Brain-Derived Neurotrophic Factor Signaling in Depression and Antidepressant Action

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ABSTRACT
Neurotrophic factors, particularly BDNF (brain-derived neurotrophic factor), have been associated with depression and antidepressant drug action. A variety of preclinical and clinical studies have implicated impaired BDNF signaling through its receptor TrkB (neurotrophic receptor tyrosine kinase 2) in the pathophysiology of mood disorders, but many of the initial findings have not been fully supported by more recent meta-analyses, and more both basic and clinical research is needed. In contrast, increased expression and signaling of BDNF has been repeatedly implicated in the mechanisms of both typical and rapid-acting antidepressant drugs, and recent findings have started to elucidate the mechanisms through which antidepressants regulate BDNF signaling. BDNF is a critical regulator of various types of neuronal plasticities in the brain, and plasticity has increasingly been connected with antidepressant action. Although some equivocal data exist, the hypothesis of a connection between neurotrophic factors and neuronal plasticity with mood disorders and antidepressant action has recently been further strengthened by converging evidence from a variety of more recent data reviewed here.

Several lines of evidence link BDNF (brain-derived neurotrophic factor) and its receptor TrkB (neurotrophic receptor tyrosine kinase 2) with mood disorders and antidepressant effects [reviewed in (1–4)]. Duman’s group (5,6) was the first to discover a connection between BDNF, depression, and antidepressant action. They first showed that BDNF levels are increased by electroconvulsive treatment in rats and that antidepressants also increase BDNF expression in the hippocampus and cortex (5), a finding that has subsequently been confirmed by several groups (1). The work of the Duman laboratory has been a major contributor to the field ever since (1,7). We review here the role of BDNF signaling in mood disorders and the antidepressant effects. While there is a large amount of convergent evidence suggesting reduced BDNF signaling in mood disorders, not all evidence supports this conclusion, and a reduction in BDNF signaling is not specific to mood disorders. On the other hand, the evidence for the critical role for BDNF signaling in the antidepressant responses is convincing and has recently been further strengthened.

BDNF is a critical mediator of activity-dependent neuronal plasticity in the brain (6,9). It has a major impact on neuronal morphology and physiology, increasing neurite sprouting and synapse stabilization and promoting long-term potentiation (3). Synthesis and release of BDNF are regulated by neuronal activity, which is consistent with the role of BDNF as a major mediator of activity-dependent neuronal plasticity. Recent data suggest that BDNF may also be linked to spontaneous, activity-independent transmission. The blockade of postsynaptic NMDA receptors involved in spontaneous transmission can rapidly increase BDNF protein translation, which can produce an increase in synaptic potentiation that resembles homeostatic scaling. This connection between spontaneous transmission and BDNF that triggers a novel form of plasticity has been linked to the rapid antidepressant action of ketamine (10–13).

BDNF-TrkB SIGNALING IN MOOD DISORDERS
BDNF signaling has been implicated in the pathophysiology of mood disorders in humans. Levels of BDNF messenger RNA (mRNA) and protein have been found to be reduced in postmortem samples taken from brains of depressed patients (14), in particular in the hippocampus (15–17) and amygdala (18). BDNF levels have also consistently been found to be reduced in brain samples of people who died as a result of suicide (19–24). Conversely, antidepressant treatment increases BDNF expression in brains of depressed patients (21). However, the numbers of examined cases are generally low, and reduction in BDNF is not specific to mood disorders, as similar reductions have been observed in other neuropsychiatric disorders, such as schizophrenia and dementia (25,26).

DNA methylation of BDNF gene promoters has been shown to be increased in peripheral blood mononuclear cells of depressed patients (27–29), which is consistent with a reduction in BDNF expression. A similar increase in BDNF promoter methylation has also been observed in brain samples from people who died by suicide (30), suggesting dysregulation of BDNF expression. This suggests that the findings in blood cells may perhaps be extrapolated to neuronal tissue, although this requires further investigation.

In addition to BDNF, levels of TrkB and TrkB mRNA have also been found to be decreased in postmortem samples of...
depressed patients (19,31), and genetic variants in the TrkB gene NTRK2 are associated with suicide attempts (32). Furthermore, the activated, phosphorylated forms of TrkB have been found to be decreased in brain samples from depressed patients (20).

**Genetic Association Between BDNF and Depression**

Valine is the predominant amino acid at position 66 of BDNF, but 25% to 50% of individuals in different populations have methionine at this position (Val66Met) (33,34). Mechanistically, this polymorphism influences intracellular BDNF trafficking and activity-dependent BDNF release (33,35), and the Met allele has been shown to impair dendritic transportation of BDNF mRNA (36). As the activity-dependent synaptic release of BDNF is critical for its action on certain types of neuronal plasticity, Met66BDNF might impede plasticity. Early studies suggested that the Met allele might be a risk factor for a number of neuropsychiatric disorders (37). However, subsequent larger studies failed to replicate these effects, and the latest meta-analyses do not support the role of BDNF Val66Met polymorphism in mood disorders (38,39) [reviewed in (4)], with perhaps an exception of increased risk of depression in male Met-carriers (40). In addition to Val66Met, several other single nucleotide polymorphisms have been detected in the human BDNF gene, and initial studies associated some of them with depression (4,41–43). However, also here, meta-analyses have not supported the initial findings (4,38).

There is evidence that Val66Met polymorphism might modulate the effects of early life adversity (44–47) or chronic stress on depression in adulthood (48). Indeed, a recent meta-analysis that examined the interaction between the Val66Met polymorphism and stressful life events or childhood adversity in more than 20,000 participants in 31 independent studies concluded that Met carriers have significantly higher risk of developing depression when exposed to stress either during childhood or in adulthood (49).

Activity-dependent BDNF release is suggested to be important for the antidepressant response. Consistently, behavioral as well as plasticity-related responses to antidepressants were lost in a mouse model of Val66Met polymorphism (55,50). Furthermore, increased spine formation in responses to ketamine and its metabolite (2R,6R)-hydroxy-ynorketamine were lost in these mice (51,52). However, similar loss has not been observed in human studies, and the Met allele, if anything, improves the response to antidepressants (53–56), and patients heterozygous for Val66Met appear to show a better response to antidepressants than patients homozygous for either the Val or the Met allele (57).

**Serum BDNF and Mood Disorders**

Levels of BDNF are high in human serum; however, levels in plasma and cerebrospinal fluid are orders of magnitude lower (58–61). More than 90% of BDNF found in blood is contained in platelets (58,59,62–64). Although it has been suggested that circulating BDNF could be derived from brain (65), it is by now clear that serum BDNF is derived from blood platelets that release it on platelet activation (58,59,62). Within platelets, BDNF is contained within the alpha granules and in the cytoplasm (60,66), and on stimulation, less than half of BDNF within platelets is released, probably representing the alpha-granule pool. Platelet BDNF is derived from megakaryocytes that transport BDNF into newly formed platelets (67,68). Whether platelets also take up BDNF from plasma is unclear; platelets do not express BDNF receptors, but uptake of labeled BDNF into platelets has been reported (64). Interestingly, mouse megakaryocytes do not synthesize BDNF, and, consequently, BDNF levels in mouse serum and plasma are very low, below detection limit (68), which speaks against uptake from plasma as a significant source of platelet BDNF.

Several studies have observed that serum or plasma BDNF levels are abnormally low in depressed patients (69) and that the levels increase back to baseline after successful treatment with antidepressants (70–79) or electroconvulsive treatment (80,81), but not after repetitive transcranial magnetic stimulation or vagus nerve stimulation (82). Although a recent meta-analysis found reduced effect sizes in more recent studies, reduction in serum BDNF remained highly significant in untreated depressed patients compared with successfully treated patients or healthy individuals (83). Unfortunately, high interindividual and intrapersonal variation in serum BDNF levels (84) prevents its use as a diagnostic marker for depression. However, as serum levels of proBDNF are not reduced in depressed patients while those of mature BDNF are (85), a ratio between mature BDNF and proBDNF has been suggested as a biomarker for bipolar disorder (86) and for discriminating between bipolar and major depressive disorder with reasonable sensitivity (87). Notably, a decrease in serum BDNF levels is not specific to depression: serum BDNF levels have been reported to be decreased also in schizophrenia (88–90) and in autism (91,92).

While serum BDNF levels were low in patients with depression and schizophrenia, whole-blood BDNF levels were not different between patients and control subjects (72,88). Therefore, the difference between patients and control subjects is not in the amount of BDNF in platelets, but in the ability of platelets to release it. Authors have proposed that instead of serum BDNF levels, a ratio between BDNF in serum and whole blood, which represents BDNF release from platelets, should be reported (72). Interestingly, serotonin is concentrated into platelets through the serotonin transporter, the target of serotonin-selective antidepressants (selective serotonin reuptake inhibitors), and, as is the case for BDNF, serotonin release is reduced in depressed patients (60,93), suggesting a link between BDNF and serotonin release. Molecular pathways that regulate vesicular release in the brain and in platelets share many components (84). It is therefore possible that reduced release from platelets could reflect compromised BDNF release also in the brain.

Susceptibility to depression can be influenced by genetic, epigenetic, and environmental risk factors. Stressful life events may contribute to an individual’s developing depression, while some individuals display resilience. In preclinical models, stress paradigms are often used to model depression-related behavior. However, the type and duration of stress can produce a range of effects on the hypothalamic-pituitary-adrenal axis, metabolism, and epigenetic and genetic effects as well as behavior. Stress has been shown to decrease BDNF expression in many brain regions, but increased expression
has also been observed in certain brain regions depending on the type and duration of stress. Given the complexity of the relationship between stress and neurotrophins, the reader is referred to articles in this special issue focusing on stress and its role in the transcriptome by Girgenti et al. (95) and the neurobiology of stress by Ploski and Vaidya (96).

Taken together, while several studies indicate abnormal expression and function of BDNF in depressed patients and a return to normal on recovery, many other studies, including genetic association studies, have failed to show a consistent relationship between BDNF and mood disorders. Therefore, a causal role for BDNF in depression remains equivocal.

**BDNF EXPRESSION AND TrkB SIGNALING ARE REQUIRED FOR ANTIDEPRESSANT DRUG ACTION**

Given the evidence that BDNF signaling may be reduced in depression, the finding that antidepressant drugs increase BDNF levels has generated interest. Duman’s laboratory was the first to find that electroconvulsive treatment as well as tricyclic and selective serotonin reuptake inhibitor antidepressants increase BDNF expression in rodent brain (5,6), which has been confirmed in numerous studies [reviewed in (1,3,97)]. Antidepressant-induced increase in BDNF levels has also been observed in human postmortem brain samples (21) as well as in serum of depressed patients (see above).

BDNF levels are increased quickly after electroconvulsive treatment, but only after several days of continuous antidepressant treatment (1,5). However, antidepressants activated TrkB autophosphorylation and downstream signaling within an hour after treatment in mice (98,99), indicating that antidepressants may initially promote BDNF release and TrkB signaling and that the increase in BDNF expression takes place only later, but it has been unclear how antidepressants activate TrkB. A recent study demonstrated that antidepressants belonging to different classes, such as fluoxetine, imipramine, and ketamine, directly bind to TrkB (100). Dimerized TrkB transmembrane domains cross each other in the transmembrane domain and create a pocket for antidepressants. Antidepressant binding stabilizes TrkB in synaptic membranes and promotes BDNF-mediated TrkB signaling (Figure 1) (100).

The affinity of antidepressants to TrkB is much lower than their affinity to the serotonin transporter, but antidepressants accumulate in brain, and concentrations needed for TrkB binding are achieved in human brain after several weeks of treatment (101), which might contribute to the slow action onset of typical antidepressants. These findings suggest a provocative hypothesis that the primary site of action of antidepressants is direct binding to TrkB instead of monoamine transporters and other classical targets.

BDNF signaling through TrkB is required for the behavioral effects of antidepressants (98,102), and several studies have investigated the brain regions and cell types where BDNF-TrkB signaling mediates antidepressant effects. Adachi et al. (103) found that deletion of BDNF from the dentate gyrus cells of mice inhibits the effects of antidepressants in behavioral paradigms. Similarly, deletion of TrkB from the progenitor cells of dentate granule neurons, but not from the mature granule neurons, prevents the effects of antidepressants on the forced swim test as well as on induced neurogenesis (104), suggesting that TrkB in the progenitor cells is the target of BDNF released from the dentate granule neurons. Cortical interneurons have been implicated as the target for both typical (105) and fast-acting (106–108) antidepressants, especially parvalbumin-containing interneurons and perineuronal nets that encase them (109–115), but somatostatin-containing neurons have also been implicated in the antidepressant action (106,116). Finally, BDNF infused into the midbrain produced an antidepressant effect in rats (117), suggesting that this effect may be mediated through monoaminergic neurons. In a recent study using an adeno-associated virus approach to inject Cre recombinase into the dorsal raphe, either BDNF or TrkB was deleted in adult mice. The deletion of BDNF did not impact antidepressant responses in behavioral paradigms, but the loss of TrkB resulted in an attenuated response to antidepressants (118), revealing a critical role for TrkB in the dorsal

**Figure 1.** Direct binding of antidepressants to TrkB (neurotrophic receptor tyrosine kinase 2). (A) Two TrkB receptors cross each other within the transmembrane region, creating a binding site for fluoxetine (inset, blue) at the outer opening of the crossed dimer of TrkB. Image courtesy of M. Grych and G. Erkovi. (B) The configuration of TrkB dimers is dependent on membrane thickness, which is regulated by cholesterol concentration. (Left panel) In moderate cholesterol concentrations, the configuration is favorable for signaling. (Right panel) At high cholesterol concentrations, such as in synaptic membranes, the crossed dimers assume a more parallel orientation, which is not compatible with signaling, and the residence time of TrkB in these membranes is short. Binding of fluoxetine (Flx) acts as a wedge that maintains the crossed transmembrane domain orientation that is compatible with signaling, which increases a probability of BDNF binding and signaling. (C) Allosteric activation of BDNF signaling by antidepressants. (Left panel) Antidepressants (ADs) promote TrkB translocation to and retention at the plasma membrane. (Right panel) BDNF (B) released from presynaptic and postsynaptic sites of active synapses efficiently signal through TrkB at the cell surface, but TrkB receptors in inactive synapses remain silent because no BDNF is released.
raphe in conventional antidepressant action and suggesting a noncell autonomous role for BDNF in the dorsal raphe in conventional antidepressant action. However, direct deletion of TrkB in serotonergic neurons did not prevent the antidepressant-like effects of fluoxetine (119), suggesting that the target for BDNF may be nonserotonergic neurons in the raphe nuclei. Taken together, these data suggest that BDNF-TrkB signaling through several different neuronal systems can mediate different effects of antidepressant drugs.

Typical Antidepressants Increase Other Growth Factors

While numerous studies have linked BDNF to antidepressant action, VEGF (vascular endothelial growth factor) and its tyrosine kinase receptor, Fk1 (fetal liver kinase 1), have also been suggested to play a critical role, although with more limited findings. VEGF is a growth factor that is important in hippocampal neurogenesis (120), although it is unclear if this is how it contributes to antidepressant action. Similar to BDNF, VEGF expression is increased by electroconvulsive and conventional antidepressant treatment (121). Conversely, pharmacological approaches that block VEGF-Fk1 signaling block the behavioral effects of conventional antidepressants, suggesting a crucial role in antidepressant-like action (121–123). Curiously, the antidepressant-like effects of BDNF and VEGF appear mutually dependent on each other (124). While additional studies are necessary to delineate the mechanistic role of VEGF in antidepressant drug action, nevertheless these data further strengthen the importance of neurotrophic factors in antidepressant action.

Rapid Antidepressants Require BDNF

The rather unexpected finding that ketamine, an NMDA receptor antagonist, produces rapid antidepressant action provides an opportunity to delineate intracellular signaling involved in the behavioral effects. Three main hypotheses have been put forth to explain the mechanism of action of ketamine. The first is often referred to as the disinhibition hypothesis. In this model, ketamine is postulated to block NMDA receptors on inhibitory neurons, which increases extracellular glutamate levels and activates AMPA receptors. This in turn causes the release of BDNF, which triggers downstream effects, such as activation of mTOR (mechanistic target of rapamycin), and ultimately synaptogenesis (106,125–128). In support of this hypothesis, it was shown that blocking mTOR with an infusion of rapamycin, an mTOR inhibitor, in the cortex blocked ketamine’s antidepressant-like effects and synaptogenesis (129). These studies suggested that mTOR was required for rapid antidepressant action and that compounds that promote mTOR activation may have therapeutic potential as rapid antidepressants. However, a separate group demonstrated that administration of rapamycin via intraperitoneal injection, to better mimic potential clinical approaches, did not prevent ketamine’s rapid antidepressant action (10). More recently, a small clinical study administered rapamycin intravenously to patients and found that it did not block ketamine’s rapid antidepressant action but rather may augment the long-term effects (130). These clinical data call into question the necessity of mTOR in the rapid antidepressant action of ketamine.

The second hypothesis focuses on how ketamine works through intracellular signaling to produce the antidepressant effects and identifies a novel form of synaptic plasticity strongly correlated with the behavioral action. Ketamine, via blockade of NMDA receptors, blocks calcium entry through these receptors, which results in the inhibition of the calcium/calmodulin-dependent kinase eEF2K (eukaryotic elongation factor 2 kinase), dephosphorylation of its sole target, eEF2 (eukaryotic elongation factor 2), and a resulting rapid increase in protein synthesis of BDNF as well as other synaptic proteins (10). This study showed that loss of BDNF or TrkB in broad forebrain regions blocked ketamine’s antidepressant action, demonstrating a requirement for BDNF-TrkB signaling in the rapid antidepressant-like effects in animal models. Anisomycin, a protein synthesis inhibitor, was also shown to block ketamine’s rapid antidepressant action, thus demonstrating a key role for protein translation that was due to eEF2K in the fast-acting behavioral effects. Ketamine, in an eEF2K-dependent manner, was also shown to trigger the insertion of AMPA receptors that resulted in an expected effect on synaptic plasticity, namely, synaptic potentiation at hippocampal Schaffer collateral inputs to CA1 synapses (10,11). The notion that an NMDA receptor antagonist produces an augmentation of synaptic responses at CA3-CA1 synapses is at first perplexing, as data over the past 2 decades have shown that brief applications of NMDA receptor antagonists on hippocampal slices results in no detectable synaptic effects. However, when ketamine is perfused for 30 minutes on a hippocampal slice, similar to the time of the ketamine infusion, and then washed out, a robust augmentation of field excitatory postsynaptic potentials is observed at CA3-CA1 synapses. This augmentation is observed by blocking NMDA receptors, suggesting that it is due to a form of homeostatic, non-Hebbian type of plasticity (13). This form of homeostatic synaptic plasticity is closely associated with ketamine’s antidepressant effects in that deletion of eEF2K inhibits ketamine’s antidepressant-like action and the augmented synaptic potentiation. Deletion of BDNF also blocks ketamine’s antidepressant-like effects as well as the synaptic potentiation. This body of work has built a crucial link between synaptic transmission and antidepressant action. The identification of the engagement of homeostatic plasticity by ketamine provides an avenue to an understanding of how ketamine may compensate circuit dysfunction or activate dormant mechanisms of patients with depression that are not evoked under normal physiological circumstances.

A third hypothesis for how ketamine exerts antidepressant effects suggests direct binding to the TrkB receptor. As described above, typical antidepressants were found to directly bind to a site formed by two transmembrane domains of TrkB within the plasma membrane, which promotes the synaptic localization TrkB, thereby increasing the probability of BDNF binding to TrkB and activating it (Figure 1) (100). Unexpectedly, ketamine and esketamine displace fluoxetine from this binding site with an affinity that is in the same range as the affinity of ketamine to NMDA receptors, suggesting that they, too, bind to this same site on TrkB. This study also reported that the Y433F mutation of the TrkB receptor blocks the binding and antidepressant-like effects of typical antidepressants as well as those of ketamine (100). This TrkB receptor
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CONCLUSIONS

Twenty-five years have passed since Duman’s group (1,5,6) proposed the connection between neurotrophic factors, mood disorders, and the antidepressant effect. Since then, converging data from a variety of preclinical and clinical studies implicate impaired BDNF signaling through TrkB in the pathophysiology of mood disorders, although especially genetic evidence has recently not supported this notion, and deficiencies in BDNF signaling are not specific to mood disorders. However, there is solid evidence to indicate that increased expression and signaling of BDNF is critical in the mechanisms of both typical and rapid-acting antidepressant drugs. As BDNF is a critical mediator of various types of synaptic plasticity, these data suggest that restricted plasticity may underlie depression and that promotion of plasticity enhances mood recovery. As plastic networks need experience-dependent activity to guide their selection (13,144,145), these data suggest a new paradigm for the treatment of mood disorders, where pharmacological and psychological approaches are closely intertwined, emphasizing the need for the active participation of the patient in successful antidepressant drug treatment.

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