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Role of BDNF in the pathophysiology and treatment of depression: activity dependent effects distinguish rapid acting antidepressants

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Abstract

The pathophysiology and treatment of depression has been the focus of intense research and while there is much that remains unknown, modern neurobiological approaches are making progress. This work demonstrates that stress and depression are associated with atrophy of neurons and reduced synaptic connectivity in brain regions such as the hippocampus and prefrontal cortex that contribute to depressive behaviors, and conversely that antidepressant treatment can reverse these deficits. The role of neurotrophic factors, particularly brain derived neurotrophic factor (BDNF) have been of particular interest as these factors play a key role in activity dependent regulation of synaptic plasticity. Here we review the literature demonstrating that exposure to stress and depression decreases BDNF expression in the hippocampus and PFC and conversely that antidepressant treatment can up-regulate BDNF in the adult brain and reverse the effects of stress. We then focus on rapid acting antidepressants, particularly the NMDA receptor antagonist ketamine, which produces rapid synaptic and antidepressant behavioral actions that are dependent on activity dependent release of BDNF. This rapid release of BDNF differs from typical monoaminergic agents that require chronic administration to produce a slow induction of BDNF expression, consistent with the time lag for the therapeutic action of these agents. We review evidence that other classes of rapid acting agents also require BDNF release, demonstrating that this is a common, convergent downstream mechanism. Finally, we discuss evidence that the actions of ketamine are also dependent on another growth factor, vascular endothelial growth factor (VEGF) and its complex interplay with BDNF.

Graphical Abstract

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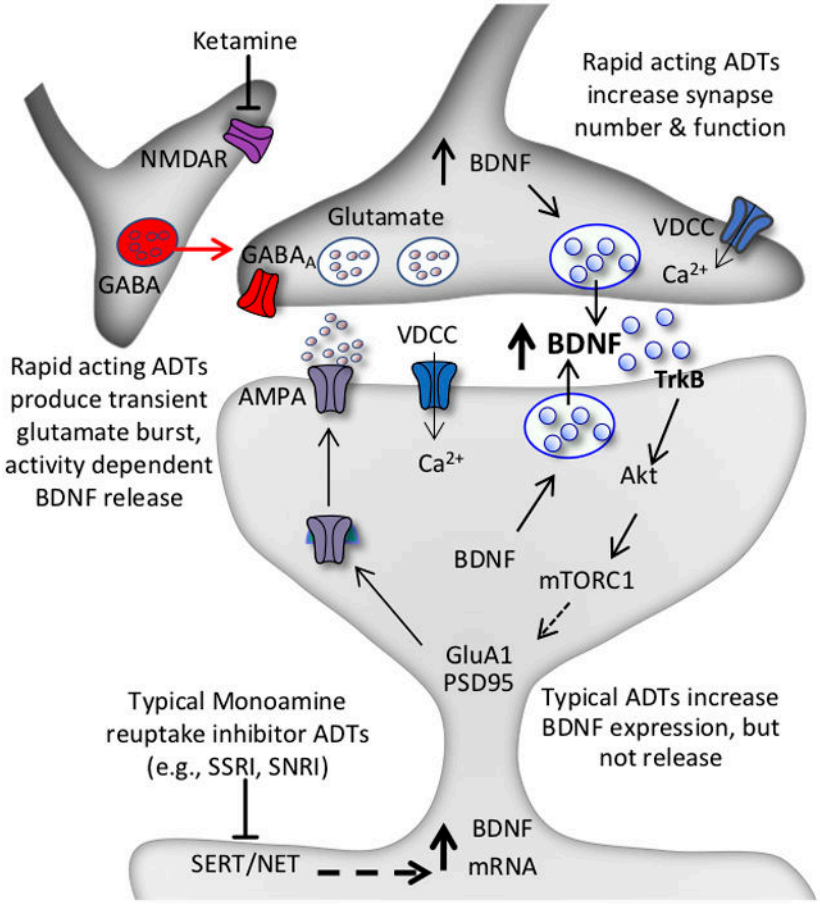
Chronic stress decreases the expression of BDNF and causes atrophy of neurons in cortical and limbic brain regions.

Rapid acting antidepressants, notably the NMDA receptor antagonist ketamine, cause activity dependent release of BDNF that contributes to rapid increases in synapse number and function.

Typical monoaminergic antidepressants cause a delayed increase in BDNF expression but not activity dependent release.



Keywords

ketamine; synaptic plasticity; stress; neurotrophic factor

Introduction

Despite the enormous personal suffering, risk of suicide, and economic consequences, our ability to diagnose and successfully treat depression has significant limitations (Flint & Kendler, 2014). Depression is a heterogeneous disorder with two-fold higher rates in women compared to men and a relatively low, 37 percent rate of heritability (Sullivan et al., 2018). These factors likely impact the difficulties in treating depression as current medications, comprised largely of monoaminergic agents, have a slow response rate of weeks to months

and are only effective in approximately two thirds of patients (Trivedi et al., 2006). These limitations highlight the discovery that ketamine, an NMDA receptor (NMDAR) antagonist, produces rapid antidepressant actions after a single dose, even in patients considered treatment resistant (Berman et al., 2000; Zarate et al., 2006; Krystal et al., 2019). The discovery of an agent that produces rapid therapeutic actions by a mechanism completely different from currently available monoaminergic agents represents one of the biggest breakthroughs for the treatment of depression in over sixty years.

The (S)-enantiomer of ketamine referred to as esketamine was recently approved in the form of a nasal application for treatment resistant depression. Although esketamine as well as ketamine represent profound, significant alternatives for depressed patients who do not respond to typical antidepressants, these drugs have an undesirable side effect profile, including dissociative and psychotomimetic effects (Krystal et al., 2019). This has prompted efforts to identify the neurobiological mechanisms underlying the antidepressant actions of ketamine and thereby inform development of novel, ketamine-like agents with fewer side effects. Initial studies demonstrated that ketamine rapidly increases synaptic number and function in the medial prefrontal cortex (mPFC), and reverses the synaptic deficits caused by chronic stress exposure (Li et al., 2010; Li et al., 2011; Duman et al., 2016). These effects could contribute to reversal of the synaptic deficits and reduced connectivity associated with depression (Drevets et al., 2008; MacQueen & Frodl, 2011; Kang et al., 2012). These findings as well as evidence from studies of typical antidepressants have led to studies of neurotrophic factors and related signaling pathways that are critical for synaptic alterations.

The focus of the current review is to discuss evidence for a role of brain derived neurotrophic factor (BDNF) in the pathophysiology and treatment of depression. A brief description of BDNF is provided, and then a review of the preclinical and clinical literature demonstrating a role for BDNF in depression is presented. This includes evidence that stress and depression are associated with decreased expression of BDNF in limbic and cerebral cortical brain regions associated with depression, and conversely that antidepressant treatments increase the expression of BDNF. Particular attention is given to ketamine, and other classes of rapid acting antidepressants, and evidence that these agents cause activity dependent release of BDNF, which is thought to underlie their rapid synaptic and antidepressant behavioral responses. This review will also discuss recent evidence that the rapid actions of ketamine involve activity dependent release of vascular endothelial growth factor (VEGF) and its interactions with BDNF signaling.

Neurobiology of BDNF

BDNF is the most highly expressed member of the nerve growth factor (NGF) family that also includes NGF, neurotrophin-3, and neurotrophin-4 (Castren & Kojima, 2017). The neurotrophins were first identified as critical regulators of cell proliferation, migration, maturation, and survival during development, but are also expressed in the adult brain where they are involved in synaptic plasticity, neuronal function and survival (Martinowich et al., 2007). BDNF is multi-exon gene with multiple 5’ promoters that control constitutive and activity regulated expression of BDNF (Adachi et al., 2014; Castren & Kojima, 2017). BDNF is constitutively expressed and released but is also controlled by neuronal activity

largely via Ca^{2+} signaling and activation of Ca^{2+}/ and cAMP response elements (Bjorkholm & Monteggia, 2016). The initial transcript is translated to pre-proBDNF which then undergoes further processing and cleavage to proBDNF and then to mature BDNF, which bind to the p75 neurotrophin receptor (p75NTR) and the tyrosine kinase receptor TrkB, respectively, to activate different downstream signaling pathways (Castren & Kojima, 2017) (Figure 1). Both are packaged into vesicles and undergo trafficking to dendrite as well as axon terminals where mature BDNF undergoes activity dependent release while proBDNF undergoes low levels of constitutive release (Figure 1).

The BDNF prodomain contains a common single nucleotide polymorphism, Val66Met expressed in approximately 30 percent of Caucasians, although higher levels, approximately 80 percent has been reported in a Chinese population (Dincheva et al., 2016; Su et al., 2017). The BDNF Val allele is required for processing of proBDNF to mature BDNF and is therefore required for activity dependent release of BDNF (Dincheva et al., 2016). The Met allele blocks the processing and activity dependent release of proBDNF and has been linked to cognitive deficits and decreased hippocampal volume, although a meta-analysis demonstrates that the effect size on hippocampal volume is smaller than originally reported (Molendijk et al., 2012; Edelmann et al., 2014; Mizui et al., 2016; Castren & Kojima, 2017). Activity dependent release of BDNF is required for long-term, protein synthesis dependent synaptic potentiation, and studies of the Met allele provide further evidence for BDNF release (Edelmann et al., 2014; Mizui et al., 2016). The Met allele is associated with reduced executive function and increased vulnerability to depression in patients exposed to early life stress (Kaufman et al., 2006; Kim et al., 2007; Gatt et al., 2009; Frodl & O'Keane, 2013). Met carriers also display increased anxiety symptoms, and PTSD patients who are Met carriers are less responsive to cognitive behavioral therapies (Dincheva et al., 2016). Together these studies indicate that carriers of the Met allele may have synaptic deficits in the hippocampus and PFC that contribute to decreased neuroplasticity and result in reduced coping mechanisms.

Role of BDNF in stress and depression

The impact of BDNF on synapse formation and synaptic plasticity, as well as neuronal survival and function led to studies of BDNF in the atrophy of neurons caused by chronic stress exposure. Chronic stress exposure causes atrophy of hippocampal CA3 pyramidal neurons as well as PFC layer 2/3 and layer 5 pyramidal neurons (Liu & Aghajanian, 2008; Popoli et al., 2011; McEwen et al., 2012; Morrison & Baxter, 2012). Early studies reported that exposure to different types of chronic stress, including unpredictable and social defeat also decreased the expression of BDNF in the hippocampus and PFC (Smith, 1995a; Duman & Monteggia, 2006; Krishnan & Nestler, 2008; 2010). In addition, BDNF expression is regulated by repeated administration of adrenal glucocorticoids (Adachi et al., 2014) and also undergoes regulation by estrogen and progesterone (Bath et al., 2013). In contrast, there is evidence that that contract stress increases BDNF expression and signaling in other brain regions, notably the nucleus accumbens and amygdala where increased function could contribute to synaptic plasticity that underlies depressive symptoms (Krishnan & Nestler, 2008; Roozendaal et al., 2009; Krishnan & Nestler, 2010). There has also been interest in

epigenetic alterations that could underlie long-lasting changes in BDNF expression (Krishnan & Nestler, 2010; Sun et al., 2013).

Studies of BDNF deletion mutant mice, either constitutive or conditional forebrain deletion mutants, do not show clear depressive-like phenotypes, as would be expected if BDNF was required for normal emotional behaviors (Duman & Monteggia, 2006; Autry & Monteggia, 2012). In addition, mice with a knock-in of the BDNF Val66Met polymorphism, which decreases the transport of BDNF transcripts to dendrite compartments, do not display overt depressive or anxiety like behaviors (Chen et al., 2006). Interesting, these mice display a reduction of dendrite length and branching, and decreased hippocampus spine-synapse number and function in the hippocampus and/or PFC (Chen et al., 2006; Liu et al., 2012). The lack of effect of global or forebrain BDNF deletion or Met knockin could be due to opposing effects of BDNF in different brain regions (i.e., PFC and hippocampus vs. depressive effects in mesolimbic dopamine system). In support of this possibility, selective knockdown of BDNF in the hippocampus is reported to be sufficient to cause depressive behaviors (Taliaz et al., 2010). Another possibility is that current rodent models have limited validity for studies of depression and are insensitive to relevant behavioral phenotypes in rodents.

The impact and relevance of these preclinical studies is supported by postmortem studies demonstrating that levels of BDNF are decreased in the cerebral cortex of depressed, as well as suicide subjects (Duman & Monteggia, 2006; Dwivedi, 2009; Duman et al., 2016). Levels of TrkB and signaling pathways downstream of BDNF-TrkB (e.g., ERK and Akt) are also decreased in suicide subjects (Castren & Kojima, 2017). There is also evidence that levels of p75NTR are increased in the PFC of suicide subjects, which could contribute to neuronal atrophy (Castren & Kojima, 2017). In addition, levels of MAP kinase phosphatase 1, a negative regulator of TrkB-ERK signaling, are increased by stress and in depressed subjects, and viral mediated expression of MAP kinase phosphatase 1 in hippocampus is sufficient to cause depressive behaviors (Duric et al., 2010). These studies are consistent with the possibility that decreased BDNF-TrkB signaling contributes to reduced volume of PFC and hippocampus in depressed patients (Drevets et al., 2008; MacQueen & Frodl, 2011), as well as synaptic loss in humans (Kang et al., 2012).

Role of BDNF in response to typical antidepressants

As studies were being carried out to test the effects of stress and depression, others were beginning to examine the role of BDNF in the actions of antidepressant treatments. This research found that in contrast to stress, administration of antidepressant drugs increased the expression of BDNF in the hippocampus and PFC (Nibuya et al., 1995; Nibuya et al., 1996; Duman & Monteggia, 2006; Castren & Kojima, 2017). The up-regulation of BDNF was observed after chronic, but not acute antidepressant administration, consistent with the time course for the therapeutic actions of these agents (Duman & Monteggia, 2006; Bjorkholm & Monteggia, 2016; Castren & Kojima, 2017). Increased expression of BDNF was observed with different classes of antidepressants, including 5-HT and norepinephrine selective reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors, as well as electroconvulsive seizure (ECS). Only administration of ECS, which causes neuronal

depolarization rapidly increased BDNF expression in the hippocampus and PFC (Nibuya et al., 1995). A role for BDNF in antidepressant induced synaptic plasticity is supported by studies demonstrating that chronic fluoxetine administration reinstates ocular dominance plasticity in the visual cortex and extinction learning in adult mice and that these effects require BDNF (Maya Vetencourt et al., 2008; Karpova et al., 2011).

The functional impact of increased BDNF expression was further examined using a number of different approaches. Infusion of BDNF into the hippocampus or PFC is sufficient to produce an antidepressant response, even after a single administration (Shirayama, 2002; Duman & Monteggia, 2006; Deyama et al., 2019a). However, as discussed above BDNF produces a depressive phenotype when infused into the mesolimbic dopamine system (Krishnan & Nestler, 2008). The role of BDNF in the actions of typical antidepressants has also been tested in BDNF mutant mice. These studies demonstrate that constitutive heterozygous deletion (homozygous deletion is lethal) or conditional forebrain deletion of BDNF blocks the antidepressant actions of typical antidepressant treatments (Duman & Monteggia, 2006; Bjorkholm & Monteggia, 2016; Castren & Kojima, 2017). In addition, mice with a knockin of the BDNF Met allele are nonresponsive to typical antidepressants such as fluoxetine (Chen et al., 2006; Dincheva et al., 2016).

Together the BDNF infusion and deletion studies demonstrate that BDNF is sufficient and necessary for the behavioral actions of typical antidepressant treatments. The delay in up-regulation of BDNF as well as the therapeutic actions of antidepressants also supports a role for BDNF in depression. The mechanisms underlying the delayed increase in BDNF are not clear but could be due to the delayed increase in intracellular signaling pathways that influence BDNF expression (Duman & Monteggia, 2006; Krishnan & Nestler, 2010; Castren & Kojima, 2017).

Role of BDNF in the response to rapid acting antidepressants

Studies of BDNF in the in the treatment of depression have been extended to rapid acting antidepressants. Initial studies reported that levels of BDNF were rapidly increased in the hippocampus after a single dose of ketamine, in contrast to the requirement for chronic administration of a typical monoaminergic antidepressant (Autry et al., 2011). Another study by this group replicated this effect and further reported that memantine, a structurally different NMDAR antagonist that does not produce rapid antidepressant therapeutic effects, does not increase BDNF levels (Gideons et al., 2014). Ketamine also increases the phosphorylated and activated form of TrkB (Kohtala et al., 2019), and racemate ketamine as well as both the (R)- and (S)-stereoisomers of ketamine reverse the deficit in BDNF and pTrkB in PFC and/or hippocampus of rodents exposed to social defeat stress or chronic unpredictable stress (Yang et al., 2015; Zhang et al., 2015; Liu et al., 2016; Sun et al., 2016). Moreover, the rapid antidepressant behavioral actions of ketamine are blocked in inducible BDNF deletion mutant mice (Autry et al., 2011). Further evidence for a role of BDNF in the actions of ketamine were provided by studies in mice with a knockin of the BDNF Val66Met polymorphism, the human variant that blocks the processing and activity dependent release of BDNF (Figure 1) (Dincheva et al., 2016). These studies demonstrate that the antidepressant behavioral actions of ketamine, as well as the increase in number and

function of synapses in the mPFC, are blocked in BDNF Met mice (Liu et al., 2012). These results suggest that the rapid synaptic and behavioral actions of ketamine require activity dependent release of BDNF, not just increased expression (Duman et al., 2016; Duman et al., 2019) (Figure 2).

To further test this hypothesis, studies were conducted to block the actions of extracellular BDNF by infusing a function blocking anti-BDNF antibody directly into the mPFC. Previous studies have demonstrated that the mPFC is necessary and sufficient for the actions of ketamine, providing the rationale for targeting this brain region (Fuchikami et al., 2015). The results demonstrate that infusion of an anti-BDNF antibody into the mPFC completely blocks the rapid antidepressant actions of a single dose of ketamine in several behavioral models (Lepack et al., 2014). Studies were also conducted to directly measure the release of BDNF, although this is problematic as in vivo microdialysis of large proteins such as BDNF are technically difficult. To address this issue we turned to primary cell cultures studies, and found that low concentrations of ketamine increase the release of BDNF into the culture media (Lepack et al., 2014; Lepack et al., 2016)(see below for further discussion of primary culture studies). Together these studies demonstrate that ketamine causes activity dependent release of BDNF and that extracellular BDNF is required for the rapid synaptic and antidepressant behavioral actions of ketamine. This differs from typical monoaminergic agents that slowly increase the expression of BDNF, but not the release of BDNF (Figure 2).

The role of BDNF release in the rapid therapeutic actions of ketamine in depressed patients is more difficult to address as it is currently not possible to measure BDNF in the brains of patients. There is a report that ketamine increases levels of BDNF in the blood of depressed patients and that levels are correlated with treatment response (Laje et al., 2012). Another approach is to examine patients carrying the BDNF Val66Met polymorphism as we would predict that Met carriers would have a decreased response to ketamine. An early study comprised primarily of Caucasian patients reported that BDNF Met carriers displayed a fifty percent reduction in their response to ketamine (Laje et al., 2012). Most of these patients were heterozygous Met carriers due to the relatively low prevalence of homozygous carriers in Caucasians. A more recent study in a Chinese population reported no effect of the BDNF Met allele on the response to ketamine (Su et al., 2017), although reanalysis of this data found that the BDNF Met allele is associated with a reduction in the sensitivity of the anti-suicidal actions of ketamine (i.e., 0.5 but not 0.2 mg/kg ketamine is effective) (Chen et al., 2019). These studies suggest a difference in the function of the BDNF Met allele depending on race, an/or that other polymorphisms interact in a race dependent manner to influence the ketamine response.

Role of BDNF in the actions of other rapid acting agents

Scopolamine: Acetylcholine Muscarinic Receptor Antagonist—Identification of other rapid acting antidepressants has been a major focus of the field to address the side effect profile of ketamine. Early studies of the acetylcholine muscarinic receptor antagonist scopolamine also demonstrate rapid antidepressant actions after a single dose (Furey & Drevets, 2006; Drevets & Furey, 2010), although a recent study reports that scopolamine is less effective for severe, treatment resistant depression (Park et al., 2019). Rodent studies

demonstrate that scopolamine has effects that are convergent with ketamine, including increased mTORC1 signaling, and increased number and function of synapses in the mPFC (Voleti et al., 2013). In addition, the rapid antidepressant behavioral actions of scopolamine are blocked in BDNF Met knockin mice and by infusion of an anti-BDNF neutralizing antibody into the mPFC (Ghosal et al., 2018). These findings indicate that the actions of scopolamine, like ketamine, require activity dependent release of BDNF into the mPFC (Ghosal et al., 2018) (Figure 2).

Rapastinel: NMDA receptor positive allosteric modulator—Another rapid acting agent is rapastinel, an NMDAR positive allosteric modulator (Burgdorf et al., 2013; Burgdorf et al., 2015). Phase 2 clinical trials reported that a single dose of rapastinel produces rapid antidepressant actions (Preskorn et al., 2008), although this has not held up in larger phase 3 clinical trials possibly due to the dosing schedule. In rodent studies rapastinel produces rapid antidepressant behavioral actions, increases mTORC1 signaling, and increases synaptic number and function in the mPFC (Burgdorf et al., 2013; Burgdorf et al., 2015; Liu et al., 2016; Kato et al., 2018). Moreover, the rapid synaptic and antidepressant behavioral actions of rapastinel are blocked in BDNF Met mice and by infusion of an anti-BDNF neutralizing antibody into the mPFC (Kato et al., 2018). This study also shows that rapastinel or ketamine increase the phosphorylated and activated form of TrkB in the mPFC and that infusion of a TrkB antagonist into the mPFC blocks the rapid antidepressant actions of rapastinel (Kato et al., 2018). Finally, the results show that infusion of an inhibitor of the Rho GTPase Rac1, which contributes to BDNF mediated synaptic plasticity (Harward et al., 2016; Hedrick et al., 2016) blocks the antidepressant actions of rapastinel (Kato et al., 2018). Another study of social defeat stress has reported that rapastinel does not reverse the BDNF and pTrkB deficits in this model of stress (Yang et al., 2016).

(2R,6R)-hydroxynorketamine (HNK): ketamine metabolite with an unidentified binding site—Due in part to the long-lasting actions of ketamine there have also been studies of metabolites that could be responsible for its long-lasting, sustained effects. One of particular interest is (*2R,6R*)-HNK. Gould and colleagues have reported that a single dose of (*2R,6R*)-HNK produces rapid antidepressant behavioral actions and increases levels of BDNF in the hippocampus (Zanos et al., 2016). Importantly, (*2R,6R*)-HNK has very low affinity for the NMDAR channel and does not have the side effect profile of ketamine in rodent models (Zanos et al., 2016; Lumsden et al., 2019), although there is evidence that high concentrations of (*2R,6R*)-HNK produce effects similar to ketamine in hippocampal slices (Suzuki et al., 2017). Rather (*2R,6R*)-HNK is thought to act via an mGlu2 receptor-like presynaptic mechanism to increase glutamate release (Riggs et al., 2019; Zanos et al., 2019). Regardless of the initial target the induction of BDNF indicates that the actions of (*2R,6R*)-HNK converge with the downstream effects of ketamine. This possibility is supported by evidence that the actions of (*2R,6R*)-HNK are blocked in BDNF Met mice and by infusion of an anti-BDNF neutralizing antibody into the mPFC (Fukumoto et al., 2019). There have also been preliminary studies of another metabolite, (S)-norketamine reporting that it reverses the deficits of BDNF and phosphor-TrkB in a social defeat model, and that infusion of a TrkB antagonist (ANA-12) blocks the antidepressant actions of (S)-norketamine (Yang et al., 2018).

Metabotropic GluR2/3 receptor antagonists—Studies of glutamatergic agents have been extended to mGluR2/3 receptor antagonists, as blockade of mGluR2/3 autoreceptors represents another approach to increase glutamate transmission. Several studies have reported that mGluR2/3 receptor antagonists, including LY341495 and MGS0039 produce rapid antidepressant actions in rodent models (Koike et al., 2011b; a; Dwyer et al., 2012; Witkin et al., 2016; Chaki, 2017). Moreover, MGS0039 reverses the deficit in BDNF and pTrkB levels in the PFC of mice exposed to social defeat stress (Dong et al., 2017). The antidepressant actions of LY341495 are blocked by pretreatment with the nonselective Trk receptor antagonist K252a (Koike et al., 2013), and another study has reported that enhancement of the antidepressant actions of ketamine by LY341495 are blocked by a selective TrkB antagonist ANA-12 (Palucha-Poniewiera et al., 2019). Primary neuronal culture studies also demonstrate that LY341495 increases the release of BDNF (Lepack et al., 2016). Further studies are needed to determine if the antidepressant actions of mGluR2 antagonists require BDNF release in the mPFC but the evidence to date is consistent with this hypothesis.

Other rapid acting agents—There has also been interest in other classes of anesthetics, including isoflurane and nitrous oxide and these agents are reported to produce rapid antidepressant actions similar to ketamine phosphor-TrkB (Antila et al., 2017; Kohtala et al., 2019). Moreover, these effects are associated with increased levels of the phosphorylated and activated form of TrkB. Further studies are needed to test the role of BDNF release in the antidepressant actions of gaseous anesthetics.

Evidence that rapid acting antidepressants increase BDNF release

Primary neuronal culture systems have been used to directly test the effects of ketamine and other rapid acting agents on the release of BDNF. Primary cerebral cortical neurons from embryonic rat brains (E18) differentiate into neurons, both glutamate and GABA, as well as glia, and form an organized system comprised of mature soma, axons, dendrites and dendritic spines (Lepack et al., 2016; Ghosal et al., 2018). Because levels of BDNF release are low and/or because BDNF binds to both TrkB and p75NTR, an immunoprecipitation step is needed to enrich BDNF for detection by ELISA (Lepack et al., 2014; Lepack et al., 2016). We have found that incubation of primary cortical cultures with several different types of rapid-acting antidepressants, including ketamine, scopolamine, rapastinel, (*2R,6R*)-HNK and LY341495, but not classical monoaminergic drugs, rapidly (15 to 60 min) increase BDNF release (Lepack et al., 2014; Lepack et al., 2016; Ghosal et al., 2018; Kato et al., 2018; Fukumoto et al., 2019). These effects are observed at low, submicromolar or nanomolar concentrations and are completely abolished by pre-incubation with an AMPAR antagonist, or muscimol, a $GABA_A$ receptor agonist and neuronal silencing agent, indicating that the release of BDNF is activity dependent (Lepack et al., 2016; Ghosal et al., 2018). In addition, BDNF release in response to ketamine, (*2R,6R*)-HNK, rapastinel and scopolamine is blocked by verapamil, an L-type VDCCs blocker, providing further evidence for a requirement of activity-dependent AMPAR- and VDDCs-mediated neuronal depolarization (Lepack et al., 2014; Ghosal et al., 2018; Kato et al., 2018; Fukumoto et al., 2019)

Recently, *d*-methadone, the *d*-isomer of methadone that acts as an NMDA receptor antagonist, was also shown to activate the mTORC1 pathway and increase BDNF release in primary cortical cultures (Fogaca et al., 2019). Methadone is best known for treatment of opiate abuse disorder, based on the activity of *l*-methadone at opiate receptors (Gorman et al., 1997). However, *d*-methadone has relatively low affinity for opiate receptor subtypes compared to *l*-methadone (Callahan et al., 2004), and early studies show that *d*-methadone produces antidepressant behavioral actions in the FST (Hanania et al., 2019) as well as several other behavioral paradigms and in the chronic unpredictable stress model (Fogaca et al., 2019). Early clinical studies have supported the possibility that *d*-methadone could be used for the treatment of depression, with fewer side effects compared to ketamine (Bernstein et al., 2019).

Taken together, the in vitro and in vivo results demonstrate that rapid-acting antidepressants stimulate BDNF release through activation of AMPAR and VDCCs, resulting in activation of mTORC1 signaling, increased levels of synaptic proteins, and increased synaptic number and function (Lepack et al., 2014; Lepack et al., 2016; Ghosal et al., 2018). These findings indicate that fast, activity-dependent BDNF release is a critical factor that distinguishes rapid-acting antidepressants from monoaminergic drugs, which induce a delayed increase in BDNF expression, but for which there is no direct evidence for BDNF release (Martinez-Turrillas et al., 2005; Seo et al., 2014; Lepack et al., 2016; Harmer et al., 2017). Typical monoaminergic antidepressants are reported to rapidly increase the phosphorylation of TrkB, which has been used as a surogate marker for increased BDNF activity (Saarelainen et al., 2003). However, recent studies demonstrate that these monoaminergic antidepressants rapidly activate TrkB receptors via interactions with other regulatory sites on the receptor, including the endocytic adaptor complex AP-2 (Fred et al., 2019) and a cholesterol regulatory site (Casarotto et al., 2019) that are independent of BDNF release. Importantly, the rapid effects of monoaminergic antidepressants on TrkB do not correspond with the time lag for the therapeutic response to these agents, and there is no direct evidence that these agents produce activity dependent synaptic effects. Further studies are needed to examine this issue, notably the ability of typical antidepressants to produce rapid, activity dependent BDNF release and synaptic plasticity.

Role of VEGF in the actions of ketamine

There has also been interest in other growth factors in the pathophysiology and treatment of depression, and here we discuss the role of VEGF, a pleiotrophic growth factor expressed by neurons, astrocytes and perivascular macrophages, as well as endothelial cells, in the brain (Greene et al., 2009; Jais et al., 2016). Several splice variants of VEGF are generated by alternative splicing, and $VEGF_{120}$ and $VEGF_{164}$ are the most abundant (about 20% and 75%, respectively) in adult mouse brain (Ng et al., 2001). Both $VEGF_{120}$ and $VEGF_{164}$ bind to high-affinity tyrosine kinase receptors, Flt-1 (VEGFR1) and Flk-1 (VEGFR2), but only $VEGF_{164}$ binds to the co-receptors, neuropilin-1 and −2 (Neufeld et al., 1999). VEGF has not only angiogenic but also potent neurotrophic and neuroprotective activity mainly through binding to Flk-1 (Rosenstein et al., 2003; Rosenstein et al., 2010).

Recent clinical studies demonstrate that VEGF levels are decreased in the cerebrospinal fluid of patients who have attempted suicide (Isung et al., 2012) and patients with at least one severe treatment-resistant depressive episode (Kranaster et al., 2019). Stress exposure is also reported to decrease VEGF in rodent models (Nowacka & Obuchowicz, 2013). In addition, viral-mediated non-cell type-specific VEGF knockdown in the hippocampal dentate gyrus is reported to produce depression-like behaviors in the forced swim test and novelty-suppressed feeding test, which were partially blocked by ketamine (Choi et al., 2016). A role for VEGF in the actions of antidepressant was first provided by evidence that chronic, but not acute, administration of a typical monoaminergic antidepressant increases VEGF expression in the hippocampus and PFC, and that the antidepressant effects of these drugs are blocked by infusion of a selective Flk-1 inhibitor (Warner-Schmidt & Duman, 2007; Greene et al., 2009).

Recently, we have demonstrated that neuronal VEGF-Flk-1 signaling plays a key role in the rapid antidepressant actions of ketamine (Deyama et al., 2019b). For these studies we generated mice with excitatory neuron-specific deletion of VEGF (CaMKIIα-Cre;VEGF$^{flox/flox}$, hereafter, VEGF$^{NEURON-/-}$) or Flk-1 (CaMKIIα-Cre;Flk-1$^{flox/flox}$, hereafter, Flk-1$^{NEURON-/-}$) in the forebrain. Similar to BDNF mutant mice (Duman et al., 2007; Advani et al., 2009; Yu et al., 2012), both VEGF$^{NEURON-/-}$ and Flk-1$^{NEURON-/-}$ mice did not show depression-like behaviors, indicating that loss of neuronal VEGF-Flk-1 signaling is not sufficient to produce a depression-like state under non-stressed conditions. However, the antidepressant behavioral effects of ketamine are blocked in VEGF$^{NEURON-/-}$ and Flk-1$^{NEURON-/-}$ mice. In addition, infusion of an anti-VEGF neutralizing antibody, which could bind and sequester extracellular VEGF, into the mPFC 30 min before ketamine administration also blocks the antidepressant actions of ketamine. In contrast, intra-mPFC infusion of the same antibody 2 hours after ketamine does not block the behavioral effects of ketamine. Further evidence for a role of VEGF in the mPFC is provided by studies demonstrating that infusion of recombinant VEGF$_{164}$ into the mPFC produces ketamine-like rapid and sustained antidepressant effects via neuronal Flk-1 (Deyama et al., 2019b). Moreover, viral-mediated knockdown of Flk-1 selectively in mPFC excitatory neurons blocks the antidepressant behavioral actions of ketamine. Together, these findings indicate that ketamine rapidly and transiently increases VEGF release in the mPFC and that neuronal VEGF-Flk-1 signaling during the initial 2-hour period is necessary and sufficient for the rapid antidepressant actions of ketamine.

In addition to these behavioral actions, neuronal VEGF-Flk-1 signaling is necessary for the ketamine-induced increase in dendritic complexity of primary cortical neurons and the number of spine synapses in layer V mPFC pyramidal neurons, as these effects are blocked by an Flk-1 inhibitor and in VEGF$^{NEURON-/-}$ mice, respectively (Deyama et al., 2019b). Together, these findings indicate that neuronal VEGF-Flk-1 signaling, as well as BDNF signaling (Liu et al., 2012; Lepack et al., 2014), plays an essential role in the neurotrophic/synaptogenic effects of ketamine.

Since both BDNF and VEGF signaling are reported to mediate the neurotrophic and behavioral actions of ketamine, we have examined whether BDNF and VEGF act in series or parallel (Deyama et al., 2019a). Intra-mPFC infusion of recombinant BDNF produces

ketamine-like antidepressant effects, and these effects are blocked by co-infusion of a VEGF neutralizing antibody or in $VEGF^{NEURON-/-}$ mice, indicating a requirement for excitatory neuron-derived extracellular VEGF. In primary cortical neurons, BDNF-TrkB signaling stimulates VEGF release (Deyama et al., 2019a), consistent with a previous study in a neuroblastoma cell line (Nakamura et al., 2006). The neurotrophic effects of BDNF on dendritic complexity also require VEGF-Flk-1 signaling in primary cortical neurons. The antidepressant actions of intra-mPFC $VEGF_{164}$ infusion are also blocked by coinfusion of BDNF neutralizing antibody. Moreover, VEGF stimulates BDNF release and requires BDNF-TrkB signaling to produce neurotrophic effects on dendritic complexity in primary cortical neurons. Together, these findings highlight an important role for interplay between BDNF and VEGF in the rapid synaptic and antidepressant behavioral actions of ketamine. Future studies of co-localization and release of BDNF and VEGF could provide further evidence for the mechanisms underlying this interplay.

Future directions

Together, these findings highlight the complex role of BDNF, as well as VEGF in the actions of different classes of antidepressant treatments. This includes typical monoaminergic agents that increase BDNF expression, as well as fast acting antidepressants like ketamine that cause rapid, activity dependent release of BDNF and VEGF. Increased expression and release of these factors reverses the deficits caused by stress and depression and provides neurotrophic support that reverses the atrophy and synaptic loss that contribute to the pathophysiology of depression. These findings also underscore the possibility of targeting BDNF and VEGF for the treatment of depression. This could include behavioral therapies to enhance activity dependent increases in BDNF and VEGF expression in brain regions implicated in depression, as well as the well-known effects of exercise on BDNF expression (Intlekofer & Cotman, 2013; Marosi & Mattson, 2014). In addition, it may be possible to develop novel therapeutic drugs that increase BDNF and VEGF expression and/or release, but with fewer side effects than ketamine. Another approach would be to develop small molecular therapeutics that target the TrkB as well as Flk-1 receptors, although this approach has been difficult to date.

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Abbreviations

BDNF	brain derived neurotrophic factor
TrkB	tropomysin receptor kinase B
p75NTR	p75 neurotrophin receptor
VEGF	vascular endothelial growth factor
Flt-1	VEGF receptor 1
Flk-1	VEGF receptor 2

NGF	nerve growth factor
NMDA	N-methyl-D-aspartate
NMDAR	NMDA receptor
PFC	prefrontal cortex
mPFC	medial prefrontal cortex
PTSD	posttraumatic stress disorder
ECS	electroconvulsive seizure
ERK	extracellular signal regulated kinase
Akt	serine threonine kinase
MAP kinase	mitogen activated protein kinase
mTORC1	mechanistic target of rapamycin complex 1
(*2R,6R*)-HNK	(*2R,6R*)-hydroxynorketamine
mGlu2/3	metabotropic glutamate 2/3 receptor
MGS0039	mGlu2/3 receptor antagonist
LY341495	mGlu2/3 receptor antagonist
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
VDCC	voltage dependent calcium channel

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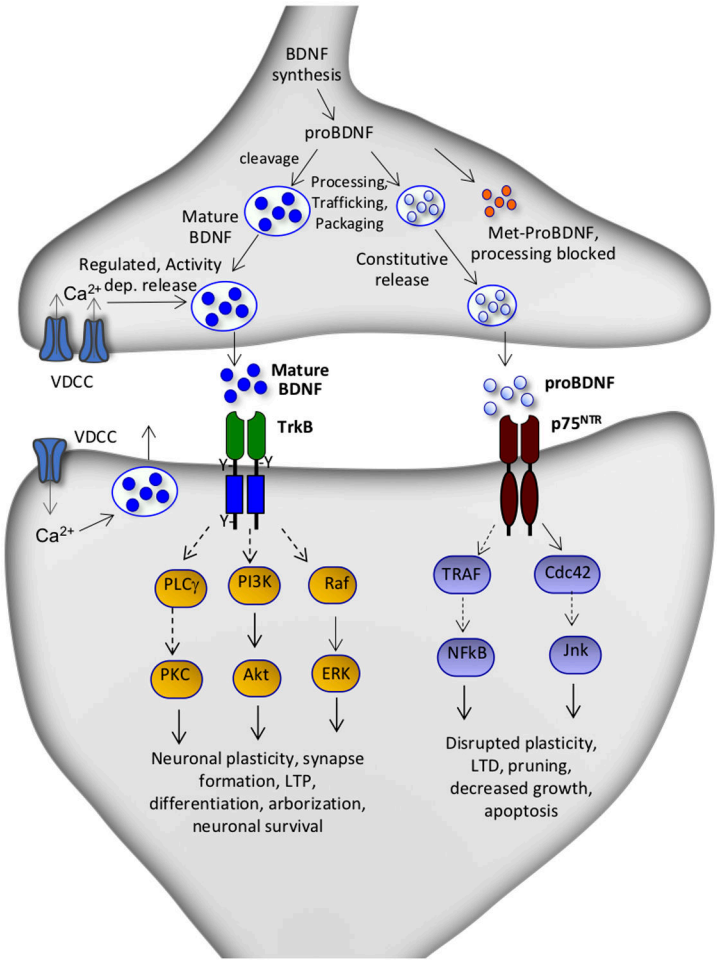

Figure 1. Processing of BDNF and receptor coupled signaling pathways.

BDNF gene expression is controlled by multiple signaling pathways included neuronal activity. BDNF transcripts can be translated in the soma or transported to other cellular compartments, notably dendrite as well as axon terminals. The transcripts are translated to pre-proBDNF which undergoes processing and cleavage to proBDNF, which is further processed by to mature BDNF. Mature BDNF is associated with synaptic plasticity and undergoes activity dependent release, while proBDNF undergoes low levels of constitutive released. The BDNF prodomain contains a common single nucleotide polymorphism, BDNF Val66Met. The Met allele impairs the trafficking and processing of proBDNF and therefore reduces activity dependent release of mature BDNF. Mature BDNF binds to the TrkB and activates downstream signaling pathways associated with synaptic plasticity, synapse formation, neuronal differentiation and survival. The proBDNF isoform binds to the p75 neurotrophin receptor (p75NTR) and activates a different set of downstream signaling pathways that are linked with disruption of synaptic plasticity, long-term depression, synaptic pruning, decreased growth and apoptosis.

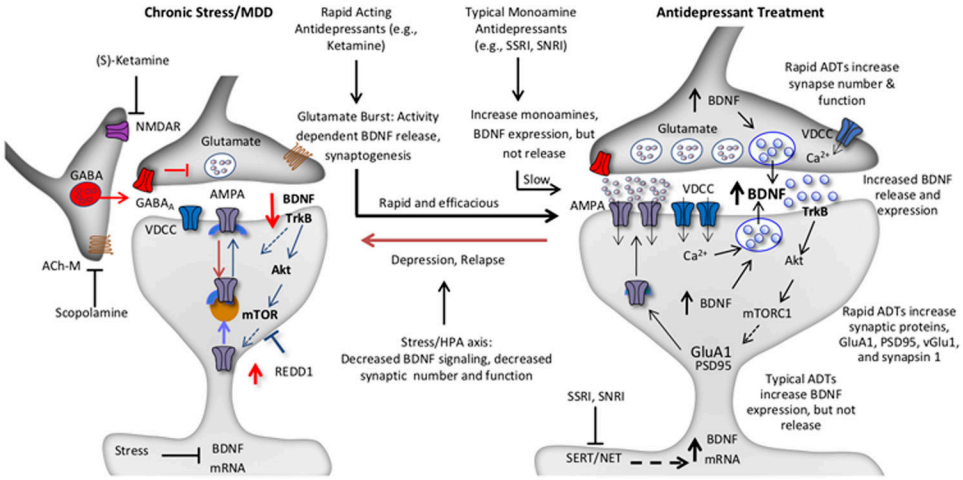

Figure 2. Model for the loss of spine synapses in stress and depression: rapid reversal by ketamine and comparison with typical monoamine reuptake inhibitor antidepressants.

Synaptic number and function in the PFC and hippocampus are maintained by homeostatic mechanisms, and proper control of synaptic connectivity in these regions is required for control of mood as well as other cortical functions. This includes activity dependent regulation of synaptic proteins, such as GluA1, PSD95, and synapsin 1. Chronic stress exposure (left) decreases the number and function of spine synapses in the PFC and hippocampus, in part via decreased BDNF expression, and decreased TrkB-mTORC1 signaling. Increased expression of a negative regulator of mTORC1 signaling, regulated in DNA damage and repair (REDD1) contributes to this effect. Antidepressant treatment (right) increases BDNF and reverses the effects of stress and depression. The NMDA receptor antagonist ketamine causes a rapid burst of glutamate that causes activity dependent release of BDNF resulting in rapid induction of synapse number and function via stimulation of TrkB-mTORC1 signaling and increased translation of synaptic proteins including GluA1. In contrast, typical antidepressants including the monoamine reuptake inhibitors (e.g., SSRI, SNRI) produce a slow induction of BDNF expression and constitutive release over several weeks of treatment, which contributes to slow adaptive changes that reverse the effects of stress and produce antidepressant responses. There is no evidence that typical antidepressants cause activity dependent release of BDNF, which is necessary for the rapid antidepressant actions of ketamine. Depression as well as relapse that occurs after 7 to 10 days in patients treated with ketamine could result from environmental factors such as sustained or uncontrollable stress or other susceptibility factors that decrease the stability of new synaptic connections.