Translational Perioperative and Pain Medicine
ISSN: 2330-4871 (Open Access)
Review Article

Role of brain-derived neurotrophic factor in the molecular neurobiology of major depressive disorder

Yi Zhang[1], Jing Shi[2], Jianxin Li[3], Renyu Liu[4], Yingcong Yu[3,*], Ying Xu[1,*]

[1]Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, the State University of New York at Buffalo, Buffalo, NY, USA; [2] School of Pharmacy and Pharmaceutical Sciences, Hangzhou Medical College, Hangzhou, Zhejiang, China; [3] Wenzhou People's Hospital, Wenzhou Third Clinical Institute Affiliated to Wenzhou Medical University, Wenzhou, Zhejiang, China; [4] Departments of Anesthesiology and Critical Care, Hospital of University of Pennsylvania, Philadelphia, PA, USA

Abstract

Major depressive disorder (MDD) is one of the most common neuropsychiatric disorders, which affects up to 20% of people in their lifetime in the United States. The exact neurobiological mechanisms of MDD remain elusive, and the diagnostics are still uncertain. Basic and clinical research from recent years demonstrated that the etiology of MDD might be associated with genetic changes of neurotrophins, particularly brain-derived neurotrophic factor (BDNF). BDNF plays a key role in neuronal development and neurogenesis. However, the detailed mechanisms related to depression and antidepressant responses are not fully understood. This review summarizes the current knowledge of the causal relationship between BDNF and MDD, and describes the important role of BDNF in the progress of depression in animal models and patients with depressive disorders.

Keywords: major depressive disorder; brain-derived neurotrophic factor; neurobiology

1. Introduction

Major depressive disorder (MDD) is the second most common debilitating neuropsychiatric disorder with a lifetime prevalence of 15-20% [1, 2]. Based on the annual report of World Health Organization in 2016, MDD would be the most prevalent cause of illness-induced disability and mortality by the year of 2030 [3]. MDD is a heterogeneous condition, and the main symptoms are continually depressed mood, cognitive disorders, one third of patients with lifetime anxiety, and even suicide. Typically, MDD subjects show the changes in appetite or body weight, loss of libido or energy, sexual dysfunction, disturbances of sleep, daytime fatigue and non-localized pain. Furthermore, commonly recognized symptoms related to the central nervous system are cognitive impairment (poor concentration and memory, and slowed reaction time), and dysfunctional thoughts (inappropriate guilt, worthlessness, and suicidal ideation) [4-6]. Although the neurobiological mechanism of MDD is complicated because of its highly variable compilation of symptoms, there is a consensus about the interaction between environmental factors and related genes, which result in optimal treatment for depression [7].

One candidate gene involved in the pathophysiology and therapy of MDD is neurotrophin, including the brain-derived neurotrophic factor (BDNF) [8]. BDNF is a major neuronal growth factor found in the whole brain, particularly abundant in the cerebral cortex and hippocampus [9]. BDNF plays a key role in neuron development and migration, axonal and dendritic growth, and synaptic plasticity [10,11]. The neurotrophin hypothesis of depression supported by recent evidence demonstrates that BDNF is involved in MDD, and seems to be a key missing link in the neurobiology of MDD [12]. The action of neurotrophins in the brain has been extensively studied, yielding results in important research findings from neuroimaging studies, the function of the hypothalamic-pituitary-adrenal axis and the neurotransmitters, as well as the effects of antidepressants [13]. Moreover, two meta-analyses including 2252 subjects also demonstrated that serum levels of BDNF in MDD

subjects are lower compared to non-depressed subjects and recovered to the normal level of the healthy control following the treatment with antidepressant [14,15]. For the aim of this review, we will summarize basic and clinical research with the focus on the relevance between BDNF and MDD.

2. Distribution of endogenous BDNF

The BDNF gene is located on the reverse strand of chromosome 11p13 and encodes a glycosylated precursor-proBDNF [16]. BDNF is firstly synthesized as proBDNF that is cleaved to generate mature BDNF (mBDNF) proteolytically [17]. BDNF acts as a regulator of stable, late phase long-term potentiation at excitatory glutamatergic synapses [18]. Some researchers have shown that both proBDNF and mBDNF aid long-term potentiation and long-term depression, respectively, suggesting the opposite cellular functions [19, 20]. Therefore, it is critical to determine whether depressive-like behaviors or anti-depressive efficacies of antidepressants are arbitrated by proBDNF or mBDNF. BDNF has been demonstrated to be produced both by pre- and post-synaptic terminals, though at various stimulation intensities [21]. In addition, mBDNF activates TrkB selectively, a typical tyrosine kinase receptor, to enhance neuronal survival and differentiation, stabilizing synaptic contacts, and increasing the branching of axons and dendrites [22]. Considering its necessity for neuronal differentiation, nerve development, and neuron survival, BDNF has been linked to many neuropsychiatric diseases, e.g. MDD.

BDNF is expressed at rather high levels by most of the tissues in the human body [23] and may cross the blood-brain barrier, and levels of serum BDNF could affect BDNF levels of the brain [24,25]. Because it is difficult to directly assess the BDNF in the brain, BDNF are exerted from blood samples to evaluate the activity of BDNF peripherally. BDNF is found within the blood, where it is mostly stored in platelets with high levels. However, it is still elusive about the origin of BDNF in the blood, platelets or lymphocytes [26].

3. BDNF in Animal Model of Depression

Animals are bred to show learned helplessness as the lack of pleasure (anhedonia) that is also shown in the depressed patients [27]. This involves in a decrease in activity of neurons in the dorsal prefrontal cortex, but the increase in activity of neurons in both the ventral anterior cingulate cortex [28] and habenula [29]. There are also other reports suggest that the metabolic changes in the habenula and ventral tegmental area (VTA) that resemble those seen in the models of depression [30], as well as reduced hippocampal serotonin and BDNF [31]. After treatment of electroconvulsive seizures or antidepressants, BDNF levels are shown to be increased [32, 33]. These preliminary results lead to the presumption that BDNF may have a key role in the pathophysiology and therapy of MDD [34]. However, deleting BDNF from broad forebrain regions in development in the mouse models did not result in profound changes in depression-related behavior [35], although BDNF conditional knockout in female mice may demonstrate the depressive-like changes in certain behavior tests [36,37].

The expression of BDNF with the obvious difference observed in the dentate gyrus (DG) of the hippocampus in animal models of depression[38], could be dysregulated by various kinds of stressors either physically or socially, including the acute social defeat [39], pre-weaning or maternal separation [40], and single and acute immobilization stress [41]. Additionally, in heterozygote BDNF knockout mice, the survival rate of immature neurons in the DG is decreased [9]. Direct bilateral microinjections of BDNF into the hippocampal DG of the rat could produce an antidepressant-like effect on behavioral changes [42], while this response to the antidepressant is reduced in BDNF receptor (TrkB)-overexpressing transgenic mice [43]. Treatment with a long-term antidepressant can enhance TrkB transcription levels in the brain of experimental rats [44], as well as signaling from TrkB receptors in the hippocampus and medial prefrontal cortex [45]. Therefore, similar to increased BDNF expression, activation of TrkB receptor is linked to the antidepressant efficacy. Additionally, a depressive phenotype is not an expression of a dominant negative TrkB or BDNF deletion mutant [43], implying that these genes are not critical genes for the disease, but may be biological markers for the disease process. The decrease in BDNF does not lead to depressive-like symptoms in BDNF heterozygous knockout mice [46], but suppresses antidepressant efficacy in BDNF conditional knock-out male mice [36]. After BDNF or TrkB is conditionally ablated in corticostriatal and nigrostriatal neuronal circuits, BDNF or TrkB

shows important cell-autonomous and paracrine roles, respectively, in the growth and maintenance of striatal neurons [47]. Moreover, TrkB overexpression reduces the symptoms of depression and anxiety [48]. However, some researchers show that the effects of BDNF are not same in various regions of the central nervous system. BDNF infusion for the VTA has a pro-depressive role, but the BDNF signaling suppression produces an antidepressant-like effect [49]. Social stresses are associated with depressive-like behaviors and result in increased BDNF levels in the nucleus accumbens (NAc), blocked by a decrease of BDNF in the VTA [50]. These results suggest that the functional properties of the VTA-NAc pathway could be opposite to that in the hippocampus [51].

According to the notion that stressful situations decrease the expression of BDNF, potential antidepressant-like effects of BDNF infusion into the brain are evaluated by depressive-like behavioral tests. After microinfusion into the midbrain of rats, BDNF could affect the analgesia, and enhance the monoaminergic activity [52]. Actually, infusion of BDNF with the intracerebroventricular or intraparenchymal administration enhances the sprouting and development of serotonin-containing neurons in the rat brain [53] and increases the synthesis and/or turnover of serotonin in the hippocampus [52]. Noradrenergic and serotoninergic systems affected by BDNF link to the monoaminergic hypothesis of depression. In the learned helplessness test, BDNF microinfusion causes significant enhancement in the conditioned avoidance behavior, compared with the positive drug imipramine or fluoxetine [42]. Infusion of BDNF into the brain acutely alleviates the depression-like behaviors in the forced swimming test, increasing the swimming time and decreasing immobility time in the tests [42,51]. These results demonstrate that treatment with BDNF at the hippocampus and midbrain area could produce obvious antidepressant-like effects, which agree with increasing stress-induced expression of BDNF in the prefrontal cortex [54]. Meanwhile, decreased BDNF expression can also be observed in the hippocampus, suggesting that antidepressant-like effects of BDNF are indeed area-dependent. However, another study demonstrates that decreased neurogenesis in the hippocampus as etiological factors of depression do not result in a hedonic-like behavior in rats [55]. Moreover, these data suggest that downstream factors of BDNF signaling could also be differentially regulated in the different brain regions. After chronic treatment with peripheral BDNF, neurogenesis in the adult hippocampus is enhanced. Moreover, pCREB, pERK and BDNF expression is also increased in the hippocampus of adult mice after peripheral BDNF administration. These imply that BDNF is not only a biological marker of MDD, but also has functional consequences on behavior, molecular signaling substrates, and neurogenesis [56]. These results might be reasons for the discord in findings regarding the impact of BDNF on depression. Clearly, there is more to the story involving elaborate specific mechanisms.

4. BDNF in Human Depression

According to basic research in animal models of depression, clinical research experience is compatible with the effects of BDNF in the pathophysiology of MDD. The BDNF levels in the serum are observed to be decreased in the MDD patients without antidepressant treatment compared to healthy controls. BDNF levels of fully remitted subjects (whether treated or unmedicated with antidepressants) are comparable to those of healthy controls, implying a correlation between BDNF levels and clinical diagnosis, but do not parallel clinical characteristics [57]. The levels of serum BDNF in MDD subjects are lower than the levels of healthy controls, and the decrease is correlated with the disease severity [58,59]. Two meta-analyses from clinical studies further demonstrate that the levels of BDNF are decreased in the MDD subjects [14,15]. The BDNF levels in platelets in both suicidal and non-suicidal patients are lower, implying the key role of BDNF in platelets [60]. Decreased contents of platelet BDNF as BDNF storage for circulation may be linked to lower serum BDNF level in MDD subjects. A clinical study shows that the levels of BDNF are significantly lower in the lymphocytes of both children/adolescents and adults with MDD compared with healthy controls, with no correlation with disease severity [26]. Therefore, decreased expression of BDNF in the lymphocytes and its bidirectional movement between the central nervous system and the periphery could possibly be a biomarker for MDD and a pharmacological target for antidepressants. In addition, the expression of BDNF is also enhanced in the NAc of MDD patients [61]. Another neuroanatomical region related to MDD in the brain is the amygdala [62-64]. Until now, it is still un-

known in MDD patients whether BDNF is involved in this structural abnormality, preclinical studies demonstrate that the expression of BDNF is increased in the amygdala in response to stress [65].

It is observed that endurance physical training caused higher BDNF levels in the hippocampus and the increased expression of BDNF in the brain. In fact, these results possibly suggest that physical training is likely to have beneficial effects on depressive subjects [66,67]. However, there is data show that the levels of plasma BDNF are increased during physical training in un-medicated moderate depression patients. However, this rise is not associated with improved scores on the Montgomery-Åsberg Depression Rating Scale, and it is also observed in healthy controls, with no differences in BDNF levels between healthy controls and patients before incremental physical training [68]. Sleep deprivation therapy combined with an antidepressant, is correlated with increased BDNF levels [69]. Moreover, depressive subjects with electroconvulsive treatment have demostrated to have an increase [70, 71] or have no role on the expression or release of BDNF [72]. The concentrations of serum BDNF are accessed from 109 MDD patients and 163 healthy controls. The research findings from the HAM-D scores show that levels of serum BDNF may be a biomarker for anxiety symptoms in the MDD patients with the treatment [73]. Levels of serum BDNF are shown to decrease with age in women subjects, whereas levels of serum BDNF remain stable in men subjects. Additionally, the findings suggest lower levels of serum BDNF with higher total scores of Beck's Depression Inventory after controlling for age and gender [74]. Some of the results from the analyses of indices in the cerebrospinal fluid of depression patients demonstrate that BDNF is dysregulated in MDD patients, and generally support the hypotheses that BDNF may have an important role in MDD [75].

Clinical research have demonstrated a correlation between MDD and a remarkable neuronal atrophy in the hippocampus [76]. The degeneration in the hippocampus is more likely correlated with the decreased neurotrophic expression; evidence is obtained from the decreased BDNF in hippocampus tissue of post-mortem suicide victims or MDD patients [77, 78]. BDNF levels in hippocampus and the increase in neurogenesis in this brain region by treatment with the antidepressant are shown to reverse or block the reductions of hippocampus volume [79-81]. Additionally, some data also demonstrate that even healthy individuals, those exposed to higher risks of developing depression including unipolar depression, have lower hippocampal volumes [82-84]. These suggest that decreased hippocampal volumes in healthy controls might display a tendency to develop the depressive disorders [82-87]. Moreover, neuroimaging acquisition and analysis may be the helpful tools as a prognosis to determine the future onset of depression. Therefore, a question raised from animal and clinical research is that decreased neurogenesis could be a causative factor to major depressive disorder. However, it is still unknown whether the function of dentate gyrus (DG) is impaired in MDD subjects and whether this is recovered after treatment with the antidepressants. Reif and his colleagues could not find any difference in the process of proliferation in the DG region after treatment with antidepressants [88]. However, Boldrini and the co-workers found a reduction in proliferation of neural progenitor cells in the DG region in patients with untreated depression while patients treated with antidepressant showed higher proliferation numbers [89].

5. BDNF and antidepressant efficacy

BDNF has been implied to have a key role in the action of antidepressants [12, 53]. The expression and release of BDNF are affected by antidepressants, and BDNF also shows an antidepressant-like effect on the animal models of depression [42]. The biochemical index has been consistent with demonstrating a restoration of BDNF after treatment with the antidepressants, and having potential use of BDNF as a biological marker for MDD or as a predictor of antidepressant efficacy [15,78,90]. Research shows that the changes in BDNF serum resulting from antidepressant treatment depend on the antidepressant administered instead of a common characteristic of the response to antidepressant therapy [91]. The mechanism involved in the increase of BDNF for antidepressant treatment is not focused on clinical research of humans. Notwithstanding, serum BDNF modulation found in MDD subjects is linked to the regulation of the mRNA levels of BDNF in leukocytes, implying that the peripheral cells could have a positive effect on the mechanisms of action of antidepressants and could be regarded as a specific biological marker [92]. Moreover, these findings also imply that an antidepressant com-

bined with an atypical antipsychotic drug is helpful and well-tolerated for the depression subjects, while atypical antipsychotics might involve as an adjuvant to enhance the levels of plasma BDNF [93].

Mimicking the effect of stress, BDNF expression is decreased in the hippocampus and frontal cortex in the rodents after exposure to corticosterone. The BDNF expression is increased after different kinds of antidepressant treatment, such as monoamine oxidase inhibitor phenelzine, which increases mRNA levels of BDNF in both the frontal cortex and hippocampus. However, the selective serotonin reuptake inhibitor fluoxetine increases BDNF mRNA only in the hippocampus, but not in the frontal cortex [94]. These results imply that BDNF plays an important role in the behavioral effect of antidepressants. Additionally, various antidepressants have significant effects on the exon-specific transcripts of BDNF in different areas of the central nervous system, suggesting that various signaling mechanisms could be involved in regulating the transcription of BDNF [94, 95]. Therefore, these findings imply that the mechanisms might be different between upregulation of BDNF by antidepressants and downregulation by corticosterone [96]. Ketamine is recently recognized as an attractive antidepressant for its rapid and effective therapeutics against MDD and the treatment-resistant depression [97,98]. Some studies demonstrate that the expression and release of BDNF regulate the antidepressant effects of ketamine, which is also necessary for the rapid-acting antidepressant effects of ketamine [99].

6. Concluding remarks

There is correlation between down-regulated expression of BDNF and depression symptoms development. The possible value of the neurotrophic factors for treatment of depression as the basic theory for designing the new antidepressants could not be excluded because of the complexity of the present experimental findings. It is obvious that BDNF/TrkB signaling is involved in the recovery of MDD, while the effects of BDNF/TrkB signaling in the pathophysiology of MDD are still conflicting rather than conclusive. Further research focusing on the signal cascade in the different brain regions could be helpful to understand the effects of BDNF in the circuitry formation and neuronal plasticity. Future clinical and post-mortem studies may better characterize the causal effects of BDNF in the context of MDD or after treatment with the antidepressants.

Competing interests

The authors declare no competing interests.

Disclosure of Funding: Dr. Renyu Liu appreciates research funding suport from NIH: NIH 1R01GM111421 (PI: RL).

Conflict Interests Disclosure: The authors have no conflicting interests to disclose.

Corresponding Authors: Xu Y: Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, the State University of New York at Buffalo, Buffalo, NY 14214, USA. Tel: +1 716-829-4361, Email: yxu9@buffalo.edu; Yu YC: Wenzhou People's Hospital, Wenzhou Third Clinical Institute Affiliated to Wenzhou Medical University, Wenzhou, Zhejiang 325000, China. Tel: +86- 577-88059910, Email: 001catherine@163.com

Editor: Zhiyi Zuo, MD, PhD Robert M. Epstein Professor of Anesthesiology, Professor of Neurological Surgery, and Neuroscience, University of Virginia. zz3c@virginia.edu

Additional publication details

Journal short name: Transl Perioper & Pain Med
Received Date: Oct 16, 2016
Accepted Date: Dec 20, 2016
Published Date: Jan 17, 2017
Transl Perioper & Pain Med 2017; 2(1):20-30

Citation and Copyright

Citation: Zhang Y, Shi J, Li J, Liu R, Yu Y, Xu Y. Role of brain-derived neurotrophic factor in the molecular neurobiology of major depressive disorder. Transl Perioper & Pain Med 2017; 2(1): 20-30

References

1. Berton O, Nestler EJ (2006) New approaches to antidepressant drug discovery: beyond monoamines. Nature Reviews. Neuroscience 7(2):137-51. DOI: 10.1038/nrn1846. PubMed PMID: 16429123.

2. Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. Nature 455(7215):894-902. DOI: 10.1038/nature07455. PubMed PMID: 18923511.

3. World Health Organization. Depression; http://www.who.int/mediacentre/factsheets/fs369/en/, last date accessed 2016-04-01.

4. Cho HJ, Lavretsky H, Olmstead R, Levin MJ, Oxman MN, et al. (2008) Sleep disturbance and depression recurrence in community-dwelling older adults: a prospective study. American Journal of Psychiatry 165(12):1543-50. DOI: 10.1176/appi.ajp.2008.07121882. PubMed PMID: 18765482.

5. Dew MA, Reynolds CR, Houck PR, Hall M, Buysse DJ, et al. (1997) Temporal profiles of the course of depression during treatment. Predictors of pathways toward recovery in the elderly. Archives of General Psychiatry 54(11):1016-24. DOI: 10.1001/archpsyc.1997.01830230050007. PubMed PMID: 9366658.

6. Naismith SL, Rogers NL, Lewis SJG, Terpening Z, Ip T, et al. (2011) Sleep disturbance relates to neuropsychological functioning in late-life depression. Journal of Affective Disorders 132(1-2):139-45. DOI: 10.1016/j.jad.2011.02.027. PubMed PMID: 21435728.

7. Lee S, Jeong J, Kwak Y, Park SK (2010) Depression research: where are we now? Molecular Brain 3(8. DOI: 10.1186/1756-6606-3-8. PubMed PMID: 20219105.

8. Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. Biological Psychiatry 59(12):1116-27. DOI: 10.1016/j.biopsych.2006.02.013. PubMed PMID: 16631126.

9. Sairanen M, Lucas G, Ernfors P, Castren M, Castren E (2005) Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. Journal of Neuroscience 25(5):1089-94. DOI: 10.1523/JNEUROSCI.3741-04.2005. PubMed PMID: 15689544.

10. Martinowich K, Lu B (2008) Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacology 33(1):73-83. DOI: 10.1038/sj.npp.1301571. PubMed PMID: 17882234.

11. Lewin GR, Barde YA (1996) Physiology of the neurotrophins. Annual Review of Neuroscience 19(289-317. DOI: 10.1146/annurev.ne.19.030196.001445. PubMed PMID: 8833445.

12. Castrén E, Võikar V, Rantamäki T (2007) Role of neurotrophic factors in depression. Current Opinion in Pharmacology 7(1):18-21. DOI: 10.1016/j.coph.2006.08.009. PubMed PMID: 17049922.

13. Palazidou E (2012) The neurobiology of depression. British Medical Bulletin 101(127-45. DOI: 10.1093/bmb/lds004. PubMed PMID: 22334281.

14. 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. International Journal of Neuropsychopharmacology 11(8):1169-80. DOI: 10.1017/S1461145708009309. PubMed PMID: 18752720.

15. Sen S, Duman R, Sanacora G (2008) Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biological Psychiatry 64(6):527-32. DOI: 10.1016/j.biopsych.2008.05.005. PubMed PMID: 18571629.

16. Greenberg ME, Xu B, Lu B, Hempstead BL (2009) New insights in the biology of BDNF synthesis and release: implications in CNS function. Journal of Neuroscience 29(41):12764-7. DOI: 10.1523/JNEUROSCI.3566-09.2009. PubMed PMID: 19828787.

17. Lu B, Pang PT, Woo NH (2005) The yin and yang of neurotrophin action. Nature Reviews Neuroscience 6(8):603-14. DOI: 10.1038/nrn1726. PubMed PMID: 16062169.

18. Panja D, Bramham CR (2014) BDNF mechanisms in late LTP formation: A synthesis and breakdown. Neuropharmacology 76(Pt C):664-76. DOI: 10.1016/j.neuropharm.2013.06.024. PubMed PMID: 23831365.

19. Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, et al. (2004) Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science 306(5695):487-91. DOI: 10.1126/science.1100135. PubMed PMID: 15486301.

20. Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, et al. (2005) Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nature Neuroscience 8(8):1069-77. DOI: 10.1038/nn1510. PubMed PMID: 16025106.

21. Matsuda N, Lu H, Fukata Y, Noritake J, Gao H, et al. (2009) Differential activity-dependent secretion of brain-derived neurotrophic factor from axon and dendrite. Journal of Neuroscience 29(45):14185-98. DOI: 10.1523/JNEUROSCI.1863-09.2009. PubMed PMID: 19906967.

22. Lee R, Kermani P, Teng KK, Hempstead BL (2001) Regulation of cell survival by secreted proneurotrophins. Science 294(5548):1945-8. DOI: 10.1126/science.1065057. PubMed PMID: 11729324.

23. Lommatzsch M, Quarcoo D, Schulte-Herbruggen O, Weber H, Virchow JC, et al. (2005) Neurotrophins in murine viscera: a dynamic pattern from birth to adulthood. International Journal of Developmental Neuroscience 23(6):495-500. DOI: 10.1016/j.ijdevneu.2005.05.009. PubMed PMID: 15978771.

24. Karege F, Schwald M, Cisse M (2002) Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. Neuroscience Letters 328(3):261-4. DOI: 10.1016/S0304-3940(02)00529-3. PubMed PMID: 12147321.

25. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ (1998) Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 37(12):1553-61. DOI: 10.1016/S0028-3908(98)00141-5. PubMed PMID: 9886678.

26. Pandey GN, Dwivedi Y, Rizavi HS, Ren X, Zhang H, et al. (2010) Brain-derived neurotrophic factor gene and protein expression in pediatric and adult depressed subjects. Progress in Neuro-Psychopharmacology and Biological Psychiatry 34(4):645-51. DOI: 10.1016/j.pnpbp.2010.03.003. PubMed PMID: 20227453.

27. Vollmayr B, Simonis C, Weber S, Gass P, Henn F (2003) Reduced cell proliferation in the dentate gyrus is not correlated with the development of learned helplessness. Biological Psychiatry 54(10):1035-40. DOI: 10.1016/S0006-3223(03)00527-4. PubMed PMID: 14625145.

28. Shumake J, Poremba A, Edwards E, Gonzalez-Lima F (2000) Congenital helpless rats as a genetic model for cortex metabolism in depression. Neuroreport 11(17):3793-8. DOI: 10.1097/00001756-200011270-00040. PubMed PMID: 11117493.

29. Shumake J, Edwards E, Gonzalez-Lima F (2003) Opposite metabolic changes in the habenula and ventral tegmental area of a genetic model of helpless behavior. Brain Research 963(1-2):274-81. DOI: 10.1016/S0006-8993(02)04048-9. PubMed PMID: 12560133.

30. Shumake J, Gonzalez-Lima F (2003) Brain systems underlying susceptibility to helplessness and depression. Behavioral and Cognitive Neuroscience Reviews 2(3):198-221. DOI: 10.1177/1534582303259057. PubMed PMID: 15006293.

31. Aznar S, Klein AB, Santini MA, Knudsen GM, Henn F, et al. (2010) Aging and depression vulnerability interaction results in decreased serotonin innervation associated with reduced BDNF levels in hippocampus of rats bred for learned helplessness. Synapse 64(7):561-5. DOI: 10.1002/syn.20773. PubMed PMID: 20222154.

32. Marais L, Stein DJ, Daniels WM (2009) Exercise increases BDNF levels in the striatum and decreases depressive-like behavior in chronically stressed rats. Metabolic Brain Disease 24(4):587-97. DOI: 10.1007/s11011-009-9157-2. PubMed PMID: 19844781.

33. Nibuya M, Morinobu S, Duman RS (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. Journal of Neuroscience 15(11):7539-47. PubMed PMID: 7472505.

34. Hashimoto K (2010) Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. Psychiatry and Clinical Neurosciences 64(4):341-57. DOI: 10.1111/j.1440-1819.2010.02113.x. PubMed PMID: 20653908.

35. Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, et al. (2004) Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proceedings of the National Academy of Sciences of the United States of America 101(29):10827-32. DOI: 10.1073/pnas.0402141101. PubMed PMID: 15249684.

36. Monteggia LM, Luikart B, Barrot M, Theobold D, Malkovska I, et al. (2007) Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. Biological Psychiatry 61(2):187-97. DOI: 10.1016/j.biopsych.2006.03.021. PubMed PMID: 16697351.

37. Autry AE, Monteggia LM (2012) Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacological Reviews 64(2):238-58. DOI: 10.1124/pr.111.005108. PubMed PMID: 22407616.

38. Sairanen M, Lucas G, Ernfors P, Castren M, Castren E (2005) Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. Journal of Neuroscience 25(5):1089-94. DOI: 10.1523/JNEUROSCI.3741-04.2005. PubMed PMID: 15689544.

39. Pizarro JM, Lumley LA, Medina W, Robison CL, Chang WE, et al. (2004) Acute social defeat reduces neurotrophin expression in brain cortical and subcortical areas in mice. Brain Research 1025(1-2):10-20. DOI: 10.1016/j.brainres.2004.06.085. PubMed PMID: 15464739.

40. Roceri M, Hendriks W, Racagni G, Ellenbroek BA, Riva MA (2002) Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. Molecular Psychiatry 7(6):609-16. DOI: 10.1038/sj.mp.4001036. PubMed PMID: 12140784.

41. Fuchikami M, Morinobu S, Kurata A, Yamamoto S, Yamawaki S (2009) Single immobilization stress differentially alters the expression profile of transcripts of the brain-derived neurotrophic factor (BDNF) gene and histone acetylation at its promoters in the rat hippocampus. International Journal of Neuropsychopharmacology 12(1):73-82. DOI: 10.1017/S1461145708008997. PubMed PMID: 18544182.

42. Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS (2002) Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. Journal of Neuroscience 22(8):3251-61. DOI: 20026292. PubMed PMID: 11943826.

43. Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, et al. (2003) Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. Journal of Neuroscience 23(1):349-57. PubMed PMID: 12514234.

44. Takahashi M, Terwilliger R, Lane C, Mezes PS, Conti M, et al. (1999) Chronic antidepressant administration increases the expression of cAMP-specific phosphodiesterase 4A and 4B isoforms. Journal of Neuroscience 19(2):610-8. PubMed PMID: 9880581.

45. Rantamaki T, Hendolin P, Kankaanpaa A, Mijatovic J, Piepponen P, et al. (2007) Pharmacologically diverse antidepressants rapidly activate brain-derived neurotrophic factor receptor TrkB and induce phospholipase-Cgamma signaling pathways in mouse brain. Neuropsychopharmacology 32(10):2152-62. DOI: 10.1038/sj.npp.1301345. PubMed PMID: 17314919.

46. MacQueen GM, Ramakrishnan K, Croll SD, Siuciak JA, Yu G, et al. (2001) Performance of heterozygous brain-derived neurotrophic factor knockout mice on behavioral analogues of anxiety, nociception, and depression. Behavioral Neuroscience 115(5):1145-53. DOI: 10.1037/0735-7044.115.5.1145. PubMed PMID: 11584927.

47. Li Y, Yui D, Luikart BW, McKay RM, Li Y, et al. (2012) Conditional ablation of brain-derived neurotrophic factor-TrkB signaling impairs striatal neuron development. Proceedings of the National Academy of Sciences of the United States of America 109(38):15491-6. DOI: 10.1073/pnas.1212899109. PubMed PMID: 22949667.

48. Groves JO (2007) Is it time to reassess the BDNF hypothesis of depression? Molecular Psychiatry 12(12):1079-88. DOI: 10.1038/sj.mp.4002075. PubMed PMID: 17700574.

49. Eisch AJ, Bolanos CA, de Wit J, Simonak RD, Pudiak CM, et al. (2003) Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: a role in depression. Biological Psychiatry 54(10):994-1005. DOI: 10.1016/j.biopsych.2003.08.003. PubMed PMID: 14625141.

50. Berton O, McClung CA, Dileone RJ, Krishnan V, Renthal W, et al. (2006) Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science 311(5762):864-8. DOI: 10.1126/science.1120972. PubMed PMID: 16469931.

51. Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM (1997) Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacology, Biochemistry, and Behavior 56(1):131-7. DOI: 10.1016/S0091-3057(96)00169-4. PubMed PMID: 8981620.

52. Siuciak JA, Boylan C, Fritsche M, Altar CA, Lindsay RM (1996) BDNF increases monoaminergic activity in rat brain following intracerebroventricular or intraparenchymal administration. Brain Research 710(1-2):11-

20. DOI: 10.1016/0006-8993(95)01289-3. PubMed PMID: 8963648.

53. Altar CA (1999) Neurotrophins and depression. Trends in Pharmacological Sciences 20(2):59-61. DOI: 10.1016/S0165-6147(99)01309-7. PubMed PMID: 10101965.

54. Lee Y, Duman RS, Marek GJ (2006) The mGlu2/3 receptor agonist LY354740 suppresses immobilization stress-induced increase in rat prefrontal cortical BDNF mRNA expression. Neuroscience Letters 398(3):328-32. DOI: 10.1016/j.neulet.2006.01.021. PubMed PMID: 16469447.

55. Jayatissa MN, Henningsen K, West MJ, Wiborg O (2009) Decreased cell proliferation in the dentate gyrus does not associate with development of anhedonic-like symptoms in rats. Brain Research 1290(133-41. DOI: 10.1016/j.brainres.2009.07.001. PubMed PMID: 19595674.

56. Schmidt HD, Duman RS (2010) Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. Neuropsychopharmacology 35(12):2378-91. DOI: 10.1038/npp.2010.114. PubMed PMID: 20686454.

57. Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Kenis G, et al. (2011) Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment. Molecular Psychiatry 16(11):1088-95. DOI: 10.1038/mp.2010.98. PubMed PMID: 20856249.

58. Gervasoni N, Aubry JM, Bondolfi G, Osiek C, Schwald M, et al. (2005) Partial normalization of serum brain-derived neurotrophic factor in remitted patients after a major depressive episode. Neuropsychobiology 51(4):234-8. DOI: 10.1159/000085725. PubMed PMID: 15897674.

59. Yulug B, Ozan E, Aydin N, Kirpinar I (2009) Brain-derived neurotrophic factor polymorphism: more than a prognostic factor during depression? Journal of Neuropsychiatry and Clinical Neurosciences 21(4):471-2. DOI: 10.1176/jnp.2009.21.4.471. PubMed PMID: 19996261.

60. Lee BH, Kim YK (2009) Reduced platelet BDNF level in patients with major depression. Progress in Neuro-Psychopharmacology & Biological Psychiatry 33(5):849-53. DOI: 10.1016/j.pnpbp.2009.04.002. PubMed PMID: 19371767.

61. Krishnan V, Han MH, Graham DL, Berton O, Renthal W, et al. (2007) Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell 131(2):391-404. DOI: 10.1016/j.cell.2007.09.018. PubMed PMID: 17956738.

62. Tebartz VEL, Woermann F, Lemieux L, Trimble MR (2000) Increased amygdala volumes in female and depressed humans. A quantitative magnetic resonance imaging study. Neuroscience Letters 281(2-3):103-6. DOI: 10.1016/S0304-3940(00)00815-6. PubMed PMID: 10704753.

63. van Eijndhoven P, van Wingen G, van Oijen K, Rijpkema M, Goraj B, et al. (2009) Amygdala volume marks the acute state in the early course of depression. Biological Psychiatry 65(9):812-8. DOI: 10.1016/j.biopsych.2008.10.027. PubMed PMID: 19028381.

64. Frodl T, Meisenzahl E, Zetzsche T, Bottlender R, Born C, et al. (2002) Enlargement of the amygdala in patients with a first episode of major depression. Biological Psychiatry 51(9):708-14. DOI: 10.1016/S0006-3223(01)01359-2. PubMed PMID: 11983184.

65. Yu H, Chen ZY (2011) The role of BDNF in depression on the basis of its location in the neural circuitry. Acta pharmacologica Sinica 32(1):3-11. DOI: 10.1038/aps.2010.184. PubMed PMID: 21131999.

66. Conn VS (2010) Depressive symptom outcomes of physical activity interventions: meta-analysis findings. Annals of Behavioral Medicine 39(2):128-38. DOI: 10.1007/s12160-010-9172-x. PubMed PMID: 20422333.

67. Pedersen BK, Pedersen M, Krabbe KS, Bruunsgaard H, Matthews VB, et al. (2009) Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. Experimental Physiology 94(12):1153-60. DOI: 10.1113/expphysiol.2009.048561. PubMed PMID: 19748969.

68. Gustafsson G, Lira CM, Johansson J, Wisen A, Wohlfart B, et al. (2009) The acute response of plasma brain-derived neurotrophic factor as a result of exercise in major depressive disorder. Psychiatry Research 169(3):244-8. DOI: 10.1016/j.psychres.2008.06.030. PubMed PMID: 19729204.

69. Gorgulu Y, Caliyurt O (2009) Rapid antidepressant effects of sleep deprivation therapy correlates with serum BDNF changes in major depression. Brain Research Bulletin 80(3):158-62. DOI: 10.1016/j.brainres-

bull.2009.06.016. PubMed PMID: 19576267.

70. Piccinni A, Del DA, Medda P, Bianchi C, Roncaglia I, et al. (2009) Plasma Brain-Derived Neurotrophic Factor in treatment-resistant depressed patients receiving electroconvulsive therapy. European Neuropsychopharmacology 19(5):349-55. DOI: 10.1016/j.euroneuro.2009.01.002. PubMed PMID: 19223156.

71. Marano CM, Phatak P, Vemulapalli UR, Sasan A, Nalbandyan MR, et al. (2007) Increased plasma concentration of brain-derived neurotrophic factor with electroconvulsive therapy: a pilot study in patients with major depression. Journal of Clinical Psychiatry 68(4):512-7. DOI: 10.4088/jcp.v68n0404. PubMed PMID: 17474805.

72. Fernandes B, Gama CS, Massuda R, Torres M, Camargo D, et al. (2009) Serum brain-derived neurotrophic factor (BDNF) is not associated with response to electroconvulsive therapy (ECT): a pilot study in drug resistant depressed patients. Neuroscience Letters 453(3):195-8. DOI: 10.1016/j.neulet.2009.02.032. PubMed PMID: 19429034.

73. Satomura E, Baba H, Nakano Y, Maeshima H, Suzuki T, et al. (2011) Correlations between brain-derived neurotrophic factor and clinical symptoms in medicated patients with major depression. Journal of Affective Disorders 135(1-3):332-5. DOI: 10.1016/j.jad.2011.06.041. PubMed PMID: 21774990.

74. Bus BA, Tendolkar I, Franke B, de Graaf J, den Heijer M, et al. (2012) Serum brain-derived neurotrophic factor: determinants and relationship with depressive symptoms in a community population of middle-aged and elderly people. World Journal of Biological Psychiatry 13(1):39-47. DOI: 10.3109/15622975.2010.545187. PubMed PMID: 21247257.

75. Martinez JM, Garakani A, Yehuda R, Gorman JM (2012) Proinflammatory and "resiliency" proteins in the CSF of patients with major depression. Depression and Anxiety 29(1):32-8. DOI: 10.1002/da.20876. PubMed PMID: 21898706.

76. Drzyzga LR, Marcinowska A, Obuchowicz E (2009) Antiapoptotic and neurotrophic effects of antidepressants: a review of clinical and experimental studies. Brain Research Bulletin 79(5):248-57. DOI: 10.1016/j.brainresbull.2009.03.009. PubMed PMID: 19480984.

77. Dunham JS, Deakin JF, Miyajima F, Payton A, Toro CT (2009) Expression of hippocampal brain-derived neurotrophic factor and its receptors in Stanley consortium brains. Journal of Psychiatric Research 43(14):1175-84. DOI: 10.1016/j.jpsychires.2009.03.008. PubMed PMID: 19376528.

78. Matrisciano F, Bonaccorso S, Ricciardi A, Scaccianoce S, Panaccione I, et al. (2009) Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine. Journal of Psychiatric Research 43(3):247-54. DOI: 10.1016/j.jpsychires.2008.03.014. PubMed PMID: 18511076.

79. Schmidt HD, Duman RS (2007) The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. Behavioural Pharmacology 18(5-6):391-418. DOI: 10.1097/FBP.0b013e3282ee2aa8. PubMed PMID: 17762509.

80. Newton SS, Duman RS (2004) Regulation of neurogenesis and angiogenesis in depression. Current Neurovascular Research 1(3):261-7. DOI: 10.2174/1567202043362388. PubMed PMID: 16181076.

81. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT (2001) Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biological Psychiatry 50(4):260-5. DOI: 10.1016/S0006-3223(01)01083-6. PubMed PMID: 11522260.

82. Baare WF, Vinberg M, Knudsen GM, Paulson OB, Langkilde AR, et al. (2010) Hippocampal volume changes in healthy subjects at risk of unipolar depression. Journal of Psychiatric Research 44(10):655-62. DOI: 10.1016/j.jpsychires.2009.12.009. PubMed PMID: 20096419.

83. Chen MC, Hamilton JP, Gotlib IH (2010) Decreased hippocampal volume in healthy girls at risk of depression. Archives of General Psychiatry 67(3):270-6. DOI: 10.1001/archgenpsychiatry.2009.202. PubMed PMID: 20194827.

84. Frodl T, Reinhold E, Koutsouleris N, Reiser M, Meisenzahl EM (2010) Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. Journal of Psychiatric Research 44(13):799-807. DOI: 10.1016/j.jpsychires.2010.01.006. PubMed PMID: 20122698.

85. Frodl T, Schule C, Schmitt G, Born C, Baghai T, et al. (2007) Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. Archives of General Psychiatry 64(4):410-6. DOI: 10.1001/archpsyc.64.4.410. PubMed PMID: 17404118.

86. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW (1996) Hippocampal atrophy in recurrent major depression. Proceedings of the National Academy of Sciences of the United States of America 93(9):3908-13. DOI: 10.1073/pnas.93.9.3908. PubMed PMID: 8632988.

87. Jessen F, Schuhmacher A, von Widdern O, Guttenthaler V, Hofels S, et al. (2009) No association of the Val-66Met polymorphism of the brain-derived neurotrophic factor with hippocampal volume in major depression. Psychiatric Genetics 19(2):99-101. DOI: 10.1097/YPG.0b013e32832080ce. PubMed PMID: 19668114.

88. Reif A, Fritzen S, Finger M, Strobel A, Lauer M, et al. (2006) Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Molecular Psychiatry 11(5):514-22. DOI: 10.1038/sj.mp.4001791. PubMed PMID: 16415915.

89. Boldrini M, Underwood MD, Hen R, Rosoklija GB, Dwork AJ, et al. (2009) Antidepressants increase neural progenitor cells in the human hippocampus. Neuropsychopharmacology 34(11):2376-89. DOI: 10.1038/npp.2009.75. PubMed PMID: 19606083.

90. Umene-Nakano W, Yoshimura R, Ikenouchi-Sugita A, Hori H, Hayashi K, et al. (2009) Serum levels of brain-derived neurotrophic factor in comorbidity of depression and alcohol dependence. Human Psychopharmacology 24(5):409-13. DOI: 10.1002/hup.1035. PubMed PMID: 19548207.

91. Hellweg R, Ziegenhorn A, Heuser I, Deuschle M (2008) Serum concentrations of nerve growth factor and brain-derived neurotrophic factor in depressed patients before and after antidepressant treatment. Pharmacopsychiatry 41(2):66-71. DOI: 10.1055/s-2007-1004594. PubMed PMID: 18311687.

92. Cattaneo A, Bocchio-Chiavetto L, Zanardini R, Milanesi E, Placentino A, et al. (2010) Reduced peripheral brain-derived neurotrophic factor mRNA levels are normalized by antidepressant treatment. International Journal of Neuropsychopharmacology 13(1):103-8. DOI: 10.1017/S1461145709990812. PubMed PMID: 19835669.

93. Yoshimura R, Ikenouchi-Sugita A, Hori H, Umene-Nakano W, Katsuki A, et al. (2010) Adding a low dose atypical antipsychotic drug to an antidepressant induced a rapid increase of plasma brain-derived neurotrophic factor levels in patients with treatment-resistant depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry 34(2):308-12. DOI: 10.1016/j.pnpbp.2009.12.003. PubMed PMID: 20005280.

94. Dwivedi Y, Rizavi HS, Pandey GN (2006) Antidepressants reverse corticosterone-mediated decrease in brain-derived neurotrophic factor expression: differential regulation of specific exons by antidepressants and corticosterone. Neuroscience 139(3):1017-29. DOI: 10.1016/j.neuroscience.2005.12.058. PubMed PMID: 16500030.

95. Dias BG, Banerjee SB, Duman RS, Vaidya VA (2003) Differential regulation of brain derived neurotrophic factor transcripts by antidepressant treatments in the adult rat brain. Neuropharmacology 45(4):553-63. DOI: 10.1016/S0028-3908(03)00198-9. PubMed PMID: 12907316.

96. Dwivedi Y (2009) Brain-derived neurotrophic factor: role in depression and suicide. Neuropsychiatric Disease and Treatment 5(433-49. DOI: 10.2147/NDT.S5700. PubMed PMID: 19721723.

97. Malinow R (2016) Depression: Ketamine steps out of the darkness. Nature 533(7604):477-8. DOI: 10.1038/nature17897. PubMed PMID: 27144350.

98. DeWilde KE, Levitch CF, Murrough JW, Mathew SJ, Iosifescu DV (2015) The promise of ketamine for treatment-resistant depression: current evidence and future directions. Annals of the New York Academy of Sciences 1345(1):47-58. DOI: 10.1111/nyas.12646. PubMed PMID: 25649308.

99. Lepack AE, Fuchikami M, Dwyer JM, Banasr M, Duman RS (2015) BDNF release is required for the behavioral actions of ketamine. International Journal of Neuropsychopharmacology 18(1):1-6. DOI: 10.1093/ijnp/pyu033. PubMed PMID: 25539510.