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Review

The role of BDNF in depression on the basis of its location in the neural circuitry

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Depression is one of the most prevalent and life-threatening forms of mental illnesses and the neural circuitry underlying depression remains incompletely understood. Most attention in the field has focused on hippocampal and frontal cortical regions for their roles in depression and antidepressant action. While these regions no doubt play important roles in the mental illness, there is compelling evidence that other brain regions are also involved. Brain-derived neurotrophic factor (BDNF) is broadly expressed in the developing and adult mammalian brain and has been implicated in development, neural regeneration, synaptic transmission, synaptic plasticity and neurogenesis. Recently BDNF has been shown to play an important role in the pathophysiology of depression, however there are controversial reports about the effects of BDNF on depression. Here, we present an overview of the current knowledge concerning BDNF actions and associated intracellular signaling in hippocampus, prefrontal cortex, nucleus accumbens (NAc) and amygdala as their relation to depression.

Keywords: BDNF; depression; antidepressant; neural circuitry

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Introduction

Depression is a clinically and biologically heterogeneous disease, with 10%–30% of women and 7%–15% of men likely to suffer from depression in their life-time[1]. The symptoms of depression are the loss of interest or pleasure in virtually all activities (anhedonia) and a long-lasting depressed mood, feelings of guilt, anxiety, and recurrent thoughts of death and suicide[2]. The genetic contribution to the manifestation of depression has been estimated as 40%–50%[3]. However, combinations of multiple genetic factors may be involved in the development of depression, because a defect in a single gene usually fails to induce the expression of multifaceted symptoms of depression[4]. Also, various non-genetic factors such as stress, affective trauma, viral infection, and neurodevelopmental abnormalities increase the complexity of the pathogenesis of the disease. Thus, extensive studies have led to a variety of hypotheses for the molecular mechanism of depression, but a definite pathogenic mechanism has yet to be defined. The objective of this review is to investigate the contribution of brain-derived neurotrophic factor (BDNF) and its intracellular signaling in different brain regions to depression and antidepressant treatments.

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Neurobiology of depression

As a basic understanding of depression the monoamine hypothesis was formulated in the mid 1960s based on the antidepressant efficacy of the monoamine reuptake inhibitors, monoamine oxidase inhibitors and the depressogenic effects of reserpine as a monoamine depleter[5]. This hypothesis suggests a deficiency or imbalances in the monoamine neurotransmitters, such as serotonin (5-HT), dopamine and norepinephrine (NE), as the cause of depression. Among therapeutic agents, antidepressants including tricyclics, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors (SSRIs) exert their therapeutic action through their ability to increase the synaptic content of monoamine neurotransmitters[6]. However, antidepressants exert their therapeutic action only after chronic treatment, indicating that enhanced 5-HT or NE neurotransmission *per se* is not responsible for the clinical actions of these drugs. Second, antidepressants are effective in less than 50% of patients[2], which suggests that additional biological substrates could provide potential therapeutic targets.

Based on clinical and animal studies it has been suggested that depression are associated with neuronal atrophy and neuronal cell loss, especially in the hippocampus and cerebral cortex[7]. Therefore the neurotrophic factors are recognized as an

important new lead in the quest for a deeper understanding of depression and the mechanisms of antidepressants effect[8]. The neurotrophic hypothesis of depression states that a deficiency in neurotrophic support may contribute to hippocampal pathology during the development of depression, and the reversal of this deficiency by antidepressant treatments may contribute to the resolution of depressive symptoms. Of various neurotrophins, most studies have focused on BDNF, one of the most prevalent neurotrophic factors in adult brain.

BDNF and depression

Studies in humans have shown decreased plasma levels of BDNF in bipolar disorder, manic and depressed patients[9, 10]. Many preclinical and clinical studies provide direct evidence suggesting that modulation in expression of BDNF could be involved in behavioral phenomenon associated with depression. Recently, a variant in the human BDNF gene, which leads to a valine to methionine change in the pro-domain of the BDNF protein (position 66), was found to decrease activity-dependent secretion of BDNF[11, 12] and be associated with increased susceptibility to neuropsychiatric disorders including depression, anxiety-related dysfunction and bipolar disorder[13–17]. People with the Met allele have been found to have a relatively small hippocampus and poor hippocampus-dependent memory function[18]. In our previous work, we have generated a BDNF knock-in mouse containing the BDNF Val66Met polymorphism, which provided a valuable tool to assess the *in vivo* consequence of $BDNF^{Met}$ polymorphism[19]. We found that $BDNF^{Met/Met}$ mice showed increased anxiety-related behaviors, which could not be reversed by fluoxetine treatment[19]. Furthermore, we found $BDNF^{Met/Met}$ mice had decreased ventromedial prefrontal cortex volume and displayed aversive memory extinction deficit[20]. These studies suggest that the BDNF Val66Met polymorphism might be at risk to develop smaller prefrontal cortex and hippocampus and thus lead to susceptibility to mood disorders, which strengthens the hypothesis that BDNF plays an important role in depression.

The role of BDNF in depression has also been supported by the hypothesis that BDNF mediates the action of antidepressant. The most widely accepted hypothesis assuming that antidepressants restore the compromised neurotransmission in mainly noradrenergic and serotoninergic system has dominated our thinking of antidepressant action. Indeed, speaking of depression, a key question has always been why therapeutic responses with antidepressants could only be achieved after at least 2–3 weeks of treatment, whereas antidepressants alter synaptic monoamine levels within hours. Since the monoaminergic hypothesis cannot fully explain this delay of antidepressant effect, it has been suggested that this delay is required in order to produce neuroadaptive mechanisms that may enhance neuronal plasticity and resilience[21, 22]. Along this line of reasoning, several studies have shown that BDNF may mediate the therapeutic action of antidepressants[23–25]. There is a plethora of evidence documenting that antidepressant treatments, including SSRIs and electroconvulsive shock (ECS) increase the expression of BDNF and tropomyosin receptor kinase B (TrkB) in the hippocampus in animal models. These effects are dependent on chronic administration of antidepressant therapy, consistent with the time course of antidepressant treatments[26, 27]. This suggests that the regulations of BDNF and TrkB are involved in the pathology and development of depression and antidepressant treatments.

However, although BDNF exerts antidepressant-like effects in hippocampus, its actions might be different or even opposite, in different brain regions. The best example is the ventral tegmental area-nucleus accumbens (NAc) dopaminergic reward circuit, in which chronic stress increases BDNF expression[28]. Local BDNF infusion into NAc exerts a prodepression-like effect in the forced swim test, and blockade of BDNF function in NAc exerts an antidepressant-like effect[28]. Thus the differential role of BDNF in depression might be attributed to its location in the depression neural circuits. In the following parts of the review, we would like to summarize the local contribution of BDNF/TrkB signaling to depression on the basis of its location in the neural circuitry.

Neural circuitry of depression

Disturbances in the detection of, response to, and interpretation of emotion are common in depression. The affective fronto-limbic circuitry including the prefrontal cortices, the cingulate cortex, several limbic structures including the hippocampus, amygdala, lower brainstem structures and the basal ganglia are highly involved in mediating these stages of emotion processing, and evidence indicates that these regions show structural and functional alterations in depression[29].

A greater understanding of the neural circuitry underlying normal mood and abnormalities in mood has been identified as one of the critical needs in the field of depression research. The hippocampus and frontal cortex are implicated in learning and memory, attention and impulse control, which suggests they may mediate cognitive aspects of depression, such as memory impairments and feelings of hopelessness, guilt, doom, and suicidality[2, 30]. The striatum (particularly the NAc) and amygdala, and related brain areas, are important in emotional memory, and could as a result mediate the anhedonia, anxiety, and reduced motivation that predominated in many patients[31]. Hypothalamic abnormalities likely contribute to altered appetite and autonomic symptoms. Thalamic and brainstem dysregulation contribute to altered sleep and arousal states[32]. Of course, these various brain areas cannot be thought of as distinct, they operate in a series of highly interacting parallel circuits, which perhaps begins to formulate a neural circuitry involved in depression.

Brain imaging studies of depressed patients indicate a significant reduction in hippocampal volume compared with healthy subjects[33, 34]. Magnetic resonance imaging (MRI) studies consistently show that the ventral prefrontal cortex is reduced in size in adult patients with major depressive disorder (MDD) compared with healthy controls. Postmortem data support this finding, and suggest that fewer glia cells may contribute to the overall reduced size of the region[35]. To the

striatum, MRI and postmortem studies showed volumetric reductions in the caudate and the ventral region of the striatum in individuals with depression[36], but other studies have found no differences[37]. In the amygdale, findings are not entirely consistent across studies. It has been reported that amygdala volumes were increased in patients during first episode with MDD, but patients with recurring MDD had smaller amygdala[38]. Other study reported that adult patients with MDD have increased amygdala volume than healthy comparison subjects[39]. Thus, inconsistencies in the data may relate to stage of the disorder. In summary, the anatomical data suggest that adult MDD is associated with reduced hippocampus, ventral prefrontal cortex volume and altered amygdala volume in comparison with healthy controls.

BDNF signaling in hippocampus involved in depression

The hippocampus, a key structure for the encoding of emotionally relevant data into memory, interacts with the amygdala to provide input regarding the context in which stimuli occur[40]. In addition, the hippocampus plays an inhibitory role in the regulation of the amygdala and hypothalamic– pituitary–adrenal (HPA) axis activity, which is the major mediator of systemic stress responses[41]. Evaluation of the mean changes of hippocampal volumes shows that the hippocampus is about 4%–5% smaller in patients with MDD than in healthy controls[42]. Using *in situ* DNA end-labeling demonstrated slightly increased rate of apoptosis in the dentate gyrus, CA1 and CA3 areas of the hippocampus in depressed patients[43]. In another postmortem study, Stockmeier *et al* found that hippocampal sections from depressed patients shrank more than sections from control subjects after histologic processing[44]. Hence, it suggests that both apoptosis and atrophy may occur in depression. BDNF clearly has a role in survival of neurons during hippocampal development, and this may relate to its putative role in depression. Decreased levels of BDNF may contribute to the atrophy of hippocampus that has been observed in depressed patients. Moreover, consistent data suggest that serum BDNF levels are reduced in depressed patients and are negatively correlated with depression severity while antidepressant treatment restores the basal level of serum BDNF[45, 46]. Decreased BDNF mRNA and protein levels, TrkB and cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) have been found in postmortem brains of suicide victims[47]. Consistently, suicidal behavior has been associated with lower plasma BDNF level[48]. In postmortem hippocampal sections, BDNF expression has been observed to be increased in dentate gyrus and subgranular regions in subjects treated with antidepressants prior to death as compared with non-treated subjects[49].

Postmortem studies have a number of limitations in assessing depression-related molecular or cell turnover. Particularly, it is difficult to rule out the effects of antidepressant medication and other drugs or factors that are not known to investigators. Therefore, animal models were applied to investigate clear depression-induced hippocampal changes. Stress is widely used as a model for mood disorders in experimental animals. A summary of studies demonstrate that many different types of acute (single stress) and chronic (7 to 21 d) stress paradigms decrease the expression of BDNF in the hippocampus. In chronically stressed tree shrews, an animal model with high validity for depression, demonstrated reduced hippocampal volume and cell proliferation, and these alterations were prevented by tianeptine treatment[50]. Immobilization stress significant decreases BDNFmRNA expression in the major subfields of the hippocampus, with the greatest effects observed in the dentate gyrus granule cell layer. Subsequent work found that other types of stress, including unpredictable, footshock, swim stress, and maternal deprivation, also decreased the expression of BDNF in the hippocampus[51, 52]. Genetic studies support the role of BDNF Val66Met polymorphism in depression[13, 14]. In our previous study, $BDNF^{Met/Met}$ mice have smaller hippocampal volumes and increased anxiety-related behaviors[19]. Moreover, music treatment could decrease anxiety state in $BDNF^{Met/Met}$ mice by increasing BDNF levels in the hippocampus and prefrontal cortex[53].

In contrast to the actions of stress, different classes of antidepressants significantly increased the expression of BDNF in the major subfields of the hippocampus, including the granule cell layer and the CA1 and CA3 pyramidal cell layers[54]. Chronic pretreatment with antidepressants blocks the stress-induced decrease in BDNF mRNA expression in the hippocampus[55]. Distinct classes of antidepressants appear to regulate the BDNF gene through differential recruitment of individual BDNF promoters[56]. In addition, they appear to be capable of reversing the epigenetic shut down of the BDNF III and IV promoters caused by stress. Indeed, overexpression of histone deacetylases, which would derepress the epigenetic control of the BDNF promoters, is shown to upregulate hippocampal BDNF expression and exert antidepressant-like effects in animal models[57]. Furthermore, truncated TrkB overexpressing mice, which show reduced BDNF signaling, are resistant to the effects of antidepressants in the forced swim model of depression[58]. Several lines of evidence suggest that increased BDNF signaling is associated with antidepressant-like behaviors in rodent depression models. Specifically, Siuciak and colleagues were the first to report that short-term (6–7 d), microinfusion of BDNF into the dentate gyrus of hippocampus produces antidepressant-like effect in forced swim test (FST) and learned helpless (LH)[59]. Furthermore, a single intracerebroventricular injection of BDNF (10 μg) produces similar changes in the modified rat FST[60]. Compared with the classical antidepressants, the effects of BDNF on these behaviors are long lasting[60, 61]. Unfortunately, relatively high doses of BDNF need to be administered to achieve these behavioral responses. Taken together, these reports clearly implicate BDNF in both the pathogenesis of depression and as a target/mediator of antidepressant action.

Several studies have suggested that normal BDNF signaling is both necessary and sufficient for antidepressant drug action. Antidepressant-induced tyrosine phosphorylation of TrkB does not induce activity of the extracellular signal-regulated kinase pathway, but does activate phospholipase-Cγ signaling

and lead to the phosphorylation of CREB, a major transcription factor directing gene expression of plasticity-related molecules[62]. In the hippocampus, increased activity of the BDNF-CREB cascade results in antidepressive responses. Chronic, but not acute, administration of several different types of antidepressants, including SSRIs, a NE-selective reuptake inhibitor, a monoamine oxidase inhibitor, an atypical antidepressant, ECS, and lithium, increase the levels of CREB mRNA and immunoreactivity in hippocampus[55]. *In situ* hybridization and immunohistochemical analysis demonstrate that the expression of CREB is increased in the major cell layers of hippocampus (*ie*, CA3 and CA1 pyramidal and dentate gyrus granule cell layers). In contrast, chronic administration of nonantidepressant psychotropic drugs (*ie*, morphine, cocaine, and haloperidol) does not influence the expression of CREB in hippocampus, demonstrating the pharmacologic specificity of this effect for antidepressants. This does not imply that the cAMP system and CREB are not involved in the actions of these drugs. In fact, chronic opiate or psychostimulant treatments are reported to regulate CREB in striatum and locus coeruleus[63]. This demonstrates that CREB is regulated in a region-specific manner depending on the neurotransmitter systems influenced by these psychotropic drug treatments.

Hippocampal overexpression of BDNF or CREB is capable of mimicking both the structural consequences of sustained antidepressant treatment as well as exerting antidepressant-like behavioral effects[61, 64]. Indeed, activation of the cAMP-CREB cascade results in increased neurogenesis of dentate granule cell progenitors, and increased dendritic length and branching[65]. It is possible that CREB, a transcriptional activator of BDNF, recruits this neurotrophin to mediate its effects on structural plasticity. BDNF, in addition to being a target of CREB, can itself recruit this particular transcription factor by activating the mitogen-activated protein (MAP) kinase cascade[66], thus setting up a potential positive feed-back loop. Taken together, elevated BDNF-CREB, through their protective influences on vulnerable hippocampal neurons and their ability to directly promote structural reorganization, could result in repair of this region known to be damaged in depression. In addition, BDNF can alter neurotransmitter release and itself elicit an activation of postsynaptic neurons, and may thus have potential protective functional consequences on hippocampal circuitry known to be dysfunctional in depression[67]. A direct consequence of enhanced hippocampal function would be a restoration of the inhibitory control exerted on the stress response pathway of the HPA axis. In addition, the well-established role of BDNF and CREB in hippocampal-dependent learning and memory may play a critical role in ameliorating the cognitive symptoms associated with depression[67, 68]. Therefore, reduced BDNF levels result in neuronal atrophy and cell death in the hippocampus whereas enhanced BDNF levels are associated with neurogenesis, cell survival and dendritic arborization. Thus, changes in hippocampal BDNF levels and the resulting downstream signaling pathways may play an essential role in regulating depression related behaviors.

BDNF signaling in prefrontal cortex involved in depression

Several lines of evidence suggest that the prefrontal cortex (PFC) is involved in the neuropathology of depression and the response to stress. Perhaps the most widely accepted division of PFC, based on anatomical connectivity and functional specialization, is the dorsolateral and ventromedial sectors[69]. The ventromedial prefrontal cortex (vmPFC) includes the ventral portion of the medial prefrontal cortex and medial portion of the orbital surface. Targets of vmPFC projections include the hypothalamus and periaqueductal gray, which mediate the visceral autonomic activity associated with emotion, and the ventral striatum, which signals reward and motivational value. In addition, vmPFC has dense reciprocal connections with the amygdala, which is involved in threat detection and fear conditioning[29]. By contrast, the dorsolateral prefrontal cortex (DLPFC), which includes portions of the middle and superior frontal gyri on the lateral surface of the frontal lobes, receives input from specific sensory cortices, and has dense interconnections with premotor areas, the frontal eye fields, and lateral parietal cortex[70]. The distinct patterns of connectivity in these two regions of PFC suggest disparate functionality. Indeed, DLPFC has primarily been associated with "cognitive" or "executive" functions, whereas vmPFC is largely ascribed "emotional" or "affective" functions.

Volumetric changes in the PFC in depression are similar to those described in the human hippocampus. The earliest functional imaging studies of depression compared the resting state brain activity (*eg* blood flow or glucose metabolism) of depressed patients with that of non-depressed comparison subjects. Results from these studies associate depression with abnormally high levels of vmPFC activity[71], but abnormally low levels of DLPFC activity in resting brain activity[72]. Recent, a type of functional imaging study compares task-related brain activations (blood flow) of depressed patients to that of non-depressed comparison subjects. Data from these studies demonstrate that depressed patients exhibit greater task-related activation in DLPFC during tests of working memory and cognitive control when performance is matched to non-depressed subjects[73]. In light of the resting state data indicating DLPFC hypoactivity in depression, these results suggest dysfunction (or at least inefficiency) in the DLPFC of depressed patients. In sum, the functional imaging studies converge to suggest that depression is associated with seemingly opposite activity profiles in vmPFC and DLPFC. The vmPFC is hyperactive at rest, whereas the DLPFC is hypoactive at rest. These imaging data hint that an imbalance in vmPFC/DLPFC activity may contribute to depression. However, functional imaging data alone cannot adjudicate whether the abnormal activity profiles observed in vmPFC and DLPFC are a cause or consequence of the disorder.

In humans, postmortem studies have shown that both BDNF and TrkB levels are significantly decreased in the prefrontal cortex and hippocampus of suicide patients compared with controls and antidepressant therapy restores brain BDNF levels to the normal range[74]. In addition, there were signifi-

cant decreases in the phosphorylation of TrkA and TrkB in both PFC and hippocampus of suicide subjects, whereas the phosphorylation of TrkC was decreased only in hippocampus without any change in PFC[75]. Stress is used as a model to study alterations of molecules and brain structure because mood disorders are often precipitated or exacerbated by acute or chronic stressful life events[76]. Repeated stress causes dendritic shortening in medial prefrontal cortex, as well as in hippocampus[77]. As with in the hippocampus, stress decrease BDNF levels in the PFC. Prenatally stressed rats had significantly less BDNF protein than nonstressed rats in PFC by Western blotting analysis[78]. Furthermore, Roth showed that infant maltreatment results in methylation of *BDNF* DNA through the lifespan to adulthood that dovetails reduced *BDNF* gene expression in the adult PFC in rat[79].

Many different antidepressants produce a modest increase in BDNF mRNA levels in PFC after a few days of treatment. BDNF mRNA and protein levels, as well as TrkB mRNA levels, were increased significantly in post-natal day 13 rats in hippocampus and PFC after escitalopram treatment as compared to control, but desipramine failed to increase either BDNF or TrkB, which suggests that SSRIs are able to positively modulate BDNF and TrkB expression, whereas desipramine is not able to. The failure of desipramine to positively modulate BDNF and TrkB expression in postnatal day 13 rats is consistent with the lack of efficacy of desipramine in children and adolescents[80]. The BDNF gene consists of four 5′ noncoding exons (I–IV) each with a separate promotor and one 3′ exon (exon-V) encoding the mature BDNF protein. The exon-III and IV BDNF promoters are regulated as immediate early genes. Previous work showed that BDNF-LTP is associated with rapid upregulation of exon-III specific and exon-V (total) BDNF mRNA. In PFC exon-III and exon-V BDNF mRNA levels were significantly elevated about 3- and 2-fold, respectively, after chronic but not acute fluoxetine treatment. In hippocampus, chronic fluoxetine administration led to a 2.5-fold increase in exon-III expression, but no significant change in exon-V expression. These studies demonstrate that chronic administration of fluoxetine leads to brain region specific upregulation of BDNF in the adult brain, which suggests that chronically administered antidepressants could promote BDNF-induced gene expression and synaptic plasticity in multiple brain regions.

Animals work shows that stress decreases phosphorylated CREB and antidepressants treatment increases the expression of phosphorylated CREB specifically in the hippocampus and prefrontal cortex[81]. Experimental studies demonstrated that chronic forced swim stress decreased the expression of phosphorylated-extracellular signal-regulated kinase 2 (p-ERK2), ERK1 and ERK2 in the hippocampus and prefrontal cortex in rats; fluoxetine reversed the stress-induced disruption of the p-ERK2, which is indicated by the increased level of the p-ERK2 in the hippocampus and prefrontal cortex in stress-fluoxetine group compared to stress group, but exhibited no effect on the stress-induced decrease of the ERK1 and ERK2. It thus appears that the major effect of fluoxetine is to activate the ERK and CREB to increase the levels of p-ERK2 and p-CREB, but not to increase the ERK and CREB expression[82].

BDNF signaling in nucleus accumbens involved in depression

The NAc is a target of the mesolimbic dopamine system, which receives dopamine input from dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain. Furthermore, the ventral striatum also has been noted to have extensive connections with the amygdala and the orbital, subgenual, and ventrolateral PFC[83]. The NAc, and its dopaminergic inputs, play critical roles in reward. Virtually all drugs of abuse increase dopaminergic transmission in the NAc, which partly mediates their rewarding effects[84]. On the other hand, the VTA neurons also innervate several other limbic structures, including the amygdala and limbic regions of neocortex. The relationship of VTA-NAc pathway to mood disorders requires further study, but it seems plausible that disturbances in this pathway would be related to abnormalities in hedonic tone and motivation[2], which are central features of mania and depression. This is supported by the finding of decreased striatal response to happy stimuli associated with level of anhedonia in depressed subjects as well as the observation of increased striatal activity in mania[85].

However, increasing BDNF levels in the NAc or VTA pathway produces depression-like phenotype and animals with a selective knockout of BDNF in the VTA are protected from the depressive effects produced by the social defeat stress[23]. At the same time, intra-VTA infusion of BDNF exerts a depression-like effect in the forced swim test, while blockade of BDNF action in the NAc, by use of viral-mediated overexpression of a dominant negative mutant of TrkB, causes an antidepressant-like effect in the same test[86]. These data suggest that BDNF plays opposite roles in the VTA-NAc circuit compared with in the hippocampal-prefrontal circuit.

While dysfunction of the VTA-NAc circuit is thought to be associated with depression, antidepressants have been postulated to reverse this dysfunction. In stark contrast to the effects of CREB-BDNF in the hippocampus, activation of the CREB-BDNF cascade in the VTA-NAc pathway results in pro-depressive like behavior[64]. Increased CREB activity in the NAc results in a phenotype characteristic of depression, including reduced reward experience or "anhedonia" and increased immobility in the forced swim test, symbolizing behavioral "despair"[87]. The effects of BDNF are thought to be mediated via up-regulating CREB expression, through activation of the MAPK/ERK pathway[66]. Thus BDNF, upstream of CREB, would recruit specific target genes with promoter CRE elements, and then affect the functioning of the VTA-NAc circuitry, resulting in a depression-like phenotype. CREB is known to positively modulate levels of dynorphin within the NAc[88], and this upregulation of the endogenous opioid dynorphin could mediate the pro-depressive effects of CREB. Although at present it is unknown if CREB induction in the NAc results in enhanced dynorphin release within the VTA, it has been hypothesized that such a change in the context of

the VTA-NAc pathway could result in dysphoria and lack of pleasure seeking[89]. This raises the possibility that enhanced BDNF-CREB in the NAc may, through a regulation of opioid signalling, result in an anhedonic state thus contributing to the pro-depressive effects, whereas an abrogation of BDNF-CREB signalling in this region could have beneficial consequences on behavior and exert an antidepressant-like effect. The opposite behavioral response for infusion BDNF to hippocampus versus NAc suggests that depression and antidepressant effects are related to the functional consequences of different downstream regulation in different neuronal networks.

BDNF signaling in amygdala involved in depression

Recent years, the amygdala has emerged as the key forebrain structure mediating inborn and acquired emotional responses, as well as processing, interpreting, and integrating various aspects of biologically and/or emotionally important information[90]. The amygdala is a complex structure that is comprised of many subnuclei. Two such units that have been particularly implicated in the control of emotional processes are the central nucleus (CeA) and the basolateral amygdala (BLA). A prevailing view is that the BLA is responsible for emotional learning; receiving sensory information and acts as a site of conditioned and unconditioned stimulus associations and uses this learned information to control the activity of the CeA. In turn, the CeA acts as a 'controller of the brainstem', by using its widespread projections to the hypothalamus, midbrain reticular formation and brainstem to orchestrate behavioral, autonomic, and neuroendocrine responses. Different regions within the amygdala are specialized, on the basis of connections with cortical, hippocampal, thalamic, hypothalamic, and other subcortical structures, to detect objects salient to the prevailing emotional state, and to modulate an appropriate response[91, 92]. Dysfunction in amygdala plasticity can be related theoretically to depression and bipolar disorder (BD)[91]. Neuroimaging studies of the amygdala in patients with BD are characterized by an interesting age-related dichotomy of findings. In adults, the predominant pattern is one of increased amygdala volume while in children and adolescents the reverse applies, which suggest that amygdala size may vary in relation to illness duration[93, 94]. Resting state functional analyses have been largely limited to the adult population and are indicative of increased baseline amygdala activity which correlates positively with severity of depression[95].

The link between stress and depression has long been observed, particularly at the clinical level, where chronic exposure to stressful life events has been associated with the development of depressive symptoms. Stress also causes structure changes in amygdala. Both acute and chronic stress increases spine synapse formation in amygdala[96] but chronic stress decreases it in hippocampus[97]. Moreover, chronic stress for 21 days or longer impairs hippocampal-dependent cognitive function and enhances amygdala-dependent unlearned fear and fear conditioning[98], which are consistent with the opposite effects of stress on hippocampal and amygdala structure and suggest that the effect of chronic stress on dendritic remodeling is regionally specific.

BDNF mRNA increased in the amygdala 1 h after the final exposure to intermittent water immersion stress. Consistent with this, repeated intermittent social stress increased BDNF mRNA in the BLA and CeA but not in the medial amygdala (MeA) 2 h after termination of social stress. However, repeated restraint or acute social stress exposure reduced amygdala BDNF mRNA 24 h later[99, 100]. This suggests that stress-induced changes in BDNF are transient in the amygdala. BDNF-overexpressing transgenic mice showed increased BLA spine density and increase anxiety-like behavior in open field test and elevated-plus maze test[101]. Furthermore, previous studies have reported that chronic stress-induced anxiety is accompanied by increases in dendritic area and spine density in the BLA[102, 103]. This increase in the BLA spine density may be a reason for the increased amygdala size and functional output.

The amygdala has been the focus of a great deal of work in the anxiety, post-traumatic stress disorder (PTSD), and drug addiction fields, but has received relatively little attention in depression. It would be interesting to use behavioral tests that focus on the amygdala, as well as direct manipulations of specific proteins in the amygdala (*eg*, CREB and BDNF, among many others), to explore the role played by these circuits in depression and antidepressant action.

Conclusions and future directions

In summary, the data herein reviews the role of BDNF in critical neural networks underlying depression/stress and antidepressant treatment (Table 1). The main studies suggest four points: First, depression or stress could reduce BDNF levels in the hippocampus and PFC; Second, depression or stress induces dentritic atrophy in the hippocampus and PFC, while leads to increased spine density in the BLA; Third, successful antidepressant treatments increase BDNF levels in the hippocampus and PFC and inhibit depression-like behavior; Fourth, BDNF levels increase in the BLA and NAc produce anxiety-like or depression-like phenotype. Thus the diverse roles of BDNF in depression depend on its location in the neural circuitry, namely, in the hippocampus and PFC BDNF inhibits depressive symptoms and whereas in the NAc and amygdala facilitates depression-like or anxiety-like symptoms.

Regardless of the role of BDNF in the etiology of depression

Table 1. Regulation of BDNF by depression/stress, and antidepressant treatment in different brain regions.

Brain regions	Depression/Stress	Antidepressant
Hippocampus	BDNF↓	BDNF↑
PFC	BDNF↓	BDNF↑
NAc	BDNF↑	BDNF↓
Amygdala (BLA)	BDNF↑	—

Symbols: ↓, decrease; ↑, increase; —, inconsistent.

and in the mechanism of action of current antidepressants, advances in understanding how specific molecular mechanisms within the hippocampus, PFC, NAc, amygdala, and other brain regions regulate mood will provide novel avenues. A major need of future research is to better define the detailed circuitry of the numerous and diverse molecular pathways in these brain regions.

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