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·Review·

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

Shangli Cai, Shucai Huang, Wei Hao

Mental Health Institute and Key Laboratory of Psychiatry of Hunan Province, The Second Xiangya Hospital, Central South University, Changsha 410011, China

Corresponding author: Wei Hao. E-mail: weihao57@gmail.com

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[1]. According to the statistics of the World Health Organization, there are 300 million patients with MDD[2]. 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[3].

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[4]. First, antidepressant treatment has an efficiency of only 60%–65% with a remission rate of ~30%[5, 6], 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-HT_{1A} autoreceptors. So far, one of the main directions of antidepressant development is to inhibit the function of 5-HT_{1A} 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 (AMPAR) agonists. Drug

development based on this strategy is the major direction for future antidepressant agents. Moreover, the inhibition of factors that decrease BDNF expression and function can also indirectly maintain BDNF levels and function. Post-translational modification is an important procedure for BDNF maturation. After synthesis in the ribosomes, pro-BDNF is processed in the rough endoplasmic reticulum to become the mature and active form *via* a variety of proteins including furin, proconvertase, and P11-tPA-plasmin[30].

The Sigma-1 receptor (σ1R) is an important chaperone located at the endoplasmic reticulum-mitochondria junction and is involved in the maturation process of pro-BDNF[31] (Fig. 1). This association indicates that the σ1R may serve as a therapeutic target in the treatment of depression. In the brain, σ1Rs are mainly distributed in the dentate gyrus, thalamus, and hypothalamus; activation and up-regulation of this receptor facilitates neurogenesis and neural differentiation as well as having anti-apoptotic effects. Several studies have shown that activation of the σ1R enhances BDNF expression[32], while others claim that the agonists of this receptor actually promote the maturation

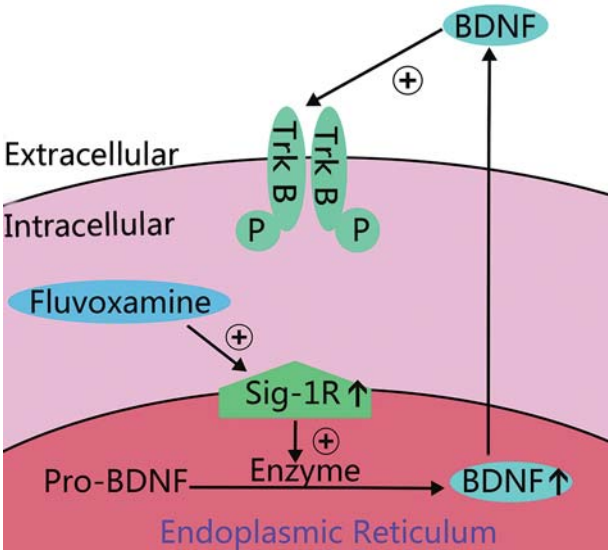

Fig. 1. Activation of the Sigma-1 receptor enhances the secretion of mature BDNF. The Sigma-1 receptor (Sig-1R) facilitates the maturation of pro-BDNF into BDNF and increases the secretion of mature BDNF, which could partially explain the fluvoxamine-mediated antidepressant effect. Increased BDNF secretion activates TrkB, which leads to enhancement of downstream signaling pathways.

of BDNF in the endoplasmic reticulum (i.e., the conversion of pro-BDNF to BDNF). Despite the increases of BDNF synthesis and secretion, its mRNA levels do not change. Moreover, an increase of mature BDNF is accompanied by decreased pro-BDNF levels after treatment with a σ1R agonist[33]. Clearly, the mechanism of BDNF upregulation by the σ1R is different from the antidepressant-mediated BDNF mRNA increase. In addition, the evidence below suggests that the σ1R is also involved in the pathogenesis of depressive disorders: (1) compared with healthy participants, the plasma level of the σ1R declines in patients with depression and increases after treatment with antidepressants[34]; (2) σ1R-knockout mice show a prolonged immobility time in the forced swimming test, an animal model of depression, indicating that deletion of σ1Rs exacerbates the severity of depression[35]; (3) administration of σ1R agonists reduces the immobility time in the forced swimming and tail-suspension tests in a dose-dependent manner, exhibiting a good antidepressant-like effect. In contrast, σ1R antagonists blocks its antidepressant-like effect[36]; and (4) the σ1R has a regulatory effect on monoamine neurotransmitters: σ1R agonists in rats up-regulate DA levels in the frontal cortex, increase the discharge of serotonergic neurons in the dorsal raphe nucleus, and enhance 5-HT release[37, 38]. σ1R agonists also enhance the antidepressant-like effects of NMDAR antagonists (amantadine and memantine) and other antidepressants such as fluvoxamine, venlafaxine, and buspirone[39].

In fact, many factors can affect BDNF synthesis, release, and function, such as changes in inflammatory cytokines and glutamate receptors, and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. All these have crucial regulatory effects on the expression and function of BDNF, and serve as new targets for antidepressants.

The Inflammatory Cytokine Hypothesis of Depression and Related New Therapeutic Targets

Cytokines are a class of signaling polypeptides secreted by the immune system, and are widely distributed in the immune and nervous systems. When the immune system responds to stressors such as disease, injury, infection, or psychosocial factors, cytokines are secreted to regulate body functions[40].

Much evidence indicates that changes in inflammatory cytokines are closely associated with the occurrence of depression, leading to the cytokine hypothesis of depression which proposes that depression is often associated with immune disorders, activation of the inflammatory response system, and elevated inflammatory cytokines under stress conditions. Under psychological stress or physical illness, the release of inflammatory cytokines can be dramatic, leading to significant increases in interleukin-1 (IL-1), IL-2, IL-6, tumor necrosis factor-α, and C-reactive protein[41-43]. Increased IL-1 and IL-2 can lead to apoptosis, attenuate neuronal differentiation, suppress synaptic transmission, and inhibit the induction and maintenance of long-term potentiation, which represents an impairment in learning, and finally result in MDD[44, 45]. The anti-inflammatory drug celecoxib, a specific inhibitor of COX-2, has a synergistic antidepressant effect. Combined treatment with celecoxib and antidepressant has shown an increased response rate and symptom remission rate compared with antidepressant alone[46] (Fig. 2).

Moreover, inflammatory cytokines are an important cause of glucocorticoid resistance, glutamate excitotoxicity, and reduced BDNF expression. Specifically, they block the functions of glucocorticoid receptors (GRs)[47], producing an effect similar to glucocorticoid resistance. Furthermore, by interfering with GR functions, inflammatory cytokines attenuate the negative feedback inhibition of glucocorticoid release mediated by GRs[47]; excessive secretion of glucocorticoids ultimately results in hyper-glucocorticoidemia, which reduces the BDNF levels in the

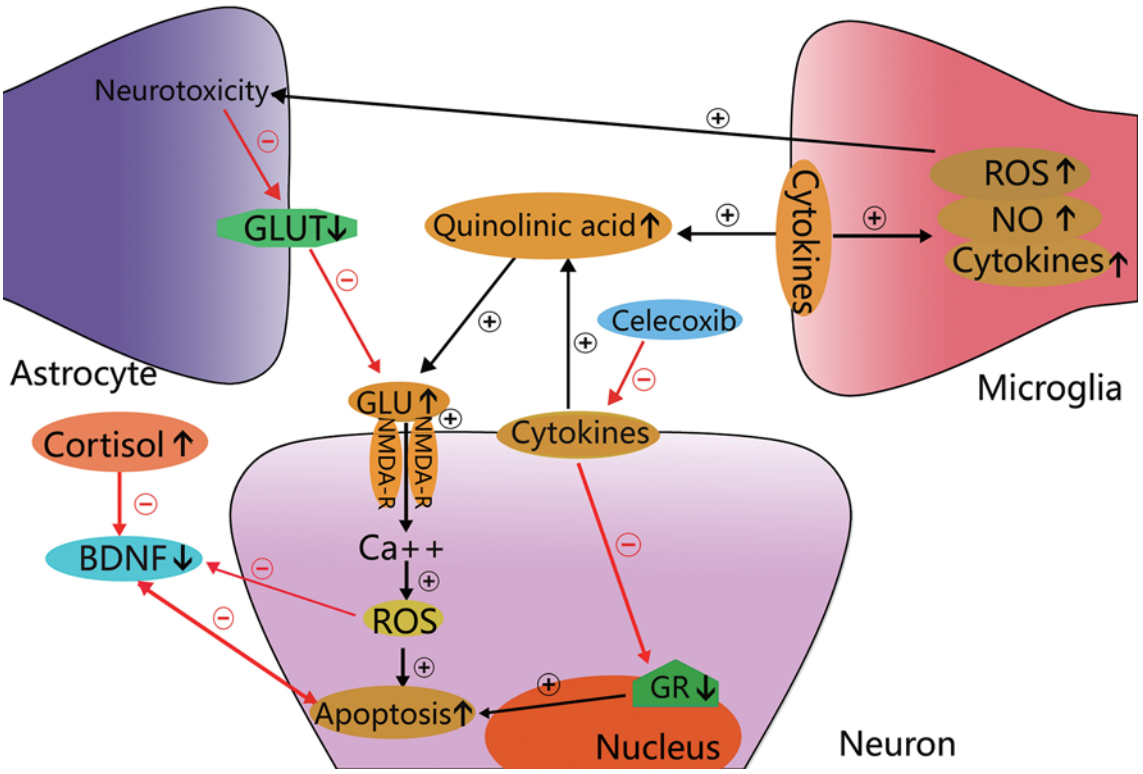

Fig. 2. Pro-inflammatory cytokines facilitate glucocorticoid resistance and glutamate excitotoxicity. The immune system activated by stressors releases excessive pro-inflammatory cytokines. The increased cytokines block glutamate receptors (GLUT), attenuating the negative feedback inhibition of glucocorticoid release. Excessive glucocorticoids ultimately reduce BDNF secretion, leading to apoptosis or degeneration in neurons. Specifically, activation of microglia and up-regulation of pro-inflammatory cytokines result in increased quinolinic acid, which contributes to excessive glutamate release into the synaptic cleft and less glutamate reuptake into astrocytes, ultimately leading to extrasynaptic NMDAR-mediated excitotoxicity. Celecoxib could exert adjunctive antidepressant effects by suppressing the pro-inflammatory cytokines.

brain, leading to apoptosis or degeneration of neurons[48]. Besides, the increased inflammatory cytokines in the CNS are closely associated with the elevation of glutamate as well as excitotoxicity mediated by NMDARs. When central microglial cells and inflammatory cytokines are activated, the activity of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase is enhanced, leading to reduced tryptophan, a precursor of 5-HT synthesis, and increased quinolinic acid synthesis[49]. Then the increased quinolinic acid enhances the release of glutamate, resulting in excessive glutamate in the synaptic cleft. Moreover, elevated quinolinic acid can directly activate extrasynaptic NMDARs, which are involved in excitotoxic injury. This scenario leads to the activation of extrasynaptic NMDARs and excitotoxicity characterized by Ca^{2+} overload[49]. Additional studies showed that the increases of inflammatory cytokines and glucocorticoids caused by stress lead to a reduction of central astrocytes, causing a decreased capacity of the glutamate transporters in astrocytes to transport intracellular glutamate and thus increasing extrasynaptic glutamate[50, 51]. Notably, the excitatory neurotoxicity caused by glutamate (mainly oxidative stress) can also lead to reduced BDNF expression, which is the core mechanism of the occurrence of depression[52, 53] (Fig. 2).

The Abnormal Glutamate Receptors Hypothesis and Related New Therapeutic Targets

Inotropic glutamate receptors, NMDARs and AMPARs, are closely associated with the occurrence of depression. Activation of these receptors permits the passage of cations such as Na^+ and Ca^{2+}. Moreover, there is a glycine-binding site at the outer membrane area of the NMDAR and a Mg^{2+}-binding site at the inner side of the channel. Under physiological conditions, the activation of AMPARs and NMDARs in the postsynaptic membrane (mainly NR2A receptor subtypes) is a crucial electrophysiological mechanism for synaptic plasticity as well as learning and memory. But under pathological conditions, particularly when stimulated by excessive glutamate, activation of extrasynaptic NMDARs (mainly NR2B receptor subtypes) results in a series of adverse events, including Ca^{2+} overload, oxidative stress injury, and apoptosis or degeneration[54]. In fact, recent research has revealed that the levels of AMPARs and NMDARs decrease in both depressed patients and depressive animal models after long-term stress, and this decline may be attributed to the over-activation of GRs and degradation of glutamate receptors[55, 56]. Decreased AMPARs in the postsynaptic membrane can result in the impairment of glutamate receptor-related cascades for cell survival and synaptogenesis and further induce MDD. All the above are key points of the abnormal glutamate receptors hypothesis of MDD.

Currently, the development of antidepressants is mainly focused on NMDAR antagonists. The key mechanisms of decreased BDNF induced by inflammatory cytokines are the quinolinic acid-mediated release of glutamate and the overactivation of extrasynaptic NMDARs. Therefore, blocking NMDARs to inhibit the over-activation of extrasynaptic NMDARs caused by glutamate and quinolinic acid is one of the important antidepressant mechanisms of NMDAR antagonists. More importantly, blocking NMDARs may enhance the activation of AMPARs *via* blocking NMDAR-mediated signal pathways (Fig. 3). This is because pretreatment with NBQX, an AMPAR antagonist, blocks the rapid antidepressant effects mediated by ketamine, an NMDAR antagonist[57], indicating that such antagonists are more likely to exert fast antidepressant effects by enhancing AMPAR signaling. But how does the activation of AMPARs lead to rapid antidepressant effects? Studies have shown that the fast antidepressant effects of NMDAR antagonists are dependent on the rapid synthesis of BDNF. Also, 4 h after treatment with ketamine for refractory depression, the plasma levels of BDNF rapidly and significantly increase; this is considered to be due to activation of the PI3K-AKT-mTOR pathway caused by AMPAR activation. Activation of mTOR deactivates eukaryotic elongation factor-2 kinase (eEF2K), which results in the activation of its substrate eEF2 and ultimately promotes the translation of BDNF[58, 59]. In addition, the increased BDNF can further act on mTOR through the TrkB-PI3K-AKT cascade to achieve positive feedback regulation of BDNF expression. In light of the importance of eEF2 in the facilitation of BDNF, inhibitors of eEF2 kinase are currently being developed, and preliminary results show that they have a rapid antidepressant effect by facilitating BDNF expression[60].

In addition to the PI3K-AKT-mTOR pathway, downstream pathways such as the PI3K-AKT-Wnt (GSK-3β-

catenin) pathway of TrkB and the BDNF receptor are also involved in the rapid antidepressant effects of ketamine. To exert an antidepressant effect, ketamine can both activate AKT and inhibit GSK-3β. Transgenic mice carrying a GSK-3 sustained-activation gene show complete resistance to the ketamine-mediated antidepressant effect[61]. The influence of GSK-3β activity on the efficiency of antidepressants is probably through its downstream molecule β-catenin. As a key signaling molecule in the Wnt pathway, β-catenin plays an important regulatory role in maintaining the genesis and proliferation of neurons as well as synaptic functions. AKT-mediated inhibition of GSK-3β reduces the phosphorylation levels of β-catenin and thereby blocks the degradation of phosphorylated β-catenin mediated by the ubiquitin-proteasome pathway, enabling a stable intracellular level of β-catenin that enters the nucleus to participate in the transcriptional activation of specific genes and the facilitation of neurogenesis. In addition, inhibition of the ubiquitin-proteasome degradation system is crucial for stabilizing the content of AMPARs, although this needs to be further confirmed. The latest research shows that the Wnt/β-catenin signaling pathway is crucial for the BDNF promotion of proliferation and differentiation of neural stem cells; treatment with IWR1, an inhibitor of the Wnt pathway, blocks the neuroprotective effects of BDNF[62].

Previous studies have shown that NMDAR antagonists have a promising effect on patients with treatment-resistant depression, but we need to be aware of their side-effects such as sedation and sensory gating disorders, especially the fact that NMDAR antagonists induce psychosis in healthy volunteers[63]. Furthermore, NMDAR antagonists including ketamine enhance the activity of acetylcholinesterase, thereby promoting the degradation of acetylcholine and leading to cognitive disorders[64]. Therefore, it will be very difficult to determine whether it is necessary to provide patients with long-term maintenance therapy of NMDAR antagonists.

Owing to the potential adverse effects of NMDAR antagonists, research has switched to studying NMDAR-related targets that can indirectly inhibit NMDARs. Two targets have received much attention: mGluR2/3 (metabotropic glutamate receptor 2/3 subtypes) and glycine binding sites. Currently, it has been confirmed that mGluR2/3 antagonists have antidepressant effects[65] that have many features in common with those of ketamine. This is because mGluR2/3 regulates glutamate release by negative feedback; hence, glutamate release in the synaptic cleft is largely enhanced after blocking mGluR2/3, and the increased glutamate further activates AMPARs and facilitates the activation of the downstream PI3K-AKT-mTOR pathway to exert antidepressant effects. Pretreatment with rapamycin (an mTOR inhibitor) or NBQX (an AMPAR antagonist) completely blocks the antidepressant effect of mGluR2/3 antagonists[66]. In addition, GLYX-13, a partial agonist of the NMDAR at glycine-binding sites, also has a strong antidepressant effect. If NMDARs are over-activated, GLYX-13 can exert its antidepressant effect mainly by blocking them; if NMDARs are insufficiently activated, it can enhance their function and facilitate long-term potentiation[67, 68].

The Hypothalamus-Pituitary-Adrenal Axis Hyperactivity Hypothesis and Related New Therapeutic Targets

As one of the important components of the neuroendocrine system, the HPA axis consists of three parts, the hypothalamic hypophysiotropic area, the pituitary, and the adrenal cortex. The hypothalamic hypophysiotropic area contains neurons that synthesize and release corticotropin-releasing hormone (CRH). The pituitary synthesizes and releases adrenocorticotropic hormone (ACTH), and the adrenal cortex is mainly responsible for the synthesis and release of glucocorticoids (mainly cortisol).

The HPA axis hyperactivity hypothesis is based on the postulate that enhancement of HPA axis activity is a key mechanism for depression when the body is exposed to stressors. The increased secretion of CRH, ACTH, and glucocorticoids has been reported in the cerebrospinal fluid of patients with depression[69]. High concentrations of glucocorticoids can have long-term adverse effects, which include: (1) imbalance of negative feedback in the HPA axis, including downregulation of negative feedback and dysfunction of GRs, disinhibition in the dexamethasone suppression test, and high concentrations of glucocorticoids in the blood; (2) excessive activation of GRs in its target cells in the CNS leads to neuronal apoptosis and degeneration[48] which is explained by the attenuation of BDNF expression and proliferation[70, 71]. In

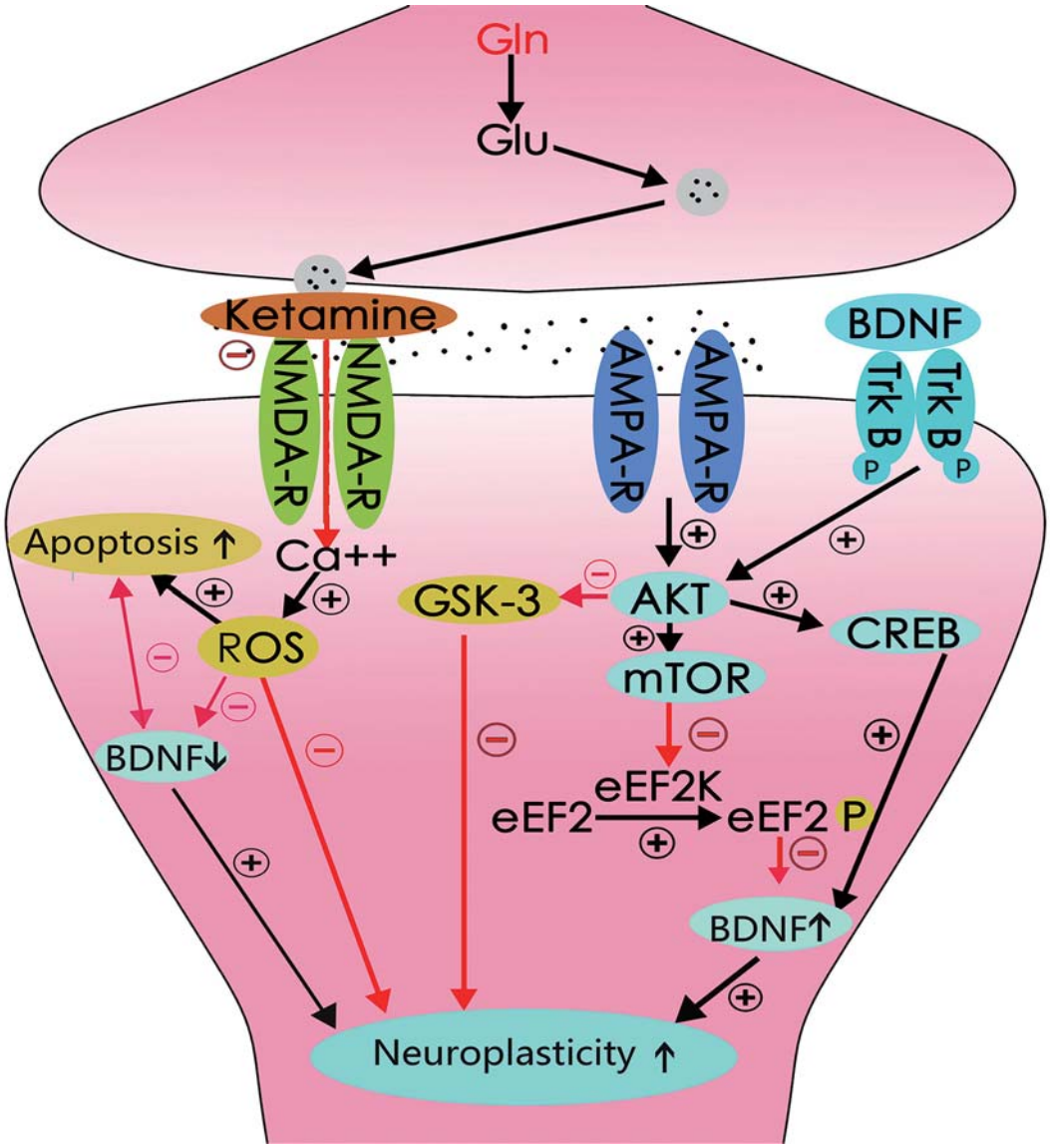

Fig. 3. Abnormal glutamate receptor hypothesis of MDD and mechanisms underlying the rapid antidepressant effects of NMDA receptor (NMDAR) antagonists. NMDARs and AMPARs are closely associated with depression. Blocking NMDARs to inhibit the over-activation of extrasynaptic NMDARs caused by glutamate and quinolinic acid is one of the important antidepressant mechanisms of NMDAR antagonists. More importantly, blocking NMDARs may enhance the activation of AMPARs *via* blocking NMDAR-mediated signal pathways. Activation of AMPARs results in enhancement of the PI3K-AKT-mTOR cascade and leads to inactivation of eEF2K and increased eEF2 phosphorylation, which ultimately promotes the eEF2-dependent translation of BDNF. Increased BDNF further achieves positive feedback regulation of BDNF expression through the TrkB-PI3K-AKT-mTOR and TrkB-PI3K-AKT-CREB pathways. In addition, suppression of GSK3 mediated by AKT contributes to the antidepressant actions of ketamine.

addition, the increased glucocorticoid levels enhance the expression of 5-HT transporters in the hippocampus, the frontal cortex, the amygdala, the dorsal raphe nucleus, and other brain regions in a GR-dependent manner, resulting in reduced 5-HT in the synaptic cleft and aggravation of depressive symptoms[72]. Accordingly, the strategy for MDD treatment is either restoring the negative feedback in the HPA or blocking the over-activated GRs. GR antagonists have demonstrated potential therapeutic properties for mood disorders, but risks also exist as the GR antagonist

mifepristone (RU-486) mediates significantly elevated cortisol and ACTH levels[73].

Recently, the macrophage migration inhibitory factor (MIF) has been found to be a key intermediate that links the activities of inflammatory cytokines and the HPA axis (Fig. 4). MIF is a pro-inflammatory factor that inhibits macrophage migration, and is present in many cell types, but it is mainly expressed in lymphocytes, macrophages, monocytes, and fibroblasts. In contrast to other pro-inflammatory factors that are inhibited by glucocorticoids, MIF expression can be induced by stimulation with glucocorticoids[74], and the induced MIF can reduce the sensitivity of immune cells such as lymphocytes and macrophages to glucocorticoids[75], thereby combating its anti-inflammatory and immunosuppressive effects. Evidence from clinical trials has shown that the MIF expression in leukocytes from patients with severe depression is 40% higher than that in patients with moderate depression[76], while in patients who are insensitive to antidepressants, the MIF mRNA levels are 48% higher[77]. In addition, depressed patients have reduced glucocorticoid sensitivity during and after stress events[76], which is likely related to the upregulation of MIF induced by glucocorticoids. After treatment with antidepressants, the inflammatory levels in the peripheral circulation as well as MIF expression levels in macrophages and lymphocytes are reduced[77]. Although MIF expressed by inflammatory cells (such as macrophages) in the peripheral circulation can act against glucocorticoids and inflammation, inhibition of MIF cannot stop depression; instead, it induces anxiety- and depression-like phenotypes in laboratory animals, leading to a decline in hippocampus-dependent learning and memory[78]. This indicates that high levels of MIF expressed by leukocytes in the peripheral circulation can facilitate the development of depression, and MIF expressed in the CNS is essential for neurogenesis, mood regulation, as well as learning and memory, which is contradictory to its role in inflammatory cells of the peripheral circulation.

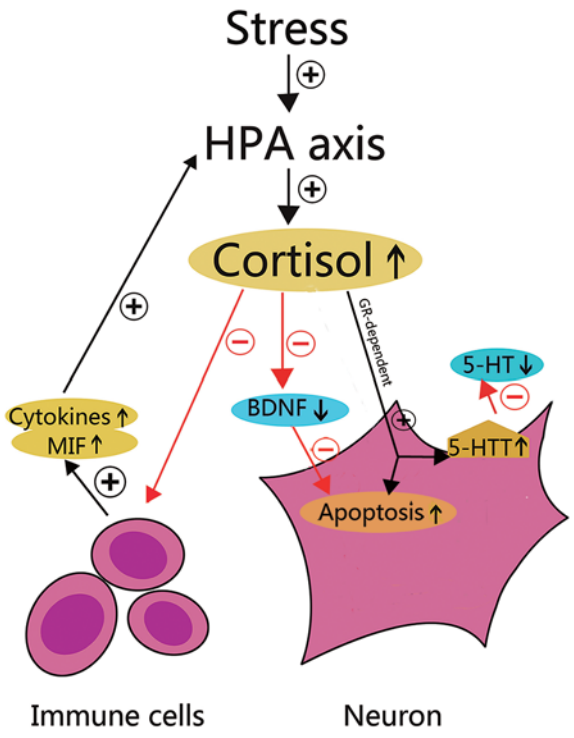

Fig. 4. Over-activation of the immune system and HPA axis synergistically disturb the normal physiological functions of neurons. Stress factors trigger excessive activation of the HPA axis, including the excessive secretion of CRH, ACTH, and glucocorticoids. Up-regulation of glucocorticoid release suppresses BDNF expression, leading to hypo-function of BDNF and attenuated synaptic plasticity. Excessive glucocorticoids result in decreased 5-HT levels in the synaptic cleft by overexpression of the serotonin transporter (5HTT). Interestingly, glucocorticoids stimulate MIF expression, which induces glucocorticoid resistance through inhibition of the response of immune cells to glucocorticoids.

MIF is also involved in mediating the pharmacological effects of antidepressants. Neuronal proliferation induced by fluoxetine can be blocked by MIF inhibition and MIF knockout[78], which suggests that MIF plays a role in the neurogenesis induced by antidepressants. Further studies have shown that the MIF-mediated cell proliferation is mediated by BDNF. Macrophage MIF induces BDNF gene expression both *in vitro* and *in vivo*, thereby restoring the reduced BDNF levels in patients with depression. This is likely to be the potential mechanism for antidepressants, electroconvulsive therapy, and long-term exercise in enhancing BDNF levels in the hippocampus, maintaining neuronal survival and promoting the growth and differentiation of newborn neurons[79].

The Circadian Rhythm Disorder Hypothesis and New Targets for Drug therapy

Substantial studies have shown that up to 80% of

depressed patients have varying degrees of sleep problems[80]. Their main symptoms include early wake-up, usually 2–3 h earlier than usual, and inability to sleep again after wake-up, which is important for diagnosis. Patients with depression might also have disorders in the sleep-wake rhythm. Furthermore, most patients with depression have diurnal mood variation, severe in the morning and mild at night. All the evidence indicates that the disturbance of biological or circadian rhythms is closely associated with the development of depression[81].

In mammals, the site of biological rhythm control is in the suprachiasmatic nucleus in the hypothalamus, which receives a variety of inputs, mainly light signal transduction from the retina, 5-HT produced by the raphe nuclei, and melatonin secreted by the pineal. Its main output is to the paraventricular nucleus of the hypothalamus, which relays signals to the HPA axis, the autonomic nervous system, and the pineal, to allow biological rhythms to regulate glucocorticoids, melatonin, and other hormones. Among these, CRH and cortisol produced by the HPA axis, and melatonin secreted by the pineal are most related to biological rhythms and sleep: CRH inhibits slow-wave sleep and triggers the sleep-wake transition; reduced CRH synthesis or CRH receptor blockade increases the duration of non-rapid eye movement (NREM) sleep and suppresses arousal[82]. Moreover, high concentrations of cortisol have effects similar to CRH, which include inhibiting NREM and prolonging arousal time. Meanwhile, it also reduces the latency of rapid eye movement (REM) sleep and increases the sleep density in REM sleep[82]. In contrast, melatonin has the opposite effects; it not only shortens the time to fall asleep and improves sleep quality, but also directly regulates the biological rhythms in the suprachiasmatic nucleus, especially the sleep-wake rhythm, through a melatonin receptor-GABA mechanism, thereby improving sleep rhythm disorders and endocrine disorders.

In as early as 1985, it was proposed that depression might be a syndrome with low melatonin[83], characterized by low levels of melatonin at night, abnormal dexamethasone suppression, and disorder of the 24-h cortisol rhythm. A cross-sectional study in 2012 further supported the low melatonin hypothesis[84] by showing that nocturnal melatonin levels in patients with depression are significantly lower than in controls. Other than the concentration changes, a change in the biological rhythm of melatonin is also an important factor. Although the abnormal rhythm in depression has high variability (phase advance, phase delay, or changes in amplitude), phase advance appears to be common in depressed patients[85] as manifested by shortened latency to REM sleep, earlier wake-up, and significantly elevated ACTH and cortisol levels at night (compared with normal controls). All these reflect a disturbance of circadian rhythms and enhancement of alertness in stress responses in patients with depression, while all these clinical manifestations are based on the advance in secretion of melatonin and cortisol, i.e., earlier reduction in melatonin levels and earlier increase in cortisol levels make it difficult to maintain sleep during the sleep period. This earlier wake-up is not only the start of a whole day of depressed mood, but also a strong indicator of relapse of depression[86].

Currently, reshaping the normal biological rhythms in depressed patients is a new approach to the treatment of depression. This includes non-drug treatments such as light therapy and sleep deprivation as well as drug treatments using melatonin and agomelatine. Melatonin inhibits ACTH-mediated cortisol secretion[87], decreases the cortisol release, and enhances the negative feedback in the HPA axis to restore this system[88]. It should be noted that the time of administration of melatonin is extremely important[89]: taking it before bedtime leads to an earlier sleep-wake cycle, which may improve the sleep difficulties and other symptoms, but aggravate the earlier wake-up symptoms; taking it at a relatively late time might postpone the sleep-wake cycle, which helps to improve the symptom of earlier wake-up. However, a number of studies have shown that melatonin can only improve sleep, but does not relieve the symptoms of depression[85].

Agomelatine has recently been added to the list of antidepressants. It is a novel antidepressant that works on melatoninergic (MT1 and MT2), 5-HT_{2B}, and 5-HT_{2C} receptors, which might function against anxiety and thereby improve sleep and regulate biological rhythms. Agomelatine regulates the sleep-wake rhythm[90], shortens the REM sleep latency, and reduces the REM sleep time and REM sleep ratio. The sleep symptoms, along with the depressive symptoms, are improved, which might be due to the overlap in antidepressant mechanisms and biological rhythm regulation. In addition, blocking the 5-HT_{2c} receptor indirectly enhances the DA and NE levels to

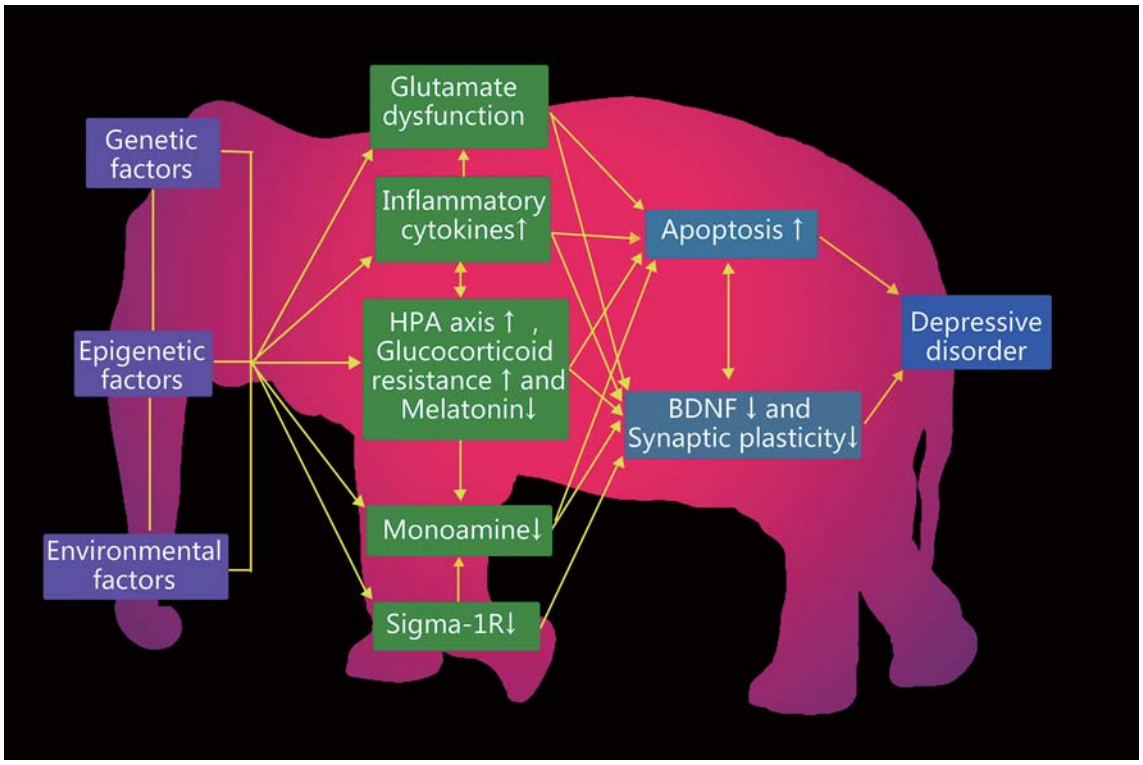

Fig. 5. Schematic of the pathogenesis of depression. The pathogenesis of depression is complex. Like the proverbial blind men exploring an elephant, different hypothesis have been proposed for the etiology and pathogenesis of depression. It is important to have an integrated view of the mechanisms. Genetic and stress vulnerabilities interplay to initiate a cascade of neurobiological changes that disrupt a dynamic system. The decrease BDNF with associated synaptic plasticity and increased apoptosis may play an important role in the onset and maintenance of depression, and may be considered as a common pathway in various hypotheses of depression.

improve depressive symptoms caused by the deficiency of monoamine neurotransmitters[85].

Summary and Outlook: Integrated View of the Pathogenesis of Depression

Like the proverbial blind men exploring different parts of an elephant, different hypotheses interpret the etiology and pathogenesis of depression from different viewpoints that are complimentary and mutually linked, rather than contradictory. It is important to have an integrated view of the mechanisms underlying depression. Genetic and stress vulnerabilities interplay to initiate a cascade of neurobiological changes that disrupt a dynamic system. As shown in Fig. 5, two factors, decreased BDNF with an associated decrease in synaptic plasticity and increased apoptosis may play an important role in the onset and maintenance of depression. Both are considered to be a common pathway in various hypotheses of depression. Although there is still much to elucidate, research progress in the pathogenesis of depression is promising for a cure of MDD.

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