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The effects of aerobic training on brain-derived neurotrophic factor level of brain premotor cortex of young male rats following an acute bout of exhaustive endurance exercise

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Abstract:

Purpose: *The aim of this study was to investigate whether 8-week treadmill training could modulate BDNF in the brain premotor cortex of rats following an acute bout of exhaustive endurance exercise.*

Methods: *For this reason the study was carried out with 12 week-old male rats (N =32) were randomly divided into two groups (N=16): non-runners control (SED), running exercise (ET).The exercise schedule consisted of progressive treadmill running for 5 days week^{-1} over 8 weeks. To see the effects of endurance training on acute*

exhaustive exercise on BDNF level of brain premotor cortex, (SED) and (ET) rats were further divided into two groups: animals killed at rest and those killed after an acute bout of exhaustive endurance exercise, in which the rats run at 30 m/min (10% uphill) until exhaustion.

Results: *After a single bout of exhaustive treadmill running, decreased significantly the BDNF level of brain premotor cortex in (SED) and (ET) rats ($p<0.05$).*

Conclusion: *As a result, it is concluded that the performed 8 weeks exercise could not prevented the decreased significantly the BDNF level of brain premotor cortex response to acute bout of exhaustive exercise. These results indicate that intense exercise can have some deleterious effect on brain premotor cortex.*

Key words: acute exercise**,** BDNF, premotor cortex

Introduction

Neurological functions and plasticity are well influenced by experiences that intrinsically affect the brain bioenergetics status, such as learning (1), dietary restriction (2) and enriched environment (3).The benefits that physical exercise can produce on the brain function and on mental health are well documented. For instance, exercise enhances hippocampal-dependent learning and memory and improves executive functioning (4). These exercise effects seem to be associated with adaptive responses in the central nervous system (CNS) such as the upregulation of neurotrophic factors, most notably the brain-derived neurotrophic factor (BDNF) (5). BDNF is an important intercellular signal that mediates neurogenesis, synaptic plasticity and cell survival (6). There is extensive literature indicating that wheel running programs, voluntary and low-intensity exercise, result in an upregulation of BDNF protein and mRNA levels in different brain areas of rodents such as the hippocampus (4) and the striatum (7). Moreover,

Soya et al. (2007) have recently documented that moderate-intensity exercise and forced-treadmill schedule increase BDNF levels in the rat's hippocampus (8). However, the effects of high-intensity forced-treadmill schedule on premotor cortex BDNF remain unclear.

The intensity of exercise should be considered when we design programs to optimize physical performance (9, 10) or health benefits because their effects are dose-dependent (11). Intense physical exercise may cause deleterious biologic adjustments and adaptations like exhaustion and over-training, respectively. Exhaustion and lack of training (12) showed high free radical formation during training and competition. Exercise produces high reactive oxygen species levels only when it is exhaustive (13). High ROS levels induce oxidative damage near the radical production sites, mainly in tissues with high mitochondrial energy metabolism and poor antioxidant defenses, like the brain. Mitochondrial oxidative phosphorylation generates most of the ROS in the neuron increased by inhibition of the electron transport chain (ETC). Additionally, the oxidative phosphorylation system itself is vulnerable to damage by ROS (14). Impaired ETC, in turn, leads to decreased ATP production, increased formation of toxic oxygen species, and altered calcium homeostasis, leading to neuron degeneration and death (15). These situations are associated with low-brain function. An inhibition of 75% on ETC complexes II–IV and 25% on ETC complex I induces oxidative stress by decreasing BDNF levels (16). The importance of BDNF in impacting energy metabolism is seen in disorders of energy balance, evidenced by mitochondrial involvement in aging and neurodegenerative diseases (17). In accordance with this notion, previous researches shown that high-intensity training schedule results in brain mitochondrial dysfunction and decreased BDNF levels in the frontal cortex of mice (18-22). However, humans mostly engage in regimental

physical training instead and the neurological mechanisms of adaptations to intense exercise remain unclear.

On the other hand, regular training is known to increase the resistance against ROS induced lipid peroxidation, and to decrease the accumulation of oxidative protein and DNA damage (23). In addition, the activity of poteasome complex increases due to exercise training, which means that the repair of oxidative damage in proteins is also up-regulated (23).

A standing question for planning the design of studies using the therapeutic potential of exercise is whether after 8 weeks of regular aerobic training influences the BDNF level of brain premotor cortex of rats caused by an acute bout of exhaustive endurance exercise. To resolve these questions, in this study, we investigated the separate and combined effects of chronic and acute treadmill running protocols on premotor cortex brain-derived neurotrophic factor levels in rats. In the present study, we employ a forced treadmill running regimen. The aim was to analyze the BDNF level, on the premotor cortex after exposure to 8 weeks aerobic training and following an acute bout of exhaustive endurance exercise.

Methodology

Animal care

Male Wistar rats weighing 200–232 g (n = 32, 12 weeks old) were purchased from Shahid Beheshti University of Medical Sciences and Health Services and were used in this study. All rats were housed in conventional clear Polycarbonate cages, four rats per cage, in a room with the temperature regulated at 22 ±2°C, humidity 45-65% and in daily light / dark cycle (12h) (0700-1900 h dark; 1900-0700 h light), given standard rat chow and tap water ad libitum. All procedures were approved by the Tehran University Animal Care and Usage Committee and

followed the guidelines established by American Physiological Society.

Experimental design

The animals were housed for two weeks prior to any special treatment. In the third-week all the animals were randomly divided mainly into two groups, group1, sedentary (Sed N=16), group2, exercise trained (ET n=16). Two groups were further divided equally into two groups where the rats were studied at rest and immediately after exhaustive exercise. During the training period, the animals in the group2, was run on the treadmill 5 days a week for 8 weeks. Experiments were conducted between 10:00 and 12:00 h.

Training and Acute Exhaustive Exercise

After divided, the animals in the group (ET) were performed aerobic exercise on a treadmill for a period of eight weeks before the training, the group (ET) rats were introduced to treadmill running through the use of one 5-25 minute running session on a rodent treadmill at a speed of 16/7 m/min and a 0-2% uphill grade (1 session a day, 5 times/wk, 1 wk) (24).The treadmill was equipped with an electric shock grid on the rear barrier to provide exercise motivation to the animals. The exercise protocol was performed in inclined treadmill one session a day during five days a week for 8 weeks. The exercise protocol was arranged as follows: in the first two weeks animals run with a speed of 16/67-18/33 m/min for 35-40 minutes and 3-4% uphill grade, in the following 3 weeks running speed was increased to 20 m/min and 5% grade uphill for 40 minute and in the last 3 weeks, treadmill speed was adjusted to 25 m/min for one hour and 8-10% uphill grade. During the eighth week of the training program, the groups (Sed) were also introduced to treadmill running at speed of 16/7-20 m/min, for 15 min day, for 5 days, before sample collection. This regimen was used to ensure that

untrained rats could also tolerate the acute exhaustive exercise without having a significant training effect (24). At the end of the training period and after 2 days at rest, half of all rats were randomly selected into the acute exhaustive exercise group (each group N=8 , totality N=16). In acute exhaustive exercise, running speed was 25 m/min (10% uphill gradient) for the first 10 min; after that the speed was increased gradually to 30 m/min , and kept constant until the rats were exhausted. The loss of the righting reflex when the rats were turned on their backs was the criterion of exhaustion. To eliminate diurnal effects, the experiments were performed at the same time (08.30–12.30 hours) (25). Immediately after exhaustion exercise, animals were sacrificed with Chloroform and then their brain was quickly removed. From the whole brain, the premotor cortex carefully separated by the Cuello AC,1983 surgical procedure (26). The specimens were stored at -20˚ C until assay. The other half of all rats (N=16) underwent anesthesia immediately before the acute exhaustive exercise, the premotor cortex was obtained according to the same program. These samples were used for the measurement levels of total protein concentration and BDNF.

Biochemical analysis

Measurement of premotor cortex BDNF protein levels

The BDNF protein concentration in the premotor cortex homogenate was determined in duplicate using an enzyme-linked immunosorbent assay (ELISA) kit (Promega, Madison, WI, USA) following the manufacturer's instructions.

Protein determination

Quantitative protein determination was achieved by absorbance measurements at 595 nm according to Bradford's method (1976), with bovine serum albumin as standard (27).

Data Analysis

The Statistical Package for Social Sciences (SPSS, Ins, Chigaco, IL) version 17 was used for all analyses. Statistical significance was set at a level of $P< 0.05$, and data were expressed as the mean ± SEM. One-way ANOVAs with Tukey's post-hoc tests and Independent and dependent t-test, were used to compare group means.

Results

Body weight and time of exhaustion

There were no significant differences in mean weight among the two groups in the beginning of experiments (Table 1). At the end of the 8 weeks of the experimental period the mean weight of the ET group was significantly higher than ET group ($p<0.05$) (Table 1). The mean exhaustion time of treadmill running to exhaustion was 12/57±1/74, 39/66±8/28, min for SED and ET groups respectively. Exhaustion time was significantly longer in ET group compared with SED group ($p<0.05$) (Table 1).

BDNF level

BDNF results are presented in (Table. 1). The results shows that there were significant differences in BDNF level of brain premotor cortex among Sed and ET groups before but not after Exhausted. BDNF level of brain premotor cortex of rats was significantly increased after exhaustion in the Sed and ET groups ($p<0.05$).

Table 1. Effects of 8-week training and acute exercise protocols on body weight and BDNF levels in the brain premotor cortex. Values are expressed as mean ± SEM.

	body weight (g)		**BDNF (Pq BDNF / μg protein)$^{-1}$**	
Group	Beginning of	End of	before	after

	Experiments	Experiments	Exhausted	Exhausted
SED	211±10	257±22† #	264.36 ±21	226.68 ±17†
ET	218±14	235±16†	252.85 ±16*	231.08±23†

BDNF, brain-derived neurotrophic factor; **SED**, sedentary; **ET**, exercise trained. # Significant difference between two groups ($p<0.05$).† Significant difference between two time measured in the each group ($p<0.05$).

Discussion and Conclusion

Corroborating with previous literature (18-21) the current results indicate that decreased BDNF levels in the premotor cortex of mice after 8 weeks of intense exercise. On the other hand, previous studies investigating the effects of exercise in BDNF levels in rat brain have been inconsistent, with some authors demonstrating increased BDNF levels (28-33) while others have reported no significant differences (34, 35). Vaynman et al. (2006) showed that 3 days of free access to voluntary wheel running increased BDNF protein and mRNA levels in the hippocampus of adult rats (28). Nepper et al. (1996) have reported that the 2-7 nights of running resulted in a significant increase of mRNA for BDNF in the rat hippocampus (35). These original findings by Neppher *et al.* (1995,1996) were confirmed by others, who showed that, indeed, physical activity/training is able to up-regulate the BDNF expression in animal brains (29, 35). For example, Oliff *et al.* (1998) have found that the brain mRNA expression in rats correlates with the distance run during voluntary activity (31). 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 (31). Radak et al. (2006) who also found increased BDNF protein and mRNA levels in the rat brain when aged rats were subjected to 8 weeks of swimming training, 5 days/week, with the first 4 weeks for periods of 60 min/day and the last 4 weeks,

120 min/day (32). Ogonovszky et al. (2005) did not find oxidative damage to DNA and lipids in the brain of old rats that performed strenuous training (the swimming duration increased by 30 min each week until it reached 4.5 h in the last week) and over-training (1 h swimming/day, five times/week, for 6 weeks, when the duration was abruptly increased to 4.5 h for the remaining 2 weeks) (33) Also, Ogonovszky et al. (2005) showed increased BDNF and decreased brain protein oxidation (33).

It is well known that different forms of exercise result in different levels of tissues stress (36). Treadmill running is usually chosen over swimming because swimming causes other forms of stress and aerobic responses are highly variable (37). Radak et al. 2006 (32) and Ogonovszky et al. 2005 (33) utilized a swimming model of exercise that imposes less mechanical stress due to water pressure, recruitment of different muscles and reduced effects of gravity, according to Neppher *et al* .1995,1996 (29, 35), used the running wheel, an intermittent physical activity, voluntary and free access model of exercise (28, 31) with low-intensity levels of running activity (38). A substantial evolutionary increase in daily movement distances can be achieved by increasing running speed in the running wheel, without remarkable increases in total energy expenditure (39). The treadmill forces the animal to run according to the exercise demands: time, duration and intensity (36) .The intensity and mode of running exercise induce different effects on important modulators of synaptic plasticity (40). Treadmill running may be considered a stressor to rodents (41) .In this case, the high intensity mode of exercise generally is a stressor model of exercise, associated with greater fiber damage, soreness, inflammation, fatigue, and other functional deficits (42). The excessive repetition of the training stimulus the local inflammation can generate a systemic inflammatory response (43). The main actors in these processes are the

cytokines – polypeptides that modulate the hypothalamic-pituitary – adrenal axis function inside and outside the brain at nearly every level of activity. These results are consistent with previous studies reporting a decrease in BDNF mRNA expression in the hippocampus induced by stress and glucocorticoids, as well as immobilization and exhaustive exercise (22). BDNF is intimately connected with brain energy metabolism (28) and has been shown to impact mitochondrial activity (44). Low-intensity running wheel increased BDNF mRNA and protein and COX-II levels in the hippocampus (28). We chose 8 weeks of high intensity treadmill running for adult mice with daily exercise duration of 60 min, this intense physical training decreased BDNF levels. But incomplete corresponding exercise designs, especially concerning exercise intensity, as well as the exercise responses of trained and untrained controls, may be responsible for the inconsistent results found in literature (20).

The other findings derived from present study shown that BDNF level of brain premotor cortex decreased significantly after a single bout of exhaustive treadmill running in the Sed and ET groups compared to pre- exhaustive. The results of this research are in line with those of the researchers who argue that intense and/or acute exercise decreased the level of BDNF in the brain (18-22). Although the exact molecular mechanisms and signaling pathways through which exhaustion training downregulates mice premotor cortex BDNF levels remains to be elucidated, there is considerable evidence supporting the role of oxidative stress in this response. The molecules typically implicated in synaptic plasticity such as brain-derived neurotrophic factor, are affected by cellular energy metabolism (45). New findings indicate that the interaction between oxidative stress and brain-derived neurotrophic factor can affect neuronal plasticity. These studies indicate that elevated reactive oxygen species level decreases

brain-derived neurotrophic factor (45). A previous study has shown that under extreme conditions, such as in high-intensity physical exercise, ROS production may be more strongly and persistently increased, and the antioxidant response may not be sufficient to reset the system to the original level of brain redox homeostasis (18, 46). Oxidative stress induces energy depletion (47) and can result in impairments to the NMDA channel function (48) related to decreased BDNF levels (49).

Conclusion:

The performed 8 weeks high-intensity physical exercise decreasing premotor cortex BDNF protein levels, (2) BDNF protein is decreased significantly in the premotor cortex after acute bout of exhaustive exercise, (3) 8 weeks exercise could not prevented the decreased significantly the BDNF level of brain premotor cortex response to acute bout of exhaustive exercise. These results indicate that intense exercise can have some deleterious effect on brain premotor cortex.

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