Letter to the Editor
Clinical Psychopharmacology and Neuroscience 2012;10(1):59-60
pISSN 1738-1088 / eISSN 2093-4327


# A BDNF Val66Met Polymorphism and Ketamine-induced Rapid Antidepressant Action

Kenji Hashimoto

Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, Chiba, Japan

## TO THE EDITOR

Accumulating evidence suggests that brain-derived neurotrophic factor (BDNF) plays a key role in the pathophysiology of major depression, as well as the therapeutic action of antidepressants.[1,2] Serum levels of BDNF in drug naïve patients with major depression are significantly lower than those in normal controls. Additionally, serum levels of BDNF in drug naïve patients can be returned to control levels with antidepressant treatment,[3] suggesting that serum BDNF may be a biomarker for major depression. This finding is supported by a meta-analysis study.[4]

A single nucleotide Val66Met polymorphism is located within the BDNF precursor proBDNF, but not the mature BDNF protein. This polymorphism is associated with cognition (e.g., episodic memory and extinction learning) and hippocampal volume in humans.[5,6] Knowing that ketamine is the most effective drug for treating refractory depression, I read with interest the article by Liu *et al*.[7] that described the role of this BDNF Val66Met polymorphism in ketamine-induced synaptogenic and antidepressant responses in mice. Using knock-in mice with the BDNF Val66Met mutation,[6,8] the authors found that mice with the Met allele displayed constitutive atrophy of distal apical dendrites and decreases in apically targeted, excitatory postsynaptic currents in layer V pyramidal cells of the prefrontal cortex. Additionally, mice with the Met allele showed decreased spine density and diameter, as well as impaired synaptic formation/maturation (synaptogenesis). Interestingly, no ketamine-induced antidepressant or synaptogenic effects were detected in Met/Met mice. These findings imply that expression of the BDNF Met allele results in basal synaptic deficits that block the synaptogenic and antidepressant actions of ketamine. The authors concluded that the therapeutic response to ketamine may be attenuated or blocked in patients with depression if they carry the Met allele.

A recent study using conditional *BDNF* gene knock-out mice showed that ketamine increases the level of BDNF in the hippocampus, and that ketamine-induced antidepressant effects are absent in BDNF null mice,[9] again, suggesting a role for BDNF in the ketamine mechanism of action. Originally, Chen *et al*.[8] reported no differences in the levels of BDNF between the brains of mice with the Met allele and those in wild-type (Val/Val) mice, although the hippocampal volume of mice with the Met allele was significantly lower than in wild-type mice. Furthermore, mice carrying the Met allele showed anxiety-related rather than depressive behavior.[8,10] Mature BDNF and proBDNF activate two distinct receptors, the tropomyosin-related kinase B receptor and the p75 neurotropin receptor ($p75^{NTR}$), respectively.[2,10] Therefore, it is likely that disturbances in $p75^{NTR}$ signaling, mediated by proBDNF with a Met allele, may result in a lack of synaptogenic and antidepressant effect of ketamine in mice, although a further study will be needed to examine this in more detail.

The Met allele occurs at a 40-50% frequency within the Asian population, which is significantly higher than the 20-30% frequency seen in Caucasian populations.[11,12] This would indicate an ethnic-based difference in the distribution for this polymorphism.[11] Given the role of the Met allele in susceptibility to stress-related major depression,[12] these results imply a higher prevalence of depression in Asian populations compared with Caucasian populations. However, this is not the case, indicating the involvement of other genetic and environmental factors, along with BDNF, in disease pathogenesis.

In conclusion, proBDNF proteins carrying the Val and Met polymorphism may be present in the serum of sub-

**Received:** November 22, 2011 / **Accepted:** November 28, 2011
**Address for correspondence:** Kenji Hashimoto, PhD
Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, 1-8-1 Inohana, Chiba 260-8670, Japan
Tel: +81-423-226-2517, Fax: +81-423-226-2561
E-mail: hashimoto@faculty.chiba-u.jp

jects with a BDNF Val66Met mutation. Therefore, it would be of great interest to determine whether proBDNF proteins with either the Val or Met amino acid or mature BDNF could be used as novel biomarkers for major depression.[2] In addition, it may be of interest to examine whether patients who are resistant to the rapid antidepressant effects of ketamine carry the Met allele.

## REFERENCES


1. Hashimoto K, Shimizu E, Iyo M. *Critical role of brain-derived neurotrophic factor in mood disorders. Brain Res Brain Res Rev 2004;45:104-114.*
2. Hashimoto K. *Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. Psychiatry Clin Neurosci 2010;64:341-357.*
3. Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, *et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 2003;54:70-75.*
4. Sen S, Duman R, Sanacora G. *Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol Psychiatry 2008;64:527-532.*
5. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, *et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003;112:257-269.*
6. Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, *et al. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. Science 2010;327:863-866.*
7. Liu RJ, Lee FS, Li XY, Bambico F, Duman RS, Aghajanian GK. *Brain-Derived Neurotrophic Factor Val66Met Allele Impairs Basal and Ketamine-Stimulated Synaptogenesis in Prefrontal Cortex. Biol Psychiatry 2011. Epub ahead of print.*
8. Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, *et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science 2006;314:140-143.*
9. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, *et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 2011;475:91-95.*
10. Hashimoto K. *BDNF variant linked to anxiety-related behaviors. Bioessays 2007;29:116-119.*
11. Shimizu E, Hashimoto K, Iyo M. *Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: the possibility to explain ethnic mental traits. Am J Med Genet B Neuropsychiatr Genet 2004;126B:122-123.*
12. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Kim YH, *et al. Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders. Biol Psychiatry 2007;62:423-428.*