Hormones (2022) 21:295–303
https://doi.org/10.1007/s42000-022-00364-z

ORIGINAL ARTICLE

The regulation of adipokines related to obesity and diabetes is sensitive to BDNF levels and adipose tissue location

İmran İnce Akça[1] · Akın Bodur[2] · Cemil Kahraman[3] · İsmail Abidin[4] · Selcen Aydın-Abidin[4] · Ahmet Alver[5]

Received: 7 July 2021 / Accepted: 9 March 2022 / Published online: 17 March 2022

Abstract

Purpose The role of BDNF in adipose tissue metabolism is poorly understood. We investigated the effects of decreased levels of BDNF on the expression of major adipokines in different fat depots (e.g., subcutaneous and epididymal) of mouse groups fed three different diet protocols.

Methods BDNF heterozygous (+/−) mice were used to evaluate the effect of reduced BDNF levels. Six groups of C57BL/6 J breed wild type (WT) and BDNF (+/−) mice were formed. These groups were fed, respectively, a control diet (CD), a high-fat diet (HFD), and a high-sucrose diet (HSD) for 4 months. Serum samples and adipose tissues were used for biochemical assays. The serum concentrations and tissue expression levels of leptin, adiponectin, and resistin were measured.

Results Compared to the CD-fed WT group (control group), serum leptin and leptin expression levels were found to be higher in all experimental groups. Serum adiponectin levels were lower in the BDNF (+/−) groups and HFD-fed WT group than in the control group. Epididymal adiponectin expression was found to be lower in the HFD-fed BDNF (+/−) group and higher in HSD-fed groups than in the control group. Compared to the control group, adiponectin expression increased in the WT groups in subcutaneous adipose tissue. Serum resistin levels were elevated in the HFD-fed groups. Resistin expression in epididymal adipose tissue was lower in the CD-fed and HFD-fed groups than in the control group.

Conclusions BDNF levels and diet differentially affect the expression of adipokines in different fat tissues in the body. BDNF may play a protective role in obesity and diabetes.

Keywords Brain-derived neurotrophic factor (BDNF) · Epididymal adipose tissue · High-sucrose diet · High-fat diet · Subcutaneous adipose tissue

Abbreviations

BDNF	Brain-derived neurotrophic factor
WT	Wild type
CD	Control diet
HFD	High-fat diet
HSD	High-sucrose diet
ICV	Intracerebroventricular

Introduction

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays an important role in the morphological and physiological development of the central nervous system. BDNF regulates crucial neuronal functions such as differentiation, survival, and synaptic plasticity via binding to its physiological receptor, TrkB [1]. Apart from its neuronal effects, BDNF has central and peripheral roles in the regulation of food intake, energy expenditure, and the control of glucose metabolism [2–4]. Intracerebroventricular (ICV) BDNF administration to experimental animals causes suppression of food intake and weight loss [5], while hyperphagia, obesity, and diabetes are observed in animals with low BDNF expression [6]. Other symptoms of the metabolic syndrome

✉ İmran İnce Akça
narmince@hotmail.com

1 Department of Medical Biochemistry, Faculty of Medicine, Tokat Gaziosmanpasa University, 60100 Tokat, Turkey

2 Department of Nutrition and Dietetics, Faculty of Health Sciences, Rumeli University, İstanbul, Turkey

3 Department of Nutrition and Dietetics, Faculty of Health Sciences, Düzce University, Düzce, Turkey

4 Department of Biophysics, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

5 Department of Medical Biochemistry, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

including leptin and insulin resistance, dyslipidemia, and hyperglycemia develop in BDNF (+/−) mice [7].

Adipose tissue is crucial in the regulation of metabolism and stores the excess energy as triglycerides and, if necessary, catabolizes triglycerides to fatty acids and glycerol. Adipose tissue also secretes adipokines which have various biological functions in inflammation, immunity, reproduction, angiogenesis, fibrinolysis, regulating appetite, coagulation, and insulin sensitivity [8]. Depending on their anatomical location and physiological, cellular, and molecular features, white adipose tissue is divided into two sub-types, subcutaneous and visceral. Each anatomical depot differs in terms of metabolic and secretory profiles. They also have different physiological roles [9].

The alteration of lipid metabolism and the secretion of adipokines in adipose tissue is critical for the development of such diseases as obesity, hyperlipidemia, diabetes, and atherosclerosis [10]. Obesity and related metabolic disorders have for years been closely associated with the Western-style diet, which includes excessive intake of high-fat and high-sucrose foods [11, 12].

In experimental models of obesity, a high-fat diet inducing obesity proved to be a model that mimicks obesity in humans more reliably than genetically engineered obesity models [13, 14]. A long-term, high-fat diet, which in the above model is frequently used to induce experimental obesity, increases circulating insulin, leptin, glucose, and triglyceride levels and leads to symptoms similar to those observed in human obesity such as insulin resistance, hepatic adiposity, visceral fat accumulation, and hyperglycemia. Obesity has thus been demonstrated to increase the risk for insulin resistance, diabetes, atherosclerosis, dyslipidemia, cardiovascular diseases, chronic kidney disease, hypertension, cancer, reproductive disorders, respiratory disorders, inflammatory diseases, joint diseases, metabolic syndrome, vascular diseases, and osteoarthritis [15–17].

Adipose tissue is an energy source, but it is in addition, an active organ with the ability to secrete cytokines and adipose tissue-derived peptides. It is therefore evident that the presence and effects of novel metabolic markers could beneficially be investigated in fat tissue. As they play important roles in regulating many metabolic pathways, adipokines synthesized from adipose tissue are promising target molecules for the future treatment of obesity and obesity-related diseases that arise with the increase of fat mass. Although BDNF and its receptor are synthesized in adipose tissue, the role of this signaling pathway has to date been poorly investigated. Hence, in this study, to test our hypothesis that BDNF may be involved in the metabolism of adipose tissue, the largest endocrine organ, and to investigate the physiological role of BDNF, we used BDNF (+/−) mice that lack one of the BDNF coding alleles and express less BDNF than wild type littermates. In order to mimic dietary pathological conditions and induce metabolic alterations, we fed experimental groups normal, high-fat, and high-sucrose diets. Changes in expression of the main adipokines (leptin, adiponectin, and resistin) with major metabolic effects were determined in different fat depots (subcutaneous and epididymal).

Materials and methods

Animals and experimental procedures

The study was approved by the Animal Experiments Local Ethics Committee of Karadeniz Technical University and animals were obtained from Karadeniz Technical University Surgical Research and Application Center (CAM), Trabzon, Turkey. All animal experiments were carried out in accordance with the European Communities Council Directive of 24 November, 1986 (86/609/EEC) for experimental animal care. A total of 48 wild type (WT) and BDNF (+/−) male mice of the C57BL/6 J breed were used. At the beginning of the diet protocol, the mice were 6 weeks old and weighed 13–15 g. The transgenic mouse model, first established by Korte et al. [18], is characterized by lacking one of the BDNF coding alleles.

Six experimental groups were formed from the genotyped mice. The mice were individually placed in a specially ventilated caging system (RAIR IsoSystem, Delawera, USA). Each group consisted of 8 mice. Specifically, the mice were fed a HFD (D12492), HSD (D12450B), and CD (D12550J). Two groups (WT and BDNF (+/−)) were fed a control diet, the two groups (WT and BDNF (+/−)) were fed a high-fat diet, and the other two groups (WT and BDNF (+/−)) were fed a high-sucrose diet. The diets were purchased from the Research Diet (Research Diets Inc, New Brunswick, NJ, USA): the composition of the experimental diets were presented in Supplementary Table 1. The CD-fed BDNF WT group was evaluated as the control group. The animals were given ad libitum access to food and water. The experimental period lasted 16 weeks. Following the diet period, all mice were decapitated. Serum samples were separated and stored at − 80 °C in a deep freezer. Total RNA isolation was performed in tissue specimens taken from subcutaneous and epididymal adipose tissues. Total RNAs were immediately converted to cDNA.

Assays

Fasting glucose and triglyceride parameters in serum were measured using commercial kits in the AU 5800 Beckman Coulter auto-analyzer. Levels of insulin (Crystal Chem Inc. 16MAUM1388), BDNF (Abnova, 381238504), leptin (R&D Systems, 338346), adiponectin (R&D Systems, 340850), and

resistin (R&D Systems, 336359) in serum samples were determined byusing enzyme-linked immunosorbent assay (ELISA) kits as recommended by the manufacturer.

Total RNA isolation from epididymal and subcutaneous adipose tissues

RNA isolation in subcutaneous and epididymal adipose tissues was performed by combining Roche Tripure Isolation Reagent (Cat No:11 667 165 001) and SIGMA Mammalian Total RNA Miniprep Kit (lot: SLBM3520V) [19].

The Nanodrop ND-2000 device was used to measure the concentrations and purity of the obtained total RNAs for quality check and quantitation. The Roche Transcriptor First Strand cDNA Synthesis Kit (Cat No: 04 896 866 001, lot: 10842322) was used for cDNA synthesis.

Quantitative real-time PCR

Real-time ready catalog assays, which are short FAM-labeled hydrolysis probes containing locked nucleic acid, were used to quanitfy RT-PCR reactions. Expression levels of beta actin, leptin, adiponectin, and resistin were determined using relative quantitative RT-PCR with a Light Cycler 480 II system (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions. The primers used in the study for beta actin, leptin, adiponectin, and resistin are shown in Supplementary Table 2. To quantitate the results obtained by RT-PCR, the $2^{-\Delta\Delta Cp}$ method was used.

Statistical analysis

The test results were analyzed on SPSS (Statistical Package for the Social and Sciences) version 23.0 statistical software. The Mann–Whitney U-test was performed to test the significance of pairwase differences using Bonferroni correction to adjust for multiple comparision. Analysis results were expressed as median and interquartile range (MED-IQR). An overall p-value of less than 0.05 was considered to show a statistically significant result.

Results

Body weight

The changes in the average weights of the groups were monitored during the 4-months feeding period. At the end of the feeding period, the final weights of the CD-fed BDNF (+/−), HFD-fed WT and BDNF (+/−), HSD-fed WT and BDNF (+/−) groups were significantly higher than those of control group ($p < 0.001$) (Table 1).

Serum metabolic measurements

Table 1 depicts the median-IQR of fasting glucose, triglyceride, insulin, HOMA-IR results, and leptin/adiponectin ratio in serum and body weights of groups before and after the feeding period.

Fasting glucose values were higher in the heterozygous groups (CD-fed BDNF (+/−), HFD-fed BDNF(+/−), HSD-fed BDNF(+/−)) than those in the control group ($p = 0.005$, $p = 0.001$, and $p = 0.022$, respectively). Serum triglycerides were significantly increased in the HFD-fed groups ($p = 0.004$). Serum insulin levels were higher in the CD-fed BDNF(+/−), HFD-fed WT, HFD-fed BDNF(+/−), HSD-fed WT and HSD-fed BDNF(+/−) groups ($p = 0.001$, $p = 0.009$, $p = 0.001$, $p = 0.002$, and $p < 0.001$, respectively). HOMA-IR values were higher in the heterozygous groups and the HFD-fed WT group than in the control group ($p = 0.011$, $p = 0.001$, $p = 0.001$, and $p < 0.001$, respectively) (Table 1).

Table 1 Body weights, glucose, triglyceride, insulin levels, HOMA-IR scores, and leptin/adiponectin ratio of experimental groups

Diet type	Control diet		High-fat diet		High-sucrose diet	
Genotype	Wild type	BDNF (+/−)	Wild type	BDNF (+/−)	Wild type	BDNF(+/−)
Initial body weight (g)	15.9 (1.75)	16.6 (3.1)	17.5 (1.1)	16.0 (2.3)	16.5 (2.2)	16.6 (2.1)
Final body weight (g)	25.7 (2.28)	32.8 (7.7)[a]	34.3 (7.9)[a]	49.4 (7.7)[a,b]	28.0 (2.7)[a]	33.1 (2.4)[a,c]
Glucose (mg/dL)	130.0 (77.5)	170 (45.0)[a]	160.0 (40.0)	235.0 (87.5)[a,b]	155.0 (62.5)	210.0 (60.0)[a,c]
Triglyceride (mg/dL)	90.0 (17.5)	95.0 (27.5)	110.0 (30.0)[a]	111.8 (27.5)[a]	80.0 (27.5)	80.8 (10.0)
Insulin (ng/mL)	3.8 (3.7)	6.3 (8.8)[a]	6.3 (11.9)[a]	45.4 (18.3)[a,b]	5.6 (7.9)[a]	18.4 (8.1)[a,c]
HOMA-IR	53.9 (45.2)	79.9 (63.6)[a]	166.8 (65.0)[a]	253.5 (424.7)[a]	34.1 (46.0)	153.5 (230.0)[a,c]
Leptin/adiponectin	0.84 (0.7)	3.2 (2.8)[a]	4.3 (2.9)[a]	13.2 (4.8)[a,b,c]	1.3 (1.1)[b]	3.8 (2.6)[a,d]

*HOMA-IR = [insulin (μU/mL) × fasting glucose (mmol/L)] / 22.5[20]

[a]significantly different from the control group. [b]values differ significantly from the HFD-fed WT group. [c]values differ significantly from the HSD-fed WT group. [d]significantly different from the HSD-fed WT group. A nonparametric test was used (Mann–Whitney U-test). A p-value of < 0.05 was considered significant. Values are median (IQR)

Circulating BDNF concentrations

Compared to the CD-fed WT group (131.7–30.6 pg/mL), the BDNF values of the CD-fed BDNF (+/−) group (93.8–49.8 pg/mL, $p=0.002$), HFD-fed BDNF (+/−) group (98.3–24.4 pg/mL, $p=0.001$), and HSD-fed BDNF (+/−) group (94.7–30.4 pg/mL, $p=0.001$) were lower (Supplementary Fig. 1).

Circulating leptin, adiponectin, and resistin concentrations and gene expression levels

Compared to the CD-WT group (5.9–5.8 ng/mL) leptin values of the CD-fed BDNF (+/−) (25.1–15.9 ng/mL), HFD-fed WT (28.6–19.5 ng/mL), HFD-fed BDNF (+/−) (68.2–38.4 ng/mL), HSD-fed WT (9.7–5.8 ng/mL), and HSD-fed BDNF (+/−) (23.6–12.2 ng/mL) groups were higher ($p<0.001$, Fig. 1A). Leptin expression of epididymal adipose tissue was higher in the CD-fed BDNF (+/−) (5.0–8.7, $p=0.005$), HFD-fed WT (7.0–4.3, $p<0.001$), HFD-fed BDNF (+/−) (5.4–4.0, $p<0.001$), HSD-fed WT (3.0–2.1, $p<0.001$), and HSD-fed BDNF (+/−) (6.4–9.3, $p<0.001$) groups than in the control group (1.0–0). Leptin expression levels in subcutaneous adipose tissue were significantly higher in the CD-fed BDNF (+/−) (8.7–12.8, $p<0.001$), HFD-fed WT (15.8–13.9, $p<0.001$), HFD-fed BDNF (+/−) (21.7–20.9, $p<0.001$), HSD-fed WT (3.4–4.9, $p=0.002$), and HSD-fed BDNF (+/−) (7.2–9.3, $p<0.001$) groups compared to those of the control group (1.0–0) (Fig. 1B).

Compared to serum adiponectin values of the control group (7.0–1.7 µg/mL), CD-fed BDNF (+/−) (6.1–1.3 µg/mL, $p=0.042$), HFD-fed WT (6.1–1.1 µg/mL, $p=0.04$), HFD-fed BDNF (+/−) (5.6–0.4 µg/mL, $p=0.001$), and HSD-fed BDNF (+/−) (5.8–0.8 µg/mL, $p=0.008$) groups were lower (Fig. 2A). Adiponectin expression of epididymal adipose tissue was lower in the HFD-fed BDNF (+/−) (0.33–0.4, $p<0.001$) group, higher in the HSD-fed WT (1.5–0.7, $p=0.012$), and HSD-fed BDNF (+/−) (1.5–1.2, $p<0.001$) groups than in the control group (1.0–0). Adiponectin expression of subcutaneous adipose tissue was higher in the HSD-fed WT (1.4–0.5, $p<0.001$), and

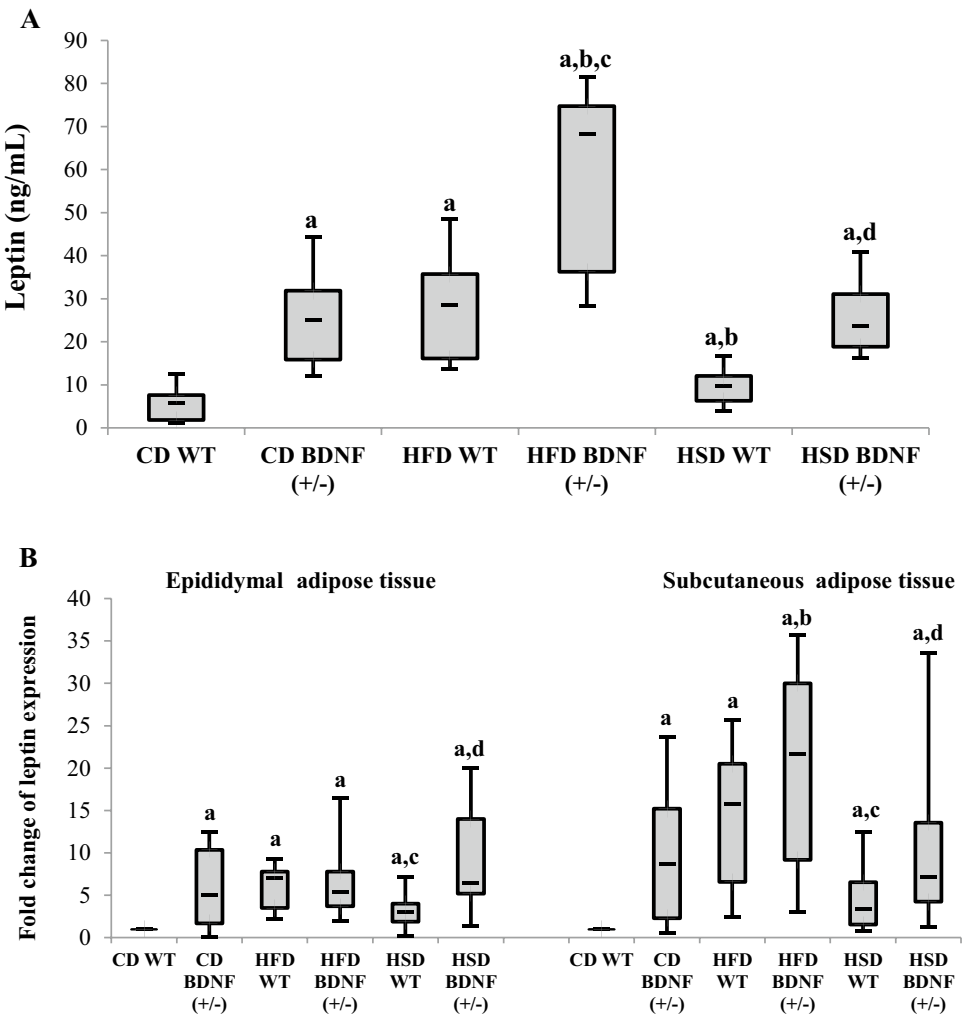

Fig. 1 **A** Leptin levels in serum samples. (a) significantly different from the control group (CD-fed WT group). (b) significantly different from the CD-fed BDNF (+/−) group ($p<0.001$). (c) significantly different from the HFD-fed WT group ($p=0.001$). (d) significantly different from the HSD WT group ($p<0.001$). **B** Leptin expression of epididimal and subcutaneous adipose tissues. (a) significantly different from the control group ($p<0.001$). (b) significantly different from the CD-fed BDNF (+/−) group ($p=0.01$). (c) significantly different from the HFD-fed WT group ($p=0.004$, $p=0.001$, respectively). (d) significantly different from the HSD-fed WT group ($p=0.001$, $p=0.013$, respectively). Statistical analysis between groups was evaluated using the Mann–Whitney U-test. p value of <0.05 was considered significant

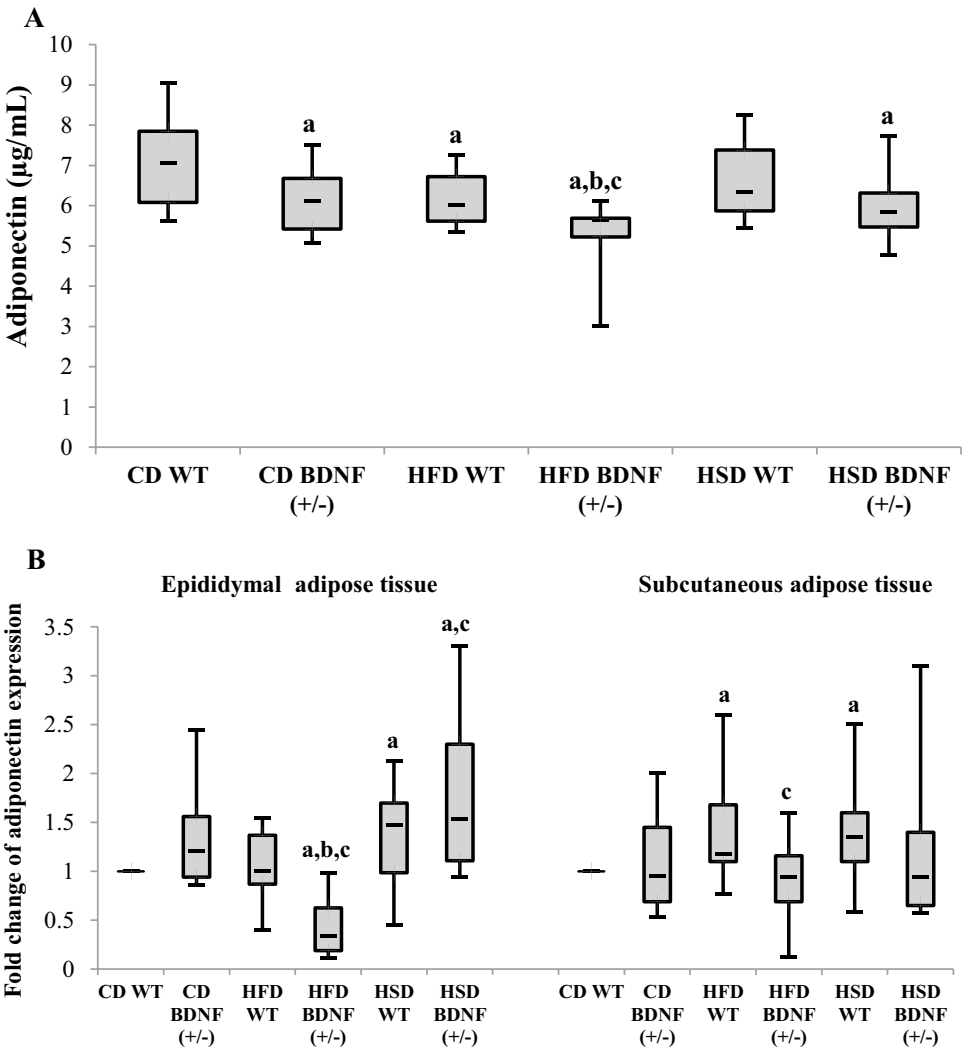

Fig. 2 **A** Adiponectin levels in serum samples. (a) significantly different from the control group. (b) significantly different from the CD-fed BDNF (+/−) group ($p=0.043$). (c) significantly different from the HFD-fed WT group ($p=0.045$). **B** Adiponectin expression of epididimal and subcutaneous adipose tissues. (a) significantly different from the control group. (b) significantly different from the CD-fed BDNF (+/−) group ($p<0.001$,). (c) significantly different from the HFD-fed WT group ($p<0.001$, $p=0.005$, $p=0.013$, respectively). Statistical analysis between groups was evaluated using the Mann–Whitney U-test. p value of <0.05 was considered significant

HFD-fed WT (1.2–0.6, $p=0.001$) groups than in the control group (1.0–0) (Fig. 2B).

The leptin/adiponectin ratio was higher in the CD-fed BDNF (+/−) (3.2–2.8), HFD-fed WT (4.3–2.9), HFD-fed BDNF (+/−) (13.2–4.8), and HSD-fed BDNF (+/−) (3.8–2.6) groups than in the control group (0.85–0.7) ($p=0.001$) (Table 1).

Resistin levels of HFD-fed WT (17.5–3.8 ng/mL, $p=0.042$), and HFD-fed BDNF (+/−) (17.2–7.3 ng/mL, $p=0.023$) groups were significantly higher compared to those of the control group (14.0–3.7 ng/mL) (Fig. 3A). Resistin expression of the epididymal adipose tissue was significantly lower in the CD-fed BDNF (+/−) (0.8–0.4, $p=0.005$), HFD-fed WT (0.7–0.6, $p=0.001$), and HFD-fed BDNF (+/−) (0.09–0.2, $p<0.001$) groups than in the control group (1.0–0). Resistin expression of subcutaneous adipose tissue was significantly lower in HFD-fed (+/−) (0.7–0.8, $p=0.034$) group than in the control group (1.0–0) (Fig. 3B).

Discussion

BDNF has critical roles in energy metabolism and feeding behavior. While its roles in the central nervous system are well-defined, the regulatory roles of BDNF in peripheral tissues (adipose tissue metabolism) are as yet poorly understood. This study was designed to demonstrate the effects of decreased BDNF concentration on adipose tissue function with different types of diets. Following a control, high-fat and high-sucrose diet protocol, the major adipokines and metabolic markers were measured in WT and BDNF heterozygous mice. Based on the findings of the present study, we can suggest that BDNF may have a protective effect against the serious health consequences of obesity and diabetes, the action of BDNF being associated with adipokine synthesis in adipose tissue.

Serum leptin levels of all the experimental groups were higher compared to those of the control group (Fig. 1A). Leptin plays key roles in nutrient intake, energy expenditure,

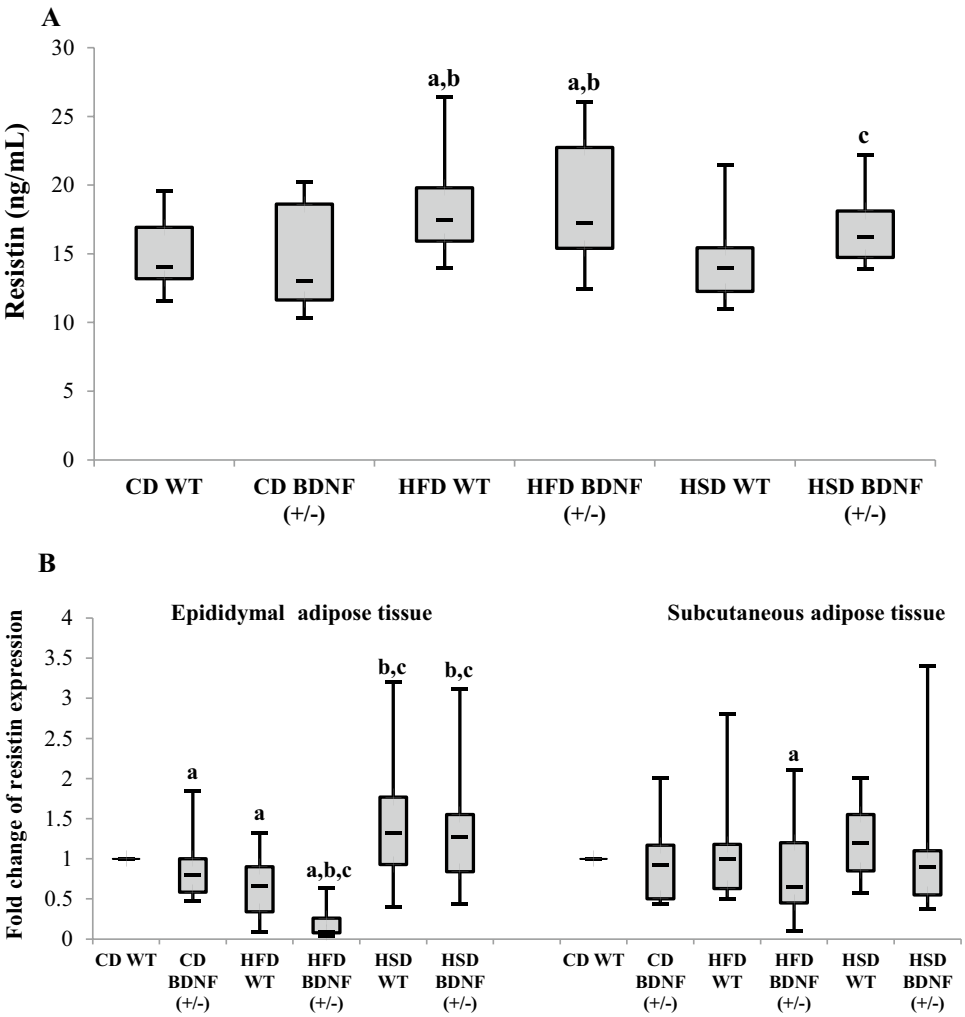

Fig. 3 **A** Resistin levels in serum samples. (a) significantly different from the control group. (b) significantly different from the CD-fed BDNF (+/−) group ($p=0.025$, $p=0.019$, respectively). (c) significantly different from the HSD-fed WT group ($p=0.01$). **B** Resistin expression of epididimal and subcutaneous adipose tissues. (a) significantly different from the control group. (b) significantly different from the CD-fed BDNF (+/−) group ($p<0.001$, $p=0.016$, $p=0.02$, respectively). (c) significantly different from the HFD-fed WT group ($p<0.001$, $p=0.002$, $p=0.002$, respectively). Statistical analysis between groups was evaluated using the Mann–Whitney U-test. p value of <0.05 was considered significant

and regulation of growth. Notably, while leptin levels are decreased in fasting, they are increased with food intake and in obesity. In a study in which Sprague-Dawley rats were fed either a standard laboratory chow diet (3% fat) or a HFD (60% fat) for 2 or 5 weeks, plasma leptin levels were significantly increased in rats fed the HFD compared with those of the chow-fed animals [21]. Kernie et al. [22] found that serum leptin levels were significantly higher in the BDNF heterozygous mice than in the WT mice. Parallel to this study, another observed a 15-fold increase in serum leptin levels was found in mutant mice, which was induced by deletion of BDNF in the postnatal brain [23]. Consistent with serum leptin levels, the leptin expression was found to be increased in epididymal and subcutaneous adipose tissues (Fig. 1B). Leptin enhances BDNF synthesis in some regions of the hypothalamus [24]. While leptin enhances hypothalamic BDNF, it reduces the production of leptin in adipocytes via the sympathetic-beta adrenergic signaling of BDNF and the hypothalamic–pituitary–adrenal axis (HPA) [25]. Wang et al. demonstrated that leptin increased sympathetic innervation in adipose tissues (iWAT and BAT) through an increase in BDNF synthesis in the paraventricular nucleus in the hypothalamus [26]. An enriched environment known to increase BDNF hypothalamic expression results in the suppression of leptin expression and oscillation by leading to activation of sympathetic innervation of white adipose tissue, which then suppresses the expression and secretion of leptin via β-adrenergic receptors. Consistent with leptin changes observed in serum, leptin expression of mice living in an enriched environment decreases by about 50% in white adipose tissue [27]. Thus, decreased BDNF values in BDNF heterozygous mice are likely to lead to an increase of leptin synthesis in adipose tissues.

Adiponectin, an adipokine that increases fatty acid oxidation and insulin sensitivity, has anti-atherogenic and anti-inflammatory properties. It increases the beta oxidation of free fatty acids in the skeletal muscle and enhances the inhibition of hepatic gluconeogenesis by insulin [28]. Adiponectin serum concentrations are an important indicator of glucose tolerance and metabolic homeostasis [29]. In our study, the heterozygous groups and HFD-fed WT displayed a significant decrease in serum adiponectin levels

compared to the control group (Fig. 2A). A similar tendency was observed in epididymal adipose tissue expression, the decrease reaching significant levels only in HFD-fed BDNF (+/−) mice. Adiponectin expression was increased in subcutaneous adipose tissue of the WT groups and in epididymal adipose tissue of the HSD-fed groups (Fig. 2B).

Mazzoli et al. showed that a Western diet led to reduction of adiponectin in epididymal adipose tissue, the hippocampus, and the frontal cortex. In addition, when BDNF levels were measured in the hippocampus and frontal cortex, a significant decrease was observed depending on the diet [12]. In a study investigating the efficacy of BDNF for diabetes and obesity, BDNF gene transfer was shown to significantly increase the expression of adiponectin, which exerts a potent insulin-sentizing effect [30]. Decreasing levels of BDNF in heterozygous mice may be the main cause of this decrease in adiponectin levels. In addition, adiponectin expression is inhibited by such factors as proinflammatory cytokines, hypoxia, and oxidative stress increase due to weight gain [31, 32]. In our study, in the HSD-fed groups, the adiponectin expression-serum discrepancy may have arisen due to post-transcriptional modifications.

Leptin and adiponectin have adverse effects on inflammation and insulin resistance. Leptin stimulates insulin resistance as well as proinflammatory cytokines related to type 2 diabetes, such as tumor necrosis factor-α and interleukin-6. On the other hand, adiponectin has anti-inflammatory properties and suppresses the expression and secretion of a number of proinflammatory immune regulators. The leptin/adiponectin ratio is strongly associated with insulin resistance and inflammation [33, 34]. In our study, the leptin/adiponectin ratio was significantly increased in the heterozygous groups and HFD-fed WT group compared to the control group (Table 1). The higher levels of leptin/adiponectin in the HFD-fed BDNF (+/−) group may be an indicator of increased inflammation and this may be the reason for the observed low adiponectin levels.

Serum resistin levels were found to be significantly higher in the HFD-fed groups than in the control group (Fig. 3A). In general, in rodents, high resistin levels are associated with glucose intolerance, decreased insulin sensitivity, hyperglycemia, increased free fatty acids, obesity, and diabetes, whereas in humans, high resistin levels are associated with atherosclerosis and cardiometabolic disease [35]. There are some studies demonstrating that a HFD increases the levels of resistin in circulation in various animal models [36, 37]. Regarding the BDNF effect, no change in serum resistin levels of the HSD-fed WT and the CD-fed and HSD-fed BDNF (+/−) groups were observed, while serum resistin levels of HFD-fed WT and BDNF (+/−) mice were found to be very similar. These results indicate that serum resistin levels were affected by diet rather than by BDNF deficiency. In epididymal adipose tissue, expression levels of resistin, which has a higher synthesis in visceral adipose tissue, decreased significantly in the HFD-fed and CD-fed BDNF(+/−) groups compared to the control group (Fig. 3B).

In this study, an inverse relationship was found between levels of resistin in circulation and expression of resistin in adipose tissue. The correlation between resistin gene expression in adipose tissue with BMI or insulin resistance biomarkers has not yet been elucidated. In many studies, while circulating levels of resistin increased with lipoidosis in genetic and diet-induced obese mouse models, mRNA levels have been found to be suppressed in adipose tissue [38, 39]. Similarly to the results of our study, mRNA expression of resistin in the epididymal adipose tissue of C57BL/6 J mice fed diets with different amounts of fat (i.e., low-fat 10% and high-fat 45%) was suppressed as the fat ratio increased, while serum resistin levels were significantly increased [40]. Furthermore, resistin mRNA levels were decreased by the addition of insulin to 3T3-L1 cells [41]. In the present study, it is likely that increasing insulin levels also contributed to decreasing resistin expression. These factors may suppress resistin expression after reaching a certain level. Therefore, resistin expression of HSD-fed groups may be high.

Conclusion

The results of this study showed that diet is able to differentially regulate the expression of adipokines in fat tissues depending on the location of adipose tissue in the body. Furthermore, their synthesis and secretion may be related to BDNF concentration. BDNF deficiency may be associated with various metabolic diseases, especially diabetes and obesity. Our data also suggest that BDNF may have a protective role against pathological symptoms associated with obesity via mechanisms involving the synthesis of adipokines.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s42000-022-00364-z.

Author contribution The authors' responsibilities were as follows: AA, İA, and CK designed the research; İİA and AB conducted research; SAA, İİA, and AB analyzed the data and performed statistical analysis; İİA, AA, and İA wrote the paper; AA, İİA, and AB provided essential reagents; İİA and AA had primary responsibility for the final content: and all authors read and approved the final manuscript.

Funding This work was supported by The Scientific and Technological Research Council of Turkey (TÜBİTAK) [Grant No. 114S553].

Declarations

Ethics approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. Ethics

committee approval was received for this study from the Karadeniz Technical University Animal Care And Ethics Commitee, 2013/6.

Consent to participate Not applicable.

Conflict of interest The authors declare no competing interests.

References

1. Cordeira J, Rios M (2011) Weighing in the role of BDNF in the central control of eating behavior. Mol Neurobiol 44:441–448
2. Marosi K, Mattson MP (2014) BDNF mediates adaptive brain and body responses to energetic challenges. Trends Endocrinol Metab 25(2):89–98
3. Gray J, Yeo GS, Cox JJ et al (2006) Hyperphagia, severe obesity, impaired cognitive function, and hyperactivity associated with functional loss of one copy of the brain-derived neurotrophic factor (BDNF) gene. Diabetes 55(12):3366–3371
4. Abidin I, Aydin-Abidin S, Bodur A, Ince I, Alver A (2018) Brain-derived neurotropic factor (BDNF) heterozygous mice are more susceptible to synaptic protein loss in cerebral cortex during high fat diet. Arch Physiol Biochem 124(5):442–447
5. Rosas-Vargas H, Martinez-Ezquerro JD, Bienvenu T (2011) Brain-derived neurotrophic factor, food ıntake regulation, and obesity. Arch Med Res 42:482–494
6. Bodur A, İnce İ, Kahraman C, Abidin İ, Aydin-Abidin S, Alver A (2019) Effect of a high sucrose and high fat diet in BDNF (+/−) mice on oxidative stress markers in adipose tissues. Arch Biochem Biophys 665:46–56
7. Bengi V, Riva MA, Cattaneo A (2016) Cellular and molecular mechanisms of the brain-derived neurotrophic factor in physiological and pathological conditions. Clin Sci 131:123–138
8. Vázquez-Vela ME, Torres N, Tovar AR (2008) White adipose tissue as endocrine organ and its role in obesity. Arch Med Res 39(8):715–728
9. Kwok K, Lam KSL, Xu A (2016) Heterogeneity of white adipose tissue: molecular basis and clinical implications. Exp Mol Med 48 e215
10. Sumiyoshi M, Sakanaka M, Kimura Y (2006) Chronic intake of high-fat and high-hucrose diets differentially affects glucose ıntolerance in mice. J Nutr 136(3):582–587
11. Yang ZH, Miyahara H, Takeo J, Katayama M (2012) Diet high in fat and sucrose induces rapid onset of obesity-related metabolic syndrome partly through rapid response of genes involved in lipogenesis, insulin signalling and inflammation in mice. Diabetol Metab Syndr 4(1):32
12. Mazzoli A, Spagnuolo MS, Gatto C et al (2020) Adipose tissue and brain metabolic responses to western diet-is there a similarity between the two? Int J Mol Sci 21(3):786
13. Jequier E (2002) Pathways to obesity. Int J Obes 26:12–17
14. Hill JO, Melanson EL, Wyatt HT (2000) Dietary fat intake and regulation of energy balance: implications for obesity. J Nutr 130:284–288
15. Jung U, Choi MS (2014) Obesity and ıts metabolic complications: the role of adipokines and the relationship between obesity, ınflammation, ınsulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci 15:6184–6223
16. Wozniak SE, Gee LL, Wachtel MS, Frezza EE (2009) Adipose tissue: the new endocrine organ? A review article. Dig Dis Sci 54:1847–1856
17. Sethi JK, Vidal-Puig AJ (2007) Adipose tissue function and plasticity orchestrate nutritional adaptation. J Lipid Res 48:1253–1262
18. Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T (1995) Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc Natl Acad Sci USA 92:8856–8860
19. Yang K (2008) Adipose tissue protocols, 2nd edn. New Jersey, Humana Press
20. Garg MK, Dutta MK, Mahalle N (2011) Study of beta-cell function (by HOMA model) in metabolic syndrome. Indian J Endocrinol Metab 15:44–49
21. Fam BC, Morris MJ, Hansen MJ, Andrikopoulos S, Proietto J, Thorburn AW (2007) Modulation of central leptin sensitivity and energy balance in a rat model of diet-induced obesity. Diabetes Obes Metab 9:840–852
22. Kernie SG, Liebl DJ, Parada LF (2000) BDNF regulates eating behavior and locomotor activity in mice. Embo J 19:1290–1300
23. Rios M, Fan G, Fekete C et al (2001) Conditional deletion of brain-derived neurotrophic factor in the postnatal brain leads to obesity and hyperactivity. Mol Endocrinol 15:1748–1757
24. Nonomura T, Tsuchida A, Ono-Kishino M, Nakagawa T, Taiji M, Noguchi H (2001) Brain-derived neurotrophic factor regulates energy expenditure through the central nervous system in obese diabetic mice. Int J Exp Diabetes Res 2:201–209
25. Noble EE, Billington CJ, Kotz CM, Wang CF (2011) The lighter side of BDNF. Am J Physiol Regul Integr Comp Physiol 300:R1053–R1069
26. Wang P, Loh KH, Wu M et al (2020) A leptin-BDNF pathway regulating sympathetic innervation of adipose tissue. Nature 583(7818):839–844
27. Cao L, Liu X, Lin D et al (2010) Environmental and genetic activation of a brain-adipocyte BDNF/leptin axis causes cancer remission and inhibition. Cell 142(1):52–64
28. Yamauchi T, Kamon J, Waki H et al (2001) The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 7(8):941–946
29. Altomonte J, Harbaran S, Richter A, Dong H (2003) Fat depot-specific expression of adiponectin is impaired in Zucker fatty rats. Metabolism 52:958–963
30. Cao L, Lin EJ, Cahill MC, Wang C, Liu X (2009) During MJ (2009) Molecular therapy of obesity and diabetes by a physiological autoregulatory approach. Nat Med 15(4):447–454
31. Ohashi K, Ouchi N, Matsuzawa Y (2012) Anti-inflammatory and antiatherogenic properties of adiponectin. Biochimie 94:2137–2142
32. Brunn JM, Lihn AS, Verdich C et al (2003) Regulation of adiponectin by adipose tissue derived cytokines: in vivo and in vitro investigations in human. Am J Physiol Endocrinol Metab 285:E527–E533
33. P, López–Jaramillo, D, Gómez-Arbeláez, J, López-López et al (2014) The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. Horm Mol Biol Clin Invest 18(1):37–45
34. Finucane FM, Luan J, Wareham NJ et al (2009) Correlation of the leptin: adiponectin ratio with measures of insulin resistance in non-diabetic individuals. Diabetologia 52(11):2345–2349
35. Kusminski CM, McTernan PG, Kumar S (2005) Role of resistin in obesity, insulin resistance and type II diabetes. Clin Sci (Lond) 109(3):243–256
36. Steppan CM, Bailey ST, Bhat S et al (2001) The hormone resistin links obesity to diabetes. Nature 18 409 6818 307 12
37. Kim D, Lee JE, Jung YJ et al (2013) Metformin decreases high-fat diet-induced renal injury by regulating the expression of adipokines and the renal AMP-activated protein kinase/acetyl-CoA carboxylase pathway in mice. Int J Mol Med 32(6):1293–1302

38. Way JM, Gorgun CZ, Tong Q et al (2001) Adipose tissue resistin expression is severely suppressed in obesity and stimulated by peroxisome proliferator-activated receptor gamma agonists. J Biol Chem 276:25651–25653
39. Rajala MW, Lin Y, Ranalletta M et al (2002) Cell type-specific expression and coregulation of murine resistin and resistin-like molecule-alpha in adipose tissue. Mol Endocrinol 16:1920–1930
40. Le-Lay S, Boucher J, Rey A (2001) Decreased resistin expression in mice with different sensitivities to a high-fat diet. Biochem Biophys Res Commun 289:564–567
41. Haugen F, Örgensen AJ, Drevon CA, Trayhurn P (2001) Inhibition by insulin of resistin gene expression in 3T3-L1 adipocytes. FEBS Lett 507:105–108