

# THE ROLE OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN THE PATHOPHYSIOLOGY OF SUICIDAL BEHAVIOR

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## SUMMARY

Suicidal behaviour is a major public health concern. It is known that the pathogenesis of suicidal behaviour involves altered neural plasticity, resulting in the aberrant stress response of the central nervous system to environmental factors. Indeed, altered brain structure and function was found in suicide victims. Neurotrophins are growth factors that are involved in the regulation of structural, synaptic, and morphological plasticity and in the modulation of the strength and number of synaptic connections and neurotransmission. Brain-derived neurotrophic factor (BDNF) the most studied and the most widely distributed among neurotrophins binds to a tropomyosin-related kinase B (TrkB) receptor and to a pan75 neurotrophins receptor. It has been reported that BDNF production is decreased in all patients with suicidal behaviour and in all suicide victims regardless of a psychiatric diagnosis. It was also found that the mRNA and protein level of BDNF was significantly lower in both the prefrontal cortex and the hippocampus of suicide subjects. Different mechanisms could be involved in the regulation of BDNF gene expression, among which epigenetic mechanisms seem to play a key role. However, also for a functional polymorphism (rs6265) Val66Met it has been shown that the Met allele is associated with the reduced BDNF activity. Further, a recent meta-analysis including 12 studies showed a trend for the Met-carrying genotypes and Met allele conferring risk for suicide. Among included studies, our study with the largest sample size, indicated 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. In accordance with previous reports, our findings demonstrate that aberrant regulation of BDNF synthesis is associated with suicidal behaviour.

**Key words:** suicide - Brain-Derived Neurotrophic Factor - Tropomyosin-related kinase B - suicidal behaviour - polymorphism

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## INTRODUCTION

Suicide alone represents the 10<sup>th</sup> leading cause of death in the world and it is estimated that 1.5 million will die from suicide in 2020 worldwide (Levi et al. 2003). It is known that suicidal behaviour has multiple causes that could be broadly divided into proximal stressors or triggers and predisposition (Mann & Currier 2010). If triggers could be mainly attributed to environmental factors, predisposition could be associated with early stressors such as childhood adversities on one side and genetic predisposition such as specific combination of different genetic variants on the other. Nevertheless, clinical risk factors have a low predictive value on suicide (Costanza et al. 2013). Structural changes were observed in patients with mental disorders associated with increased suicide risk such as depression, schizophrenia and bipolar disorder, indicating that aberrant neuroplasticity could be involved in patients with suicidal behaviour (van Heeringen et al. 2011). A recent systematic review of comparative imaging studies of brains of suicide victims shows that changes in the structure and functions of the brain in association with suicidal behaviour are mainly found in the orbitofrontal and dorsolateral parts of the prefrontal cortex (van Heeringen et al. 2011). Further it is known that neuronal activity plays a pivotal role in synaptic

plasticity and that neurotrophins such as brain-derived neurotrophic factor (BDNF) are potent factors for synaptic modulation. Especially during childhood and adolescence BDNF plays an important role in the regulation and growth of neurons (Sher 2011). The serotonin dysfunction found in adolescent and adult suicidal behaviour could be related to the low level of BDNF, which impedes the normal development of serotonin neurons during brain development (Sher 2011). It was speculated that BDNF dysfunction could play a more significant role in the pathophysiology of psychiatric disorders and suicidal behaviour in adolescents than in adults. In the recent review it was reported that except for the serotonergic system, particularly with respect to the polymorphism of the gene coding for the serotonin transporter (5-HTTLPR) and BDNF, data did not converge to produce an univocal consensus regarding suicidal behaviour and different biomarkers (Costanza et al. 2013).

## BDNF AND NEUROPLASTICITY

BDNF influences a variety of neural processes during the development such as: neurogenesis, neuronal survival and maturation of neural development pathways (Russo-Neustadt 2003). It is reported that BDNF is involved in morphological plasticity, neurite

outgrowth, phenotypic maturation, and synthesis of proteins for differentiated functioning of neurons and for synaptic formation and functioning (Huang & Reichardt 2001). Further, BDNF is involved in nerve regeneration, structural integrity, and maintenance of neuronal plasticity in the adult brain, including regulation of synaptic activity, and in neurotransmitter synthesis (Reichardt 2006, for review see Dwivedi 2012). BDNF levels and its intracellular localization in neurons are regulated via several different mechanisms, including BDNF transcripts, messenger RNA (mRNA) and protein transport, and regulated cleavage of pro-BDNF to mature BDNF (Dwivedi 2012). A pathological alteration of the BDNF regulation may lead to aberrant neural maintenance and regeneration and, therefore, structural abnormalities in the central neuronal system with a reduced neural plasticity and, therefore, impaired stress response of an individual (Dwivedi 2012).

The neurotrophic/plasticity hypothesis of depression (Duman et al. 1997), proposed more than a decade ago, is now supported by multiple basic and clinical studies focused on the role of intracellular-signalling cascades that govern neural proliferation and plasticity with a central role of BDNF (van Heeringen et al. 2011). The neurogenesis hypothesis of depression was based upon the demonstration that stress decreased adult neurogenesis in the hippocampus and that decreased expression of BDNF and possibly other growth factors contributes to depression (Duman & Monteggia 2006). On the contrary, chronic administration of antidepressants produces an increase in hippocampal BDNF mRNA expression and BDNF protein levels (Duman & Monteggia 2006). Further it is known that psychiatric illness is a major contributing factor and more than 90% of suicide victims have a psychiatric illness at the time of suicide with depressive syndromes being the most prevalent (Lönnqvist et al. 1995).

## **FUNCTIONAL POLYMORPHISM OF THE BDNF GENE AND SUICIDALITY**

The BDNF gene harbours a functional polymorphism; a Val66Met variant (rs6265) resolving in a substitution of valine with methionine in codon 66. It has been shown that the Met allele is associated with the reduced BDNF activity (Egan et al. 2003). A recent meta-analysis including 12 studies indicated a trend for the Met-carrying genotypes and Met allele conferring risk for suicide (Zai et al. 2011). Among included studies the study with the largest sample size indicated 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 (Pregelj et al. 2011). We genotyped the BDNF Val66Met polymorphism on 560 DNA samples from 359 suicide victims and 201 control subjects and subdivided according to sex, method of suicide, and influence of childhood

adversity. Although a similar frequency of BDNF Val66Met variants was found between all included suicide victims and the control groups and also between the male groups the frequency of the combined Met/Met and Met/Val genotypes and the homozygous Val/Val genotype was significantly different between the female suicide victims and female controls, between the female suicide victims who used violent suicide methods and female controls, and between all included suicide victims with or without severe stressful life events in childhood (Pregelj et al. 2011). It could be suggested that 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 (Pregelj et al. 2011).

However a recent association study with completed suicide in the Japanese population and meta-analyses exploring the association between the brain-derived neurotrophic factor gene with suicide using 307 Japanese completed suicides, 380 healthy controls, and data from previously published samples indicated that the Met-allele tended to be associated with attempted suicide in Asian populations, but not with the completed suicide (Ratta-Apha et al 2013).

## **EPIGENETIC REGULATION OF BDNF AND TRKB EXPRESSION AND SUICIDALITY**

Epigenetic information is defined as the information carrying molecular processes that is inherited through mitosis or meiosis influencing gene expression independently of the DNA sequence (de León-Guerrero et al. 2011). Environmental factors could via specific intracellular signalling pathways, such as gene expression regulation by transcription factors, control neuronal differentiation at multiple levels, such as neuronal precursor cell cycle control, migration, synaptogenesis, neuronal survival and neurotransmitter phenotype (de León-Guerrero et al. 2011). Binding of the transcription factors to the specific regions of the DNA is influenced by different mechanisms such as DNA sequence, especially in the promoter regions, on one hand and epigenetic mechanisms, such as histone modulation or methylation of the DNA molecule, on the other (Riccio 2010). The third known epigenetic mechanisms are micro ribonucleic acids (abbreviated miRNA). miRNA is a short RNA molecule on average of 22 nucleotides long found in eukaryotic cells (Kusenda et al. 2006).

The number of studies on methylation patterns of BDNF promoter regions in association with psychiatric disorders are growing. However, so far there is only one study performed on suicide completers done by Keller et al. (2010). Interestingly, they were able to show that methylation degree of the promoter/exon IV corresponds to the mRNA levels of BDNF. Higher

methylation level reflected in lower levels of mRNA expression in suicide victims compared to the control group (Keller et al. 2010). Further finding that gave the study another important point was that global methylation levels were not associated with suicidality, sex or age, which supports the results that the methylation state of BDNF promoter/exon IV is related to suicide particularly (Keller et al. 2010).

BDNF activates receptors such as TrkB and the low-affinity nerve growth factor receptor (LNGFR - also known as p75) and modulates others such as alpha-7 nicotinic receptor (Patapoutian & Reichardt 2011; Fernandes et al. 2001). Nevertheless, one of the major receptors to which BDNF binds with high affinity and mediates its action is TrkB which is also regulated in an activity-dependent manner (Dwivedi 2012). In a postmortem case-control study it was found that 10 of 28 suicide victims demonstrated significant decreases in different probe sets specific to TrkB T1 splice variant in Brodmann areas 8 and 9 and were generalizable to other frontal regions. It was also reported that the methylation state at particular CpG dinucleotides of the promoter region of the gene has an effect on TrkB.T1 expression indicating the involvement of epigenetic factors in the gene expression. Methylation and mRNA levels of TrkB and suicide were so far studied in two independent studies by Ernst et al. (2009) and Keller et al. (2010). In the study by Ernst et al. (2009) reduction of TrkB.T1 expression in the frontal cortex of a subpopulation of suicide completers was associated with the methylation state of the promoter region (Ernst et al. 2009). While on the other hand in the study of Keller et al. (2010) the levels of mRNA expression and methylation status of TrkB and TrkB-T1 did not correlate (Keller et al. 2010). Both studies were performed on relatively small samples and also on different brain regions, the first with 28 suicide victims and 11 control subjects on Brodmann area 8/9 and eight other frontal cortical regions (Ernst et al. 2009) and the second with 18 suicide victims and 18 controls on Wernicke area (Keller et al. 2010). The first study performed the analysis also on the cerebellum samples, but did not find a significant association (Ernst et al. 2009). Although the two studies have a similar approach we cannot compare their results, since the sample origin was different. This could also support the idea that there is brain-area specificity present in epigenetic patterns. Completing a brain-area map on methylation patterns would therefore be crucial before further search for causes of altered methylation levels.

## CONCLUSIONS

Genetic and epigenetic studies confirm a major role of BDNF and also the role of BDNF receptor TrkB in pathophysiology of suicidal behaviour. Aberrant regulation of BDNF gene expression resulting in decreased BDNF activity could alter the vulnerability to stress and directly and/or indirectly increase the risk for suicidal behaviour.

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