Commentary

Brain-derived neurotrophetic factor and suicidal behavior

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Summary

Studies of the neurobiology of suicidal behavior have become an important and integral part of psychiatric research. Over the past several years, studies of the role of brain-derived neurotrophic factor (BDNF) in the pathophysiology of suicidality have attracted significant interest of researchers. Multiple lines of evidence including studies of levels of BDNF in blood cells and plasma of suicidal patients, postmortem brain studies in suicidal subjects with or without depression, and genetic association studies linking BDNF to suicide suggest that suicidal behavior may be associated with a decrease in BDNF functioning. Studies of the BDNF function are important for suicide research and prevention because of the multiple reasons including the following: (i) BDNF plays a role in the pathophysiology of depression, post-traumatic stress disorder, substance use disorders and other conditions associated with suicidal behavior. Treatment-induced enhancements of BDNF can facilitate neural integrity and recovery of function in psychiatric disorders, and consequently prevent suicidal behavior; (ii) abnormal BDNF function may be associated with elevated suicidality independently of psychiatric diagnoses. It is possible that treatment-induced improvement in the BDNF function prevents suicidal behavior independently of improvement in psychiatric disorders; (iii) BDNF may be a biological marker of suicidal behavior in certain patient populations. It is to be hoped that the studies of the neurobiology of suicidal behavior will lead to the development of new methods of suicide prevention.

Introduction

Suicidal behavior is a multifaceted medical and social problem. 1,2 Each year ~1 million people in the world die by suicide, including ~35 000 people in the USA and ~6000 people in the UK. 1-5 It is estimated that there are from 10 to 20 times as many suicide attempts as suicide deaths. More than 90% of suicides are associated with psychiatric illnesses, and 60% of them occur in the context of depression, although almost all psychiatric disorders are characterized by an increased risk of suicidal behavior. 1,2 The existence of suicidal traits independently of psychiatric disorders has been proposed. 1,6 Suicidal behavior may be conceptualized as a function of the interplay between state-dependent factors, such as psychiatric, neurological or medical illness and life events, and trait-dependent factors, which include biological markers for suicidal behavior. Studies of the neurobiology of suicidal behavior have become an important and integral part of psychiatric research.
Over the past several years, studies of the role of brain-derived neurotrophic factor (BDNF) in the pathophysiology of suicidality have attracted significant interest of researchers.\textsuperscript{7,8}

**BDNF**

Neurotrophic factors are homodimeric proteins known to have a wide range of roles in development and function of the nervous system.\textsuperscript{7–10} They promote neuronal survival, regulate many aspects of neuronal development and function, including synapse formation and synaptic plasticity. Mammalian neurotrophins include BDNF, nerve growth factor (NGF), neurotrophin (NT) 3 and NT 4/5 and continued to be a focus for research. The neurotrophins have similar structure, biochemical characteristics and bind to two types of receptors: tyrosine kinase receptors TrkA, TrkB or TrkC, or a common low-affinity neurotrophin receptor p75 (p75NTR) that has no tyrosine kinase domain. Of various neurotrophins, BDNF has attracted a lot of interest because of its potential role in the pathophysiology of different psychiatric and neurological disorders including depression, schizophrenia, obsessive-compulsive disorder, Alzheimer’s disease, Huntington’s disease, Rett syndrome, dementia, anorexia nervosa, bulimia nervosa and suicidal behavior. BDNF was discovered in the beginning of 1980s by Yves Barde, Hans Thoenen and their colleagues.\textsuperscript{11} They succeeded in identifying and purifying a factor from the brain that they named brain-derived neurotrophic factor (BDNF). BDNF plays critical roles in the survival, maintenance, and growth of the brain and peripheral neurons. BDNF is found in different tissues and cell types, not just in the brain. Existing scientific evidence suggests that abnormal BDNF function may result in suicidal behavior because (i) it contributes to the pathophysiology of depression, posttraumatic stress disorder (PTSD), substance dependence and other psychiatric disorders associated with suicidal behavior; and (ii) it may contribute to the neurobiology of suicidal behavior independently of other psychiatric conditions.\textsuperscript{7,8}

**BDNF and the pathophysiology of psychiatric disorders associated with suicidal behavior**

Many preclinical and clinical studies provide direct evidence suggesting that modulation in the expression of BDNF could be involved in the biological mechanisms of stress, depression and substance use disorders.\textsuperscript{12–14} There is a link between overactive stress system and BDNF expression in the brain. Chronic stress or prolonged exposure to glucocorticoids can reduce BDNF levels and impair hippocampal function, by producing dendritic retraction, restructuring, and disconnection.\textsuperscript{15} Repeated stress can lead to neuronal atrophy and loss in several brain regions, including the hippocampus\textsuperscript{16} and it reduces the BDNF mRNA expression. It has been demonstrated that immobilization stress significantly decreased BDNF mRNA expression in the hippocampus, most notably in the dentate gyrus.\textsuperscript{17} A human study demonstrated significantly lower plasma BDNF levels in PTSD patients compared with healthy controls suggesting its possible involvement in the pathophysiology of PTSD in humans.\textsuperscript{18}

BDNF has been found to be decreased in serum and the hippocampus of depressed patients and successful antidepressant treatment increases BDNF back to normal levels.\textsuperscript{13,19–21} A recent study suggests that the absence of an early increase of BDNF in conjunction with early non-improvement might be a highly specific peripheral marker predictive for treatment failure in patients with MDD.\textsuperscript{22} Based on these and other studies, the BDNF 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. The antidepressant-induced BDNF signaling does not make changes itself.\textsuperscript{23} Antidepressants improve plasticity and allow the activity-dependent environmental signals to alter the network so that it can model the outside world. This indicates that antidepressants should be combined with psychosocial treatments such as psychotherapy and physical exercise. It is of interest to note that an indirect approach for enhancing BDNF is through exercise. In one study, brain-injured rats showed increased levels of BDNF and enhancement of cognitive performance following exercise.\textsuperscript{24} This indicates that exercise might enhance BDNF function in individuals with psychiatric disorders.

BDNF is expressed in the dopaminergic mesocorticolimbic pathway beginning in the ventral tegmental area and nucleus accumbens, known as the reward pathway.\textsuperscript{14,25,26} Recent findings implicate BDNF as a key mediator of reward processes and substance dependence. For example, psychoactive drugs such as cocaine, amphetamine or ethanol, either injected or self-administered, increase BDNF mRNA and protein levels in the paraventricular hypothalamus and in several mesocorticolimbic areas including the prefrontal cortex, the basolateral amygdala, the piriform and cingulate cortices and the striatum.
Studies of BDNF in individuals with suicidal behavior

BDNF and suicide attempts

A recent study examined plasma BDNF levels in major depressive disorder (MDD) patients who had recently attempted suicide, non-suicidal MDD patients and normal controls and found that reduction of plasma BDNF level was related to suicidal behavior in depression. The authors proposed that BDNF level may be a biological marker of suicidal depression. Another recent study examined BDNF mRNA expression in peripheral blood mononuclear cells (PBMCs) of patients with major depression who had or had not recently attempted suicide. The BDNF mRNA expression was reduced in PBMCs of patients with major depression compared to healthy controls. Among depressed patients, BDNF mRNA expression was lower in suicide attempters.

BDNF and completed suicides

Post-mortem studies showed significantly lower BDNF levels in the hippocampus and prefrontal cortex of suicide victims regardless of psychiatric diagnosis. It has recently been reported that BDNF promoter/exon IV is frequently hypermethylated in the Wernicke area of the post-mortem brain of suicide patients irrespective of genome-wide methylation levels, indicating that a gene-specific increase in DNA methylation could cause or contribute to the downregulation of BDNF expression in suicide patients. It has also been observed that the combined Met/Met and Met/Val genotypes of the BDNF Val66Met variant could be the risk factor for violent suicide in female subjects and for suicide in victims exposed to childhood trauma.

Discussion

Multiple lines of evidence including studies of levels of BDNF in blood cells and plasma of suicidal patients, post-mortem brain studies in suicidal subjects with or without depression and genetic association studies linking BDNF to suicide suggest that suicidal behavior may be associated with a decrease in BDNF functioning. The low-BDNF levels in suicidal patients can be explained by the fact that decreased serotonin function in suicidal depression could down-regulate BDNF expression. BDNF and serotonin are known to regulate synaptic plasticity, neurogenesis and neuronal survival, and these two signals co-regulate one another. Abnormal serotonin signaling could decrease expression of BDNF in suicidal depression. Another possible explanation for low-BDNF levels in suicidal depression is that the stress associated with a suicide attempt could suddenly decrease BDNF after the attempt. Also, stressful events such as a suicide attempt may alter the responsiveness of the HPA system and stress-induced elevation of glucocorticoids reduces expression of BDNF levels in blood and brain.

Conclusion

Studies of the BDNF function are important for suicide research and prevention because of the multiple reasons including the following.

- BDNF plays a role in the pathophysiology of depression, post-traumatic-stress disorder, substance use disorders and other conditions associated with suicidal behavior. Treatment-induced enhancements of BDNF can facilitate neural integrity and recovery of function in psychiatric disorders, and consequently prevent suicidal behavior.
- Abnormal BDNF function may be associated with elevated suicidality independently of psychiatric diagnoses. It is possible that treatment-induced improvement in the BDNF function prevents suicidal behavior independently of improvement in psychiatric disorders.
- BDNF may be a biological marker of suicidal behavior in certain patient populations.

It is important to note that biological markers for suicide may be in fact indicators of psychiatric disorders and/or personality traits associated with suicidal behavior. For example, we cannot rule out a possibility that BDNF is a marker of a subtype of depression. Despite increasing insight into the neurobiology of suicidal behavior, it is not clear to what extent current treatment interventions are actually associated with a reduced occurrence of suicidal behavior. It is to be hoped that the studies of the neurobiology of suicidal behavior will lead to the development of new methods of suicide prevention. We should prevent thousands and thousands of unnecessary deaths.

Conflict of interest: None declared.

References

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