Obesity Research & Clinical Practice (2014) 8, e63—e69

ORIGINAL ARTICLE

Decreased plasma levels of brain-derived neurotrophic factor and its relationship with obesity and birth weight in obese Japanese children

Shunsuke Araki[a,*], **Yukiyo Yamamoto**[a], **Kazushige Dobashi**[b], **Kohtaro Asayama**[c], **Koichi Kusuhara**[a]

[a] *Department of Pediatrics, School of Medicine, University of Occupational and Environmental Health, Yahatanishi-ku, Kitakyushu 807-8555, Japan*
[b] *Department of Pediatrics, Showa University School of Medicine, Shinagawa-Ku, Tokyo 142-8666, Japan*
[c] *Faculty of Health Nutrition, Tokyo Kasei-Gakuin University, Tokyo 194-0292, Japan*

Received 2 March 2012; received in revised form 27 July 2012; accepted 31 July 2012

KEYWORDS
Adipocytokines;
Visceral adipose tissue;
Metabolic syndrome;
Children and adolescents;
Developmental origins of health and disease (DOHaD)

Summary
Background: Brain-derived neurotrophic factor (BDNF) plays important roles in the central regulation of food intake and body weight control. However, little is known about the role of BDNF in childhood obesity.
Objective: To investigate the relationship between plasma levels of BDNF and anthropometric factors, metabolic derangements due to obesity, adipocytokine levels and birth weight in obese Japanese children.
Subjects and methods: Sixty-six obese Japanese children aged from 5 to 15 years old were enrolled. The age-matched control group consisted of 32 non-obese healthy children. The plasma levels of BDNF and adipocytokines (leptin and adiponectin) were assayed using ELISA techniques.
Results: The mean BMI Z-scores were −0.67, +2.15 and +3.39 for the non-obese control children, obese (BMI ≥ 90th percentile, <99th percentile) and morbidly obese (BMI ≥ 99th percentile), respectively. The plasma levels of BDNF were significantly decreased in the morbidly obese children compared with the levels in the obese and non-obese control children (507 ± 33 pg/ml vs. 626 ± 46 pg/ml, 621 ± 35 pg/ml, $p < 0.05$). Univariate linear regression analysis showed that the plasma level of BDNF was positively correlated with birth weight ($r = 0.264$, $p < 0.05$) and inversely

* Corresponding author at: Department of Pediatrics, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. Tel.: +81 93 691 7254; fax: +81 93 691 9338.
E-mail address: arashun@med.uoeh-u.ac.jp (S. Araki).

http://dx.doi.org/10.1016/j.orcp.2012.07.003

correlated with the BMI *Z*-score ($r = -0.314$, $p < 0.05$). Multivariate forward stepwise linear regression analysis revealed that the birth weight and BMI *Z*-score are independent predictors of the plasma BDNF level.
Conclusion: The plasma level of BDNF, which is decreased in morbidly obese children, is associated with birth weight and the BMI *Z*-score. Our results suggest that BDNF may play important roles in the development and pathophysiology of childhood obesity.

Introduction

Brain derived neurotrophic factor (BDNF) belongs to the neurotrophin family, the members of which play a key role in the regulation of the survival, growth, and maintenance of neurons [1]. Several studies have revealed that BDNF and its high-affinity receptor, tropomyosin-related kinase B (TrkB), are involved in the central regulation of food intake and energy homeostasis [2,3]. Mice with BDNF haploinsufficiency are hyperphagic and develop obesity [4]. Furthermore, both central and peripheral infusion of BDNF decrease food intake, increase energy expenditure and lead to weight loss [5,6]. In humans, BDNF is also considered to be important for energy homeostasis. Indeed, several reports have demonstrated that the serum levels of BDNF were low in obese adults and children and in subjects with metabolic syndrome (MS) [7—10]. Among subgroup with WAGR syndrome, those with BDNF haploinsufficiency have low levels of serum BDNF and become hyperphagic and develop child-onset obesity [11,12]. Additionally, recent studies also revealed that single-nucleotide polymorphisms (SNPs) in BDNF genes are strongly related with BMI and childhood obesity [13,14].

The dysregulation of the expression of adipocytokines, such as leptin, adiponectin, interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), which are secreted from adipose tissue [15], contributes to the development of obesity-related metabolic derangements and is linked to MS [16]. It has been revealed that the level of adipocytokines can be changed in even obese children, as in obese adults [17]. Neurotrophins (NTs), such as BDNF, nerve growth factor (NGF), NT3 and NT 4/5, have also been considered as potential adipocytokines. For example, NGF has been shown to be directly secreted from both murine and human adipocytes grown in culture [18]. In addition, Hristova et al. reported that the plasma levels of NGF and BDNF were significantly lower in subjects with MS [7]; therefore, NTs were assumed to be involved in the pathogenesis of MS [8]. However, no reports have been published about the relationship between circulating BDNF levels and either visceral fat accumulation or adipocytokine levels in obese subjects.

Several studies have reported the serum BDNF levels in children with autism [19,20] and with a variety of childhood diseases [21—23]. Regarding childhood obesity, El-Gharbawy et al. reported that the serum BDNF levels are lower in overweight children than in normal weight children and that the serum BDNF concentration is correlated with age and platelet count but not with the BMI *Z*-score [9]. However, the changes in the plasma BDNF levels in obese children are still unclear. The present study was designed to elucidate the impact of obesity on plasma BDNF levels in children. Additionally, recent studies showed that a small size for gestational age at birth might be a risk factor for MS and type 2 diabetes mellitus [24]. To our knowledge, the relationship between plasma BDNF levels in obese children and birth weight has not yet been reported. Therefore, we also examined the relationship between birth weight and plasma BDNF levels in obese Japanese children.

Subject and methods

Sixty-six obese Japanese children, 43 boys and 23 girls, who visited the Clinic for Obese Children, University of Occupational and Environmental Health Hospital, were consecutively enrolled in the study. The ages of the subjects ranged from 5 to 15 (10.3 ± 0.34; mean $\pm$ SEM) years old. The BMI, BMI-percentile and BMI *Z*-score by age and sex were calculated from the national statistics for Japanese school children in 2000 (Ministry of Health, Labor and Welfare, Japan). A child was defined as obese if his or her BMI percentile for age and sex was between the 90th and 99th percentiles and as morbidly obese if his or her BMI exceeded the 99th percentile. No indications of endocrine, metabolic or kidney diseases were detected in the study subjects. The age-matched control group consisted of 32 non-obese children, 17 boys and 15 girls.

Anthropometric measurements were performed using previously described methods [25]. Visceral