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THE EFFECT OF 4 WEEKS AEROBIC TRAINING ON SPATIAL MEMORY AND BRAIN-DERIVED NEUROTROPHIC FACTOR IN SEDENTARY YOUNG GIRLS.

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ABSTRACT

There are numerous evidences that verify the beneficial effects of physical exercise on the central nervous system and cognition. Therefore, the aim of this study was to evaluate the effect of aerobic training on spatial memory and the possible mechanism of this effect, i.e. the brain-derived neurotrophic factor in sedentary girls. For this purpose, 12 sedentary females (mean age, 1/92 ± 23/90), voluntarily participated in the study and after giving blood samples and spatial memory test, they started their workout exercise under the aerobic protocol which continued for four weeks. At the end, the memory test and blood sampling were conducted 24 hours after the last session in order to remove the temporary effects of exercise. To analyze the data, t-test and Pearson's correlation coefficient were applied at a significance level of $p \leq 0.05$. The results showed that exercise led to meaningful progress memory scores ($p<0.05$). Also, the serum BDNF levels were significantly negatively correlated with aerobic training. The correlation between changes in the spatial memory test and expression of BDNF was not statistically significant ($p>0.05$). Generally, the results of this study showed that physical activity can lead to an improvement in spatial memory.

***Keywords*: Aerobic physical exercise, BDNF, Spatial memory, sedentary**

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INTRODUCTION

Although the positive impact of physical activity on cardiovascular system, musculoskeletal has long been known, but its impact on the mental and cognitive function is a novel realm of sports science and behavioral research and there are many research ongoing in the field(Zoladz&Pilc, 2010). Meanwhile, researchers have recently tried to shift the focus from the physical benefits of exercise to the possible positive impact of these activities on cognitive functions(Brutvan,2011). Several studies have shown that physical activity can have a positive impact on some aspects of cognition [Hillman, Ericksonand Kramer,2008]. In addition, it was recently shown that a vigorous exercise and workout improves long-term retention of new motor skills(Roig et al., 2012). Brain significantly responds to exercise and changes in anatomical, cellular and molecular body levels (Rezaee et al.,2013). The question that involved the minds of researchers in this field much more than the effect of exercise on cognitive functions is about the mechanisms mediating the effects of exercise on cognitive functions. Three hypotheses have been proposed in this field. One of these questionsis on the regulation of neurotrophineinvolved in neuronal survival, differentiation of neurons in the developing brain, and branches of the dendritic and synaptic systems of adult brain, as a result of exercise (Ploughman, 2008). In animal studies, the behavioral effects of exercise on memory and motor memory is clear, as in animals the use of aggressive techniques such as brain biopsy is permitted while the use of such methods in humans is not possible. An alternative method or shortcut is the application of biomarkers which play an important role in memory formation and retention (Winteret al., 2007).Although the concentration of biomarkersdoes not necessarily mean that these compounds have a direct effect on memory, but increase of each compound reflects the activity of a specific molecular pathway which is potentially involved in the process of memory formation (Langetal., 2007). There are several biomarkers that mediate the effects of physical exercise on motor memory and learning the skills. One of the most important molecular mediators in the field of complex and proven relationships between exercise and memorywhich have been studied, is brain driven neural growth factor (BDNF) (Cotmanetal.,2007;Vivar, Potter & van Praag, 2013). Because the BDNF crosses the blood-brain barrier (Pan &etal., 1998), there is a positive relationship between its serum and brain levels(Karege, Schwald&Cisse, 2002). BDNF exists in plasma, serum and platelets. Platelets save it and then release it in the plasma. Thus, there is a positive correlation between the amount of platelets and BDNF(Lommatzschetal., 2005).Many studies have examined the effect of physical activity on BDNF levels. There are conflicting evidences regarding the effects of exercise onthe BDNF blood level at rest. Some studies have reported that endurance training increases the basic plasma levels of BDNF, while others have reported that none of resistance training and endurance training do not change the basic level of BDNF in blood circulation(Yarrow, 2010). Thus, there has been uncertainty in BDNF response to exercise training program (Knaepenetal., 2010) and available information in this area seems inadequate (Matthews etal., 2009). The majority of studies that examined the effect of exercise training in this area have been mainly focused on protein and limited number of researches consider its effects on BDNF and memory at the same time. Thus, given the importance and novelty of the BDNF issue in healthand cognitive functionresearch of the brain and the possibility of a linkage between thisneutrophine and physical activity and cognitive function, this study seeks an answer to the question that whether there is a correlation between the changes resulting from the exercise in neurotrophic factors and memory in sedentary university students.

Methodology

This study applies quasi-experimental methods. The subjects in this study were 12 volunteer sedentary female students of Shiraz University who were selected after filling a special questionnaire to determine the level of physical activity and participation consent form in the study.Exclusion criteria were ages under 21 or over 25 years, history of mental, neurological disorder, and also record the current consumption of drugs affecting the nervous system and the history of participation in regular physical activity during the past six months. A week before the study, an introduction to the training session was held where participants became familiar with how to run on a treadmill. The exercise was conducted at a certain time of the day (afternoon) and under the supervision of the researcher. In the first 10 minutes of each session, there was jogging and stretching to warm up. Then, the main program which was running on a treadmill (3 sessions per week for four weeks) was carried out. Based on the methodology of training, we started with exercise intensity of 60% of maximum heart rate for 30 minutes in the first week and ended with 75 percent of maximum heart rate for 45 minutes in the 4th week. 5 minutes were allocated at the end of each training session to cool down. Pre-test and post-test (after 4 weeks) blood and spatial memory tests were performed on all participants. To determine the concentration of serum BDNF, blood samples were collected from the brachial vein after 12 hours of overnight fasting. Measurements were conducted by ELISA kit for human samples, according to the manufacturer's instructions (Bioassay Technology Laboratory, China) with response factor of 0.01 (ng/ml).

Spatial working memory test N-BACK

Spatial memory performance of all participants was analyzed using SPATIAL N-BACK TEST software for both pre-test and post-test. There are several tests to assess working memory, among which the most famous is the N-BACK test (Jaeggi, 2010). The main reason to prefer the N-BACK over other tests is that the test is less complicated than others, and is easy to use and ready for analysis in cognitive neuroscience by means of imaging, phenomenologyand behavioral. In this test, the subjects were presented a sequence of stimuli. Then, the task is to decide, the presented stimuli are in accordance with its N predecessor in the sequence or not. The task becomes more difficult by increasing the N, and speed and subject’s accuracy become negatively affected (Janidesetal., 1997). This program allows you to choose the color and the number of stimuli, stimulus duration and the time between the presentations of two stimuli. Obviously, to compare subjects with each other, the same terms of performance and application settings are required to be observed. The test must be conducted in a very favorable location and time and psychometric conditions of this experiment must be met. The objective is that the subject uses the maximum of its ability and keep the same pace while presenting the best performance. It is recommended that before the test officially starts, the meeting is made intimate with some informal talks. Before the experiment began, the necessary adjustments to color, number, duration of stimulus presentation and the interval between the two offers on the results page should be done (in the present case green color, long time presentation of stimuli, 500 ms, and the interval between two stimuli 2000 ms was considered). After entering the personal information of participants, test runs. Before the main test run, pilot (example) is run. At the beginning of both main and example run, an explanation is provided on screen. (To make the subject understand the task the test can be repeated several times, if necessary) and the test should be made fully clear for patients. The test begins when the subjects state their readiness. The duration of the experiment is set between 4 to 25 minutes, according to the time setting and the number of stimuli and taking into account the experimental stage. During the run skip the pilot phase, if necessary, or run out of the screen by pressing Esc.

Statistical methods

Descriptive statistics were applied for central tendency and dispersion parameters such as mean and standard deviation. In order to ensure normal distribution of the records, the Kolmogorov-Smirnov verification test were applied. In addition, paired t-test and Pearson correlation were used for data analysis. The significance level for all variables $p<0.05$ were considered. All statistical analysis was performed on SPSS 22 software.

FINDINGS

The mean and standard deviation of the data relating to spatial memory and serum BDNF level test results in the pre-test and post-test are shown in Table 1.

Paired t-test results illustrate that the spatial memory post-test data variables that are measured in terms of average error and time have a significant reduction (p=0.02) that means the enhancement of spatial memory.

Comparing BDNF data to pre-test and post-test also showed that 4 weeks of aerobic training significantly reduced (p=0.03) serum levels in sedentary female university students (Table 2).

As can be seen in Table 3, the Pierson correlation results showed no meaningful correlation between changes in memory scores and changes in neurotrophic factors, (p=0.61).

Table 1: Mean and standard deviation of variables in the pre-test and post-test data

Varibles	Pre-test	Post-test
Spatial memory(mean of error and time)	383/90±100	324/40±61
BDNF(ng/ml)	7/23±4/14	5/34±4/15

Data are expressed as mean and standard deviation (M ± SD).

Table 2: Paired-t test results in memory and BDNF.

Variables	Mean	Std.Diviation	P	df	t
BDNF(ng/ml)	1.89	1.6	0.003	10	3.91
Spatial memory (mean of error and time)	59.5	76.01	0.02	10	2.59

P ≤ 0.05

Table 3: Correlation between memory changes with changes BDNF.

Differences	pearson	p
BDNF -memory	172	0.61

DISCUSSION

The aim of the present study was an investigation of the effect of aerobic exercise on memory and neuronal brain-derived growth factor (BDNF) in sedentary young female university students, as a possible mechanism mediating this effect. The results show the benefits of aerobic exercise on spatial memory.

The positive impact of aerobic exercise on spatial memory

This study found that aerobic exercise improves spatial memory. According to research, the positive role of aerobic exercise on cognitive actions is well-supported. Cross-sectional studies have shown that people with high physical activity possess better cognitive function than their sedentary counterparts(Hillman et al,2006).Physical activity through molecular mechanisms such as neurogenesis can prevent the lack of cognitive activity(Lista& Sorrentino, 2010). Our results confirmed that physical exercise can help in maintaining the cognitive function and overall structure of the brain. In the investigation of Shayanet all(2013), which examined the impact of both endurance and resistance exercise on the attention and BDNF of sedentary students, concluded that physical exercise can lead to improvement in cognitive functions.Abedi, Kazemi and Shooshtari (2013) in their study on kids with neuropsychological learning disabilities stated that aerobics improves executive function and attention in such kids. In another study by Sadeghiet al (2013) on 50-70 year old women reported that implementation of the three-month aerobic and rhythmic exercise increase the memory level in women. According to Zeidabadiet al (2014) to evaluate the effect of short-term and long-term physical activity on spatial learning and memory, both types of physical activity were shown to significantly improve spatial memory.Irandoost,Seghatoleslam (2013) in their study of evaluation of the effect of aerobic exercise on memory, executed eighteen session aquatic exercise program on 45 years men. They stated that aerobic training has a positive effect on spatial memory. Haghighiet al (2013) expressed in their research on medium-term effects of exercise on learning and memory that it seems that running on a treadmill is helpful and useful in prevention and relief of cognitive impairments. Therefore, all these researches show the positive effect of aerobic exercise on cognitive functions.

The effect of aerobic exercise on brain driven nerve growth factor (BDNF)

In this study, four weeks of moderate-intensity aerobic exercise was shown to cause the significant decrease in serum BDNF level in sedentary female university students. A recent survey of research on BDNF level response to exercise in the human circulatory concluded that most previous studies have not confirmed the effect of exercise on resting levels of BDNF(Knaepen, 2010). In one study, the increase in secretion of BDNF in the brain was visible only in cervical vein after 12 weeks of aerobic exercise(Seifert, 2010). In another study, resting BDNF level had a transient increase following 4 weeks of training, which was disappeared during the next 4 weeks of training(Castellano., & White, 2008). Although numerous studies have been conducted, the results are not quite clear about the effects of endurance and resistance exercise on neurotrophic factors(Shahbazi et al.,2013). Various research findings in this field were not consistent, so that in some studies of physical activity, significant increase in BDNF levels was reported (Barari& et al., 2014; Tsai & et al., 2013; Ma& et al., 2012;Babaei, Damirchi, AzaliAlamdari, 2013)while in some others no significant changes in these variables was observed(Vosadiet al, 2013; Swift et al.,2012; Schiffer et al.,2009; Goekint et al., 2010).Differences in the exercise activity types (voluntary or mandatory), intensity and duration of exercise(Seifert et al., 2010), may be the main cause of the differences in the results of various research. The results of this study were antithetic with the results of Nofuji(2008),and his research colleagues stated that physical activity is effective on serum BDNF levels and there might be an inverse relationship between the concentration of BDNF and daily activity.The habit of exercise decreases serum BDNF levels. Also, according to Huang et al(2006), imposed mandatory running on a treadmill as training requirements for the animal causes the stress and negatively affects the BDNF mediated signals.In examining the relationship between physical activity, cardiorespiratory fitness, cardiovascular autonomic health and BDNF concentrations in healthy men (n = 28) and women (n = 16),Ramsbottoma, Curriea&Gilder(2010), concluded that cardiac autonomic health was negatively correlated with the concentration of brain-derived neurotrophic factor;however, this association was not statistically significant. One possible explanation on the decreasing in BDNF level can be consumption of BDNF in some tissues for the purpose of repairing the tissue damage which in this case the probable release of BDNF from platelets increase. More than 90% of BDNF protein in the blood is stored in the platelets that can be released through the processes of activation or clotting) Fujimura, 2002; Radka, 1996). Since protein synthesis in platelets has not been confirmed, it is possible that the platelets absorb the BDNF from the brain or other parts through the blood circulation.It seems that physical activity increases the accumulation of free radicals and active forms of oxygen (Carmeli, Laviam, &Reznick, 2000)such as superoxide anion and hydrogen peroxide as a response to greater use of oxygen which causes muscle damage and inflammation(Liu et al,2005; Alessio&Goldfar, 1998).Exercise is also shown to cause mechanical stress that makes damage to the nerves and muscles(Kuipers, 1994). It has been found that BDNF plays a role in the process of the reconstruction of the site of injury(Ebadi, 1994). It seems platelets free up BDNF to activate in the place of injury in order to facilitate regeneration of peripheral nerves or other tissues that contain high-affinity TrkB that accept BDNF (Fujimura, 2002). Interestingly, the BDNF protein is significantly increased in the Soleus muscle where the TrkBis expressed after exercise (Gomez-Pinilla, 2001). These reports confirm the possible release of BDNF from platelets to damaged tissues in order to facilitate the restructuring process during which the storage amount of BDNF in platelets is reduced. Since that BDNF is a dynamic variable the additional laboratory manipulation might reverse the results and such manipulations are feasible in the lab (Whiteman, 2013). Since it is shown that BDNF proteins are released from tissues other than the brain, such as skeletal muscle, the increase in BDNF in physical practice cannot only be attributed to the brain and the hippocampus area in the antithetic investigations(mojtahedi, 2014).This is due to the nature of some exercises like resistance training, which includes much of skeletal muscle tissue. It increases the possibility that the effect of exercise on muscles leads to increased blood levels of BDNF rather than its effect on the brain.Moreover, decreased serum BDNF in response to exercise have been reported in some previous investigations on not-trained people and atherosclerosis patients (Nofuji,2008; Ramsbottom, Currie & Gilder, 2010) and it is attributed to an increase in its cell processing (synthesis, secretion, and absorption analysis (Geroldi, Minoretti& Emanuele, 2006). Another reason for the reduction of BDNF in response to exercise, maybe its unnecessariness. BDNF influence on the reduction in appetite, food intake and weight control as well as its involvement in the improvement of metabolic fuels and an increase in fuel costs (Mojtahedi, 2014). So it is likely that BDNF increases to improve the process of reduction in energy intake. So, with the loss of fat, improvement in the mechanism of fuels and increase in energy expenditure in response to aerobic exercise, the reduction in participants' body needs to BDNF is a physiologic natural regulation.

The lack of correlation between variations in spatial memory and brain-derived neurotrophic factor (BDNF)

The data analysis showed that there is no significant correlation in the changes in mean response time and error to N-BACK test and changes in BDNF. Although the precise mechanism of physiological and psychological effects of exercise on the brain function, attention and executive control is not known, three hypotheses have been proposed in the context of this study, and for certain explained reasons, only the third hypothesis examined which finally was not confirmed. These hypotheses include: (1) increasing oxygen saturation and angiogenesis in brain levels task related performance;(2) an increase in neurotransmitter in the brain, such as serotonin that facilitate data analysis process; (3) the regulation of neurotrophins involved in neuronal survival, neuronal differentiation of the developing brain, and branches of the dendritic and synaptic devices in adults' brain (Ploughman, 2008).The results of this research work in this field are matched with result Ferris et al (2007). Perhaps the reason of the lack of correlation between these two variables are two other possible mechanisms. In fact, aerobic exercise may be improving memory due to an increase in oxygen saturation and angiogenesis in the brain critical levels or increase in brain neurotransmitter other the increase the neurotrophic factors.In addition, it is likely that due to the small number of subjects, Pearson correlation coefficient failed to properly assess the relationship between these two variables. The results of the present study showed that physical activity can lead to memory improvement, but there was no significant correlation between changes in memory and neurotrophic factors. Perhaps more research is necessary to prove this as well as investigation of other possible mechanisms is required.

Therefore, it is recommended longer physical protocols, other cognitive functions and role of different receptors of neurotrophic factors are also be investigated.

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