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ScienceDirect

Journal of Sport and Health Science xx (2016) 1–6

www.jshs.org.cn

Original article

Obesity promotes oxidative stress and exacerbates blood-brain barrier disruption after high-intensity exercise

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Received 6 November 2015; revised 25 March 2016; accepted 6 April 2016
Available online

Abstract

Purpose: The purpose of this study was to investigate the effects of obesity and high-intensity acute exercise on oxidant-antioxidant status, neurotrophic factor expression, and blood-brain barrier (BBB) disruption.
Methods: Twenty-four healthy, untrained men (12 non-obese (mean 14.9% body fat) and 12 obese subjects (mean 29.8% body fat)) performed 20 min of continuous submaximal aerobic exercise at 85% maximal oxygen consumption. Blood sampling was performed to examine the oxidant-antioxidant status (reactive oxygen species (ROS) and superoxide dismutase (SOD)), neurotrophic factors (brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)), and BBB disruption (S100β and neuron-specific enolase) before and after acute exercise.
Results: The obese group showed significantly higher pre-exercise serum ROS levels and significantly lower pre-exercise serum SOD levels than the non-obese group ($p < 0.05$). Serum ROS, SOD, BDNF, NGF, and S100β levels were significantly increased post-exercise compared with pre-exercise levels in both the non-obese and the obese groups ($p < 0.05$). The obese group showed significantly higher serum ROS, BDNF, NGF, and S100β levels post-exercise compared to the non-obese group ($p < 0.05$).
Conclusion: Our study suggests that episodic vigorous exercise can increase oxidative stress and blood neurotrophic factor levels and induce disruption of the BBB. Moreover, high levels of neurotrophic factor in the blood after exercise in the obese group may be due to BBB disruption, and it is assumed that oxidative stress was the main cause of this BBB disruption.

Keywords: Antioxidant enzyme; Blood-brain barrier; Exercise; Neurotrophic factor; Obesity; Oxidative stress

1. Introduction

Cerebral vessels have a structure called the blood-brain barrier (BBB) composed of tight endothelial cell junctions, pericytes, astrocyte end-feet, and a basal lamina. The selective permeability of the BBB restricts the passage of harmful substances that can threaten normal brain function into the brain parenchyma from the extracerebral blood. Thus, the BBB provides a protective function for the brain against rapid changes in blood components.[1,2] On the other hand, a breakdown of the BBB caused by aging or other factors can induce cognitive impairment.[3] In addition, almost all the factors that contribute to the deterioration of the BBB's protective function have been reported to contribute to the pathogenesis of neurologic diseases such as epilepsy, multiple sclerosis, and Alzheimer disease.[2,4]

The main factors involved in BBB disruption are endoplasmic reticulum stress, glutamate excitotoxicity, and formation of reactive oxygen species (ROS).[5] Increased oxidative stress caused by excessive ROS production and compromised intrinsic antioxidant defense contribute to BBB disruption through several mechanisms, including oxidative damage to cellular molecules, cytoskeletal reorganization, and upregulation of inflammatory mediators.[6] When BBB disruption occurs, high concentrations of S100β and neuron-specific enolase (NSE), brain-specific proteins circulating inside the brain, are observed in the peripheral blood. The concentrations of these proteins have been reported as an index for estimating the extent of the increase in BBB permeability and brain damage.[7,8]

Obesity not only causes diabetes, high blood pressure, and cardiovascular disease but also has recently been reported to

Peer review under responsibility of Shanghai University of Sport.
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http://dx.doi.org/10.1016/j.jshs.2016.06.005

Please cite this article in press as: Hee-Tae Roh, Su-Youn Cho, Wi-Young So, Obesity promotes oxidative stress and exacerbates blood-brain barrier disruption after high-intensity exercise, Journal of Sport and Health Science (2016), doi: 10.1016/j.jshs.2016.06.005

be closely associated with the onset of neurodegenerative disorders.[9,10] A suggested cause of such diseases is an obesity-induced high oxidative stress level in the body.[11] According to Vincent et al.,[12] obesity was accompanied by chronically high oxidative stress levels because of the imbalance between tissue ROS and antioxidants. Olusi[13] also reported that compared to obese subjects with a body mass index (BMI) ≥ 40 kg/m^2, healthy subjects showed significantly lower plasma malondialdehyde concentrations and significantly higher activities of the antioxidant enzymes erythrocyte superoxide dismutase (SOD) and glutathione peroxidase. In addition, it was reported that the brain was less resistant to oxidative stress-induced damage than other tissues because of its relatively lower content of antioxidant enzymes against ROS; therefore, oxidative stress-induced damage to the brain could lead to neuronal apoptosis, triggering the onset of neurodegenerative disorders.[14,15] All these reports suggest a role for obesity in BBB disruption and the pathogenesis of neurodegenerative disorders.

Not only is participation in regular exercise effective for prevention and alleviation of obesity, but it can also reduce oxidative stress levels that have been elevated because of obesity.[16,17] It has also been reported that both regular exercise training and acute exercise were effective for maintaining and enhancing brain function by increasing the expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), regardless of the presence of a variety of diseases.[18] However, excessively intense acute exercise can metabolically impair dynamic cerebral autoregulation by overproducing free radicals, leading to the mechanical disruption of the BBB.[19] It is also possible that high oxidative stress levels damage the microtubule cytoskeleton, interfering with vesicular transport and inducing the downregulation of neurotrophic factors.[20] In addition, according to a report by Vincent et al.[21], the concentrations of plasma hydroperoxides and thiobarbituric acid reactive substances were significantly higher after acute exercise in obese subjects than in non-obese subjects. This suggests that the oxidative stress level of an obese individual can be higher than that of a healthy individual, not only at rest but also immediately after exercise.

Thus, compared to a non-obese individual, in an obese individual it is considered to be a higher risk that acute exercise will decrease the brain protective function of the BBB by increasing the oxidative stress level in the body while also affecting neurotrophic factor expression. However, there have been no reports concerning the effect of obesity and acute high-intensity exercise on oxidative stress levels in the body, neurotrophic factor expression, and BBB disruption. Accordingly, the present study aimed to examine the changes in oxidant-antioxidant status, neurotrophic factor expression, and BBB disruption in non-obese and obese subjects performing high-intensity acute exercise.

2. Methods

2.1. Subjects

Twenty-four healthy untrained men volunteered as subjects for the present study. All subjects met the following criteria before enrollment in the study: (1) no participation in regular physical activity, (2) no chronic health problems or smoking, (3) no history of cardiovascular, metabolic, or respiratory disease, and (4) no consumption of antioxidant supplements within the past 3 months. Subjects attended a brief orientation meeting before data collection, and all subjects read and signed a written informed consent statement consistent with university guidelines. Subjects were placed into 1 of 2 groups based on BMI and %body fat. Subjects with ≥25% body fat and a BMI ≥25 kg/m^2 were placed into the "obese" group, and those who had <25% body fat and BMI <25 kg/m^2 were placed into the "non-obese" group (Table 1). All study procedures were approved by the National Research Foundation of Korea (NRF-2013S1A5B5A07049580).

Table 1
Subject characteristics and anthropometric measures (mean ± SD).

Variables	Non-obese (n = 12)	Obese (n = 12)	p
Age (year)	22.9 ± 2.2	22.9 ± 2.2	1.000
Height (cm)	174.5 ± 3.9	173.2 ± 4.6	0.461
Weight (kg)	65.6 ± 4.2	87.9 ± 10.4	<0.001**
Fat mass (kg)	9.8 ± 2.3	26.1 ± 5.8	<0.001**
BMI (kg/m^2)	21.5 ± 1.6	29.3 ± 3.0	<0.001**
Body fat (%)	14.9 ± 3.2	29.8 ± 3.6	<0.001**
Resting SBP (mm Hg)	116.5 ± 4.8	123.1 ± 6.3	0.009*
Resting DBP (mm Hg)	74.2 ± 5.6	82.9 ± 7.3	0.003*
VO_{2max} (mL/kg/min)	54.3 ± 3.8	41.8 ± 6.8	<0.001**

*p < 0.01, **p < 0.001 as determined using the independent t test.
Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure.

2.2. Anthropometric measurements

Anthropometric measures taken 1 week before beginning exercise testing included the measurement of height, body composition, resting blood pressure (BP), and maximal oxygen consumption (VO_{2max}). Height and body composition were measured using a stadiometer (seca 213; seca, Hamburg, Germany) and a bioimpedance analysis device (InBody 220; BioSpace, Seoul, Republic of Korea), respectively. BP was measured in a seated position using standard auscultation procedures and a mercury sphygmomanometer (TRIMLINE; PyMaH, Somerville, NJ, USA). VO_{2max} was measured on a treadmill (Q65; Quinton, Seattle, WA, USA) according to the Bruce protocol based on the breath-by-breath method,[22] with each participant wearing a gas analyzer (METAMAX 3B; Cortex, Leipzig, Germany).

2.3. Acute exercise test

The exercise test was carried out by means of a treadmill run of 20 min at an intensity of 85% of the anthropometrically measured VO_{2max}. According to the Bruce protocol, with each subject wearing a gas analyzer, VO_2 measurement began with exercise onset and continued until each subject's VO_2 reached the target value of 85% VO_{2max}. At that point, exercise intensity was controlled by adjusting the speed and slope of the treadmill to maintain a VO_2 steady state at 85% VO_{2max}.

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