Review Article

Brain-Derived Neurotrophic Factor and Suicide in Schizophrenia: Critical Role of Neuroprotective Mechanisms as an Emerging Hypothesis

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ABSTRACT

Suicide is a common occurrence in psychiatric disorders and is a cause of increased healthcare utilization worldwide. Schizophrenia is one of the most common psychiatric disorders worldwide and posited to be seen in 1% of the population worldwide. Suicide is a common occurrence in schizophrenia with 25%–30% patients with schizophrenia attempting suicide and 8%–10% completing it. There is a need for valid biological markers to help clinicians identify patients with schizophrenia that may be at a risk of suicide and thus help in them receiving better care and interventions at the earliest even before a suicide attempt occurring. There are clear neurobiological changes at a genetic, neuroimaging, and neurochemical level that occurs in patients with schizophrenia that attempt suicide. There is a new theory that postulates neuronal plasticity and neuroprotection to have a role in the biological changes that ensue when suicidal thoughts and feelings occur in patients with schizophrenia. Neurotrophic growth factors like brain-derived neurotrophic factor (BDNF) have been documented to play a role in the protection of neurons and in the prevention of neurobiological changes that may lead to suicide both in schizophrenia and depression. The present paper presents a commentary that looks at the role of BDNF as a protective factor and neurobiological marker for suicide in schizophrenia.

Key words: *Brain-derived neurotrophic factor, neurobiology, neuronal plasticity, neuroprotection, schizophrenia, suicide*

INTRODUCTION

Suicide is a public health problem which is commonly noted in 35%–40% of psychiatric disorders worldwide.[1] It causes severe burden, loss of financial resource increased health care utilization. Suicide rates have not declined over the past decade.[2] It continues to increase despite revolutionary advances in treatments. It has been noted that 20% beds in intensive care, 50% beds in acute psychiatric wards, and 50% beds in psychiatric community care units may have patients with current or at least one past suicide

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attempt.[3] About 15%–20% patients attending the emergency room of a general hospital, 20%–25% of the student population, and 50% psychiatric patients in primary care may have suicidal ideations.[4] Despite commendable advances in mental health care, which has demonstrated path breaking changes, the rates of suicide are every increasing while there is no specific treatment for suicide and its occurrence is highly unpredictable.[5]

In every individual who attempts suicide, there are risk and protective factors that interact leading to the attempt or the prevention of an attempt.[6] The recent concept originates from complex interaction of factors from genetics, structural and functional brain imaging, neurochemistry, knowledge of psychosocial factors and interventions in suicide.[7]

NEUROBIOLOGICAL RISK FACTORS FOR SUICIDE

There are some factors which increase the vulnerability of an individual to develop suicidal thoughts which progress into an attempt depending on several risk factors, however, the pathway of psychopathology involved in the process of transition from suicidal ideation to attempt remains undetermined.[8] Neurobiological underpinnings, genetic predisposition,[9] functional changes abnormalities in neuronal architecture and neurochemical function[10] in the brain which appear at an early age are some of individual's susceptibility for suicide as well as for mental disorder as one of the theories to explain that suicide is a process based on neurobiological changes.[11] Neurobiological changes appear much earlier than a manifestation of earliest symptoms of mental disorder. A significant number of at-risk candidates develop ideation and make an attempt in prodromal stage. Although neurobiological changes are seen in patients with suicidality, it is likely that shared brain changes between mental disorder and suicide increase the risk for suicide. An argument has now been made that neuroprotection and neuroplasticity are involved in maintaining the health and architecture of neuronal cells.[12]

BRAIN DERIVED NEUROTROPHIC FACTOR AND SUICIDE

It has been observed that neuroprotective factors such as nerve growth factor and brain-derived neurotrophic factor (BDNF) are particularly involved protection of neurons which remain biologically vulnerable in the early phase of suicidality with or without the presence of mental disorder.[13] Accordingly, BDNF levels are low in various psychiatric disorders and patients that attempt suicide, patients with an at-risk phase (at risk mental state), and it has been demonstrated that only about 40% individuals in the prodromal or clinical high-risk states for psychiatric disorders develop the disorder finally.[14] It is presumed that increased BDNF levels may offer the possibility of prediction or act as a biomarker and play a role in treatments. This is an area that needs further exploration.[15] The psychopathological processes and pathways involved in suicide are multifactorial, and we need to research efficient biomarkers that shall serve as a means to predict accurately the risk of suicide in schizophrenia.

SUICIDE AND SCHIZOPHRENIA

About 5%–10% patients suffering from schizophrenia usually complete suicide while about 25%–35% attempt suicide at some point in their lifetime, irrespective of their clinical recovery and condition.[16] This phenomenon has a neurobiological basis and these neurobiological changes appear during early age well before the onset of clinical symptoms. Information on the nature of these changes in high-risk individuals is extremely limited.[17] Postmortem studies and neuroimaging studies in schizophrenia indicate a biological basis for stress-diathesis programming in these patients.[18] Early life adversity and epigenetic mechanisms might explain some of the links between suicide risk and brain circuitry and neurochemistry abnormalities.[19]

Impairment of the serotonin neurotransmitter system has been implicated in suicidal behavior both in schizophrenia and the general population.[20] There is also a relation between stress-diathesis and suicidal behavior that points toward abnormalities in the hypothalamo-pituitary-adrenal axis and posits a neuroendocrine hypothesis for schizophrenia.[21] A detailed explanation of these neurobiological changes is beyond the scope of the current review. The biochemical changes that occur in the early phase of schizophrenia can serve as a marker for identifying vulnerable candidates because only 15%–30% of "high-risk" individuals develop psychosis over time.[22] The postdischarge phase remains a particularly high-risk condition, where the risk of suicide increases by 80–100 times and though 25% of patients recover well, they may still have significant ideas of suicide.[23] Suicide attempts take place across all age-groups, phases of illnesses, and socioeconomic condition while it is not clearly known if changes in neuronal structure and function are reversible.[24] However, studies indicate that neuronal circuits in the early phase of the illness appear to be intact but are functionally impaired. Impairment of neuronal integrity does not arise until later stages of the illness.[25] Functional brain abnormalities

correspond to changes in neurochemical factors and associated neurotransmitter function.[26] An increase in cell membrane breakdown, reduced membrane generation, and synaptogenesis at the onset of psychosis has been repeatedly reported.[27]

Magnetic resonance imaging studies have shown that prodromal patients who convert to schizophrenia or psychosis have less gray matter in the cerebral cortex[28] while magnetic resonance spectroscopy studies have shown that there are changes in different brain metabolites in these patients.[29] It is a well-established fact that the early stage of schizophrenia is associated with progressive changes in brain structure and function, and this highlights the importance of neurobiological investigation into the "transition" to psychosis from an "at-risk" stage.[30] Sophisticated imaging has shown structural brain changes present in the prodromal phase as well as in first episode psychosis within drug naïve and medicated patients.[31] These neurobiological impairments may manifest clinically as impaired cognitive control of mood, pessimism, reactive aggressive traits, impaired problem solving, over-reactivity to negative social signs, excessive emotional pain, and suicidal ideation, finally leading to suicidal behavior.[32]

BRAIN DERIVED NEUROTROPHIC FACTOR AND SCHIZOPHRENIA

There is an ever growing body of information on abnormalities in the expression of neurotrophins in schizophrenia.[33] BDNF is a protective neurotrophic factor that regulates the survival and growth of neurons and influences synaptic efficiency and plasticity.[34] BDNF is located throughout the cortex but is predominantly found in the hippocampus.[35] BDNF promotes the survival of a wide range of neuronal cells and is known to modulate dopamine, GABA, and serotonin receptors.[36] Neuroprotective factors such as BDNF play a role in maintaining the health of neurons in the brain.[37] Psychosocial stress plays some role in this process and studies have shown that BDNF is lower in individuals in the early phase of psychosis compared to healthy controls.[38] Several studies report reduced blood levels of BDNF in both medicated and drug-naïve patients with schizophrenia.[39] Treatment with atypical antipsychotics increases BDNF levels suggesting its role in the clinical improvement process in schizophrenia.[40] Although this information is compelling, the role of neuroprotective factors needs to be further investigated to be able to predict psychosis for the implementation of therapeutic intervention early before the illness gains a strong foothold.[41]

BRAIN DERIVED NEUROTROPHIC FACTOR, PSYCHOPATHOLOGY, AND THE NEUROPROTECTIVE THEORY

Over the past several years, studies on the role of BDNF in the pathophysiology of suicidality have attracted the significant interest of researchers.[42] Multiple lines of evidence including studies of the 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.[43] Studies of BDNF function are important for suicide research and prevention because of the multiple reasons including the following, namely.

- BDNF plays a role in the pathophysiology of depression, posttraumatic stress disorder, substance use disorders, and other conditions associated with suicidal behavior.[44] 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 suicidal behavior independently of psychiatric diagnoses.[45] 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.[46] 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.

Overall, it appears that abnormalities in BDNF signaling may serve as an important biological risk factor in the etiology and pathogenesis of suicide. The gene-environmental interaction is associated with or reflects the neuroprotective factors like BDNF and neuroglia in the early phase of psychiatric illness.[47] There are changes in *in vivo* brain metabolites, cell membrane and reduced cell generation as shown by imaging and neurochemical studies, and these changes are associated with substances such as essential poly-saturated fatty acids, which modulate chemical neurotransmission.[48]

Overall, these studies indicate that "neuronal integrity" in the early phase of the illness appears to be intact, but neuronal circuits are functionally impaired. Studies support a progressive impairment of neuronal integrity as the illness progresses.[49] It is important to note that the role of BDNF and other neuroprotective factors

are not causative. It appears that they are involved in the "process of brain changes" which leads to the development of symptoms. The neuroprotective factors are involved in maintaining neuronal architecture and circuits.[50]

BRAIN DERIVED NEUROTROPHIC FACTOR AND SUICIDE IN SCHIZOPHRENIA

BDNF have gained the most attention in suicide research, and these studies show impairment in many physiological functions in the brain, including synaptic and structural plasticity.[51] Several studies consistently show that expression of BDNF is reduced in blood cells of suicidal patients and in brains of subjects who committed suicide.[52] There is evidence of the role of BDNF in suicide as numerous studies show a strong association of suicidal behavior with BDNF functional polymorphism.[53] The lower levels of BDNF in subjects suffering from schizophrenia with suicide attempts suggest that the serum BDNF level is a potential marker of suicidal behavior, independently of the presence of mental disorders. The latest literature shows that there are abnormalities in neurotrophic expression in schizophrenia.[54] In particular, BDNF is reduced in the early phases of psychosis.[55] Neurotrophins such as BDNF are proteins that serve as survival factors for CNS neurons. Deficits in the production and utilization of these proteins can lead to CNS dysfunctions, and BDNF is a protective neurotrophic factor that is important to the survival and growth of neurons, and in synaptic efficiency/plasticity.[56]

NEUROPROTECTIVE THEORY AND ITS MERIT AND LIMITATION

Evidence suggests that BDNF is involved in major depression, such that the level of BDNF is decreased in depressed patients and that antidepressants reverse this decrease. Stress, a major factor in depression, also modulates BDNF expression.[57] It is well established that neurobiological changes are present in the early phase of the illness, indicating that neuroprotective factors like BDNF are deficient and thus are adversely affecting the maturation of neurons. However, the onset of these changes during psychosis is not clearly known.[58]

Although suicide in early phases in schizophrenia is common, it is not clearly known whether suicide is an independent syndrome or a part of the process of schizophrenia.[59] Studies show that neuroprotective factors like BDNF play an important role in neuronal protection in both schizophrenia and suicide. It is also not known if changes seen in suicide behavior are neuronal progression of neurobiological changes from the early phase.[60] It is not known if there is any difference in the level of neuroprotective factors among patients with schizophrenia with and without suicidality, suicide crisis, or attempt.

Suicidal thought patterns and ideation in schizophrenia showing varying patterns in keeping with the phases of the illness as well as symptomatology.[61] This gap in knowledge has significant implications for management of suicide behavior, for example, whether treatment of schizophrenia will also work for suicide behavior or suicide behavior would need any other specific intervention.

CONCLUSION

The following paper posits the role of BDNF as a protective factor in the genesis of suicide and suicidal behavior in patients with schizophrenia. Thus, further research is warranted in patients with schizophrenia with varying degrees of Suicidality to ascertain the levels of BDNF in these subjects and whether there are specific changes related in BDNF in relation to suicide risk in this group. It is also important to study whether early treatment with antipsychotic drugs helps in raising BDNF levels which may be neuroprotective in nature. There is also a need for studying BDNF in patients with first-episode psychosis and chronic schizophrenia to determine the role of BDNF as schizophrenia progress. Results obtained from these studies if conclusive may serve in determining BDNF as a protective marker of both treatment response and suicide risk in schizophrenia.

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Conflicts of interest
There are no conflicts of interest.

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