THE BRAIN DERIVED NEUROTROPHIC FACTOR 
AND INFLUENCES OF STRESS IN DEPRESSION

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SUMMARY
Brain derived neurotrophic factor (BDNF) is a member of the neurotrophin family and is widely expressed throughout the central nervous system (CNS). BDNF is involved in proliferation, differentiation, survival and death of neuronal and non-neuronal cells in the developing and adult CNS. The BDNF hypothesis of depression postulates that a reduction in BDNF is directly involved in the pathophysiology of depression, whilst anti-depressant mediated restoration of BDNF is responsible for the alleviation of the depressive state. This hypothesis is drawn from several studies implicating BDNF in depression and has received considerable support, which will be reviewed in this paper. This review will also discuss the implications of the functional Val66Met polymorphism of the gene encoding BDNF, which may reduce BDNF expression particularly when exposed to stress and thus may play a critical role in the pathogenesis of depression.

Key words: brain derived neurotrophic factor – depression - stress

INTRODUCTION
Brain derived neurotrophic factor (BDNF) is a neuro-protective protein that regulates neuronal survival, growth and differentiation (Huang & Reichardt 2001, Lipsky & Marini 2007). The BDNF hypothesis of depression postulates that stress reduces BDNF concentrations in limbic system structures and this underpins the central pathogenic process in depression, whilst anti-depressants restore BDNF concentrations and through this alleviate depressive symptoms (Duman & Monteggia 2006). This theory has been derived from a rich literature and has drawn considerable support, which will be reviewed in this paper. In addition this paper investigates the influence of a common single nucleotide polymorphism (Val66Met) within the gene encoding BDNF, which has a functional role in BDNF expression and may confer susceptibility to depression.

THE ROLE OF BDNF IN DEPRESSION
Several converging lines of research provide compelling evidence to support the BDNF hypothesis of depression. Firstly, stress is a potent risk factor for depression (Kessler 1997, Stirling & Amaya-Jackson 2008, Widom et al. 2007) and is associated with reduced BDNF concentrations in animal models (Barrientos et al. 2003, Murakami et al. 2005, Pizarro et al. 2004, Scaccianoce et al. 2006, Ueyama et al. 1997) and humans (Lee & Kim 2010). This may be because stress causes activation of the hypothalamic-pituitary-adrenal (HPA) axis with a corresponding increase in cortisol secretion and at excessive concentrations cortisol can suppress BDNF production (Nessler et al. 2002). Depression has consistently been associated with heightened stress reactivity and hypercortisolaemia (Knorr et al. 2010, Stetler & Miller 2011) and reduced BDNF concentrations are well documented findings (Blugeot et al. 2011, Karege et al. 2005, Karege et al. 2002, Lee et al. 2007, Molendijk et al. 2011). Anti-depressants have been shown to improve the depressive state both through regulation of the HPA-axis and restoration of BDNF concentrations (Altar et al. 2003, Garza et al. 2004, Lee et al. 2007, MacQueen & Frodl 2011, Molendijk et al. 2011, Russo-Neustadt et al. 1999). This suggests that stress induced reductions of BDNF may confer risk for depression and restoration of HPA-axis and BDNF homeostasis may be responsible for the improvement of mood.

THE INFLUENCE OF THE VAL66MET POLYMORPHISM
A common single nucleotide polymorphism in the BDNF gene called Val66Met impairs the packaging and secretion of BDNF (Egan et al. 2003). The minor Met allele has been associated with features of depression, such as impaired memory (Goldberg et al. 2008, van Wingen et al. 2010) and reduced hippocampal volume (Bueller et al. 2006, Frodl et al. 2007, Hajek et al. 2012, Pezawas et al. 2004), and risk of depression (Pei et al. 2012). However, results have not been consistently replicated and some studies have demonstrated that the Met allele is not a risk factor for depression (Chen et al. 2008, Gratacos et al. 2007) or only confers a weak association with depression in males (Verhagen et al. 2007). This may be because there are other genetic and environmental risk factors that influence the pathway to MDD, such as early life stress (Bergstrom et al. 2008) or recent life events through interactions with genetic variation in the serotonin transporter gene (Bukh et al. 2009). Thus, the role of Val66Met as a susceptibility factor for depression is complex and likely to involve interactions with several other genetic and environ-
mental risk factors. Therefore, there is a need for further studies to investigate the association of Val66Met and environmental risk factors (especially childhood adversity and recent negative life events) in order to improve our understanding of the complex genetic and environmental pathways to depression.

CONCLUSION

The evidence implicating BDNF in the pathogenesis of depression is convincing, with several lines of research supporting the BDNF hypothesis of depression. Furthermore, the Val66Met polymorphism within the gene encoding BDNF may confer susceptibility to depression both directly and through interactions with stress. Further research should be conducted to clarify the association of Val66Met and depression, with a particular focus on the effect of stress in early life on later depressive symptoms.

Acknowledgements: None.

Conflict of interest: None to declare.

REFERENCES


