Brain-derived neurotrophic factor in mood disorders and antidepressant treatments

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Abstract

Levels of brain-derived neurotrophic factor (BDNF) are reduced in the brain and serum of depressed patients and at least the reduction in serum levels is reversible upon successful treatment. These data, together with a wealth of reports using different animal models with depression-like behavior or manipulation of expression of BDNF or its receptor TrkB have implicated BDNF in the pathophysiology of depression as well as in the mechanism of action of antidepressant treatments. Recent findings have shown that posttranslational processing of BDNF gene product can yield different molecular entities that differently influence signaling through BNDF receptor TrkB and the pan-neurotrophin receptor $p75_{NTR}$. We will here review these data and discuss new insights into the possible pathophysiological roles of those new BDNF subtypes as well as recent findings on the role of BDNF mediated neuronal plasticity in mood disorders and their treatments.

Introduction

Mood disorders are among the leading causes of suffering world-wide (Collins et al., 2011; Murray et al., 2012) and they are particularly prevalent in Western societies (Wittchen et al., 2011). Traditionally, mood disorders are treated by either drugs or psychotherapy or by their combination, but many patients for not benefit from any of these treatment options (Insel and Wang, 2009). During the last decades, insufficient signaling by neurotrophic factors has been recognized as a potential underlying factor for depression and promotion of neurotrophin signaling have been linked with antidepressant responses (Duman et al., 1997; Martinowich et al., 2007; Castrén and Rantamäki, 2010a; Castrén and Rantamäki, 2010b; Autry and Monteggia, 2012).

Neurotrophins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4), act by binding to their cognate tyrosine kinase receptors (NGF to TrkA, BDNF and NT-4 to TrkB, NT-3 to TrkC) as well as to a common low-affinity neurotrophin receptor ($p75_{NTR}$) (Bothwell, 2014). Since the vast majority of the literature linking neurotrophins to mood disorders deals with BDNF, other neurotrophins showing only very minor role (Castrén, 2014), we will here focus on the role of BDNF and its receptors. It should be noted, however, that the role for BDNF is by no means restricted to depression; it has also been implicated in anxiety and schizophrenia, as well as in neurodegenerative disorders (Lu et al., 2013; Castrén, 2014).

BDNF, like other neurotrophins, is synthetized as a precursor protein (pro-BDNF) that is proteolytically processed into a mature BDNF (mBDNF) by intracellular and/or extracellular proteases (Seidah et al., 1996), most prominently by the proprotein convertase PC7 (Wetsel et al., 2013), but also extracellularly by metalloproteinases and plasmin (Deinhardt and Chao, 2014b). Lee et al. (2001) initially reported that precursor NGF (proNGF) promoted neuronal death while mature form of NGF enhanced neuronal survival (Lee et al., 2001). It was further shown that proBDNF promoted cell death, growth cone retraction, spine shrinkage and long-term depression (LTD), whereas mBDNF promoted spine formation, neuronal survival, and LTP (Teng et al., 2005; Woo et al., 2005; Zagrebelsky et al., 2005; Koshimizu et al., 2009; Deinhardt et al., 2011).

Pro-forms of neurotrophins preferentially bind to the $p75_{NTR}$ whereas mature neurotrophins show higher affinity towards Trk receptors (Lee et al., 2001; Lu et al.,

2005; Hempstead, 2014). Remarkably, the activation of Trk and p75NTR show very different, in many cases opposite effects: Trk receptors enhance neuronal survival, synaptogenesis and plasticity, whereas activation of p75NTR promotes cell death and synaptic pruning (Lu et al., 2005; Deinhardt and Chao, 2014a; Kraemer et al., 2014). The biological actions of proNGF and proBDNF require the activation of a receptor complex consisting of p75NTR and sortilin (sortilin-related VPS10 domain-containing receptor) to initiate cell death (Nykjaer et al., 2004; Teng et al., 2005; Deinhardt et al., 2011). Furthermore, Pang et al. (2004) showed that the extracellular conversion from proBDNF into BDNF occurred as a cellular mechanism determining BDNF-dependent LTD (Pang et al., 2004). Woo et al (2005) further showed that proBDNF facilitates hippocampal LTD by the activation of p75NTR (Woo et al., 2005). These findings suggest that (1) precursor and mature BDNF subtypes exert opposing biological functions and (2) a post-translational control, processing of proBDNF could be a key mechanism for altering the biological action of BDNF.

Given a dramatic alteration of the BDNF action by adding the pro-domain, the pro-region may have more potential functions. It was previously shown that the BDNF pro-domain assists in the folding of BDNF (Kolbeck et al., 1994). Recently, it was demonstrated that a BDNF polymorphism Val66Met, which substitutes a valine to a methionine at codon 66 in the pro-region of human BDNF, affects human memory function as well as secretion mechanism of BDNF protein (Egan et al., 2003). Thus, these findings suggest that the BDNF pro-domain is more functional region.

Indeed, several recent reports indicated that the BDNF pro-domain is endogenously present and acts as a ligand. Dieni et al. (2012) reported that BDNF and its pro-peptide both stained large dense core vesicles in excitatory presynaptic terminals of the adult mouse hippocampus (Dieni et al., 2012). Second, Mizui et al. (2015) showed that the BDNF pro-peptide is a new synaptic modulator in the central nervous system: the BDNF pro-peptide allow facilitation of hippocampal LTD (Mizui et al., 2015). To understand the molecular and cellular mechanism, Lee's laboratory generated a transgenic mouse line with the Val66Met mutation and showed that this polymorphism alters anxiety-related behavior (Chen et al., 2006). They further reported that mice with the Val66Met mutation are defective in NMDAR-dependent plasticity in the hippocampus (Ninan et al., 2010). Recently, Mizui et al. (2015) demonstrated that treatment of hippocampal slices with the BDNF pro-peptide with the Met mutation completely inhibited LTD (Mizui et al., 2015). Anastasia et al. (2013) showed that application of the BDNF pro-peptide with the Met mutation

induces acute growth cone retraction and a decrease in Rac activity in hippocampal neurons (Anastasia et al., 2013).

Given these distinct and multiple biological actions of proBDNF and its pro-peptide, a post-translational mechanism of BDNF, proteolytic cleavage of proBDNF and a BDNF polymorphism Val66Met could be new mechanisms for the development of brain diseases.

BDNF in depressed patients

BDNF levels have been found to be reduced in the postmortem samples of brains of depressed patients (Dunham et al., 2009; Thompson Ray et al., 2011; Guilloux et al., 2012; Tripp et al., 2012). Furthermore, BDNF levels are also reduced in the brains of suicide victims, many of which suffer from severe depression (Chen et al., 2001; Dwivedi et al., 2003; Dwivedi et al., 2009). In addition to BDNF, levels of its receptor TrkB have also been reported to be downregulated in the brains of depressed patients (Tripp et al., 2012) and the levels of active, phosphorylated form of TrkB are reduced in suicide victims (Dwivedi et al., 2003), indicating reduced BDNF signaling through TrkB in depression. Conversely, increased levels of mRNA for the $p75^{NTR}$ neurotrophin receptor have been reported in the brains of suicide victims (Dwivedi et al., 2009). In the adult brain, $p75^{NTR}$ is mostly expressed the cholinergic neurons, but upon neuronal trauma, $p75^{NTR}$ expression is increased in cortical and hippocampal neurons and mediates degeneration and death of injured neurons (Harrington et al., 2004; Volosin et al., 2008). Increase in $p75^{NTR}$ levels in suicide victims suggests that a severe psychological stress, such as leading to suicide, may represent a brain trauma. $p75^{NTR}$ signaling may promote synaptic depression and pruning and other "antitrophic" effects that might at least partially underlie the pathophysiology of depression (Lu et al., 2005; Martinowich et al., 2012; Zagrebelsky and Korte, 2014).

BDNF is found in human serum at high levels that would be sufficient to saturate the binding to TrkB receptors in cultured neurons (Radka et al., 1996). In contrast, BDNF levels in human plasma are orders of magnitude lower than in human serum, and relationship of plasma BDNF to depression is variable (Karege et al., 2005; Bocchio-Chiavetto et al., 2010), suggesting that a vast majority of serum BDNF originates from blood platelets that release BDNF upon activation (Fujimura et al., 2002; Karege et al., 2005; Turck and Frizzo, 2015). Indeed, a recent study identified BDNF

expression in human megakaryocytes, precursors for blood platelets, and showed that the regulation of BDNF synthesis in megakaryocytes was very similar to that characterized in neurons (Chacon-Fernandez et al., 2016).

Several reports and meta-analyses clearly demonstrate that depressed patients have reduced serum BDNF levels (Shimizu et al., 2003; Karege et al., 2005; Sen et al., 2008; Bocchio-Chiavetto et al., 2010; Molendijk et al., 2014) and those levels are restored after successful recovery (Shimizu et al., 2003; Sen et al., 2008). A very recent study reported that hippocampal volume was transiently increased in severely depressed patients after successful electroconvulsive shock treatment, but that serum BDNF levels were not associated with this change and were not altered by the treatment (Bouckaert et al., 2016). However, reduced serum BDNF levels are not specific to depression since similar reduction has been observed in schizophrenia and autism, for example (Hashimoto et al., 2006; Katoh-Semba et al., 2007; Fernandes et al., 2014) and has also been identified as a risk factor for dementia (Weinstein et al., 2014). Conversely, exercise increases serum BDNF levels, which is associated with improved cognition in elderly and in schizophrenia (Leckie et al., 2014; Kimhy et al., 2015). Notably, however, it was recently reported that assays for BDNF serum levels are associated with high within-individual, inter-individual as well as between-assays variation (Polacchini et al., 2015), which together prevents the use of serum BDNF levels as a reliable biomarker for mood disorders.

The significance of the lower BDNF levels in depression is currently unclear but the temporal correlation between serum BDNF levels and the antidepressant effect is not direct: ketamine and electroconvulsive shock treatment increase serum BDNF levels only gradually while their antidepressant effect appears quickly (Allen et al., 2015). Remarkably, while BDNF levels in serum are reduced, the whole blood BDNF levels are not different from euthymic controls, suggesting that it is not the concentration of BDNF within blood platelets but the ability of platelets to release their BDNF that is reduced in depressed patients (Karege et al., 2005), although reduced platelet BDNF levels have also been reported (Lee and Kim, 2009). Taken together, these studies strongly suggest that changes in serum BDNF levels reflect altered BDNF release from blood platelets, however, given the similarities in the regulation of BDNF synthesis between megakaryocytes and neurons, there may be parallels between brain and serum BDNF content and release. Unfortunately, in contrast to human platelets, mice express hardly detectable levels of BDNF in megakaryocyte and platelets, which precludes the use of transgenic mice in the examination of the

mechanisms and sources of blood BDNF (Chacon-Fernandez et al., 2016). However, rat platelets do contain BDNF (Radka et al., 1996).

As mentioned above, BDNF gene displays a common polymorphism with either valine or methionine at the position 66 within the BDNF pro-region (Val66Met) (Egan et al., 2003). Mice expressing the human met-BDNF allele show increased anxiety and sensitivity to stress (Chen et al., 2006; Yu et al., 2009; Bath et al., 2012a) and show a similar deficit in fear extinction as the human Met allele carriers do (Soliman et al., 2010). Although early clinical studies suggested that the Val66Met polymorphism increases susceptibility to a variety of brain disorders (Bath and Lee, 2006; Chen et al., 2006), including depression in a subset of patients (Anttila et al., 2007) as well as in bipolar disorder (Sklar et al., 2002) and neuroticism (Sen et al., 2003), subsequent studies and meta-analyses have failed to consistently demonstrate an association between BDNF Val66Met polymorphism and mood disorders (Gyekis et al., 2013), although there may be an association with depression in men (Verhagen et al., 2010). Furthermore, while patients with depression have significantly smaller hippocampal size when compared to controls, hippocampi of both Val and Met carriers were similarly reduced (Harrisberger et al., 2015). However, there are reports indicating that Met-allele carriers may be more sensitive to adverse experiences during early life (Bukh et al., 2009; Hosang et al., 2014).

BDNF in animal models of depression

Stress is a recognized risk factor for depression and stress is therefore widely used as an experimental model for depression. It was recognized already two decades ago that BDNF levels in the cortex and hippocampus are reduced in stress (Smith et al., 1995; Duman and Monteggia, 2006; Molteni et al., 2009). BDNF levels are also reduced in mice after exposure to social stress (Tsankova et al., 2006; Martinowich et al., 2007). However, reduction of BDNF levels or TrkB signaling alone does not directly correlate with depression-like behavior: Heterozygous mice lacking one allele of BDNF and expressing about half of normal BDNF levels do not show depression-related behaviors (MacQueen et al., 2001; Saarelainen et al., 2003; Lindholm and Castrén, 2014). However, female mice with forebrain specific loss of BDNF expression do display behaviors associated with depression, although males show normal depression-like behavior (Monteggia et al., 2007; Lindholm and

Castrén, 2014). Furthermore, conditional deletion of TrkB from the newly-born neurons in the adult dentate gyrus increases anxiety-like behavior (Bergami et al., 2008) and knockdown of BDNF in the dentate gyrus in rats produces depression-like effects (Taliaz et al., 2010).

Recent series of elegant studies by Jeanneteau, Chao and colleagues have shed light on the mechanisms of interaction between stress hormones and BDNF (Jeanneteau and Chao, 2013). They first showed that dexamethasone, an agonist of the glucocorticoid receptor (GR) can activate TrkB signaling in the rat dentate gyrus, in cultured neurons and neuronal cells (Jeanneteau et al., 2008), which indicates that glucocorticoids may under certain conditions act as TrkB activators. TrkB activation by GR requires protein synthesis but apparently does not to require BDNF release. In addition, they showed that BDNF increases serine phosphorylation of the GR, which promotes the transcriptional activity of GR. Furthermore, coadministration of dexamethasone and BDNF induces the expression of a unique set of genes involved in neuronal growth and differentiation and distinct from those activated by dexamethasone alone (Lambert et al., 2013), suggesting a functional interaction of TrkB and GR signaling pathways in the cytoplasm and at genomic level. Remarkably, when BDNF levels are low or TrkB activation is inhibited, GRs in brain are downregulated, promoting vulnerability to stress, whereas when TrkB is activated, GR agonists result in neurotrophic effects and stress resilience, through simultaneous activation of mitogen-activated kinase and suppression of GR-protein phosphatase-5 pathways (Arango-Lievano et al., 2015). Such an interaction between TrkB and GR signaling may play a role in the dual effects of GR activation on dendritic spine dynamics, where short-term glucocorticoid treatment promotes spine turnover and thereby adaptability, whereas chronic treatment with glucocorticoids promotes excess spine loss (Liston and Gan, 2011).

The relationship between stress and BDNF is complex, however. While stress generally reduces BDNF levels in the cortex and hippocampus, stress increases BDNF levels in the nucleus accumbens (Berton et al., 2006; Krishnan et al., 2007). Stimulation of dopaminergic projection to the nucleus accumbens promotes depression-like behavior after social defeat stress and this effect can be blocked by inhibiting TrkB activation, but not by dopamine receptor antagonists, suggesting that BDNF released from dopaminergic neurons critically regulates susceptibility to social defeat stress (Wook Koo et al., 2015). Furthermore, infusion of BDNF into nucleus accumbens increases immobility in forced swim test, while inhibition of TrkB

signaling in this brain region decreases immobility, indicating that BDNF in the nucleus accumbens promotes depression-like behavior (Eisch et al., 2003). Thus, BDNF may have opposite effects on depression-like behavior depending on the network involved, emphasizing that BDNF is not a “happiness molecule”, but acts by promoting the effects of the networks active in depression-like or antidepressant-like behavior (Castrén, 2005; Castrén, 2013).

BDNF in the antidepressant responses

Whereas the causal role of neurotrophins in the symptoms of mood disorders is somewhat controversial, their role in the mechanism of antidepressant treatments is much clearer (Lindholm and Castrén, 2014). Neuronal activity, such as seizures (Zafra et al., 1990; Isackson et al., 1991), increases BDNF expression and the first antidepressant treatment that was shown to increase BDNF expression is electroconvulsive shock treatment (Nibuya et al., 1995; Altar et al., 2003). Subsequently, several studies have demonstrated that chronic treatment with various antidepressant drugs increase BDNF mRNA and protein levels in the cerebral cortex and hippocampus (Nibuya et al., 1995; Duman et al., 1997; Altar, 1999; Russo-Neustadt et al., 1999; Coppell et al., 2003; Jacobsen and Mork, 2004; Duman and Monteggia, 2006; Calabrese et al., 2007; Calabrese et al., 2011; Autry and Monteggia, 2012). This increase involves activation of BDNF promoters at least partly through reduced histone acetylation in these promoter regions (Russo-Neustadt et al., 2001; Dias et al., 2003; Tsankova et al., 2006; Karpova, 2014). Interestingly, in human, activity-dependent expression of BDNF is regulated by the activation of promoter I of BDNF gene (Pruunsild et al., 2011). A recent report analyzed the methylation profile of 2 CpG islands located at promoters I and IV of BDNF gene with genomic DNA from peripheral blood of patients with major depression and indicated that the methylation profiles of CpG I, but not IV, matched the classification of healthy controls and patients in clinical diagnosis (Fuchikami et al., 2011).

Representatives of essentially all pharmacological classes of clinically used antidepressants increase TrkB autophosphorylation and signaling in hippocampus and forebrain and this effects is observed within hours after the administration of the drug (Saarelainen et al., 2003; Rantamäki et al., 2007). Similar increase in BDNF mRNA and TrkB phosphorylation has been seen after acute treatment with a rapid-

acting antidepressant ketamine (Li et al., 2010; Autry et al., 2011; Lepack et al., 2014; Abdallah et al., 2015; Monteggia and Zarate, 2015). These data demonstrate that antidepressant drugs, essentially without exception, increase BDNF signaling in the rodent forebrain (Castrén and Rantamäki, 2010a; Castrén and Rantamäki, 2010b; Autry and Monteggia, 2012).

Injection of BDNF into the midbrain region or into hippocampus reduces depression-like behavior and mimics the effects of antidepressants (Siuciak et al., 1997; Altar, 1999; Shirayama et al., 2002; Hoshaw et al., 2005) and similar effects are found when TrkB activity is promoted by overexpressing TrkB in cortical neurons (Koponen et al., 2005). Furthermore, increased expression of BDNF counteracts the effects of stress (Shirayama et al., 2002; Duman and Monteggia, 2006). These data suggest that BDNF signaling is sufficient for antidepressant-like behavioral effects in rodents. However, consistent with the central role of BDNF signaling in the nucleus accumbens in the development of social defeat stress phenotype (Berton et al., 2006), injection of BDNF into the nucleus accumbens promotes depression-like behavior (Eisch et al., 2003), again demonstrating the network-dependent effect of BDNF in mood regulation.

Finally, BDNF and TrkB signaling are also necessary for the behavioral effects of antidepressant drugs, at least in rodents (Lindholm and Castrén, 2014). Deletion of BDNF gene or reduction of the levels of BDNF in forebrain regions blocks the behavioral effects of several different antidepressant drugs (Saarelainen et al., 2003; Monteggia et al., 2004; Lepack et al., 2014). Inhibition of TrkB signaling by a dominant-negative TrkB receptor or conditional deletion of TrkB in the dentate gyrus similarly blocks the effects of antidepressants (Saarelainen et al., 2003; Li et al., 2008). The antidepressant effects of ketamine appear to be lost in mice completely lacking BDNF in the forebrain regions (Autry et al., 2011), however, similar loss of effect was not seen in heterozygous BDNF null mice (Lindholm et al., 2012), indicating that, in contrast to classical antidepressants, low levels of BDNF are sufficient for an antidepressant response to ketamine.

Mice with the Met allele of the human Val66Met polymorphism of the BDNF gene are insensitive to antidepressants, which is consistent to reduced activity-dependent release of BDNF in these mice (Chen et al., 2006; Bath et al., 2012b; Liu et al., 2012). Controversial data has been published concerning the response rate in human Met-allele carriers to antidepressant treatments (Anttila et al., 2007; Domschke et al., 2010; Laje et al., 2012), but recent meta-analyses indicate that, if

anything, the Met carriers respond better to typical antidepressant treatments than Val homozygous do (Kato and Serretti, 2010; Zou et al., 2010; Yan et al., 2014). However, the response to the fast-acting antidepressant ketamine may be more widespread in Val-homozygous than in Met-carriers (Laje et al., 2012). Taken together, these data provide compelling evidence for the necessary role for BDNF and TrkB signaling in antidepressant responses in rodents (Lindholm and Castrén, 2014), however, the data reviewed above suggest that a similar clear relationship may not exist in humans.

BDNF, antidepressants and neuronal plasticity

How does BDNF signaling bring about antidepressant responses? Although many details remain to be investigated, increasing body of literature supports the idea that neurotrophins promote neuronal plasticity that then translates into antidepressant responses in depressed patients (Nestler et al., 2002; Calabrese et al., 2009; Castrén and Hen, 2013). Furthermore, recent evidence suggests that promotion of neuronal plasticity by antidepressants is alone not sufficient for an antidepressant response but that drug treatment may need to be supplemented with behavioral treatments that beneficially guide the plastic networks (Castrén, 2013).

Activity-dependent regulation of BDNF expression was connected with neuronal plasticity early on (Thoenen, 1995). When antidepressants were shown to promote BDNF expression and signaling, a connection between neuronal plasticity and the antidepressant response was proposed (Duman et al., 1997; Castrén, 2004; Castrén, 2005). Indeed, antidepressants promote neuronal plasticity at several levels (Castrén and Hen, 2013): First, antidepressants increase neurogenesis in the dentate gyrus and this effect is required for the behavioral effects of at least some antidepressants (Santarelli et al., 2003; Sahay and Hen, 2007). Increase in neurogenesis requires chronic antidepressant treatment (Malberg and Duman, 2003; Wu and Castrén, 2009) and is dependent on BDNF signaling (Sairanen et al., 2005). Second, antidepressants increase axon elongation and dendritic sprouting (Vaidya et al., 1999; Wang et al., 2008; Bessa et al., 2009; Chen et al., 2011) as well as expression of plasticity-related proteins (Sairanen et al., 2007). Although BDNF is known to influence both axonal and dendritic sprouting (Cohen-Cory et al., 2010), it is currently unknown whether these effects of antidepressants are mediated by BDNF or TrkB signaling. Finally, chronic antidepressant and acute ketamine

treatment promotes synaptogenesis (Hajszan et al., 2009; Li et al., 2010; Chen et al., 2011) and synaptic strength (Stewart and Reid, 2000; Wang et al., 2008) and at least the effects of ketamine are BDNF-dependent (Liu et al., 2012). These data show that there is a strong correlation and in some cases causal relationship between neuronal plasticity and the antidepressant effect and that at least partially, the effects of plasticity are mediated by BDNF signaling.

Recent studies have cast light on how neuronal plasticity is translated into an antidepressant effect. Using developing visual cortex, it was shown that chronic treatment with an antidepressant fluoxetine reactivates a state of plasticity within the adult cortex that is indistinguishable from the elevated plasticity typically found in juvenile cortex (Maya Vetencourt et al., 2008). When this promoted state of plasticity is combined with rehabilitation, plastic networks can reorganize so that impaired vision of one eye, due to developmental visual deprivation, can be fully restored. Fluoxetine increases BDNF expression in the visual cortex as it does in the hippocampus and the effects of antidepressant treatment are mediated by and are dependent on BDNF signaling (Maya Vetencourt et al., 2008). Serotonin and regulation of neuronal inhibition are also required for the effects of fluoxetine-induced plasticity (Maya Vetencourt et al., 2011; Maya-Vetencourt et al., 2012), but how these different systems interact to promote plasticity remains unclear.

Fluoxetine also reactivates juvenile-like plasticity in the fear extinction circuitry: long-term extinction of a fear response was seen in the adult mice only when fluoxetine-induced promoted plasticity was combined with the fear extinction training (Karpova et al., 2011). The need of combination of fluoxetine treatment with fear extinction resembles the synergistic effects of antidepressants and psychotherapy in the treatment of phobia and posttraumatic stress disorder (Schneier et al., 2012), and might in fact represent the neurobiological mechanism that explains the enhanced effect of the combined treatment (Castrén, 2013).

Finally, chronic fluoxetine treatment promotes developmental plastic state in the dentate gyrus of the hippocampus (Kobayashi et al., 2010; Hagihara et al., 2013). This phenomenon, coined dematuration, is characterized by increased expression of markers of immature dentate granule neurons with a coincident reduction of markers of maturity not only in the newly-born granule neurons, but also in older ones (Kobayashi et al., 2010; Hagihara et al., 2013).

Conclusions:

The data reviewed above suggests a close relationship between BDNF signaling, neuronal plasticity and mood disorders. These findings open several potentially translational avenues. First, BDNF might become a biomarker for mood disorders. While serum BDNF levels appear to be too variable between individuals to become a reliable biomarker, the usefulness of other molecules derived from the BDNF gene (pro-BDNF and BDNF pro-peptide) alone or in combination should be investigated. For example, a recent report measured the amounts of BDNF and proBDNF in serum of severely injured patients vulnerable to posttraumatic stress disorder (PTSD) and depression with a novel ELISA of proBDNF/BDNF (Matsuoka et al., 2015). Measuring the amount of BDNF, its pro-peptide and proBDNF, and the ratio of these BDNF subtypes in blood might advance our understanding of the roles of neurotrophins in mood disorders and potentially become a useful biomarker.

Second, as reviewed above, the BDNF pro-peptide and proBDNF exhibit negative effects on neurons while the effect of BDNF are positive. Given the negative effects of proBDNF and its pro-peptide, it could be speculated that the amount and/or biological effects of these two molecules may be increased in mood disorders, restricting plasticity and potentially producing antidepressant-resistance in patients. Third, since essentially all antidepressant treatments increase BDNF-TrkB signaling, this signaling pathway could become a useful tool for screening or novel antidepressant drugs.

Finally, the findings reviewed above suggest that BDNF-mediated plasticity induced by antidepressant treatments is only effective when it is combined with therapy or rehabilitation that guides the rewiring of plastic networks. Efforts should be made to optimize plasticity-promoting drug treatments and psychotherapeutic approaches, also taking into account effects that may restrict plasticity, into a new treatment framework that optimally promotes mood recovery and prevents relapses to depression.

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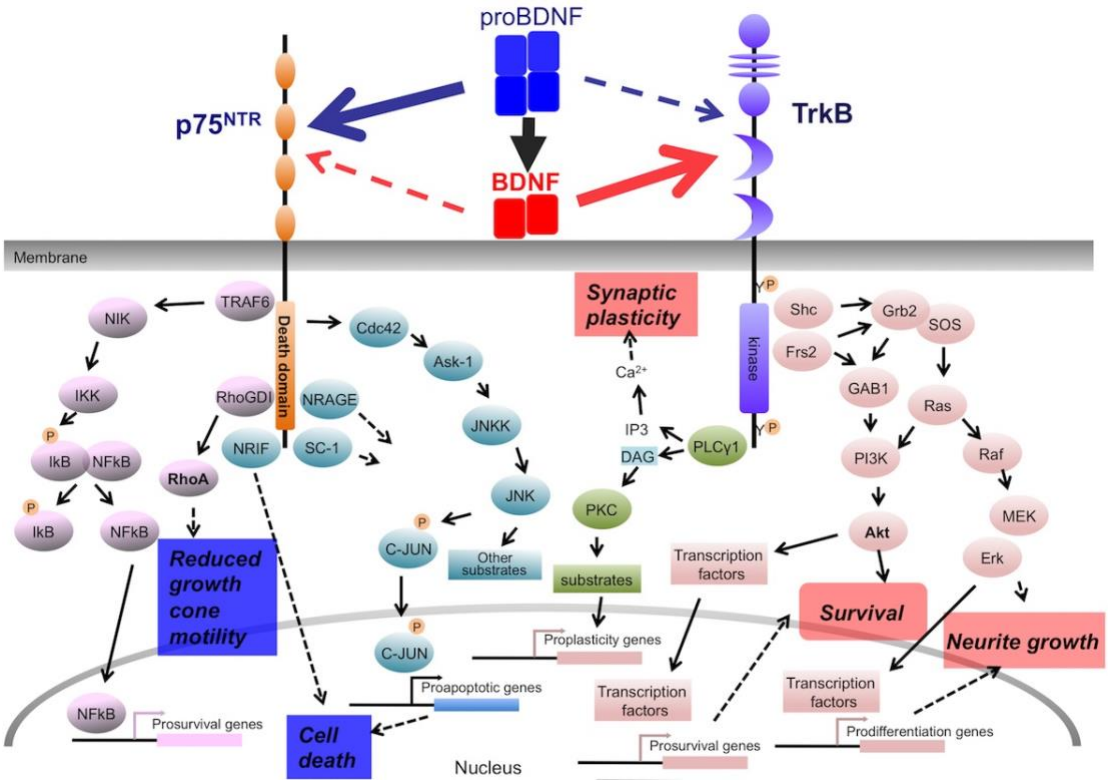
Figure legends:

Figure 1: Signaling pathways activated by proBDNF and mature BDNF (BDNF).



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