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The Role of Neurotrophins in Major Depressive Disorder

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Abstract

Neurotrophins and other growth factors have been advanced as critical modulators of depressive behavior. Support for this model is based on analyses of knockout and transgenic mouse models, human genetic studies, and screens for gene products that are regulated by depressive behavior and/or antidepressants. Even subtle alteration in the regulated secretion of brain-derived neurotrophic factor (BDNF), for example, due to a single nucleotide polymorphism (SNP)-encoded Val-Met substitution in proBDNF that affects processing and sorting, impacts behavior and cognition. Alterations in growth factor expression result in changes in neurogenesis as well as structural changes in neuronal cytoarchitecture, including effects on dendritic length and spine density, in the hippocampus, nucleus accumbens, and prefrontal cortex. These changes have the potential to impact the plasticity and stability of synapses in the CNS, and the complex brain circuitry that regulates behavior. Here we review the role that neurotrophins play in the modulation of depressive behavior, and the downstream signaling targets they regulate that potentially mediate these behavioral pro-depressant and antidepressant effects.

Keywords

Antidepressant; Arc; Brain-Derived Neurotrophic Factor (BDNF); Depression; Ketamine; Nerve Growth Factor (NGF); Neuritin; Neurotrophin-3 (NT-3); Trk; VGF

Overview of Neurotrophins

Neurotrophins are a family of secreted growth factors that regulate survival, growth, differentiation and maintenance of neurons in both CNS and PNS [1-3]. Four neurotrophins, nerve growth factors (NGF) [4], brain-derived neurotrophic factor (BDNF) [5], neurotrophin-3 (NT-3) [6] and neurotrophin-4/5 (NT-4/5) [7] have been identified and their function in the nervous system has been widely explored. The various effects of different neurotrophins on neurons can be attributed to their selective binding to two classes of receptors, the Trk family of receptor tyrosine kinases and the p75 neurotrophin receptor (p75NTR). Specifically, NGF binds to TrkA, BDNF and NT-4/5 bind to TrkB, NT-3 to TrkC and all four neurotrophins interact with p75NTR [8]. Recent studies have further

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revealed that immature pro-neurotrophins, which have not been proteolytically processed, and mature neurotrophins bind to different receptors. For example, pro-BDNF selectively binds p75NTR with the aid of sortilin to induce apoptosis [9], long-term depression (LTD) [10], and reduce dendritic complexity and spine density [11] in the hippocampus. The binding of neurotrophins to their cognate receptors activates different intracellular signaling cascades, including the Ras/ERK (MAPK) pathway, the PLC γ pathway and the PI3K/Akt pathway [12], which mediate both unique and overlapping functions of neurotrophins in the CNS and PNS [13]. Thus there are multiple levels by which neurotrophin actions can be modulated to impact depression and the response to antidepressants, including regulation of their synthesis, secretion, and signaling, all of which are discussed below.

Is BDNF a Biomarker of Human Depression?

Recognition by Duman and colleagues [14] that antidepressant treatment was associated with increased BDNF expression in the hippocampus led to further investigation of the role that neurotrophins play in depression and in the response to antidepressant treatment, both in human subjects and animal models of depression. Analysis of postmortem human brain tissues has revealed reduced BDNF mRNA and protein levels in hippocampus, prefrontal cortex and amygdala of depressed patients and suicide subjects [15-17]. Moreover, antidepressant treatments were found to increase BDNF protein levels in different areas of hippocampus [18].

Given the limitations of human postmortem studies, BDNF levels in blood samples have been widely studied. Reduced levels of mature BDNF, but not its precursor proBDNF, were reported in sera and plasma from depressed patients [19-22], and this reduction of BDNF was normalized by antidepressant treatment [23-25]. In addition, reduced BDNF content in platelets and decreased BDNF mRNA expression in peripheral blood lymphocytes and mononuclear cells were also reported in depressed patients [26-28]. Reduced BDNF levels in both serum and plasma have also been found in depressed patients who have attempted suicide, compared to non-suicidal depressed patients or healthy controls, and in subjects with depressive episodes of longer duration or recurrent episodes of depression [29, 30]. The association of lower serum BDNF levels with depressive personality traits in healthy human subjects suggests a possible link between BDNF levels and the susceptibility of healthy humans to depression [31]. Circulating BDNF may therefore be a potential biomarker for major depression, and although this could reinforce the relevance of identifying therapeutic targets in the peripheral circulation, recent studies demonstrate a positive correlation between BDNF levels in blood and hippocampus [32]. Further investigation of the mechanistic importance of CNS BDNF in depression and antidepressant efficacy, and the determination of its site of action within the brain, have relied on the animal studies that are discussed below.

Does Depressive Behavior Regulate BDNF Expression in Animal Models of Depression?

Previous studies have shown that many stressors including immobilization, electrical foot shock, restraint, forced swimming, social deprivation and chronic social defeat down-regulate BDNF mRNA and protein levels in different brain regions, in particular hippocampus [33-39]. This reduction in BDNF expression is associated with the development of depressive-like behavior. What are the underlying mechanisms that control BDNF levels in depressed and antidepressant-treated animals? Stress-induced down-regulation of BDNF splice variant mRNAs in hippocampus was found to be associated with increased histone methylation of the respective BDNF promoters [40]. Antidepressant treatment reversed this down-regulation by promoting histone acetylation at these

promoters, indicating that stress and antidepressants exert their effects on BDNF expression at least in part via chromatin modification.

However, a number of reports demonstrate opposing changes or no change in BDNF expression in animal models of depression and antidepressant efficacy [41, 42]. Moreover, many studies have shown that both acute and chronic stress increase BDNF mRNA and protein levels in hippocampus [43-47], evoking speculation that increased BDNF levels after stress might serve as a protective mechanism to offset the destructive effects of stress on the hippocampus. Alternatively, these discrepant findings could have resulted from the use of different stressors to induce behavior, or the different procedures used to quantify BDNF levels [48]. Age might also influence BDNF levels following stress, as social defeat up-regulates hippocampal BDNF mRNA expression in adolescent but not adult rats [49].

In other brain regions, increased BDNF mRNA levels were detected in medial prefrontal cortex and amygdala within 2 hours of the last social defeat episode [50], in agreement with previous studies showing that BDNF mRNA levels were initially induced in these regions but were reduced 24 hours later [37]. Berton et al. [51] reported increased BDNF expression in nucleus accumbens (NAc) following social defeat, correlating this increase of BDNF mRNA and protein in NAc to the development of susceptibility to depression. Taken together, these human and animal studies demonstrate depression-associated and region-specific changes in BDNF protein and mRNA levels. Manipulation of BDNF expression in animal models with regional specificity should therefore provide insight into potential mechanisms that underlie major depressive disorder in humans, and these studies are described below.

What Role does BDNF play in Antidepressant Treatment?

Altered levels of BDNF are correlated with depression, and antidepressant treatments exert their effects by reversing this alteration [52-54]. Many studies have demonstrated that almost all antidepressant treatments or activities, including electroconvulsive therapy, antidepressant drugs, exercise and environmental enrichment up-regulate BDNF mRNA and protein expression in specific brain regions and blood, and reverse depressive-like behavior [14, 55-60]. The necessity of having normal BDNF function to permit antidepressants to act was demonstrated by the observed attenuated actions of antidepressant in the forced swim test (FST) after deletion of BDNF in the forebrain [61]. Consistent with these results, BDNF^{+/-} germline knockout mice showed an impaired response to fluoxetine treatment [62], further supporting the role that BDNF plays in antidepressant actions. Other than their inductive effects on BDNF expression, antidepressant drugs are also able to initiate BDNF signaling by promoting the activation of TrkB receptors and the phosphorylation of cyclic AMP response element binding (CREB) protein in rodent brain [63, 64]. However, and of considerable interest, BDNF is not necessarily involved in antidepressant drug-induced activation of TrkB receptors [65], suggesting that antidepressants can regulate alternative signaling pathways that increase TrkB phosphorylation.

Antidepressant and Pro-Depressant Effects of BDNF: Location, Location, Location

Altered BDNF expression impacts behavior and antidepressant responses, but the region within the brain and the neurons and circuits involved define whether BDNF acts in a prodepressant or antidepressant manner. For example, localized ablation of BDNF in the ventro tegmental area (VTA), the brain region believed to be the source of NAc BDNF protein, mimicked the effects of antidepressant treatment, resulting in attenuated depressive-like behavior [51], while intra-VTA infusion of BDNF produced depressive-like behavior

[66]. On the other hand, bilateral infusion of BDNF into the hippocampal dentate gyrus of rats reversed the depressive-like behaviors shown in the learned helplessness (LH) and FST paradigms with a similar efficacy to antidepressant drugs [67], and intracerebroventricular BDNF infusion induced sustained antidepressant-like effects [68]. Similarly, transgenic overexpression of BDNF in the hippocampus, which also protected dendrites in the CA3 region from atrophy [69], decreased immobility in the FST, and virally-mediated BDNF overexpression in adult rat hippocampus reversed anhedonia and reduced immobility in the FST [70]. Thus the antidepressant or pro-depressant effects of modulating BDNF expression are very much dependent on CNS location. Antidepressant-like effects of peripherally-administered BDNF have also been observed, including dose-dependent reduction in immobility in the FST and latency to drink in novelty-induced hypophagia (NIH) [71]. Peripheral BDNF administration further rescued the anhedonia induced by chronic unpredictable stress, facilitated the survival of immature neurons in the dentate gyrus and prefrontal cortex, and induced BDNF protein and mRNA expression in hippocampus, suggesting a possible function of peripheral BDNF in the pathogenesis of depression, in addition to its role as a potential biomarker.

Behavioral Effects of BDNF Downregulation

Because of the severely impaired coordination and short life span of BDNF germline homozygous knockout mice [72], BDNF^{+/-} heterozygous mice have been studied, and these did not show any depressive-like behaviors in the FST, learned helplessness (LH), tail suspension test (TST) or sucrose preference test (SPT) [63, 73-75]. Interpretation of these early efforts was complicated by subsequent discoveries of additional functional roles for BDNF in pain pathways, including reduced pain sensitivity in BDNF^{+/-} mice [73], which could have impacted the LH paradigm. However, recent studies indicate that BDNF^{+/-} mice have a pro-depressive phenotype: male BDNF^{+/-} mice showed increased immobility in the FST after exposure to mild stress, suggesting higher vulnerability of BDNF deficient mice to stress [76]. Moreover, Magarinos et al. observed retracted dendritic arborization in the CA3 region and reduced hippocampal volume in unstressed BDNF^{+/-} mice, similar to the phenotypes of stressed wild type mice [77]. Behavioral sequelae of global BDNF reduction may therefore reflect the summation of antidepressant-like effects of BDNF in the hippocampus and prefrontal cortex, and pro-depressive effects of BDNF in the VTA [51, 78], consistent with the region- and circuit-specific role of this neurotrophin.

In order to circumvent the embryonic lethality and developmental abnormalities caused by targeted deletion of *Bdnf* in the germline, and to study gene function in specific tissues or regions, BDNF conditional knockout mice have been generated. Forebrain deletion of BDNF resulted in decreased sucrose preference and longer immobility time in FST in female mice compared to wild type littermates, while male conditional knockout mice are indistinguishable from wild types, suggesting a gender difference in vulnerability to depressive-like behavior that was not applicable to antidepressant responses, as both male and female conditional knockout mice failed to attenuate their depressive-like behavior following desipramine treatment [79]. However, BDNF conditional knockout in the dentate gyrus did attenuate antidepressant efficacy [80]. Lastly, mice with conditional knockout of BDNF in the VTA have been reported to show reduced social avoidance in the social interaction test following social defeat [51], reinforcing region-specific effects of BDNF on depressive behavior.

BDNF knockdown by RNA interference in dorsal dentate gyrus resulted in depressive-like behaviors in the SPT, FST, and home-cage locomotion as well as impaired neuronal differentiation [81]. Interestingly, the same group reported that BDNF knockdown in VTA leads to decreased immobility time in the FST and increased sucrose preference [78],

consistent with previous reports demonstrating that conditional deletion of BDNF in VTA induced antidepressant-like effects [51].

Defects in Regulated BDNF Secretion and Depression: the BDNF Val66Met Polymorphism

The Val66Met BDNF polymorphism is the most widely studied variation in the *BDNF* gene and has been correlated with BDNF function, hippocampal activity, and depression. This single nucleotide polymorphism (SNP) at nucleotide 196, leading to substitution of methionine (Met) for valine (Val) at codon 66, interferes with BDNF protein sorting and secretion, and BDNF mRNA trafficking to dendrites [82-84]. Abnormal memory and hippocampal function have been observed in human subjects carrying the Met-allele [82, 85]. Many studies also suggest a pro-depressive role of the BDNF Met-allele, which has been correlated with smaller volumes of the hippocampus [86], parahippocampus, amygdala, and frontal gyrus [87], but higher BDNF levels in serum [88]. However, reduced hippocampal volume was not only observed in depressed patients, but also in healthy subjects [89], and no effect on hippocampal volume and BDNF levels in both plasma and serum by the Val66Met SNP have also been reported [90-92], suggesting a complex phenotype.

In addition, depressed patients carrying the Met-allele (BDNF^{Val/Met} and BDNF^{Met/Met}) are more likely to suffer from suicidal ideation and to attempt suicide [93]. Met-allele carriers exposed to greater early life stress had smaller hippocampal volume and higher syndromal depression, while the experience of early life stress in BDNF^{Val/Val} homozygotes had no effect on depression [94]. BDNF^{Val/Met} and BDNF^{Met/Met} subjects also respond better to antidepressant treatment compared to BDNF^{Val/Val} homozygotes [95, 96].

Study of the BDNF Val66Met polymorphism in rodent models has facilitated mechanistic understanding of this sorting and secretory defect. BDNF^{Met/Met} mice were more resilient to chronic social defeat stress than BDNF^{Val/Val} [97], which may be attributed to reduced BDNF levels in NAc. BDNF^{Met/Met} rodents fail to respond to ketamine administration, having impaired synaptogenesis and longer immobility time in the FST [98]. Compared to BDNF^{Val/Val} mice, BDNF^{Met/Met} mice also had lower basal BDNF protein levels as well as impaired NMDA-receptor dependent LTP and LTD, and decreased survival of newly generated neurons in hippocampus, which could not be reversed by fluoxetine administration [99, 100]. Recent studies further demonstrate that BDNF^{Val/Met} mice have increased depressive- and anxiety-like behaviors and impaired working memory following restraint stress, and show antidepressant responses to acute administration of desipramine but not fluoxetine, perhaps suggesting more effective treatment options for depressed patients with this genetic variant [101]. Thus a relatively subtle deficit in BDNF sorting and secretion can lead to profound behavioral modification and altered responses to antidepressants, alcohol and drugs of abuse [102, 103], perhaps reflecting in part altered neural plasticity in response to both adverse and rewarding life events [104].

Modulation of Depressive Behavior and Antidepressant Efficacy by BDNF/TrkB Signaling

Mice with reduced BDNF/TrkB activation are resistant to antidepressant treatment [63]. Moreover, conditional forebrain TrkB knockout mice manifest decreased spine densities and increased spine length on apical and basal dendrites in the CA1 region [105], as well as decreased neurogenesis in hippocampus and impaired behavioral improvements induced by chronic antidepressant administration or by exercise [106]. Conversely, transgenic mice with over-expressed catalytic TrkB receptors in brain showed decreased immobility in the FST

[107]. These findings are consistent with the important role of BDNF/TrkB signaling in depression and antidepressant efficacy.

Binding of BDNF to TrkB activates different intracellular signaling cascades, including the Ras/ERK (MAPK), PLC γ and PI3K/Akt pathways [12] (see Figure 1), each of which have been linked to depression. Reduced levels of different effectors of the Ras/ERK (MAPK) pathway were reported in postmortem hippocampus and frontal cortex of depressed and suicide subjects [108, 109]. Consistent with postmortem studies, animal studies showed that inhibition of ERK signaling in hippocampus and prefrontal cortex was sufficient to induce depressive-like behaviors [110], and activation of ERK signaling in hippocampus was necessary for the antidepressant-like effects of intrahippocampal BDNF infusion [67]. Moreover, chronic mild stress-induced reduction of ERK signaling in hippocampus and prefrontal cortex could be rescued by fluoxetine administration [111, 112]. Consistent with the importance of ERK signaling in depression and antidepressant efficacy, hippocampal overexpression of MAPK Phosphatase-1 (MKP-1), a negative regulator of the MAPK pathway, induced depressive behavior, while local deletion of MKP-1 in hippocampus led to a resilient response to stress [113]. And as noted previously, the effects of BDNF signaling pathways on depression and antidepressant efficacy are location-dependent: chronic unpredictable stress promoted ERK signaling in VTA [114], while viral-mediated overexpression of ERK2 in VTA increased susceptibility to stress and ERK2 blockade in VTA produced resilience [114].

Studies of PI3K/Akt signaling in the brain provide further evidence for its modulation of depressive behavior, but a simple, region-specific pattern of signaling pathway contributions to depression does not emerge. Reduced Akt signaling has been found in hippocampus and prefrontal cortex of depressed and suicide subjects [115, 116], and in animals, chronic social defeat stress and chronic unpredictable stress reduced Akt phosphorylation in the VTA [117, 118], while viral-mediated blockade of Akt signaling in VTA increased susceptibility to social defeat-induced depressive behavior [118]. Recently, decreased Akt phosphorylation was also observed in basolateral amygdala following FST [119], suggesting that a generalized decrease in Akt signaling is associated with depression, distinct from region-specific ERK2 signaling described above. Lastly, blockade of the PI3K/Akt pathway was sufficient to offset increased hippocampal neurogenesis following exercise [120], and to prevent the antidepressant-like effects of folic acid [121] and ketamine [122]. Since BDNF acts through the PI3K/Akt pathway (see Figure 1), this finding suggests the involvement of BDNF in the antidepressant actions of ketamine. Interestingly, ketamine treatment failed to induce synaptogenesis in prefrontal cortex of BDNF^{Met/Met} mice, and its antidepressant actions were also impaired in these mice [123]. Similarly, ketamine administration did not produce antidepressant-like effects in BDNF conditional knockout mice, but in wild type mice, ketamine induced BDNF translation by deactivating eukaryotic elongation factor 2 (eEF-2) kinase, which in turn resulted in fast-acting antidepressant-like effects [124].

One of the downstream targets of PI3K/Akt pathway, GSK-3, has drawn much attention due to its involvement in depression. Akt can phosphorylate both GSK-3 α and GSK-3 β isoforms in their N-terminal domains, thus inhibiting their activities. In clinical studies, increased GSK-3 β activity and decreased phosphorylated GSK-3 β protein levels were observed in ventral prefrontal cortex of depressed subjects [115, 125], and a GSK-3 β polymorphism has been correlated with altered hippocampal structure in depressed patients [126]. In rodent studies, intraperitoneal and intracerebroventricular administration of GSK-3 inhibitors induces antidepressant-like behaviors [127, 128]. Similar antidepressant-like effects were also observed in both GSK-3 α and GSK-3 β deficient mice [129, 130]. Moreover, GSK-3 knock-in mice that lack inhibitory phosphorylation of GSK-3 (GSK-3 α/β ^{21A/21A/9A/9A}) were found to be more vulnerable to stress-induced depressive-like behaviors [131]. Does

GSK also play a role in antidepressant efficacy? Recent studies demonstrate that ketamine administration enhances phosphorylation of both GSK-3 α and GSK-3 β in hippocampus and prefrontal cortex, and this inhibition of GSK-3 is required for the antidepressant effects induced by ketamine [132]. The effects of GSK-3 on depressive- and antidepressant-like behaviors are mediated by phosphorylation of β -catenin, resulting in its degradation. Consistent with the GSK-3 studies described above, reduced β -catenin protein levels were reported in ventral prefrontal cortex of depressed patients [125], mice with a conditional knockout of β -catenin in the forebrain displayed depressive-like behavior in the TST [133], and mice with β -catenin overexpression in brain showed antidepressant-like effects in the FST [134].

How do Neurotrophins and their Signaling Pathways Modulate Depressive Behavior?

Regulation of Neuronal Plasticity

Disruption of neuronal plasticity has been linked to impaired learning and memory, as well as mood disorders such as major depression and bipolar disorder [135]. Clinical evidence has supported reduced hippocampal volumes in depressed patients [136-141], while animal studies provide related data demonstrating that stress induces retraction of pyramidal cell dendrites in hippocampus [77, 142], and the loss of pyramidal neuron dendritic spines in medial prefrontal cortex [143, 144]. Working in an opposing manner, antidepressant treatments, including ECT and drugs, increase plasticity by inducing hippocampal dendritic sprouting [145], increasing dendritic spine density [146], and promoting synaptogenesis [147].

Many studies have explored the role of BDNF in the regulation of neuronal plasticity. Study of BDNF^{+/-} heterozygous knockout mice revealed dendritic retraction in the hippocampus and reduced hippocampal volume [62, 77]. Similarly, BDNF^{Val/Met} mice were found to have impaired spine formation and synaptic function, and decreased spine density and dendritic length [62, 98, 101], in different brain regions, including hippocampus, prefrontal cortex and amygdala. These changes in neuronal plasticity of Met-allele carriers have been attributed to a deficiency in BDNF mRNA dendritic trafficking [84], which in turn resulted in impaired local protein translation that is required for normal synaptogenesis and spine maintenance [148]. Moreover, BDNF overexpression was shown to be sufficient to enhance dendritic complexity of dentate granule cells [149] and dendritic density in basolateral amygdala, and to prevent dendritic atrophy in CA3 induced by chronic stress [69].

The important roles that the Ras/ERK (MAPK) and PI3K/Akt pathways play downstream of BDNF/TrkB to modulate depressive behavior and antidepressant responses are likely realized in part by modulation of synaptogenesis and synaptogenesis. Overexpression of PI3K or Akt is sufficient to increase dendritic complexity and soma size as well as to induce production of filopodia-like protrusions, whereas mTOR inhibition has the opposite effects [150]. In addition, Ras/ERK (MAPK) and PI3K/Akt pathways are believed to be upstream of Rho family GTPases, including RhoA, Rac and Cdc42, which are involved in the regulation of actin polymerization, thus mediating dendritic spine plasticity [151-153]. Ras/ERK (MAPK) and PI3K/Akt pathways were also demonstrated to be necessary for ketamine-induced activation of mTOR signaling, which is functionally correlated with synapse formation [122]. Lastly, Ras/ERK (MAPK) pathway-dependent phosphorylation of synapsin regulates synaptogenesis [154]. Many of the pro-depressant and antidepressant effects of BDNF are therefore mediated by signaling pathways downstream of the TrkB receptor that impact the plasticity of neural circuits in a regionally-specific manner.

Regulation of Neurogenesis

Malberg and Duman first reported that fluoxetine could reverse the stress-induced reduction in hippocampal neurogenesis [155], establishing a correlation between neurogenesis and depression. Impaired neurogenesis in hippocampus, caused by irradiation, prevented the antidepressant effects of fluoxetine and imipramine, which were observed in non-irradiated controls [156]. These findings were supported by several subsequent studies [157, 158], although neurogenesis-independent effects of antidepressant treatment were also suggested [159]. *In vivo* studies have revealed that BDNF is required for antidepressant-induced hippocampal neurogenesis. Heterozygous BDNF^{+/-} knockout mice showed reduced proliferation and survival of hippocampal neuronal progenitor cells [160], and reduced hippocampal neurogenesis induced by dietary restriction or environmental enrichment [160, 161]. Also studying BDNF^{+/-} knockout mice, Sairanen et al. did not find a major role for BDNF in promoting hippocampal progenitor cell proliferation induced by antidepressant treatment, although BDNF was required for long-term survival of newborn neurons [162]. On the other hand, viral-mediated BDNF overexpression was sufficient to enhance hippocampal neurogenesis [163], and intraventricular and intrahippocampal BDNF infusions increased neurogenesis in rat olfactory bulb [164] and hippocampus [165], respectively, while intravenous BDNF administration in a rat stroke model increased neurogenesis in the dentate gyrus and improved recovery [166].

In addition to BDNF, NT-3 deletion in dentate gyrus reduced the number of differentiated hippocampal progenitor cells [167], while intracerebroventricular NGF infusion promoted survival of newborn neurons in adult dentate gyrus [168]. Downstream of Trk receptors, PI3K/Akt and Ras/ERK (MAPK) signaling pathways have been suggested to converge on nuclear transcription factor CREB [169], which is responsible for regulating expression of genes involved in neurogenesis, such as CCNA (cyclin A) and CCND2 (cyclin D2) [170]. In addition, and relevant to the role of Akt signaling in depression, impaired neurogenesis was also observed in GSK-3 α/β 21A/21A/9A/9A knock-in mice [171] and in GSK-3 β overexpressing mice [172].

Secretory and Cytoskeletal Targets of BDNF: Potential Roles in Depression and Antidepressant Responses

BDNF modulates depressive behavior and the response to antidepressant treatment. Many of these effects are likely mediated by gene products that are transcriptionally regulated by this growth factor. VGF (non-acronymic) is a secreted protein and neuropeptide precursor that is robustly regulated by BDNF and NT-3 in CNS neurons [173]. Hippocampal VGF expression is decreased by depressive behavior and in pro-depressive SERT knockout rats, is increased by exercise and antidepressant treatment, and intrahippocampal or intracerebroventricular infusion of C-terminal VGF-derived peptides AQEE30 or TLQP62 attenuates depressive-like behavior [174-176]. Consistent with these antidepressant effects, TLQP62 regulates hippocampal neuronal progenitor proliferation and synaptic plasticity, and heterozygous VGF knockout mice have increased immobility in the TST and FST [174, 175, 177]. The mechanism of action of VGF in regulating depressive behavior and antidepressant responses could depend on autocrine or paracrine effects of VGF peptides on regulated BDNF secretion [177], or the role that this chromogranin/secretogranin-like protein plays in dense core secretory vesicle biogenesis, both potentially impacting regulated BDNF secretion, much as does the Val66Met BDNF polymorphism.

Arc (activity-regulated cytoskeleton-associated protein), is an immediate early gene that is regulated by BDNF and synaptic activity, and is localized to neuronal dendrites [178, 179]. Chronic, but not acute, antidepressant administration [180-182] and electroconvulsive

stimulation (ECS) [183] induce Arc mRNA expression in hippocampus and parietal cortex. Arc mRNA expression in the hippocampus and frontal cortex was transiently down-regulated by chronic mild stress [184], and significantly reduced Arc mRNA expression was also observed in the medial prefrontal cortex of mice that were susceptible to chronic social defeat [185], and also in three rodent models that manifest depressive-like behavior [184, 186, 187]. Although other studies demonstrate increased Arc mRNA levels following acute stress and social defeat stress [49, 181, 188, 189], findings generally support a correlation between increased Arc expression and antidepressant effects, and decreased Arc levels and depressive behavior, suggesting that its role in depression is a result of its function in regulating synaptic plasticity. Consistent with the importance of dysregulated synaptic plasticity in depression, knockdown of neuritin (CPG15), an activity- and BDNF-regulated gene product that is involved in synaptic plasticity, maturation, and stabilization [190] in the hippocampus, was sufficient to block the antidepressant-like effects in the FST caused by BDNF infusion into dentate gyrus [191], indicating that the antidepressant-like effects of BDNF may also depend on other regulators of synaptic plasticity including neuritin.

Conclusions

Neurotrophins in general and BDNF in particular modulate depressive behavior and the response to antidepressant treatment, in part through the regulation of synaptic plasticity, synaptogenesis, spinogenesis, and neurogenesis. BDNF levels are affected by depression, stress and antidepressant treatment, in both CNS and blood. Region-specific modulation of BDNF levels in brain can lead to depressive behavior or antidepressant-like responses—location and synaptic circuit are critical. Neurotrophin actions are transduced primarily via PI3K/Akt and Ras/ERK (MAPK) signaling pathways, and importantly the genes they transcriptionally regulate. A better understanding of the proteins that control synaptic plasticity and the regulated secretion of neurotrophins, and their role in the pathogenesis of depression and the control of antidepressant efficacy, in different areas of the brain including hippocampus and NAc/VTa, should improve the design of more effective treatments for this prevalent, extremely debilitating disease.

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Figure 1.

Hippocampal BDNF/TrkB signaling pathways that modulate depressive behavior and antidepressant responses. Binding of BDNF to TrkB activates different intracellular signaling cascades, including the PI3K/Akt, Ras/ERK (MAPK) and PLC γ pathways [12]. Phosphorylation of Y490 of TrkB leads to recruitment of adaptor proteins such as Shc, Grb2 and Gab1 and subsequent activation of the PI3K/Akt pathway [192] and Rho family of GTPases (RhoA, Rac, Cdc42), which positively regulate actin polymerization through downstream signaling including ROCK/PAK, LimK and Cofilin [151-153]. Another downstream effector of the PI3K/Akt pathway is GSK-3, whose activity is negatively regulated by Akt-mediated phosphorylation [193]. One of the downstream targets of GSK-3 is β -catenin, which can be translocated into the nucleus to promote gene expression. The mTOR pathway, which facilitates local translation and the rapid antidepressant effects of ketamine, is also regulated by PI3K/Akt signaling [122]. Activation of PI3K/Akt signaling is believed to positively modulate spinogenesis, synaptogenesis and neurogenesis, thus inducing antidepressant effects. In addition to inductive effects on gene expression, the Ras/ERK (MAPK) pathway also acts through Rho family of GTPases, mTOR signaling, and synapsin to induce spinogenesis, synaptogenesis and neurogenesis (not shown) [122, 153, 154]. Phosphorylation of Y816 of TrkB recruits PLC γ [194], inducing the hydrolysis of PIP2 to IP3 and DAG. IP3 regulates calcium release and CAMK activation, while DAG activates PKC. Both IP3/CAMK and DAG/PKC signaling regulate synaptic plasticity [195], however their roles in depression remain largely unknown.