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Review article

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THE EFFECT OF PHYSICAL ACTIVITY ON THE BRAIN DERIVED NEUROTROPHIC FACTOR: FROM ANIMAL TO HUMAN STUDIES

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It is well documented that physical activity can induce a number of various stimuli which are able to enhance the strength and endurance performance of muscles. Moreover, regular physical activity can preserve or delay the appearance of several metabolic disorders in the human body. Physical exercise is also known to enhance the mood and cognitive functions of active people, although the physiological backgrounds of these effects remain unclear. In recent years, since the pioneering study in the past showed that physical activity increases the expression of the brain derived neurothophic factor (BDNF) in the rat brain, a number of studies were undertaken in order to establish the link between that neurothrophin and post-exercise enhancement of mood and cognitive functions in humans. It was recently demonstrated that physical exercise can increase plasma and/or serum BDNF concentration in humans. It was also reported that physical exercise or electrical stimulation can increase the BDNF expression in the skeletal muscles. In the present review, we report the current state of research concerning the effect of a single bout of exercise and training on the BDNF expression in the brain, in both the working muscles as well as on its concentrations in the blood. We have concluded that there may be potential benefits of the exercise-induced enhancement of the BDNF expression and release in the brain as well as in the peripheral tissues, resulting in the improvement of the functioning of the body, although this effect, especially in humans, requires more research.

Key words: *brain derived neurothophic factor, cognitive function, exercise, learning, mood, training*

INTRODUCTION

It is well known that physical activity provides a number of various stimuli which are able to enhance both the metabolic and functional status of the human body. Physical training within a relatively short period of time (weeks or months) is able to increase the expression of a number of genes involved in any enhancement of a physical capacity (1). Perhaps the most spectacular discovery concerning the adaptation of the body to physical training was presented by John Holloszy, who has shown that regular physical activity/training can induce mitochondria biogenesis in skeletal muscles, leading to an improvement of physical performance (2-4). An increase in muscle mitochondria density enhances the metabolic stability of the muscle during exercise and increases muscle performance (5-7).

For a long period of time physical training was almost exclusively associated with athletes and their preparation for top sports events. However, during the last few decades the amount of studies concerning the effect of physical activity/training and its effects on the health status of healthy yet untrained people as well as of patients has substantially increased (8). They were mainly focused on the effect of training on the adaptation of the cardiovascular, hormonal and muscle systems. The new vision of the benefits of regular physical activity has been presented in a series of experiments showing the anti-inflammatory action of physical exercise (for review see (9, 10)). It was demonstrated that the moderate intensity of physical exercise can be an important factor in the prevention as well as in the healing of several metabolic disturbances of the human body (1, 8, 11).

Physical exercise is also known to enhance the mood and cognitive functions in humans (12-15), although the physiological backgrounds of those effects remain unclear. In recent years there has been a growing interest in research concerning the effect of physical exercise and training on the functioning of the brain, with a special focus on its effect on the brain derived neurotrophic factor (BDNF). Several of these studies showed that exercise induced an up-regulation of the BDNF in the hippocampus and might therefore play an important role in the enhancement of cognitive functions in humans (for review see. (16)).

The BDNF, its isoforms and their receptors

BDNF is most abundant in the growth factor family (17-20). This protein, to begin with, was purified from the brain of a pig (21). The BDNF is widely expressed in the rodent brain, and is especially abundant in the hippocampus, cerebral cortex,

cerebellum, striatum and the amygdala (22, 23). A recent study by Zhang *et al.* (24), showed an intense expression of the BDNF in various parts of an adult monkey brain including: cerebral cortex (layers III and IV), hipocampus (granular cell layer), midbrain (substantia nigra), pons (abducent and facial nucleus), medulla oblongata (hypoglossal nucleus, cuneate and gracile nucleus) and thalamus and hypothalamus nuclei (arcuate) as well as a moderate and mild expression in several other regions of the brain (for an overview, see *Table 1* in (24)). BDNF expression was also reported in various parts of the human brain, including the hippocampus, claustrum, amygdala, bed nucleus of the stria terminalis, septum and the nucleus of the solitary tract (25).

It has been demonstrated that the BDNF plays a critical role in the activity-dependent processes, including synapse development and plasticity (26-28). It was reported that BDNF, by acting *via* the protein tyrosine kinase receptor (TrkB) (20, 29) regulates a number of processes including neuronal development and its functions (19, 30-32). BDNF is involved in memory formation, including learning and behavior, synaptic plasticity, synaptic efficacy and neuronal connectivity, plus it promotes the development of immature neurons and enhances the survival of adult neurons (19, 33, 34). According to Monteggia *et al.* (31) the role of BDNF in the adult brain may be different from that in the developing brain. It was demonstrated that the loss of BDNF selectively in the brain of adult mice resulted in impaired hippocampal function, whereas the loss of BDNF during the early stages of development contributed to hyperactivity as well as to the more severe impairments in hippocampal-dependent learning (31).

BDNF, similar to other neurothropins, is initially synthesized as a precursor (pro-BDNF with MW of 32 kDa), which is subsequently cleaved to generate the mature BDNF (mBDNF with MW of 14 kDa) (see, (35, 36). Additionally, a third BDNF isoform with MW of 28 kDa was recognized as well (see *Fig. 1* in (35)). This BDNF isoform, known as truncated BDNF, is not further cleaved (37). It is well documented that the mBDNF and the pro-BDNF are biologically active, whereas the function of the truncated BDNF is still unknown.

BDNF exerts its biological effects in the neural system *via* two types of receptor: the tyrosine kinase receptor (Trk) B receptor and the pan-neurotropin receptor p75 ($p75^{NTR}$) (for an overview see (38)). It was demonstrated that pro-BDNF preferentially interacts with the $p75^{NTR}$, whereas mBDNF selectively binds and activates the TrkB (39, 40). In this way various BDNF isoforms generate sometimes opposite effects. For example, it has been reported that the activation of $p75^{NTR}$ by an endogenous pro-BDNF results in long term depression (LTD) in the hippocampus (41, 42) and induces apoptosis in peripheral neurons (43), whereas activation of the TrkB receptors by mBDNF is essential for long term potentiation (LTP) (44, 45) and regulates the neuronal development and its functions (31). Moreover, it has been recently demonstrated that the exogenous pro-BDNF suppresses synaptic transmission and structurally causes axonal retraction by activation presynaptic $p75^{NTR}$ (46). These authors also showed that muscle stimulation induces a secretion of pro-BDNF, which elicits either synaptic potentiation or depression, depending on whether it is proteolitically cleaved (46). For an overview of the major intracellular signaling pathway activated throughout TrkB and $p75^{NTR}$ receptors see *Fig. 2* in (38). It is of interest how the two receptors communicates with each other in order to provide optimal cell functioning. This issue has been recently reviewed by Reichardt (38) showing that the signaling pathways initiated thought Trk receptors act at several steps to suppress the major pro-apoptotic-signaling pathway stimulated by $p75^{NTR}$ to maintain a proper cell functioning (see also (47)). For this reason, in order to evaluate the effect of the BDNF release on physiological functions, it is important to determine both the amount of proBDNF and the mature BDNF release from the neurons. However, relatively little data on the measurements of all the above mentioned BDNF isoforms has been reported so far.

The effect of exercise on the BDNF expression in a rodent's brain

It was demonstrated that physical activity/training can increase BDNF gene expression in the brain (48-53). The interest in this area of research was initiated by Nepher *et al.* (48), who originally reported a significant positive correlation between the mean distance run on a running wheel and the mRNA for BDNF in the hippocampus and caudal neocortex of the studied rats. The authors concluded that physical activity could increase the availability of BDNF to these cells by up-regulating its expression in the hippocampus, and as a result it was proposed that exercise induced the up-regulation of BDNF and could help to increase the brain's resistance to damage and degeneration through BDNF's support of neuronal growth, function and survival (48). Subsequently, Nepper (49) have reported that the 2-7 nights of running resulted in a significant increase of mRNA for BDNF in the rat hippocampus. These original findings by Neppher *et al.* (48, 49) were confirmed by others, who showed that, indeed, physical activity/training is able to up-regulate the BDNF expression in animal brains. For example, Oliff *et al.* (54) have found that the brain mRNA expression in rats correlates with the distance run during voluntary activity. Furthermore, the authors have reported that as little as 6 hours of voluntary wheel running resulted in a significant up-regulation of the hippocampal BDNF mRNA expression in rats, which remained elevated after 12 hours of voluntary running Oliff *et al.* (54). Recently, Rassmussen *et al.* (55) reported that a single bout of exercise resulted in the significant up-regulation of BDNF mRNA in the hippocampus and cortex of a mouse, with a peak occurring at about 2 hours after finishing the treadmill exercise bout.

An interesting observation concerning the dynamics of the changes in the BDNF protein levels in rats during the time course of training and detraining was published by Berchtold *et al.* (52). The authors reported that a daily exercise training (voluntary running exercise performed on a running wheel) resulted in a significant increase in the BDNF protein level after 14 days of training, which continued to rise until the end of the training period (*i.e.* up to 90 days). Moreover, it remained significantly elevated (above the level found in the sedentary rats) up to the 7^{th} day after finishing the daily training (see *Fig. 2A* and *3A* in (52)). The authors have also studied the effect of the same kind of training performed on alternating days. It was found that this training can also significantly increase the BDNF protein level in the hippocampus of the rats, although this increase is slower and it decays much faster when compared to the daily exercise training (see, *Fig. 2B* and *3B* in Berchtold *et al.* (52)). This data suggests that physical training can up-regulate the BDNF protein level in the brain, but the most beneficial seems to be when the daily training is performed for at least several months.

An interesting observation concerning the various types of exercise: treadmill running *vs.* voluntary wheel running on cognitive functions was recently reported by Liu *et al.* (53). These authors have demonstrated that although both moderate treadmill running and wheel running up-regulated the BDNF-TrkB pathway in the hippocampus, both forms of the training protocols exerted varied effects in the different regions of the brain and on its functions. The authors concluded that different forms of exercise induced changes of the neuroplasticity in different brain regions and also exerted diverse effects on

various forms of learning and memory. This effect should be taken into consideration when interpreting the effect of exercise on brain plasticity and its functioning.

Exercise-induced BDNF and learning benefits

It was postulated by Figurov *et al.* (45) that BDNF may regulate LTP in the developing hippocampus as well as the adult hippocampus by enhancing synaptic responses to tetanic stimulation. The authors demonstrated that BDNF promoted the induction of LTP by tetanic stimulation in young hippocampal slices, which with their absence of BDNF showed only short-term potentiation (STP) (45). The LTP is considered to be a form of synaptic plasticity involved in long-term memory formation (56, 57). The importance of BDNF in LTP was also reported by others (see *e.g.* (32, 58-61)). Additional evidence for the role of BDNF in the cognitive function of the brain comes from the study by Alonso *et al.* (62), which shows that an intrahippocampal administration of recombinant human BDNF facilitated long-term memory (LTM) formation in the rat brain (62), whereas bilateral infusion of the function-blocking anti-BDNF antibody in to the CA1 region of the dorsal hippocampus impaired LTM retention scores in rats. Lee *et al.* (63) have shown that the process of memory consolidation in rats is strictly dependent upon the presence of BDNF in the hypothalamus. It was also recently postulated that plasma BDNF concentration can be considered as a biomarker of memory and general cognitive function in women (64).

Since physical activity is able to up-regulate the BDNF expression in the rat hippocampus (48-50), it was postulated that this increase may play an important role in the cognitive functions, including learning and memory (65). Indeed, the exercise-induced up-regulation of BDNF in the hypothalamus was related to an improvement of cognitive function, including memory, in rodents (51, 66, 67), whereas the inhibition or down-regulation of BDNF or TrkB impaired memory formation (67-70). This data suggests that, indeed, regular physical activity might potentiate the cognitive functions *via* the exercise-induced up-regulation of the hippocampus BDNF (32, 53, 71). It was also recently reported that the training-induced BDNF expression in the peripheral cortex of exercising rats was strongly correlated with object recognition memory (72). This is the first evidence whereby the changes in the BDNF level are associated with the voluntary exercise-induced improvement in non-spatial memory, which is itself mediated by structures outside the hippocampus (72).

BDNF polimorphism

Additional evidence for the importance of BDNF in learning and cognitive functions in humans is provided by recent studies (73), initiated by Egan *et al.* (74), who have found that the presence of the Val^{66}Met BDNF polymorphism in humans (a methionine (Met) substitution for valine (Val) at codon 66), found in one or in both alleles in approximately 30% of people (73), was associated with poorer episodic memory and abnormal hippocampal activation. Further studies by this group (75) provided additional evidence for the importance of the BDNF Val^{66}Met polymorphism in memory performance. Subsequently, Kleim *et al.* (76) reported that the subjects lacking the BDNF Val^{66}Met polymorphism showed an expansion of the motor map with training, whereas subjects with the BDNF Val^{66}Met polymorphism in one or both alleles showed only a little of such plasticity. Cheeran *et al.* (77) recently found that the response of healthy subjects to three different plasticity-inducing protocols in the motor cortex is associated with the polymorphism of the BDNF gene that they carry. According to Cheeran *et al.* (77), the polymorphism in the BDNF gene may be one factor that influences the natural response of the brain to injury and disease. Moreover, it was reported that the Val^{66}Met polymorphism may play a key role in the genetic predisposition to anxiety and depressive disorders (Chen *et al*. (78)). These observations were further developed by Soliman *et al.* (79), who demonstrated that variant BDNF alleles may play a role in anxiety disorders, showing an impaired learning of the cues that signal safety versus threat and in the efficacy of treatments that rely on the extinction mechanism, such as exposure therapy. According to Ninan *et al.* (80) the BDNF Val^{66}Met polymorphism has a direct effect on NMDA receptor transmission, which may account for the changes in the synaptic plasticity in the hippocampus.

These studies clearly demonstrate that the disturbances in the BDNF structure, such as the Val^{66}Met polymorphism, affects memory and learning and that it might also be involved in the origin of several neurological and psychiatric conditions (77).

Plasma and/or serum BDNF level in healthy humans

It was originally demonstrated by Rosenfeld *et al.* (81), that the BDNF can be detected in both the human serum and in the plasma, besides its concentration in the serum is more than 200-fold higher than in the plasma. Currently, based on a larger sample of subjects, it is well established that the serum BDNF concentration $[BDNF]_s$ in healthy humans is higher by about 100-fold than in plasma $[BDNF]_p$ (82, 83). Most of the BDNF circulating with the blood is stored in the platelets (84, 85). Therefore, a close correlation exists between the count of the platelets and the serum BDNF concentration in humans (82). The circulating BDNF is produced by a number of peripheral non-neuronal tissues, including vascular human endothelial cells (86-89), T cells, B cells and monocytes (90). Additionally, it was shown that BDNF mRNA in the skeletal muscles of rodents increases in response to contraction (65, 91). The recent study by Matthews *et al.* (92), confirmed the previous observations showing that skeletal muscles can indeed produce BDNF, although in the light of their study the muscle-produced BDNF is not released into the circulation and cannot therefore account for its changes in serum or plasma.

According to Fujimura *et al.* (85), the platelets can bind, store and release BDNF upon activation at the site of traumatic injury in order to facilitate the repair of peripheral nerves or other tissues that contain TrkB. Moreover, these authors (85) question the role of platelets produced by the circulating BDNF. Rojas Vega *et al.* (93), and have recently postulated that the elevated serum BDNF concentrations might be beneficial for improving recovery after spinal cord injury. However, the contribution of varied sites where BDNF is periphally produced is not established yet. According to Nakahashi *et al.* (87) the endothelial cells may significantly contribiute to circulating BDNF. It was demonstrated that BDNF can cross the blood-brain barrier (94, 95) in both directions, *i.e*. from the brain to the periphery and from the periphery to the brain (95), *via* the high capacity saturable transporter system (95). Furthermore, it was reported that the BDNF level in the brain correlates with the serum BDNF concentration (96), therefore it has been suggested that the blood level of the BDNF may reflect the brain level and *vice-versa*. According to Lommatzch *et al.* (82), the changes in $[BDNF]_p$ are reflecting its changes in the brain. It should be mentioned, however, that some authors (42, 97) challenged the finding of Poduslao and Curran (94) and of Pan *et al.* (95) where the exchange of BDNF between the brain tissue and blood is concerned. It was recently reported that during physical exercise the increase in the $[BDNF]_p$ concentration in humans was due to an enhanced release of BDNF from the brain (55). These authors have shown that in humans, both at rest and during exercise, the

brain contributed to 70-80% of the circulating BDNF, while the other contribution decreased following 1 hour of recovery. According to Rasmussen *et al*. (55), the brain is a major but not sole contributor to the circulation of BDNF both at rest and during exercise. This is an important new observation, although the magnitude of the contribution of the brain to peripheral BDNF concentration, as reported by Rasmussen *et al.* (55), should be considered with caution, since the contribution from other peripheral sources of BDNF release during exercise, such as the platelets, vascular endothelial cells, smooth muscle cells and other cells, requires more research.

Plasma and/or serum BDNF level in mental disorders

Since BDNF plays a critical role in the functioning of the brain (19, 28, 31), some studies have attempted to relate the BDNF with major mental disorders: depression (98, 99) and schizophrenia (100). A number of studies were undertaken to assess the levels of BDNF in plasma $[BDNF]_p$ and/or in serum $[BDNF]_s$ in patients with depression or schizophrenia. Moreover, Komulainen *et al.* (64) have recently reported that plasma BDNF is a biomarker of impaired memory and general cognitive function in ageing women.

Depression

It was reported that the basal $[BDNF]_s$ in untreated patients suffering from major depressive disorders is significantly lower than in control subjects (101-105). Additionally, low plasma BDNF was reported to be associated with suicidal behavior in depressed patients (Kim *et al.* (104)). Interestingly, it was reported that 8-12 weeks of treatment with antidepressant drugs resulted in a significant increase in serum BDNF concentration in the studied patients (102, 103, 105). It was also recently shown that the basal $[BDNF]_p$ in patients suffering from post-traumatic stress disorder was significantly lower than in the healthy subjects (106).

Schizoprenia

A large body of data concerning the serum $[BDNF]_s$ was collected from schizophrenic patients, although the emerging picture is not clear. While most of the studies showed a lower $[BDNF]_p$ or $[BDNF]_s$ concentrations in patients with schizophrenia, when compared to healthy controls (107-110), but some research (111, 112) reported similar $[BDNF]_p$ or $[BDNF]_s$ concentrations in both groups. Occasionally, even higher than normal levels of $[BDNF]_s$ where observed in schizophrenic patients (113, 114). Some of the differences in the $[BDNF]_s$ levels in schizophrenic patients found in different studies might be due to the various stages and the level of severity of the illness besides the treatment methodology.

Some interesting observations concerning the $[BDNF]_s$ levels in schizophrenic patients were recently reported by Carlino *et al.* (115). These authors measured both the total BDNF levels (as in most of the above mentioned studies) as well as three BDNF isoforms (pro-BDNF, truncated BDNF and mat-BDNF) levels in serum. The total BDNF concentration in the studied schizophrenic patients was slightly lower than in the control group, although the most interesting findings of this study were the clear differences in the pro-BDNF, truncated BDNF and the mat-BDNF isoforms in patients *vs.* the control group. Namely, the serum pro-BDNF and mat-BDNF concentrations were significantly higher in schizophrenic patients, whereas the level of the truncated BDNF isoform was significantly lower in the schizophrenic patients. Moreover, the reduced levels of the serum truncated BDNF / total BDNF ratio correlated with the worst PANSS negative and positive symptoms and with the poorer neurocognitive performance (see Carlino *et al.* (115)).

BDNF and type 2 diabetes mellitus

It was shown that serum BDNF concentrations in type 2 diabetes mellitus (T2DM) patients are significantly lower than in non-diabetic controls (116, 117). Opposite results were reported by Suwa *et al.* (118), showing that serum BDNF levels in newly diagnosed female patients with T2DM were significantly higher than those in the control subjects. According to Hristowa *et al.* (119), elevated plasma and/or serum BDNF concentration may be an early marker of pathological metabolic changes in the body. On the other hand, it was recently reported that 6 weeks of endurance training has induced an improvement in the physical capacity of humans, involving an increase in maximal oxygen uptake (VO_{2max}), an increase in the power generating capability at the VO_{2max}, a decrease in lipid peroxidation, and that a slight decrease in insulin resistance was accompanied by a significant increase in basal as well as the exercise induced plasma BDNF concentrations in young healthy men (120). Furthermore, it was reported that the administration of BDNF to diabetic mice improved glucose (121-123) and lipid metabolism (124). These recent findings suggest that an elevated serum and/or plasma BDNF concentration in healthy individuals may have opposite meaning than in patients with metabolic disorders (see (118, 120, 125, 126). Additionally, the systematic study of the changes in serum BDNF in patients at various stages of the T2DM are needed in order to establish its role in the origin of this metabolic disorder.

The effect of a single bout of physical exercise and training on the plasma or serum BDNF concentrations in humans

It was reported that a single bout of physical exercise can increase the plasma or serum BDNF concentrations in healthy humans. It was originally demonstrated by Gold *et al.* (127) that a single session of prolonged exercise (30 minutes cycling at 60% VO_2max), resulted in a significant increase in the serum BDNF concentration both in healthy individuals as well as in multiple sclerosis patients. Subsequently, in the study by Rojas Vega *et al.* (128), it was shown that a single bout of maximal incremental exercise resulted in a significant increase in the serum BDNF in recreational athletes, whereas 10 minutes of moderate aerobic cycling was not sufficient to increase the serum BDNF concentration above the pre-exercise level. This finding is in accordance with the study by Ferris *et al.* (129), which shows that the magnitude of the increase in the serum BDNF concentration during exercise is dependent on the intensity of the exercise. A significant increase in the serum BDNF concentration in young healthy men has also been reported by Winter *et al.* (130), after very high intensity running for a small duration (2 runs until exhaustion, lasting 3 minutes each, with 2 minutes break). Similarly, Tang *et al.* (131) reported a significant increase in the serum BDNF concentration in young and healthy men after short term high intensity of 15 minutes step-exercise. No effect of a single bout of maximal incremental cycling exercise - (up to VO_{2max}, lasting about 30 minutes), on the plasma BDNF concentration was found in young healthy men (120). Recently it was reported that a prolonged - 4 hours rowing exercise resulted in a significant increase in the plasma BDNF concentration in humans (55). Additionally, Yarrow *et al.* (132) have reported that a single session of resistance exercise resulted in a significant increase in the serum BDNF concentration in young and healthy men.

Regarding the effect of physical training on the basal and exercise-induced changes of plasma or serum BDNF

concentrations, the picture is more complex. Both the effects of the endurance as well as the strength training program in a varied groups of subjects on the basal and exercise induced plasma or serum BDNF concentrations were evaluated. Firstly considering the effects of endurance training on the basal and the exercise-induced plasma or serum BDNF concentrations, Schulz *et al.* (133), who studied the effect of 8-week aerobic bicycle training on the serum BDNF concentration in patients with multiple sclerosis, found no effect of the training on the basal as well as the exercise-induced serum BDNF concentration. Similarly, Castellano and White (134), who studied the effect of endurance cycling training on the serum BDNF concentration in multiple sclerosis patients, found a temporary (after 4 weeks of training) increase in the serum BDNF concentration, which returned to the pre-training level after 8 weeks of training. Zoladz *et al.* (120), who studied the effect of 5 weeks of moderate intensity training, have found a significant increase in the basal plasma BDNF concentration as well as a significant exercise-induced increase in the plasma BDNF concentrations in young and healthy men. Recently, Seifert *et al.* (135) reported that 3 months of endurance training in young and healthy men enhanced the resting release of BDNF from the brain but had no effect on the magnitude of the exercise-induced increase in the plasma BDNF concentration.

Where the effect of the strength training on the on basal and the exercise-induced plasma or serum BDNF concentrations is concerned, the reported results are not consistent. Levinger *et al.* (126) have shown that 10-week resistance training did not affect the plasma baseline BDNF concentration in middle aged subjects. Likewise, Goekint *et al.* (136) have found no effect from 10-week strength training on the basal and post exercise serum BDNF concentration in young and healthy men. On the other hand, Yarrow *et al.* (132) have recently reported that a 5-week resistance training augments the exercise-induced transient increase in serum BDNF concentration in young and healthy yet previously untrained males.

The training-induced an increase in the $[BDNF]_p$ and $[BDNF]_s$ might play a role in the exercise-induced improvement of mood (137), as well as in the protection and regeneration of various tissues (93, 138). The training-induced enhancement of the circulating BDNF might be involved in the neoangiogenesis of the cardiac and skeletal muscles after training (86, 88). Furthermore, the training-induced elevation of BDNF may be beneficial to the efficacy of pharmacological antidepressant treatment (139, 140). It was also postulated (120) that the training-induced increase in $[BDNF]_p$ *via* its action in the central nervous system may also enhance motor learning ability in athletes. In the light of these recent studies (141), the training-induced up-regulation of the skeletal muscle BDNF, as shown by Matthews *et al.* (92) might increase fat oxidation in skeletal muscles in an AMPK-dependent fashion.

Further studies in humans are needed to establish first of all the effect of the single bout of exercise and training on the changes in the serum levels of the pro-BDNF, truncated BDNF and the mat-BDNF isoforms in humans and to relate their levels to the mood state and the cognitive performance. More data is needed to establish the role of BDNF in the enhancement of the metabolic status of skeletal muscles.

CONCLUSIONS

We have concluded that in the light of the available data collected mainly from rodents, physical training is able to up-regulate the BDNF expression in some regions of the brain. The existing evidence indicates that the training-induced up-regulation of BDNF expression in the brain may play a role in the improvement of mood as well as in an enhancement of cognitive functions. Moreover, physical exercise, similar to pharmacological treatment with antidepressant drugs, is able to enhance the level of plasma and/or serum BDNF concentrations in humans. However, the physiological importance of the training-induced changes in plasma and/or serum BDNF concentrations in humans remains to be established. Further studies are required to determine the effect of a single bout of exercise and training on the three BDNF isoforms (pro-BDNF, truncated BDNF and mat-BDNF) levels in serum, especially in relation to the mental state and cognitive performances in humans.

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