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R E V I E W

Brain-derived neurotrophic factor: role in depression and suicide

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Abstract: Depression and suicidal behavior have recently been shown to be associated with disturbances in structural and synaptic plasticity. Brain-derived neurotrophic factor (BDNF), one of the major neurotrophic factors, plays an important role in the maintenance and survival of neurons and in synaptic plasticity. Several lines of evidence suggest that BDNF is involved in depression, such that the expression of BDNF is decreased in depressed patients. In addition, antidepressants up-regulate the expression of BDNF. This has led to the proposal of the "neurotrophin hypothesis of depression". Increasing evidence demonstrates that suicidal behavior is also associated with lower expression of BDNF, which may be independent from depression. Recent genetic studies also support a link of BDNF to depression/suicidal behavior. Not only BDNF, but abnormalities in its cognate receptor tropomycin receptor kinase B (TrkB) and its splice variant (TrkB.T1) have also been reported in depressed/suicidal patients. It has been suggested that epigenetic modulation of the *Bdnf* and *Trkb* genes may contribute to their altered expression and functioning. More recently, impairment in the functioning of pan75 neurotrophin receptor has been reported in suicide brain specimens. pan75 neurotrophin receptor is a low-affinity neurotrophin receptor that, when expressed in conjunction with low availability of neurotropins/Trks, induces apoptosis. Overall, these studies suggest the possibility that BDNF and its mediated signaling may participate in the pathophysiology of depression and suicidal behavior. This review focuses on the critical evidence demonstrating the involvement of BDNF in depression and suicide.

Keywords: BDNF, neurotrophins, p75[NTR], Trk receptor, depression, antidepressants, suicide, genetics, epigenetics

Introduction

Depression and suicide are important public health concerns. Depression affects about 15% of the population at some point in their lives and is the leading cause of disability worldwide.[1] About 9 million people are diagnosed as having depression each year in the United States alone, and the lost productivity and treatment expenses burden the US economy by more than US$43 billion per year.[2,3] Depression is associated with an increased number of suicide attempts and increased lethality[4,5] Suicide accounts for almost 2% of the world's deaths.[6] In most of the developed world, suicide is among the top 10 leading causes of death for individuals of all ages, and is the third leading cause of death among adolescents, after motor vehicle accidents and homicide.[7–9] Several arguments suggest that suicidal behavior is a disorder of its own, although psychiatric disturbances, including depression, are major contributing factors.[9,10] Autopsy studies of suicide victims have identified a high rate of major depressive disorder (MDD)

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as one of the main causes of increased mortality among suicide victims.[11] The presence of psychopathology is a strong predictor; however, only a minority of people with such diagnoses commits suicide, which indicates that there is a certain predisposition to suicide that is independent of the main psychiatric disorders.[9,12–14] Despite the devastating impact of depression and suicide on numerous lives, there is still a dearth of knowledge concerning the mechanisms underlying their pathogenesis.

Overwhelming evidence points to altered synaptic and structural plasticity in patients with depression and in suicidal patients. In fact, it has been proposed that depression/suicide results from an inability of the brain to make appropriate adaptive responses to environmental stimuli as a result of impaired synaptic plasticity and structural plasticity[15–18] Support for this comes from a variety of studies in major depressed/suicidal subjects demonstrating altered brain structure, such as reduction in cell number, density, cell body size, neuronal and glial density in frontal cortical or hippocampal brain areas and decrease in parahippocampal cortex cortical/laminar thickness.[19–27] In addition, changes in synaptic circuitry,[28] decreased dorsolateral prefrontal cortical activity,[29,30] impaired synaptic connectivity between the frontal lobe and other brain regions,[31,32] changes in the number and shape of dendritic spines,[33,34] changes in the primary location of synapse formation, altered dendritic morphology of neurons in the hippocampus, decrease in length and number of apical dendrites,[35] neuronal atrophy and decreased volume of the hippocampus,[36–38] decreased number of neurons and glia in cortical areas,[39] and spatial cognition deficits[40] have also been reported during stress and depression. Furthermore, depression is associated with negative impact on learning and memory;[41–43] and stress, a major factor in depression and suicide, hinders performances on hippocampal-dependent memory tasks and impairs induction of hippocampal long-term potentiation. These studies clearly demonstrate impaired structural and functional plasticity in depression and suicide; however, the precise molecular and cellular nature of events that lead to such altered plasticity in these disorders remains unclear.

Survival and development of neurons in the central nervous system (CNS) depends on the influence of a variety of extracellular signals. One set of signals is provided by neurotrophins. The role of neurotrophins in directing brain growth and neuronal functioning is being increasingly recognized. Neurotrophins not only play an important role in cellular proliferation, migration, and phenotypic differentiation and/or maintenance in the developing CNS,[44,45] but their presence is required in the adult CNS for maintenance of neuronal functions, structural integrity of neurons, and neurogenesis[46,47] which suggests that neurotrophins are biologically significant over the entire life span. In addition, a number of studies have demonstrated that neurotrophic factors regulate structural, synaptic, and morphological plasticity to modulate the strength or number of synaptic connections and neurotransmission.[48,49] Thus, a pathological alteration of the neurotrophic factor system may not only lead to defects in neural maintenance and regeneration and, therefore, structural abnormalities in the brain, but may also reduce neural plasticity and, therefore, impair the individual's ability to adapt to crisis situations.

Mammalian neurotrophins are homodimeric proteins that include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin (NT) 3, and NT 4/5. Most functions of neurotrophins are mediated by the tropomycin receptor kinase (Trk) family of tyrosine kinase receptors. The interaction of neurotrophins with the Trk receptors is specific: NGF binds with TrkA, BDNF and NT 4 both bind with TrkB, and NT 3 binds with the highest affinity to TrkC but is also capable of signaling through TrkA and TrkB. In addition to the full length TrkB receptor, several non-catalytic truncated TrkB isoforms have also been identified; these isoforms lack the signaling domain, preventing the induction of a signal transduction mechanism. Binding of a neurotrophin to the appropriate Trk receptor leads to the dimerization and transphosphorylation of tyrosine residues in the intracellular domain of the Trk receptors and subsequent activation of cytoplasmic signaling pathways.[50,51] All neurotrophins can bind to the pan75 neurotrophin receptor (p75^{NTR}), which plays a role in neurotrophin transport, ligand binding specificity, and Trk functioning.[44,52,53]

Of various neurotrophins, BDNF has attracted a great deal of interest as a functional candidate gene in various mental disorders. The *Bdnf* gene lies on the reverse strand of chromosome 11p13 and encodes a precursor peptide pro-BDNF.[54] In fact, all neurotrophins, including BDNF, are synthesized as a pre-pro-neurotrophin precursor that undergo posttranslational modifications before giving rise to mature homodimeric protein. The pro-BDNF is produced in endoplasmic reticulum, which is accumulated in trans-Golgi network via Golgi apparatus. It has been suggested that pro-BDNF binds to sortilin in the Golgi, which facilitates the correct folding of the mature domain. The mature domain of BDNF binds to carboxypeptidase E, thereby sorting BDNF to the regulated secretary pathway.[55] A substitution of valine (Val) to methionine (Met) at codon 66 in the

prodomain impairs this sorting of BDNF.[56] The pro-BDNF is the main form of neurotrophin,[57–59] and the mature form originates through proteolytic cleaving. Plasmin is the major extracellular protease that cleaves pro-BDNF.[60,61] The expression of the *BDNF* gene is tightly regulated by neuronal activity, through mechanisms dependent on calcium.[62] In addition to BDNF, the function of a receptor for BDNF (ie, TrkB) is also regulated in an activity-dependent manner. TrkB is primarily localized in the synaptic sites. Further localization of TrkB occurs at the synaptic sites after neuroanal activity.[55] Neuronal activity, therefore, is critical for synthesis and intracellular targeting of TrkB receptors.[55] Thus, BDNF release and expression of TrkB receptors in a coordinated fashion are important for optimal synaptic response.

The role of BDNF in depression has gained broad attention because many pre-clinical and clinical studies provide direct evidence suggesting that modulation in expression of BDNF could be involved in behavioral phenomenon associated with depression. Based on these studies, the neurotrophin hypothesis of depression was proposed, which suggests that stress and depression is associated with decreased expression of BDNF and that antidepressants alleviate depressive behavior by increasing its level.[15,16] This is quite relevant given that BDNF is involved in synaptic plasticity and, as earlier mentioned, compromised synaptic and structural plasticity have been shown to be associated with depression. Because stress and depression are the major contributory factors in suicide, recently, a number of studies have attempted to investigate the role of BDNF in suicidal behavior. These studies, albeit in infancy, provide strong support for the idea that abnormalities in BDNF could be an important contributory factor in suicidal behavior. This review focuses on the critical assessment of the involvement of BDNF and its functioning in depression and suicidal behavior.

BDNF in stress

Several clinical and epidemiological studies have identified stressors as important risk factors in depression and suicide.[63–70] An overactive hypothalamus-pituitary-adrenal axis has been well established in stress. On the other hand, there is strong evidence for a connection between stress system overactivity and suicidal behavior. For example, in suicide victims, hypothalamus-pituitary-adrenal axis hyperactivity has been linked with elevated corticotrophin-releasing hormone levels in the cerebrospinal fluid, reduced corticotrophin-releasing hormone binding sites in the frontal cortex, augmented pro-opiate-melanocortic RNA density in the pituitary, large corticotrophic cell size, and alterations in the mineralocorticoid to glucocorticoid receptor messenger RNA (mRNA) ratio in the hippocampus of suicide victims.[71–76] Also, a consistent association has been found between subsequently completed suicide and nonsuppression of cortisol in the dexamethasone suppression test.[77–82]

Studies in pre-clinical models have shown stress-induced dysregulation of BDNF expression. Several types of stressors have been used to examine the role of BDNF in stress-related disorders. The very first study that examined the role of stress was from Smith and colleagues,[83] who demonstrated that immobilization stress used for 1 or 7 days (for 2 hours per day) significantly decreased BDNF mRNA expression in the hippocampus. This decrease was present throughout the hippocampus; however, the dentate gyrus showed the most significant response. This was later confirmed by other investigators.[84,85] Similar changes were observed when other types of stressors were used. For example, Rasmusson et al[86] demonstrated that exposure to twenty 0.5-second 0.4-mA foot shocks coterminating with 70-dB, 5-second-long pure tones over 60 minutes decreased dentate gyrus BDNF mRNA. Some of the stressors, such as social defeat, decreased BDNF not only in hippocampus but also in cortical and subcortical areas of mice.[87] Interestingly, it has been shown that maternal separation led to depression like behavior in adulthood, which was correlated with decreased BDNF expression.[88] This study suggests that early developmental insult causes depression in later life, which is mediated through abnormalities in BDNF-mediated signaling.

Several studies have shown that exposure of exogenous corticosterone (to mimic the stress effect) also reduces BDNF expression in rodent hippocampus, similar to that observed in various pre-clinical stress models.[83,89–91] Recently, we examined the effects of corticosterone treatment on BDNF expression in detail and found that the mRNA level of BDNF was not only decreased in the hippocampus but that the frontal cortex also showed significantly reduced expression of BDNF.[92] This suggests that the effects of glucocorticoids on BDNF are not limited to the hippocampus; other brain areas are also equally affected. When endogenous corticosterone was removed by adrenalectomy, the level of BDNF in the hippocampus increased.[89,93] On the other hand, dexamethasone replacement to adrenalectomized rats restored the level of BDNF to control levels.[93] These studies demonstrate that expression of BDNF expression is regulated via glucocorticoids.

On a molecular level, BDNF is highly regulated. The rat *Bdnf* gene contains 4 separate promoters that are linked

to 4 main transcript forms.[94,95] Each transcript has 4 short 5' noncoding exons (I-IV) containing separate promoters and 1 shared 3' exon (exon V) encoding the mature BDNF protein. Although the biological significance of these BDNF transcripts is not clear, it appears that these transcripts can facilitate multi-level regulation of BDNF expression and may determine the tissue-specific expression. To examine the molecular basis of stress regulation of BDNF, we determined mRNA levels of exons I through IV. We observed that corticosterone selectively decreased the expression of transcripts II and IV, but not transcripts I or III, in both the frontal cortex and hippocampus.[92] Two other recent studies suggest that immobilization stress decreases total BDNF expression, along with a specific decrease in exon IV in the hippocampus[96] and hypothalamus.[97] These studies suggest that the decrease of BDNF mRNA expression by glucocorticoids may be due to a decrease in expression of the specific BDNF transcripts that contain exons II and IV.

BDNF in depression

In addition to stress, several lines of evidence point to the involvement of BDNF in depression. These include indirect evidence demonstrating that antidepressants regulate BDNF/TrkB expression and that BDNF itself shows antidepressant-like effects. In addition, depressed patients show alterations in expression of BDNF both in blood cells and in postmortem brain tissues. Genetic studies also link BDNF polymorphism to depression. Each of these aspects are detailed further.

Regulation of BDNF expression by antidepressants

The effects of antidepressants on the expression of the *Bdnf* gene have been investigated extensively. In general, it has been shown that when given to healthy rodents, several classes of antidepressants, including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic agents, noradrenaline reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants, all increase expression of BDNF in the brain.[98–108] In addition, several other agents known to have antidepressant properties also increase expression of BDNF in rodent brain. These agents include α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and *N*-methyl-D-aspartate antagonists, electroconvulsive shock, and transcranial magnetic stimulation.[98,109–114] Chronic treatment with antidepressants not only increases expression of BDNF in healthy rodents, but also reverses downregulation of BDNF caused by stress.[98,115,116] However, these

effects depend on various factors, including length of administration, class of antidepressant, route of administration, age of animal, and doses of the drugs. In general, an increase in BDNF expression occurs only after long-term treatment and, in most cases, short-term treatment with antidepressants causes no change in the expression of BDNF.[98,101,106,117,118] However, short-term treatment with antidepressants has also been shown to cause an increase in BDNF expression in the cortex[119,120] and even a decrease in the hippocampus.[101,119,120]

The effects of antidepressants such as desipramine or fluoxetine have also been studied in BDNF-deficient mice. These studies show that the behavioral effects of antidepressant are abolished in BDNF-deficient mice,[121,122] suggesting that BDNF plays an important role in the behavioral effects of antidepressants.

Regulation of BDNF exons by antidepressants

To examine how BDNF is regulated in response to antidepressants, we administered different classes of antidepressants (serotonin uptake blocker, fluoxetine, norepinephrine blocker, desipramine, monoamine oxidase inhibitor, or phenelzine) to healthy rats and examined whether antidepressants regulate the expression of BDNF via specific BDNF transcript(s).[92] We observed very interesting results such that treatment of healthy rats with desipramine or phenelzine increased mRNA levels of total BDNF in both the frontal cortex and hippocampus, whereas fluoxetine increased the mRNA level of BDNF only in the hippocampus.[92] More interestingly, when we examined the effects of antidepressants on the expression of individual exons containing BDNF transcripts, we found that desipramine specifically increased exons I and III in both the frontal cortex and hippocampus; fluoxetine increased only exon II in the hippocampus; and phenelzine effectively increased exons I and IV in the hippocampus but only exon I in the frontal cortex. In another study, Dias et al[102] examined the effects of long-term antidepressants on BDNF transcript levels in the rat hippocampus, amygdala, and cortex. They observed that desipramine increased exon III in different cortical areas, whereas fluoxetine had no significant effects on BDNF exons in any of the brain areas studied. Another recent study by Altieri et al[118] also showed no effect of long-term fluoxetine treatment on BDNF transcripts in the hippocampus. Our observation of increased exon III by desipramine is similar to the findings of Dias et al[102] but we also noted an increase in the expression of exon I. In addition, contrary to reports

by Dais et al[102] and Altieri et al[118] we found a selective increase in exon II by fluoxetine in both the frontal cortex and hippocampus. Although some of these discrepancies can be attributed to route of administration or doses of drugs, these findings suggest that there is no unified mechanism for the regulation of BDNF exon(s) by antidepressants and that various classes of antidepressants may affect BDNF exon expression differently.

We further examined whether antidepressants reverse the corticosterone-mediated decrease in BDNF and whether similar BDNF exons are involved in this mechanism by which antidepressants upregulate BDNF expression.[92] We observed that long-term treatment with desipramine completely reversed the corticosterone-induced decrease in BDNF in both the frontal cortex and hippocampus. Fluoxetine was able to partially reverse the changes in hippocampal BDNF, but did not cause any change in the frontal cortex. Phenelzine, on the other hand, reversed the corticosterone-induced decrease in BDNF partially in the frontal cortex and completely in the hippocampus. Interesting results were noted when individual BDNF transcripts were examined after antidepressant treatment of corticosterone-implanted rats: the antidepressants were able to increase mRNA levels of only those BDNF transcripts that were affected when the respective antidepressant was given to healthy rats without corticosterone pellet implantation. Thus, desipramine increased exons I and III in the frontal cortex and hippocampus, fluoxetine increased exon II in the hippocampus, and phenelzine increased exon I in the frontal cortex and exons I and IV in the hippocampus. Surprisingly, except for the changes in exon II by fluoxetine in the frontal cortex and in exon IV by phenelzine in the hippocampus, the corticosterone-mediated decrease in exons II and IV persisted even after antidepressant treatment. However, the overall observation was that all the antidepressants increased the level of total BDNF mRNA in the brain of corticosterone-treated rats. Although it is difficult to assess the extent of involvement of a particular exon in regulation of overall BDNF expression, there is complete reversal by desipramine in both the frontal cortex and hippocampus because the increase in exon III was very robust in these brain areas. On the other hand, in the hippocampus, fluoxetine was able to reverse the corticosterone-mediated decrease of only exon II, but not exon IV; therefore, the reversal was partial. However, no effect of fluoxetine on total BDNF expression was observed in the frontal cortex, because fluoxetine was not able to increase either exon II or IV in the frontal cortex. On the other hand, phenelzine was partially effective in the frontal cortex because of its effects on exon II, but complete

reversal was noted in the hippocampus because phenelzine increased the levels of both corticosterone-decreased exons II and IV. Thus, it appears that antidepressants are effective in causing an increase in total BDNF expression in corticosterone-treated rats; however, the mechanisms for the down-regulation of BDNF transcripts by corticosterone and those that affect their upregulation by antidepressants are quite different.

TrkB studies in relation to antidepressant treatment

In addition to BDNF, TrkB receptors have also been studied in relation to antidepressant treatment. The *Trkb* gene can give rise to at least 2 isoforms of TrkB, encoding the "full-length," or catalytic, form of TrkB, the receptor mediating the main biological actions of BDNF,[123,124] and the "truncated" TrkB receptors (TrkB.T1), which lack a large part of the intracellular domain and do not display protein–tyrosine kinase activity.[125] Binding with BDNF leads to activation of the full-length TrkB receptors by ligand-induced dimerization and autophosphorylation of tyrosine residues in the intracellular region.[126] Full-length TrkB receptors also mediate retrograde transport of BDNF to neuronal cells.[127] The activated receptors become able to interact and phosphorylate several intracellular targets. Although catalytic TrkB is considered as the receptor mediator of the main biological actions of BDNF, the truncated TrkB is also a predominant isoform in the adult brain,[128,129] functioning as a cellular adhesion molecule regulating synaptic plasticity and axonal outgrowth, modulating signaling by catalytic TrkB through the formation of heterodimers, and regulating the extracellular availability of its endogenous ligands.[125] It has been shown that BDNF signaling is impaired as a consequence of the formation of receptor heterodimers,[130] which suggests that the truncated form of TrkB can act as a negative modulator of BDNF signaling.

It has been shown that long-term treatment with electroconvulsive shock, desipramine, fluoxetine, tranylcypromine, and sertraline all increased mRNA levels of TrkB in the rat brain.[98] Recently, Rantamäki et al[131,132] reported that not only the expression, but TrkB signaling, is rapidly activated by a variety of antidepressants in mouse medial prefrontal cortex (PFC) and hippocampus. This occurs through antidepressant-mediated autophosphorylation of TrkB. These studies suggest that the behavioral effect of antidepressants requires TrkB activation along with an increase in BDNF expression. Interestingly, the TrkB-mutant mice do not exhibit depression-like behaviors such as increased "despair" in

the forced swim test.[133] However, TrkB.T1-overexpressing transgenic mice, which show reduced TrkB activation in the brain, and heterozygous BDNF null (BDNF+/−) mice both are resistant to the effects of antidepressants in the forced swim test, indicating that normal TrkB signaling is required for the behavioral effects typically produced by antidepressants.[121]

Antidepressant-like effect of BDNF

The role of BDNF in depression also stems from preclinical studies demonstrating that BDNF not only regulates expression of BDNF but shows antidepressant-like effects in animal models. In a learned helplessness model of depression, infusion of BDNF reduces escape latencies and failure rates in rodents,[134,135] suggesting the effectiveness of BDNF in reducing inescapable random shock-induced depressive behavior. Similarly, intra-midbrain infusion of BDNF in rodents produces antidepressant-like effect in the forced swim test and learned helpless models of depression.[134] Infusion of BDNF in the dorsal raphe nucleus also resulted in antidepressant-like effect in the learned helpless model of depression.[136] Interestingly, the effects of BDNF on these behavioral paradigms were much longer lasting compared with classic antidepressants.[135,137]

Clinical studies of BDNF response in depressed patients before and after antidepressant treatment

Consistent with animal studies, studies in humans provide evidence that BDNF plays an important role in depression. Although BDNF is highly expressed in the brain, studies regarding the expression level of BDNF in the human brain of depressed subjects are limited. In an earlier study, Chen et al[138] showed that the expression of BDNF is increased in the postmortem brain of depressed subjects treated with antidepressants compared with those who were untreated. Recently, many studies have attempted to examine the level of BDNF in serum or platelets of depressed subjects with and without antidepressant treatment. Although the significance of measurement of BDNF in blood cells is unclear, it was demonstrated that BDNF may cross the blood-brain barrier and that platelet BDNF shows similar changes postnately similar to the brain,[139] suggesting that there are parallel changes in the blood and brain levels of BDNF. Karege and colleagues[140] were the first to compare BDNF levels in the serum of depressed subjects and healthy controls. In 15 male and 15 female depressed patients, they found that BDNF level was significantly lower compared with healthy controls. This decrease was negatively

correlated with the severity of depression. Moreover, they found a sex effect such that female depressed patients were more severely depressed and released less BDNF than males. Recently, the same group of investigators suggested that the decrease in serum BDNF in depressed patients is related to release mechanisms of BDNF because no change was found in the level of BDNF in blood, but serum and platelet BDNF were decreased in depressed patients.[141] Since then, several studies have examined BDNF level in these peripheral tissues before and after antidepressant treatment. For example, Gonul et al[142] and Piccinni et al[143] reported decreases in serum BDNF level in depressed patients. On the other hand, Matrisciano et al[144] examined serum BDNF levels in healthy subjects and depressed patients at baseline and after 5 weeks and 6 months of sertraline, escitalopram, or venalfaxine treatment. They found that the BDNF level was lower in depressed patients and that sertraline increased BDNF level after 5 weeks and 6 months, whereas escitalopram increased BDNF level only after 6 months. Venalfaxine did not change the level of BDNF. There was a negative correlation between increase in BDNF level and decrease in Hamilton Depression Rating Scale score. On the other hand, Gonul et al[142] reported that depressed patients show increased BDNF level in serum after treatment with a variety of antidepressants for 8 weeks, including venalfaxine, sertraline, fluoxetine, paroxetine, and citalopram. Similarly, increases in serum BDNF level by amitriptyline after 36 days, paroxetine after 4 or 8 weeks, or venalfaxine after 12 weeks of treatment to depressed patients were reported.[145–147] Not only antidepressants but vagus nerve stimulation, repetitive transcranial magnetic stimulation,[148] or electroconvulsive therapy[149] to depressed patients also cause an increase in serum BDNF level in depressed patients. In a recent meta-analysis, Brunoni et al[150] and Sen et al[151] concluded that BDNF levels are lower in depressed patients than healthy controls and that BDNF levels are significantly higher after antidepressant treatment. Overall, these findings provide strong evidence of modulation in BDNF in depression and in response to antidepressants.

Role of BDNF in genetic basis of depression

The gene encoding human BDNF is localized at chromosome 11p13. In humans, a common single nucleotide polymorphism at nucleotide 196 within the 5' pro-BDNF sequence encodes a variant BDNF at codon 66 (Val66-Met). As mentioned earlier, this Met66 variant affects activity-dependent BDNF secretion.[56,59] This is critical for dendritic trafficking and synaptic localization of BDNF. Interestingly, knockout

mice carrying the Val66Met polymorphism show reduced activity-dependent secretion of BDNF, without any change in the level of total BDNF.[152] More interestingly, mice carrying the BDNF Met/Met or Val/Met allele show a reduced volume of hippocampus compared with wild-type mice, and BDNF Met/Met knock-in mice have reduced dendritic arbor complexity.[152] These studies are quite relevant to depression, because structural abnormalities, particularly structural abnormalities in the brain, including reduced hippocampal volume during stress and in depressed patients, have been reported,[153,154] which increases the risk for depression. Recently, Frodl et al[155] examined the effect of the BDNF Val66Met polymorphism on hippocampal and amygdala volumes in patients with depression and in healthy control subjects. They found that depressed patients had significantly reduced hippocampal volumes. They also found smaller hippocampal volumes for depressed patients and for healthy controls carrying the Met-BDNF allele when compared with subjects homozygous for the Val-BDNF allele. No significant difference in amygdala volume was found between depressed patients and healthy controls and no significant main effects for the BDNF Val66Met polymorphism were observed. They concluded that the Met-BDNF allele carriers might be at risk of developing smaller hippocampal volumes and might be susceptible to depression. Interestingly, human magnetic resonance imaging studies in normal healthy subjects showed that Val/Val homozygotes had a larger hippocampal volume than Val/Met heterozygotes.[156–158]

People with the Met allele also have poor hippocampal-dependent memory function and hippocampal hyperactivation during learning,[56,159] which could be associated with hippocampal hypersensitivity to stress. On the other hand, Kliem et al[160] demonstrated that training-dependent increases in the amplitude of motor-evoked potentials and motor map reorganization are reduced in healthy subjects with a Val66Met polymorphism in the *Bdnf* gene, compared with subjects without the polymorphism. These results suggest that BDNF is involved in mediating the experience-dependent plasticity of the human motor cortex. Furthermore, the Val66Met polymorphism in the *Bdnf* gene modulates human cortical plasticity and the response to transcranial magnetic stimulation.[161]

Earlier, Tsai et al[162] studied the *Bdnf* gene Val66Met polymorphism in 152 patients with MDD and in 255 healthy controls. They also examined the association of this polymorphism and fluoxetine therapeutic response in 110 patients with MDD who received a 4-week fluoxetine treatment. They found no significant differences for the

genotype or allele frequency of the BDNF polymorphism comparing the MDD and control groups. Further, no significant differences were noted comparing the 3 genotype groups for depressive-cluster symptoms. However, a trend to improved 4-week fluoxetine antidepressant response was demonstrated for heterozygous patients compared with homozygous analogs. Similarly, Choi et al[163] reported that the genotype, allele, and allele-carrier distributions for the Val66Met polymorphism did not differ significantly between patients with MDD and healthy controls; however, they showed that the Val66Met polymorphism of BDNF was associated with citalopram efficacy, with Met-allele carriers responding better to citalopram treatment.

Very recently, Licinio et al[164] studied novel genetic polymorphisms in the BDNF gene and assessed their frequencies and associations with MDD or antidepressant response. They identified 83 novel single-nucleotide polymorphisms (SNPs): 30 in untranslated regions, 4 in coding sequences, 37 in introns, and 12 in upstream regions; 3 of 4 rare novel coding SNPs were nonsynonymous. Association analyses of patients with MDD and controls showed that 6 SNPs were associated with MDD (rs12273539, rs11030103, rs6265, rs28722151, rs41282918, and rs11030101) and 2 haplotypes in different blocks (one including Val66, another near exon VIIIh) were significantly associated with MDD. One recently reported 5′ untranslated region SNP, rs61888800, was associated with antidepressant response.

Hwang et al[165] reported that the BDNF Val66Met genotype distribution was significantly different between geriatric depressed patients and healthy subjects and there was a significant excess of the Met allele in these patients compared with the control group. Very recently, Duncan et al[166] found that the Val/Val genotype was associated with higher scores on the Cognitive-Affective factor of the Beck Depression Inventory-II, Cognitive-Affective factor scores, and Somatic-Vegetative factor scores, suggesting an association between the Val/Val genotype and higher levels of depression symptoms. In a similar line of investigation, Savitz et al[167] showed that bipolar patients, who were met-allele carriers, and were exposed to sexual abuse, performed more poorly on memory test, suggesting that functional BDNF polymorphism and cognition would moderate the effect of psychological trauma on memory. Similar findings were later reported by other investigators.[168,169] Interestingly, Childhood adversity per se predict higher levels of adult depressive symptoms and BDNF Val66Met polymorphisms moderate the effect of childhood sexual abuse on adult depressive symptoms.[170]

Another piece of evidence demonstrating role of BDNF in depression comes from studies showing an association of personality traits and BDNF polymorphism.[171–174] It is pertinent to mention that personality traits have been linked to major depression as well as suicide.[175]

Do epigenetics play any role in BDNF modification in depression and antidepressant responses?

Recent studies suggest that epigenetic regulation of the gene may be crucial in the pathophysiology of depressive behavior.[176] Histone modifications along with DNA methylation play a major role in gene silencing through chromatin remodeling. Methyl-CpG binding protein MeCP2, which encodes a protein that functions as a transcriptional repressor, selectively binds to BDNF promoter III and represses expression of the *Bdnf* gene. Membrane depolarization triggers the calcium-dependent phosphorylation and release of MeCP2 from BDNF promoter III, thereby facilitating transcription.[177] On the other hand, membrane depolarization causes increased BDNF transcription, which involves dissociation of the MeCP2-histone deacetylase-mSin3A repression complex from its promoter,[177,178] which suggests that DNA methylation-related chromatin remodeling is important for activity-dependent *Bdnf* gene regulation. Recently, Fuchikami et al[179] reported that single immobilization stress (a model for depression) decreased the levels of BDNF mRNA, which was associated with decreased expression of exons I and IV. They also reported that the levels of acetylated histone H3 were decreased in the promoters of I, IV, and VI exons, suggesting that histone acetylation is involved in regulation of the *Bdnf* gene in the immobilization stress model. Earlier, in an important study, Tsankova et al[180] found that social defeat stress caused down-regulation of BDNF exons III and IV and robustly increased histone methylation at their corresponding promoters. Long-term imipramine treatment reversed this down-regulation and increased histone acetylation at these promoters. This hyperacetylation by long-term imipramine treatment was associated with a selective down-regulation of histone deacetylase. Overexpression of HDAC5 blocked the ability to reverse depression-like behavior. Altogether, these studies suggest that although BDNF expression is repressed or induced by stress or antidepressants by different mechanisms, epigenetic regulation of the *BDNF* gene plays an important role in depression and in the mechanisms of action of antidepressants.

BDNF in suicide

Because depression is an important causative factor in suicidal behavior, it is interesting to examine whether suicidal behavior is associated with alterations in BDNF and its cognate receptors. It is more interesting to examine whether alterations in BDNF in suicidal subjects are independent of depression. In this regard, postmortem brain studies in suicide subjects with or without depression, levels of BDNF in blood cells of suicidal patients, and genetic association studies linking BDNF to suicide have been performed. These studies indicate a possible role of BDNF to suicidal behavior.

Human postmortem brain studies

To my knowledge, we were the first to examine of the role of BDNF in suicide. We determined mRNA and protein expression of BDNF in the PFC (Brodmann's area 9) and hippocampus from specimens obtained from 21 fully characterized suicide subjects and 27 nonpsychiatric healthy control subjects.[181] We observed that mRNA level of BDNF was significantly reduced, independently and as a ratio to neuron-specific enolase (a housekeeping gene), in both the PFC and hippocampus of suicide subjects compared with nonpsychiatric healthy control subjects. These reductions were associated with a significant decrease in the protein level of BDNF. Interestingly, when we divided suicide subjects into those who had depression and those who had another psychiatric disorder, we found that the decrease in expression of BDNF was present in all suicide subjects regardless of psychiatric diagnosis. Our findings demonstrate that suicidal behavior may be associated with a decrease in BDNF functioning. More recently, Karege et al[182] examined the expression of BDNF in the PFC, hippocampus, and entorhinal cortex in suicide subjects. Similar to our findings, they reported that the level of BDNF was significantly decreased in the PFC and hippocampus. No change was found in the entorhinal cortex, suggesting that a decrease in BDNF may be specific only to certain brain areas. In addition, Karege et al[182] found that suicide subjects who were receiving antidepressant treatment did not show any change in the level of BDNF, suggesting that psychotropic drugs normalize the decreased level of BDNF in suicide subjects. Interestingly, Kozcicz et al[183] reported sex-specific changes in the level of BDNF in suicide subjects. They found that BDNF level was much lower in the midbrain (nonpreganglionic Edinger-Westphal nucleus) of male suicide subjects, whereas female suicide subjects showed an increased level of BDNF in this brain area, suggesting a possible sex effect in the regulation of BDNF expression in suicide subjects. Although the previous studies did not find sex-specific changes in BDNF expression in the hippocampus or cortical areasb,[181,182] whether sex-specific effect in BDNF expression is specific to the midbrain area needs further studies.

In addition to adult suicide subjects, we recently examined the expression of BDNF in postmortem brain samples obtained from teenaged suicide subjects.[184] Protein and mRNA expression of BDNF was determined in samples from the PFC, Brodmann's area 9, and hippocampus obtained from 22 teenaged suicide victims and 22 matched nonpsychiatric healthy control subjects. As with adult suicide subjects, we found that protein expression of BDNF was significantly decreased in the PFC of teenaged suicide subjects. Interestingly, no significant change in BDNF protein expression was observed in the hippocampus. On the other hand, a decrease in BDNF mRNA was observed both in the PFC and hippocampus of teenaged suicide subjects. Whether this subtle difference in the protein expression of BDNF represents differences in some characteristics between teenage and adult suicide is not clear. Nonetheless, this study further suggests that BDNF is involved in suicidal behavior.

Blood cell studies

As in depressed patients, the BDNF level in blood cells has also been examined in patients with suicidal ideation or in those who have attempted suicide. Deveci et al[185] investigated whether their serum BDNF levels differ among suicide attempters without a major psychiatric disorder compared with patients with MDD and healthy subjects. Ten suicide attempters, 24 patients with MDD, and 26 subjects without any psychiatric diagnosis and any psychiatric treatment were examined. They found that serum BDNF levels were lower in both the attempted suicide group and the MDD group vs the control group. In another study, Kim et al[186] measured plasma BDNF levels in 32 depressed patients who had recently attempted suicide, 32 nonsuicidal depressed patients, and 30 healthy controls. They found that BDNF levels were significantly lower in suicidal depressed patients than nonsuicidal depressed patients or healthy controls. Interestingly, BDNF levels were not different between fatal and nonfatal suicide attempts. Similarly, Lee et al[187] found that plasma BDNF level was decreased in depressed suicidal patients vs depressed nonsuicidal patients. These studies suggest that reduction of plasma BDNF level is related to suicidal behavior in depression and that BDNF level may be a biological marker of suicidal depression. However, when BDNF level was determined in platelets, it was found that platelet BDNF levels were lower in both nonsuicidal and suicidal depressed patients compared with healthy controls, whereas no significant differences were noted between nonsuicidal and suicidal depressed patients.[188] Interestingly, Dawood et al[189]

used direct internal jugular vein blood sampling methods to circumvent the issue of whether BDNF is released from other sources than the brain and they examined the relationship between brain BDNF production and suicide risk in untreated patients with depression. They used veno-arterial BDNF plasma concentration gradient as an index of brain BDNF production. Of the patients, 11 had low suicide risk and 8 had a moderate to high suicide risk. The veno-arterial BDNF concentration gradient was significantly reduced in patients at medium to high suicide risk and there was a significant negative correlation between suicide risk and the internal jugular venous veno-arterial BDNF concentration gradient. This study suggests an association between internal jugular venous BDNF overflow and suicide risk.

Genetic studies linking BDNF to suicide

Hong and colleagues[190] were the first to study an association of BDNF with suicide. They did not find any significant association of Val66Met polyorphism and suicidality in bipolar patients of Chinese origin. Recently, Kim et al[191] examined BDNF Val/Met polymorphism in bipolar disorder in Korean subjects and whether clinical features vary according to genotype. They found that allelic distributions did not differ significantly between bipolar patients and healthy normal controls; however, the rate of suicide attempts among the Val/Val, Val/Met, and Met/Met genotype groups was significantly different. Relative to patients with the Val/Val genotype, those with the Met/Met genotype had a 4.9-fold higher risk of suicide attempts, suggesting that BDNF Val/Met is related to the suicidal behavior in bipolar patients. On the other hand, Sarchiapone et al[192] genotyped 170 depressed patients for their history of suicide attempts and BDNF Val/Met polymorphism. Depressed patients who carried the BDNF Val/Met polymorphism variant (GA + AA) showed significantly increased risk of suicidal behavior. The risk of a suicide attempt was also significantly higher among those reporting higher levels of childhood emotional, physical, and sexual abuse. Secondary analyses suggested that depression severity was a significant risk factor only in the wild-type BDNF genotype, and that the risk of suicide attempts was more predictable within the wild-type group. The same group of investigators extended this study in postmortem samples of subjects who completed suicide and healthy controls.[193] They did not find a significant association of BDNF Val/Met polymorphism with suicide. They argued that even if family studies showed a shared inheritability of suicidal tendencies between suicide attempters and completers, completed suicide and attempted suicide may have two distinct phenomena

and different molecular genetic components may be involved. They also analyzed two other polymorphisms in the *Bdnf* gene, −270C > T and −281C > A, and found their occurrence as less than 5%. Interestingly, Perroud et al[194] examined whether a Val/Met BDNF polymorphism could moderate the effect of childhood maltreatment on the onset, number, and violence of suicidal behavior in suicide attempters. They reported that childhood sexual abuse was associated with violent suicide attempts in adulthood only among Val/Val individuals and not among Val/Met or Met/Met individuals. The severity of childhood maltreatment was significantly associated with a higher number of suicide attempts and with a younger age at onset of suicide attempt. This result suggests that Val/Met modulates the effect of childhood sexual abuse on the violence of suicidal behavior and that BDNF dysfunction may enhance the risk of violent suicidal behavior in adulthood. Altogether, these studies clearly link BDNF polymorphisms to suicidal behavior.

TrkB studies in suicide

Apart from BDNF, TrkB receptors have also been studied in relation to suicidal behavior. We examined the expression levels of TrkB in the same postmortem brain samples in which we determined the expression levels of BDNF. We found that the expression of full-length TrkB was significantly decreased in the PFC and hippocampus of suicide subjects compared with nonpsychiatric healthy controls. Interestingly, we did not find changes in expression of truncated isoform of TrkB (TrkB.T1). We found similar changes in PFC and hippocampus of teenaged suicide subjects.[184] Our finding of decreased full-length TrkB expression in the suicide brain specimen may have serious implications. The decrease in full-length TrkB would not only affect BDNF-induced signaling but also the supply of BDNF to neurons and, thus, the loss of trophic maintenance of a variety of neuronal types, because the catalytically active full-length TrkB is present predominantly within neuronal axons, cell soma, and dendrites.[195] In addition, the undiminished numbers of truncated TrkB would only exacerbate any effects as a result of the loss of catalytically active full-length TrkB, because truncated TrkB inhibits BDNF-mediated neurite outgrowth via the internalization of BDNF. More recently, we examined the functionality of full-length TrkB. We found that tyrosine phophorylation of TrkB was significantly compromised in the brain specimens of suicide subjects.[196] These studies suggest that not only BDNF and TrkB are less expressed, but the functioning of TrkB is also impaired, in suicide brain specimens.

In a recent study, Ernst et al[197] studied truncated TrkB (TrkB.T1) in frontal cortical regions and the cerebellum of suicide subjects. They found that about 36% of suicide completers had significant decreases in different probe sets specific to TrkB.T1 in frontal cortical areas but not the cerebellum. The decrease in TrkB expression was specific to the T1 splice variant. There was no effect of genetic variation in a 2500-base pair promoter region or at relevant splice junctions; however, an effect of methylation state at particular CpG dinucleotides on TrkB.T1 expression was noted. These results suggested a reduction in TrkB.T1 expression in suicide subjects, which was associated with the epigenetic modification of the TrkB.T1 promoter region.

p75^NTR studies in suicide

p75^NTR, initially discovered as a low-affinity receptor for NGF, is now known as a class of receptor that can bind to all neurotrophins with equivalent nanomolar affinities.[198] The 3.8-kb mRNA for p75^NTR encodes a 427-amino acid protein containing a 28-amino acid single peptide, a single transmembrane domain, and a 55-amino acid cytoplasmic domain.[199] Although p75^NTR receptors do not contain a catalytic motif, they interact with several proteins, including Trk receptors, which causes enhancement of ligand specificity and ligand affinities for Trk receptors.[200–202] Functionally, in contrast to Trk receptors, which contain autophosphorylation sites and are involved in cell survival, p75^NTR lacks intrinsic enzymatic activity and can transmit both positive and negative signals.[203] It has been shown that p75^NTR can mediate neuronal apoptosis when the cognate Trk receptor is less activated or not activated.[204] Similarly, p75^NTR can cause developing hippocampal neuronal death induced by neurotrophins in the absence of a Trk receptor.[205–207] In the adult CNS, it has been shown that excitotoxin-induced neuronal apoptosis is accompanied by the induction of p75^NTR in the dying neurons,[208] which suggests that p75^NTR may represent a general stress-induced apoptotic mechanism.[209] However, the apoptotic mechanisms of p75^NTR are active only when Trk receptors are less expressed or less active. Moreover, ectopic expression of the appropriate Trk receptor can convert a proapoptotic neurotrophin to a prosurvival neurotrophin. Thus, it appears that the ratio of expression levels and/or activation states of Trk receptors and p75^NTR is quite relevant in neurotrophin-mediated functions. Recently, we observed that the expression ratio of p75^NTR to Trk receptors is increased in the postmortem brain specimens of suicide subjects. Reduced expression of neurotrophins[181,210] together with reduced expression and activation of Trk and

concomitant increased expression of p75[NTR] indicate that the possible consequence is a tipping of the balance away from cell survival, which could be associated with structural abnormalities and reduced neuronal plasticity in suicide brain specimens.

The two major signaling pathways activated by Trks are Ras-Raf extracellular signal–regulated kinase (ERK) and phosphoinositide 3-kinase (PI3-kinase)-Akt. In addition, phospholipase Cγ binds to activated Trk receptors and initiates an intracellular signaling cascade that results in the activation of protein kinase C. On the other hand, p75[NTR] stimulates several proapoptotic pathways, which include C-Jun kinase signaling, sphingolipid turnover, and association with adaptor proteins, such as neurotrophin receptor–interacting MAGE homolog (NRAGE) and p75[NTR]-associated cell death executor (NADE), that directly promote cell cycle arrest and apoptosis.[211–214] Trk receptors suppress the major proapoptotic signaling pathway, c-Jun kinase, initiated by p75[NTR].[215] In sympathetic neurons, Ras-mediated activation of PI3-kinase is required to suppress this signaling pathway.[216] Activation of Trk receptors completely suppresses the activation by p75[NTR] of sphingomyelinase through the association of activated PI3-kinase with acidic sphingomyelinase.[217,218] Sphingomyelinase activation results in generation of ceramide, which promotes apoptosis by inactivating ERK and PI3-kinase pathways.[219–221] Interestingly, we have reported less-activated ERK1/2[222,223] and PI-3 kinase[224] in both the PFC and the hippocampus of suicide subjects. These findings could be associated with less activation/expression of Trks. These findings also indicate suboptimal activation of prosurvival pathways. Conversely, if p75[NTR] is more abundantly expressed, this may lead to proapoptotic signaling. Further studies are required to determine whether proapoptotic pathways are activated in the brain specimens of suicide subjects and how Trk- and p75[NTR]-mediated signal transduction pathways interplay in the pathophysiology of suicide.

Recently, it has been shown that pro-BDNF binds preferentially to p75[NTR] and elicits apoptosis as opposed to mature BDNF, which binds weakly with p75[NTR] but with high affinity to TrkB, where it exerts neuroprotective activity.[60,225] Thus, pro-BDNF and mature BDNF cause opposite physiological actions through binding to p75[NTR] and TrkB receptors, respectively.[55] In fact, it has been shown that pro-BDNF facilitates long-term depression via activation of p75[NTR].[226] On the other hand, TrkB plays a critical role in early-phase long-term potentiation[227] and conversion of pro-BDNF to mature BDNF is essential for TrkB-mediated late-phase long-term potentiation.[61] In a recent preliminary study, we observed that the level of pro-BDNF is increased PFC and hippocampus of suicide subjects (unpublished observation), whereas a recent genetic study suggests that the S205L polymorphism, which substitutes a serine with a leucine residue, of the p75[NTR] gene is associated with attempted suicide.[228] These studies reveal the crucial roles of pro-BDNF and p75[NTR] in suicidal behavior.

Conclusion and future studies

Several preclinical and clinical observations indicate that depression may be associated with the inability of neural systems to exhibit adaptive plasticity. Given the role of BDNF and its cognate receptors in neural and structural plasticity, and that depression and antidepressants exert opposite actions on BDNF and TrkB expression and functions, it is apparent that BDNF signaling may be crucial in the pathophysiology of depression and in the mechanism of action of antidepressants. It is still unclear how a decrease in BDNF expression leads to depression. Genetic BDNF knock-in and knock-out models could possibly answer this question. However, recent studies suggest that a reduction in BDNF level in BDNF heterozygous knockout mice does not produce depression-like symptoms,[229] although overexpression of TrkB reduces anxiety and depressive behavior in mice.[230,231] On the other hand, overexpression of TrkB.T1 fails to induce a depression-like effect in the forced swim test.[121] Thus, more in-depth studies are required to answer this question.

For suicidal behavior, the studies showing abnormalities in BDNF signaling in suicide are compelling. Many postmortem brain studies in patients who complete suicide and in those with suicidal ideation or attempted suicide show decreased BDNF expression and abnormalities in its cognate TrkB/TrkB.T1 receptor. Although depression is an important factor in suicide, some studies were able to differentiate suicidal behavior vs depressive behavior in terms of decreased level of BDNF. Genetic studies also indicate an association of BDNF to suicidal behavior. Not only BDNF, but signaling mechanisms to which BDNF mediates its functions are also impaired in the brain specimens of suicide subjects. From these studies, it can be assumed that a decrease in BDNF in suicide subjects is independent of psychiatric illness and stress diathesis; however, further studies will be required to answer this complex question.

There are many avenues in BDNF research in depression/suicide that need further attention. For example, what role does dendritic localization of BDNF/TrkB play in altered plasticity in these disorders? What is the significance of enhanced

expression of pro-BDNF and p75[NTR] in the development of depressive/suicidal behavior? Recently, it has been shown that BDNF and TrkB regulate translational machinery in dendrites.[232] Moreover, BDNF induces the expression of Lim kinase 1, a protein kinase whose mRNA translation is inhibited by brain-specific microRNA-134. microRNA 134 is localized in dendrites and its overexpression leads to a decrease in spine size through repression of Lim kinase 1 mRNA translation.[233] Thus, studying BDNF/TrkB and other interacting proteins in dendrites will further reveal their novel mechanistic roles in the development of depression/suicidal behavior.

Acknowledgments and disclosures

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