Neuroscience Letters 437 (2008) 29–32

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Decreased serum brain-derived neurotrophic factor in trained men

Yu Nofuji[a], Masataka Suwa[b], Yoshihiko Moriyama[a], Hiroshi Nakano[c], Atsushi Ichimiya[b], Reiko Nishichi[d], Haruka Sasaki[b], Zsolt Radak[e], Shuzo Kumagai[b,*]

[a] Graduate school of Human-Environment Studies, Kyushu University, Kasuga, Fukuoka 816-8580, Japan
[b] Institute of Health Science, Kyushu University, Kasuga, Fukuoka 816-8580, Japan
[c] Department of Human-Development, Nakamura Gakuen University, Fukuoka 814-0198, Japan
[d] Department of Nursing, St. Mary's University, Kurume, Fukuoka 830-8558, Japan
[e] Faculty of Physical Education and Sports Sciences, Semmelweis University, Budapest 1123, Hungary

ARTICLE INFO

Article history:
Received 30 January 2008
Received in revised form 20 March 2008
Accepted 20 March 2008

Keywords:
Brain-derived neurotrophic factor
Physical activity
Energy expenditure

ABSTRACT

The purpose of this study was to clarify the effect of physical activity on the level of serum brain-derived neurotrophic factor (BDNF). The serum BDNF level in trained men who have participated in regular sport activity ($n = 12$) was compared to that in sedentary subjects ($n = 14$). The physical activity levels expressed as total energy expenditure, move-related energy expenditure and walking count in the trained were significantly higher than those in the sedentary. The serum BDNF level in the trained men was found to be lower than that in the sedentary (19.54 ± 4.53 ng/ml vs. 23.63 ± 2.94 ng/ml, respectively, $P < 0.01$). The serum BDNF level showed a significant negative correlation with daily total energy expenditure ($r = -0.507$, $P < 0.05$), movement-related energy expenditure ($r = -0.503$, $P < 0.05$), and walking count ($r = -0.480$, $P < 0.05$). These results may suggest that vigorous habitual physical activity decrease the serum BDNF level.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors and found in the nervous system and periphery. BDNF is known to promote the growth, development, maintenance and function of survival of the neuronal system [2,4,30,35]. In addition, accumulating evidence suggests that BDNF may play important roles in memory, learning [20,21], mood disorder [7], food intake, and energy metabolism [23].

BDNF is also present in human and rat plasma, and much more concentrated in the serum [31]. Although the role of circulating BDNF remains unclear [9,22,32], since BDNF can cross the blood–brain barrier [28], consequently, the serum BDNF could reflect the expression and/or action of BDNF in the brain and other organs, and some clinical conditions. Indeed, serum BDNF is decreased in patients with severe Alzheimer's disease [17], depression [12,33], and eating disorders [24] in comparison to healthy controls. Furthermore, BDNF has a possible link with metabolic status [5,6]. A previous study demonstrated that serum BDNF was increased in patients with type 2 diabetes mellitus [34].

BDNF level is also affected by exercise. It has been shown in humans that there is a transient augmentation of serum BDNF concentration immediately after moderate exercise [10] and short duration high-intensity exercise to exhaustion [36]. In animals, exercise training has been reported to increase BDNF mRNA in several brain areas [25–27]. Moreover, BDNF mRNA expression in the hippocampus was positively correlated with running distance. These findings suggest the possibility that daily physical activity may thus have an impact on the serum BDNF level. This study determined whether the serum BDNF level in trained men differs from that in age-matched control subjects.

Twelve Japanese trained males and 14 sedentary male volunteers participated in this study. All trained men had participated in regular sports activities more than four times and 16 h per week for more than 3 years. The control subjects had not participated in any regular exercise for more than 1 year. The trained group included distance runners ($n = 7$), a sprinter ($n = 1$), tennis players ($n = 3$), and a badminton player ($n = 1$). The details of the training frequency, volume and playing experience were obtained by questionnaires. We interviewed the subjects to obtain their medical history and current life style. Subjects who were on medication for any medical or psychological condition and/or smokers were excluded from this study. This study was conducted in accordance with the Declaration of Helsinki, and approved by the ethics committee of the Institute of Health Science, Kyushu University, Fukuoka, Japan. Written informed consent was received from all participants prior to participation.

After overnight fasting, venous blood samples were collected between 9:00 and 10:30 A.M. After the blood was centrifuged,

* Corresponding author at: Kasugakoen 6-1, Kasuga, Fukuoka, Japan.
Tel.: +81 92 583 7853; fax: +81 92 583 7853.
E-mail address: shuzo@ihs.kyushu-u.ac.jp (S. Kumagai).

0304-3940/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2008.03.057

the serum and plasma were stored at −80 °C until analyses. The BDNF assessment was performed within 1 month of the sample collections. The serum and plasma BDNF level was measured using an enzyme-linked immunoassay (ELISA) kit (Promega, Madison, WI). Hemoglobin A_{1c} (HbA_{1c}) was measured by high-performance liquid chromatography. The fasting blood glucose (FBG) and the lipid profiles including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were determined using enzymatic methods.

Morphologic and psychological measurements were conducted because the serum BDNF level has been reported to be affected by various conditions such as obesity [22] and depression [12,33]. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The percentage of body fat (%Fat) was measured by electrical impedance (Tanita, Tokyo, Japan) [29]. Waist circumstance measured at the level of the umbilicus was divided by the circumference of the hip measured at its greatest gluteal protuberance to calculate the waist–hip ratio (WHR). The psychological state such as depressive mood and anxiety was assessed using the 30 items version of the General Health Questionnaire (GHQ-30) and the self-ratable State-Trait Anxiety Inventory (STAI) were performed in all subjects.

To evaluate physical activity, the participants attached the Lifecorder® (Suzuken Co., Nagoya, Japan) for 1 week just before the day of blood collection. The Lifecorder® is a small solid state recorder (62.5 mm × 46.5 mm × 26 mm, 40 g), containing an acceleration sensor, an amplifier, a microprocessor and memory. Based on the memorized intensity and times of movements, weight, and basal metabolic consumption, daily total energy expenditure (TEE) and movement-related energy expenditure (MEE) is calculated [32].

The data were presented as the mean ± standard deviation (S.D.). The comparisons between the control subjects and trained were performed using the unpaired Student's *t*-test. The relationship between two variables was examined using Pearson's correlation coefficient. A stepwise multiple regression analysis was performed to assess the influence of the following independent variables on serum BDNF level: age, BMI, GHQ score, WC, FBG, TC, TG. Statistical significance was defined as $P < 0.05$.

Table 1 shows the morphologic, psychological and metabolic characteristics of the subjects. There were no differences in age, height, weight, BMI, %Fat, FBG, HbA_{1c}, HDL-C or TC and the scores of the GHQ and STAI between the two groups. A difference observed between the two groups in the TG and WHR. The average TEE, MEE, WC in the trained group was distinctly higher than those in the control group (Table 2).

Table 1
Characteristics of the subjects

	Control ($n = 14$)	Trained ($n = 12$)
Age (years)	22.4 ± 1.2	21.8 ± 0.9 ns
Height (cm)	171.7 ± 7.0	172.5 ± 7.2 ns
Weight (kg)	60.9 ± 7.7	62.6 ± 8.0 ns
BMI (kg/m^2)	20.6 ± 2.1	21.0 ± 2.0 ns
%Fat	17.1 ± 4.3	15.0 ± 2.6 ns
WHR	0.85 ± 0.08	0.77 ± 0.05*
TC (mg/dl)	173.8 ± 26.4	159.5 ± 19.8 ns
HDL-C (mg/dl)	61.4 ± 14.3	69.2 ± 12.8 ns
TG (mg/dl)	91.1 ± 41.2	59.2 ± 23.7*
HbA1c	4.8 ± 0.2	4.7 ± 0.03 ns
FBG (mg/dl)	91.4 ± 8.9	88.7 ± 7.0 ns
GHQ-30	4.6 ± 4.4	5.8 ± 3.0 ns
STAI (Trait)	42.5 ± 9.4	42.4 ± 7.0 ns
(State)	40.7 ± 9.1	39.3 ± 7.8 ns

Data are expressed as the mean ± S.D. BMI, body mass index; %Fat, percentage of body fat; WHR, waist–hip ratio; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA_{1c}, Hemoglobin A_{1c}; FBG, fasting blood glucose; GHQ-30, 30 items version of the General Health Questionnaire; STAI, self-ratable State-Trait Anxiety Inventory; ns, non-significant.
* Significantly different between the groups ($P < 0.05$).

Table 2
Physical activity level of the subjects

	Control ($n = 14$)	Trained ($n = 12$)
TEE (kcal/day)	2199.6 ± 228.3	2532.7 ± 270.5*
MEE (kcal/day)	261.5 ± 108.6	556.0 ± 174.5*
WC (steps/day)	9171.0 ± 2861.2	15517.9 ± 4227.6*

Data are expressed as the mean ± S.D. TEE, total energy expenditure; MEE, movement-related energy expenditure; WC, walking count.
* Significantly different between the groups ($P < 0.05$).

Fig. 1 indicates the serum BDNF level in the both groups. The serum BDNF level in the trained was significantly lower than that in the control subjects (19.54 ± 4.53 ng/ml vs. 23.63 ± 2.94 ng/ml). No difference was detected in the plasma BDNF levels between the groups (controls: 1440.61 ± 1090.28 pg/ml vs. trained: 1143.64 ± 600.53 pg/ml). Correlation analyses were conducted with the measurements obtained from all of the subjects. Significant negative correlations between serum BDNF and TEE ($r = -0.507$, Fig. 2A), MEE ($r = -0.503$, Fig. 2B), WC ($r = -0.480$, Fig. 2C) and GHQ scores ($r = -0.551$) were detected. GHQ-30 provides six subscales: general illness, somatic symptom, insomnia, social dysfunction, anxiety and dysphoria, and depression. Only the scale of anxiety and dysphoria was associated with serum BDNF level ($r = -0.52$). The serum BDNF was not significantly associated with age, height, weight, BMI, %Fat, WHR, FBC, HbA_{1c}, HDL-C, TG, TC and STAI score. None of measurements significantly correlated with plasma BDNF level. In a multiple regression model with serum BDNF as the dependent variable (model $r^2 = 0.46$, $P < 0.01$), GHQ score ($\beta = -0.48$, $P < 0.01$) and WC ($\beta = -0.42$, $P = 0.01$) were significant independent predictors, but there were no significant contributions from age ($P = 0.51$), BMI ($P = 0.17$), FBG ($P = 0.65$), TC ($P = 0.90$) and TG ($P = 0.61$).

This is the first report to investigate the serum BDNF level in trained men. The serum BDNF level in trained men was lower than that in age-matched subjects and was negatively correlated with the physical activity level. The serum BDNF level has been reported to change according to age [37], body weight, BMI [22] and depressive state [16]. In the current study, no significant difference was observed in age, anthropometric and psychological parameters between the two groups, suggesting such parameters were not related to the difference of the serum BDNF level between the groups.

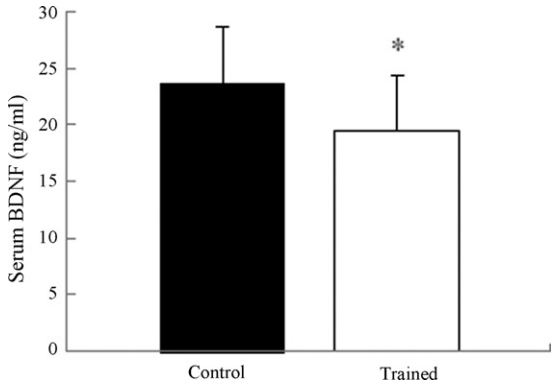

Fig. 1. The serum BDNF level in the control ($n = 14$) and the trained groups ($n = 12$). Data are expressed as the mean ± S.D. *; $P < 0.05$ vs. control.

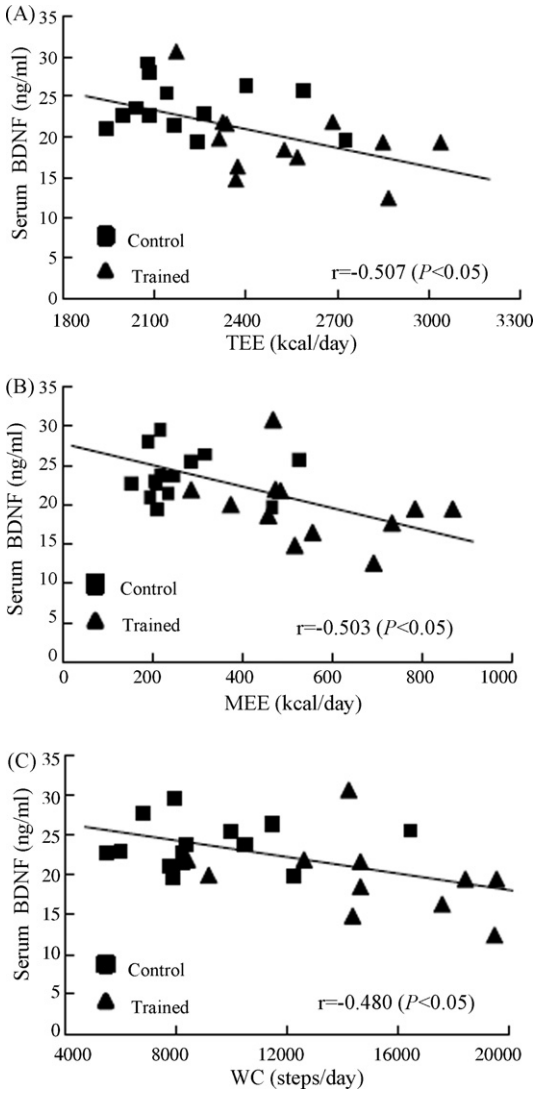

Fig. 2. Relationship between the serum BDNF level and total energy expenditure (A), move-related energy expenditure (B), and walking count (C). TEE, total energy expenditure; MEE, movement-related energy expenditure; WC, walking count.

The serum BDNF concentration increased immediately after moderate [10] and high-intensity [36] acute exercise and rapidly returned to basal concentration [10,36]. In the present study, the blood sample was collected at least 24 h after the last exercise. Therefore, the significant reduction of serum BDNF in trained men was the effect of chronic physical activity rather than that of acute exercise.

There is accumulating evidence in animals that exercise training increases the expression of BDNF mRNA and protein expression in several regions of the brain [25,26]. Since BDNF can cross the blood–brain barrier in both directions [28] and the cortex BDNF correlates with the serum BDNF [13], the serum BDNF is considered to reflect the expression and/or action of BDNF in the brain. Therefore, high level of serum BDNF in the trained was expected. In this study, however, BDNF concentration in the trained was lower than that in the control.

Why did the serum BDNF decrease in the trained men? One of the explanations is that BDNF utilization in some tissues might be increased to repair the injured tissues and then the release of BDNF from platelets might be increased. More than 90% of blood BDNF proteins are stored in platelets, from which it can be released through activation or the clotting processes [9,31]. Since protein synthesis in platelet has not been confirmed, it is possible that platelets take up BDNF from the brain and/or other specific organs *via* the blood circulation. Physical exercise seems to increase accumulation of free radicals and reactive oxygen species such as superoxide anion and hydrogen peroxide as a response to the increased oxygen utilization [3] and they cause muscular damage and inflammation [1,18]. Exercise also induces mechanical stress, which causes injury to both muscles and nerves [15]. BDNF is known to play a role in repair processes at the site of traumatic injury [8]. Platelets appear to release BDNF upon activation at the site of traumatic injury to facilitate the repair of peripheral nerves or other tissues that contain the high-affinity BDNF receptor TrkB [9]. Interestingly, BDNF protein in the soleus muscle, where TrkB is expressed, significantly increased after training [11]. Such reports raise the possibility that the release of BDNF from platelets to damaged tissues increases in order to facilitate the repair process, and then the BDNF stored in platelets decreases.

Another possibility is that BDNF production is decreased because it is not necessary for the trained men. Several lines of evidence suggest that BDNF contributes to food intake and body weight control, acting as anorexigenic factor [14,19]. In addition, BDNF has been shown to improve glucose and lipid metabolism and increase energy expenditure [23]. The serum BDNF level in newly diagnosed female patients with type 2 diabetes mellitus is higher than that in healthy subjects and associated with the total and abdominal subcutaneous fat mass and lipid and glucose metabolism [34]. It is therefore likely that the BDNF level increases in obese diabetic patients to compensate for such pathophysiologic conditions because of its potential roles in improving energy metabolism and suppressing food intake. On the other hand, it is well established that exercise induces body fat reduction and improvement of lipid and glucose metabolism. In the current study, the trained group showed high energy expenditure and low TG level. Taken together, it is reasonable that habitual physical activity enhances energy expenditure and then less BDNF is needed for controlling energy balance or eating behavior.

The limitations of this study were the cross-sectional design itself, the small sample size and the lack of the data of fitness levels such as maximal oxygen consumption. Further studies focused on such problems are called for.

In conclusion, the serum BDNF level was lower in trained men than that in sedentary subjects. In addition, the serum BDNF level was found to be correlated with the daily physical activity level. These results suggest that the daily physical activity affects the serum BDNF level.

References

[1] H.M. Alessio, A.H. Goldfarb, Lipid peroxidation and scavenger enzymes during exercise: adaptative response to training, J. Appl. Physiol. 64 (1988) 1333–1336.
[2] M. Bibel, Y.A. Barde, Neurotrophins: key regulators of cell fate and cell shape in the vertebrate nervous system, Genes Dev. 14 (2000) 2919–2937.
[3] E. Carmeli, G. Laviam, A.Z. Reznick, The role of antioxidant nutrition in exercise and aging, in: Z. Radák, (Ed.), Free Radicals in Exercise and Aging, Human Kinetics, Champaign, 2000, pp. 73–115.
[4] A.R. Carter, C. Chen, P.M. Schwartz, R.A. Segal, Brain-derived neurotrophic factor modulates cerebellar plasticity and synaptic ultrastructure, J. Neurosci. 22 (2002) 1316–1327.
[5] G.N. Chaldakov, M. Fiore, M.G. Hristova, L. Aloe, Metabotrophic potential of neurotrophins: implication in obesity and related diseases? Med. Sci. Monit. 9 (2003) HY19–HY21.
[6] G.N. Chaldakov, M. Fiore, A.B. Tonchev, D. Dimitrov, R. Pancheva, G. Rancic, L. Aloe, Homo obesus: a metabotrophin-deficient species. Pharmacology and nutrition insight, Curr. Pharm. 13 (2007) 2176–2179.
[7] R.S. Duman, Synaptic plasticity and mood disorders, Mol. Psychiatry 7 (Suppl.) (2002) S29–S34.
[8] M. Ebadi, R.M. Bashir, M.L. Heidrick, F.M. Hamada, H.E. Refaey, A. Hamed, G. Helal, M.D. Baxi, D.R. Cerutis, N.K. Lassi, Endogenous neuroprotection factors

and traumatic brain injury: mechanisms of action and implications for therapy, J. Neurotrauma 11 (1994) 3–33.
[9] H. Fujimura, C.A. Altar, R. Chen, T. Nakamura, T. Nakahashi, J. Kambayashi, B. Sun, N.N. Tandon, Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation, Thromb. Haemost. 87 (2002) 728–734.
[10] S.M. Gold, K.H. Schulz, S. Hartmann, M. Mladek, U.E. Lang, R. Hellweg, R. Reer, K.M. Braumann, C. Heesen, Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls, J. Neuroimmunol. 138 (2003) 99–105.
[11] F. Gómez-Pinilla, Z. Ying, P. Opazo, R.R. Roy, V.R. Edgerton, Differential regulation by exercise of BDNF and NT-3 in rat spinal cord and skeletal muscle, Eur. J. Neurosci. 13 (2001) 1078–1084.
[12] F. Karege, G. Perret, G. Bondolfi, M. Schwald, G. Bertschy, J.M. Aubry, Decreased serum brain-derived neurotrophic factor levels in major depressed patients, Psychiatry Res. 109 (2002) 143–148.
[13] F. Karege, M. Schwald, M. Cisse, Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets, Neurosci. Lett. 328 (2002) 261–264.
[14] S.G. Kernie, D.J. Liebl, L.F. Parada, BDNF regulates eating behavior and locomotor activity in mice, EMBO J. 19 (2000) 1290–1300.
[15] H. Kuipers, Exercise-induced muscle damage, Int. J. Sports Med. 15 (1994) 132–135.
[16] U.E. Lang, R. Hellweg, J. Gallinat, BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits, Neuropsychopharmacology 29 (2004) 795–798.
[17] C. Laske, E. Stransky, T. Leyhe, G.W. Eschweiler, A. Wittorf, E. Richartz, M. Bartels, G. Buchkremer, K. Schott, Stage-dependent BDNF serum concentrations in Alzheimer's disease, J. Neural Transm. 113 (2006) 1217–1224.
[18] J.F. Liu, W.Y. Chang, K.H. Chan, W.Y. Tsai, C.L. Lin, M.C. Hsu, Blood lipid peroxides and muscle damage increased following intensive resistance training of female weightlifters, Ann. N. Y. Acad. Sci. 1042 (2005) 255–261.
[19] W.E. Lyons, L.A. Mamounas, G.A. Ricaurte, V. Coppola, S.W. Reid, S.H. Bora, C. Wihler, V.E. Koliatsos, L. Tessarollo, Brain-derived neurotrophic factor-deficient mice develop aggressiveness and hyperphagia in conjunction with brain serotonergic abnormalities, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 15239–15244.
[20] Y.L. Ma, H.L. Wang, H.C. Wu, C.L. Wei, E.H.Y. Lee, Brain-derived neurotrophic factor antisense oligonucleotide impairs memory retention and inhibits long-term potentiation in rats, Neuroscience 82 (1998) 957–967.
[21] M. Mizuno, K. Yamada, A. Olariu, H. Nawa, T. Nabeshima, Involvement of brain-derived neurotrophic factor in spatial memory formation and maintenance in a radial arm maze test in rats, J. Neurosci. 20 (2000) 7116–7121.
[22] P. Monteleone, A. Tortorella, V. Martiadis, C. Serritella, A. Fuschino, M. Maj, Opposite changes in the serum brain-derived neurotrophic factor in anorexia nervosa and obesity, Psychosom. Med. 66 (2004) 744–748.
[23] T. Nakagawa, A. Tsuchida, Y. Itakura, T. Nonomura, M. Ono, F. Hirota, T. Inoue, C. Nakayama, M. Taiji, H. Noguchi, Brain-derived neurotrophic factor regulates glucose metabolism by modulating energy balance in diabetic mice, Diabetes 49 (2000) 436–444.
[24] M. Nakazato, K. Hashimoto, E. Shimizu, C. Kumakiri, H. Koizumi, N. Okamura, M. Mitsumori, N. Komatsu, M. Iyo, Decreased levels of serum brain-derived neurotrophic factor in female patients with eating disorders, Biol. Psychiatry 54 (2003) 485–490.
[25] S.A. Neeper, F. Gómez-Pinilla, J. Choi, C.W. Cotman, Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain, Brain Res. 726 (1996) 49–56.
[26] H. Ogonovszky, I. Berkes, S. Kumagai, T. Kaneko, S. Tahara, S. Goto, Z. Radák, The effects of moderate-, strenuous- and over-training on oxidative stress markers, DNA repair, and memory, in rat brain, Neurochem. Int. 46 (2005) 635–640.
[27] H.S. Oliff, N.C. Berchtold, P. Isackson, C.W. Cotman, Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus, Brain Res. Mol. Brain Res. 61 (1998) 147–153.
[28] W.M. Pardridge, Y.S. Kang, J.L. Buciak, Transport of human recombinant brain-derived neurotrophic factor (BDNF) through the rat blood–brain barrier in vivo using vector-mediated peptide drug delivery, Pharm. Res. 11 (1994) 738–746.
[29] J.A. Pasco, I.H. Rutishauser, Body fat estimated from anthropometric and electrical impedance measurements, Hum. Nutr. Clin. Nutr. 39 (1985) 365–369.
[30] M.M. Poo, Neurotrophins as synaptic modulators, Nat. Rev. Neurosci. 2 (2001) 24–32.
[31] S.F. Radka, P.A. Holst, M. Fristche, C.A. Altar, Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay, Brain Res. 709 (1996) 122–130.
[32] N. Saito, T. Yamamoto, Y. Sugiura, S. Shimizu, M. Shimizu, Lifecorder: a new device for the long-term monitoring of motor activities for Parkinson's disease, Intern. Med. 43 (2004) 685–692.
[33] E. Shimizu, K. Hashimoto, N. Okamura, K. Koike, N. Komatsu, C. Kumakiri, M. Nakazato, H. Watanabe, N. Shinoda, S. Okada, M. Iyo, Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants, Biol. Psychiatry 54 (2003) 70–75.
[34] M. Suwa, H. Kishimoto, Y. Nofuji, H. Nakano, H. Sasaki, Z. Radak, S. Kumagai, Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus, Metabolism 55 (2006) 852–857.
[35] H. Thoenen, Neurotrophins and neuronal plasticity, Science 270 (1995) 593–598.
[36] R.S. Vega, H.K. Struder, V.B. Wahrmann, A. Schmidt, W. Bloch, W. Hollmann, Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans, Brain Res. 1121 (2006) 59–65.
[37] A.A. Ziegenhorn, O. Schulte-Herbruggen, H. Danker-Hopfe, M. Malbranc, H.D. Hartung, D. Anders, U.E. Lang, E. Steinhagen-Thiessen, R.T. Schaub, R. Hellweg, Serum neurotrophins—a study on the time course and influencing factors in a large old age sample, Neurobiol. Aging 28 (2007) 1436–1445.