Psychiatria Danubina, 2012; Vol. 24, Suppl. 1, pp 169–171 *Conference paper*

THE BRAIN DERIVED NEUROTROPHIC FACTOR AND INFLUENCES OF STRESS IN DEPRESSION

Jessica Kimpton

The University of Manchester, Oxford Road, Manchester, UK

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 susceptibly 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

1. *Altar C, Whitehead R, Chen R, Wortwein G and Madsen T. "Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain." Biological Psychiatry 2003; 54:703-709.*
2. *Barrientos R, Sprunger D, Campeau S, Higgins E, Watkins L, Rudy J and Maier S. "Brain-derived neurotrophic factor mRNA downregulation produced by social isolation is blocked by intrahippocampal interleukin-1 receptor antagonist." Neuroscience 2003; 121: 847-853.*
3. *Bergstrom A, Jayatissa M, Mork A and Wilborg O. "Stress sensitivity and resilience in the chronic mild stress rat model of depression; an in situ hybridization study." Brain Research 2008; 1196:41-52.*
4. *Blugeot A, Rivat C, Bouvier E, Molet J, Mouchard A, Zeau B, Bernard C, Benoliel J and Becker C. "Vulnerability to depression: from brain neuroplasticity to identification of biomarkers." Journal of Neuroscience 2011; 31:12889-12899.*
5. *Bueller J, Aftab M, Sen S, Gomez-Hassan D, Burmeister M and Zubieta J. "BDNF Val66Met is associated with reduced hippocampal volume in healthy subjects." Biological Psychiatry 2006; 59:812-815.*
6. *Bukh J, Bock C, Vinberg M, Werge T, Gether U and Vedel Kessing L. "Interaction between genetic polymorphisms and stressful life events in first episode depression." Journal of Affective Disorders 2009; 119:107-115.*
7. *Chen L, Lawlor D, Lewis S, Yuan W, Abdollahi M, Timpson N, Day I, Ebrahim S, Smith G and Shugart Y. "Genetic association study of BDNF in depression: Finding from two cohort studies and a meta-analysis." American Journal of Medical Genetics 2008; 147B:814-821.*
8. *Duman R and Monteggia L. "A neurotrophic model for stress-related mood disorders." Biological Psychiatry 2006; 59:1116-1127.*
9. *Egan M, Kojima M, Callicott J, Goldberg T, Kolachana B and Bertolino A. "The BDNF Val66Met polymorphism affects activity dependent secretion of BDNF and human memory and hippocampal function." Cell 2003; 112:257-269.*
10. *Frodl T, Shule C, Schmitt G, Born C, Baghai T and Zill P. "Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression." Archives of General Psychiatry 2007; 64:410-416.*
11. *Garza A, Ha T, Garcia C, Chen M and Russo-Neustadt A. "Exercise, antidepressant treatment, and BDNF mRNA expression in the aging brain." Pharmacology, biochemistry and behaviour 2004; 77:209-220.*
12. *Goldberg T, Ludicello J, Russo C, Elvevag B, Straub R, Egan M and Weinberger D. "BDNF Val66Met polymerphism significantly affects d' in verbal recognition memory at short and long delays." Biological Psychiatry 2008; 77:20-24.*
13. *Gratacos M, Gonzalez J, Mercader J, de Cid R, Urretavizcaya M and Estivill X. "Brain-derived neurotrophic factor Val66Met and psychiatric disorders: Meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia." Biological Psychiatry 2007; 61:911-922.*
14. *Hajek T, Kopecek M and Hoschl C. "Reduced hippocampal volumes in healthy carriers of brain-derived neurotrophic factor Val66Met polymorphism: meta-analysis." World Journal of Biological Psychiatry 2012; 13:178-187.*
15. *Huang E and Reichardt L. "Neurotrophins: roles in neuronal development and functionNeurotrophins: roles in neuronal development and function." Annual Review of Neuroscience 2001; 24:667-736.*
16. *Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubury J and Bertschy G. "Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity." Biological Psychiatry 2005; 57:1068-1072.*
17. *Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G and Aubury J. "Decreased serum brain-derived neurotrophic factor levels in major depressed patients." Psychiatry Research 2002;109:143-148.*
18. *Kessler R. "The effects of stressful life events on depression." Annual Review of Psychology 1997; 48:191-214.*
19. *Knorr U, Vinberg M, Kessing L and Wetterslev J. "Salivary cortisol in depressed patients versus control persons: a systematic review and meta-analysis." Psychoneuroendocrinology 2010; 35:1275-1286.*
20. *Lee B, Kim H, Park S and Kim Y. "Decreased plasma BDNF level in depressive patients." Journal of Affective Disorders 2007; 101:239-244.*
21. *Lee B and Kim Y. "The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment." Psychiatry Investigation 2010; 7:231-235.*
22. *Lipsky R and Marini A. "Brain-Derived Neurotrophic Factor in Neuronal Survival and Behavior-Related Plasticity." Annals New York Academy of Sciences 2007; 1122:130-143.*

23. *MacQueen G and Frodl T. "The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research." Molecular Psychiatry 2011; 16:252-264.*
24. *Molendijk M, Bus B, Spinhoven P, Penninx B, Kenis G, Prickaerts J, Voshaar R and Elzinga B. "Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment." Molecular Psychiatry 2011; 16:1088-1095.*
25. *Murakami S, Imbe H, Morikawa Y, Kubo C and Senba E: "Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly." Neuroscience Research 2005; 53:129-139.*
26. *Nessler E, Barrot M, DiLeone, Eisch A, Gold E and Monteggia L. "Neurobiology of Depression." Neuron 2002; 34:13-25.*
27. *Pei Y, Smith A, Wang Y, Pan Y, Yang J, Chen Q, Pan W, Bao F, Zhao L, Tie C, Wang Y, Wang J, Zhen W, Zhou J and Ma X. "The brain-derived neurotrophic-factor (BDNF) val66met polymorphism is associated with geriatric depression: A meta-analysis." American Journal of Medical Genetics 2012; 159:560-566.*
28. *Pezawas L, Verchinski B, Mattay V, Callicott J, Kolachana B and Straub R. "The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology." Journal of Neuroscience 2004; 24:10099-10102.*
29. *Pizarro J, Lumley L, Medina W, Robinson C, Chang W, Alagappan A, Bah M, Dawood M, Shah J, Mark B, Kendall N, Smith M, Saviolakis G and Meyerhoff J. "Acute social defeat reduces neurotrophin expression in brain cortical and subcortical areas in mice." Brain Research 2004; 1025:10-20.*
30. *Russo-Neustadt A, Beard R and Cotman C. "Exercise, Antidepressant Medications, and Enhanced Brain Derived Neurotrophic Factor Expression." Neuropsychopharmacology 1999; 21:679-682.*
31. *Scaccianoce S, Del Bianco P, Paolone G, Caprioli D, Modafferi A, Nencini P and Badiani A. "Social isolation selectively reduces hippocampal brain-derived neurotrophic factor without altering plasma corticosterone." Behavioural Brain Research 2006; 168:323-325.*
32. *Stetler C and Miller G. "Depression and Hypothalamic-Pituitary-Adrenal Activation: A Quantitative Summary of Four Decades of Research." Psychosomatic Medicine 2011; 73:114-126.*
33. *Stirling K and Amaya-Jackson L. "Understanding the behavioral and emotional Consequences of child abuse." Pediatrics 2008; 122:667-673.*
34. *Ueyama T, Kawai Y, Nemoto K, Sekimoto M, Tone S and Senba E. "Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain." Neuroscience Research 1997; 28:103-110.*
35. *van Wingen G, Rikpkema M, Franke B, van Eijndhoven P, Tendolkar I, Verkes R, Buitelaar J and Fernandez G. "The brain-derived neurotrophic factor Val66Met polymerphism affects memory formation and retrieval of biologically salient stimuli." Neuroimage 2010; 50:1212-1218.*
36. *Verhagen M, van der Meij A, van Duerzen P, Janzing J, Arias-Vasquez A, Buitelaar J and Franke B. "Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity." Molecular Psychiatry 2007; 15:260-271.*
37. *Widom C, DuMont K and Czaja S. "A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up." Archives of General Psychiatry 2007; 64:49-56.*

Correspondence:
Jessica Kimpton
The University of Manchester
Oxford Road, Manchester M13 9PL, UK
E-mail: Jessica.kimpton@doctors.org.uk