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Brain-Derived Neurotrophic Factor and Suicide Pathogenesis

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Abstract

Suicide is a major public health concern. The etiology and pathogenic mechanisms associated with suicidal behavior are poorly understood. Recent research on the biological perspective of suicide has gained momentum and appears to provide a promising approach for identifying potential risk factors associated with this disorder. One of the areas that has gained the most attention in suicide research is the role of brain-derived neurotrophic factor (BDNF), which participates in many physiological functions in the brain, including synaptic and structural plasticity. Several studies consistently show that expression of BDNF is reduced in blood cells of suicidal patients and in brains of subjects who committed suicide. Recent studies also demonstrate abnormalities in the functioning of BDNF, because its cognate receptors (tropomyosin receptor kinase B and pan75 neurotrophic receptor) are abnormally active and/or expressed in the postmortem brains of suicide subjects. There is further evidence of the role of BDNF in suicide as numerous studies show a strong association of suicidal behavior with BDNF functional polymorphism. Overall, it appears that abnormalities in BDNF signaling may serve as an important biological risk factor in the etiology and pathogenesis of suicide.

Keywords

BDNF; genetics; neurotrophins; p75^{NTR}; suicide; TrkB

Introduction

Suicide is a major public health concern. About one million people commit suicide worldwide each year (1). The lifetime suicide attempt rate among adults is about 10% (2). On the other hand, among adolescents, it is the 3rd leading cause of death after motor vehicle accidents and homicide (3). More than 90% of suicides are associated with mental illnesses (4), and 60% of them occur in the context of depressive disorder, although almost all psychiatric disorders are characterized by an increased risk of suicidal behavior. Therefore, the existence of suicidal syndromes independently of psychiatric illnesses has been proposed (5). Recently, Mann et al. (6) proposed a stress-diathesis model, which postulates that suicidal behavior may be understood as a function of the interplay between state-dependent factors, such as illness and life events, and trait-dependent factors, which include biological markers for suicidal behavior. Previously, most of the studies of suicidal behavior were focused on the roles of psychosocial and sociocultural factors; however, these factors are of too little predictive value to be of clinical use. Recently, research on the biological perspective of suicide has gained a stronghold and appears to provide a promising approach to identify potential risk factors associated with suicide.

An emerging hypothesis suggests that the pathogenesis of suicide/depression involves altered plasticity of neuronal pathways (7). 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 and structural plasticity (8,9). Support for this theory comes from studies demonstrating altered brain structure during stress and in depressed and suicidal patients. For example, Altshuler et al. (10) reported that suicide subjects had smaller parahippocampi than did normal controls. In another study, using three-dimensional cell counting, Rajkowska (11,12) reported that suicide completers had increased neuronal density, and reduced laminar width and neuronal size in dorsolateral prefrontal cortex. Using magnetic resonance imaging, Bremner et al. (13) found that the volume of the hippocampus in patients with major depression had a statistically significant smaller hippocampal volume than normal control subjects. Anatomical studies also show structural changes in brains of depressed subjects such that reductions in spine density and arborization of subicular apical dendrites (14) and glial cell density in layer V and neuronal size in layer VI of frontal cortex (15) have been reported. As far as synaptic plasticity is concerned, Aganova (16) reported reduced synaptic contacts in the anterior limbic cortex in psychoses patients, whereas antidepressant treatment triggers pyramidal dendritic spine synapse formation (17). On the other hand, Honer et al. (18) reported reduced expression of several synaptic-enriched proteins in psychosis patients, whereas stress causes shortening and debranching of dendrites in the CA3 region of the hippocampus and suppresses neurogenesis of dentate gyrus granule neurons (19) and synapse formation (20). In addition, chronic stress causes neuronal atrophy (20) and spatial cognition deficits (21). Altogether, these studies clearly demonstrate altered structural and synaptic plasticity in depression and suicide.

Neurotrophins are growth factors that are critical in regulating structural, synaptic, and morphological plasticity and in modulating the strength and number of synaptic connections and neurotransmission (22). In addition, the role of neurotrophins in the adult central nervous system is quite important because they participate in the maintenance of neuronal functions, the structural integrity of neurons, and neurogenesis (23), suggesting their biological role over the entire life span. Neurotrophins are homodimeric proteins and are categorized into 4 different classes: nerve growth factor, brain-derived neurotrophic factor (BDNF), neurotrophin 3, and neurotrophin 4/5. Of these four classes, the most important and widely distributed member is BDNF (24). The *BDNF* gene lies on the chromosome 11p13 and encodes pro-BDNF, a precursor peptide of mature BDNF (25). The pro-BDNF is produced in the endoplasmic reticulum, which is accumulated in the trans-Golgi network via the Golgi apparatus. It has been suggested that pro-BDNF binds to sortilin in the Golgi apparatus, which facilitates the correct folding of the mature domain. The mature domain of BDNF binds to carboxypeptidase E, thereby sorting BDNF to the regulated secretory pathway (26). A substitution of valine (Val) to methionine (Met) at codon 66 in the prodomain impairs this sorting of BDNF (27). Mature BDNF originates through proteolytic cleavage mediated by plasmin (28).

BDNF mediates its biological action after binding to tropomyosin receptor kinase B (TrkB). Binding of BDNF to the TrkB receptor leads to the dimerization and transphosphorylation of tyrosine residues in the intracellular domain of the TrkB receptors and to subsequent activation of cytoplasmic signaling pathways (29). Another class of receptor to which BDNF binds is p75 neurotrophin receptor (p75^{NTR}), which plays an important role in neurotrophin transport, ligand binding specificity, and Trk functioning (30).

BDNF is directly involved in neurite outgrowth, phenotypic maturation, morphological plasticity, and synthesis of proteins for differentiated functioning of neurons and for synaptic functioning (24). BDNF is also involved in nerve regeneration, structural integrity, and

maintenance of neuronal plasticity in adult brain, including regulation of synaptic activity, and in neurotransmitter synthesis (31). Thus, a pathological alteration of the BDNF 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. Because of the role played by BDNF in regulating structural, synaptic, and morphological plasticity, there has been great interest in its role in the pathogenic mechanisms of depression. The role of BDNF in depression has gained broad attention because many preclinical and clinical studies provide direct evidence suggesting that modulation in the expression of BDNF could be involved in behavioral phenomena associated with stress and depression. Based on these studies, the neurotrophin hypothesis of depression was proposed, which suggests that depression is associated with decreased expression of BDNF and that antidepressants alleviate depressive behavior by increasing its level (32,33). More recently, it has been suggested that the relationship of BDNF with depression is not straightforward, although the role of BDNF in the mechanisms of action of antidepressants is a consistent phenomenon (34).

In recent years, there has been a great interest in examining the role of BDNF in suicide. This is because: 1) depression is a major component of suicide, 2) there is a strong association of stress with suicide, and 3) both depression and stress regulate BDNF expression. In this context, whether the role of BDNF in suicide is independent of depression has been the major focus of research. This review comprehensively discusses the recent findings of a possible role of BDNF in suicide pathogenesis. We have discussed BDNF studies in postmortem brain of suicide subjects with or without depression, levels of BDNF in blood cells of suicidal patients, and genetic association studies linking BDNF to suicide. Because BDNF binds to TrkB and p75^{NTR} receptors, the implications of these molecules in suicidal behavior have also been discussed. At the current state of research on BDNF in suicide, it is impossible to perform meta-analysis. All the information pertaining to the role of neurotrophins in suicide, therefore, came from searches of the MEDLINE database (1990 to the present) and from literature cited in review articles.

Role of BDNF in Stress: A Major Factor in Suicidal Behavior

Stress pathway and suicidal behavior

One of the primary responses to stress is the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Briefly, in response to a stress, hypothalamus releases corticotropin-releasing hormone (CRH), which in turn causes secretion of adrenocorticotropin hormone (ACTH) into the bloodstream from the anterior pituitary gland. ACTH travels to the adrenal glands where it stimulates the production and release of cortisol. HPA axis is a closed-loop system, in which cortisol acts to regulate its own secretion through feedback inhibition. Cortisol acts on mineralocorticoid receptors and glucocorticoid receptors to maintain the circadian variation of the HPA axis. Mineralocorticoid receptors are high-affinity receptors which are predominantly occupied under basal conditions and help maintain HPA axis tone, whereas glucocorticoid receptors are bound during times of stress and play a major role in turning off the HPA axis.

Several studies show that stress is a major risk factor in suicidal behavior (reviewed in 35). For example, there is strong evidence for a connection between the HPA axis and suicidal behavior. This is evident from studies showing elevated corticotrophin-releasing hormone levels in the cerebrospinal fluid, reduced corticotrophin-releasing hormone binding sites in the frontal cortex, augmented pro-opiate-melanocortin RNA density in the pituitary gland, large corticotrophic cell size, and alterations in the mineralocorticoid to glucocorticoid receptor messenger RNA (mRNA) ratio in the hippocampus of subjects who committed suicide (36,37,38,39,40). Also, a consistent association has been found between subsequently

completed suicide and nonsuppression of cortisol in the dexamethasone suppression test (41,42,43).

Stress and BDNF

There is a strong connection between overactive stress system and BDNF expression in the brain. Smith et al. (44) demonstrated that immobilization stress significantly decreased BDNF mRNA expression in the hippocampus, most notably in the dentate gyrus, which was later confirmed by other investigators (45,46). Using a different stress paradigm, Rasmusson et al. (47) demonstrated that exposure to foot shocks decreased dentate gyrus BDNF mRNA in the rat hippocampus. Other stressors, such as social defeat, decreased BDNF not only in the hippocampus but also in cortical and subcortical areas of mice (48).

Another approach to examine the role of BDNF in stress is to expose the rodents with exogenous glucocorticoids. As with stress paradigms, exposure of exogenous corticosterone to rats reduced BDNF expression in the hippocampus (44,49). Recently, we examined the effects of corticosterone treatment on BDNF expression 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 (50). Interestingly, removal of corticosterone by adrenalectomy increased the level of BDNF in the hippocampus (51,52), whereas supplementation of the synthetic glucocorticoid dexamethasone to adrenalectomized rats restored the level of BDNF to normal (51). These studies demonstrate that expression of BDNF is under regulation of circulating glucocorticoids.

How BDNF is regulated by glucocorticoids is not clearly known; however, on a molecular level, BDNF is highly regulated. The rat *bdnf* gene contains 4 distinct promoters that are linked to 4 main transcript forms (53). Each transcript has 4 short 5' noncoding exons (I-IV) containing separate promoters and one shared 3' exon (exon V) encoding the mature BDNF protein. These transcripts facilitate multilevel regulation of BDNF expression and determine the tissue-specific expression. Recently, we observed that corticosterone decreased the expression of only transcripts II and IV, but not transcript I or III, in the rat frontal cortex and hippocampus (50). Two other studies also suggest that immobilization stress decreased total BDNF expression, along with a specific decrease in exon IV in the hippocampus (54) and hypothalamus (55). These studies suggest that expression of BDNF is regulated by glucocorticoids, which is the result of a decrease in the expression of the selective BDNF transcripts.

BDNF Studies in Blood Cells of Subjects with Suicidal Ideation and Suicide Attempters

Very recently, many studies have examined BDNF levels in the blood cells of suicidal subjects. Although the significance of BDNF in blood cells is not clear, it has been shown that BDNF may cross the blood-brain barrier and that platelet BDNF postnatally shows changes similar to the brain (56), suggesting that there are parallel changes in the blood and brain levels of BDNF. Kim et al. (57) measured plasma BDNF levels in depressed patients who had recently attempted suicide, nonsuicidal depressed patients, and healthy controls. They found that the BDNF level was significantly lower in suicidal depressed vs nonsuicidal depressed patients or healthy controls. Interestingly, BDNF levels were not different between fatal and nonfatal suicide attempts. Similarly, Lee et al. (58) found that the plasma BDNF level was significantly decreased in depressed suicidal patients vs depressed nonsuicidal patients. Interestingly, Dawood et al. (59) used direct internal jugular vein blood sampling methods to circumvent the issue of whether BDNF is released from sources other than the brain. They examined the relationship between brain BDNF production and suicide

risk in patients with depression who were free of medication. They found that the venoarterial BDNF concentration gradient was significantly reduced in patients at medium to high suicide risk and that there was a significant negative correlation between suicide risk and the internal jugular venous venoarterial BDNF concentration gradient. In contrast to these studies, Deveci et al. (60) reported that the serum BDNF level was lower in both the attempted suicide group and the depressed group vs the control group. Similarly, the platelet BDNF level was lower in both nonsuicidal and suicidal depressed patients compared with healthy controls (61).

BDNF Studies in Postmortem Brain of Suicide Completers

Because of the limited availability of postmortem brain tissues, there have been only a few studies examining BDNF in suicide completers. To our knowledge, we were the first to examine the role of BDNF in postmortem brain tissues of subjects who committed suicide. We determined mRNA and protein expression of BDNF in the prefrontal cortex (PFC) and hippocampus of suicide subjects and nonpsychiatric healthy control subjects (62). We found that the mRNA level of BDNF was significantly lower in both the PFC and hippocampus of suicide subjects. Using antibody that recognizes mature BDNF, we also found significantly decreased protein level of BDNF in the PFC and hippocampus of suicide subjects. The decreased protein level of BDNF was significantly correlated with its mRNA level, which suggests that there is less synthesis of BDNF in brains of suicide subjects. Interestingly, when we divided suicide subjects into those who had a history of depression and those who had other psychiatric disorders, we found that a decrease in expression of BDNF was present in all suicide subjects regardless of psychiatric diagnosis. Thus, our findings demonstrate that a reduced level of BDNF is associated with suicidal behavior. More recently, Karege et al. (63) examined the expression of BDNF in the PFC, hippocampus, and entorhinal cortex of suicide subjects. Similar to our findings, they reported that the level of BDNF was significantly decreased in the PFC and hippocampus; however, they did not find any change in the entorhinal cortex, suggesting that a decrease in BDNF may be specific only to brain areas that are related to emotion and cognition. Karege et al. (63) also 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, Kozicz et al. (64) examined the gender difference in the expression of BDNF in suicide subjects. They found that the BDNF level was much lower in the midbrain 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 other studies did not find sex-specific changes in BDNF expression in the hippocampus or cortical areas of suicide subjects (62,63), whether the sex-specific effect in BDNF expression is specific to the midbrain area needs to be further studied.

In a recent study, we attempted to delineate the pathogenic mechanisms of adult suicide vs teenage suicide, because the epiphenomenon of teenage suicide may be different than that of adults (65). As with adult suicide, we found that the expression of BDNF mRNA was decreased in the PFC and hippocampus of teenage suicide subjects; however, the protein expression of BDNF was decreased only in the PFC but not in the hippocampus. Thus, there is a disconnection between mRNA and protein expression of BDNF in the hippocampus of teenage suicide subjects. There is a possibility that differences in expression of BDNF between the PFC and hippocampus of teenage suicide subjects could be associated with defective translation of BDNF in the hippocampus. Further studies are needed to clarify this important issue.

Genetic Studies of BDNF in Patients with Suicidal Behavior

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 (Val66Met). As mentioned earlier, this Met66 variant affects activity-dependent BDNF secretion (27). 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 (66). More interestingly, the BDNF Met/Met or Val/Met allele is associated with reduced hippocampus volume (67). Furthermore, the Val66Met polymorphism in the *BDNF* gene modulates human cortical plasticity and the response to transcranial magnetic stimulation (68).

In a Chinese population of bipolar subjects (69), there was no association of the BDNF Val66Met polymorphism with suicidal behavior; however, recently, Kim et al. (70) reported that in a Korean population, although the allelic distributions did not differ between bipolar patients and healthy controls, 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 suicidal behavior in bipolar patients. Similarly, Iga et al. (71) reported that BDNF polymorphisms were not associated with depression but were significantly associated with suicidal behavior. More recently, Sarchiapone et al. (72) studied depressed patients for their history of suicide attempts and BDNF polymorphism. They found that there was a significantly increased risk of suicidal behavior in depressed patients who carried the BDNF Val/Met polymorphism variant (GA + AA). 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. In a postmortem brain study of subjects who committed suicide, Zarrilli et al. (73) found no significant association of the BDNF Val/Met polymorphism and suggested that completed suicide and attempted suicide may have two distinct phenomena and that different molecular genetic components may be involved. Zarrilli et al. (73) also analyzed two other polymorphisms in the *BDNF* gene, -270C > T and -281C > A, and found their occurrence as less than 5%. Vincze et al. (74) genotyped the BDNF polymorphism in bipolar patients and healthy controls. They found G196 alleles and severity of suicidal behavior in bipolar patients. In another study, Perroud et al. (75) 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 found 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.

TrkB Studies in Postmortem Brains of Suicide Completers

As mentioned in the "Introduction," BDNF mediates its physiological actions via interaction with the TrkB receptors. The *TRKB* gene gives rise to two isoforms: the full-length or catalytic form and truncated or noncatalytic form. The main biological actions of BDNF are mediated via full-length TrkB, which is catalytically active. On the other hand, the "truncated" TrkB" (TrkB.T1) lacks a large part of the intracellular domain and does not display protein-tyrosine kinase activity (76). Binding with BDNF leads to activation of the

full-length TrkB by ligand-induced dimerization and autophosphorylation of tyrosine residues in the intracellular region. The activated TrkB interacts and phosphorylates several intracellular targets. The truncated TrkB is also a predominant isoform in the adult brain (77) and functions 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 (76). It has been shown that BDNF signaling is impaired as a consequence of the formation of receptor heterodimers (78), which suggests that the truncated form of TrkB can also act as a negative modulator of BDNF signaling.

TrkB has been studied in postmortem brains of suicide subjects, although not extensively. We reported that the expression of full-length TrkB was significantly lower in the PFC and hippocampus of adult suicide subjects compared with age-matched healthy controls (62). On the other hand, no significant change was noted in the expression of TrkB.T1 (62). When examined in brains of teenage suicide subjects, we found similar changes in the expression of full-length TrkB (65). Our findings suggest that suicide is not only associated with a decreased level of BDNF, but that functions of BDNF via TrkB are also impaired. In addition, a decrease in full-length TrkB may also affect 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 (79). In addition, the presence 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 functional status of full-length TrkB in these suicide subjects. We observed that tyrosine phosphorylation of TrkB was significantly lower in the brains of suicide subjects (80). These studies suggest that both BDNF and TrkB are less expressed; also, the functioning of TrkB is impaired in suicide brain.

Recently, Ernst et al. (81) studied TrkB.T1 in the postmortem brains of suicide subjects and found that a significant population of suicide completers had a decrease in different probe sets specific to TrkB.T1 in frontal cortical areas. The decrease 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, the effect of the methylation state at CpG dinucleotides on TrkB.T1 expression was noted, suggesting that a reduction in TrkB.T1 expression in suicide subjects may be associated with the epigenetic modification of the TrkB.T1. This was further confirmed by the same group of investigators, who found a significant increase in methylation state at Lysine 27 (H3) of TrkB.T1 promoter in the prefrontal cortex of suicide subjects which was inversely correlated with expression level of TrkB.T1 (82).

p75^{NTR} Expression: Relationship to Suicidal Behavior

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 (30). 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 (83). On the other hand, p75^{NTR} can send negative signals. For example, p75^{NTR} can cause developing hippocampal neuronal death, induced by neurotrophins in the absence of a Trk receptor (84). In the adult central nervous system, excitotoxin-induced neuronal apoptosis is accompanied by the induction of p75^{NTR} in the dying neurons (85), which suggests that p75^{NTR} may represent a general stress-induced apoptotic mechanism. Interestingly, the apoptotic mechanisms of p75^{NTR} are active only when Trk receptors are less expressed or less active. Moreover, ectopic expression of the Trk receptor can convert a proapoptotic neurotrophin to a prosurvival neurotrophin. Thus,

the ratio of expression levels and/or activation states of Trk receptors and p75^{NTR} is quite important in neurotrophin-mediated functions. Recently, we observed that the expression ratio of p75^{NTR} to Trk receptors is increased in the postmortem brain of suicide subjects (80). Reduced expression of neurotrophins, together with reduced expression and activation of Trk and concomitant increased expression of p75^{NTR}, indicates 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. The mechanisms responsible for p75^{NTR}-induced apoptotic functions are still not very clear. However, several studies demonstrate that p75^{NTR} includes c-Jun kinase signaling, sphingolipid turnover, and association with adaptor proteins, such as the neurotrophin receptor-interacting MAGE homolog and p75^{NTR}-associated cell death executor, which directly promote cell cycle arrest and apoptosis (86). In contrast, Trk receptors suppress c-Jun kinase and activation of sphingomyelinase, initiated by p75^{NTR}. Sphingomyelinase activation results in the generation of ceramide, which promotes apoptosis by inactivating extracellular signal-regulated kinase and phosphoinositide 3-kinase pathways (87). Interestingly, we have reported less-activated extracellular signal-regulated kinase 1/2 (88,89) and phosphoinositide 3-kinase (90) signaling in the postmortem brains of suicide subjects, which could be associated with less activation/expression of Trks.

In addition to Trks, pro-BDNF also plays an important role in p75^{NTR}-mediated apoptosis (91). Thus, pro-BDNF and mature BDNF can cause opposite physiological actions through binding to p75^{NTR} and TrkB receptors, respectively (92). In a recent study, we observed that the level of pro-BDNF is increased postmortem brains of suicide subjects (unpublished data, Dwivedi et al., 2009) whereas a genetic study suggests that the S205L polymorphism, which substitutes a serine with a leucine residue of the p75^{NTR} gene, is associated with a attempted suicide (93). These studies suggest that mature BDNF, pro-BDNF, and p75^{NTR} may also play an important role in suicide pathogenesis. Further studies are required to determine whether p75^{NTR}-mediated proapoptotic pathways are active in the brain of suicide subjects and how Trk- and p75^{NTR}-mediated signal transduction pathways interplay in the pathophysiology of suicide.

Summary and Conclusion

In this review, we have summarized and integrated recent findings that implicate BDNF in suicide. The evidence demonstrating the involvement of BDNF in suicide ranges from human postmortem brain studies of subjects who committed suicide to studies of those who attempted suicide or had suicidal ideation. In general, it appears that the expression and functioning of BDNF are down-regulated in suicidal patients. Although depression is an important factor in suicide, several studies were able to differentiate suicidal behavior from depression in terms of abnormalities in BDNF. Studies also show that stress causes similar changes in BDNF, as in suicidal subjects, suggesting that stress may be playing an important role in BDNF down-regulation in suicidal patients. Most genetic studies also implicated an association of the BDNF functional polymorphism with suicidal behavior. On one hand, these studies provide compelling evidence linking BDNF with suicide. On the other hand, these studies raise several questions: 1) How is BDNF regulated and how does a reduction in BDNF expression or the Val66Met polymorphism induce suicidal behavior? 2) What is the significance of enhanced expression of pro-BDNF and p75^{NTR} in the development of depressive/suicidal behavior? 3) Is there a role of p75^{NTR}-mediated apoptotic signaling in the development of suicidal behavior? 4) What is the significance of dendritic localization of TrkB and how can that affect BDNF signaling in suicide brain? Recently, it has been shown that 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 (94). Thus, studying BDNF/TrkB and other interacting proteins in dendrites will further reveal their novel mechanistic roles in the development of suicidal behavior. Overall, in view of the current findings, a novel concept of the neurobiology of suicide is evolving in which disruptions in BDNF signaling could be seen as important biological risk factors that may be useful in delineating the etiology of this disorder and that may eventually result in site-specific therapeutic interventions.

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Abbreviations

BDNF	brain-derived neurotrophic factor
ERK	extracellular signal-regulated kinase
HPA	hypothalamic-pituitary-adrenal axis
p75^{NTR}	pan 75 neurotrophic receptor
TrkB	tropomyosin receptor kinase B
TrkB.T1	truncated TrkB receptor

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Key Messages

- BDNF is a member of the neurotrophin family that is involved in neuronal growth, phenotypic maturation, morphological plasticity, and synthesis of proteins for differentiated functioning of neurons and synaptic functioning.
- BDNF expression is decreased in the postmortem brain of subjects who committed suicide and in the blood cells of those patients who attempted to commit suicide or had suicidal ideation.
- There is a strong association of functional BDNF polymorphism and suicidal behavior.
- There appears to be abnormalities in BDNF signaling in suicide brain, because altered expression and/or functions of BDNF receptors (tropomyosin receptor kinase B and pan 75 neurotrophic receptor) have been noted in the brain of suicide subjects.
- Overall, it appears that BDNF may be playing a role in the pathogenic mechanisms of suicide. Further in-depth studies are required to delineate how BDNF is involved in suicidal behavior.

Figure 1. Postulated hypothesis for the role of BDNF and p75^{NTR} in suicidal behavior
 Reductions in BDNF and TrkB and upregulation of pro-BDNF and p75^{NTR} may cause altered structural and neural plasticity, which may be crucial in the etiology and pathogenesis of suicidal behavior. Abbreviations: BDNF, brain-derived neurotrophic factor; LTD, long-term depression; LTP, long-term potentiation; p75^{NTR}, pan 75 neurotrophin receptor; TrkB, tropomyosin receptor kinase B.

Table 1Summary of BDNF, TrkB, and p75^{NTR} studies in suicide

Studies	Outcome	Reference
BDNF STUDIES		
Blood cell studies	Decrease	57, 58, 59, 60, 61
Postmortem Brain studies		
PFC	Decrease	62, 63, 65
Hippocampus	Decrease	62, 63
Hippocampus	No change	65
Entorhinal cortex	No change	63
Genetic Association Studies (Val66Met polymorphism)	No association	69, 73
	Positive association	70, 71, 72
TrkB STUDIES		
Full-length TrkB	Decrease	62, 80
Truncated TrkB.T1	No change	62, 65
Truncated TrkB.T1	Decrease	81
p75^{NTR} STUDIES		
Postmortem Brain Studies	Increase	80
Genetic Association (S205L polymorphism)	Positive association	93