



Original Article

# Effects of aerobic exercise training on peripheral brain-derived neurotrophic factor and eotaxin-1 levels in obese young men

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**Abstract.** [Purpose] The aim of the present study was to investigate the effects of aerobic exercise training on the levels of peripheral brain-derived neurotrophic factor and eotaxin-1 in obese young men. [Subjects and Methods] The subjects included sixteen obese young men with a body mass index greater than 25 kg/m<sup>2</sup>. They were randomly divided between control and exercise groups (n = 8 in each group). The exercise group performed treadmill exercise for 40 min, 3 times a week for 8 weeks at the intensity of 70% heart rate reserve. Blood collection was performed to examine the levels of serum glucose, plasma malonaldehyde, serum brain-derived neurotrophic factor, and plasma eotaxin-1 before and after the intervention (aerobic exercise training). [Results] Following the intervention, serum BDNF levels were significantly higher, while serum glucose, plasma MDA, and plasma eotaxin-1 levels were significantly lower than those prior to the intervention in the exercise group. [Conclusion] Aerobic exercise training can induce neurogenesis in obese individuals by increasing the levels of brain-derived neurotrophic factor and reducing the levels of eotaxin-1. Alleviation of oxidative stress is possibly responsible for such changes.

**Key words:** Aerobic exercise, BDNF, CCL11

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## INTRODUCTION

Chemokines are a family of small cytokines that regulate leukocyte migration by inducing chemotaxis of specific cells. Chemokines are produced in almost all eukaryotic cells that constitute blood and other tissues. For example, chemokines of the CC subfamily are secreted by epithelial cells and fibroblasts during inflammatory reactions<sup>1)</sup>. Eotaxin-1 (CCL11), a member of the CC chemokine family secreted by epithelial cells, fibroblasts, macrophages, and eosinophils, has been reported to play an important role in eosinophil infiltration during allergic inflammation<sup>1)</sup>. Accordingly, majority of previous studies on the function and role of CCL11 focused mainly on inflammatory airway diseases, such as asthma<sup>1, 2)</sup>. However, recently, studies have provided evidence regarding the neurobiological relevance of CCL11<sup>3)</sup>. For example, in the study of Villeda et al., a decrease in long-term potentiation of synaptic transmission, a neurophysiological index related to learning ability, has been observed in the brains of mice injected with CCL11<sup>4)</sup>. In addition, that study revealed that CCL11 is a blood-borne factor inhibiting neurogenesis<sup>4)</sup>.

On the other hand, it has been reported that regular exercise not only reduces high oxidative stress level caused by obesity, but also induces neurogenesis by increasing expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF)<sup>5, 6)</sup>. Dramatic changes in oxidative stress levels could play an important role in neurotrophic factor expression as well as in CCL11 release<sup>7, 8)</sup>. In addition, Loughrey et al. revealed increased circulating CCL11 levels in patients with a

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metabolic syndrome that included obesity as a clinical manifestation<sup>9</sup>). Choi et al. reported that although CCL11 levels were significantly higher in patients with central obesity, regular exercise training could reduce their plasma CCL11 levels<sup>10</sup>. However, there has been very limited research into dynamics of neurogenesis in obese human subjects and the relationship between CCL11 levels and regular exercise has not been properly studied.

Therefore, for the present study, obese young men were recruited with the objective of defining the effect of regular aerobic exercise intervention on the content of malonaldehyde (MDA), an oxidative stress marker, and on the resulting changes in peripheral BDNF and CCL11 levels.

## SUBJECTS AND METHODS

Sixteen obese young men between 20–26 years of age volunteered as subjects for the present study. All subjects had to meet the following criteria before enrollment in the study: 1) BMI above 25 kg/m<sup>2</sup> and waist circumference above 90 cm, 2) no participation in regular physical activity programs, and 3) no history of cardiovascular, metabolic, or respiratory diseases. Subjects were randomly assigned into a control (CON) group or an exercise (EX) group, with 8 subjects in each group. The characteristics of the subjects are shown in Table 1. The study conformed to the standards set by the latest revision of the Declaration of Helsinki. All subjects read and signed a written informed consent statement consistent with the guidelines set by the Department of Physical Education at Yonsei University.

Anthropometric measurements included measurements of height, body composition, resting blood pressure (BP), and maximal oxygen uptake (VO<sub>2</sub>max). Height and body composition were measured using a stadiometer (SECA213; SECA, Hamburg, Germany) and a bioimpedance analysis (BIA) device (Inbody720; Biospace, Seoul, Korea), respectively. BP was measured in a seated position using standard auscultation procedures and a mercury sphygmomanometer (Trimline; PyMaH, Somerville, NJ, USA). Each subject was wearing a gas analyzer (MetaMax 3B; Cortex, Leipzig, Germany) that evaluated respiratory parameters using the breath-by-breath method and VO<sub>2</sub>max was measured on a treadmill (Q65; Quinton, Seattle, WA, USA) according to the Bruce protocol.

All subjects in the EX group had undergone the supervised treadmill running exercise [70% of the heart rate reserve (HRR), 40 min each] sessions 3 times a week for 8 weeks, while those in the CON group just maintained their usual lifestyles.

Ten milliliters of blood was collected from the antecubital vein of each subject before and after the intervention using a 22-gauge needle, a serum separator tube (Becton Dickinson, Franklin Lakes, NJ, USA), and an ethylenediamine tetra-acetic acid tube (Becton Dickinson, Franklin Lakes, NJ, USA). Collected blood samples were centrifuged for 15 min at 1,000 × g and then stored at –80 °C until further analysis. Serum glucose was determined by the hexokinase method using a commercially available glucose/hexokinase assay kit (Pointe Scientific, Canton, MI, USA). The analyses of plasma MDA, serum BDNF, and plasma CCL11 levels were carried out using an OxiSelect™ MDA Adduct Competitive ELISA Kit (Cell Biolabs, San Diego, CA, USA), a human BDNF ELISA Kit (R&D Systems, Minneapolis, MN, USA), and a human CCL11/Eotaxin Immunoassay Kit (R&D Systems, Minneapolis, MN, USA), respectively. A microplate reader (EMax; Molecular device, Sunnyvale, CA, USA) was used to measure absorbance at 450 nm.

Statistical analyses were performed with SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as the means ± standard deviation (SD), unless otherwise stated. Independent Student's *t*-tests were conducted to compare baseline levels of all variables between the CON and EX groups. To reveal differences between normally distributed data, the two-way repeated analysis of variance (ANOVA) was employed. When significant time by group interactions occurred, simple main effects were assessed using independent and paired Student's *t*-tests. Level of significance was set at 0.05.

**Table 1.** Characteristics of the subjects

| Variables                       | CON (n = 8) | EX (n = 8) |
|---------------------------------|-------------|------------|
| Age (years)                     | 22.3±2.1    | 22.9±2.5   |
| Height (cm)                     | 173.6±6.3   | 172.8±4.4  |
| Weight (kg)                     | 83.8±10.3   | 85.6±8.3   |
| Fat mass (kg)                   | 24.3±4.5    | 24.6±5.2   |
| BMI (kg/m <sup>2</sup> )        | 27.7±2.2    | 28.7±2.5   |
| Body fat (%)                    | 28.8±2.3    | 28.7±4.4   |
| Waist circumference (cm)        | 99.8±4.8    | 100.0±5.8  |
| Resting SBP (mmHg)              | 126.0±7.3   | 126.9±9.4  |
| Resting DBP (mmHg)              | 81.4±5.3    | 83.8±5.9   |
| VO <sub>2</sub> max (mL/kg/min) | 43.9±7.2    | 42.4±5.9   |

Data are presented as mean ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

## RESULTS

The comparison of anthropometric and biochemical characteristics for the two groups before and after intervention is shown in Table 2. Following intervention, repeated measures ANOVA demonstrated a significant effect of treatment for weight ( $F = 29.546$ ,  $p < 0.001$ ), BMI ( $F = 26.859$ ,  $p < 0.001$ ), fat mass ( $F = 31.632$ ,  $p < 0.001$ ), body fat ( $F = 19.947$ ,  $p = 0.001$ ), waist circumference ( $F = 29.126$ ,  $p < 0.001$ ),  $VO_2$ max ( $F = 18.613$ ,  $p = 0.001$ ), serum glucose levels ( $F = 12.754$ ,  $p = 0.003$ ), plasma MDA levels ( $F = 5.218$ ,  $p = 0.038$ ), serum BDNF levels ( $F = 12.834$ ,  $p = 0.003$ ), and plasma CCL11 levels ( $F = 9.178$ ,  $p = 0.009$ ). Following the intervention, BMI, fat mass, body fat, waist circumference, serum glucose levels, plasma MDA levels, and plasma CCL11 levels were significantly lower, while  $VO_2$ max and serum BDNF levels were significantly higher when compared to values prior to the intervention in the EX group ( $p < 0.05$ ).

## DISCUSSION

Obesity not only increases the rate of occurrence of type 2 diabetes mellitus, hypertension, and cardiovascular disease<sup>11, 12</sup>, but it has also been recently reported to be closely associated with the development of neurodegenerative disorders<sup>13, 14</sup>. One of plausible causes of neurodegeneration is obesity-induced increase in the level of high oxidative stress in the body<sup>15</sup>. In our study, to examine the effect of regular aerobic exercise on oxidative stress level and neurogenesis in obese subjects, the peripheral levels of MDA, BDNF, and CCL11 were measured. It was found that plasma MDA and CCL11 levels were decreased, whereas serum BDNF levels were significantly increased after 8 weeks of aerobic exercise. This result corroborates observations in previous studies that showed significantly lower plasma MDA and CCL11 levels and, at the same time, significantly higher serum BDNF levels after regular exercise training in patients with a metabolic syndrome that included obesity as a clinical feature. Tunkamnerdthai et al. reported that 8 weeks of low-intensity exercise significantly decreased plasma MDA levels in overweight patients with type 2 diabetes<sup>5</sup>, while Choi et al. found that 12 weeks of exercise training significantly reduced plasma CCL11 levels in patients with obesity<sup>10</sup>. In addition, Lee et al. observed significantly increased serum BDNF levels in obese patients after 12 weeks of aerobic exercise<sup>6</sup>.

In the present study, changes in the indexes related to obesity and levels of serum glucose and plasma MDA suggested that the significantly lower plasma CCL11 levels and significantly higher serum BDNF content were due to regular aerobic exercise. By inducing the improvement of body composition and reducing fasting glucose level, regular exercise alleviated oxidative stress in the body. This interpretation is supported by previous studies, which had reported that obesity elevates oxidative stress levels and induces CCL11 release following the increase in the reactive oxygen species (ROS) production<sup>8, 15</sup>. Increased oxidative stress could, in turn, induce down-regulation of neurotrophic factors<sup>7</sup>. In addition, it was reported that high blood glucose concentration induces ROS production via various biochemical signaling cascades, such as glucose autoxidation, increase in advanced glycation end-products synthesis, and activation of the polyol pathway, thereby leading to increased oxidative stress in a variety of tissues<sup>16</sup>. On the other hand, it has been reported that in addition to improving obesity symptoms, regular exercise could reduce fasting glucose concentration and levels of MDA, an indirect oxidative stress marker<sup>17, 18</sup>.

In conclusion, it is suggested that regular exercise can induce neurogenesis in obese individuals by increasing BDNF levels, while concomitantly reducing CCL11 levels. Alleviation of oxidative stress could be a principal mediator of these physiological and biochemical changes.

**Table 2.** Comparison of anthropometric and biochemical characteristics before and after intervention

| Variables                | CON (n = 8) |           | EX (n = 8) |                       |
|--------------------------|-------------|-----------|------------|-----------------------|
|                          | Before      | After     | Before     | After                 |
| Weight (kg)              | 83.8±10.3   | 83.5±10.0 | 85.6±8.3   | 79.5±7.3*             |
| BMI (kg/m <sup>2</sup> ) | 27.7±2.2    | 27.6±2.1  | 28.7±2.5   | 26.6±1.9*             |
| Fat mass (kg)            | 24.3±4.5    | 24.0±4.7  | 24.6±5.2   | 19.1±4.5*             |
| Body fat (%)             | 28.8±2.3    | 28.7±2.0  | 28.7±4.4   | 25.1±4.4*             |
| Waist circumference (cm) | 99.8±4.8    | 99.0±4.4  | 100.0±5.8  | 91.6±4.3*             |
| $VO_2$ max (ml/kg/min)   | 43.9±7.2    | 43.4±5.4  | 42.4±5.9   | 49.1±4.3 <sup>†</sup> |
| Glucose (mg/dl)          | 94.6±2.6    | 94.5±3.2  | 94.4±4.2   | 91.7±4.3*             |
| MDA (mmol/ml)            | 5.7±0.5     | 5.7±0.6   | 5.7±0.4    | 5.1±0.8*              |
| BDNF (ng/ml)             | 24.8±4.9    | 25.1±4.9  | 24.8±4.1   | 29.9±5.3 <sup>†</sup> |
| CCL11 (pg/ml)            | 71.7±12.5   | 72.7±10.9 | 72.8±14.2  | 68.5±11.9*            |

Data are presented as the mean ± SD. BMI, body mass index. Symbols \* and <sup>†</sup> indicate significantly lower or significantly higher values, respectively, in the same subjects compared to the values obtained before the start of the intervention period ( $p < 0.05$ )

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