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BDNF — a key transducer of antidepressant effects

Carl Björkholm[a] and **Lisa M. Monteggia**[b,*]

[a] Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

[b] Department of Neuroscience, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract

How do antidepressants elicit an antidepressant response? Here, we review accumulating evidence that the neurotrophin brain-derived neurotrophic factor (BDNF) serves as a transducer, acting as the link between the antidepressant drug and the neuroplastic changes that result in the improvement of the depressive symptoms. Over the last decade several studies have consistently highlighted BDNF as a key player in antidepressant action. An increase in hippocampal and cortical expression of BDNF mRNA parallels the antidepressant-like response of conventional antidepressants such as SSRIs. Subsequent studies showed that a single bilateral infusion of BDNF into the ventricles or directly into the hippocampus is sufficient to induce a relatively rapid and sustained antidepressant-like effect. Importantly, the antidepressant-like response to conventional antidepressants is attenuated in mice where the BDNF signaling has been disrupted by genetic manipulations. Low dose ketamine, which has been found to induce a rapid antidepressant effect in patients with treatment-resistant depression, is also dependent on increased BDNF signaling. Ketamine transiently increases BDNF translation in hippocampus, leading to enhanced synaptic plasticity and synaptic strength. Ketamine has been shown to increase BDNF translation by blocking NMDA receptor activity at rest, thereby inhibiting calcium influx and subsequently halting eukaryotic elongation factor 2 (eEF2) kinase leading to a desuppression of protein translation, including BDNF translation. The antidepressant-like response of ketamine is abolished in BDNF and TrkB conditional knockout mice, eEF2 kinase knockout mice, in mice carrying the BDNF met/met allele, and by intra-cortical infusions of BDNF-neutralizing antibodies. In summary, current data suggests that conventional antidepressants and ketamine mediate their antidepressant-like effects by increasing BDNF in forebrain regions, in particular the hippocampus, making BDNF an essential determinant of antidepressant efficacy.

Keywords

Brain-derived neurotrophic factor; Hippocampus; Synaptic plasticity; Behavior; Depression

* Corresponding author. Ginny and John Eulich Professorship in Autism Spectrum Disorders, Department of Neuroscience, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9111, USA. lisa.monteggia@utsouthwestern.edu (L.M. Monteggia)..

1. Introduction

1.1. Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a well-studied growth factor that serves many critical functions within the central nervous system (CNS). BDNF has a role in processes such as neuronal maturation, synapse formation and synaptic plasticity among others in the brain (see e.g. Park and Poo, 2013). BDNF has also been implicated in a number of psychiatric disorders, including schizophrenia, intellectual disability and autism, and the development of mood disorders such as depression and its treatment (Autry and Monteggia, 2012).

BDNF is a member of the neurotrophin family that includes nerve growth factor (NGF), neurotrophin-3 (NT3), and neutorophin-4 (NT4). BDNF is widely expressed in the CNS and can exert profound effects on development, morphology, and synaptic plasticity and function in the brain. The *BDNF* gene has nine promoters that drive expression of distinct *Bdnf* transcripts that each encode the same BDNF protein (Aid et al., 2007; Pruunsild et al., 2007). These individual *Bdnf* transcripts may contribute to regional and temporal specific effects of BDNF and is an active area of investigation. The transcription of BDNF mRNA can be regulated by neuronal activity via Ca^{2+} influx, through Ca^{2+} permeable glutamate receptors (mainly N-Methyl-D-aspartate [NMDA] receptors) and voltage gated Ca^{2+} channels (Ghosh et al., 1994; Zafra et al., 1991). Previous work has shown that Ca^{2+} initiates the binding of transcription factors such as cyclic AMP response element binding protein (CREB) and Ca^{2+} response factor (CaRF) to the BDNF promoters (Tao et al., 1998, 2002). Activity-dependent BDNF transcription can also be regulated by epigenetic changes of the chromatin structure, adding yet another level of regulation (Kumar et al., 2005; Zhou et al., 2006).

BDNF is synthesized in cell bodies of neurons and glia and transported to terminals where it is released (Lessmann and Brigadski, 2009). However, BDNF can also be directed to dendrites, where activity dependent local translation of BDNF takes place (Lau et al., 2010). BDNF is first synthesized into pre-pro-BDNF, which is cleaved to mature BDNF, however, the exact location of this conversion (inside the cell or after secretion extracellularly) remains unclear (see e.g. Leal et al., 2014). BDNF secretion is activity dependent, and BDNF has been shown to be secreted both by presynaptic and postsynaptic terminals, although at different stimulation intensities (Matsuda et al., 2009). The cell biology of BDNF processing and trafficking is complex and remains an open question therefore we refer the readers to a recent review on this topic (please see e.g. Karpova, 2014).

BDNF binds with high affinity to the tropomycin receptor kinase B (TrkB) receptor (Soppet et al., 1991). BDNF, like other members of the neurotrophin family, can also bind to the p75 neurotrophin receptor although with lower affinity (Meeker and Williams, 2015). Many studies have established a critical role for BDNF-TrkB in synaptic plasticity mechanisms. TrkB receptors are expressed both pre- and postsynaptically and BDNF has been shown to regulate neurotransmitter release as well as postsynaptic responses (Madara and Levine, 2008). BDNF binding to TrkB can regulate at least three intracellular signaling pathways (Park and Poo, 2013). One pathway involves phospholipase C-γ (PLC- γ) leading to protein

kinase C (PKC) activation. A second involves mitogen-activated protein (MAP) kinase, which can activate Ras leading to downstream effects. A third signaling pathway involves phosphatidylinositol-3′OH-kinase (PI3K) that can activate the AKT-mTOR pathway.

As mentioned previously, BDNF-TrkB signaling can modulate neurotransmission and enhance synaptic efficacy both via presynaptic and postsynaptic mechanisms in a variety of ways. BDNF facilitates high frequency activity induced long-term potentiation (LTP) in the Schaffer collaterals of the hippocampus in young animals by enhancing presynaptic neurotransmitter release (Figurov et al., 1996). BDNF infusion into the hippocampus may also induce LTP in vivo (Ying et al., 2002), confirming the physiological relevance of this finding. Presynaptic release of BDNF has been shown to be critical for LTP-induction in the hippocampus Schaffer collaterals (Zakharenko et al., 2003). In the dentate gyrus (DG) subregion of the hippocampus, BDNF can facilitate LTP though postsynaptic mechanisms (Kovalchuk et al., 2002). BDNF may also increase the postsynaptic response by increasing conductance of NMDA receptors (Levine et al.,1995,1998). BDNF has been shown to increase α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) responses by enhancing AMPA receptor translation and cell surface expression (Caldeira et al., 2007; Fortin et al., 2012). In addition, BDNF can facilitate excitatory transmission indirectly by attenuating inhibitory neurotransmission by, for example, reducing the surface expression of $GABA_A$ receptors (Jovanovic et al., 2004). BDNF via TrkB signaling has been found to increase spine density in the hippocampus via several signaling pathways (Alonso et al., 2004; Amaral and Pozzo-Miller, 2007; Kumar et al., 2005). Moreover, LTP-induced enlargement of hippocampal dendritic spine volume is dependent on BDNF signaling and local protein translation (Tanaka et al., 2008). Recent studies have also identified a key role for BDNF in synaptic potentiation seen after sustained blockade of NMDA receptor activity, where BDNF action appears to upregulate postsynaptic AMPA receptors (Autry et al., 2011; Nosyreva et al., 2013).

1.2. Single nucleotide polymorphisms in the BDNF gene

Given the crucial importance of BDNF in the developing and mature CNS, it is not surprising that disturbances in BDNF expression can affect brain function. Single nucleotide polymorphisms (SNPs), have been identified in the *BDNF* gene, which has provided an opportunity to study individuals carrying these SNPs (See e.g. Egan et al., 2003; Hing et al., 2012). The best characterized SNP in the *BDNF* gene is located in the pro-BDNF region, changing codon 66 from a valine (val) to methionine (met; i.e. val66met). Individuals with the val66met SNP have reduced episodic memory and aberrant hippocampal function that is believed to be due to disturbed intracellular trafficking and activity dependent secretion of BDNF (Egan et al., 2003). The val66met SNP has also been suggested to play a role in the vulnerability to several psychiatric disorders and traits; including mood disorders and impaired cognition (Notaras et al., 2015). Interestingly, symptoms analogous to their human counterparts have been found in genetically modified mice carrying the human *BDNF* val66met alleles. These mice display working memory deficits as well as an anxious and depressive-like phenotype in response to stress (Yu et al., 2012). In addition, these mutant mice have reduced synaptic plasticity and synaptic transmission in both hippocampus and the medial prefrontal cortex (mPFC; Ninan et al., 2010; Pattwell et al., 2012). Another SNP,

BE5.2, located in a cis-regulatory region that controls the activity of a *BDNF* promoter in the hippocampus, cortex and the amygdala, has been identified (Hing et al., 2012). This SNP reduces evoked release of BDNF in the hippocampus and cortex and is also associated with mood disorders. In contrast, in the amygdala, *BE5.2* increases BDNF release, which may provide a mechanistic explanation for this SNP's linkage to the development of anxiety disorders (Hing et al., 2012).

2. BDNF and the response to conventional antidepressants

Clinically used antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs), mediate their antidepressant effect by modulating the extracellular levels of monoamines mainly serotonin or norepinephrine. It is generally thought that these drugs enhance the extracellular levels of monoamines rather quickly, within hours; however, the antidepressant response is delayed and typically requires weeks of treatment before a sufficient antidepressant response is obtained (Trivedi et al., 2006). Therefore, other mechanisms downstream of the enhancement of extracellular level of monoamines are believed to mediate the antidepressant response. In this context, BDNF has been linked to the mechanism of action of antidepressants (Duman et al., 1997; Ghosh et al., 1994; Monteggia et al., 2004; Duman and Monteggia, 2006).

The first studies to implicate BDNF in antidepressant responses showed that conventional antidepressant drugs, as well as electroconvulsive therapy (ECT), enhanced BDNF and TrkB mRNA expression in the hippocampus and cortical regions in a timeframe similar to the onset of the antidepressant-like response (Nibuya et al., 1995, 1996). To more directly examine the causal involvement of BDNF in antidepressant responses, Siuciak and colleagues infused BDNF protein directly into the midbrain and observed an antidepressant-like effect in rodents (Siuciak et al., 1997). Subsequent work showed that a single bilateral infusion of a low dose of BDNF directly into the DG or CA3, but not CA1, region of the hippocampus was sufficient to induce an antidepressant-like effect within three days (Shirayama et al., 2002), suggesting that these regions may be key regions for antidepressant effects acting through BDNF. In this latter study, the antidepressant effects of BDNF were suggested to be mediated by TrkB activation of mitogen-activated protein kinase kinase (MEK), acting through the extracellular signal-regulated protein kinase (ERK) pathway. Rather surprisingly, this study also noted that BDNF produced an antidepressant effect for up to 10 days after the infusion, well past the time frame of the degradation of the protein, suggesting that BDNF may be triggering a sustained plasticity mechanism to mediate the long-term antidepressant effects. In separate work, peripheral, subcutaneous injections of BDNF were reported to produce antidepressant- and anxiolytic-like effects in rodents, prevent depression-related effects of chronic stress, and to increase cell survival in the hippocampus and prefrontal cortex (Schmidt and Duman, 2010). However, the exact mechanism of this finding remains to be determined, as BDNF is poorly transported across the blood-brain barrier leaving it unclear as to how peripheral administration mediates the reported effects.

Over the past decade, several studies have examined whether BDNF is required for antidepressant responses. Constitutive BDNF null knockouts die early in postnatal

development precluding their use for behavioral studies assessing depression-related behavior and antidepressant responses. Heterozygous BDNF null (BDNF+/−) mice have been examined and do not show alterations in depression-like behavior, suggesting that an ~50% reduction in BDNF levels does not impact depression-related behavior per se (Saarelainen et al., 2003). In this same study, the antidepressant imipramine was ineffective in behavioral tests, suggesting that BDNF is required for the antidepressant effects of imipramine. However, the ~50% reduction in BDNF throughout the body may have complicated the interpretation of the data. To examine a potential role for BDNF selectively in the brain in mediating antidepressant effects, studies have utilized inducible and conditional knockout mice in which the deletion of BDNF is controlled in a regional and temporal manner. The Monteggia laboratory generated an inducible knockout mouse in which BDNF was selectively deleted in broad forebrain regions and these mice did not show alterations in depression-related behavior. However, these mice had an attenuated response to the antidepressant desipramine suggesting forebrain BDNF was required for antidepressant efficacy (Monteggia et al., 2004). In a subsequent study, two independent lines of conditional BDNF knockout mice in which BDNF was deleted in the forebrain were generated and it was found that while loss of BDNF increased depression-related behavioral measures after chronic stress in females, these effects were largely absent in male mice (Monteggia et al., 2007). To directly examine the requirement of BDNF specifically in the adult hippocampus in mediating antidepressant effects, a viral mediated gene transfer approach was employed. Using an adeno-associated virus (AAV) expressing Cre recombinase or AAV expressing green fluorescent protein (GFP) as a control, BDNF was selectively deleted in subregions of the hippocampus in adult floxed BDNF mice. The loss of BDNF in either the DG or CA1 subregion of the hippocampus did not alter depression-related behavior (Adachi et al., 2008). However, loss of BDNF selectively in DG, but not the CA1, was crucial for the antidepressant-like effect of conventional antidepressants such as SSRIs and TCAs (Adachi et al., 2008). These results were the first in demonstrating that BDNF in the hippocampus, specifically the DG, was required for antidepressant efficacy. This finding is in agreement with post mortem data showing that BDNF immunoreactivity is increased in several hippocampal regions including the DG in patients treated with antidepressants at the time of their death (Chen et al., 2001) suggesting that BDNF in the hippocampus, specifically in particular subregions, may be critical for antidepressant responses in humans.

The requirement for BDNF in antidepressant responses has also been investigated using mice expressing the val66met SNP in the *BDNF* gene. Mice homozygous for this BDNF SNP (BDNF met/met) recapitulate the memory phenotypes reported in humans with this SNP (Chen et al., 2006). The BDNF met/met mice were also unresponsive to chronic treatment with the antidepressant fluoxetine presumably through deficits in BDNF secretion (Chen et al., 2006). In mice with the BDNF met/met allele SSRI-induced enhancement of BDNF levels and synaptic plasticity was impaired (Bath et al., 2012) suggesting that the lack of response to SSRIs may be tied to the observed deficits in synaptic plasticity. In patients with major depressive disorder, the BDNF val66met SNP, as well as two other BDNF SNPs, were linked to a reduced response to antidepressant treatment suggesting that these SNPs may impact treatment responses to antidepressants (Kocabas et al., 2011).

Further support for the involvement of BDNF signaling in the response to antidepressants has come from studies examining the high affinity BDNF receptor, TrkB. Antidepressant drugs require functional TrkB receptors to mediate antidepressant-like response in preclinical models (Rantamäki et al., 2007; Saarelainen et al., 2003). Rather intriguingly, chronic antidepressant treatment increases the phosphorylation of the TrkB receptor, thus increasing its activity, in the hippocampus and anterior cingulate cortex suggesting that BDNF-TrkB signaling in these brain regions may be critical in mediating antidepressant effects (Rantamäki et al., 2007). The latter study also confirmed that conventional antidepressants require monoamines to impact BDNF intracellular signaling as monoamine depletion prevented the antidepressant induced activation of TrkB (Rantamäki et al., 2007).

While there is strong evidence to suggest that BDNF in the hippocampus and prefrontal cortex is involved in mediating antidepressant responses, other brain regions have also been implicated in antidepressant responses. For example, BDNF signaling in the ventral tegmental area (VTA) to nucleus accumbens pathway seems to produce effects that are in many ways opposite to effects of BDNF in the hippocampus (Nestler and Carlezon, 2006). BDNF injected directly into the VTA induces depression-like behavior and, conversely, blocking BDNF signaling in nucleus accumbens, a brain region, which receives afferents from the VTA, induces an antidepressant-like effect (Eisch et al., 2003). BDNF signaling in this region has also been found to be important for the development of the molecular and behavioral manifestations of stress (Berton et al., 2006; Lippmann et al., 2007), thus further supporting the involvement of BDNF in the mesolimbic pathway in the expression of at least a subset of the depressive symptoms. Another brain region that has received attention for its involvement in mood disorders is the lateral habenula. The lateral habenula signals negative valence to monoaminergic systems and over-activation of the lateral habenula has recently been proposed to be involved in depression as well as to be a site of antidepressant action of conventional antidepressant drugs (Proulx et al., 2014; Sartorius and Henn, 2007). However, it remains to be determined whether BDNF in this region plays a role in antidepressant responses or depression-related behavior.

Collectively, BDNF-TrkB signaling in the hippocampus appears to be a critical component of antidepressant responses to conventional antidepressants, at least in preclinical animal models. The involvement of the hippocampus in antidepressant efficacy does not preclude the involvement of other brain regions, as undoubtedly diverse neural circuits are required for antidepressant responses. However, the requirement for BDNF in the hippocampus in mediating antidepressant responses allows one a starting point to elucidate the neural circuitry involved in this process.

3. BDNF is required for the rapid antidepressant effects of ketamine

The discovery that an acute low dose of ketamine, a noncompetitive NMDA receptor antagonist, can trigger rapid antidepressant effects in patients with depression, including treatment-resistant depression, has generated a great deal of interest in unraveling the underlying biological mechanisms mediating the fast acting response (Berman et al., 2000; DiozGranados et al., 2010a; 2010b; Price et al., 2009; Zarate et al., 2006a). Acute intravenous administration of low dose ketamine elicited a rapid antidepressant effect within

2 h that in some patients persisted for more than two weeks. Ketamine has a half-life of ~3 h suggesting that the longer lasting antidepressant effects were not mediated by NMDA receptor blockade per se but rather may involve some type of synaptic plasticity mechanisms. Given the critical role for BDNF in conventional antidepressant effects, and the well-documented effects of BDNF on synaptic plasticity and transmission, it was well conceived to investigate whether BDNF was involved in ketamine's antidepressant effects.

Our laboratory demonstrated a critical role for BDNF and TrkB in the antidepressant action of ketamine and showed that the antidepressant-like effect of ketamine was attenuated in inducible forebrain specific BDNF and conditional TrkB knockout mice (Autry et al., 2011). In this study, ketamine was shown to rapidly increase the phosphorylation of TrkB, an indicator of TrkB activation, in the hippocampus suggesting this brain region was involved in the antidepressant response of ketamine. Intriguingly, the antidepressant effects of ketamine and other NMDA receptor antagonists required a rapid increase in BDNF protein translation, but not BDNF mRNA expression, in the hippocampus as blockade of the former, but not the latter abolished the antidepressant-like action of the NMDA receptor antagonists. This data is in agreement with prior work showing that acute ketamine that induces an antidepressant effect increases BDNF protein levels in the hippocampus (Garcia et al., 2008). However, this rapid increase in BDNF protein expression while required, was not maintained at 24 h after ketamine treatment, suggesting that BDNF working through TrkB was triggering intracellular signaling, and possibly synaptic plasticity effects, required for the antidepressant response (Autry et al., 2011). Work from our laboratory went on to show that ketamine, through blockade of NMDA receptors, was targeting a specific intracellular signaling pathway in order to rapidly increase BDNF protein expression. Low dose ketamine, and other NMDA receptor antagonists, by blocking the activation of NMDA receptors by spontaneous neurotransmission (i.e. non action potential-dependent neurotransmitter release), dampened the flow of calcium through the receptor, thereby inhibiting eukaryotic elongation factor 2 kinase (eEF2K). The eEF2K has only one known substrate, eukaryotic elongation factor 2 (eEF2), which when phosphorylated by eEF2K, halts protein translation. Previous in vitro work has shown that blocking spontaneously activated NMDA receptors inhibits eEF2K such that there is an overall decrease in the phosphorylation of eEF2 and thereby desuppressing protein translation in a rapid manner (Sutton et al., 2007). In vivo work demonstrated that low dose ketamine in mice blocks NMDA receptors at rest to desuppress protein translation resulting in a rapid increase in BDNF protein expression in the hippocampus (Autry et al., 2011). The importance of this pathway in the rapid antidepressant effects were tested by the administration of eEF2K inhibitors in mice which resulted in decreased phosphorylation levels of eEF2, a rapid upregulation of BDNF protein, and a rapid antidepressant effect in mice that was dependent on BDNF expression (Autry et al., 2011). Subsequent work confirmed the importance of this pathway in the rapid antidepressant response to ketamine as eEF2K null knockout mice that are administered an acute low dose of ketamine do not have increased BDNF protein expression and do not show an antidepressant response to the drug (Nosyreva et al., 2013). Collectively, these studies to date have proposed a novel mechanism for how acute low dose ketamine blocks the NMDA receptor to trigger changes on intracellular signaling that mediate the antidepressant effects.

Several lines of evidence have confirmed the finding that BDNF is required for the antidepressant response to ketamine. Preclinical studies have found that an infusion of a BDNF- neutralizing antibody into the mPFC abolishes ketamine's antidepressant-like effects also suggesting that BDNF in the mPFC may also be an important site of action (Lepack et al., 2014). Mice expressing the human *BDNF* val66met SNP have also been examined following acute ketamine administration and shown to have an attenuated antidepressant response (Liu et al., 2012a) further corroborating the finding that functional BDNF is indeed required for the rapid antidepressant action of ketamine.

These preclinical findings linking BDNF to the antidepressant response to ketamine have started to impact clinical studies. A small trial investigated ketamine treatment outcomes in patients with major depression carrying either the functional BDNF val66val allele against met carriers found an increased antidepressant response to ketamine in individuals with the val/val than met carriers (Laje et al., 2012) suggesting that alterations in BDNF function can impact ketamine's antidepressant effects. Low dose ketamine infusion has also been found to increase the serum concentration of BDNF especially in responders to treatment (Haile et al., 2014) suggesting plasma BDNF may be a potential biomarker for the antidepressant effects of ketamine (Haile et al., 2014). However, conflicting clinical results have also been reported (Machado-Vieira et al., 2009). The relationship between BDNF in the brain and peripheral levels of BDNF are unclear. However, given the critical need for biomarkers in the field of depression, the potential ability to correlate BDNF plasma levels with antidepressant responses to ketamine may warrant further investigation.

3.1. BDNF-TrkB activation and downstream effects of ketamine

Several intracellular signaling pathways, in addition to eEF2 kinase signaling, such as mammalian target of rapamycin (mTOR) and glycogen synthase kinase 3 (GSK-3) have been implicated in the antidepressant effects of ketamine (Beurel et al., 2011; Li et al., 2010). However, neither of these targets has been directly linked to NMDA receptor blockade by ketamine in explaining their involvement. The fact that ketamine can trigger a rapid antidepressant response within two hours allows one to mechanistically link the target of the drug, NMDA receptor blockade, with intracellular signaling to elucidate the antidepressant effect. Initial studies had suggested that ketamine activates mTOR through disinhibition of glutamate transmission, resulting in a rapid burst of glutamate that triggers BDNF release to increase synapse formation (see Duman, 2014). However, studies directly examining the disinhibition hypothesis have failed to support its involvement in ketamine's antidepressant response. Specifically, loss of the GluN1 subunit of the NMDA receptors on parvalbumin expressing GABAergic interneurons did not alter the behavioral response to ketamine, suggesting that NMDA receptors on parvalbumin containing interneurons are not the target for ketamine's antidepressant effects (Pozzi et al., 2014). Moreover, the loss of GluN2B from principal cortical neurons resulted in an attenuated response to the antidepressant effects of ketamine (Miller et al., 2014). It is quite possible that ketamine by blocking NMDA receptors at rest, inhibiting eEF2K and desuppressing protein synthesis of BDNF, and other targets, may then be triggering activation of mTOR. Previous work examining the antidepressant effects of ketamine demonstrated that mTOR was downstream of BDNF (Autry et al., 2011). Indeed, BDNF mice with the met/met SNP do not response to

the antidepressant effects of ketamine and have impaired synaptogenesis that is believed to be mediated through mTOR (Liu et al., 2012a) supporting the notion that BDNF is upstream of this signaling pathway. Previous work has shown that BDNF is a potent activator of mTOR signaling (Jourdi et al., 2009; Takei et al., 2004; Slipczuk et al., 2009), and mTOR is a key integrator for many signaling pathways (see Costa-Mattioli and Monteggia, 2013). In addition, BDNF has been found to inhibit the activity of GSK-3 in the hippocampus (Johnson-Farley et al., 2006). Thus, the role of mTOR and GSK-3 may be more in the downstream effects rather than the initiation of the antidepressant effect of ketamine. Indeed, it is not difficult to imagine that the rapid upregulation of BDNF protein synthesis and activation of TrkB could then trigger various intracellular signaling pathways that activate mTOR and GSK-3 as well as other molecules that are involved in ketamine's antidepressant effects.

Work to date suggests that the rapid upregulation of BDNF protein and subsequent TrkB activation triggers an increase in synaptic efficacy that is required for the antidepressant action of ketamine. It is well documented that activation of NMDA receptors can impact BDNF expression resulting in enhanced LTP (Kovalchuk et al., 2002). However, ketamine blocks NMDA receptors making it more difficult to explain the link between NMDA receptor antagonism, increased BDNF expression, and changes in synaptic efficacy. Recent work has shown that a 30-min treatment of slice preparations with ketamine potentiates synaptic efficacy in the Schaffer collateral pathway from CA3 to CA1 subregions of the hippocampus (Autry et al., 2011; Nosyreva et al., 2013, 2014). This increase in synaptic efficacy produced by ketamine treatment was dependent on eEF2K, protein translation, as well as BDNF expression suggesting this signaling pathway in rapid antidepressant efficacy and the synaptic effects (Autry et al., 2011; Nosyreva et al., 2013). The ketamine triggered rapid increase in BDNF protein expression was shown to rapidly increase surface expression of the AMPA receptor subunits, GluA1 and GluA2, in the hippocampus that were required for the increase in synaptic efficacy as well as the antidepressant effects of ketamine (Nosyreva et al., 2013). This ketamine induced increase in synaptic efficacy was age dependent as young mice did not exhibit this increase in synaptic potentiation or display an antidepressant response to ketamine (Nosyreva et al., 2014).

The hypothesis that the mechanism of action of ketamine is via blockade of the spontaneous, non-action potential dependent, NMDA receptor-mediated neurotransmission, which leads to an inhibition of eEF2K and a consequently a desuppression of BDNF protein expression was directly tested when our laboratory compared ketamine to memantine, another NMDA receptor antagonist. Interestingly, memantine is similar to ketamine in that they are both noncompetitive NMDA receptor antagonists; however, clinical data has persistently shown that memantine does not trigger a rapid antidepressant effect, or even a delayed antidepressant effect, in patients with major depression (Ferguson and Shingleton, 2007; Lenze et al., 2012; Zarate et al., 2006b). While ketamine and memantine have similar effects on evoked neurotransmission, their effects on spontaneous, non action potential dependent, NMDA receptor-mediated transmission was unknown. Work done in our laboratory demonstrated that memantine has little effect on the function of NMDA receptors activated by spontaneous neurotransmitter release, in contrast to ketamine. This differential effect of ketamine and memantine extended to intracellular signaling coupled to spontaneous NMDA

receptors, in that memantine does not inhibit eEF2K nor alter BDNF protein expression in the hippocampus, key determinants of ketamine mediated rapid antidepressant effects (Gideons et al., 2014). These data highlight the complexity of targeting the NMDA receptor in that not all noncompetitive NMDA receptor antagonists can mediate antidepressant effects, but also support the hypothesis of eEF2K's and BDNF's crucial importance of in the antidepressant effects of ketamine.

4. Discussion and future perspectives

Current evidence strongly implicates BDNF-TrkB signaling in the response to clinically used antidepressant drugs including ketamine. Indeed, as stated above, conventional antidepressants as well as ketamine require BDNF to mediate their antidepressant effects. Thus, it is possible that while there may be differences in how conventional antidepressants and ketamine trigger an antidepressant response, BDNF may be the point of convergence for the antidepressant effect of these drugs.

While BDNF has been extensively studied for its role in the CNS, there is still a great deal of work needed in delineating the regional specificity of BDNF signaling which will be important in better understanding antidepressant efficacy. Future studies utilizing regionally discrete and cell type specific gene deletions of both BDNF and its receptor TrkB will need to be conducted to elucidate the precise location and pathways involved in BDNF signaling that mediate antidepressant responses. This information will be crucial in starting to elucidate the neural circuitry involved in antidepressant responses.

While BDNF is necessary for the antidepressant responses to antidepressant drugs, is it sufficient? As previously discussed, bilateral BDNF-infusions into the hippocampus or the ventricles induces antidepressant-like effects in preclinical animal models that can persist for several days (Shirayama et al., 2002; Siuciak et al., 1997). However, infusions of BDNF into the brain are not practical for wide treatment. BDNF does not readily cross the blood brain barrier so there has been a great deal of interest on the development of small molecules directly targeting TrkB signaling. These molecules have shown promising antidepressant-like results in preclinical studies (Liu et al., 2010, 2012b). However, BDNF-TrkB signaling is tightly regulated thus administering exogenous BDNF or TrkB agonists may not result in the expected outcomes and prolonged use may, due to BDNF's trophic effects, entail the risk of side effects (see Price et al., 2007). Since BDNF-TrkB signaling may contribute differently to the symptomatology of depression depending on brain region (c.f. above), it is not certain that a global increase in BDNF expression or TrkB activation induces an overall antidepressant effect, although experiments conducted to date support this hypothesis (Duman and Voleti, 2012; Schmidt and Duman, 2010). Nevertheless, even though promising preclinical results have been obtained with molecules directly targeting BDNF-TrkB signaling, indirectly acting drugs that modulate the physiological BDNF signaling, or drugs that act on signaling pathways downstream of BDNF may provide more fruitful targets to pursue.

Data to date consistently suggests that BDNF is a critical mediator of conventional antidepressant responses, as well as ketamine mediated rapid antidepressant efficacy. From

this work, the hippocampus also emerges as a critical site of BDNF action to mediate these effects. Moreover, electrophysiological studies with ketamine suggest that BDNF is triggering changes in synaptic efficacy that are strongly correlated with the antidepressant effects. The link between BDNF and antidepressant responses may be mediated by augmentation of synaptic efficacy. Further elucidation of these synaptic plasticity mechanisms that link BDNF action to antidepressant responses will enable us to better understand what is required to trigger antidepressant effects in hopes of developing better treatment options.

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Abbreviations

AAV	adeno-associated virus
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	brain derived neurotrophic factor
CA1	cornu ammonis area 1
CA3	cornu ammonis area 3
CNS	central nervous system
DG	dentate gyrus
ECT	electroconvulsive therapy
eEF2	eukaryotic elongation factor 2
eEF2K	eukaryotic elongation factor 2 kinase
ERK	extracellular signal-regulated protein kinase
GABA	γ-Aminobutyric acid
GFP	green fluorescent protein
GSK-3	glycogen synthase kinase 3
LTP	long-term potentiation
MAP	mitogen-activated protein
MEK	mitogen activated protein kinase kinase
MET	methionine
mPFC	medial prefrontal cortex
mRNA	messenger ribonucleic acid

mTOR	mammalian target of rapamycin
NMDA	N-Methyl-D-aspartate
NGF	nerve growth factor
NT3	neurotrophin-3
NT4	neurotrophin-4
PI3K	phosphatidylinositol-3′OH-kinase
PKC	protein kinase C
PLC-γ	phospholipase C-γ
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TrkB	tropomycin receptor kinase B
VAL	valine

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