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REVIEW ARTICLE

Targeting the Neuronal Activity of Prefrontal Cortex: New Directions for the Therapy of Depression

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Abstract: Depression is one of the prevalent psychiatric illnesses with a comprehensive performance such as low self-esteem, lack of motivation, anhedonia, poor appetite, low energy, and uncomfortableness without a specific cause. So far, the cause of depression is not very clear, but it is certain that many aspects of biological psychological and social environment are involved in the pathogenesis of depression. Recently, the prefrontal cortex (PFC) has been indicated to be a pivotal brain region in the pathogenesis of depression. And increasing evidence showed that the abnormal activity of the PFC neurons is linked with depressive symptoms. Unveiling the molecular and cellular, as well as the circuit properties of the PFC neurons will help to find out how abnormalities in PFC neuronal activity are associated with depressive disorders. In addition, concerning many antidepressant drugs, in this review, we concluded the effect of several antidepressants on PFC neuronal activity to better understand its association with depression.

Keywords: Depression, prefrontal cortex, circuit, molecular, synapse, drug.

1. INTRODUCTION

PFC in primates is divided into three subregions: dorsal PFC, ventral PFC, and orbitofrontal cortex (OFC). It can also be subdivided into dorsolateral, ventrolateral and medial prefrontal cortex (mPFC). The mPFC further can be divided into three regions, which are anterior cingulate cortex, prelimbic cortex (PrL) and infralimbic cortex (IL) [1]. In mammalian brain anatomy, PFC is the prefrontal cortex which contains the anterior frontal lobe. It is reported that the PFC covers the Brodmann areas BA8-14, BA24-25, BA32 and BA44-47 in humans [2]. The corresponding relationship is shown in Table **1**. Many research studies have illustrated an intact relationship between a person's willpower, motivation, individuality, and the functions of the PFC. The PFC has also been indicated in planning complicated cognitive and learning behavior, individuality development, decision making and regulating social activity. The PFC is highly associated with much of the brain, including extensive links with other cortical, subcortical, brain lobe and brain stem [3]. The dorsal PFC is peculiarly connected with brain regions related to consideration, cognition and activity [4], while the ventral PFC connects with brain regions linked with emotion [5]. Recently, the Prefrontal Cortex (PFC) has been indicated to be a pivotal brain region in the pathogenesis of depression.

Major Depressive Disorder (MDD) seems to involve many brain regions, but there is abundant evidence which suggested that PFC plays a crucial role. Basic and clinical studies have demonstrated the reduced size of PFC indicated in depression, along with neuronal hypoplasia or atrophy, such as loss of synapses in Chronic Unpredictable Mild Stress (CUMS) models. And it has been demonstrated that optogenetic activation of PFC showed antidepressant-like actions in the social defeat stress animal model [6]. In this article, we review major findings concerning the molecular and cellular mechanisms by which the PFC neuronal activity becomes aberrant and the effects of typical antidepressant drugs on PFC synaptogenesis. We also summarize the efferent regions of the PFC, as well as the afferent regions of the PFC, which may improve symptoms of depression.

We will begin with a brief introduction to the existing animal models of depression. An ethologically valid model that has been shown to be effective in studying depression is the chronic social defeat stress model (CSDS). In this model, C57BL/6J mice are subjected to chronic social defeat stress induced by CD-1 aggressor mice for 10 consecutive days [7]. A subsequent social interaction testing suggested that social avoidance is performed as an indication of depression-like behaviors. Chronic unpredictable mild stress model (CUMS) is another widely used animal paradigm. Adult male rats

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Table 1. The following table shows the corresponding relation of the PFC in human Brodmann areas and rodents.

8	Lateral 9	12	44	45	46	47	Medial 9	Medial 10	24	25	32	11	13	14
caudal	lateral						media					orbitofrontal		
	ventrolateral			dorsolateral			anterior cingulate cortex		prelimbic cortex		infralimbic cortex			

Table 2. The effect of typical antidepressant drugs on PFC synaptogenesis.

Drug	Classification	Usage	Function	Mechanism
Desipramine	Tricyclic antidepressants (TCAs)	Monoamine neurotransmitter reuptake inhibitors	Enhances synaptic transmission and/or long-termpotentiation (LTP) (Bath, Jing *et al*. 2012); increases spine density (Ampuero, Rubio *et al*. 2010) or blocks the dendrites and spines atrophy (JM Bessa, D Ferreira 2009); increases cFos expression in the vmPFC (Chang, Chen *et al*. 2015).	Acting *via* presynaptic alpha-2 receptors, moderating the release and activity of norepinephrine directly (Garcia, Barrera *et al*. 2004) or through cortical GABAergic interneurons indirectly (Andrews and Lavin 2006).
Fluoxetine	Selective serotonin reuptake inhibitors (SSRIs)	The reabsorption of 5-HT in synaptic space by neurons was selectively inhibited, and the concentration of 5-HT in synaptic space was increased	Induces an increase in the expression of cFos in the vmPFC (Chang, Chen *et al*. 2015); increases dendritic complexity, spine density, and the BDNF/ TrkB signaling expression levels (Song, Wu *et al*. 2019).	Acting on the most PFC PNs with 5-HT1A and 2C receptors directly (Puig and Gulledge 2011); Acting through inhibition of the expression of 5-HT1A of fast-spiking interneurons. Indirectly.
Ketamine	NMDA receptor antagonist	Anesthetic agent	Increases the function and number of synaptic connections; promotes synaptic proteins production rapidly (within hours); increases the number and function of synapse spines in layer V PNs of the PFC (Nanxin Li 2010); increases the expression of cFos in the dmPFC and vmPFC (Chang, Chen *et al*. 2015); elevates levels of BDNF, increases extracellular glutamate, activates the mTORC1 cascade, and increases number and function of spine synapses in PFC (Eric S. Wohleb 2017).	Blocking excitation by NMDA glutamate receptors, disinhibition of PNs *via* inhibitory interneurons (Chang, Chen *et al*. 2015). Antagonizing the stimulation of NMDA receptors, dampened the eEF2K function (Autry, Adachi *et al*. 2011).

were randomly exposed to an array of unpredictable mild stressors for weeks to drive the animals into depression. The unpredictable mild stressors contain forced swimming, restraint, water deprivation, isolation, food deprivation, foot shock or tail pinch [8]. Chronic restraint stress (CRS) is a paradigm that mice are periodically constrained from moving by placing them in a tube for days or weeks. The restraint apparatus restricted the movement but did not interfere with normal breathing, as it was modified with numerous holes [7, 9]. Over the years, numerous animal models have been established to elucidate the pathophysiology underlies depression and to test novel antidepressant treatment strategies, however, the animal models available currently are of limited utility for these purposes [10].

2. ACTIVITY OF PFC NEURONS IN DEPRESSIVE CONDITIONS

Basic and clinical studies have demonstrated the reduced size of PFC indicated in depression, along with neuronal hypoplasia or atrophy, such as loss of synapses, decreased synaptic density and neuron decrease in depression and stress models [11, 12]. CUMS causes a decrease in the length and branching of apical dendrites and a reduction in the number and effect of spine synapses in layer V pyramidal neurons of the medial PFC (mPFC). CRS also causes dendritic atrophy, including decreased total numbers and length of apical dendrites branches in rat mPFC pyramidal cells [13-16]. Other chronic stress paradigms and models can lead to a similar decrease in dendrite complexity and spine density in the PFC neurons [17-19]. It is interesting that acute stress exposure promotes cognitive function and glutamate transmission in PFC, however, chronic stress has the opposite effect [20]. Hyo Jung Kang and his colleagues suggested that synapses number, by electron microscopy, was reduced in the dorsal-lateral PFC (dlPFC) of depressed patients [21].

The conclusion is that GABAergic interneurons (GABA, g-aminobutyric acid) are reduced in the dorsal-lateral PFC (dlPFC), as well as a decreased number of glia cells [22, 23].

Magnetic resonance spectroscopy proves the changed activities of glutamate and GABA cycling, showing the imbalance of these pivotal neurotransmitters in MDD individuals [24]. CUMS causes a decrease in excitatory postsynaptic potentials and serotonin (also named as 5-HT) in mPFC layer V pyramidal neurons (PNs). Chronic stress also suppresses glutamate signaling and the transmission through ubiquitin-mediated degradation of glutamate receptors associated with emotional and cognitive activity [20].

Brain-imaging of depressed patients present compelling and consistent evidence of the reduced the size of cortical and limbic brain areas, including the PFC and hippocampus [12, 25, 26]. Volume reduction has also been indicated in the subgenual and orbitofrontal cingulate cortices of depressed individuals [27, 28], and post-mortem brain analyses of depressed patients which indicate a meaningful loss of the glial cells [22, 29] and a decrease in neuronal size [30]. Functional imaging of depressed individuals showed a decrease in connectivity of hippocampus and PFC, along with other regions, though there are also studies of increased activity in the ventrolateral and subgenual PFC in depressed individuals compared to the non-depressed [31, 32], and these alterations are contrary in individuals in remission [28, 33], possibly because of dysregulation of mutual connection [26]. Moreover, early-life stress impairs the capacity of the ventromedial PFC (vmPFC) to maintain activity in response to resistant stressors [34]. Accordingly, studies suggested that disturbance rather than an integral increase or a decrease in connection within PFC and their targeted limbic regions taking the responsibility for the dysregulations in cognitive and emotional regulation in emotion disorders [26].

3. MAJOR MOLECULAR MECHANISM OF THE PFC DURING DEPRESSION

Mechanisms underlying the disruption of synaptic homeostasis and depression behavior is unclear. Brain-derived neurotrophic factor (BDNF), a well-researched factor, has important functions in the central nervous system (CNS). BDNF has been indicated to be involved in some psychiatry disorders, such as autism, schizophrenia, intellectual disability, as well as mood disorders like depression [35]. BDNF plays a critical role in synapse formation, and neuronal maturation synaptic plasticity in the brain [36]. It has been demonstrated that glucocorticoid or stress exposures could reduce BDNF expression in the hippocampus and PFC, and BDNF levels are reduced in postmortem brains of depression individuals [37, 38]. Inversely, chronic administration of a typical antidepressant drug rescues the expression of BDNF, and the function of antidepressants is diminished in BDNF deletion mutant mice [38]. Besides, BDNF deletion mutant mice are more sensitive to stress and BDNF mainly affects spine density and dendrite complexity [38, 39]. The rapid and continuing antidepressant-like effect of BDNF are prohibited by infusion of a vascular endothelial growth factor (VEGF) neutralizing antibody, and the neuron-specific deletion of VEGF in mPFC prohibits the antidepressant activity of BDNF [40]. Research studies in primary cortical neurons indicate that BDNF motivates the delivery of VEGF and that the dendrite complexity induced by BDNF is prohibited by a selective VEGF receptor inhibitor. Surprisingly, the conclusions also indicate reciprocal connections, showing that the neurotrophic and behavioral activities of VEGF depend on BDNF [40].

Depression and stress reduced BDNF and tropomyosin related kinase (TrkB) receptor signaling pathway, as well as decrease the extracellular signal regulated kinase (ERK) in downstream and protein kinase B (Akt) signaling in hippocampus and the PFC [41] (Fig. **1**). These signaling pathways positively influence the stability and maturation of synaptic through regulating the synthesis of synaptic protein and the cycling of glutamate receptor [42, 43]. Besides, depression and stress increase the level of mitogen-activated protein kinase phosphatase 1 (MAPK1), that negatively regulates ERK pathway, which sufficiently leads to depression-like behaviors [41] and decrease neuritin, one downstream target of BDNF, that is essential to the antidepressant action [44]. In humans and varieties of chronic depression models, the ERK signaling pathway was significantly downregulated in PFC and hippocampus, suppressing the ERK signaling in these regions led to depression-like behavior [45]. In addition, a transcription factor downstream to ERK, the cAMP response element-binding protein (CREB), and the MAPK phosphatase (MKP) are sensitive to depression [45]. Chronic antidepressant treatment reversed these neurochemical alterations [45].

Glygocen synthase kinase 3 (GSK3) is another signaling molecule indicated in synaptic homeostasis and regulated by BDNF-Akt signaling pathway. The imbalance of GSK3 could lead to a decrease in spine synapses in PFC according to stress and depression [46] (Fig. **1**). The activity of GSK3 in the nucleus accumbens (Nac) is also linked with chronic social defeat stress, and the inhibition of GSK3 in Nac or administration of GSK3 inhibitor causes antidepressant action in the behavior of depression models [46, 47]. Studies have indicated that prenatal stress gives rise to the down-regulation of mRNA expressions and protein levels of several critical signal molecules, such as sonic hedgehog, Notch and β-catenin that block neurogenesis [48]. GSK3 has two main subtypes, GSK3α and GSK3β. Findings concluded that GSK-3β was up-regulated that hold the responsibility for interference between different neurodevelopmental molecules like β-catenin, sonic hedgehog, BDNF and Notch which affected the neuronal development due to prenatal stress [48]. GSK-3β has been proved to be a regulator of cellular function including apoptosis, stem cell renewal, and cell proliferation. Evidence showed that the dysregulation of GSK-3β prohibits sonic hedgehog, Notch and Wnt/β-catenin signaling [49, 50]. Studies showed that conditional overexpression of GSK-3β in the forebrain of mice leads to damaged spatial learning and memory in mice [51]. Meanwhile, GSK-3β overexpression caused neuronal cell death, the increase of astrocyte, glial and decreased LTP that was rescued by decreasing the level of GSK-3β to normal either by transgene silencing or by lithium administration [52]. GSK-3β inhibits sonic hedgehog signaling by mediating the degeneration of G proteins [53]. Correlation between the Notch and GSK-3β is also reflected in GSK-3β binding and phosphorylating the intracellular region of Notch, which stabilizes the protein by decreasing its degeneration *via* the proteasome [54].

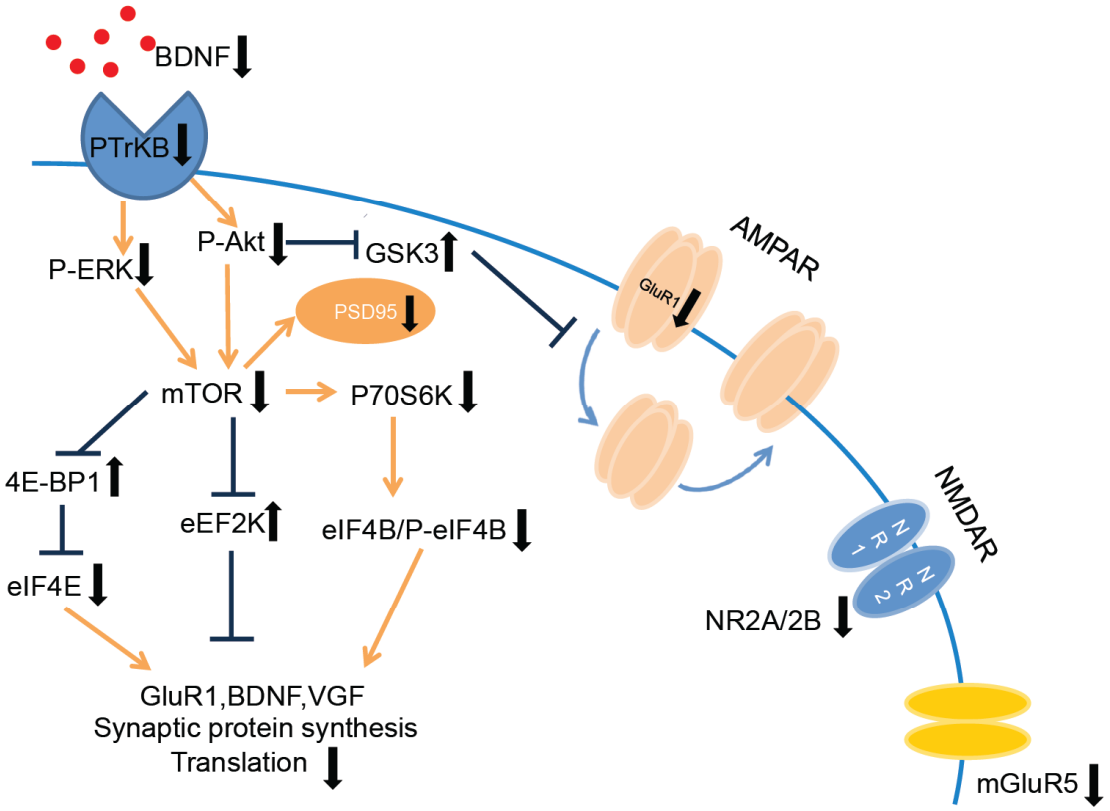

Fig. (1). Major molecular mechanisms of the PFC during depression. Stress and depression disrupt BDNF-TrkB receptor signaling, including reductions of the downstream ERK and Akt pathways. These pathways positively influence synaptic maturation and stability via regulation of synaptic protein synthesis. Stress and depression also cause deficits in synthesis of postsynaptic proteins including NMDA receptor subunits (NR2A, NR2B), mGluR5 and PSD-95. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Different cell culture researches also proved that the synaptogenesis which results in glutamate receptor stimulation needs the expression of BDNF to activate TrkB-mTOR (the mammalian target of rapamyc) pathway and synaptogenesis [55]. The functional association between mTOR stimulation and the synthesis of synaptic protein was illustrated by intracerebroventricular (ICV) infusion of rapamycin, a selective mTOR inhibitor that absolutely blocked the synthesis of glutamate receptor subtype 1 (GluR1), postsynaptic density protein 95 kDa (PSD95), and synapsin I [56, 57]. Physiologically, the activation of mTOR phosphorylates p70-kDa ribosomal protein S6 kinase (p70S6K), following p70S6K-induced eIF4B phosphorylation that facilitates the protein translation initiation [58]. The mTOR phosphorylates eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), as well as inactivates, thus reducing its combination with eIF4E and releasing eIF4E to promote the initiation of translation [59]. Stimulated translation initiation factors, especially eIF4E and eIF4B, are in charge of the ribosome recruitment of the 5'end of mRNA [57]. But there was an important decrease in p70S6K, eukaryotic initiation factor 4B (eIF4B), mTOR, and eukaryotic phosphorylated initiation factor 4B protein (p-eIF4BP) expression in the MDD relative to controls [57]. Postmortem studies also illustrate evident deficits in metabotropic glutamate receptor subtype 5 (mGluR5), prominent postsynaptic proteins including the subunits (NR2A, NR2B) of N-methyl-D-aspartate (NMDA) receptor, and PSD-95 in the PFC in MDD [57].

Vincent Vialou and his colleagues showed that transcription factor ΔFosB induction in mPFC, especially in PrL area, mediates the susceptibility to stress in CSDS model [60]. The level of ΔFosB in PrL increased selectively in susceptible mice after CSDS, and ΔFosB overexpression in PrL, but not in IL, boosted the susceptibility to stress. These effects of ΔFosB partly depend on the cholecystokinin (CCK)-B receptor induction as the blockade of CCKB in mPFC induces resilience to stress, while CCK overexpression in mPFC causes anxiogenic and depressant effects of social stress. Therefore, ΔFosB mediates the expression of CCKB induced by stress [60].

The mature neuropeptide Y (NPY), which is a 36 amino acid peptide, exists widely in the central nervous system [61] and can be categorized into two types of NPY mRNA, which is a "long" and a "short" NPY [62]. Both genetic analysis and functional studies have indicated that NPY is a key regulator of mentality and emotion including depression [63, 64]. The PFC and hippocampus have both the "short" and the "long" NPY mRNAs levels, however only the "short" NPY mRNA was indicated to be downregulated in depression rats [65].

The neuropeptide precursor VGF plays a pivotal role in the etiology of depression and antidepressant action [66]. Research studies have shown that the levels of VGF were decreased in BA25 (a part of human vmPFC) of MDD individuals and in the vmPFC of mice which experienced CRS

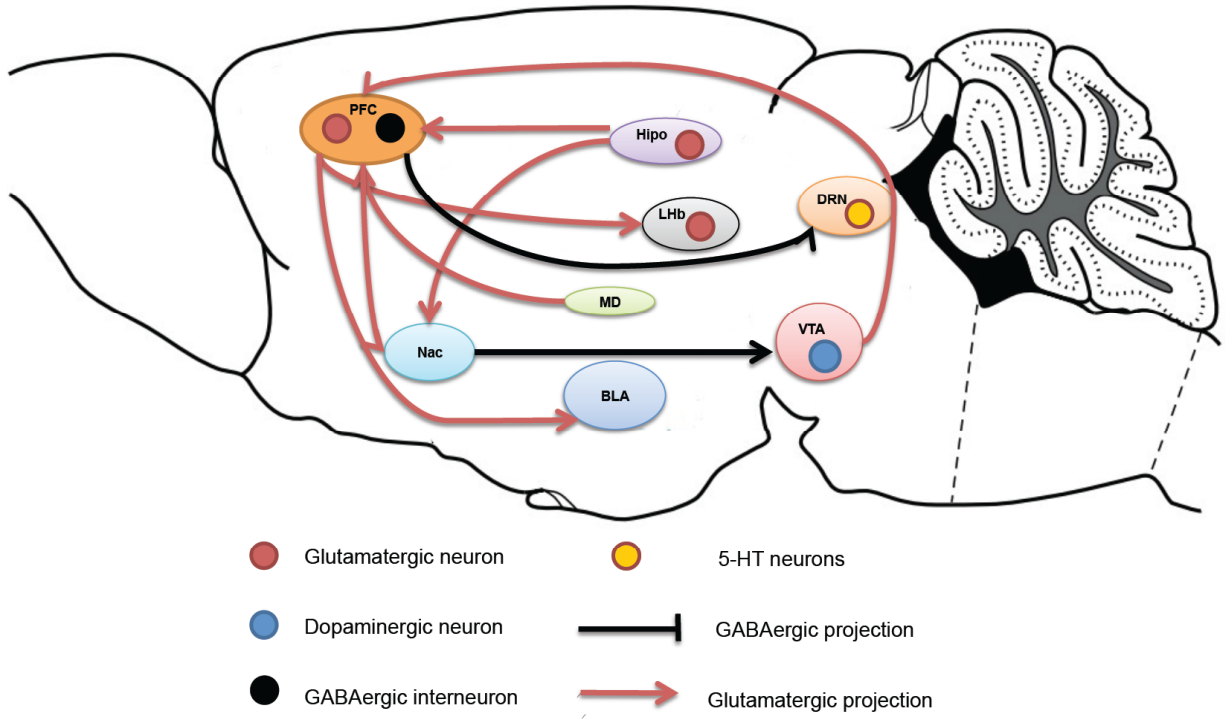

Fig. (2). Efferent and afferent regions of the PFC. The neuronal activity of PFC can be regulated by multiple brain regions via different projections. Targeting those circuits and related molecules might be the potential therapeutic directions for depression. Projections to the PFC, as shown above, include the hippocampus (Hippo), the ventral tegmental area (VTA), mediodorsal thalamus (MD). Efferent regions of the PFC include the lateral habenula (LHb), the dorsal raphe nucleus (DRN), the nucleus accumbens (Nac) and the nucleus reuniens (RE). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

training, while they were elevated by ketamine in mice vmPFC [66]. The overexpression of VGF in vmPFC rescued behavioral deficits induced by CRS, and the knockdown of VGF in vmPFC increased the susceptibility to subchronic variable stress (SCVS) and inhibited the antidepressant efficacy of ketamine [66]. However acute infusion of TLQP-62, VGF-derived peptide [67], into vmPFC induced behavioral phenotypes that mimic the effect produced by antidepressant administration [66].

Complex neural mechanisms are thought to be involved in depression. Reports showed that inflammation may have a crucial role in the pathophysiology of depression [68]. Cytokines are pleiotropic molecules with important roles in inflammatory responses. Sustained stress and the subsequent release of pro-inflammatory cytokines lead to chronic neuroinflammation, which contributes to depression. The glucocorticoid receptors (GRs) in PFC and the associated hypothalamus–pituitary–adrenal (HPA) axis have close interactions with pro-inflammatory cytokines and neuroinflammation [69]. Studies indicated that animals exposed to CRS show enhanced expression of GR^{+} cells in both PrL and ACC regions of the PFC [70]. The levels of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, are increased in patients with depression [71, 72]. In a meta-analysis, Dowlati *et al*. suggested that the levels of TNF-α and IL-6 were significantly higher in patients with MDD than in healthy controls, although other cytokines, such as IL-1β, interleukin-2 (IL-2), IL-4, IL-10, and interferon-γ (IFN-γ), were not significantly altered in MDD [71].

4. EFFERENT REGIONS OF THE PFC

Depression has been suggested to be the result of maladaptive changes in specific brain circuits. The prefrontal cortex (PFC) has been indicated to be a pivotal brain region in the pathogenesis of depression (Fig. **2**). Studies show that optogenetic and electrical manipulation of mPFC in rats ameliorated depressive-like behavior [73]. Moreover, specific optogenetic stimulation of mPFC neurons which project to nucleus accumbens (Nac) promoted resiliency in CSDS animals [6]. The Nac commonly has an effect on motivated and reward behavior with regard to either conditioned or unconditioned stimulation, and the dysfunction of Nac is indicated to play a role in the MDD symptom [74, 75].

The mPFC was also shown to afferent to some other brain areas, such as dorsal raphe nucleus (DRN), and lateral habenula (LHb), that are also indicated to be involved in several depression symptoms [76]. DRN is a serotonergic nucleus that is indicated in MDD [77]. The mPFC gets command of the activity of neurons in the DRN and the levels of extracellular 5-hydroxytryptamine (5-HT; serotonin) [78], and the antidepressant-like action of mPFC electrical stimulation appears to be dependent on an intact 5-HT system. By using optogenetic projection to govern neurons with specific efferent circuit patterns, researchers announced that selective stimulation of those mPFC cells which project to DRN had a significant, rapid and invertible effect on active behavioral state selection. Besides, they targeted the mPFC projection to LHb, a region which is known to have a significant effect on motivated behavior and

depression [79], and found that stimulation of this projection had the contrary role in escape-related behavior in the FST.

There are also excitatory afferent inputs from the basolateral amygdala (BLA) densely arborizing in mPFC superficial layers [80, 81] and forming synapses within layer II pyramidal neurons [82]. It has been identified by optogenetic manipulation that there are two different pyramidal cell populations in layer II of PrL, that project to the BLA or to the contralateral mPFC [82]. PrL-BLA afferent inputs that target spines near BLA neurons soma trigger greater excitatory postsynaptic potentials (EPSPs) than projections to the dendrite cells [82]. Destruction of the PrL-BLA projection caused large, risky rewards [83]. This particular interaction between the BLA and PrL may promote highly efficient mutual connectivity, which may be pivotal for control of mood, fear [84], emotion and anxiety [85]. PrL strongly connects with a comparatively small group of regions, and have been called the "PrL circuit". These regions mainly contain the hippocampus, insular cortex, Nac, BLA, the mediodorsal thalamus (MD), the reuniens nuclei of thalamus and ventral tegmental area (VTA) of the midbrain [86].

Rodent studies have indicated that the vmPFC presents glutamatergic projections directly to the ventral striatum [87]. Moreover, the inactivation of vmPFC affects neuronal activity in ventral striatum [88]. Humans with vmPFC abnormity exhibit emotional blunting and decreased physiological reactivity to an aversive stimulus, and increased susceptibility to depression [89]. Combination of biochemical and resting-state functional magnetic resonance imaging analyses, MDD individuals showed abnormal connectivity of PFC and striatum [90]. MDD individuals presented significantly stronger striatal connectivity in the mPFC and middle/superior temporal cortices compared to controls [90]. Then, a significant role of 'TNF-α' was reported in mPFC-striatum functional connectivity in MDD individuals. The treatment-related brain connectivity influence depends on the level of TNF-α in MDD individuals [90].

The principal region of thalamus, nucleus reuniens (RE) was also indicated to receive the afferent inputs from mPFC and transmits processed messages with monosynaptic projection to hippocampus [91]. Particularly, the vmPFC solely targets medial parts of the thalamus. However, the dmPFC distributes mainly to the ventral, intralaminar, and lateral parts of thalamus. RE fibers constitute excitatory connections mainly on terminal dendrites of pyramidal cells in CA1 [92], making a circuit as vmPFC-RE-hippocampus.

5. AFFERENT REGIONS CONTROLLING PFC ACTIVITY

Depression is involved in abnormal anatomy, morphology, and pathophysiology in PFC and hippocampus [93]. In Individuals suffering depression rumination and persistent thoughts are linked with reduced hippocampal volume [94-96], disturbed activation of the mPFC [97], and dysregulation with PFC and hippocampus [98]. Similarly, functional magnetic resonance imaging studies indicated decreased Hippocampus-PFC interconnectivity [98]. Recent studies illustrated that reduction in theta phase and theta-gamma cross-frequency may reflect the impairment of synaptic plasticity in Hippocampus-PFC circuit in the depression state [99]. So, the interconnections between the PFC and hippocampus are strongly associated with the neurobiology of psychiatric and neurodegenerative disorders. It is worth mentioning that there are direct and indirect Hippocampus-PFC pathways. In rodents, immunohistology research studies showed that the hippocampus efferent to GABAergic interneurons and excitatory pyramidal cells of PFC in a monosynaptic manner [100]. Adhikari found that the theta oscillation in the ventral hippocampus (vHPC) is highly associated with that of mPFC where theta power in both mPFC and vHPC was enhanced in anxiety-relevant condition including the open field (OF) and elevated plus-maze test (EPM) [101]. Furthermore, following a study from the same team indicated that optogenetic inhibition of vHPC to the mPFC projection alleviated anxiety and aversion [102]. Other studies have also illustrated that anxiety-associated firing is selectively enhanced in vHPC neurons which project to the mPFC [103] and that optogenetic inhibition to the vHPC-mPFC circuit ameliorated anxiety [102]. A The vHPC efferent cells were indicated almost primarily in the CA1. Along with the monosynaptic Hippocampus-PFC projections, there are complicated multisynaptic circuits between the hippocampus and PFC.

The PFC receives projections from some regions of thalamic nuclei, such as the ventral anterior, the anterior medial, the mediodorsal, and the intralaminar nuclei [104, 105]. It is worth to note that the projections from thalamic and hippocampal to the mPFC present different distribution, as the ventral CA1 projects mainly to the PFC deep layers [106], while the mediodorsal thalamus, the major thalamic afferent nucleus of the mPFC, primarily targets layer III [107]. Meanwhile, the layer I of PFC was reported to receive projections from those neurons predominantly located in the paralaminar, intralaminar, and midline thalamus [108, 109]. Anatomical research studies have indicated that mediodorsal thalamus (MD) primarily excitably projects to interneurons that express parvalbumin (PVIs) in layer III and PNs in layer V of mPFC, indicating that MD may exert double impact on PN neurons in PFC. Ferguson and Gao's study [110] indicated that the projection intensity of thalamocortical synapses onto layer V PNs may be less robust than that onto PVIs. Ferguson and Gao have provided comprehensive data regarding feedback inhibition principle from the MD to the PVIs of mPFC, which is vital to control excitation/inhibition (E/I) balance and improve mPFC-associated behaviors. Both mPFC GABAergic neurons and PNs are directly regulated by the hippocampal [111] and thalamic glutamatergic projections [112, 113], so that thalamic along with hippocampal projections induce EPSPs and/or Inhibitory postsynaptic potentials (IPSPs) in mPFC neocortical pyramidal neurons [112]. Short-latency AMPA -receptor evoked potentials excitation in PrL by electrical stimulation in vHPC [114] is followed by inhibition caused by activating monosynaptic GABAergic interneurons [112], contributing to feedback inhibition of these PNs [113]. Research studies demonstrated that repeated intracranial stimulation of lateral hypothalamus-medial forebrain connection ameliorates clomipramine which could induce deficits in learning, as well as reverses aberrant monoamine metabolism and neuronal atrophy in PFC [115]. These results proved the presupposition that chronic brain stimulation reward experiment might be indi-

cated as a potential treatment method for rescuing learning deficits in depression and related disorders [115].

6. EFFECTS OF TYPICAL ANTIDEPRESSANT DRUGS ON PFC SYNAPTOGENESIS

As is well known that there are various kinds of drugs for depression treatment. Evidence shows that typical antidepressants, including SSRIs, could affect synaptic plasticity [116]. Chronic antidepressant treatment can increase the density of spines [117] or inhibit the dendrites and spines atrophy induced by chronic stress exposure [118, 119]. Through electrophysiological manipulations, chronic fluoxetine (a typical SSRIs) treatment elevates long-term potentiation (LTP) and/or synaptic transmission [120]. Fluoxetine can also increase the expression of cFos, which is regarded as a neuronal activity marker, and 5-bromodeoxyuridine-positive (BrdU+) cells in the vmPFC [74]. Over the past few years, some reports have verified whether BDNF is essential to antidepressant responses. The necessity of BDNF in antidepressant action has been demonstrated in mice which expressed the val66met single nucleotide polymorphism (SNP) in the BDNF gene [121]. The BDNF SNP mice were irresponsive to treatment with fluoxetine [121]. In mice with BDNF allele mutation, SSRI-caused elevated levels of BDNF and synaptic plasticity was attenuated [122]. Chronic SSRIs administration also causes 5-HT1A autoreceptors desensitization to elevate 5-HT neurotransmission. Gene knockout of 5-HT1A autoreceptors (1AcKO) in mice adult 5-HT neurons were brought to test the response to SSRIs. The 1AcKO mice showed a decrease of 5-HT1A autoreceptor-related hypothermia and aberrant electrophysiological responses and subchronic fluoxetine treatment enhanced 5-HT metabolism in PFC of 1AcKO mice [123]. Fluoxetine was also proved to affect plasticity of the prefrontal cortex in the chronic stress paradigm, studies showed increased level of plasticity marker, polysialic neural cell adhesion molecule, after chronic stress and it could be reduced by fluoxetine treatment [124]. In conclusion, all the existing studies showed that the mPFC with Fluoxetine-treatment had significant increases in dendritic complexity, spine density, and the BDNF/TrkB signaling expression levels [125].

The NMDA receptor antagonist, ketamine has rapid antidepressant effects on drugs-resistant depressed individuals [126-128]. Ketamine plays a part in decreasing suicide ideation and bipolar depression [128]. Acute intravenous low dose ketamine administration induced antidepressant effect rapidly within 2 hours and this effect could persist for more than two weeks in some patients. Ketamine has a half-life of no more than 3 hours indicating that the long lasting antidepressant effects might not be regulated by NMDA receptor blockage but might involve some other synaptic plasticity mechanisms. The finding that ketamine could rapidly increase the function and number of synaptic interconnections has regarded synaptogenesis as a significant process of the depression treatment, as well it indicates that dysregulation of synaptogenesis and decrease of association works in the pathophysiology mechanism of depression [129]. It was reported that ketamine induces rapid antidepressant behavioral actions in rodent depression models, and the responses depend on the rapid production of synaptic proteins and the function and number of spine synapses of PNs in layer V of the PFC [130].

Researchers have also demonstrated the pivotal role of BDNF and TrkB in the action of ketamine and indicated that the antidepressant action of ketamine was impaired in inducible specific BDNF, as well as conditional TrkB knockout mice [131, 132]. Furthermore, elevated levels of BDNF, increase of extracellular glutamate, activation of the mTORC1 cascade, and increased number and function of spine synapses in PFC have been occurred after ketamine treatment in preclinical work [132]. It has also been demonstrated that ketamine rescues the deficits in spine density rapidly, anxiety and anhedonia induced by chronic stress exposure [133]. Ketamine could also increase the expression of cFos in both the dmPFC and vmPFC [74]. Low dose ketamine, as well as other NMDA receptor inhibitors, antagonized the stimulation of NMDA receptors, which prohibited the flow of calcium, thereby dampened the function of eukaryotic elongation factor-2 kinase (eEF2K). The eEF2K has one substrate, called eEF2, which ceases the translation of protein when phosphorylated by eEF2K. When ketamine or other NMDA receptor antagonists were given, the eEF2 was rapidly reduced [134]. To verify the function of eEF2 in the rapid antidepressant action of ketamine, the researchers found that BDNF expression in brain tissue elevated rapidly after administration of an inhibitor of eEF2K that the phosphorylation level of eEF2 decreased significantly. After administration of eEF2K inhibitor, the immobility time in forced swimming test (FST), a sign of desperation, was significantly reduced, but after administration of eEF2K inhibitor to BDNF knockout mice, it did not reduce the immobility time in FST [134]. These evidence confirm that ketamine inhibits eEF2K pathway. It also increases the translation level of BDNF and produces rapid antidepressant effects. Furthermore, the significance of this signaling in the rapid antidepressant actions was verified *via* the administration of eEF2K antagonists resulting in reduced eEF2 phosphorylation levels, BDNF protein upregulation, and a rapid antidepressant response depends on the expression of BDNF [131].

Meanwhile, the antidepressant actions of ketamine have been indicated to require glutamate AMPA receptors [135]. In accordance with this, they illustrated that pretreatment with a selective AMPA receptor antagonist, which is called NBQX (abbreviation), completely inhibited the production of phosphorylated ERK, Akt and mTOR, along with the phosphorylation of 4E-PB1 and p70S6K in the PFC [135]. Besides, different research studies found that the behavioral alterations of systemic administration ketamine are inhibited by deleting either VEGF or its receptor, Flk-1 in forebrain excitatory neuron or by infusing a VEGF neutralizing antibody into mPFC [136]. Furthermore, infusions of VEGF into mPFC are sufficient to induce ketamine-like rapid antidepressant-like behavioral effects, and these actions are inhibited by neuron-specific the receptor of VEGF, Flk-1 deletion. The results also indicated that Flk-1 knockdown in excitatory neurons of adult mPFC prohibits the effects of ketamine administration. Moreover, inhibition of neuronal VEGF signaling inhibits the synaptogenic and neurotrophic effects of ketamine [136].

A metabolite of ketamine, (2R, 6R)-HNK is demonstrated to induce rapid antidepressant actions, and does not have the side effects of ketamine [137]. Furthermore, it does not prohibit the receptors of NMDA as ketamine, though the underlying molecular signaling mechanisms remain unknown, but it increases AMPA-mediated currents and BDNF expression [138]. Researchers have demonstrated that the mTORC1 signaling is involved in the mechanism of antidepressant actions. Systemic (2R, 6R)-HNK infusion or administration into mPFC has been proved to produce long-lasting and rapid antidepressant effects through behavioral tests, demonstrating the mPFC as a crucial region for the effects of (2R, 6R)-HNK [137]. Moreover, the antidepressant effects of (2R, 6R)-HNK are antagonized in BDNF Val66Met allele knockin mice (in which the release and activity-dependent processing of BDNF is blocked) or through an anti-BDNF neutralizing antibody microinjection into mPFC. Administration of pharmacological inhibitors of mTORC1 or TrkB pathway into mPFC, the known downstream of BDNF, also has been reported to inhibit the effects of (2R, 6R)-HNK. Moreover, (2R, 6R)-HNK has been indicated to increase the synaptic function of the mPFC [137].

In addition to two classic antidepressants mentioned above, the tricyclic antidepressant, norepinephrine uptake inhibitor, desipramine (DMI) is administrated to adult male rats to find out whether the antidepressants target the PFC. Results showed that rats with DMI administration presented a distinct and remarkable increase in the expression of cFos compared to controls in the vmPFC [74]. As it is known that the vmPFC consists of superficial layers (I-III) and deep layers (V-VI) [139]. Counting the numbers of cFos stained cells within these layers, they indicated that the statistically increased expression of cFos in the vmPFC after DMI administration primarily exhibited in the deep layers. There are also studies which showed chronic, but not acute desipramine administration which increased the cFos expression in PFC [140]. Of the brain areas projected from the vmPFC, the lateral septum, insular cortex, nor BLA were significantly activated after DMI administration compared to saline injections [140]. However, the Nac presented increased cFos expression after DMI treatment. These conclusions indicate that the vmPFC-Nac projection may play a part in DMI's effects [74]. To figure out if the Nac receives projection from vmPFC neurons activated by DMI, the cholera toxin subunit B (CTB), a retrograde tracer was injected into the Nac unilaterally. The results were in accordance with their hypothesis that DMI activates this projection, which may thus play a part in the regulation of emotion and antidepressant effects of the antidepressants [74]. DMI exerts significant short-term and long-term effects on the mRNA levels of genes involved in spine plasticity within mPFC [141].

Besides these classic antidepressants, tactile stimulation (TS) has been indicated to have beneficial impacts on neuropsychiatric disorders, though the underlying mechanism is not very clear [142]. The most recent research shows that reserpine, used to treat hypertension and psychosis, elevated plasma adrenocorticotropic hormone and corticosterone, reduced the levels of BDNF and TrkB, and increased the immunoreactivity of proBDNF in the PFC, which were also indicated after TS. Besides, TS restored the levels of glial fibrillary acidic protein and glucocorticoid receptor, which were decreased by reserpine, however, glial cell-derived neurotrophic factor was elevated by TS [143].

Reduced levels of BDNF in PFC could promote depression-like phenotype in rodents, and BDNF- TrkB signaling plays a role in the pathophysiology of depression [144]. Then, researchers reported that the TrkB agonist, 7, 8-dihydroxyflavone (7, 8-DHF), show antidepressant effects [145-147]. It could significantly improve the reduced phosphorylation of TrkB in the PFC, furthermore, it could significantly attenuate the reduction of synaptogenesis markers, PSD-95 in the PFC after CSDS [148].

CONCLUSION AND PERSPECTIVE

In conclusion, there are abundant evidences that the homeostasis of synaptic connections plays a critical role in emotion-related circuits in the pathogenesis and treatment of depression. In this article, we review major studies illuminating the cellular and molecular mechanisms by which the PFC neurons become aberrant and the effects of typical antidepressant drugs on PFC synaptogenesis. We also summarize the efferent brain areas downstream of the PFC, and the source of afferent inputs into the PFC, which may mediate depression-like symptoms. There is no doubt that further researches are required for the illumination of the impacts of stress and the effects of antidepressants on synaptogenesis in some other circuits including PFC, anterior cingulate cortex, Nac, amygdala and so on, as well as to reveal the significance of synaptic dysfunction on behavior, cognition, learning, and memory in depression and anxiety models. These researches will further explain the neuronal and synaptic dysfunction in the etiology of depression and will conduce to the meaningful development of safer, more effective antidepressant agents that last longer and work more rapidly.

LIST OF ABBREVIATIONS

4E-BP1	=	Eukaryotic initiation factor 4E-binding protein 1
5-HT	=	5-Hydroxytryptamine
Akt	=	Protein kinase B
AMPA	=	α-Amino-3-Hydroxy-5-Methyl-4-Isoxazoleproprionic acid
BA	=	Brodmann areas
BDNF	=	Brain-derived neurotrophic factor
BLA	=	Basolateral amygdala
CA1	=	Field CA1 of hippocampus
CA3	=	Field CA3 of hippocampus
CCK	=	Cholecystokinin
CCKB	=	Cholecystokinin –B receptor
CNS	=	Central nervous system
CREB	=	The cAMP response element-binding protein

CRS	=	Chronic restraint stress
CSDS	=	Chronic social defeat stress
CTB	=	Cholera toxin subunit B
CUMS	=	Chronic unpredictable mild stress
DG	=	Dentate gyrus
dlPFC	=	The dorsal-lateral prefrontal cortex
DMI	=	Desipramine
DRN	=	Dorsal raphe nucleus
E2	=	Estrogen
eEF2	=	Eukaryotic elongation factor 2
eEF2K	=	Eukaryotic elongation factor-2 kinase
eIF4B	=	Eukaryotic initiation factor 4B
EPM	=	Elevated plus-maze test
EPSPs	=	Excitatory postsynaptic potentials
ERK	=	Extracellular signal-egulated kinase
FST	=	Forced swimming test
GABA	=	G-aminobutyric acid
GAL	=	Galanin
GALRs	=	GAL receptors
GluR1	=	Glutamate receptor subtype 1
GSK3	=	Glygocen synthase kinase 3
HPLC	=	High-performance liquid chromatograph
ICV	=	Intracerebroventricular
IL	=	Infralimbic cortex area
IPSPs	=	Inhibitory postsynaptic potentials
KIN	=	The kinase catalytic domain
LHb	=	Lateral habenula
LTP	=	Long-term potentiation
MAPK	=	Mitogen-activated protein kinase
MD	=	Mediodorsal thalamus
MDD	=	Major depressive disorder
mGluR5	=	Metabotropic glutamate receptor subtype 5
MKP	=	MAPK phosphatase
mPFC	=	The medial PFC
mTOR	=	The mammalian target of rapamyc
Nac	=	The nucleus accumbens
NMDA	=	N-methyl-D-aspartate
NPY	=	Neuropeptide Y
NRD	=	Negative regulatory domain
OF	=	Open field
OFC	=	The orbitofrontal cortex
p70S6K	=	P70-kDa ribosomal protein S6 kinase
p-eIF4B	=	Phosphorylated eukaryotic initiation factor 4B
PFC	=	the prefrontal cortex
PI3Ks	=	Phosphoinosmde-3-kinase
PNs	=	Pyramidal neurons
PrL	=	Prelimbic cortex area
PSD95	=	Postsynaptic density protein 95 kDa
PVIs	=	Parvalbumin-expressing interneuron
RE	=	Reuniens
SCVS	=	Subchronic variable stress
SNP	=	Single nucleotide polymorphism
SSRIs	=	Selective serotonin reuptake inhibitors
TCAs	=	Tricyclic antidepressants
TrkB	=	Tropomyosin related kinase
VEGF	=	Vascular endothelial growth factor
vHPC	=	Ventral hippocampus
vmPFC	=	The ventromedial PFC
VTA	=	Ventral tegmental area

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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