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

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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

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[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

Table 1
Characteristics of the subjects

	Normal (n = 7)	Diabetes (n = 24)
Age (y)	47.6 ± 7.5	51.0 ± 6.6
BMI (kg/m^2)	24.1 ± 6.3	26.1 ± 3.3
%Fat	34.3 ± 15.6	36.4 ± 7.9
WHR (cm/cm)	0.88 ± 0.07	0.94 ± 0.06*
VFA (cm^2)	90.6 ± 26.4	164.2 ± 60.6*
SFA (cm^2)	213.3 ± 147.8	220.5 ± 79.0
$\dot{V}O_2$max (mL · kg^{-1} · min^{-1})	30.7 ± 11.2	29.1 ± 6.7
TC (mg/dL)	216.0 ± 31.5	241.3 ± 33.5
HDL-C (mg/dL)	70.4 ± 23.1	58.4 ± 15.5
TG (mg/dL)	78.0 ± 18.9	144.6 ± 114.4*
HbA_{1c} (%)	4.80 ± 0.35	6.52 ± 0.90*
FBG (mg/dL)	96.0 ± 9.7	145.2 ± 29.8*
FIRI (μU/mL)	5.19 ± 2.07	7.14 ± 4.18
AUC_{BG} (mg/dL)	349.7 ± 55.9	681.3 ± 154.6*
AUC_{IRI} (mg/dL)	122.5 ± 42.0	96.2 ± 39.4
HOMA-IR	1.22 ± 0.49	2.32 ± 1.38*

Data are expressed as mean ± SD.
*$P < .05$ vs healthy subjects.

HOMA-IR in the diabetic patients were significantly higher than those in subjects with normal glucose tolerance ($P < .05$).

3.2. Comparison of serum BDNF level between the groups

Fig. 1 indicates a comparison of the serum BDNF level in the groups. The serum BDNF level in the diabetic patients was significantly higher than that in the healthy subjects (40.6 ± 9.9 and 30.6 ± 7.2 ng/mL, respectively, $P = .019$).

3.3. Relationships between serum BDNF level and other variables

In the patients with type 2 diabetes mellitus, as shown in Fig. 2, the serum BDNF level positively correlated with the BMI ($r = 0.535$, $P = .006$, Fig. 2A), %fat ($r = 0.552$, $P = .004$, Fig. 2B), SFA ($r = 0.480$, $P = .017$, Fig. 2C), TG ($r = 0.470$, $P = .019$, Fig. 2D), FBG ($r = 0.437$, $P = .032$, Fig. 2E), and HOMA-IR ($r = 0.506$, $P = .011$, Fig. 2F). The serum BDNF level was inversely correlated with age ($r = -0.486$, $P = .015$). The serum BDNF had a positive but weak correlation with HbA_{1c} ($r = 0.396$, $P = .055$). On the other hand, WHR ($r = 0.135$, $P = .534$), $\dot{V}O_2$max ($r = -0.063$, $P = .772$), TC ($r = 0.048$, $P = .826$), HDL-C ($r = -0.219$, $P = .307$), AUC_{BG} ($r = 0.200$, $P = .352$), IRI ($r = 0.342$, $P = .102$), AUC_{IRI} ($r = 0.038$, $P = .863$), or VFA ($r = 0.102$, $P = .641$) was not associated with the serum BDNF. In addition, although the number of the subjects was small (n =7), the serum BDNF closely correlated with FBG in the healthy subjects ($r = 0.754$, $P = 0.0496$). Partial correlation analyses were performed to eliminate the influence of age. Correlations between the BDNF level and the BMI ($r = 0.423$, $P = .045$), %fat ($r = 0.504$, $P = .014$), and TG ($r = 0.426$, $P = .043$) remained significant after adjusting for age. In addition, the serum BDNF level and HOMA-IR tended to show a positive correlation ($r = 0.408$, $P = .054$). When the influences of both age and SFA were eliminated, the partial correlation coefficient between serum BDNF and TG remained significant ($r = 0.479$, $P = .043$)

4. Discussion

This is the first report to investigate the serum BDNF level in patients with type 2 diabetes mellitus and age-matched subjects with normal glucose tolerance. We found the serum BDNF in the newly diagnosed female patients with type 2 diabetes mellitus to be significantly higher than that in healthy subjects. In the patients with type 2 diabetes mellitus, the serum BDNF level was associated with the indices of obesity including the BMI, %fat, and SFA, but not with the WHR or VFA. Because the %fat and SFA were estimated from the subcutaneous fat volume, these results imply that the increased serum BDNF level may thus be related to the subcutaneous or total fat mass. The serum BDNF level was also associated with the TG, blood glucose, and insulin tolerance in the patients. Moreover, the serum BDNF was closely correlated with FBG in the healthy subjects. These results suggest that the serum BDNF level thus reflected the lipid and glucose metabolism.

Brain-derived neurotrophic factor expressed in ventromedial hypothalamus neurons has been shown to apparently suppress food consumption and maintain energy balance downstream of melanocortin-4 receptor [3]. Brain-derived neurotrophic factor inhibited the glucagon secretion from pancreatic alpha cells, which expressed BDNF and its receptor trkB [17]. Brain-derived neurotrophic factor heterozygous mice ($BDNF^{+/-}$) indicated hyperphagic, obese, hyperglycemic, and insulin-resistant phenotypes [18-22]. It was therefore plausible that a decreased BDNF level accelerated the development of obesity and type 2 diabetes mellitus. On the other hand, we found the serum

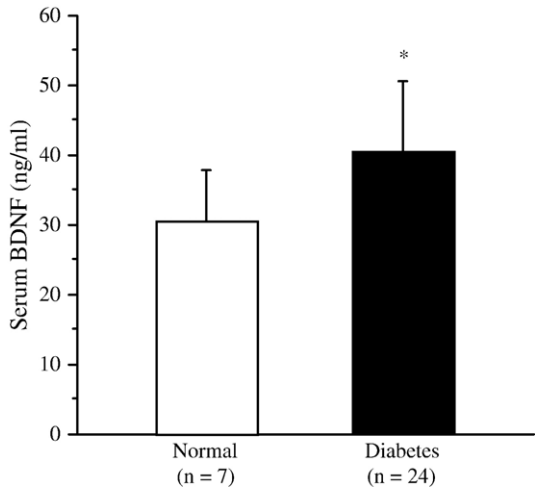

Fig. 1. The serum BDNF level in the subjects with normal glucose tolerance and patients with type 2 diabetes mellitus. Data are expressed as the mean ± SD. *$P < .05$ vs healthy subjects.

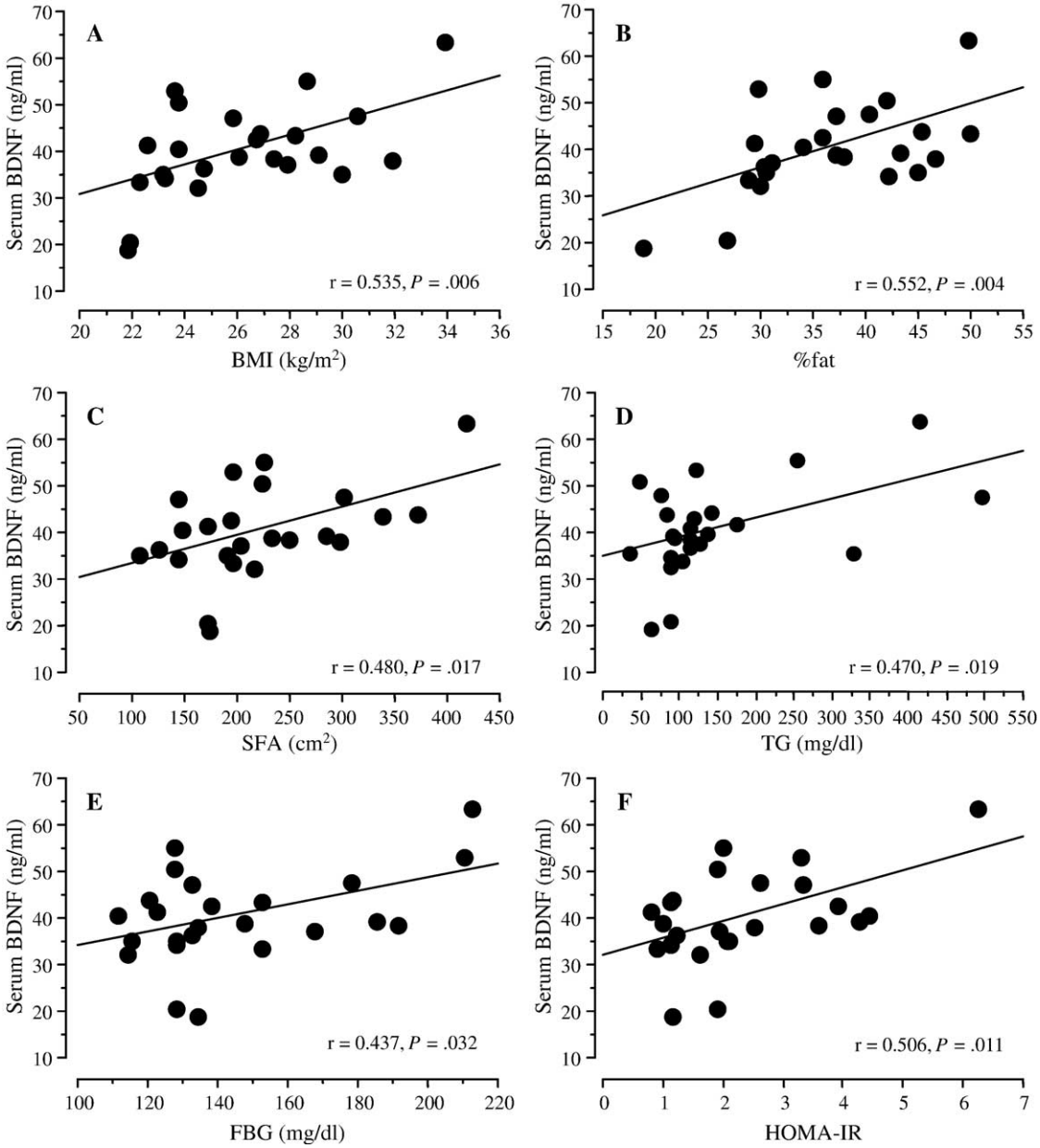

Fig. 2. Relationships between the serum BDNF level and the BMI (A), %fat (B), SFA (C), TG (D), FBG (E), and HOMA-IR (F) in 24 patients with type 2 diabetes mellitus.

BDNF to increase in patients with type 2 diabetes mellitus, and an increased serum BDNF level was thus found to be associated with obesity in the patients with type 2 diabetes mellitus. There are several observations that BDNF treatment to obese diabetic animals ameliorated such pathophysiologic conditions. The long-term subcutaneous administration of BDNF significantly decreased the body weight via a reduced food intake in obese diabetic *db/db* mice [4] and KKA^y mice [23]. Such treatment also reduced the blood glucose, HbA_{1c}, nonesterified free fatty acid, TC, and phospholipid levels independent of food intake in *db/db* mice [4,5,24]. Moreover, the subcutaneous or intracerebroventricular injection of BDNF improved the regulation of body temperature and increased oxygen consumption, glucose oxidation, and the expression of uncoupling protein 1 messenger RNA (mRNA) and protein in brown adipose tissue at least partially via the activation of the sympathetic nervous system in *db/db* mice [4,6,25]. It is therefore possible that the BDNF level increases in obese diabetic patients to compensate for such pathophysiologic conditions because of its potential roles in improving energy metabolism and suppressing food intake.

A previous study clearly demonstrated that BDNF heterozygous mutant mice resulted in hyperphagia before the onset of obesity [22]. Moreover, BDNF treatment in obese diabetic animals led to a reduced food intake and body weight and improving hepatic insulin sensitivity [4,23,26]. These results suggest that the BDNF primarily

regulates the food consumption followed by a change in body weight and insulin sensitivity. However, it remains unknown whether the obese diabetic conditions influence the BDNF expression. The results in this study that the serum BDNF level in the newly diagnosed female patients with type 2 diabetes mellitus increased and it was associated with obesity in such patients thus suggest the possibility that the obese diabetic conditions up-regulates the BDNF expression as an ameliorating factor for such pathophysiologic conditions.

The origin of an increased serum BDNF level in the obese diabetic patients remains unclear. The platelets contained a high concentration of BDNF [27]. The serum BDNF level was at least 10-fold higher than the platelets free plasma BDNF level [27,28]. Fujimura et al [27] suggested that most or all the BDNF in the blood was contained within the platelets based on the analysis of the platelet and blood BDNF contents. Collectively, these data suggest that almost all of the increased serum BDNF in the obese diabetic patients thus originated from platelets. The serum BDNF level was strongly associated with cortical BDNF (r = 0.81) in rats [8]. The BDNF bound and apparently internalized the washed platelets, whereas no BDNF receptor trkB was detected in the platelets [27]. It is thus possible that platelets gain BDNF from brain and/or other specific organs.

The BDNF mRNA expression of the soleus muscle, L4 and L5 dorsal root ganglia, and sciatic nerve significantly increased in streptozotocin-treated diabetic rats [29]. Therefore, skeletal muscle and peripheral nerve are the possible candidates for the origin of the increased serum BDNF level in the obese diabetic patients. In addition, the pancreas [30,31] and vascular endothelial cells synthesized BDNF [32]. Aorta [33], kidney, submandibular gland, ovary [34], heart, lung [35], retina [36], and immune cells [37] also expressed BDNF mRNA. Further studies are called for to clarify the origin of such increased level of BDNF in obese type 2 diabetic patients.

Up to ~50% of the platelet BDNF was released by the stimulation of agonists including thrombin, calcium ionophore A23187, collagen, and shear stress [27]. Presumably, the platelets might release BDNF in the trkB-expressed tissues by platelet activation. TrkB was expressed in the hypothalamus [9], pancreas [17,30], and skeletal muscle [38] that are associated with regulating the energy balance and metabolism. Such reports raise the possibility that platelets play a role in the release of BDNF in such tissues to prevent or compensate for individuals with obese diabetic conditions. It is hypothesized that the suppressed release of platelet BDNF by some unknown mechanisms increases the platelet BDNF store and the serum BDNF level, thereby accelerating the obese diabetic conditions. The fact that the plasma BDNF level decreased in the patients with metabolic syndrome and obesity [39] may possibly reflect an impaired release of platelet BDNF in such patients, which would support this hypothesis.

The previous studies [9,10] demonstrated the serum BDNF level to be associated with the BMI in female subjects. These previous studies [9,10] also indicated that the serum BDNF level decreased in the female patients with eating disorders including anorexia nervosa and bulimia nervosa, which mostly occurred in females. Such evidences imply that the serum BDNF reflects the eating behavior and development of obesity in females. Therefore, we hypothesized that serum BDNF level was related to type 2 diabetes mellitus as well as obesity at least in part via bad eating behavior especially in females and then performed the present study. As expected, in this study we demonstrated the serum BDNF level in female patients with type 2 diabetes mellitus to increase in association with obesity. On the other hand, in males, such eating disorders are scarcely observed and then it still remains unclear as to whether such an association between eating behavior and the serum BDNF level is also observed in males. Further studies to clarify the relationship among BDNF, eating behavior, obesity, and type 2 diabetes mellitus in male subjects are thus called for.

The patients in this study were all newly diagnosed and had not received either any pharmaceutical treatment or behavior-modifying intervention. It remains unknown regarding whether such an association between the serum BDNF and obese diabetic conditions as seen in this study also exists for patients who have had a longer duration of diabetes mellitus or who have received medication or intervention therapy. In this regard, BDNF treatment suppressed the blood glucose level in *db/db* mice, but not in lean *db/m* mice [40], thus suggesting the possibility that the BDNF level contributes to either improving or compensating for obesity and glucose metabolism according to their level and other factors such as intervention. To elucidate the association between the serum BDNF level and obese diabetic conditions will require further studies focusing on the duration of diabetes and the effects of medication and intervention.

In conclusion, we have shown the serum BDNF level to increase in newly diagnosed female obese patients with type 2 diabetes mellitus who had not previously received either any medication or intervention therapy. In addition, the serum BDNF level was found to be associated with the total and abdominal subcutaneous fat mass and lipid and glucose metabolism in such patients. These results suggest that the BDNF plays a potentially important role in compensating for such obese diabetic conditions. However, it is also possible that a suppressed release of BDNF from the platelets due to some unknown mechanism increases the serum BDNF level, while thereafter promoting obese diabetic conditions.

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