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Serum Brain-Derived Neurotrophic Factor Concentrations in Lean and Overweight Children and Adolescents

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Abstract

Context— Brain-derived neurotrophic factor (BDNF) and its receptor appear to be important components of the leptin-signaling cascade involved in energy homeostasis, and mice with *BDNF* or *TrkB* gene haploinsufficiency have excessive adiposity. Little is known about the relationship between adiposity and BDNF, particularly in children.

Objective— The objective of the study was to study the association of serum BDNF with measures of adiposity in children.

Design/Setting/Patients— BDNF was determined by a sandwich-type ELISA after an overnight fast in convenience sample of 328 subjects, aged 3–19 yr enriched for extreme obesity. In 43, BDNF was also measured before, and again 1 h after, consuming a high-energy content (787 kcal) milkshake.

Main Outcome Measures— Measures included associations between BDNF and measures of adiposity.

Results— There were no significant univariate associations between log BDNF and adiposity measured by body mass index (BMI), BMI-Z score, or fat mass. However, in an analysis of covariance accounting for age, sex, race, pubertal status, and platelet count, BDNF was lower in overweight children (mean ± SD, 39.8 ± 24.8 *vs.* 47.0 ± 25.4 ng/dl, $P = 0.03$); in multiple regression analyses with log BDNF as the dependent variable, BMI ($P = 0.03$), BMI-Z ($P = 0.01$), and body fat ($P < 0.02$) were all negatively associated with BDNF once age, pubertal status, and platelet count were included in the model. Ingestion of a meal did not significantly alter serum BDNF 1 h later ($P = 0.26$).

Conclusions— Serum BDNF is lower in extremely overweight children and adolescents than those of normal weight. It remains to be determined whether obese individuals with low serum BDNF for age and platelet count have mutations that alter BDNF function.

Brain-derived neurotrophic factor (BDNF) is a 119-amino-acid, 13.6-kDa protein (1) belonging to the neurotrophin family of signaling proteins that appears to be involved in the central regulation of energy homeostasis. BDNF and its receptor, tropomyosin-related kinase B (TrkB), are abundantly expressed in hypothalamic regions believed to be important for the maintenance of normal body weight (2,3). Mice with *BDNF* haploinsufficiency (4) are hyperphagic and develop obesity, hyperactivity, and aggressiveness. Conditional BDNF mutant mice, in whom BDNF is deleted after birth, develop mature-onset obesity and aspects of the metabolic syndrome (5). Furthermore, central infusion of BDNF in melanocortin 4

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receptor-deficient mice suppresses their hyperphagia and reverses their obesity (6). BDNF infusions also ameliorate the hyperglycemia, hyperinsulinemia, and hyperleptinemia seen in mice with *BDNF* haploinsufficiency (7). In humans, the BDNF gene has been hypothesized to play a role in the obesity found in patients with the Wilm's tumor, aniridia, genitourinary anomalies, and mental retardation contiguous gene syndrome (8), and a mutation in *TrkB* has been described in a child with severe obesity and developmental delay (9).

Few studies have examined serum concentrations of BDNF protein. Low serum BDNF has been reported in women with depression (10,11) or eating disorders such as anorexia nervosa (12), particularly when compared with obese patients (13), but also when women with anorexia nervosa or bulimia nervosa are compared with normal-weight individuals (12–14). Studies evaluating serum BDNF in children are rare (15,16); to our knowledge, no prior reports have studied serum BDNF concentrations in overweight children.

To establish age-appropriate norms for serum BDNF in children and evaluate possible differences in BDNF in overweight and normal-weight children, we examined fasting serum BDNF in a large cohort of lean and overweight children and studied the relationships between BDNF and body composition. We hypothesized that serum BDNF would be positively related to both body mass index (BMI) and body fat mass.

Subjects and Methods

A convenience sample of generally healthy children and adolescents age 3–19 yr was recruited using newspaper advertisements and mailings to families and physicians for studies of the physiological, metabolic, and molecular basis of childhood obesity as previously described (17). Subjects were recruited for investigations of the natural history of weight gain and weight reduction trials. Both nonoverweight children, with BMI between the fifth and 95th percentile for age and sex (18), and overweight children (BMI $\geq$ 95th percentile) were studied. Exclusion criteria included recent weight loss, known genetic or endocrine causes of obesity, significant medical illness, and use of medications affecting body weight. These studies were carried out in accordance with the Declaration of Helsinki and were approved by the National Institute of Child Health and Human Development Institutional Review Board, which serves as the ethics committee for pediatric studies conducted by National Institute of Child Health and Human Development investigators. Each child gave written assent, and a parent gave written consent, for protocol participation.

Weight and height were measured as described previously (19) using calibrated electronic instruments so that BMI (kilograms per square meter) could be calculated. BMI SD scores (BMI-Z) and percentile ranks were calculated according to the Centers for Disease Control and Prevention 2000 growth standards (18). Pubertal stage was assessed by a pediatric endocrinologist or trained nurse practitioner, with breast stage according to Tanner assessed for girls and testicular volume measured using an orchidometer for boys. Pubertal staging was then further categorized into three groups for analysis: prepubertal (Tanner 1 breast stage for girls and testis size < 4 ml for boys), midpubertal (Tanner II and III breast stages for girls and testes 4–12 ml for boys), and late pubertal (Tanner IV and V breast stages and testes > 12 ml for boys). Body composition was determined using dual-energy x-ray absorptiometry (DXA; QDR2000 or QDR4500A; Hologic, Bedford, MA) in most subjects. For 59 children (7% prepubertal, 34% midpubertal, and 59% late pubertal) for whom DXA was not available, air displacement plethysmography (Life Measurement Inc., Concord, CA) was performed according to the manufacturer's instructions and procedures as previously described (17,19, 20) so that lean body mass and body fat mass could be determined. Measurements of fat mass by air displacement plethysmography and DXA have previously been shown to be well correlated (19,21).

Fasting blood samples were collected between 0800 and 1100 h in serum separator tubes for BDNF assay and routine chemistry studies. A second sample of heparinized plasma was obtained to determine platelet count because BDNF is stored in and released from platelets (22,23). To examine the acute impact of food intake on serum BDNF, we also carried out a pilot study of 43 consecutive children studied under one protocol (24), who had a second blood sample collected 1 h after they consumed a standard liquid breakfast (Scandishake; Axcan Pharma Inc., Birmingham, AL; 787 kcal, 52% carbohydrates, 11% protein, 37% fat). All samples were centrifuged at 4 C for 15 min and the serum stored at −20 C until assayed.

Assays

Serum BDNF was measured using a commercial kit (BDNF Emax immunoassay system; Promega, Madison, WI). Briefly, 96-well flat-bottom immunoplates (Nalge Nunc International, Rochester, NY) were coated with an anti-BDNF monoclonal antibody overnight at 4 C for 16–18 h. The sandwich enzyme immunoassay was then performed using aliquots of subjects' serum samples diluted in the range of 1:25 to 1:2000. BDNF concentration in serum was calculated based on a standard curve, which was linear between 7.8 and 125 pg/ml. Intra- and interassay variability were less than 9 and less than 18%, respectively; the lower limit of detection was 7.8 pg/ml. Platelet count was measured in heparinized samples by automated two-dimensional optical analysis with automatic verification by focused-flow impedance (CELL-DYN 4000; Abbott Laboratories, Abbott Park, IL) using standard methodology in the National Institutes of Health clinical laboratory.

Statistical analysis

Statistical analyses were conducted using SuperAnova (version 1.11; Abacus Concepts, Inc., Berkeley, CA) and StatView (version 5.01; SAS Institute Inc., Cary, NC) software. The BDNF concentrations of overweight and nonoverweight children were log transformed and then compared by analysis of covariance. Age, sex, race, pubertal status, and platelet count were used as covariates, and least squares means retransformed to conventional units are reported from this analysis. Multiple linear regressions were also used to determine whether BMI-Z score, body fat mass, or lean body mass significantly contributed to the prediction of the log of BDNF after the aforementioned demographic factors and platelet count were taken into account. Statistical significance was set at $P = 0.05$. Mean (SD) is reported unless otherwise noted.

Results

A total of 328 healthy children and adolescents, age 3–19 yr, were studied, including 224 overweight and 104 nonoverweight children (Table 1). As expected, the mean BMI, BMI-Z score, and body fat mass of the two groups differed significantly. Among the overweight group, 45% had BMI in excess of the 99th percentile for age and sex. The mean age and the gender distribution of the overweight and nonoverweight children were not significantly different. As expected (25), pubertal development was significantly more advanced among overweight children. The racial/ethnic distribution of the two groups was also significantly different in the anticipated direction (26), with more African-American children in the overweight group (50.9 *vs.* 22.1%, $P < 0.001$). As has been found previously among overweight children (27) cross-sectionally and among overweight adults who are gaining weight rapidly (28), platelet count was significantly greater among overweight children ($P < 0.001$).

There were no significant univariate associations between BDNF and BMI (Fig. 1A), BMI-Z (Fig. 1B) or percent body fat mass (Fig. 1C). There was a small but significant association between age and BDNF ($r = +0.11$, $P = 0.05$). Serum BDNF was, however, significantly associated with platelet count ($r = 0.16$, $P < 0.006$; Fig. 1D). However, by analysis of

covariance, serum BDNF adjusted for sex, age, pubertal status, and platelet count was significantly lower in overweight subjects (39.8 ± 24.8 *vs.* 47.0 ± 25.4 ng/dl, $P = 0.03$; Fig. 2). In a multiple regression model with fasting serum BDNF as the dependent variable (model $r^2 = 0.065$, $P = 0.002$), there were no significant contributions from sex ($P = 0.61$), race ($P = 0.38$), or adiposity expressed as BMI, BMI-Z, or percentage body fat (all $P \geq 0.16$), but platelet count (beta = +0.21, $P < 0.001$) and age (beta = +0.14, $P = 0.006$) were significant predictors, with each accounting for approximately 3% of the variance in fasting serum BDNF. Separate analyses seeking a relationship between BDNF and BMI for white children, black children, and children of other races or ethnicities found no significant differences in the relationships between BMI and BDNF for any group. Removal of the three subjects with BMI between the fifth and 10th percentiles and the 12 subjects with BMI between the 90th and 95th percentiles did not alter these results (data not shown).

Compared with fasting values, postprandial serum BDNF concentrations measured in 43 children 1 h after drinking a high-calorie milkshake (Fig. 3) were not significantly different from baseline values in either nonoverweight ($P = 0.24$) or overweight children ($P = 0.39$).

Discussion

We measured serum BDNF in a large cohort of nonoverweight and overweight children to examine the importance of demographic and auxologic factors as predictors of circulating BDNF. Because conditions that are often associated with energy restriction, such as anorexia nervosa (12), bulimia nervosa (13), and untreated major depression (10,11), have been found to be associated with low serum BDNF and because serum BDNF has been reported to reflect central BDNF levels in rats (29,30), we hypothesized that serum concentrations of BDNF would be positively related to BMI or body adiposity. Contrary to our initial hypothesis, children's serum BDNF concentrations were not significantly associated with BMI, BMI-Z, or fat mass in univariate models, and in multivariate models, in which chronological age and platelet count (22,23) were the strongest factors associated with fasting serum BDNF concentrations, we found a negative association between BDNF and measures of adiposity, such that BDNF concentrations, adjusted for sex, race, pubertal status, age, and platelet count, were 15% lower in severely overweight youth than in those of normal weight. These results differ from those of Nakazato *et al.* (12), who reported a significant, positive relationship between BMI and serum BDNF in adults but only when patients with anorexia nervosa were included in the analysis. Within the group of normal-weight individuals studied, a positive relationship between BMI and BDNF was not found. Interestingly, adults in the study by Nakazato *et al.* who had bulimia nervosa, whose weight did not differ from those of his healthy controls, had lower BDNF, a result that may be consistent with the findings reported in the present investigation for severely obese children. Eating-disordered psychopathology involving loss of control over eating may be reported by as many as 30% of such children (31–36). Alternatively, it is possible that some extremely overweight children may have relative deficiencies of BDNF and, like the BDNF haploinsufficient mouse (4), may have hyperphagia as a consequence of BDNF insufficiency. Further studies seeking function-altering mutations in the BDNF gene among severely overweight children with low serum BDNF would thus seem indicated.

We also conducted a pilot investigation of the effect of food intake on serum BDNF 1 h after food consumption. In rats that have undergone a percussive head injury, a 4-wk exposure to a high-fat sucrose diet suppresses BDNF synthesis in some hippocampal neurons (37). However, in the present study of children, eating a meal did not acutely change serum BDNF. We therefore conclude that circulating BDNF concentrations in children are not rapidly affected by food intake. We hypothesize that the reason we saw relatively little impact of food intake on BDNF concentrations is because serum BDNF most closely reflects platelet stores rather

than neuronal secretion of BDNF. It remains possible, however, that serum BDNF might require a longer time period before the effects of food intake might be detected. It is also possible that some individuals have substantial circulating quantities of pro-BDNF, which cross-reacts with all currently available BDNF assays and might thus have affected these results (38).

BDNF serves as a neurotransmitter modulator and participates in plasticity mechanisms such as long-term potentiation (39) and learning (40). Serum BDNF has therefore previously been investigated in children with autistic disorders and mental retardation (15,16). Miyazaki *et al.* (15) reported high serum BDNF in a small group of children with autistic disorders and mental retardation, compared with adult controls. Additional studies comparing serum BDNF in overweight children without neurocognitive difficulties and age- and BMI-matched children who have well-characterized learning and/or mood problems are required to elucidate the relationship between serum BDNF and neurocognitive deficiencies in children.

In conclusion, serum BDNF is not positively related to body adiposity in youth aged 3–19 yr. The current investigation suggests that serum BDNF is positively associated with platelet count and negatively associated with both BMI and age. Thus, serum BDNF concentrations in children may need to be interpreted with age-specific and platelet count-specific standards.

Prospective studies of individuals with phenotypes that include childhood-onset obesity in combination with learning or mood disorders are needed to define the role of serum BDNF as a biological marker for abnormalities in the BDNF-TrkB signal transduction system. Mutations in the *BDNF* and *TrkB* genes that can be shown to be associated with overweight appear to be rare in obese children (9,41). It remains to be determined whether individuals with mutations expected to change BDNF expression or function have significant alterations in serum BDNF or whether serum BDNF will be useful to identify individuals anticipated to have resistance to the actions of BDNF at its receptor.

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Abbreviations

BDNF
Brain-derived neurotrophic factor

BMI
body mass index

BMI-Z
: BMI SD score

DXA
: dual-energy x-ray absorptiometry

TrkB
: tropomyosin-related kinase B

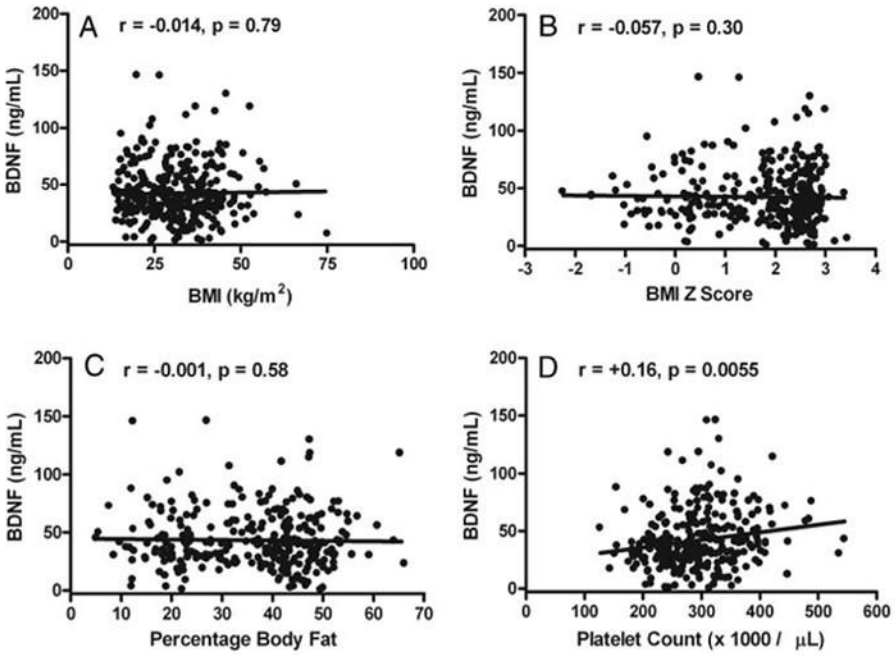

Fig. 1.

Univariate associations in 328 children between fasting serum BDNF concentrations and BMI (A), BMI-Z score for age and sex (B), percentage body fat (C), and platelet count (D).

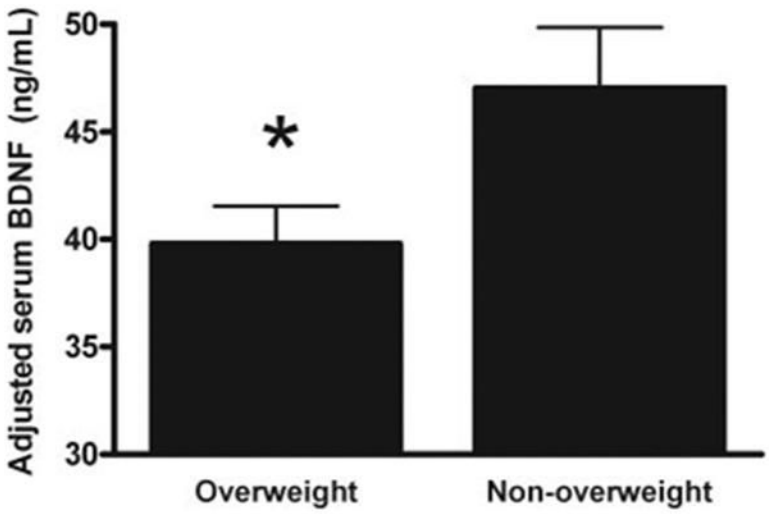

Fig. 2.
Serum BDNF adjusted for covariates in overweight (n = 224) and nonoverweight (n = 104) children and adolescents. *, $P = 0.03$.

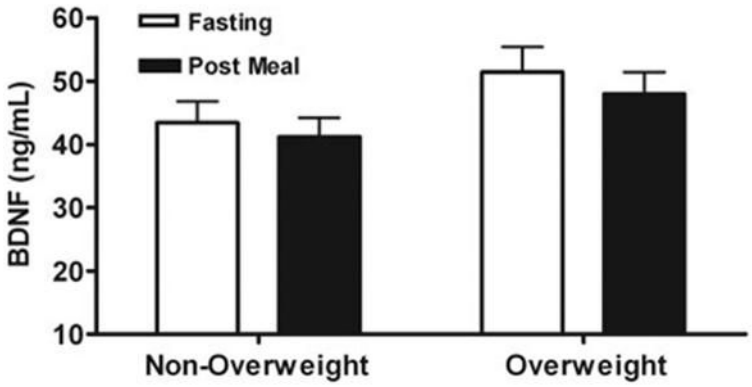

Fig. 3.

Children's serum BDNF concentrations in the fasted state and 1 h after consumption of a 787-kcal milkshake meal. There were no significant differences in BDNF after the meal for either nonoverweight (n = 19) or overweight (n = 24) children.

TABLE 1

Subject characteristics

	Not overweight: BMI fifth to 95th percentile (n = 104)	Overweight: BMI ≥ 95th percentile (n = 224)
Age (yr)	12.5 (3.1)	12.7 (2.7)
Range	4.1–19.1	3.5–19.1
Sex (%)		
Female	52.9	59.4
Male	47.1	40.6
Pubertal stage (%)[a]		
Prepubertal	25.0	12.5
Midpubertal	22.1	39.7
Late pubertal	52.9	47.8
Race/ethnicity (%)[a]		
Black/African-American	22.1	50.9
White/Caucasian	67.3	44.6
Other	10.6	4.5
BMI (kg/m^2)[a]	19.9 (3.6)	36.2 (8.5)
BMI-Z score[a]	0.378 (0.805)	2.441 (0.362)
Range	−2.24–1.59	1.67–3.43
Body fat mass (%)[a]	22.3 (7.8)	42.2 (9.3)
Platelet count (× 1000/μl)[a]	270 (77)	306 (62)

Mean (SD) unless otherwise indicated. For body fat mass, n = 286; for platelet count, n = 254.

[a] $P < 0.001$, overweight *vs.* normal-weight children.