Asian Journal of Psychiatry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

# Brain derived neurotrophic factor (BDNF) and suicidal behavior: A review of studies from Asian countries

Akanksha Sonal[a], Vijaya Raghavan[b,*]

[a] Department of Geriatric Psychiatry, King George Medical University, Lucknow, Uttar Pradesh, India
[b] Schizophrenia Research Foundation, R/7A, North Main Road, Anna Nagar West Extension, Chennai, Tamil Nadu, 600101, India

ARTICLE INFO

*Keywords:*
Suicide
Suicide attempt
BDNF
Genetics
Serum
Neuropsychiatric disorders

ABSTRACT

The biological basis of suicide and suicidal behavior is actively researched. Recently, the role of Brain Derived Neurotropic Factor (BDNF) in suicidal behavior has gained attention and significant results are observed. In this review, we aimed to focus on the studies from Asian countries that have explored the role of BDNF and suicidal behavior. The review highlights the findings from these studies and discusses the possible avenues that should be explored in future studies from Asian countries to understand more on suicidal behavior and possible prevention.

## 1. Introduction

Suicide is a major public health issue worldwide. As per World Health Organization (WHO), the number of people dying by suicide is over 800,000 and the recent trend shows the number is increasing (Organization and others, 2014). Suicide and attempted suicide has a major impact not only on the individual but also on the family and society at large. Estimates indicate that for each completed suicide the number of attempted suicide is very high (10–20 times more) (Isometsä, 2017). Various biopsychosocial factors have been implicated for suicide and suicidal behavior. These factors act at multiple levels and their interaction lead to the suicidal behavior. Some of the important factors implicated for suicidal behavior are psychiatric disorders, substance use, chronic physical illness, impulsivity, unemployment, unmarried status and poor social support (Chan et al., 2016; Cox Lippard et al., 2014; Krause et al., 2013; Tucker et al., 2015). Even though most the individuals with psychiatric disorders do not attempt suicide, majority of the individuals attempting suicide have psychiatric disorders (Milner et al., 2013; Windfuhr and Kapur, 2011).

Though various demographic and clinical factors are shown to be associated with suicide, prediction of suicidal behavior with these variables is poor and not reliable (Goldstein et al., 1906; Tran et al., 2013). This has triggered the search for more valid and reliable biological markers that could predict the suicidal behavior and possible prevention. This research direction has indicated biological variables such as genetic vulnerability, neurotransmitter levels in brain and hormonal changes could be possible biomarkers for future suicidal behavior (Costanza et al., 2014; Oquendo et al., 2014; Pandey and Dwivedi, 2012). Also, it has been shown that these factors could play a role in the pathophysiological mechanism behind suicide and suicidal behavior. One such biological variable that has been extensively studied in association with suicide is brain derived neurotropic factor (BDNF) (Dwivedi, 2010; Paska et al., 2013).

BDNF belongs to a family of neurotrophin proteins present in brain and circulating in blood (Liu et al., 2015). BDNF is found to be involved in various biological processes such as neurogenesis, neural plasticity and regeneration (Cowansage et al., 2010; Mizui et al., 2016; Zhao et al., 2017). Altered BDNF levels are seen in various neuropsychiatric disorders (Autry and Monteggia, 2012). For example, altered BDNF levels are seen in depression and found to correlate with the cognitive deficits present in depression (Dwivedi, 2013; Hashimoto, 2010; Kuhn et al., 2014). Similarly, BDNF changes in the brain are seen in schizophrenia, anxiety disorders, addiction disorders, Rett syndrome and other neurodevelopmental disorders (Domingos da Silveira da Luz et al., 2013; Katz, 2014; McGinty et al., 2010; Zhang et al., 2012).

The role of BDNF in suicide is actively researched. Recent studies show the relationship between suicide, stress, depression and BDNF (Masi and Brovedani, 2011). The results of these studies indicate the important role played by BDNF in suicidal behavior and its possible role as biomarker in predicting suicide. This could lead to the possible utilization of BDNF as a therapeutic target in the treatment and prevention of suicidal behavior.

Even though the literature on BDNF and suicidal behavior is increasing, only one study has systematically reviewed the results (Eisen

* Corresponding author.
*E-mail address:* vijayaraghavan@scarfindia.org (V. Raghavan).

https://doi.org/10.1016/j.ajp.2018.03.004
Received 30 April 2017; Received in revised form 25 December 2017; Accepted 1 March 2018

et al., 2015). Moreover, only few studies from the Asian countries have been included in these reviews. Hence, the aim of the current review is to summarize the role of BDNF in suicidal behavior in general and highlight the research findings from Asian countries. This could lead to further research in Asian countries in the biological aspects of suicide and suicidal behavior especially BDNF.

## 2. Materials and methods

Literature search was conducted in online Medline/PubMed and Google Scholar from the date of first available article up to March 2017. The search strategy included clinical trials, systematic reviews and case-reports. We searched the following terms (Suicide OR Suicide attempt OR Suicidal behavior OR Self injurious behavior) AND (BDNF OR Brain derived neurotropic factor). The references cited in the identified publications were searched for additional studies. We reviewed the studies specifically from Asian countries with regards to the following characteristics such as aim of the study, methods of sampling, research design, and results.

## 3. Results

### 3.1. BDNF and suicidal behavior: world

Genetic studies on suicide and suicide attempts have identified a strong association between BDNF Val66Met polymorphism and suicidal behavior (Bresin et al., 2013; de Luca et al., 2011; González-Castro et al., 2015; Iga et al., 2007; Sarchiapone et al., 2008; Schenkel et al., 2010; Zarrilli et al., 2009). In one study, a possible interaction between B*DNF* Val66Met and *DRD3* Ser9Gly SNPs was found to increase the risk of suicide attempts in individuals with schizophrenia was observed (Zai et al., 2015).

Epigenetic mechanisms have been found to play an important role in suicidal behavior. Aberrant DNA methylation of BDNF gene and microRNA-185 have emerged as two important epigenetic pathways influencing neuronal and circuit formation by negatively regulating gene expression (Schneider et al., 2015; Serafini et al., 2014). Post-mortem brain studies, specifically pertaining to Wernicke area, indicates a frequent BDNF promoter/exon IV hyper-methylation. This indicates a gene-specific increase in DNA methylation of BDNF could play a role in the etiology of suicidal behavior (Keller et al., 2010). Also, BDNF-NTRK2-CREB pathway is found to be involved along with DICER1 in the pathogenesis of suicide. Interestingly, DICER1 involved in the normal processing of microRNAs (Pulay and Réthelyi, 2016). This indicates that microRNAs could have a possible role in the neurobiology of suicide.

In the post-mortem brain studies done on individuals died of suicide, BDNF protein levels in prefrontal cortex, hippocampus and amygdala were found to significantly lower when compared with normal control samples (Ernst et al., 2009; Maheu et al., 2013; Pandey et al., 2008). Similarly, in another study, reduced expression of BDNF and Tropomycin receptor kinase B (TrkB) in postmortem brain in suicide subjects is observed (Pandey et al., 2008).

In a study examining the plasma BDNF and HPA-axis by Dexamethasone Suppression Test (DST) in female suicide attempters, an inverse relationship was observed (Ambrus et al., 2016).

In one cross-sectional study, serum BDNF were not found to be significantly different between the suicide attempters and non-attempters. While significant difference in serum BDNF levels is observed between depressed individuals (with or without suicide attempt) and controls, no significant difference is found between depressed individuals with suicide attempt and depressed individuals without suicide attempt (Deveci et al., 2007). In a recent meta-analysis which has considered various studies investigating the serum BDNF levels and attempted suicide found the pooled estimate ($p = 0.36$) to be not significant and has substantial heterogeneity ($I^2 = 73\%$, $p = 0.02$) (Eisen et al., 2015). A study examined the CSF BDNF levels and correlated with Scale for Suicidal Ideation (SSI). This revealed a significant positive correlation between BDNF levels and SSI score (Martinez et al., 2012). In the studies that have measured the plasma levels of BDNF in depressed individuals with suicide attempts, it was found that BDNF levels were significantly lower when compared with the control normal group while no significant difference was found when compared with depressed individuals with no suicide attempts. The serum BDNF levels in women with postpartum affective disorder (PPAD) with suicidal risk are significantly lower when compared with women with PPAD without suicidal risk (Pinheiro et al., 2012). The lower levels of BDNF is not only observed in depression with suicide but also in Parkinson's and Alzheimer's disorder with suicide attempts, suggesting that the serum BDNF level is a potential marker of suicidal behavior, independent of mental disorders (Ventriglia et al., 2013).

### 3.2. BDNF and suicidal behavior: Asian countries

#### 3.2.1. Genetic studies

A study explored the associated between the BDNF gene Val66Met polymorphism, mood disorders and suicidal behavior in a Chinese sample population. But no significant association was observed BDNF gene Val66Met polymorphism and mood disorders when compared with normal controls. Also, there was no association between BDNF gene Val66Met polymorphism and suicidal behavior (Hong et al., 2003). Similarly, in another study from China, BDNF Val66Met polymorphism was not affected by age-of-onset, depression severity, cognitive function or suicidal attempt history in the study subjects but there was a significant difference between the depressed group when compared with the control group ($P = 0.003$) (Hwang et al., 2006). This is in contrast from other studies done on Caucasian population where a significant association is observed. This indicates that the association could be dependent on ethnicity.

A meta-analysis from Japan has showed that BDNF gene Val66Met polymorphism is associated with suicidal attempts but not completed suicide in Asian population (Ratta-Apha et al., 2013). In a study from Korea, BDNF Val66Met polymorphism was found to be significantly associated with suicidal behavior in Bipolar disorder and indicated the possible role of BDNF Val66Met polymorphism as a marker for suicide risk in Bipolar disorder (Kim et al., 2008). Similarly, BDNF *met* allele is found to be associated with suicidal ideation in breast cancer survivors (Kim et al., 2013).

In Taiwanese population, the relationship between BDNF G196A gene polymorphism and clinical phenotypes in individuals with schizophrenia were explored. The results indicate a significant difference in BDNF G196A polymorphism between individuals with schizophrenia patients with and without a suicide history (Huang and Lee, 2007).

In an age and sex matched case-control study comparing between individuals with attempted suicide and normal controls, no association was found between BDNF polymorphism and attempted suicide in the overall study subjects. But, BDNF 196G/G genotype was significantly associated with elderly suicide attempters indicating the possible use of this genotype as a risk marker for suicide attempts in the elderly ($p = 0.038$) (Wang et al., 2015).

### 3.3. Epigenetic studies

One study has explored the association between the DNA methylation pattern of BDNF gene in depressed individuals. The results indicated that a higher BDNF promoter methylation status was significantly associated with a previous suicidal attempt history and suicidal ideation measured by Beck Scale for Suicide Ideation (BSS) and poor treatment outcomes for suicidal ideation. This study highlights the possibility of BDNF methylation status as a proxy for previous suicidal attempts and as a biomarker for poor outcomes in depression with suicidal ideation (Kang et al., 2013). In another study from Korea,