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

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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.

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Keywords

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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 (Trk-B)-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 serotonergic 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 unknown 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 demonstrated to have an increase [70, 71] or have no role on the expression or release of BDNF [72]. The concentrations of serum BDNF are assessed 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 combined 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.

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