16.7; $[BDNF]_{p\ vena\ jug}$: 34.1; HI at wk 12 vs rest at wk 12: $[BDNF]_{p\ arterial}$: 100.0; $[BDNF]_{p\ vena\ jug}$: 7.3
Zoladz et al.[75] (2008)	H	At rest: ↑ in $[BDNF]_p$ at 5 wk After GXT: ↑ in $[BDNF]_p$ at 5 wk vs rest at wk 5 ↑ in $[BDNF]_p$ at 5 wk vs GXT at wk 0	At rest: 63.1 GXT at wk 5 vs rest at wk 5: 307.1 GXT at wk 5 vs GXT at wk 0: 527.5

Continued next page

Table VI. Contd

Study (year)	Subjects	Result ($p < 0.05$)	[BDNF] increase or decrease (%)[a]
Baker et al.[50] (2010)	D	At baseline: $[BDNF]_p$ in M > $[BDNF]_p$ in F (not significant $p = 0.09$)	NS
		At rest: ↓ in $[BDNF]_p$ in M and ↑ in $[BDNF]_p$ in F vs controls[k]	NS
Castellano and White[51] (2008)	D	At baseline: $[BDNF]_s$ in MS < $[BDNF]_s$ healthy controls at wk 0	NS
		At rest: → in $[BDNF]_s$ at 8 wk (>–< ↑ $[BDNF]_s$ at 4 wk)	NS NS
		After LMI: ↓ in $[BDNF]_s$ at 0, 4 and 8 wk vs rest at 0, 4 and 8 wk	NS
		→ in $[BDNF]_s$ at wk 8 vs LMI at wk 0 and 4	
Schulz et al.[67] (2004)	D	At rest: → in $[BDNF]_s$ at 8 wk	At rest: 36.2
		After LMI: ↑ in $[BDNF]_s$ at 0 and 8 wk vs rest[g]	LMI at wk 8 vs rest at wk 8: 365.2
		→ in $[BDNF]_s$ at wk 8 vs LMI at wk 0	LMI at wk 8 vs LMI at wk 0: 24.3
Trained/untrained subjects			
Chan et al.[52] (2008)	H	$[BDNF]_s$ highly trained subjects < $[BDNF]_s$ moderately trained subjects	ND
Currie et al.[53] (2009)	H	$[BDNF]_s$ in high cardio-respiratory fit subjects < $[BDNF]_s$ in low cardio-respiratory fit subjects	ND
Floël et al.[55] (2010)	H	No correlation between $[BDNF]_s$ and level physical activity	ND
Nofuji et al.[61] (2008)	H	$[BDNF]_s$ trained subjects < $[BDNF]_s$ untrained subjects $[BDNF]_p$ trained subjects = $[BDNF]_p$ untrained subjects	ND
Zoladz et al.[75] (2008)	H	$[BDNF]_p$ trained subjects > $[BDNF]_p$ untrained subjects	ND

a Percentage of increase or decrease of [BDNF] immediately following the acute exercise or training protocol (i.e. 0 min post-exercise and within a week post-training), compared with baseline measurements. To get an idea of the order of magnitude of the effects of an acute exercise or training protocol on peripheral levels of BDNF, percentages of increase or decrease in BDNF compared with basal values were calculated. However, 8 studies did not provide point values of BDNF levels, therefore percentages of increase or decrease of BDNF can only be estimated from graph values. An increase in BDNF is expressed as a positive value; a decrease in BDNF is expressed as a negative value.[47,51,54,60,63-65,71]

b No significant decrease 30 min following exercise, yet significant decrease after 2 h and 3 h post-exercise.[51]

c BDNF was not assessed at 0 min post-exercise, values that are given here, are those of 30 min post-exercise at wk 0.[51]

d These values account for the control subjects, not the experimental group (administration of reboxetine).[56]

e In contradiction with the significant decrease 2 h and 3 h post-exercise, an increase in $[BDNF]_s$ (not significant) could be found 30 min post-exercise.[51]

f Rojas Vega et al.[65] did not include a control group of healthy subjects in their study. Consequently, the finding that baseline $[BDNF]_s$ is increased compared with able-bodied subjects can not be verified.

g Schulz et al.[67] found no statistically significant differences at week 0 and 8 of aerobic training at rest or after LMI between the MS group and the MS control group. Yet, a significant increase in BDNF following an acute exercise was observed in both groups at wk 0 and 5.

h No studies available on the effects of acute strength exercises on BDNF in disabled or diseased subjects.

i No significant differences between groups.[57,72]

j No studies available on the effects of strength training on BDNF in disabled or diseased subjects.

k This is a sex-specific effect of aerobic training vs stretching on $[BDNF]_p$ (i.e. group X sex ANOVA, $F_{1,23} = 4.68$; $p = 0.04$).[50]

$[BDNF]_{arterial}$ = arterial [BDNF]; **$[BDNF]_{p\ a\text{-}v\ diff}$** = difference between arterial and jugular venous plasma BDNF concentration; **$[BDNF]_{vena\ jug}$** = vena jugular [BDNF]; **D** = persons with a disease or disability; **ECC+** = eccentric-enhanced resistance exercise/training; **F** = female; **GXT** = graded exercise protocol; **H** = healthy subjects; **HI** = high-intensity exercise; **HiMF** = high metabolic risk group; **LMI** = low to moderate intensity; **LoMF** = low metabolic risk group; **M** = male; **MDD** = major depression disorder; **MS** = multiple sclerosis; **ND** = no data; **NS** = not specified; **rpm** = rounds per minute; **SCI** = spinal cord injury; **T** = moment of BDNF collection, e.g. T60 after exercise = 60 min following the end of the exercise; **TC** = trained condition (at the thirtieth strength training session); **UC** = untrained condition (at the sixth strength training session); ↑ indicates significant increase; ↓ indicates significant decrease; → indicates no significant differences; [] indicates concentration; $[]_s$ indicates serum concentration; $[]_p$ indicates plasma concentration; >–< indicates as opposed to.

subjects and persons with a disease or disability.[3][54,56,58,62-64,68,71] Acute aerobic exercise of low to moderate intensity is less effective to increase basal BDNF concentrations in healthy subjects (i.e. in only 44% of the studies),[51,54,58,63,64,69] but not in persons with a disease or disability. In these subjects an exercise of low to moderate intensity almost always increases basal BDNF concentration (i.e. in 83% of the studies in persons with a disease or disability[4]).[47,58,65,67,69] Remarkably, in the study on SCI subjects of Rojas Vega et al.,[65] the intensity-dependent character of the BDNF response is inverse to that reported in healthy subjects; a low to moderate acute exercise increases basal BDNF concentration while the immediately following high-intensity exercise decreases this concentration again to baseline. Furthermore, the study of Castellano and White[51] reported very different effects of an acute exercise of low to moderate intensity on concentration of BDNF (table VI).[51,67] Castellano and White[51] measured a decrease in BDNF concentration in healthy subjects and persons with MS compared with baseline BDNF values. An explanation for this odd result can be found in the assessment of peripheral BDNF; blood samples were not taken immediately following the acute exercise trial but 30 minutes, 2 hours and 3 hours post-exercise. In 73% of the studies, serum concentration of BDNF was analysed; only in the studies of Zoladz et al.,[75] Rasmussen et al.,[62] Gustafsson et al.[58] and Seifert et al.[68] plasma concentration of BDNF was measured (tables V and VI). Thus, acute exercise induces a transient increase in peripheral BDNF in both healthy subjects and in persons with a chronic disease or disability. Moreover, a dose-response relationship exists between the intensity of the exercise and peripheral BDNF concentration. In persons with a chronic disease or disability BDNF concentration increases already following an acute exercise of low to moderate intensity whereas BDNF concentration in healthy subjects benefits significantly more from high-intensity exercise.

2.6.2 Effect of an Acute Strength Exercise

Goekint et al.[57] and Yarrow et al.[72] were the first to study the exercise-induced BDNF response following an acute strength exercise. Yarrow et al.[72] reported a significant strength exercise-induced increase of 32% in serum BDNF while Goekint et al.[57] did not find a significant change (i.e. 3.6%) in BDNF following an acute strength exercise session. Goekint et al.[57] speculated that exercise intensity in their study was too low (i.e. six strength exercises of 3×10 repetitions at 80% of 1 repetition maximum (1RM) with relatively large resting periods between efforts). However, Yarrow et al.[72] implemented two strength exercise protocols of different intensity as follows: (i) traditional resistance exercise/training (TRAD), which incorporates two strength exercises of 4×6 repetitions at 52.5% 1RM concentrically and eccentrically; and (ii) eccentric-enhanced resistance exercise/training (ECC+), which incorporates two strength exercises of 3×6 repetitions at 40% 1RM concentrically and 100% 1RM eccentrically. They found similar transient increases in BDNF in both groups, independent of training intensity. However, the groups were matched for training volume. Presumably, an acute strength exercise stimulates peripheral BDNF on the condition that the exercise load is intensive enough.

2.6.3 BDNF Response during Passive Recovery

The increase of peripheral BDNF following an acute aerobic or strength exercise is transient. In most studies BDNF concentration returned to baseline within 10–60 minutes post-exercise, showing a fast disappearance rate of circulating BDNF after cessation of an aerobic or strength exercise. Castellano and White[51] and Yarrow et al.[72] observed a significant decrease below baseline concentration in peripheral BDNF concentration 2- and 3-hours post-exercise, both in

3 In the study of Gustafsson et al.,[58] a significant increase in $[BDNF]_p$ following an acute exercise of high intensity was only found in male control subjects.

4 In the study of Gustafsson et al.,[58] a significant increase in $[BDNF]_p$ following an acute exercise of low to moderate intensity was only found in male persons with MDD.

persons with MS and healthy (control) subjects. The exercise-induced response of peripheral BDNF seems to include an elevated release of BDNF into the blood circulation on the one hand and a greater tissue absorption on the other hand.

2.6.4 Effect of Aerobic Training

Schiffer et al.,[66] Castellano and White[51] and Schulz et al.[67] reported no training-induced effect on basal BDNF concentration in healthy subjects[51,66] and in persons with MS, respectively.[51,67] Only Zoladz et al.[75] and Seifert et al.[68] observed an increase in basal plasma BDNF[5] concentration following a period of aerobic training. However, Zoladz et al.[75] did not include a control group. Furthermore, Seifert et al.[68] found that BDNF from the brain (vena jugularis) was increased but no differences were seen in plasma BDNF concentration in a peripheral artery. Also, they included overweight men in their study who lost weight and body fat due to aerobic training. Furthermore, the training group experienced a higher loss in adipose tissue than the control group so that elevated basal BDNF concentration in the training group could be the result of altered energy metabolism.[10-12] Baker et al.[50] reported an elevated basal plasma BDNF concentration in men with mild cognitive impairment following aerobic training as compared with a stretching programme. In women they reported the inverse phenomenon. In both sexes plasma cortisol concentration fluctuated accordingly to plasma BDNF (i.e. plasma cortisol concentration increased in men and decreased in women relative to controls). When the change in BDNF from rest to post-acute exercise was assessed at the end of an aerobic training period, Zoladz et al.,[75] Schulz et al.[67] and Seifert et al.[68] reported a significant increase in peripheral BDNF concentration (307.1%, 365.2% and 100.0%, respectively) following an acute exercise compared with basal BDNF concentrations at the end of the training period. Nevertheless, Schulz et al.[67] and Seifert et al.[68] observed the same acute exercise-induced increase (i.e. 100.0%) at baseline. Thus, only according to Zoladz et al.[75] an aerobic training programme elevates the BDNF response to an acute exercise; however, they did not use a control group in their study.[75] The findings of Zoladz et al.,[75] Schulz et al.[67] and Seifert et al.[68] are in contradiction with those of Castellano and White,[51] where a decrease in serum BDNF concentrations following an acute exercise was found at the end of the training period. However, also at baseline, BDNF concentration decreased following an acute exercise; assessment of peripheral BDNF was not performed immediately following the acute exercise, but 30 minutes, 2 hours and 3 hours following the acute exercise. Similar results could be found in persons with MS and healthy (control) subjects, although the disappearance rate of BDNF in persons with MS following the acute exercise differed significantly between week 4 (86%) and week 8 (59%).[51]

Thus, results differ when it comes to the point of a BDNF response to aerobic training. Three studies[6] observed an elevated basal plasma BDNF concentration following a training period.[50,68,75] Remarkably, these studies use a more intensive training protocol as compared with the other studies[51,66,67] (i.e. training ratio, respectively, 4–7 ×/week as compared with 2–3 ×/week and training intensity at a higher percentage of the heart rate reserve or $\dot{V}O_{2max}$) [table IV]. As with strength training, only one study on aerobic training observed a greater plasma BDNF response to acute exercise following a period of aerobic training (i.e. as compared with the BDNF response to acute exercise at baseline).[75] However, this study lacked a control group.[75] More studies are requested to unravel the benefits of aerobic training on peripheral BDNF concentration and/or cellular processing.

2.6.5 Effect of Strength Training

Four studies examined the effect of strength training on peripheral BDNF concentration in

5 Seifert et al.[68] found an increase in $[BDNF]_p$ measured in the vena jugularis but not in arterial $[BDNF]_p$ following an aerobic training programme.

6 Baker et al.[50] only found an increase in men with mild cognitive impairment.

healthy subjects.[57,60,66,72] Protocols can be found in table IV. The studies of Goekint et al.,[57] Levinger et al.,[60] and Schiffer et al.,[66] used similar strength training protocols. Yarrow et al.[72] limited strength training to two exercises and used two groups who trained the same volume but at different training intensities (i.e. traditional versus eccentric-enhanced strength training).

All studies agree that strength training has no effect on basal peripheral BDNF concentration. However, Goekint et al.[57] and Yarrow et al.,[72] also studied the BDNF response to a single strength exercise following a strength training programme. Only Yarrow et al.[72] reported a significant increase of serum BDNF concentration post-acute exercise, both at baseline and after completion of a strength training programme. Moreover, the change in BDNF from rest to immediately post-acute exercise was 98% greater at the completion of the 5-week strength training programme than at baseline. Except for the study of Levinger et al.,[60] who investigated middle-aged individuals with clusters of metabolic risk factors, no other study investigated the effects of strength training on peripheral BDNF concentration in persons with a chronic disease or disability. From four studies, the inquiry for whether strength training influences peripheral concentrations of BDNF remains inconclusive. It can be assumed that a strength training programme does not elevate basal BDNF concentration; therefore, maybe strength training protocols are not strenuous enough (i.e. training ratio of 3 ×/week) [table IV]. Strength training could possibly trigger a greater BDNF response to acute exercise in trained as compared with untrained subjects, although more research is necessary to support this hypothesis.

2.6.6 Basal BDNF in Trained versus Untrained Subjects

Zoladz et al.[75] reported a lower concentration of plasma BDNF in untrained subjects compared with trained subjects. The other studies concerning this topic did not perform an experimental intervention protocol but observed the concentration of peripheral BDNF in trained and untrained subjects.[52,53,61] Moderately trained, untrained or low cardio-respiratory fit subjects seem to have higher concentrations of serum levels of BDNF than trained subjects. This was observed in athletes and untrained subjects at rest by Currie et al.,[53] Nofuji et al.[61] and Chan et al.[52] As suggested earlier (section 2.5.1), a lower level of BDNF in trained subjects and athletes could indicate that BDNF clearance is more effective (i.e. a higher disappearance rate) than in untrained subjects. However, no clinical trial has been performed to support this hypothesis. Moreover, Floël et al.[55] could not find a correlation between BDNF concentration and level of physical activity. A longitudinal randomized clinical trial with trained and untrained subjects in a crossover design could give a more definite answer to whether basal BDNF concentration in trained subjects is lower than in untrained subjects. Moreover, it is also possible that lower concentrations of BDNF could represent the shift in blood volume instead of a true increase in BDNF as plasma volume increases by 10–20% following regular physical training.[90,91]

2.7 Guidelines for Future Research

An acute aerobic exercise induces an increase in peripheral BDNF concentration in healthy subjects, as well as in persons with a chronic disease or disability. Most studies found a statistically significant dose-response relationship between the intensity of an acute aerobic exercise protocol and concentration of BDNF. Although, Seifert et al.[68] measured BDNF concentration at different exercise intensities (i.e. starting from 60% to 100% of $\dot{V}O_{2max}$) and could not observe a change in BDNF response. Independently of the intensity of the exercise, BDNF concentration generally returns back to baseline within 15–60 minutes and tends to decrease below baseline after 60 minutes.

From the results of the 24 included studies, it is difficult to determine the essential exercise parameters (i.e. intensity, duration and mode) that are necessary to induce an increase in peripheral BDNF concentration. It is most likely that exercise parameters are related to each other and that BDNF response is triggered when exercise becomes strenuous. Therefore, it would be interesting to

objectivate exercise intensity and relate it to ratings of perceived exertion following exercise[53] and to monitor mean and maximal heart rate values. When it comes to the mode of acute exercise, we can conclude from the included studies that acute aerobic exercise is more likely to elevate BDNF concentration than acute strength exercise. Presumably, in the two studies on acute strength exercise, the load of the exercise is not intensive enough for the given subjects to influence basal BDNF concentration. Moreover, in strength exercise resting periods between efforts are often implemented, which results in a decrease in heart rate, lactate, minute ventilation etc. between repetitions and between sessions. Within acute aerobic exercise cycling, hand cycling, running, rowing and stepping all bring on an exercise-induced BDNF response. To better understand the relationship between the nature of an acute exercise and peripheral BDNF concentrations, future studies should look at dose-response relationships between percentages of increase in BDNF on the one hand, and exercise parameters such as intensity, duration and mode of exercise on the other. The nature of an acute exercise and also subject characteristics, determine the BDNF response; in healthy subjects high-intensity exercise is more likely to induce a BDNF response, while in persons with a chronic disease or disability an exercise of low to moderate intensity seems already strenuous enough to trigger a BDNF response. Metabolic response to exercise or training is known to differ between healthy subjects and persons with a disease or disability and, therefore, probably also BDNF response, will be different. Thus, more studies are required on the BDNF response to different exercise intensities, both in healthy subjects and in persons with a disease or disability. Next to this, Chen et al.[110] and Egan et al.[22] point out that activity-dependent secretion of BDNF is diminished in subjects with the BDNF polymorphism, Val66Met. Future studies should, whenever possible, identify whether subjects are carriers of the genetic variant of the *BDNF* gene (Val66Met) [i.e. 20–30% of human population[24,25]]. Also, for an appropriate comparison between studies, it would be better if changes in BDNF concentration would be expressed in relative units (e.g. in percentages of changes ± the standard deviations). Finally, it would not only be interesting to determine the amount of increase in BDNF, but also the disappearance rate of peripheral BDNF following acute exercise (e.g. BDNF assessment at 0, 30, 60 and 120 minutes post-exercise or by marking BDNF protein *in vivo*).

Three of six studies reported an aerobic training-induced response on basal BDNF while none of the four studies on strength training was capable of elevating basal BDNF concentration. Two of six training studies (i.e. one on aerobic and one on strength training) observed an elevated circulating BDNF response to an acute exercise following a training period. Because of the greater effect of strength training on insulin-like growth factor (IGF)-1 production[111] compared with aerobic training,[112] there could be a possible differential effect of aerobic and strength exercise and/or training on peripheral concentration of BDNF. It is well known that IGF-1 is needed to transform pro-BDNF into BDNF in the CNS[113] and that IGF-1 easily crosses the blood-brain-barrier. Nevertheless, with regard to training-induced effects on peripheral concentration of BDNF, inconsistent findings and too few studies impede to draw a distinct conclusion whether a training period elevates basal BDNF concentration and/or upregulates the cellular processing of BDNF. Future studies on training-induced BDNF response should systematically investigate effects on basal BDNF concentration but also on BDNF response to an acute exercise. Another issue which demands some attention, is whether exercise-induced BDNF increase is limited or not and which physiological and/or environmental factors determine the ceiling effect.

2.8 Origin of Exercise-Induced BDNF Response

The cellular origin of the exercise-induced BDNF response remains partially unclear. Recently, Rasmussen et al.[62] found evidence for a release of BDNF from the brain, as BDNF is able to cross the blood-brain barrier.[114,115] They reported that the brain has a significant BDNF production both at rest and during prolonged

exercise (i.e. 2- to 3-fold increase of the production at rest) in healthy subjects. Confirming these results, Seifert et al.[68] very recently showed that indeed BDNF is released from the brain (vena jugularis), and that aerobic training in obese subjects increases basal BDNF concentration. The brain contributes for almost 75% of circulating BDNF, suggesting that the brain is the major, but not sole, contributor to circulating BDNF in healthy subjects.[62] Yet, it remains to be elucidated from which regions in the CNS and the brain (e.g. hippocampus, cerebral cortex, prosencephalon, cerebellum, hypothalamus) BDNF originates. Animal studies agree that exercise principally upregulates messenger RNA (mRNA) expression in the hippocampus.[4,68,116] A quarter of circulating BDNF seems to stem from a peripheral source. It has been speculated that the exercise-induced BDNF response originates partially from the contracting muscle cells. However, Matthews et al.[10] showed that, *in vitro*, BDNF is indeed synthesized by skeletal muscle cells during contraction, and that muscle-derived BDNF is not released into circulation but used to enhance fat oxidation in the muscle cell. However, more studies are necessary to confirm that, *in vivo*, skeletal muscles do not release BDNF into the circulation following high-intensity contractions. Several other studies revealed some sources of BDNF within the blood circulation. Initially, low concentrations of BDNF in plasma suggest that BDNF is normally not present in the circulation but it is stored in the blood platelets until activation.[117] Yamamoto and Gurney[118] stated that platelets contain BDNF mRNA derived from the cytoplasm of the megakaryocyte and that they release BDNF protein upon agonist stimulation.[96] Consequently, platelets might also synthesize BDNF protein. However, platelets have limited protein synthesis capacity[119] and Fujimura et al.[96] found extremely low or no concentration of BDNF mRNA in blood platelets. Therefore, it is more likely that BDNF is sequestered from the blood circulation, and originates for a major part in the brain and for some part elsewhere.[62,96,119] Other sources of human BDNF circulating in blood plasma and serum or stored in blood platelets could be peripheral cells or endocrine organs such as vascular endothelial cells,[119] immune or peripheral blood mononuclear cells (e.g. T and B lymphocytes,[120-122] eosinophils,[123,124] monocytes,[121,122,125] vascular smooth muscle cells,[126] the pituitary gland,[127] salivary glands such as the submandibular glands).[128,129]

Synthesis and release of BDNF into the blood circulation increases as a result of a physical stimulus in a dose-response manner. The more intense the acute stimulus or (positive) stress is, the greater the BDNF response. Normalization of the BDNF concentration occurs when the stressor disappears, indicating that BDNF is used or stored elsewhere or/and that elevated BDNF secretion has ceased. Following exercise, peripheral BDNF clearance could be elevated indicating that circulating BDNF is used in the periphery or that BDNF is transported via the blood circulation to the brain where it crosses the blood-brain barrier to enhance neural health.[82] When the same stimulus or stressor is repeatedly administered, for example an exercise training programme, it is possible that a ceiling effect occurs because subjects become accustomed to the stimulus or enriched condition and homeostatic mechanisms take over again.[130] To verify this hypothesis, it would be interesting to perform a longitudinal study comparing training-induced BDNF response in well trained subjects to sedentary subjects. Recently, Berchtold et al.[82] showed that both daily exercise and alternating days of exercise increased rat hippocampal BDNF protein, and concentrations progressively increased with longer running duration. They found that hippocampal BDNF protein remained elevated for several days after exercise ceased and could easily be induced again by another brief exercise exposure.[82] These findings could indicate that peripheral BDNF is indeed retrogradely transported and used in the brain following exercise, and that long lasting effects of exercise on BDNF are only traceable in the CNS.

3. Conclusions

This review gives a summary of the current knowledge on the exercise-induced response of

BDNF in healthy subjects and persons with a chronic disease or disability. When interpreting the results of this review, the selection process must be kept in mind. Taken together, it is difficult to compare studies because of varying study populations, sample sizes, different acute exercise and training protocols and different biochemical analysis techniques. Research concerning acute exercise or training interventions should clearly define protocol parameters that result in a functional benefit regarding peripheral BDNF concentration. Also, exercise-induced changes in BDNF should be expressed in relative units (for example in percentages of changes ± the standard deviations).

Overall, an acute aerobic exercise unmistakably influences circulating BDNF concentration, although the effect is transient. In healthy subjects it is rather unlikely that regular exercise (i.e. training) results in an elevated basal BDNF concentration, although the current amount of studies is insufficient to be able to exclude any training-induced effect on basal BDNF. However, the BDNF response to exercise is most probably an epiphenomenon of what happens centrally, and exercising regularly could induce central effects without elevating peripheral basal BDNF concentration. Circulating BDNF probably originates for a large part in the brain; we can only speculate where the other part of circulating BDNF originates from, where it is transported to and for what purpose it is used or stored at its final destination. Furthermore, future research has to show whether repeated administration of an enriched condition, stimulus or stressor (i.e. acute exercise, training and/or reduced-calorie diet) influences the efficiency of the cellular processing of BDNF or basal BDNF concentration (i.e. increase of basal BDNF and disappearance rate). Instead of a training programme consisting of the same exercise protocol during each training session, a protocol with a new exercise stimulus for every few sessions could be implemented.

Whether the use of acute exercise and training is viable for the treatment of neurodegenerative and metabolic diseases (seen from its effects on peripheral BDNF), seems plausible. Recent studies show that BDNF plays a role in regulating central (i.e. through interaction with leptin and through the hypothalamic pathway that controls bodyweight and energy homeostasis) and peripheral energy metabolism (i.e. BDNF as a contraction-inducible protein in skeletal muscle). As a result, central and/or peripheral BDNF could possibly mediate some of the health benefits of exercise in metabolic disorders. On the other hand, effects of repeated exercise on peripheral BDNF concentration could be important with regard to the treatment and prevention of neurological diseases and impairments such as MS, Parkinson's disease and SCI. Long-term effects of exercise on symptoms of neurodegenerative diseases and neurological disorders and its relation with BDNF, have not yet been investigated. The synergistic effect of a combination of BDNF-stimulating factors such as acute exercise or training, changes in the nutrient content of a diet, and key pharmaceuticals could be a next step to study.

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