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Comparing sprint and endurance training on anxiety, depression and its relation with brain-derived neurotrophic factor in rats

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ABSTRACT

Although the response of brain-derived neurotrophic factor (BDNF) has been shown to low intensity exercise training, but the effect of intensive exercise training is not clear. Also, there is insufficient information about relationship between BDNF and depression and anxiety following intensive exercise. This study aimed to investigate the effects of 6 weeks of intensive endurance training (ET) and sprint interval training (SIT) on brain BDNF and its relationship with anxiety and depression in Albino Wistar rats. Anxiety and depression of rats were measured by elevated plus maze (EPM) and tail suspension test (TST), respectively. All data were analyzed using one-way ANOVA and Pearson's correlation coefficient at $P < 0.05$ level. Both SIT and ET regimens increased BDNF content in the brain, and the alterations made were greater following SIT than ET. Also, both SIT and ET regimens increased number of entries and the time spent in the open arm significantly in EPM, with a higher elevation following SIT than ET. In addition, both SIT and ET regimens decreased number and duration of immobility significantly in TST, with a higher reduction following SIT than ET. Furthermore, BDNF content correlated positively with number of entries and the time spent in the open arm in EPM and negatively with number and duration of immobility in TST. Collectively, sprint interval training regimen, rather than intensive endurance training regimen, is highly potential to improve anxiety and depression through a greater increase in BDNF contents in brain.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is one of the most important neurotrophic factors plays an important role in mental states [1]. By interaction with its receptors, BDNF up-regulates the expression and activity of antioxidant enzymes and anti-apoptosis factors [2]. In addition, BDNF modulates brain development and neuroplasticity and neurite outgrowth, thereby improving memory and preventing Alzheimer and depression [3].

Accumulating evidence has pointed to exercise training as a non-pharmacologic approach for increasing the neurotrophins in the brain which in turn improves memory [4–6]. In this context, it has been shown that swimming training with moderate intensity [4], voluntary wheel running [5] and running on treadmill [6] elevated BDND contents of hippocampus in adults [4,5] and old animals [6] which in turn improves cognitive functions. In contrast, beneficial effects of training disappeared with detraining [4].

In reality, studies suggest that low to moderate intensity exercise increases brain BDNF content [4–6], but the effect of intensive endurance and sprint exercise on brain BDNF content is not well studied. In addition to improving memory, studies suggest that BDNF is involved in reducing incidents of depression and anxiety [7–9]. In this regard, it has been shown that BDNF content in depressive subjects is significantly lower than in control subjects [7]. Notably, it has been reported that stress can lead to neuronal atrophy (8), down-regulation of BDNF expression in the hippocampus [8,9] and reduction in hippocampal volume [10]. In contrast, treatment with antidepressant drugs [11,12], as well as, electroconvulsive shock treatment [13], resulted in a significant increase in BDNF content of serum [12], hippocampus and prefrontal cortex [11,13], there by leading to the reversal of neuronal atrophy and cell loss [8]. Furthermore, direct hippocampal infusions of BDNF protein can produce antidepressant effects [14]. Many people do not have enough time for exercise, and it is necessary to examine the effects of exercise training intensity on

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health improvement [3], especially depression and anxiety behaviour. Understanding the effects of different exercise training on these behaviours will help trainers in prescribing the best approach. Hence, the aim of the present study was to compare the effects of intensive endurance and sprint exercise training on depression and anxiety behaviour and determine their relations with BDNF as one possible modulating mechanism.

2. Materials and methods

2.1. Animals

This experimental study was approved by ethics committee of Birjand University of Medical Sciences in Iran and followed the guidelines for the use and care of laboratory animals ("Principles of laboratory animal care", NIH publication No. 86-23. Revised 1996). Twenty-four sexually mature male Albino Wistar rats (282 ± 14 g) were obtained from the laboratory of bearing and multiplying at the Mashhad University of Medical Scinces (Iran). Animals were housed with 12:12-h reverse light–dark cycles under controlled temperature (22 ± 2◦C) and had free access to tap water and standard rat food (Javaneh Khorasan Company, Iran). Initially, rats were familiarized with labratory envierment and running on motor-driven treadmill (5 days, 10 min/day at a speed of 10 m/min) (3) and then were randomly assigned into three equal groups of control (C), endurance training (ET), and sprint interval training (SIT).

2.2. Exercise training protocols

ET and SIT protocols were performed on a 12-line motor-driven treadmill on the basis of an overload principle for 6 weeks, 6 sessions per week [3]. To minimize novelty confound, each rats run in a fixed lane during the entire training program. Animals were motivated to run by a mild electrical shock at the end of the belt [15]. Because of handling effects on neurologicl characteristics, the rats in C group were placed and removed from the treadmill each day as ET and SIT rats but did not run [16]. At the beginning and end of ET and SIT protocols, warm-up and cool-down were performed at 16 m/min (correspond to 68% maximal oxygen uptake (VO_2max)) [3].

Rats in ET group run on treadmill at a speed of 27 m/min (correspond to 80% VO_2max) for 20 min at first session, increased with 2 min per day until 60 min was achieved by the 4th week; and was maintained for the two following weeks. Rats in SIT group, in odd days, run on treadmill at 40 m/min for 3 min (correspond to 95% VO_2max), alternated with active rest for 60 s at 16 m/min. The interval in the first session was 2 and increased to 6 repetitions in the 4th week and was maintained for the following two weeks. Rats in even days run on treadmill at 54 m/min for 30 s (correspond to 100% VO_2max), alternated with active rest for 60 s at 16 m/min. The interval in the first session was 3 and increased to 20 repetitions in 4th week and was maintained for the two following weeks [3].

2.3. Behavioral procedures

Animal anxiety and depression of rats was measured 24 h [17] after the last exercise training session by elevated plus maze (EPM) [17] and tail suspension test (TST) [18], respectively. It has been reported that albino rats present higher activity during the night [19]. Therefore, rats were examined at 19:00 pm to 22:00 pm.

The EPM apparatus consisted of two open arms (50 cm long, 10 cm wide) and two closed arms (50 cm long, 10 cm wide, with a wall 50 cm high) that standing at 50 cm above the floor. Each rat was placed in the central part of the EPM facing one of the open arms. The number of entries and the time spent in the open arm were recorded for 5 min [17,20]. Count criterion was entrance of each four paws of rats into open arm [20]. To avoid any smell interference, both of open and close arms of EPM were cleaned with alcohol at the end of each animal performance [17,20]. Also, noise and level of light can influence behavior in the elevated plus maze [20]. Therefore, EPM test performed in separate quiet and brightly lit room with consistent illumination.

In TST, animals were suspended by the tail with bands and hung from a mounted hook. The number and duration of immobility were recorded during the total 6 min [18]. Count criterion of immobility was lack of any movement except for respiration and whisker movement [18].

2.4. Tissue preparation and biochemical assays

To eliminate the effect of the last exercise session, the animals were sacrificed by decapitation under deep anesthesia (Ketamine, 60–80 mg/kg and Xylazine, 8 mg/kg; IP) 48 h after the last exercise session between 10:00 and 11:00 am [3]. Then, animal brain was dissected and washed by normal saline and rapidly submerged in liquid nitrogen and stored at −80 ˚C for further analysis. To inhibit protease activity, we added Protease Inhibitor Cocktail (#GB-326-1, ProBlock™-50, Goldbio technology CO, USA) to the microtube containing brain tissue powdered by liquid nitrogen (Afzalpour et al., 2015). Total protein of BDNF in brain were measured using commercially available kit (#CSB-E04504r, Cusabio Biotech CO., LTD. Sino-American). The sensitivity of the kit was less than 7.81 pg/ml. The absorbance of BDNF was measured at 450 nm by Anthos 2020 microplate reader (Biochrom CO, England). The data are presented as mg tissue weight [3].

2.5. Statistical analysis

Statistics analyses were carried out using Statistical Program for the Social Sciences (Version 17.0, SPSS Inc, Chicago, USA). All data were tested for homogeneity of variance and normality by Levene's and Shapiro–Wilk's test, respectively, at first and then analyzed using one-way ANOVA followed by Bonferroni post hoc test. Also, Pearson's correlation coefficient was used to examine the relationship between BDNF content and parameters of anxiety and depression. Data were presented as mean ± standard deviation. The significance level was set at $p < 0.05$.

3. Results

Body weights were not significantlt different between the SIT (332 ± 4 g), ET (338 ± 16 g) and C (343 ± 9 g) groups ($F_{2,23} = 2.11$, $P = 0.14$) (Fig. 1).

The results indicated that the brain BDNF contents, as the most abundant neurotrophins, increased significantly in SIT (33.79 ± 2.23 pg/mg tissue) ($P = 0.001$) and ET (24.02 ± 4.27 pg/mg tissue) ($P = 0.001$) groups more than in C (13.58 ± 1.46 pg/mg tissue) group, while the SIT resulted in a greater increase in the level of brain BDNF than those of ET ($P = 0.001$) (Fig. 2).

In the context of anxiety, the number of entries into open arms

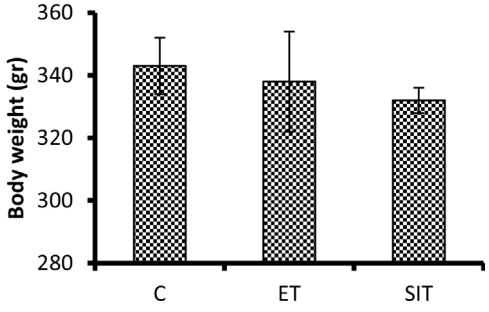

Fig. 1. Body weights of rat in Sprint interval training (SIT), Endurance training (ET) and Control (C) groups. No significant difference between the groups ($P = 0.14$).

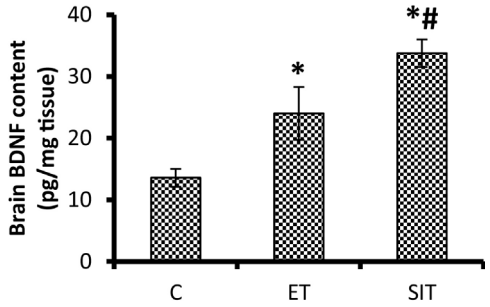

Fig. 2. Comparisons of brain BDNF contents ($^{*}P = 0.001$, $^{\#}P = 0.001$) between C, ET, and SIT groups. The asterisk (*) indicates a significant difference from C. The hash sign (#) indicates a significant difference from ET. Abbreviations are the same as are denoted in the legend of Fig. 1.

increased significantly in SIT (10.62 ± 2.61) (P = 0.001) and ET (7.87 ± 1.72) (P = 0.001) groups than in C (3.57 ± 1.13) group (Fig. 3A). In addition, the time spent into open arms increased significantly in SIT (115.12 ± 18.21 s) (P = 0.001) and ET (81.50 ± 15.67 s) (P = 0.014) groups than in C (53.71 ± 16.69 s) group (Fig. 3B). Besides, SIT induced a greater increases in the number of entries into open arms (P = 0.032) (Fig. 3A) and the time spent into open arms (P = 0.002) (Fig. 3B) than ET.

In the context of depression, the number of immobility decreased significantly in SIT (19.37 ± 4.59) (P = 0.001) and ET (28.00 ± 5.70) (P = 0.022) groups than in C (37.00 ± 7.11) group (Fig. 3C). In addition, the duration of immobility decreased significantly in SIT (125.38 ± 18.89 s) (P = 0.001) and ET (151.25 ± 13.72 s) (P = 0.017) groups than in C (177.43 ± 15.91 s) group (Fig. 3D). Besides, SIT induced a greater decreases in the number of immobility (P = 0.023) (Fig. 3C) and the duration of immobility (P = 0.015) (Fig. 3D) than ET.

Furthermore, our results showed a significantly positive correlation between BDNF and number of entries into open arms (r = 0.71, P = 0.001) (Fig. 4A), BDNF and time spent into open arms (R = 0.77, P = 0.001) (Fig. 4B). In contrast, our findings showed a significantly negative correlation between BDNF and number of immobility (R = − 0.72, P = 0.001) (Fig. 4C) and duration of immobility (R = −0.70 P = 0.001) (Fig. 4D).

4. Discussion

There are growing evidences that low to moderate-intensity exercise training is an important factor in improving memory and cognitive function through increases in brain neurotrophins [4]. In addition, depression and anxiety disorders are among the most disabling of all medical disorders. They frequently appear early in life, run a chronic course and adversely affect the prognosis of other medical illnesses [9]. Here, in an experimental animal model, we showed that both of SIT and ET improve depression and anxiety behaviors in rats.

BDNF is more likely than other neurotrophins to be involved in mood disorders [9]. Therefor, BDNF changes and its relationship with and anxiety behavior studied in present study. It was revealed that SIT and ET resulted in significant increases in brain BDNF contents in Albino Wistar rats. BDNF, as the most abundant neurotrophins with 14 kDa, is widely distributed in the central nervous system and is associated with memory and learning processes [3]. Our findings are inconsistent with other studies that reported no significant differences in BDNF contents of hippocampus because of short-term exercise training period [21]. In addition, no significant change in BDNF contents of hippocampus and basal forebrain has been attributed to learning induced by Morris maze task at the last week of the exercise training [15]. Because of learning effects on BDNF, researchers tried to minimize the effects of new stimulus-induced learning. Running is a relatively simple task and easily learned [22]. Therefore, it was not necessary to familiarize rats with running on treadmill with high intensity and long duration that may be interferingwith the results induced by exercise trainings [3]. In reality, observed changes in BDNF concentration in this study may be due to the exercise training itself.

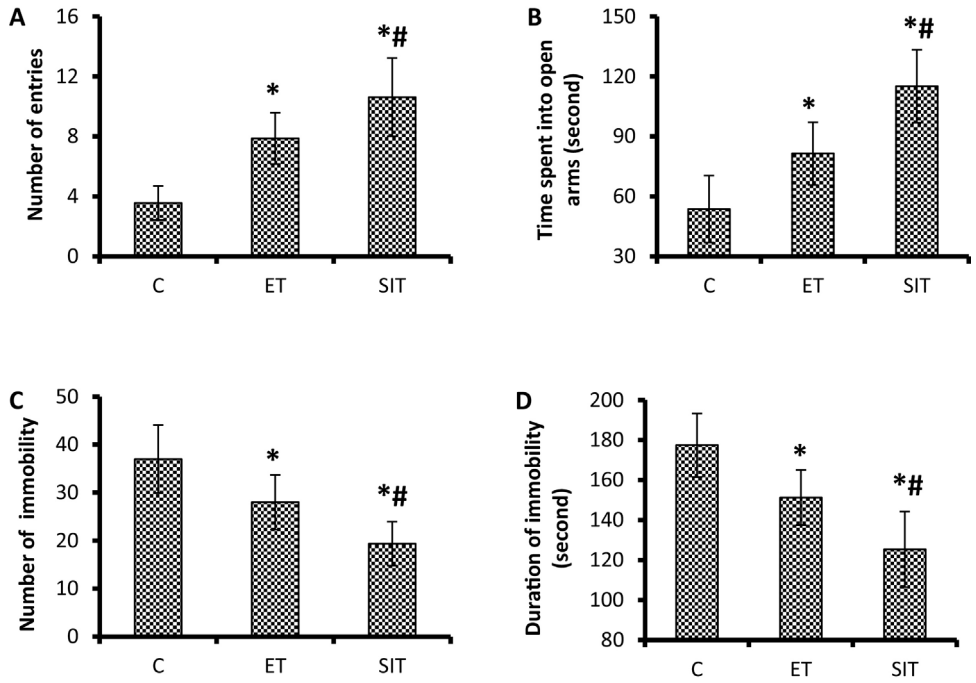

Fig. 3. Comparisions of number entries into open arms ($^{*}P = 0.001$, $^{\#}P = 0.032$) (A) and time spent into open arms ($^{*}P = 0.001$ and *P = 0.014 for SIT and ET groups respectively, $^{\#}P = 0.002$) (B) in EPM test between C, ET, and SIT groups. Comparisions of number immobility ($^{*}P = 0.001$ and $^{*}P = 0.022$ for SIT and ET groups respectively, $^{\#}P = 0.023$) (C) and duration of immobility ($^{*}P = 0.001$ and $^{*}P = 0.017$ for SIT and ET groups respectively, $^{\#}P = 0.015$) (D) in TST test between C, ET, and SIT groups. The asterisk (*) indicates a significant difference from C. The hash sign (#) indicates a significant difference from ET. Abbreviations are the same as are denoted in the legend of Fig. 1. Also, EPM and TST point out to elevated plus maze and tail suspension test, respectively.

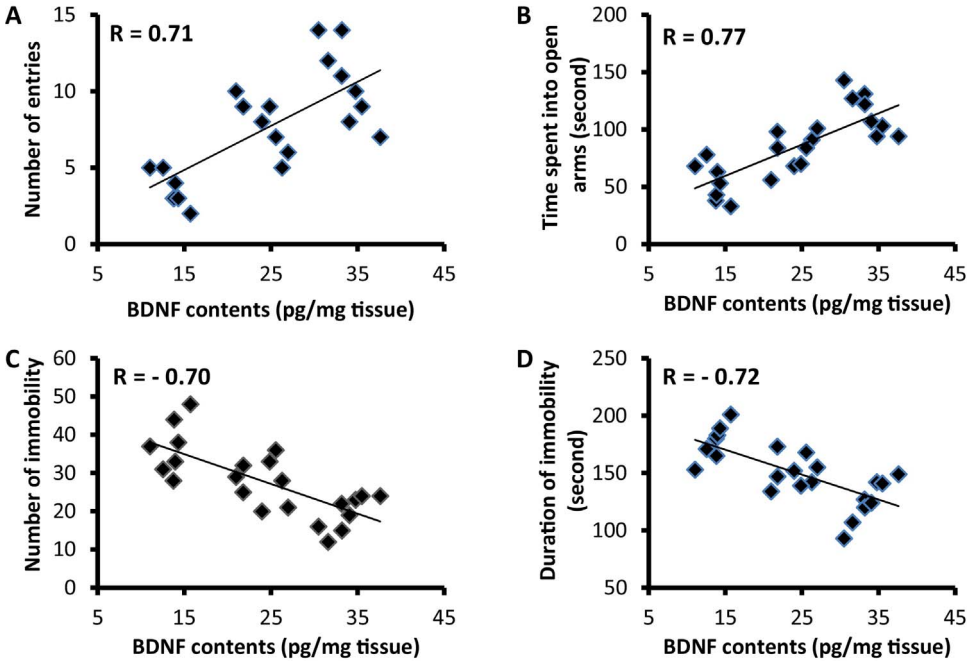

Fig. 4. Correlations between BDNF and number entries into open arms (P = 0.001) (A), BDNF and time spent into open arms (P = 0.001) (B), BDNF and number of immobility (P = 0.001) (C), BDNF and duration of immobility (P = 0.001) (D).

Overtraining is associated with decreased levels of BDNF [23]. However, animals in current study were not experiencing overtraining because of no significant changes in body weight. Furthermore, estrogen and its receptors increased BDNF levels in the hippocampus of female rats through activation of PKA/Akt/CREB and MAPK/CREB pathways [6]. Therefore, due to up-regulating effects of estrogen on the BDNF [6,24], male rats are examined in present study. In contrast, testosterone does not have significant effects on BDNF content in male rats [24]. Exercise protocols in the present study were intense (with 80–100% VO_2max). Accumulating evidence has shown that more hydrogen peroxide (H_2O_2) and tumor necrosis factor alpha (TNF-α) is produced following sprint training than endurance training [3]. H_2O_2 and TNF-α upregulates BDNF expression by increasing translocation of p65:p50 of nuclear factorkappa B (NF-κB) complex from cytoplasm to nucleus and activation of cAMP response element bind protein (CREB) [1,3]. Therefore, the higher content of BDNF following SIT compared to ET may be associated with higher levels of oxidative stress and pro-inflammatory factors induced by SIT.

In addition, our results showed that both of SIT and ET improve anxiety and depression behaviors in rats. Our findings are consistent with one study that improving in estrogen deficiency-induced depression-like behavior has been attributed to increasing content of BDNF induced by running on treadmill in hippocampal and prefrontal cortex rats [16]. Besides, combination of reboxetine (antidepressant treatment) and voluntary exercise (wheel running), led to more rapid and sustained increases in hippocampal BDNF mRNA expression than reboxetine alone [11]. Furthermore, Martinowich et al., in a review, have pointed out to neurotrophins theory of depression [9]. Althought, a significant positive correlation has been reported between BDNF protein and performance in the radial water maze [5], the results of present study also showed a significant correlation between BDNF and improving of anxiety and depression behaviors. In reality, a large proportion of BDNF is secreted in the pro-form (pro-BDNF), which is subsequently converted to mature BDNF (mBDNF) by extracellular proteases [9]. In this context, it has been reported that voluntary wheel-running increases convertion of pro-BDNF to mBDNF [25]. Notably, it has been shown that pro-BDNF and mBDNF can lead to Long-term depression and long-term potentiation, respectively [9]. Besides, SIT induced a greater improvement in anxiety and depression behaviors than ET that may be resulted from greater increases in BDNF content in SIT than ET. Beside, it has been reported that swimming exercise ameliorates depression-like behavior in chronically stressed rats through increases in 5-Hydroxytryptophan and reduction of corticosterone level [26]. Moreover, it has been shown that increases in estrogen levels induced by running on treadmill lead to improvement in total distance, number of crossing squares and immobile episodes in Open field test, and immobile time in TST [18]. In general, BDNF is not the only factor involved in improving of depression and anxiety behaviors following exercise training. Rather, a combination of factors may be involved in these events. Therefore, it is necessary to examine tht collective effect of these variables in future studies.

5. Conclusions

Although numerous and direct evidence is not available in support of this notion, it appears that the SIT, through further increases in BDNF contents, can result in greater improvements in animal anxiety and depression behavior. This means that the separation of the training sessions to various bouts of exercise with maximum effort will lead to greater mood gains.

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