Available online at www.sciencedirect.com

SCIENCE DIRECT

Metabolism Clinical and Experimental 55 (2006) 852–857

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus

Masataka Suwa[a,*], Hiroyo Kishimoto[b], Yu Nofuji[b], Hiroshi Nakano[c], Haruka Sasaki[d], Zsolt Radak[e], Shuzo Kumagai[a]

[a]*Institute of Health Science, Kyushu University, Kasuga, Fukuoka 816-8580, Japan*
[b]*Graduate School of Human-Environment Studies, Kyushu University, Kasuga, Fukuoka 816-8580, Japan*
[c]*Department of Human Development, Nakamura Gakuen University, Jonan-ku, Fukuoka 814-0198, Japan*
[d]*Second Division of Internal Medicine, Chikushi Hospital, Fukuoka University, Chikushino, Fukuoka 818-8502, Japan*
[e]*Faculty of Physical Education and Sports Science, Semmelweis University, Budapest, Hungary*

Received 29 July 2005; accepted 16 February 2006

Abstract

Previous studies have demonstrated that brain-derived neurotrophic factor (BDNF) played a role in the eating behavior and glucose and lipid metabolism. In this study we measured the serum BDNF levels in newly diagnosed female patients with type 2 diabetes mellitus (n = 24, aged 34-59 years) and female subjects with normal glucose tolerance (n = 7, aged 34-56 years). The serum BDNF level was found to significantly increase in diabetic patients in comparison to that in healthy subjects ($P < .05$). In these patients, the serum BDNF level showed positive correlation with the body mass index ($r = 0.535$, $P < .01$), the percentage of body fat ($r = 0.552$, $P < .01$), the subcutaneous fat area based on computed tomography scan ($r = 0.480$, $P < .05$), the triglyceride level ($r = 0.470$, $P < .05$), the fasting blood glucose level ($r = 0.437$, $P < .05$), and the homeostasis model assessment of insulin resistance score ($r = 0.506$, $P < .05$), whereas it showed a negative correlation with age ($r = -0.486$, $P < .05$). The partial correlation coefficients adjusted by age showed significant differences regarding the body mass index ($r = 0.423$, $P < .05$), percentage of body fat ($r = 0.504$, $P < .05$), and triglyceride level ($r = 0.426$, $P < .05$). These results provide the first evidence that an increased BDNF is associated with a prevalence of type 2 diabetes mellitus. In addition, the BDNF is related to the total and abdominal subcutaneous fat mass and energy metabolism in the newly diagnosed female patients with type 2 diabetes mellitus.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family expressed in the nervous system and periphery. Brain-derived neurotrophic factor is known to play an important role in such factors as neuronal outgrowth, differentiation, synaptic connection, and neuronal repair [1].

In the matured central nervous system, the expression of BDNF and its receptor trkB were observed in various hypothalamus nuclei associated with eating behavior and obesity [2]. An increased BDNF level in the ventromedial hypothalamus seemed to suppress food consumption and maintain an energy balance downstream of melanocortin-4 receptor [3]. Recent studies have demonstrated that BDNF treatment to obese and diabetic animals significantly suppressed the blood glucose, food consumption, and dietary body weight gain, while also enhancing the energy expenditure, glucose and lipid metabolism, and the activity of sympathetic nervous system [4-6]. Based on these data from animal experiments, it is possible that BDNF affects the morbid state of obesity and type 2 diabetes mellitus via its function on eating behavior and metabolism. However, whether BDNF is associated with obesity and type 2 diabetes mellitus in humans remains to be elucidated. Brain-derived neurotrophic factor can cross the blood-brain barrier [7]. The brain and serum BDNF levels underwent similar changes during maturation, and the serum BDNF level has been reported to closely correlate with the cortical BDNF level

* Corresponding author. Tel.: +81 92 583 7853; fax: +81 92 583 7853.
E-mail address: suwa-m@students.ihs.kyushu-u.ac.jp (M. Suwa).

0026-0495/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.02.012

[8], thus suggesting that the serum BDNF can reflect the brain BDNF level. The serum BDNF level has been reported to be positively correlated with the body mass index (BMI) in female patients with eating disorders [9]. Furthermore, the serum BDNF level in women with anorexia nervosa was lower, whereas it was higher in obese women than in normal-weight healthy women [10]. These results seem to imply that the serum BDNF level reflects the eating behavior and obese condition, and it is possible that the BDNF level thus play a role in these conditions for humans.

Because both obesity and a bad diet are significant risk factors for development of type 2 diabetes mellitus [11], it is hypothesized that a change of serum BDNF level is associated with prevalence of type 2 diabetes mellitus as well as obesity in such patients. One purpose of the present study was to compare the serum BDNF level in newly diagnosed female type 2 diabetic patients with that of female subjects with normal glucose tolerance. In addition, another purpose of the present study was to estimate the relationships between the serum BDNF level and the indices of obesity including the percentage of fat and abdominal visceral and subcutaneous fat distribution as well as the BMI. Furthermore, the relationships between the serum BDNF level and the indices of diabetes and lipid profiles in these patients were also examined.

2. Materials and methods

2.1. Subjects

Twenty-four newly diagnosed Japanese female patients with type 2 diabetes mellitus aged 34 to 59 years and 7 age-matched female subjects with normal glucose tolerance aged 34 to 56 years participated in this study. The pathologic state was classified according to the diagnostic criteria of the Committee of Japan Diabetes Society [12]. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Institute of Health Science, Kyushu University, Fukuoka, Japan. Written informed consent for all procedures was obtained from all subjects. All subjects had not previously received either any pharmaceutical treatment or behavior-modifying intervention.

2.2. Measurement of the metabolic parameters and serum BDNF levels

The subjects had been diagnosed based on the 75-g oral glucose tolerance test (OGTT). After overnight fasting of at least 12 hours, fasting blood samples were taken and then OGTT was performed. Blood samples were obtained at 30, 60, 90, 120, and 180 minutes. The blood glucose and serum insulin concentrations at fasting and during OGTT were measured by the enzymatic method and a radioimmunoassay, respectively. The area under the curves for glucose (AUC_{BG}) and insulin (AUC_{IRI}) during OGTT were calculated by the trapezoidal rule using absolute values. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated from the fasting blood glucose (FBG) and fasting serum insulin (FIRI) concentrations by the formula: HOMA-IR = FIRI (μU/mL) × FBG (mmol/L)/22.5. The serum BDNF level was measured using an enzyme-linked immunoassay kit (Promega, Madison, WI). Hemoglobin A_{1c} (HbA_{1c}) was measured by high-speed liquid chromatography. The lipid profiles including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were determined using the enzymatic method.

2.3. Measurement of anthropometric parameters

The BMI was calculated as the weight in kilograms divided by the square of height in meters. The percentage of body fat (%fat) was estimated based on the sum of the triceps and subscapular skinfolds measured with a skinfold caliper using the formula of Brozek and Henschel [13]. Waist circumference, measured at the level of the umbilicus, was divided by the circumference of the hip, measured at its greatest gluteal protuberance, to obtain the waist-to-hip ratio (WHR). The abdominal visceral fat area (VFA) and subcutaneous fat area (SFA) at the level of the umbilicus were automatically calculated by a computer system connected to a computed tomography scan (VIGOR LAU DATOR, Toshiba, Japan) as described by Tokunaga et al [14].

2.4. Evaluation of cardiovascular fitness

The maximal oxygen uptake ($\dot{V}O_2max$), which was an index of cardiovascular fitness and an important risk factor for the incidence of type 2 diabetes mellitus [15], was predicted. In brief, graded exercise tests using a cycle ergometer (Monark, Stockholm, Sweden) were performed. The heart rate and electrocardiograms were monitored and recorded during the test. The exercise intensity was increased 3 or 4 times every 4 minutes until the heart rate reached 70% of maximum or above. $\dot{V}O_2max$ was predicted by the nomogram of Åstrand and Ryhming [16], a modality that is generally used to predict $\dot{V}O_2max$.

2.5. Statistical analyses

The data were expressed as the mean ± SD. The comparisons between the healthy subjects and the patients with type 2 diabetes mellitus were performed using the unpaired t test. The relationships between the serum BFNF and other parameters were ascertained using Pearson correlation coefficients and partial correlation coefficients. Statistical significance was defined as $P < .05$.

3. Results

3.1. Characteristics of subjects

Table 1 shows the physical and metabolic characteristics of the subjects. WHR, VFA, TG, HbA_{1c}, FBG, AUC_{BG}, and