Review Article

The Role of Neural Plasticity in Depression: From Hippocampus to Prefrontal Cortex

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Neural plasticity, a fundamental mechanism of neuronal adaptation, is disrupted in depression. The changes in neural plasticity induced by stress and other negative stimuli play a significant role in the onset and development of depression. Antidepressant treatments have also been found to exert their antidepressant effects through regulatory effects on neural plasticity. However, the detailed mechanisms of neural plasticity in depression still remain unclear. Therefore, in this review, we summarize the recent literature to elaborate the possible mechanistic role of neural plasticity in depression. Taken together, these findings may pave the way for future progress in neural plasticity studies.

1. Introduction

The establishment and realization of neural functions are based on generation, transformation, and storage of information in neural networks. The brain is developing and progressing at high speed in the six- to nineteen-year-old age group, and the unique plasticity of neural development is crucial to mature neural function. In a neural network, neurons are the fundamental functional units that integrate and transmit signals in response to intrinsic and extrinsic information [1]. Neuronal functions are dynamic processes that occur in response to environmental stimuli, emotions, injury, and so forth. This is the theoretical basis of neural plasticity, which is an umbrella term to describe structural and functional changes in the brain in response to various stimuli, including stress and depression. Depression is a prevalent, chronic, and recurrent disease. Depression, one of most devastating diseases, has a worldwide lifetime prevalence of 20%. Moreover, to patients with depression, depression not only brings profound mental agony but also causes pathophysiological disorders and enhances susceptibility to some diseases, for instance, cardiac diseases and cerebrovascular illness [2]. Therefore, patients with depression suffer from higher mortality than the healthy population. Unfortunately, to date, no completely effective treatments for depressed patients have been developed. Currently available antidepressant treatments, whether medications, psychotherapies, or other methods, have limited efficacy in depression and can cause significant side effects [2]. Hence, it is profoundly significant to explore the pathophysiology of depression. Though a large number of studies on the correlation between depression and neural plasticity have revealed some of their mechanisms, the neurobiological mechanisms of depression are still not well known. Negative stimuli, such as stress, pain, and cognitive impairment, can result in both depression and changes in neural plasticity. The neuropsychology hypothesis of major depressive disorder proposes the theory that dysfunction of neural plasticity is a basic pathomechanism of the disorder [3]. However, depression is not an inexorable outcome of dysfunction of neural plasticity. To our knowledge, there are no authoritative research results or expert consensus to confirm whether depression or changes
in neural plasticity are the initial factor. Most of the studies suggest that depression and dysfunction of neural plasticity act on and influence each other. In this perspective, we review the recent literature to elaborate what is known about neural plasticity in depression to pave the way for ongoing and future studies.

2. Hippocampal Plasticity in Depression

The hippocampus is the most commonly studied brain region in depression research. From a structural point of view, the hippocampus is part of the limbic system and develops nerve fiber connectivity with emotion-related brain regions, for instance, the prefrontal cortex and amygdala. In addition, the hippocampus contains high levels of glucocorticoid receptors and glutamate and regulates the hypothalamus-pituitary-adrenal (HPA) axis, which makes it more susceptible to stress and depression. Changes in hippocampal plasticity can result from stress and other negative stimuli. Stress impacts hippocampal plasticity in many ways. Chronic and severe stress has been shown to impair hippocampus-dependent explicit memory in animal models of depression [4]. This effect can be explained by changes in hippocampal synaptic plasticity modeled by long-term potentiation (LTP) and long-term depression (LTD). Hippocampal synaptic plasticity is widely considered to play an important role in hippocampus-dependent explicit memory formation [5]. Severe stress can impair LTP and enhance LTD in the hippocampi of rodent models [6, 7]. Stress can also decrease neuronal dendrite branching and plasticity in the hippocampus [8]. In addition, stress can trigger activation of the hypothalamic-pituitary-adrenal axis, increase level of corticosteroids, and downregulate hippocampal neurogenesis [9]. Cognitive impairment can enhance long-term potentiation in the CA1 region and markedly elevate protein levels of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluA1 in the mouse hippocampus and then induce depression in mouse models [10]. In addition, neuropathic pain-induced depressive-like behavior may be associated with hippocampal neurogenesis and plasticity through tumor necrosis factor receptor I signaling [11]. Hippocampal plasticity in depression involves hippocampal volumetric changes, hippocampal neurogenesis, and apoptosis of hippocampal neurons.

2.1. Synaptic Plasticity in the Hippocampus. Synaptic plasticity is one of the most fundamental and important functions of the brain. The efficacy of transmission at a synapse depends on modulation of the connectivity between neurons and neuronal circuits during adaptation to the environment [12]. Stress has profound effects on synaptic plasticity in the hippocampus and presents different influences in different subfields of the hippocampus. Stress can impair LTP in CA3 while facilitating LTD and spike-timing-dependent LTD (tLTD) in CA1 [12]. In addition, depression can downregulate synaptic proteins and growth factors required for hippocampal LTP in animal models.

Electroacupuncture can alleviate depression-like behaviors and reverse the impairment induced by long-term potentiation in the CA1 synapses of the hippocampus in depressive rats [13]. Physical exercise may prevent changes in synaptic plasticity and increases in synaptic transmission in hippocampal CA1 pyramidal neurons caused by stress but cannot reverse the present glutamatergic synaptic alterations induced by depression [14]. Glucocorticoid receptor antagonists and monoaminergic antidepressants can protect against negative synaptic plasticity in CA1 induced by stress. TJZLI84, a monoacylglycerol lipase inhibitor, exhibited antidepressant effects by enhancing adult neurogenesis and long-term synaptic plasticity in the dentate gyrus of the hippocampus [15]. Lycium barbarum was found to reduce depression-like behavior mediated by enhanced synaptic plasticity in the hippocampus of rats [16].

2.2. Hippocampal Volumetric Changes in Depression. It has been widely reported that there is a significant reduction in hippocampal volume in depression patients [17]. This situation was found in both adult and adolescent depressed patients, whether they were in their first or recurrent depressive episodes. A recent study reported that, in female patients with recurrent familial pure depressive disorder (rFPDD), volumetric reductions of the right hippocampal body and tail were significantly larger than those of the left, while the whole brain volume was approximately equal to that of healthy subjects [18]. Consistent with this, a significant increase in right hemispheric hippocampal gray matter volume has been found in elderly patients with severe depression treated with electroconvulsive therapy [19, 20]. However, hippocampal volumetric reduction was also found in patients who had recovered from depression [17]. The volumetric changes may result from a neurodegenerative reaction to increased glucocorticoid levels in depression [20]. The changes in synaptic plasticity induced by depression are associated with structural and functional changes in the hippocampus. The volume reduction of the prefrontal cortex and hippocampus may also result from the disruption and atrophy of neurons and glia in depression [21, 22]. Nonetheless, the hippocampal volumetric changes are not associated with the severity of depression [18]. Evidence supports that larger hippocampal volumes indicate quicker recovery in depressed individuals [23]. This can be explained by hippocampal regulation in stress reactivity. Reduced hippocampal volumes may be a neural scar marker of depression and a vulnerability marker for future episodes [17]. The clinical application of hippocampal volumetric changes still needs large-sample research to confirm.

2.3. Hippocampal Neurogenesis. Brain neurogenesis lasts from birth to adulthood in many animals, including humans. Hippocampal neurogenesis occurs markedly in the dentate gyrus, with approximately 700 granule cells born daily, corresponding to an annual turnover of 1.75% of the neurons within the renewing fraction [24]. The rate of hippocampal neurogenesis decreases modestly with age. Compared with the millions of granule cells in the granular layer of the hippocampus, newborn neurons are few in number, but they can be sufficient to achieve functional
Neural Plasticity

2.4. Hippocampal Apoptosis in Depression.

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shock produce larger increases in hippocampus volume in
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depression are larger than those in nonmedicated patients
number and dentate gyrus size in medicated patients with
lack of research data to illustrate the effects of medication on
non-human primates. In rodents, most antidepressant treatments that are
used in humans, including electroconvulsive shock and med-
ication, were subsequently shown to facilitate hippocampal
neurogenesis [30–34\]. However, the facilitation of fluoxetine treatment
was sensitive to stress, corticosterone levels, and
route of medication [29\]. The effects of fluoxetine treatment
on non-human primates are similar to those in rodents. In
addition, electroconvulsive shock can also boost hippocam-
al neurogenesis in non-human primates [35\]. There is a
lack of research data to illustrate the effects of medication on
non-human primates. In humans, total dentate granule cell
number and dentate gyrus size in medicated patients with
depression are larger than those in nonmedicated patients
based on postmortem studies [36\]. Selective serotonin reup-
take inhibitors, lithium treatment, and electroconvulsive
shock produce larger increases in hippocampus volume in
treated depressed patients than in nontreated patients [37,
38\]. In line with this observation, research evidence from
the hippocampal subfields has revealed larger dentate gyri in
medicated depressed patients [39\]. These data are relevant to
multiple forms of neural plasticity and suggest an increase
in hippocampal neurogenesis. Nevertheless, there is no ade-
quate evidence to establish that hippocampal neurogenesis
is necessary for antidepressant efficacy, and its increase is
sufficient for antidepressive therapy.

2.4. Hippocampal Apoptosis in Depression. Proliferation, dif-
erentiation, and apoptosis are continuous progressions in
adult hippocampal neurons. Many studies have demonstrated
that depression and stress can induce hippocampal apoptosis
in rodents, non-human mammals, and humans, though
hippocampal apoptosis can also be found in nondepressed
rodents [40\]. Similarly, hippocampal apoptosis may result in
depression. Evidence showed an increase of apoptosis in den-
tate gyrus of maternal rats with repeated separation of their
pups and impairment of memory capability with depression-
like behavioral changes [41\]. In maternal-separation rat
models, tadalafl, a phosphodiesterase type 5 inhibitor, exerts
antidepressant effects by suppressing maternal-separation-
induced apoptosis and increasing cell proliferation in the
dentate gyrus [42\]. Though some studies support the idea that
hippocampal apoptosis is a causative factor in hippocampal
volumetric changes, histopathological studies on depressed
patients have yielded inconsistent results [43\]. There are dif-
ferences in the stimulative effects of chronic depression and
acute depression on hippocampal apoptosis. In animal mod-
els and human studies, chronic depression showed longer
lasting apoptosis-promoting effects in the hippocampus
than acute depression [40\]. The apoptosis-promoting effects
induced by acute depression can fully subside in one day of
recovery, while the adverse effects in chronic depression may
need up to three weeks for recovery. However, it is uncertain
in what stage depression and stress start to mediate apoptosis
progression. In addition, their effects showed differences
among subfields of the hippocampus. Compared with the
apoptosis increase in the whole dentate gyrus caused by acute
depression, the number of cells in the granular cell layer can
increase even as the cell count in the whole dentate gyrus is
declinning [44\]. This discrepancy may be due to the different
sensitivities of granular cells to acute and chronic stress.

In addition to tadalafl (mentioned above), several types
of drugs may have antidepressant effects owing to hippocam-
al apoptosis. For instance, venlafaxine, a serotonin/nore-
pinephrine dual reuptake inhibitor, suppresses hippocampal
apoptosis by upregulating brain-derived neurotrophic factor
[45\]. In addition, fluoxetine, a 5-hydroxytryptamine reuptake
inhibitor, regulates hippocampal plasticity by alleviating
the upregulation of synaptosomal polysialic neural cell adhesion
molecule caused by depression and elicits an antiapoptotic
response in the hippocampus [46\].

3. The Prefrontal Cortex in Depression

The prefrontal cortex (PFC), as a significant nerve center of
thinking and behavior regulation in the brain, is also associ-
ated with depression [47\]. In view of anatomical connectivity
and functional specialization, the prefrontal cortex is divided
into two subregions: ventromedial prefrontal cortex (vmPFC)
and dorsolateral sectors (dlPFC) [48\]. VmPFC involves the
regulation of affect, including the generation of negative
emotion, and dlPFC mediates cognitive functions, such as
intention formation, goal-directed action, and attentional
control [49\]. The two sectors have both been shown to have
significant roles in depression. However, their effects present
discrepancies, according to reports in the literature. Func-
tional imaging studies have shown opposite changes of activ-
ity in the two sectors: during the progression of depression,
hyperactivity appeared in the vmPFC, while hypoactivity
appeared in dlPFC; in the recovery phase in response to
psychotherapy or medication for depression, hypoactivity
was found in the vmPFC, while hyperactivity was found in
dlPFC [48, 50–53\]. Furthermore, in lesion models, dlPFC loss
can aggravate depression, whereas vmPFC loss can exhibit an
alleviative effect on depression [54, 55\]. Dysfunction caused
by dIPFC damage in stroke is considered a predisposing factor to poststroke depression [56]. In addition, a decrease of cortical thickness in the right vmPFC, which occurs in the early stages of neurodevelopment, results in depression in preschoolers [57]. Volume reduction of the prefrontal cortex may result from the disruption and atrophy of neurons and glia in depression, as observed in the hippocampus [21, 22]. Energy and glutathione metabolic pathways in the prefrontal cortex were shown to be significant biological pathways in depressive rats [58]. Many studies have indicated that changes in glutamate metabolism were associated with depression [59–67]. In a stress-induced depressive mouse model, the prefrontal cortex in depression showed a significant reduction of glutamate in the GABAergic pathway, which may contribute to depression [62]. Activation of metabotropic glutamate receptor 3, which plays a significant role in regulating the function and cognition of the prefrontal cortex, can result in long-term depression in the medial prefrontal cortex of rats in vitro [68]. The GRIN2A gene, which encodes the glutamatergic N-methyl-D-aspartate (NMDA) receptor subunit epsilon-1 in the prefrontal cortex, is probably disturbed in the regulation of synaptic plasticity in depression [69].

In addition, a novel miRNA (miR-101b) was found to be downregulated in depression and could decrease mRNA and protein levels of glutamate transporter SLC1A1 in the prefrontal cortex [59]. In addition, in the medial prefrontal cortices of chronic unpredictable mild stress-induced depressive mice, there was a downregulation of mRNAs encoding proteins for the GABAergic synapses, dopaminergic synapses, synaptic vesicle cycle, and neuronal growth and an upregulation of miRNAs of regulating these mRNAs [70]. In a chronic corticosterone-mediated depressive rat model, the majority of the related miRNAs and associated gene networks showed glucocorticoid receptor element binding sites; this is a potential mechanism whereby corticosterone may mediate depression [71].

There is also a decrease in prefrontal hemodynamic responses in depression and a significant and positive correlation between prefrontal hemodynamic responses and the role of the emotional domain [72, 73]. In addition, the lack of activation of oxygenated hemoglobin in the prefrontal cortex indicates that it may be a mechanism of depression [74]. Observing changes in hemoglobin concentration in the prefrontal cortex detected by near-infrared spectroscopy may be a convenient approach to evaluate and predict antidepressant improvement in late-onset depression [58]. Furthermore, increases in mean oxygenated hemoglobin may be positively correlated with the severity of depression [75].

Repetitive transcranial magnetic stimulation of the dorsomedial prefrontal cortex (dIPFC) and dIPFC exhibits effectiveness and safety in treatment-resistant depression [76–80]. In electroconvulsive therapy for depression, an early decrease of intralimbic functional connectivity and a later increase of limbic-prefrontal functional connectivity were found [81]. Epidural prefrontal cortical stimulation over the PFC has also been shown to be a promising novel therapeutic method for treatment-resistant depression [82]. Positive emotional learning can facilitate N-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity in the medial prefrontal cortex and then exert positive effects on promoting rehabilitation in depressive rats [83]. Some studies have reported that NMDA receptor antagonists, such as ketamine and lamicenine, can increase mammalian target of rapamycin complex 1 (mTORC1) signaling by activating threonine kinase (AKT) and extracellular signal-regulated kinase (ERK) signaling pathways and increase synaptic number and function in the prefrontal cortex [2, 84, 85]. A recent study on protein level changes in the prefrontal cortex suggested that treatment with the tricyclic antidepressant clomipramine in neonates was a reliable model to study the effects of antidepressants on the early phase of brain development [86]. Hence, the effects of antidepressant treatment on early brain development may induce constant pathological changes in the prefrontal cortex. YY-23, a new extractive compound, and fluoxetine can reverse the inhibitory effects of chronic mild stress on spontaneous burst firing of medial prefrontal cortex pyramidal neurons in depression [87]. Mecamylamine, a nicotinic antagonist, is a novel antidepressant that exerts antidepressant actions by increasing PFC levels of BDNF and monoamines [88]. Interestingly, in a depressive rat model, nutritional supplements, such as n-3 polyunsaturated fatty acids (PUFA), may prevent the development of depression by impeding HPA axis hyperactivity [89]. This study suggests that dystrophy may be another mechanism of depression.

4. Amygdalar Changes in Depression

The amygdala plays a significant role in affective modulation and memory encoding [90]. The amygdala is also a critical site of neuronal plasticity for fear conditioning [91]. Morphological and functional changes of the amygdala associated with depression have been verified in many studies [92, 93]. In contrast, with the hippocampus and prefrontal cortex, stress and depression enhance synaptic plasticity in the amygdala and the ventral emotional network [3]. Stress was found to induce dendrite retraction in the PFC and hippocampus, while it induced dendritic arborization of pyramidal and spiny neurons in the basolateral amygdala [12]. Expression of brain-derived neurotrophic factor (BDNF), which is known to play a central role in synaptic plasticity induced by stress, increased in the basolateral amygdala but decreased in the hippocampal CA3 in rats [9, 94]. Depression disrupted glutamate signaling at the NMDA receptor in the amygdala in humans [95]. Neonatal glucocorticoid treatment enhanced LTP response and the phosphorylation level of MAPK in the lateral nucleus of the amygdala and promoted depression-like behavior in adult rats [91].

Amygdala kindling, as a classic model of temporal lobe epilepsy with convulsion, can cause depression-like behaviors in both immature rats and adult rats [96]. Amygdalar functional connectivity differs in late-life depression phenotypes, and this discrepancy may be a criterion to distinguish phenotypes of late-life depression and evaluate the severity [97].

In addition, the volume of the amygdala varied with the severity of the depression [98]. Interestingly, a recent study showed that larger gray matter volume in the bilateral amygdala was found in first-degree relatives of depressed
patients [99]. Furthermore, amygdala perturbations caused by negative stimuli, which elicit greater amygdala activation, might be an early and subtle risk marker for depression [100]. Recent evidence suggests that postpartum depression can increase amygdalar response to infant stimuli and decrease bilateral amygdala-right insular cortex connectivity [101]. The latter may have a stimulative effect on depression and anxiety. However, abnormal functional connectivity in depression is discrepant in the left amygdala [102]. In the left amygdala, the functional connectivity decreased in the amygdala positive network, while it increased in the amygdala negative network. In a clinical study of early-childhood-onset depression, functional connectivity was reduced in the bilateral amygdala [103]. Abnormal amygdala functional connectivity is also found in late-onset depressed patients [104]. Hence, a distributed neuronal network including cortical and limbic regions rather than a discrete brain region contributes to depression. The amygdala-associated frontolimbic circuits, amygdala-dorsal lateral prefrontal cortex, and amygdala-ventromedial prefrontal cortex, which integrate affective processes, may have characteristic dysfunctions in adolescent depression [104]. These circuits may change exponentially in association with depression severity and potentially be considered as a biomarker to analyze the effect of treatment on depression. Interestingly, some of the amygdalar changes in depression differ by gender. A recent study indicated that women but not men possess an IL18 haplotype that increases threat-related left centromedial amygdala reactivity and boosts susceptibility to stress-related depression by promoting proinflammatory responses [105]. Depression-associated single-nucleotide polymorphisms can regulate the expression of the bicaudal C homolog 1 (BICCI) gene and decrease its promoter activity on the PKA signaling pathway in amygdalar neurons [106]. These changes may cause mood disorders. In addition, prenatal maternal depression can influence the functional connectivity of the amygdala in early postnatal life, particularly in 6-month-old infants [107]. Prenatal maternal depression can also incur the risk of aggression in offspring [108]. In contrast, many studies have suggested that amygdala hyperactivity may improve symptoms of depression [109]. Some antidepressant treatments have been shown to play a role in amygdala regulation. Transcutaneous vagus nerve stimulation is a noninvasive peripheral neuromodulation therapy administered at the ear for depressed patients and has been shown to be effective for depression treatment [110]. It can promote amygdala-lateral prefrontal network resting state functional connectivity in the right amygdala of depressed patients [111]. Real-time fMRI neurofeedback training is another novel noninvasive treatment for depression [112]. It can enhance blood-oxygenation-level-dependent activity in the amygdala and benefit depressed patients. In addition, the effects of electroconvulsive therapy in patients with depression may also be associated with neuroplasticity changes in the amygdala, and this phenomenon may be due to neurotrophic processes, including neurogenesis [112]. Medication associated with the amygdala in depressed patients includes quetiapine, citalopram, and ketamine [113–115]. In depressive rat models, the amygdala has shown a significant role in fluoxetine-stimulated cell survival and a potential to modulate antidepressant action in hippocampal neurogenesis [116].

5. Neural Plasticity in Other Brain Regions in Depression

The ventral striatum participates in the mechanisms of natural reward, and its dysregulation contributes to symptoms of anhedonia in depression [4]. Chronic stress can cause long-term adaptations in the ventral tegmental area-accumbens pathway that may contribute to its dysregulation in major depression [4]. α1-Adrenoceptor dependent downregulation of the membrane GluR1 subunit in the mouse ventral tegmental area mediated the depressive-like behavior induced by lipopolysaccharide [117]. In rats with postpartum depression, gestational stress could decrease dendritic length, branching, and spine density on medium spiny neurons in the nucleus accumbens shell and promote depressive-like behavior in the early/mid-postpartum phase [118].

Hypothalamic synaptic plasticity in depression can be caused by increased mRNA expression of synaptotagmin I and synapsin I, and the latter may contribute to depression-like behaviors and HPA axis hyperactivity [119]. In addition, the extracellular matrix may be involved in synaptic stabilization and transmission and may modulate synaptic plasticity in the central nervous system [120]. In recent studies, modeling of bidirectional modulations in synaptic plasticity, designed to reveal the mechanism of long-term potentiation and long-term depression, suggested that Ca\(^{2+}\)/calmodulin (CaM) pool size played a critical role in coordinating LTP/LTD expression [121].

6. Summary and Conclusion

Overall, neural plasticity is a vital feature of the brain in response to intrinsic and extrinsic stimuli, including stress and depression. Mounting clinical and basic research studies have illuminated the correlations between neural plasticity and depression. As the summaries in Tables 1 and 2, the effects of depression on neural plasticity are complex pathophysiological processes, involving multiple encephalic regions, such as the hippocampus, prefrontal cortex, and amygdala as well as complicated interactions of many signal pathways, such as NMDA, glutamate, and glucocorticoid. On the other hand, the changes in neural plasticity induced by stress and other negative stimuli can contribute to the onset and development of depression. The majority of antidepressant treatments, including psychotherapies, physiotherapies, and medications, exert antidepressant effects associated with neural plasticity. Unfortunately, to date, no ideal and completely effective treatment has been found for depressed patients. Though we have done extensive work in this review, the detailed mechanisms of neural plasticity in depression still remain unclear. Targeting neural plasticity in depression may lead to novel breakthroughs.

Competing Interests

The authors confirm that this article content has no conflict of interests.
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<td>Protects against negative synaptic plasticity in CA1 induced by stress</td>
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<tr>
<td>TJZL184 (a monoacylglycerol lipase</td>
<td>Rats</td>
<td>Enhances adult neurogenesis and long-term synaptic plasticity in the DG of the hippocampus</td>
</tr>
<tr>
<td>Lycium barbarum</td>
<td>Rats</td>
<td>Enhances synaptic plasticity in the hippocampus</td>
</tr>
<tr>
<td>Lithium (selective serotonin reuptake</td>
<td>Rats and humans</td>
<td>Facilitates hippocampal neurogenesis</td>
</tr>
<tr>
<td>Fluoxetine (selective serotonin</td>
<td>Rats</td>
<td>Amygdala neuroplasticity, alleviates upregulation of synaptosomal polysialic neural cell adhesion molecule and reverses the inhibitory effects of chronic mild stress on spontaneous burst firing of medial prefrontal cortex pyramidal neurons</td>
</tr>
<tr>
<td>Tadalafil (phosphodiesterase</td>
<td>Rats</td>
<td>Suppresses maternal separation-induced apoptosis and increases cell proliferation in the dentate gyrus</td>
</tr>
<tr>
<td>Venlafaxine (serotonin/norepinephrine</td>
<td>Rats</td>
<td>Suppresses hippocampal apoptosis by upregulating brain-derived neurotrophic factor</td>
</tr>
<tr>
<td>Ketamine and lanicemine (NMDA receptor</td>
<td>Rats</td>
<td>Increases mammalian target of rapamycin complex I (mTORC1) signaling by activating threonine kinase (AKT) and extracellular signal-regulated kinase (ERK) signaling pathways and increases synaptic number and function in the prefrontal cortex</td>
</tr>
<tr>
<td>Mecamylamine (nicotinic antagonist)</td>
<td>Rats</td>
<td>Increases PFC levels of BDNF and monoamines</td>
</tr>
</tbody>
</table>

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**References**


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Neural Plasticity


