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ENDURANCE TRAINING INCREASES PLASMA BRAIN-DERIVED NEUROTROPHIC FACTOR CONCENTRATION IN YOUNG HEALTHY MEN

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It is believed that brain derived neurotrophic factor (BDNF) plays an important role in neuronal growth, transmission, modulation and plasticity. Single bout of exercise can increase plasma BDNF concentration $[BDNF]_p$ in humans. It was recently reported however, that elevated $[BDNF]_p$ positively correlated with risk factors for metabolic syndrome and type 2 diabetes mellitus in middle age group of subjects. On the other hand it is well established that endurance training decreases the risk of diabetes and development of metabolic syndrome. In the present study we have examined the effect of 5 weeks of moderate intensity endurance training on the basal and the exercise induced changes in $[BDNF]_p$ in humans. Thirteen young, healthy and physically active men (mean ± S.E: age 22.7 ± 0.5 yr, body height 180.2 ± 1.7 cm, body weight 77.0 ± 2.5 kg, Vo_{2max} 45.29 ± 0.93 ml · kg^{-1} · min^{-1}) performed a five week endurance cycling training program, composed mainly of moderate intensity bouts. Before training $[BDNF]_p$ at rest have amounted to 10.3 ± 1.4 pg · ml^{-1}. No effect of a single maximal incremental cycling up to Vo_{2max} on its concentration was found (10.9 ± 2.3 pg · ml^{-1}, P=0.74). The training resulted in a significant (P=0.01) increase in $[BDNF]_p$ at rest to 16.8 ± 2.1 pg · ml^{-1}, as well as in significant (P=0.0002) exercise induced increase in the $[BDNF]_p$ (10.9 ± 2.3 pg · ml^{-1} before training vs. 68.4 ± 16.0 pg · ml^{-1} after training). The training induced increase in resting $[BDNF]_p$ was accompanied by a slight decrease in insulin resistance (P=0.25), calculated using the homeostatic model assessment version 2 (HOMA2-IR), amounting to 1.40 ± 0.13 before and 1.15 ± 0.13 after the training. Moreover, we have found that the basal $[BDNF]_p$ in athletes (n=16) was significantly higher than in untrained subjects (n=13) (29.5 ± 9.5 pg · ml^{-1} *vs*. 10.3 ± 1.4 pg · ml^{-1}, P=0.013). We have concluded that endurance training of moderate intensity increases both basal as well as the end-exercise $[BDNF]_p$ in young healthy men. This adaptive response, contrariwise to the recent findings in patients with metabolic disorders, was accompanied by a slight decrease in insulin resistance.

Key words: *brain derived neurotrophic factor, exercise, insulin, training*

INTRODUCTION

Brain derived neurotrophic factor (BDNF) was first isolated from pig brain (1) and is the most abundant in the nerve growth factor family. BDNF is related to nerve growth factor, the first neurotrophic factor discovered (2) and acts *via* protein tyrosine kinase receptor (TrkB) (3). BDNF and other trophic factors may play a role in preventing neuronal death and in processes of neuroregeneration (4). It promotes the development of immature neurons and enhances the survival of adult ones (5). BDNF plays a role in memory formation (7), synaptic plasticity (6), synapse formation (8), synaptic efficacy and neuronal connectivity (9).

In the periphery BDNF is found in the plasma, serum and platelets (10) and it is formed by vascular endothelial cells and by peripheral blood mononuclear cells (11). Despite the size of the protein (27 kDa) BDNF can cross the blood-brain barrier (12, 13) in both directions from brain to the periphery and from the periphery to the brain (13), *via* high capacity saturable transporter system (13). A positive correlation between BDNF levels in the brain and serum was described (14), therefore the blood levels of BDNF may reflect the brain levels and *vice-versa*. It should be mentioned however, that some authors (15, 16) challenged the finding by Poduslo and Curran (12), and by Pan *et al.* (13).

Physical exercise is not only beneficial in preventing cardiovascular diseases, it also reduces the risk of developing some types of cancers including colon, breast and prostate cancer (17-20), and it is also potent to enhance brain health and its plasticity (21). Physical activity increases the expression of BDNF in the rat brain (22-25). It was shown that voluntary wheel running in rats leads to an increase in expression of BDNF mRNA level in the hippocampus (26) and this increase is sustained for several weeks after training (21). Also in humans serum BDNF levels $[BDNF]_s$ are significantly elevated in response to exercise. It was described that 30 min of moderate exercise (bicycle ergometry) increases $[BDNF]_s$ (27). An increase in $[BDNF]_s$ during the ramp test to exhaustion was observed (28) and the magnitude of its increase is exercise intensity dependent (29). On one hand, exercise improves neurological health and decreases negative mood (30, 31) also in depressed patients voluntary exercise produced antidepressant effect (32) and the positive effect was increased after acute exercise (33). On the other hand, a role for BDNF in pathogenesis of depression was proposed (34) and decreased $[BDNF]_s$ was found in depressed patients (35). Moreover, it was recently reported that low levels of $[BDNF]_p$ in humans accompanies impaired glucose metabolism as well as it was postulated that decreased $[BDNF]_p$ may be a pathogenetic factor involved not only in dementia and depression, but also in type 2 diabetes (36). It should be also mentioned, that the recent study by Han *et al*. (37), showed that among persons with the WAGR syndrome (Wilms' tumor, aniridia, genitourinary anomalies and mental retardation), BDNF haploinsufficiency is associated with lower levels of serum BDNF and with childhood-onset obesity.

However, surprisingly, it was recently shown that $[BDNF]_s$ positively correlated with risk factors for metabolic syndrome and type 2 diabetes mellitus in middle age group of subjects (38). Moreover, a significantly elevated $[BDNF]_s$ in newly diagnosed female patients with type 2 diabetes mellitus was recently shown by Suwa *et al*. (39). According to some authors (38-40) elevated levels of plasma / serum BDNF concentrations may be an early marker of pathological metabolic changes in the body.

In view of the above presented contradictory results regarding the relationship between plasma/serum BDNF concentrations and the risk of metabolic syndrome in humans (36, 38-40), in the present study we aimed to investigate the bimodal effect of moderate intensity endurance training *i.e*. on the basal and on the exercise induced plasma BDNF concentrations in young healthy men, also in relation to the changes in the insulin resistance. We have hypothesized, that this kind of training, considered as an intervention beneficial to the health status (for review see *e.g*. (20)) should result in an increase in the basal ("chronic") as well as in the exercise induced ("acute") increase in $[BDNF]_p$ without disturbances in insulin resistance in young healthy man.

MATERIALS AND METHODS

Subjects

Thirteen young, healthy and physically active men (means ± S.E: age 22.7 ± 0.5 yr, body height 180.2 ± 1.7 cm, body weight 77.0 ± 2.5 kg and BMI 23.7 ± 0.6 kg · m^{-2}) participated in five week endurance training. The maximum oxygen uptake ($\dot{V}_{O_2\,max}$) - determined before training - amounted to 45.29 ± 0.93 ml · kg^{-1} · min^{-1}.

All subjects were aware of the aims of the study and gave informed written consent. The study protocol was approved by the Local Ethical Committee and was performed in accordance with the Declaration of Helsinki.

Exercise protocol

The incremental exercise test was performed on the cycloergometer Ergo-Line GmbH & Co KG 800s (Bitz, Germany). Before the test, a 6-min resting period was allowed to determine the resting stage of the cardio-respiratory parameters. The exercise test was performed at pedalling rate of 60 rev · min^{-1} started at power output 30 W, followed by a gradual increase of power output by 30 W every 3 minutes and it was continued until exhaustion (41). The exercise incremental test was performed twice: three days before and three days after completing a 5-week endurance training.

Gas exchange variables

Gas exchange variables were measured continuously *breath by breath* using the Oxycon Champion, Mijnhardt BV (Bunnik, The Netherlands), starting from the 6th minute prior to exercise until the test was stopped. Before and after each test, gas analysers were calibrated with certificated calibration gases as previously described by Zoladz *et al*. (42).

Blood sampling

Blood samples for measurements of plasma insulin, glucose and BDNF concentrations were taken at rest in the morning hours 7:30 - 8:00 a.m. in fasting state, twice: before and after five weeks of endurance training. The blood samples were taken before and during the incremental exercise test using the Abbot Int-Catheter, Ireland (18G/1.2 ´ 45 mm) inserted (about 15 minutes prior to the onset of the incremental exercise test) into the antecubital vein. The catheter was connected to an extension set using a "T" Adapter SL Abbot, Ireland (the tube 10 cm in length). Immediately before each blood sampling, 1 mL of blood volume was drawn in order to eliminate blood from the catheter and the T-set. Blood samples for plasma lactate measurements were taken prior to the exercise test, at the end of each step of the incremental exercise (the last 15 seconds before increase of power output) and at the moment of ending the exercise protocol.

Plasma lactate measurements

The samples (0.5 mL each) for measurements of plasma lactate concentration ($[La^-]_p$) were placed in 1.8 mL Eppendorf tubes, containing 1 mg ammonium oxalate and 5 mg sodium fluoride and mixed for about 20 seconds and then centrifuged. The blood plasma (about 200 µL) was stored at -40°C for further analysis of $[La^-]_p$ using an automatic analyser Vitros 250 Dry Chemistry System, Kodak (Rochester, NY, USA). Lactate threshold (LT) in this study was defined as the highest power output above which plasma lactate concentration $[La^-]_p$ showed a sustained increase of more than 0.5 mmol · L^{-1} · $step^{-1}$ (see (42)).

Plasma BDNF measurements

Plasma BDNF concentrations $[BDNF]_p$ were analyzed by enzyme immunoassay using ELISA kit EK-033-22, by Phoenixes Pharmaceuticals, Inc, CA, USA with a detection range from 7.8 - 500 pg · ml^{-1} and with < 3% cross-reactivity with others neurothrophines. The intra-assay and inter-assay variations were < 10% and < 12%, respectively.

Plasma insulin and glucose measurements

Plasma insulin was measured by IRMA using the INS-IRMA kit (BioSource, Belgium). Analytical sensitivity for this measurement was 1 µIU/ml and intra- and interassay CV were < 2.4% and 6.8%. For IRMA method the radioactivity of the samples were measured by using gamma scintillation counter (Wallac, Finland).

Plasma glucose was measured by enzymatic method (dry chemistry) by using Vitros 950 (Johnson and Johnson, USA).

Insulin resistance

Based on the fasting plasma concentrations of glucose and insulin, the level of insulin resistance was calculated, using the homeostatic model assessment version 2 (HOMA2-IR) (see (43)).

Endurance training programme

The subjects underwent a 5-week endurance training programme (for details see (44)). Training was performed on cycloergometers Monark 874 E at pedaling rates amounting to 60 rev · min^{-1}. The programme included four training sessions per week. Two various training protocols were applied: (a) continuous endurance cycling - performed at the power output (PO) corresponding to 90% of oxygen consumption measured at previously determined lactate threshold (90% VO_2 at LT) lasting

40 minutes and (b) intermittent endurance cycling composed of 6 minute cycling without resistance (*unloaded cycling*) followed by 3 minute cycling at the power output corresponding to 50% Δ, repeated 4 times. The power output corresponding to 50% Δ was calculated for each subject as follows: 50% Δ = PO at LT + 0.5 (PO_{max} - PO_{LT}) (see *e.g.* (45)). Continuous endurance cycling training was performed on Tuesdays and Fridays, whereas intermediate endurance training on Mondays and Thursdays. On Wednesdays, Saturdays and Sundays no training was applied. During the five-week training the subjects performed 20.8 ± 0.14 training sessions lasting in total 13.9 ± 0.10 hours. The training workload applied was predominantly of moderate intensity since 85% of the training workloads (expressed in time) were performed below the LT and only 15% above the LT (at 50% Δ see above).

The athletes

For the comparison of the basal $[BDNF]_p$ in untrained and in the trained subjects, in the present study we have also involved a group of 16 athletes (means ± S.E: age 22.8 ± 0.7 yr, body height 182.3 ± 1.7 cm, body weight 74.7 ± 2.8 kg, BMI 22.5 ± 0.7 kg · m^2), specialized in various kinds of athletic events (for 8 ± 1 years), (including sprinters, jumpers and runners). Blood samples for measurements of plasma BDNF, glucose and insulin concentrations were taken at rest at 7:30 - 8:00 a.m. in fasting state. The relevant measurements were performed as described above.

Statistics

The results are expressed as mean and standard deviation (x ± SE). Statistical significance was tested using Wilcoxon-signed-rank test (for paired samples) and Wilcoxon-Mann-Whitney test (for two independent samples). Non-asymptotic, exact, two-sided *P*-values are presented (see the Results section). Correlation between two variables was tested with Spearman's correlation analysis. The statistics was done using the statistical packet StatXact 6.1 and STATISTICA 7.1.

RESULTS

Body mass, body mass index (BMI)

No significant changes in the body mass (77.0 ± 2.5 kg and 76.5 ± 2.4 kg, respectively, for pre-training and post-training values) and in BMI (23.7 ± 0.6 kg · m^{-2} and 23.5 ± 0.6 kg · m^{-2}, respectively, for pre-training and post-training values), was found after 5 weeks of the endurance training.

Maximal oxygen uptake (Vo_{2max})

Vo_{2max} increased from 3472 ± 94 ml · min^{-1} to 3585 ± 95 ml · min^{-1} (P = 0.057) in response to training. Significant increase in Vo_{2max} expressed per kg of body mass was observed (from 45.29 ± 0.93 ml · kg^{-1} · min^{-1} to 47.14 ± 1.12 ml · kg^{-1} · min^{-1}, P = 0.03).

Power output reached at Vo_{2max} (PO_{max})

PO_{max} after training was also significantly higher (277 ± 7 W *vs*. 255 ± 7 W, P = 0.0005) after the endurance training.

Plasma BDNF concentration [BDNF]p

Before training $[BDNF]_p$ at rest amounted to 10.3 ± 1.4 pg · ml^{-1}. Its concentration at the end of exercise (*i.e.* at the Vo_{2max}) amounting to 10.9 ± 2.3 pg · ml^{-1} was not significantly different (P = 0.74) from its value at rest (see *Fig. 1*). After 5 weeks of the endurance training $[BDNF]_p$ at rest amounted to 16.8 ± 2.1 pg · ml^{-1}, while at the end of exercise its concentration amounting to 68.4 ± 16.0 pg · ml^{-1} was significantly elevated (P = 0.0002). $[BDNF]_p$ at rest after training was significantly higher than before training (P = 0.01).

Moreover, the magnitude of the exercise-induced increase in $[BDNF]_p$, defined as the difference between the end-exercise minus pre-exercise plasma

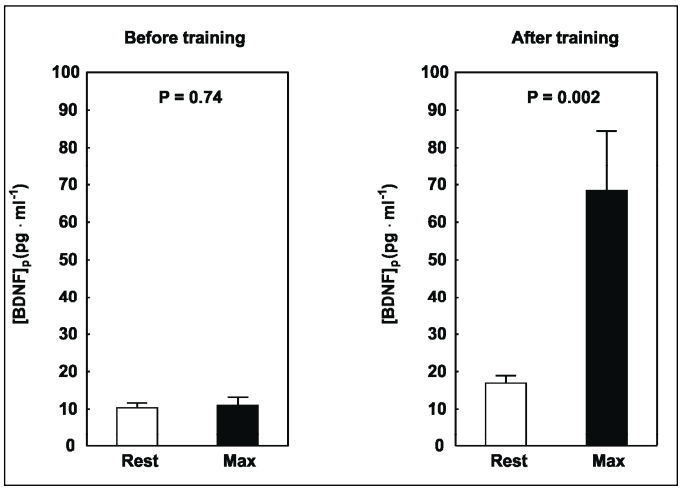

Fig. 1. Plasma BDNF concentrations in young healthy men (n = 13), measured at rest (Rest) and at the Vo_{2max} (Max) during maximal incremental cycling exercise test, determined before (left panel) and after 5 weeks of the endurance training of moderate intensity (right panel).

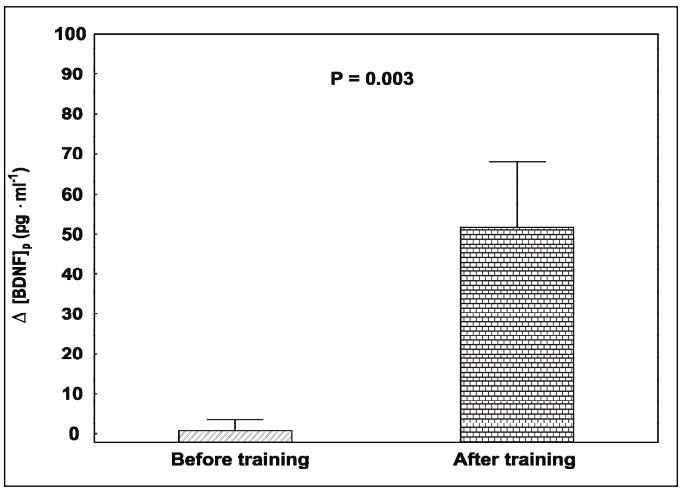

Fig. 2. Plasma BDNF concentrations ($[BDNF]_p$) in young healthy men (n =13), expressed as the difference between the end-exercise minus pre-exercise plasma concentration of BDNF (Δ $[BDNF]_p$), determined before and after 5 weeks of the endurance training of moderate intensity.

concentration of BDNF (Δ $[BDNF]_p$), was significantly higher (P = 0.003) after training (see *Fig. 2*).

Insulin resistance

The insulin resistance, calculated using the (HOMA2-IR), was not significantly affected by the endurance training, although it tended to be lower after training. It amounted to 1.40 ± 0.13 before and 1.15 ± 0.13 after the training (P = 0.25).

Plasma BDNF concentration at rest in well trained athletes vs. untrained subjects

Additionally, we have compared the basal $[BDNF]_p$ in 16 athletes *vs*. 13 untrained subjects. The basal plasma BDNF concentration $[BDNF]_p$ in athletes amounting to 29.5 ± 9.5 pg · ml^{-1} was significantly (P = 0.013) higher (3-folds) than in the untrained subjects participating in this study (10.3 ± 1.4 pg · ml^{-1}).

DISCUSSION

In the present study no "acute" effect of a single bout of maximal incremental exercise up to Vo_{2max} on the end exercise plasma BDNF concentration $[BDNF]_p$ was observed before training (P = 0.74). The main and original finding of this study was that a moderate intensity training lasting 5 weeks, resulted in a significant (P = 0.01) "chronic" increase in the basal (see *Fig. 1*) as well as in the exercise induced "acute" increase in $[BDNF]_p$ (P = 0.0002) in young healthy men (see *Fig. 2*). Moreover, significantly higher basal $[BDNF]_p$ was found in well trained athletes, when compared to the untrained young healthy man (P = 0.013).

The values of the $[BDNF]_p$ found in our subjects were substantially lower than in other studies (36) but they were close to that reported by other researches (46-48). It should be mentioned however, that a substantial variations in plasma / serum BDFN concentrations were reported in the literature even in healthy subject of similar age, which are most like related to various kits and laboratory procedures applied in these studies (for discussion of this point see *e.g*. (29, 49)). Therefore, the changes in the $[BDNF]_p$ induced by varied interventions for an appropriate comparisons should also be expressed in relative units (for example in % of changes).

Brain-derived neurotrophic factor (BDNF) is a key mediator of neuronal synaptic plasticity in adults (50). Reduced BDNF levels in the human brain are associated with cognitive function deficit, impaired memory performance and depression (51, 52). Already more that one decade ago Neeper *et al*. (22) have shown that physical exercise can increase BDNF gene expression in specific brain region of rat. Moreover, the authors postulated that physical exercise induced up-regulation of BDNF could help increase the brain's resistance to damage and degeneration through BDNF's support of neuronal growth, function

and survival. Since that time, the original findings by Neeper *et al*. (22) has been confirmed by this author (23) and by others (24, 25, 53). It was also recently reported that skeletal muscle expresses BDNF (54, 55), however the time kinetics of the BDNF expressions after single bout of exercise indicates, that the acute exercise-induced increase in $[BDNF]_s$ has its origin not in the skeletal muscle. However the training induced "chronic" increase in plasma BDNF concentration may be partly related to the up-regulation of the muscle BDNF expression.

It was shown that serum BDNF concentration $[BDNF]_s$ in healthy humans is by about 100 - fold higher than in plasma $[BDNF]_p$ (46, 56). However, the changes in $[BDNF]_p$ are considered to reflect its changes in the brain (46). It was demonstrated that platelets bind, store and release a large amount of BDNF upon agonist stimulation (57). According to Fujimura *et al*. (57) this store of the BDNF can be used at the site of traumatic injury to facilitate the repair of peripheral nervous or other tissues that contain TrkB. It was show that in the adult nervous system BDNF plays a predominant role in neuronal plasticity (51). Therefore, it was postulated by Rojas Vega *et al*. (28), that the exercise-induced peripheral increase in BDNF may help to increase the brain's resistance to damage and neurodegradation that occurs with age.

No much is known on the acute effect of a single bout of exercise on the plasma/serum BDNF concentrations in humans (28, 58), especially that the existing data come from studies involving varied groups of subjects including patients, healthy individuals as well as athletes. Gold *et al*. (27) have reported that single bout of prolonged exercise (30 minutes cycling at 60 % Vo_{2max}) resulted in a significant increase in $[BDNF]_s$ both in healthy persons as well as in multiple sclerosis patients. Rojas Vega *et al*. (28) have reported that single bout of maximal incremental exercise resulted in a significant increase in $[BDNF]_s$ in recreational athletes (Vo_{2max} = 56.6 ± 8.6 ml · kg^{-1} · min^{-1}), whereas 10 minutes moderate aerobic cycling was not sufficient to increase the $[BDNF]_s$ above the pre-exercise level. This finding is in accordance with the study by Ferris *et al*. (29) showing that the magnitude of increase in $[BDNF]_s$ during exercise is exercise intensity dependent. Recently Winter *et al*. (59) have reported that very high intensity short duration running (2 runs until exhaustion lasting 3 minutes each, with 2 minutes break) resulted in a significant increase in $[BDNF]_s$ in young healthy men. These authors postulated that the $[BDNF]_s$, dopamine and epinephrine seams to be the mediators by which physical exercise improves learning in humans. As mentioned above, in the present study we have found no acute effect of single bout of maximal incremental exercise on the $[BDNF]_p$ before training (see *Fig. 1*). The effect of single bout of exercise on the $[BDNF]_p$ may be related to the training status of the studied subjects. In view of our results training has bimodal influence on $[BDNF]_p$ and even single bout of high intensity exercise can significantly increase $[BDNF]_p$.

Even less is known regarding the effect of training on the plasma / serum BDNF concentration in humans. To our best knowledge only one training study involving strength training was performed. Ten week resistance training performed in that study however, did not affected the $[BDNF]_p$ in middle age subjects (38). As mentioned above, the 5 week endurance training applied in our study resulted in a significant increase both in the basal plasma ("chronic") as well as in the exercise induced ("acute") $[BDNF]_p$ (see *Fig. 1*).

It was recently reported that low levels of $[BDNF]_p$ in humans accompanies impaired glucose metabolism as well as it was postulated that a decreased $[BDNF]_p$ may be a pathogenetic factor involved not only in dementia and depression, but also in type 2 diabetes (36). It was reported that patients with acute coronary syndromes have reduced levels of BDNF in plasma (60). El-Gharbawy *et al*. (61), have recently reported that $[BDNF]_s$ is lower in extremely overweight children and adolescent than those of normal weight. Moreover, a negative correlation between $[BDNF]_p$ and body weight was found in healthy volunteers (46).

However, on the other hand, according to some authors (38, 39, 40) elevated levels of plasma/serum BDNF concentrations may be an early markers of pathological metabolic changes in the body. Suwa *et al*. (39), found significantly elevated $[BDNF]_s$ in newly diagnosed female patients with type 2 diabetes mellitus. This is in agreement with the recent study by Levinger *et al*. (38), who have found that elevated concentration of $[BDNF]_p$ positively correlated with risk factors for metabolic syndrome and type 2 diabetes mellitus in middle age group of subjects. These observations are in agreement with the so called "metabolic syndrome-neurotrophic hypothesis" suggesting that BDNF may pay a role in the development of risk factors associated with the metabolic syndrome (40). According to Suwa *et al*. (39) the elevated concentration of BDNF observed in the early stage of type 2 diabetes mellitus is a compensatory mechanism developed in those patients. According to Hristova *et al*. (40) an increase in the plasma / serum BDNF concentrations (over-secretion) at an early stage of the metabolic syndrome leads to the imbalances in the autonomic nervous system and in the interaction between the neuroimmuno-endocrine system, which in the later stage of the disease process may result in a reduction in BDNF concentration in relation to healthy subjects. This hypothesis can not be ruled out by the observations showing a lower plasma/serum BDNF concentrations in patients with long standing type 2 diabetes mellitus (see *e.g*. Krabbe *et al*. (36)). However, further longitudinal study are needed to establish the role of the changes in BDNF secretion in the development of the metabolic syndrome and type 2 diabetes mellitus.

As mentioned above, in the present study we have observed an increase in the basal as well as in the exercise-induced increase in the $[BDNF]_p$ after moderate intensity endurance training in young healthy men with normal insulin resistance. In our subjects, the insulin resistance calculated using the homeostatic model

assessment version 2 (HOMA2-IR), amounting to 1.40 ± 0.13 before training and 1.15 ± 0.13 (P = 0.25) was by 18% lower after training. Therefore the training induced increase in the $[BDNF]_p$, accompanied by a decrease in insulin resistance, decrease in lipid peroxidation (Majerczak *et al*. 2008, our unpublished observations), increase in the Vo_{2max}, increase in the power output at Vo_{2max}, we consider as positive effects of training. It seems to be rather unlikely, that the moderate intensity training resulting in several positive responses in the body would lead to the increase in the risk factors for the metabolic syndrome and type 2 diabetes mellitus. Therefore, we postulate that in case of young healthy subjects, opposite to middle age untrained subjects (see, (38)) as well as to the diabetic patients (see, (39)) with limited adaptive capacity in the body, the training induced increase in $[BDNF]_p$ belongs to positive adaptive responses in the body. Additionally, we have compared the basal $[BDNF]_p$ in well trained athletes of national/international level (sprinters, jumpers, runners) with its level in untrained subjects. The plasma $[BDNF]_p$ in athletes was significantly higher that in the untrained subjects (P = 0.013). Therefore, our results suggest that in case of young healthy men an elevated $[BDNF]_p$ is attributable to the trained status of humans.

The training induced increase in $[BDNF]_p$ may be beneficial to the body in several ways, including its involvement in mechanism of exercise induced improvement of mood, protection and regeneration of the peripheral and central nervous system (53, 62), as well as may play a role in training induced neoangiogenesis in the cardiac and skeletal muscles (for overview see *e.g*. (63, 64)). Moreover the training induced increase in BDNF may be beneficial to efficacy of pharmacological antidepresant treatment (for discussion of this piont see (65)). Additionally, it may also be involved in the process of regeneration and survival of the injured motor neurons after fatiguing exercise. Moreover, we postulate that the training induced increase in $[BDNF]_p$ *via* its action in the central nervous system may also enhances the motor learning ability in athletes.

We have concluded that endurance training of moderate intensity has bimodal influence on the $[BDNF]_p$: it increases both basal as well as exercise-induced plasma BDNF concentration in young healthy men. This adaptive response was accompanied by an increase in Vo_{2max}, power generating capability and no disturbances in the insulin resistance, as calculated using the homeostatic model assessment version 2 (HOMA2-IR). Therefore, the training induced increase in $[BDNF]_p$ in young healthy men, is accompanied by positive adaptive responses in the body and should not be considered as in the case of the patients with metabolic syndrome as an early marker of pathological metabolic changes in the body, as proposed recently (38).

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Conflicts of interest statement: None declared.

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