New hypothesis and treatment targets of depression: an integrated view of key findings

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Major depressive disorder (MDD) is a common and devastating psychiatric disorder characterized by persistent low mood, cognitive disorder, and impaired social function. Despite its complex mechanisms, increasing evidence has identified the involvement of neurotrophic factors, inflammatory cytokines, the hypothalamus-pituitary-adrenal axis, and glutamate receptors in the pathophysiology of this illness. The present review synthesizes recent research achievements to define the network between different hypotheses of MDD and to understand which part is most pivotal for its pathogenesis. By integrating MDD-related signal pathways, we highlight brain-derived neurotrophic factor (BDNF) dysfunction and increased apoptosis as the final common cascades, and new therapeutic strategies aiming to enhance BDNF function have been shown to exert a rapid and effective antidepressant action.

Keywords: depression; BDNF; cytokines; hypothalamus-pituitary-adrenal axis; glutamate receptor

Introduction

Major depressive disorder (MDD) is a mental disorder characterized by prominent and persistent low mood, mental retardation, cognitive impairment, volitional decline, and somatic symptoms. MDD, which has a significantly high recurrence rate, can reduce the capacity of a patient to study, work, and engage in social skills, as well as increase the disability rate and suicide risk. According to the statistics of the World Health Organization, there are 300 million patients with MDD. It is estimated that by 2020 the disease burden caused by MDD will be ranked next to ischemic heart disease, becoming the second most common cause of disability and death.

Currently, the understanding of depression is mainly based on the monoamine-deficiency hypothesis, which proposes that the occurrence of depression is associated with deficiencies of three major monoamine transmitters, 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA). By inhibiting their transporters, antidepressants block their reuptake, thereby increasing the transmitter concentration in the synaptic cleft and relieving the symptoms of depression.

However, the monoamine-deficiency hypothesis is being seriously challenged. First, antidepressant treatment has an efficiency of only 60%–65% with a remission rate of ~30%, while a high percentage of patients show no improvement, even after combination therapy with a variety of antidepressants. Second, although antidepressants rapidly increase the levels of monoamine neurotransmitters in the central nervous system (CNS) by blocking the transporters, it often takes two weeks or even longer for the onset of antidepressant efficacy. All this evidence indicates that monoamine-deficiency can only partly explain the pathogenesis of depression.

At the moment, large numbers of clinical and basic studies have provided new hypotheses for the pathogenesis of MDD. In this review, we begin with the classic monoamine hypothesis, and then review some new hypotheses of the mechanisms and therapeutic targets...
in depression. We aim to present an integrated view of depression mechanisms and new thinking about the therapeutic strategies for the development of new drugs.

**The Neurotrophic Factor Hypothesis and Related New Therapeutic Targets**

Two major factors are related to the delayed efficacy of antidepressants. First, it takes two to three weeks for the adaptation of receptor sensitivity, such as the desensitization of presynaptic 5-HT₁A autoreceptors. So far, one of the main directions of antidepressant development is to inhibit the function of 5-HT₁A autoreceptors to facilitate their rapid desensitization[7, 8]. Second, the increased synthesis of cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) often takes 2–3 weeks, which is coincident with the delayed onset of efficacy, suggesting that these are likely to be key mechanisms for the delayed efficacy of antidepressants[9]. More evidence has shown that decreased neurotrophic factors (NTFs), especially BDNF, and impaired synaptic plasticity may be the common pathways of depression[10].

NTFs are a class of small proteins with neurotrophic functions, and include nerve growth factor, BDNF, glial cell line-derived neurotrophic factor, insulin-like growth factor, and transfer growth factor[11]. The confirmed biological roles of NTFs include: maintaining neural survival in embryonic development and promoting differentiation, facilitating axonal growth, guiding nerve-growth direction, maintaining the survival of mature neurons, and accelerating neurogenesis[11].

Clinical and animal studies have shown reduced BDNF mRNA levels in the hippocampus of depressed animal models[12] and decreased levels of serum BDNF in untreated depressed patients[13]. Patients with depression often show atrophy or lack of neurons, particularly in the hippocampus and the cerebral cortex[14]. In vivo and in vitro animal experiments have shown increased BDNF levels in the limbic system and in plasma after long-term treatment with antidepressants[15]. Besides, administration of BDNF into the animal brain has antidepressant-like behavioral effects[16]. All these findings suggest that BDNF may be key in the treatment of depression. In fact, changes in the BDNF level have been widely used as a biomarker for depression. In addition, the BDNF Met allele is associated with an increased suicide risk in patients with depression[17, 18], especially in females as well as in early-onset[19] and elderly depression patients[20].

Therefore, NTFs are considered to be an important and new clue for understanding the pathogenesis of depression and the mechanisms of action of antidepressants[21]. In 2006, Duman et al.[22] proposed a neurotrophin hypothesis of depression, which claimed that NTFs promote synaptic growth and maintain neuronal survival, while their deficiency induces atrophy of brain structures and MDD. In addition, antidepressants exert their effect by enhancing the levels of NTFs in the brain, increasing synaptic plasticity, and promoting neuronal survival. As an important NTF, BDNF mainly acts on neurons in the hippocampus, cerebral cortex, cerebellum, and basal forebrain, which are associated with higher functions such as learning and memory. BDNF also promotes neural proliferation and differentiation and has an anti-apoptotic function, as well as regulating synaptic morphology, information transmission and plasticity, thereby improving the symptoms of depression[23, 24]. Interestingly, BDNF improves sleep architecture, especially slow-wave sleep, during antidepressant treatment, which reflects enhanced synaptic plasticity and the synchronization of neuronal circuits[25].

Decreased slow-wave sleep usually leads to reduced cognition and depressed emotion, which are commonly observed in depressed patients with sleep disorders[26, 27]. In addition, reduced synaptic plasticity and slow-wave sleep are commonly reported in populations carrying BDNF Val66Met polymorphisms, suggesting an association with functional defects of BDNF, and importantly, these patients are likely to be resistant to antidepressant treatments targeting BDNF[28, 29].

At present, the antidepressant effect of BDNF is not fully understood, so it is urgent to study the mechanisms of BDNF synthesis and release in order to develop new antidepressants. BDNF expression can be facilitated in two ways. One is to increase CREB-mediated BDNF expression, but it usually takes 2–3 weeks for the onset of antidepressant effects, which does not meet the demand for a rapid response. Another way is through direct action on membrane-binding receptors especially ion channel receptors, for example by N-methyl-D-aspartate receptor (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) agonists. Drug