

BDNF Measurement in Stress-Related Mood Disorders: A Review of Clinical Studies

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Abstract

Objective: The study of brain-derived neurotrophic factor (BDNF) in mood disorders and other psychiatric disorders is increasing. Of particular interest is whether or not BDNF can be a marker for psychiatric disorders. The aim of this study was to review the published findings on BDNF in stress-related mood disorders.

Method: Searches were conducted of the PubMed and Psikiyatri Dizin databases to access international and national publications, respectively. Database searches were conducted with the keywords BDNF, and stress and mood disorders.

Results: BDNF plays a role in the physiopathology of stress-related changes and is supposedly related to a decrease in the number and size of neurons. Additionally, it has been suggested that serum levels of BDNF are lower in depressive patients than in the healthy controls. Nonetheless, BDNF levels increase after antidepressant treatment, along with symptom recovery, to those seen in healthy control subjects. This increase cannot be achieved in patients that do not respond to antidepressant treatment. On the other hand, in patients with stress-related non-depressive psychiatric disorders, serum BDNF is also low.

Conclusion: To date, even though consistent findings of reduced BDNF levels have been reported, the specificity of these findings is doubtful. Serum BDNF might be considered a marker for stress-related mood disorders.

Key Words: Brain-derived neurotrophic factor, stress, mood disorders

INTRODUCTION

Monoaminergic hypotheses have an important role in our understanding of the physiopathology of psychiatric disorders. Categorizing psychopharmacological treatments according to their monoaminergic effects strengthens this role; however, it is widely thought that changes in monoaminergic transmission are only one of the steps in the formation of psychiatric disorders (Duman and Monteggia, 2006). When this process is examined in terms of cells and the interrelationship of the cells, neurotrophins are more outstanding. The role of neurotrophins in the maintenance and proliferation of neurons is widely emphasized in the physiopathology of mood disorders (Gönül and Akdeniz, 2002). Many factors with neurotrophic properties are described. Among these factors are neural

growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), neurotrophin 4/5 (NT-4/5), neurotrophin 6 (NT-6), vascular endothelial growth factor (VEGF), and glial cell-derived neurotrophic factor (GDNF). Among these, BDNF has the most research and data in the physiopathology of psychiatric disorders, especially depression. In this review, the clinical aspects of the BDNF will be discussed and the clinical studies will be given priority in order to answer the question of whether or not it is possible for BDNF to be a marker for stress-related mood disorders.

METHOD

A search of PubMed limited to only human trials using the keywords stress and BDNF found 176 studies.

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Searching again with the keywords mood disorder and BDNF located 280 studies. Among these studies, those that were a screening, review, or letter to the editor were excluded; thusly, 124 studies were selected for evaluation. The same procedure was performed in the Psikiyatri Dizini database to find Turkish studies and a total of 5 studies were found. Four of these studies were reviews and only 1 was an original research report. Additionally, 2 recent meta-analyses were found that examined the effect of antidepressant use on BDNF levels in depression, and in order to not reduplicate the results these meta-analyses were included instead of the studies covered in these meta-analyses.

BDNF in Peripheral Circulation

In vivo studies have proved that there is perfusion of BDNF in the peripheral circulation. Thus, a topic of interest is whether or not there is a correlation between peripheral and central BDNF levels, and at what level BDNF has a perfusion rate in the peripheral circulation. Platelets, eosinophils, brain neurons, and vascular endothelial cells are known to be sources of BDNF (Trajkovska et al., 2007). It is suggested that instead of BDNF being synthesized in the platelets, it is sequestered into the platelets (Shimizu et al., 2003). It is reported that circulating BDNF is not limited to the reactivity of platelets (Karege et al., 2005). The most illuminating study on this topic was performed by Pan et al. (1998), who report that BDNF can cross the blood-brain barrier and that there is a correlation between serum and brain BDNF levels. Still, it should be kept in mind that measuring serum BDNF level is only an indirect way to demonstrate the level of BDNF in the brain.

Relation between Stress and BDNF

In animal models of mood disorders stress is widely used. The precipitating role of acute or chronic stress in mood disorders is well known (Duman and Monteggia, 2006). Smith et al. (1995) were the first to demonstrate the role of neurotrophins in changes related to stress, and reported that stress decreases gene expression of BDNF in the hippocampus CA3 pyramidal cell layers and in the dentate gyrus granule cell layer. Stress causes damage and atrophy in the neurons in some brain regions, especially the hippocampus (Duman, 2004). In addition to being an important structure for learning and verbal memory, the hippocampus also plays a pivotal role in the pathophysiology of depression. It is known that the hippocampus has connections with the amygdala and prefrontal cortex (MacQueen et al., 2003). On the other hand,

the negative modulation effect of the hippocampus on the hypothalamus-pituitary-adrenal stress hormone axis may be responsible for dysregulation of the stress response (Pittenger and Duman, 2007). Due to stress there may be impairment in hippocampus-dependent memory. These changes can occur due to stress as well as glucocorticoids, and glucocorticoids may cause similar damage in the hippocampus (Sapolsky et al., 1985). In the hippocampus, increasing stress may inhibit neuronal growth (Gould et al., 1992) as well as cause neuronal death (Magarinos et al., 1996).

Due to exposure to chronic stress, in contrast to reduced hippocampal volume, the volume of the amygdala increases (Frodl et al., 2003). There is not only an increase in volume, but also hyperactivity in the function of the amygdala, as demonstrated in functional imaging studies (Drevets et al., 1992). As the hippocampus is responsible for verbal memory and impairment in verbal memory occurs in hippocampal atrophy, the amygdala is responsible for learning and memory; however, with hyperactivity of the amygdala, amygdala-dependent fear learning increases excessively (Conrad et al., 1999). Moreover, changes in the amygdala do not reverse completely, even after the cessation of exposure to chronic stressor (Vyas et al., 2004).

The difference between the effects of stress on the amygdala, and hippocampus and prefrontal cortex is significant. While both acute and chronic stress impairs hippocampal function, reduces the length and complexity of CA3 dendrites, and impairs neurogenesis, they also lead to enhanced amygdala-dependent fear learning, increased length and complexity of amygdalar dendrites, and increased amygdalar volume (Pittenger and Duman, 2007). This shows that stress does not have a unique effect on brain structure and functions, but may have various effects in various brain regions. The relationship between BDNF and stress contributes to our understanding of the pathophysiology of major depression (Pittenger and Duman, 2007).

BDNF findings in Depression

Beyond the relationship between stress and BDNF, changes in neurotrophins and BDNF in depression have been a focus of interest. In addition to the monoamine theory of depression, Popoli et al. (2002) suggest that intracellular pathways have a major role in regulating neuroplasticity and neurodegeneration in the etiology of mood disorders. According to this hypothesis, stress results in neuronal atrophy and decreased neurogenesis,

and then depression occurs. By stimulating intracellular pathways, antidepressants lead to up-regulation of the cAMP response element binding (CREB) protein and to an increase in the expression of neurotrophic factors, particularly BDNF. This hypothesis was the precursor of a new understanding of the etiology of depression and has been the inspiration for many subsequent studies.

Karege et al. (2002) reported low serum levels of BDNF in patients with major depressive disorder when compared with control subjects, as well as a negative correlation between the severity of depression and serum BDNF level. Shimizu et al. (2003) compared depressed patients that were not pharmacologically treated, depressed patients treated with antidepressants, and healthy control subjects, in terms of serum BDNF level, and reported lower serum levels of BDNF in untreated depressed patients than in the other two study groups. In accordance with the previous study, Shimizu et al. (2003) observed a significant negative correlation between serum BDNF level and Hamilton Depression Rating Scale (HAM-D) score. This result was reported in a larger study of 111 depressed patients and 107 healthy controls; serum BDNF level was significantly lower in the depressed group than in the healthy controls (Huang et al., 2008). A meta-analysis reported that serum BDNF levels are lower in patients with major depression than in healthy controls, and that low-level serum BDNF is not associated with age or gender (Sen et al., 2008). It is accepted that low-level serum BDNF in patients with major depressive disorder is a consistent finding.

While low-level serum BDNF in major depressive disorder is reported, it is suggested that some polymorphisms of the BDNF gene may be significant. Val66Met polymorphism of the BDNF gene is the most studied polymorphism and has the largest body of data. It is suggested that healthy controls with the met allele have poor performance in episodic memory and that the Val66Met allele of BDNF is associated with decreased hippocampal volume and increased activation of the hippocampus during learning and memory tasks in normal volunteers (Egan et al., 2003; Post, 2007). In a study on healthy controls, Eker et al. (2005) showed that Met-BDNF allele carriers have morphological anomalies in the frontal, parietal, and temporal cortexes, as compared to Val allele carriers, and that these brain regions are associated with working memory. Frodl et al. (2007) reported that Met-BDNF allele carriers have smaller hippocampal volume; however, in 2 larger studies no significant difference was observed between patients with major depressive disorder and healthy controls, in terms of Val66Met

polymorphism (Hong et al., 2003; Tsai et al., 2003). In a study on HPA axis dysregulation in patients with major depressive disorder it was observed that Met-BDNF allele carriers had higher levels of non-suppression, based on the dexamethasone suppression test, than other allele carriers (Schüle et al., 2006). This study sought to identify the relationship between BDNF and stress-related mood disorders. In a study on citalopram, even though there was no difference between depressed patients and healthy controls, in terms of polymorphism, Met-BDNF allele carriers had better responses to antidepressant treatment (Choi et al., 2006). On the other hand, in studies conducted with elderly samples the Met-BDNF allele was more prevalent in depressive patients than in healthy controls (Hwang et al., 2006; Taylor et al., 2007). Major depressive disorder patients with a history of attempted suicide more frequently had the BDNF Val66Met polymorphism than those without a history of attempted suicide (Sarchiapone et al., 2008). In terms of symptomatology, when 154 patients with major depressive disorder were compared with the same number of healthy controls, psychotic features, suicidal behavior, and a history of mood disorders in the family were more prevalent in Met-BDNF allele carriers. In a Japanese sample no difference was reported in the frequency of BDNF polymorphism between depressed patients and healthy controls (Iga et al., 2007).

Low-level serum BDNF in depression is a consistent finding, and while this level is correlated with the severity of depression, it is not associated with age or gender. On the other hand, BDNF polymorphism does not discriminate between depressed patients and healthy controls; however, it can discriminate between some clinical and therapeutic features of depression.

The Effect of BDNF on Antidepressant Treatment

The determination that depressive patients have low-level serum BDNF led to an interest in determining if antidepressant treatment would increase serum BDNF. The first such study was conducted in Turkey by Gönül et al. (2003) and showed that in patients with major depressive disorder antidepressant treatment with various drugs significantly increased serum BDNF level in concordance with the remission of depression, comparable to healthy subjects. Aydemir et al. (2005) evaluated serum BDNF in a group of 10 patients treated with venlafaxine and reported that along with remission of depression serum BDNF increased to the level of healthy controls. Many studies with similar methodologies followed these two initial studies. In this present review the

results of every other study will not be repeated; however, two meta-analyses will be discussed.

A meta-analysis by Ronald Duman (a pioneer in this field) et al. examined serum BDNF level in depression and its change in response to antidepressant treatment (Sen et al. 2008). In this meta-analysis 11 studies with complete data were evaluated. They reported that serum BDNF level was significantly lower in patients with depression than in healthy controls, and antidepressant treatment increased serum BDNF to the level of healthy controls. In these studies evaluated in this meta-analysis, bias for publication of meta-analyses described by Egger et al (1997) is not at significant level.

The other meta-analysis was performed by Brunoni et al. (2008); 23 studies were evaluated and data for 1504 patients were subjected to statistical analysis. The effect size was calculated as 0.62 (95% confidence interval: 0.36-0.88). In this meta-analysis, it is reported that there is no bias for publication in the studies reviewed. While the effect size of the difference in the level of serum BDNF between depressed patients prior to antidepressant treatment and healthy controls was 0.91 (95% confidence interval: 0.70-1.11), following antidepressant treatment the effect size of the comparison of depressed patients and healthy controls, in terms of serum BDNF, decreased to 0.34 (95% confidence interval: 0.02-0.66). As a result of meta-regression change in the level of serum BDNF after antidepressant treatment was independent of the change in depressive symptomatology, duration of treatment, and history of antidepressant use. Brunoni et al. (2008) suggested in their meta-analysis that the level of serum BDNF is associated with clinical changes in depression and that improvement after treatment is due to change in neuroplasticity. As clinical improvement obtained with antidepressant treatment persists, the level of serum BDNF remains unchanged. A 1-year follow-up study reported that while as from the first month of treatment patients' plasma BDNF levels did not differ significantly from those observed in healthy control subjects, serum BDNF levels in patients remained significantly high at all times (Piccinni et al., 2008).

One study on antidepressant treatment deserves a more detailed evaluation. Yoshimura et al. (2007) compared depressed patients treated with paroxetine or milnacipran to healthy controls, in terms of the level of serum BDNF. At the end of the trial, serum BDNF in the patients that responded to antidepressant treatment increased, as expected. The interesting finding of this study is that serum BDNF levels in the patients that

did not respond to antidepressant treatment remained unchanged, as compared to the index measure, and were significantly lower than in healthy controls. This finding highlights the role of BDNF in the improvement of depression.

As a result of these treatment studies, antidepressant treatment significantly increases the level of serum BDNF in patients with major depressive disorder.

BDNF and other Stress-Related Disorders

In addition to the many studies on BDNF in depression, there are many studies on BDNF in other stress-related disorders. These studies will clarify the significance of BDNF in stress-related disorders.

Among the stress-related psychiatric disorders is conversion disorder, and in a comparative study of patients with conversion disorder, patients with major depressive disorder and healthy controls, patients with conversion disorder had serum BDNF levels as low as those in depressed patients (Deveci et al., 2007a). The nonexistence of depression in these patients was confirmed both with DSM criteria and HAM-D scores. On the other hand, another study on suicide attempters without any major psychiatric disorder, but with a code V diagnosis according to DSM-IV-TR, that presented to an emergency room reported that the serum BDNF level in those that attempted suicide was lower than in healthy controls and similar to that in depressed patients (Deveci et al., 2007b). These two studies show that even though there is no depression, in stress-related disorders serum BDNF levels are as low as those seen in major depressive disorder. In post-traumatic stress disorder, which is a disorder directly associated with stress, low-level BDNF was not observed (Zhang et al., 2006). In terms of this unexpected and paradoxical finding, the authors suggest that the effect size of the sample was not sufficient to show the difference. Thus, new studies with larger well-structured samples are needed. Additionally, in another stress-related disorder—burnout syndrome—serum BDNF levels were low and this finding was independent of HPA axis dysfunction (Önen Sertöz et al., 2008).

In chronic and persistent stress conditions the case is rather different. Even though BDNF levels were low in individuals with various stress conditions, in an animal study, Kuroda and McEwen (1998) measured BDNF after 21 days of chronic restraint stress and observed that BDNF was unchanged, suggesting that this may have been due to desensitization to the effects of repeated stress (Duman and Monteggia, 2006). In a study sup-

porting the findings of this experimental study it is reported that serum BDNF level of the dysthymic group was significantly higher than in the major depressive disorder group, and did not differ from that in the control group (Aydemir et al., 2007). This finding highlights the normalization of the serum BDNF level generated by desensitization to chronic and persistent stress. The relationship between depression and pain syndromes caused by chronic stress always arouses interest. Serum BDNF levels in pain syndromes, such as migraine and fibromyalgia, is higher than those in major depressive disorder and similar to those in healthy controls (Taşkın et al., 2008). This suggests that either stress causes less change in somatizing patients or high level of BDNF is the result of desensitization to chronic stress. While interpreting this finding it should also be kept in mind that in pain syndromes platelets release BDNF.

As a result of psychiatric disorders other than mood disorders, in the presence of stress, independent of depression, serum BDNF has a tendency to decrease.

Is it Possible for BDNF to be a Marker?

We will try to answer the question we asked at the beginning of this paper based on the presented data. Identification a marker for depression, which is one of the most prevalent psychiatric disorders seen in the practice of psychiatry, is highly desired. In this respect, based on consistent evidence BDNF seems to be a good candidate. In a review of the biological markers for depression by the World Psychiatric Association Task Force it is suggested that the results provide further support for the hy-

pothesis that BDNF may be central to the development of depressive mood states (Mössner et al., 2007).

Data that show lower BDNF levels in depressed patients than in healthy controls, significant increases in BDNF with antidepressant treatment, and unchanged levels or non-normalization of BDNF in patients without a response to antidepressant treatment make BDNF a marker for depression. On the other hand, changes in the level of BDNF in several other conditions limit its specificity for depression. As in the release of BDNF from platelets, several medical conditions that cause peripheral changes in BDNF levels may also affect serum BDNF levels in psychiatric disorders. Nonetheless, the consistent finding that antidepressant treatment causes an increase in the serum BDNF level results in BDNF being considered a marker, at least in treatment studies.

CONCLUSION

BDNF is a promising marker because it is the most studied biological variable. When the data presently available is evaluated, serum BDNF level is not a strong marker for the diagnosis of depression. As serum BDNF levels may change in many different medical conditions, specificity in any disease or disorder cannot be high; however, some data indicate that BDNF can be considered as a marker in stress-related disorders or in mood disorders with a stress-related etiology. In psychiatric disorders, especially depression, studies on BDNF may again highlight the concept of “endogen-reactive”. This issue deserves additional research.

REFERENCES

- Aydemir Ö, Deveci A, Taneli F (2005) The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: a preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry* 29:261-265.
- Aydemir Ö, Deveci A, Taşkın OE, Taneli F, Esen-Danacı A (2007) Serum brain-derived neurotrophic factor level in dysthymia: a comparative study with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 31:1023-1026.
- Brunoni AR, Lopes M, Fregni F (2008) A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *Int J Neuropsychopharmacol* 28:1-12.
- Choi MJ, Kang RH, Lim SW, Oh KS, Lee MS (2006) Brain-derived neurotrophic factor gene polymorphism (Val66Met) and citalopram response in major depressive disorder. *Brain Res* 1118:176-182.
- Conrad CD, LeDoux JE, Magariños AM, McEwen BS (1999) Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. *Behav Neurosci* 113:902-913.
- Deveci A, Aydemir Ö, Taşkın O, Taneli F, Esen-Danacı A (2007a) Serum brain-derived neurotrophic factor levels in conversion disorder: Comparative study with depression. *Psychiatry Clin Neurosci* 61:571-573.
- Deveci A, Aydemir Ö, Taşkın O, Taneli F, Esen-Danacı A (2007b) Serum BDNF level in suicide attempters related to psychosocial stressors: a comparative study with depression. *Neuropsychobiology* 56:93-97.
- Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992) A functional anatomical study of unipolar depression. *J Neurosci* 12:3628-3641.
- Duman RS (2004) Role of neurotrophic factors in the etiology and treatment of mood disorders. *Neuromol Med* 5: 11-25.
- Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. *Biol Psychiatry* 59:1116-1127.
- Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 24: 257-269.

- Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in metaanalysis detected by a simple, graphical test. *BMJ* 315:629–634.
- Eker Ç, Kitiş Ö, Ozan E, Okur H, Eker ÖD, Ersoy MA, Akdeniz F, Vahip S, Akarsu N, Gönül AS (2005) İnsan beyinde BDNF geninin val66met polimorfizmine bağlı gri madde değişiklikleri. *Klinik Psikofarmakoloji Bülteni* 15:104-111.
- Frodl T, Meisenzahl EM, Zetzsch T, Born C, Jäger M, Groll C, Bottlender R, Leinsinger G, Möller HJ (2003) Larger amygdala volumes in first depressive episode as compared to recurrent major depression and healthy control subjects. *Biol Psychiatry* 53: 338-344.
- Frodl T, Schüle C, Schmitt G, Born C, Baghai T, Zill P, Bottlender R, Rupprecht R, Bondy B, Reiser M, Möller HJ, Meisenzahl EM (2007) Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Arch Gen Psychiatry* 64:410-416.
- Gould E, Cameron HA, Daniels DC, Wooley CS, McEwen BS (1992). Adrenal hormones suppress cell division in the adult rat dentate gyrus. *J Neurosci* 12: 3642–3650.
- Gönül AS, Akdeniz F (2002) Depresyon, nöroplastisite, nörogenesis ve nörotrofik faktörler. *Klinik Psikiyatri Dergisi* 5(Ek Sayı 4):51-56.
- Gönül AS, Akdeniz F, Taneli F, Donat Ö, Eker Ç, Vahip S (2003) The effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. *Eur Neuropsychopharmacol* 13 (Suppl. 4): 203.
- Gönül AS, Akdeniz F, Taneli F, Donat Ö, Eker Ç, Vahip S (2005) Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. *Eur Arch Psychiatry Clin Neurosci* 255:381-386.
- Hong CJ, Huo SJ, Yen FC, Tung CL, Pan GM, Tsai SJ (2003) Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. *Neuropsychobiology* 48:186-189.
- Huang TL, Lee CI, Liu YL (2008) Serum brain-derived neurotrophic factor levels in patients with major depression: effects of antidepressants. *J Psychiatr Res* 42:521-525.
- Hwang JP, Tsai SJ, Hong CJ, Yang CH, Linrg JF, Yang YM (2006) The Val66Met polymorphism of the brain-derived neurotrophic-factor gene is associated with geriatric depression. *Neurobiol Aging* 27:1834-1837.
- Iga J, Ueno S, Yamauchi K, Numata S, Tayoshi-Shibuya S, Kinouchi S, Nakataki M, Song H, Hokoishi K, Tanabe H, Sano A, Ohmori T (2007) The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with psychotic feature and suicidal behavior in Japanese major depressive patients. *Am J Med Genet B Neuropsychiatr Genet* 144B:1003-1006.
- Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G (2005) Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. *Biol Psychiatry* 57:1068-1072.
- Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM (2002) Decreased serum brain-derived neurotrophic factor levels in depressed patients. *Psychiatry Res* 109: 143-148.
- Kuroda Y, McEwen BS (1998) Effect of chronic restraint stress and tianeptine on growth factors, growth-associated protein-43 and microtubule-associated protein 2 mRNA expression in the rat hippocampus. *Brain Res Mol Brain Res* 59: 35–39.
- MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, Nahmias C, Young LT (2003). Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc Natl Acad Sci USA* 100: 1387–1392.
- Magarinos AM, McEwen BS, Flugge G, Fuchs E (1996) Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. *J Neurosci* 16: 3534–3540.
- Mössner R, Mikova O, Koutsilier E, Saoud M, Ehli AC, Müller N, Fallgatter AJ, Riederer P (2007) Consensus paper of the WFSBP Task Force on Biological Markers: biological markers in depression. *World J Biol Psychiatry* 8:141-174.
- Önen Sertöz Ö, Tolga Binbay İ, Köylü E, Noyan A, Yıldırım E, Elbi Mete H (2008) The role of BDNF and HPA axis in the neurobiology of burnout syndrome. *Prog Neuropsychopharmacol Biol Psychiatry* 32:1459-1465.
- Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ (1998) Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology* 37:1553-1561.
- Piccinni A, Marazziti D, Catena M, Domenici L, Del Debbio A, Bianchi C, Mannari C, Martini C, Da Pozzo E, Schiavi E, Mariotti A, Roncaglia I, Palla A, Consoli G, Giovannini L, Massimetti G, Dell'Oso L (2008) Plasma and serum brain-derived neurotrophic factor (BDNF) in depressed patients during 1 year of antidepressant treatments. *J Affect Disord* 105:279-283.
- Pittenger C, Duman RS (2008) Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology* 33:88-109.
- Popoli M, Gennarelli M, Racagni G (2002) Modulation of synaptic plasticity by stress and antidepressants. *Bipolar Disord* 4: 166-182.
- Post RM (2007) Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. *J Psychiatr Res* 41: 979-990.
- Sarchiapone M, Carli V, Roy A, Iacoviello L, Cuomo C, Latella MC, di Giannantonio M, Janiri L, de Gaetano M, Janal MN. Association of polymorphism (Val66Met) of brain-derived neurotrophic factor with suicide attempts in depressed patients. *Neuropsychobiology* 57:139-145.
- Sapolsky RM, Krey L, McEwen B (1985). Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. *J Neurosci* 5: 1221–1227.
- Schüle C, Zill P, Baghai TC, Eser D, Zwanzger P, Wenig N, Rupprecht R, Bondy B (2006) Brain-derived neurotrophic factor Val66Met polymorphism and dexamethasone/CRH test results in depressed patients. *Psychoneuroendocrinology* 31:1019-1025.
- Sen S, Duman R, Sanacora G (2008) Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol Psychiatry* 64:527-532.
- Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, Nakazato M, Watanabe H, Shinoda N, Okada S, Iyo M (2003) Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry* 54: 70-75.
- Smith MA, Makino S, Kvetnansky R, Post RM (1995) Stress alters the expression of brain derived neurotrophic factor and neurotrophins-3 mRNAs in the hippocampus. *J Neurosci* 15:1768–1777.
- Taşkın EO, Aydemir Ö, Deveci A, Taneli F, Selçuki D, Cerrahoğlu L, Esen Danacı A (yayında) Ağnrlı sendromlarda serum beyin-türevli nörotrofik faktör düzeyleri: Major depresyon ile kontrollü bir çalışma. *Klinik Psikofarmakoloji Bülteni*.
- Taylor WD, Züchner S, McQuoid DR, Steffens DC, Speer MC, Krishnan KR (2007) Allelic differences in the brain-derived neurotrophic factor Val66Met polymorphism in late-life depression. *Am J Geriatr Psychiatry* 15: 850-857.
- Trajkovska V, Marcussen AB, Vinberg M ve ark. (2007) Measurements of brain-derived neurotrophic factor: methodological aspects and demographical data. *Brain Res Bull*, 73:143-149.
- Tsai SJ, Cheng CY, Yu YW, Chen TJ, Hong CJ (2003) Association study of a brain-derived neurotrophic-factor genetic polymorphism and major depressive disorders, symptomatology, and antidepressant response. *Am J Med Genet B Neuropsychiatr Genet* 123B:19-22.
- Vyas A, Pillai AG, Chatarji S (2004) Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. *Neuroscience* 128: 667–673.
- Yoshimura R, Mitoma M, Sugita A, Hori H, Okamoto T, Umene W, Ueda N, Nakamura J (2007) Effects of paroxetine or milnacipran on serum brain-derived neurotrophic factor in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 31: 1034–1037.
- Zhang H, Ozbay F, Lappalainen J, Kranzler HR, van Dyck CH, Charney DS, Price LH, Southwick S, Yang BZ, Rasmussen A, Gelernter J (2006) Brain derived neurotrophic factor (BDNF) gene variants and Alzheimer's disease, affective disorders, posttraumatic stress disorder, schizophrenia, and substance dependence. *Am J Med Genet B Neuropsychiatr Genet* 141B:387-393.