Brain derived neurotrophic factor (BDNF) in cardiometabolic physiology and diseases

Kardiyometabolik fizyoloji ve hastalıklarda beyinden türemiş nörotrofik faktör (BDNF)

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ABSTRACT

Important advances in our understanding of the relationships between adipose tissue derived peptides, namely adipokines, and their effects on cardiovascular functions have been achieved in recent years. Growing knowledge of adipokine biology is revealing the complexity of these proteins. Adipose tissue releases some other proteins called neurotrophins that are mainly active in central and peripheral nervous system. However, secretion and activity of these hormones are not only limited to neuronal cells and tissues, but they also take part in adipose tissue development, energy metabolism, glucose utilization, insulin sensitivity, inflammation, lipoprotein synthesis, and atherosclerosis. In this review, we describe the most recent advances in the functions of brain derived nerve growth factor (BDNF), a major type of neurotrophins, focusing primarily on cardiovascular and metabolic diseases. *(Anadolu Kardiyol Derg 2012; 12: 684-8)*

Key words: Brain derived nerve growth factor, cardiovascular disease, atherosclerosis, dyslipidemia, diabetes mellitus

ÖZET

Son yıllarda, adipokinler olarak bilinen adipoz doku kaynaklı peptidler ve bunların kardiyovasküler fonksiyonlar üzerine etkileri üzerine önemli ilerlemeler sağlanmıştır. Adipokin biyolojisi hakkında bilgiler çoğaldıkça bu proteinlerin karmaşık görünümü aydınlatılmaktadır. Adipoz doku nörotrofinler olarak bilinen ve temel olarak santral ve periferal sinir sisteminde görev yapan diğer bazı proteinleri de salgılar. Bununla beraber, bu hormonların sekresyon ve aktivitesi sadece nöronal hücreler ve dokularla sınırlı olmayıp yağ dokusu gelişimi, enerji metabolizması, glikoz kullanımı, insülin duyarlılığı, enflamasyon, lipoprotein sentezi ve aterosklerozda da rol oynarlar. Bu derlemede majör bir nörotrofin olan beyinden türemiş nörotrofik faktör (BDNF) ile ilgili en son veriler, özellikle kardiyovasküler ve metabolik hastalıklar üzerinden irdelenmiştir.
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Anahtar kelimeler: Beyinden türemiş nörotrofik faktör, kardiyovasküler hastalık, ateroskleroz, dislipidemi, diyabetes mellitus

Introduction

It is well known that adipose tissue-derived peptide hormones participate in the regulation of energy metabolism in the central nervous system (1). However, during the last decade, strong evidence have been obtained that peptides and proteins, which mainly regulate central and peripheral neuronal activity and are present in the central nervous system at higher concentrations, play a significant role in the regulation of both metabolic functions and injury responses. Neurotrophins, namely nerve growth factor, brain derived nerve growth factor (BDNF), neurotrophin-3, neurotrophin-4 and neurotrophin-5, regulate development and differentiation of the nervous system starting from the prenatal period. However, secretion and activity of these substances are not only limited to central and peripheral nervous system, but they participate in various physiological and pathological processes such as development of adipose tissue, energy metabolism, glucose utilization, insulin sensitivity, inflammation, lipoprotein synthesis, and atherosclerosis.

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Atherosclerosis and adipose tissue-derived peptides

Atherosclerotic conditions are accompanied by dysregulations in the synthesis and secretion of adipokines such as adiponectin, leptin, inteleukin-6, plasminogen activator inhibitor-1, tumor necrosis factor (TNF), and resistin. As an example, blood level of the beneficial peptide adiponectin which is abundantly found in the circulation is adversely affected from the derangements in lipid (2) and glucose metabolism (3). Conversely, reduction of cholesterol in dyslipidemia (4) or correction of hyperglycemia in subjects with diabetes mellitus (DM) (5) results in increase in blood adiponectin concentration. Other adipose tissue-derived peptides such as leptin (6), apelin (7) and visfatin (8) were also reported to have some effects on the atheroclerotic diseases. Among these, synthesis and/or secretion of apelin is dysregulated in a number of conditions leading to atherosclerosis including hypertension (9), diabetes (3, 10), and hypercholesterolemia (2, 4). Since apelin receptor is expressed by a variety of cells that are involved in atherosclerotic processes, this novel peptide need to be searched thoroughly for its roles in the mechanism of cardiovascular diseases.

Neurotrophins and their metabolic effects

Nerve growth factors or neurotrophins are proteins that enhance the growth potentialities of sensory and sympathetic nerve cells. Under the definition of peptide hormones superfamily, they are defined as the intercellular messengers like adipokines (adiponectin, leptin, resistin), cytokines (chemokines, hematopoietic growth factors, hepatocyte growth factor, interferons, interleukines, lymphokines, monokines, osteopontin, transforming growth factor beta, TNF), endothelial growth factors, endothelins, fibroblast growth factor, quinines (bradykinin, kininogens, tachykinin) and platelet derived growth factor (see, http://www.ncbi.nlm.nih.gov/mesh?term=neurotrophins). Nevertheless, regardless of their presence in other sites, all peptides secreted by adipocytes are generally called adipokine or adipocytokine. The members of the "nerve growth factors" subfamily defined to date, referred as neurotrophins, are shown in Table 1 (11). These proteins are mainly involved in the neuronal growth and survival as well as signalling in the brain and in the peripheral nervous system. Whereas nerve growth factor was described first in the chronological order, BDNF is the best known member of the group regarding their functions in the non-neuronal events.

Neurotrophins show their effects through low-affinity p75 neurotrophin receptor (p75NTR) and high-affinity tyrosine kinase (Trk) receptors (TrkA, TrkB and TrkC), which belong to the TNF receptor superfamily (11). They are synthesized as proneurotrophins that can bind to p75NTR receptor, but not to Trk receptors. Once they become mature via proteolysis, neurotrophins can bind to both p75NTR and Trk receptors. Specifically, nerve growth factor binds to TrkA, BDNF to TrkB and neurotrophin-3 to TrkC. In some conditions, neurotrophin-3 may also activate TrkA and TrkB receptors with low affinity.

BDNF was first introduced about 20 years ago. Current research indicates that BDNF participates in the pathogenesis of many immune, inflammatory or metabolic events inside and outside the nervous system. Like other neurotrophins, BDNF and/or its receptor are synthesized in many non-neuronal tissues and cell types including developing heart (12), atherosclerotic vessels (13), macrophages (14), endothelial cells (12) and vascular smooth muscle cells (13), which could explain why this peptide is thought to be involved in the mechanism of atherosclerotic diseases.

Table 1. Neurotrophins

1.	Nerve Growth Factor
2.	Brain-Derived Neurotrophic Factor
3.	Neurotrophin-3
4.	Neurotrophin-4/5
5.	Neurotrophin-6
6.	Neurotrophin-7
7.	Ciliary Neurotrophic Factor
8.	Glia Maturation Factor
9.	Glial Cell Line-Derived Neurotrophic Factors
10.	Neuregulins (NRG-1, 2, 3 and 4)
11.	Pituitary Adenylate Cyclase-Activating Polypeptide

BDNF blood level and its associates

In healthy volunteers, mean plasma BDNF level was found 92.5 pg/mL (8.0-927.0 pg/mL) and closely correlated to its concentration in platelets where it's stored (15). Circulating but not the platelet level of BDNF correlated negatively with age, body mass index (BMI) and total cholesterol, whereas no difference with respect to gender was detected by the same investigators. In a study in which the subjects were screened for long years starting from a healthy period, circulating BDNF level was higher in women and it decreased with advancing age in both genders (16). Moreover, blood level of BDNF had a positive correlation with diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, adipose tissue mass, body mass index, diastolic blood pressure and triglyceride, showing some differences between men and women (16, 17). Importantly, women with low plasma BDNF had greater all-cause mortality risk than women with high plasma BDNF in a study conducted in old age individuals (18). However, blood BDNF level measurement was recently reported to be affected by a variety of technical and personal reasons, increasing with age and being higher in women (19).

Cardiac actions of BDNF

Considerable amount of research effort has been devoted to contribution of BDNF to the pathogenesis and/or recovery of major types of cardiac diseases in recent years (Fig. 1). In animal heart, BDNF expression was found to be upregulated after ischemia-reperfusion injury in the left ventricle (20), suggesting both neuronal and non-neuronal functions for neurotrophins in

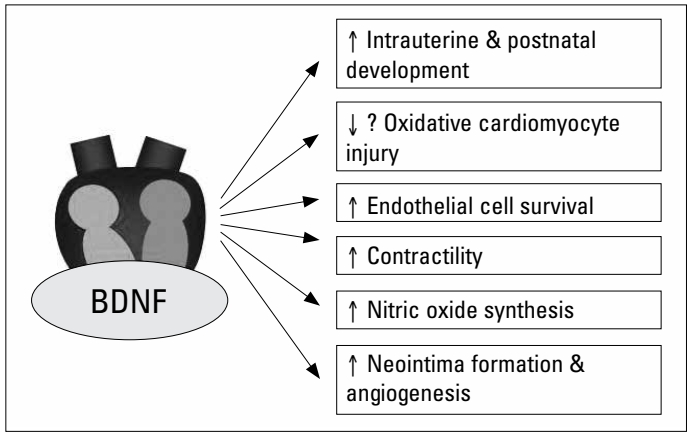

Figure 1. Cardiac actions of BDNF
BDNF - brain-derived neurotrophic factor

major types of vascular injury. Since administration of BDNF resulted in an increase in the myocardial injury and damage after artificial occlusion in the aging animal heart and this was linked to macrophage-derived inflammation (14), the action of BDNF might be thought deleterious in this case; however, it is also possible that BDNF upregulation can be a local and/or systemic response to injury, controlled by the nervous system. Because, in the ischemic myocardium, BDNF can improve angiogenesis and left ventricular function (21). Moreover, blood BDNF level was reported to decrease in subjects with acute coronary syndrome (22), while significantly greater BDNF levels were found in the coronary sinus blood samples in subjects with unstable angina compared to those with stable angina or healthy controls (13). A potential mechanism of this finding may be that BDNF is stored in the platelets and rapidly released locally as a response to damage or sheer stress (23). However, immunohistochemical investigations demonstrated marked BDNF expression in the atheromatous intima and adventitia, macrophages and smooth muscle cells in atherosclerotic coronary arteries in people with unstable angina pectoris (13). In the same study, stimulation with recombinant BDNF significantly enhanced oxidative stress in cultured human coronary artery smooth muscle cells, which was abolished by the inhibitor of NAD(P)H oxidase, suggesting that BDNF is involved in the mechanism of oxidant cardiomyocyte injury. In accordance with this, recently, increased coronary level of BDNF was linked to platelet activation and inflammatory response (24). Moreover, in a more recent investigation, plasma BDNF concentration was found inversely associated with the levels of triglyceride, LDL-cholesterol and fibrinogen, presence of DM, male sex and age, and positively with high-density lipoprotein cholesterol level and platelet count in people with angina pectoris (25). Interestingly, plasma BDNF level was detected as an independent predictor of 4-year coronary and all-cause mortality, indicating that low plasma BDNF may be associated with future coronary events and death in these patients. An inverse relationship between serum BDNF level and the status of cardiorespiratory fitness was also reported (17), suggesting serum BDNF may be associated with the effects of increased cardiorespiratory fitness on cardiovascular disease. Future studies are needed to elucidate the exact roles of BDNF and its receptor in cardiac homeostasis and injury.

BDNF and endothelial cells

BDNF was shown to prolong endothelial cell survival by stimulating Trk receptor (26). In accordance with this, animal studies showed that interaction between the endothelial cells as well as cardiac contractility could not be established in the absence of BDNF in the prenatal period, followed by early postnatal death (12). Moreover, in human pulmonary artery endothelial cells BDNF substantially increased nitric oxide levels by activating Akt and endothelial nitric oxide synthase, indicating that neurotrophins acutely modulate pulmonary endothelial nitric oxide production and contribute to relaxation of the pulmonary vasculature (27).

Involvement of BDNF in lipid and energy metabolism

BDNF also participates in lipid metabolism, energy metabolism and related disorders. Circulating BDNF was reported to correlate positively to LDL cholesterol, total cholesterol and triglyceride levels in humans (16, 17). In animal experiments, BDNF treatment reported to lower blood glucose, non-esterified free fatty acid, total cholesterol and phospholipid levels significantly in diabetic models, along with liver weight, liver triglyceride contents and fatty liver in histological examinations (28). Furthermore, administration of simvastatin elevated the expression of BDNF in the brain and accelerated the neuronal and functional recovery (29). However, the effects of statins on circulating level of BDNF in humans are unknown. Feeding with high fat chow of lab animals lacking hepatic BDNF indicated that BDNF might facilitate the emergence of insulin resistance and dyslipidemia by suppressing PPAR-alpha and fibroblast growth factor 21, both of which positively regulate fatty acid β-oxidation and catabolism, hepatic fat storage, insulin sensitivity and lipid metabolism and to which antidiabetic and lipid lowering effects have been ascribed (30). This is in contrast to actions of BDNF in the brain where it improves eating behavior thereby regulating energy balance (31). More importantly, food restriction and increased physical activity augmented the level of BDNF in the brain (32).

Actions of BDNF in diabetes and insulin metabolism

Fat tissue derived peptides are well known to contribute to the mechanism of diseases characterized by insulin resistance (33). In diabetic animals, BDNF was demonstrated to improve hepatic insulin resistance (31). It was also shown that exogenous BDNF administration displayed antiobesity and antidiabetic actions similar to thiazolidinediones (34). Moreover, it was reported that BDNF deficient mice exhibited the characteristics of metabolic syndrome observed in humans (35). Besides, animals fed with fat and carbohydrate enriched food showed decreased level of BDNF in the hippocampus (32). Clinically, while several authors showed low blood levels of BDNF in sub-

jects with type 2 DM (36), another study found that blood levels of BDNF were higher and correlated with fasting plasma glucose in subjects with newly diagnosed and untreated type 2 DM (37). Together with the data derived from animal experiments, it may be speculated that a compensatory increase in BDNF synthesis may occur in untreated hyperglycemia. In addition, BDNF polymorphism (rs6225) that is obesity predisposing was found to be associated with weight regains in humans (38), suggesting this peptide as a genetic predictor of adiposity dysregulation in these subjects. Finally, microvascular BDNF production was found to reduce in diabetic animals, indicating a reduced microvascular neuroprotection in diabetes (39).

The data regarding the relation of BDNF to the markers of insulin sensitivity are controversial. BDNF treatment lowered nonfasted serum insulin compared with vehicle treated db/db mice (40). It was also shown to activate insulin signal transduction in the liver, skeletal muscle and interscapular brown adipose tissue in diabetic mice (41). Moreover, physical exercise which is known to alleviate insulin resistance was reported to increase plasma and skeletal muscle BDNF concentrations, with a slight improvement in insulin sensitivity (42, 43).

BDNF and its relation to other adipokines

Adipokines including the neurotrophins as well as a variety of inflammatory mediators interact with each other in cardiovascular diseases (44-46) and in conditions with insulin resistance (47-49). Since, for example, low serum adiponectin was linked to an increased prevalence of coronary atherosclerosis, the association of BDNF with other adipose tissue derived peptides may be important. It was reported that leptin shows its neuroprotective effect in the brain by increasing the level of BDNF (50). In humans, plasma BDNF level inversely correlated to adiponectin level only in male gender, but it was correlated with the components of metabolic syndrome in both sexes (16). However, it is possible that such observations may be resultant from reactive mechanisms rather than direct etiological relations, and the interactions among the neurotrophins and other adipokines need to be explored further.

Conclusions and future perspectives

It is likely that BDNF, one of the major neurotrophins synthesized by nearly all of non-immune and immune cells involved in the atherogenesis, participates in the pathogenesis of cardiometabolic diseases through various mechanisms including inflammation, glucose and insulin metabolism, and atherosclerosis.

Studies that fully investigate the vascular and metabolic effects of these peptides would ensure to thoroughly understand "central" control of cardiovascular diseases. Research attempts to increase local or systemic BDNF production in cardiac or metabolic diseases might also introduce more definitive data with respect to the exact roles of this endogenous peptide in health and disease. Awaiting discovery also include identification of genetic differences in the metabolism of BDNF and other neurotrophins.

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References

1. Ahima RS, Qi Y, Singhal NS, Jackson MB, Scherer PE. Brain adipocytokine action and metabolic regulation. Diabetes 2006; 55 Suppl 2: S145-54. [CrossRef]
2. Taşçı I, Doğru T, Naharcı I, Erdem G, Yılmaz MI, Sönmez A, et al. Plasma apelin is lower in patients with elevated LDL-cholesterol. Exp Clin Endocrinol Diabetes 2007; 115: 428-32. [CrossRef]
3. Erdem G, Doğru T, Taşçı I, Sönmez A, Tapan S. Low plasma apelin levels in newly diagnosed type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes 2008; 116: 289-92. [CrossRef]
4. Taşçı I, Erdem G, Özgür G, Tapan S, Doğru T, Genç H, et al. LDL-cholesterol lowering increases plasma apelin in isolated hypercholesterolemia. Atherosclerosis 2009; 204: 222-8. [CrossRef]
5. Kim HJ, Kim SK, Shim WS, Lee JH, Hur KY, Kang ES, et al. Rosiglitazone improves insulin sensitivity with increased serum leptin levels in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2008; 81: 42-9. [CrossRef]
6. Kiliç T. Is leptin an independent risk factor for development of left ventricular hypertrophy in obese hypertensive patients? Anadolu Kardiyol Derg 2008; 8: 347-9.
7. Taşçı I. Apelin, prediabetes and atherosclerosis. Exp Clin Endocrinol Diabetes 2011; 119: 457-8. [CrossRef]
8. Doğru T, Sönmez A, Taşçı I, Yılmaz MI, Erdem G, Ertürk H, et al. Plasma visfatin levels in young male patients with uncomplicated and newly diagnosed hypertension. J Hum Hypertens 2007;21:173-5. [CrossRef]
9. Sönmez A, Celebi G, Erdem G, Tapan S, Genç H, Taşçı I, et al. Plasma apelin and ADMA Levels in patients with essential hypertension. Clin Exp Hypertens 2010; 32: 179-83. [CrossRef]
10. Taşçı I, Erdem G, Tapan S. The relation of ADMA and apelin to endothelial dysfunction and angiogenesis in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2009; 86: e37-8. [CrossRef]
11. Sofroniew MV, Howe CL, Mobley WC. Nerve growth factor signaling, neuroprotection, and neural repair. Annu Rev Neurosci 2001; 24: 1217-81. [CrossRef]
12. Donovan MJ, Lin MI, Wiegn P, Ringstedt T, Kraemer R, Hahn R, et al. Brain derived neurotrophic factor is an endothelial cell survival factor required for intramyocardial vessel stabilization. Development 2000; 127: 4531-40.
13. Ejiri J, Inoue N, Kobayashi S, Shiraki R, Otsui K, Honjo T, et al. Possible role of brain-derived neurotrophic factor in the pathogenesis of coronary artery disease. Circulation 2005; 112: 2114-20. [CrossRef]
14. Cai D, Holm JM, Duignan IJ, Zheng J, Xaymardan M, Chin A, et al. BDNF-mediated enhancement of inflammation and injury in the aging heart. Physiol Genomics 2006; 24: 191-7. [CrossRef]
15. Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, et al. The impact of age, weight and gender on BDNF levels in human platelets and plasma. Neurobiol Aging 2005; 26: 115-23. [CrossRef]
16. Golden E, Emiliano A, Maudsley S, Windham BG, Carlson OD, Egan JM, et al. Circulating brain-derived neurotrophic factor and indices of

metabolic and cardiovascular health: data from the Baltimore Longitudinal Study of Aging. PLoS One 2010; 5: e10099. [CrossRef]
17. Jung SH, Kim J, Davis JM, Blair SN, Cho HC. Association among basal serum BDNF, cardiorespiratory fitness and cardiovascular disease risk factors in untrained healthy Korean men. Eur J Appl Physiol 2011; 111: 303-11. [CrossRef]
18. Krabbe KS, Mortensen EL, Avlund K, Pedersen AN, Pedersen BK, Jørgensen T, et al. Brain-derived neurotrophic factor predicts mortality risk in older women. J Am Geriatr Soc 2009; 57: 1447-52. [CrossRef]
19. Bus BA, Molendijk ML, Penninx BJ, Buitelaar JK, Kenis G, Prickaerts J, et al. Determinants of serum brain-derived neurotrophic factor. Psychoneuroendocrinology 2011; 36: 228-39. [CrossRef]
20. Hiltunen JO, Laurikainen A, Väkevä A, Meri S, Saarma M. Nerve growth factor and brain-derived neurotrophic factor mRNAs are regulated in distinct cell populations of rat heart after ischaemia and reperfusion. J Pathol 2001; 194: 247-53. [CrossRef]
21. Liu Y, Sun L, Huan Y, Zhao H, Deng J. Application of bFGF and BDNF to improve angiogenesis and cardiac function. J Surg Res 2006; 136: 85-91. [CrossRef]
22. Manni L, Nikolova V, Vyagova D, Chaldakov GN, Aloe L. Reduced plasma levels of NGF and BDNF in patients with acute coronary syndromes. Int J Cardiol 2005; 102: 169-71. [CrossRef]
23. Fujimura H, Altar CA, Chen R, Nakamura T, Nakahashi T, Kambayashi J, et al. Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. Thromb Haemost 2002; 87: 728-34.
24. Lorgis L, Amoureux S, de Maistre E, Sicard P, Bejot Y, Zeller M, et al. Serum brain-derived neurotrophic factor and platelet activation evaluated by soluble P-selectin and soluble CD-40-ligand in patients with acute myocardial infarction. Fundam Clin Pharmacol 2010; 24: 525-30. [CrossRef]
25. Jiang H, Liu Y, Zhang Y, Chen ZY. Association of plasma brain-derived neurotrophic factor and cardiovascular risk factors and prognosis in angina pectoris. Biochem Biophys Res Commun 2011; 415: 99-103. [CrossRef]
26. Caporali A, Emanueli C. Cardiovascular actions of neurotrophins. Physiol Rev 2009; 89: 279-308. [CrossRef]
27. Meuchel LW, Thompson MA, Cassivi SD, Pabelick CM, Prakash YS. Neurotrophins induce nitric oxide generation in human pulmonary artery endothelial cells. Cardiovasc Res 2011; 91: 668-76. [CrossRef]
28. Tsuchida A, Nonomura T, Nakagawa T, Itakura Y, Ono-Kishino M, Yamanaka M, et al. Brain-derived neurotrophic factor ameliorates lipid metabolism in diabetic mice. Diabetes Obes Metab 2002; 4: 262-9. [CrossRef]
29. Wu H, Lu D, Jiang H, Xiong Y, Qu C, Li B, et al. Simvastatin-mediated upregulation of VEGF and BDNF, activation of the PI3K/Akt pathway, and increase of neurogenesis are associated with therapeutic improvement after traumatic brain injury. J Neurotrauma 2008; 25:130-9. [CrossRef]
30. Teillon S, Calderon GA, Rios M. Diminished diet-induced hyperglycemia and dyslipidemia and enhanced expression of PPARalpha and FGF21 in mice with hepatic ablation of brain-derived neurotropic factor. J Endocrinol 2010; 205: 37-47. [CrossRef]
31. Kuroda A, Yamasaki Y, Matsuhisa M, Kubota M, Nakahara I, Nakatani Y, et al. Brain-derived neurotrophic factor ameliorates hepatic insulin resistance in Zucker fatty rats. Metabolism 2003; 52: 203-8. [CrossRef]
32. Duan W, Lee J, Guo Z, Mattson MP. Dietary restriction stimulates BDNF production in the brain and thereby protects neurons against excitotoxic injury. J Mol Neurosci 2001; 16: 1-12. [CrossRef]
33. Öztekin S, Karakurt O, Yazıhan N, Ünal I. Relationship of brain natriuretic peptide with metabolic syndrome parameters: an observational study. Anadolu Kardiyol Derg 2011; 11: 678-84.
34. Yamanaka M, Itakura Y, Tsuchida A, Nakagawa T, Noguchi H, Taiji M. Comparison of the antidiabetic effects of brain-derived neurotrophic factor and thiazolidinediones in obese diabetic mice. Diabetes Obes Metab 2007; 9: 879-88. [CrossRef]
35. Duan W, Guo Z, Jiang H, Ware M, Mattson MP. Reversal of behavioral and metabolic abnormalities, and insulin resistance syndrome, by dietary restriction in mice deficient in brain-derived neurotrophic factor. Endocrinology 2003; 144: 2446-53. [CrossRef]
36. Krabbe KS, Nielsen AR, Krogh-Madsen R, Plomgaard P, Rasmussen P, Erikstrup C, et al. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. Diabetologia 2007; 50:431-8. [CrossRef]
37. Suwa M, Kishimoto H, Nofuji Y, Nakano H, Sasaki H, Radak Z, et al. Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus. Metabolism 2006; 55: 852-7. [CrossRef]
38. Delahanty LM, Pan Q, Jablonski KA, Watson KE, McCaffery JM, Shuldiner A, et al. Genetic predictors of weight loss and weight regain after intensive lifestyle modification, metformin treatment, or standard care in the Diabetes Prevention Program. Diabetes Care 2012; 35: 363-6. [CrossRef]
39. Navaratna D, Guo SZ, Hayakawa K, Wang X, Gerhardinger C, Lo EH. Decreased cerebrovascular brain-derived neurotrophic factor-mediated neuroprotection in the diabetic brain. Diabetes 2011; 60: 1789-96. [CrossRef]
40. Tonra JR, Ono M, Liu X, Garcia K, Jackson C, Yancopoulos GD, et al. Brain-derived neurotrophic factor improves blood glucose control and alleviates fasting hyperglycemia in C57BLKS-Lepr(db)/lepr(db) mice. Diabetes 1999; 48: 588-94. [CrossRef]
41. Tsuchida A, Nakagawa T, Itakura Y, Ichihara J, Ogawa W, Kasuga M, et al. The effects of brain-derived neurotrophic factor on insulin signal transduction in the liver of diabetic mice. Diabetologia 2001;44:555-66. [CrossRef]
42. Zoladz JA, Pilc A, Majerczak J, Grandys M, Zapart-Bukowska J, Duda K. Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. J Physiol Pharmacol 2008; 59 Suppl 7: 119-32.
43. Pedersen BK, Pedersen M, Krabbe KS, Bruunsgaard H, Matthews VB, Febbraio MA. Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. Exp Physiol 2009; 94: 1153-60. [CrossRef]
44. Karadurmuş N, Tapan S, Çakar M, Naharcı I, Çelik T, Taşçı I, et al. Lower plasma soluble TWEAK concentration in patients with newly diagnosed hypertension. Clin Invest Med 2012; 35: E20-6.
45. Duan W, Guo Z, Jiang H, Ware M, Mattson MP. Reversal of behavioral and metabolic abnormalities, and insulin resistance syndrome, by dietary restriction in mice deficient in brain-derived neurotrophic factor. Endocrinology 2003; 144: 2446-53. [CrossRef]
46. Işık S, Cetin M, Ciçekçioğlu H, Uçar O, Çetin ZG, Ozuğuz U, et al. Value of IGF-I levels in the evaluation of response to treatment with levosimendan in patients with severe heart failure. Anadolu Kardiyol Derg 2011; 11: 523-9.
47. Aydoğdu A, Taşçı I, Tapan S, Başaran Y, Aydoğan U, Meriç C, et al. High plasma level of long Pentraxin 3 is associated with insulin resistance in women with polycystic ovary syndrome. Gynecol Endocrinol 2012;28:722-5. [CrossRef]
48. Söylemez N, Demirbağ R, Sezen Y, Yıldız A, Akpınar O. The levels of the leptin and adiponectin according to body mass index and their relationship with oxidative parameters. Anadolu Kardiyol Derg 2010; 10: 391-6. [CrossRef]
49. Genç H, Doğru T, Tapan S, Taşçı I, Bozoğlu E, Gök M, et al. Soluble CD40 ligand, soluble P-selectin and von Willebrand factor levels in subjects with prediabetes: the impact of metabolic syndrome. Clin Biochem 2012; 45: 92-5. [CrossRef]
50. Zhang F, Chen J. Leptin protects hippocampal CA1 neurons against ischemic injury. J Neurochem 2008; 107: 578-87. [CrossRef]