Effects of BDNF Polymorphisms on Antidepressant Action

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Evidence suggests that the down-regulation of the signaling pathway involving brain-derived neurotrophic factor (BDNF), a molecular element known to regulate neuronal plasticity and survival, plays an important role in the pathogenesis of major depression. The restoration of BDNF activity induced by antidepressant treatment has been implicated in the antidepressant therapeutic mechanism. Because there is variability among patients with major depressive disorder in terms of response to antidepressant treatment and since genetic factors may contribute to this inter-individual variability in antidepressant response, pharmacogenetic studies have tested the associations between genetic polymorphisms in candidate genes related to antidepressant therapeutic action. In human BDNF gene, there is a common functional polymorphism (Val66Met) in the pro-region of BDNF, which affects the intracellular trafficking of proBDNF. Because of the potentially important role of BDNF in the antidepressant mechanism, many pharmacogenetic studies have tested the association between this polymorphism and the antidepressant therapeutic response, but they have produced inconsistent results. A recent meta-analysis of eight studies, which included data from 1,115 subjects, suggested that the Val/Met carriers have increased antidepressant response in comparison to Val/Val homozygotes, particularly in the Asian population. The positive molecular heterosis effect (subjects heterozygous for a specific genetic polymorphism show a significantly greater effect) is compatible with animal studies showing that, although BDNF exerts an antidepressant effect, too much BDNF may have a detrimental effect on mood. Several recommendations are proposed for future antidepressant pharmacogenetic studies of BDNF, including the consideration of multiple polymorphisms and a haplotype approach, gene-gene interaction, a single antidepressant regimen, controlling for age and gender interactions, and pharmacogenetic effects on specific depressive symptom-clusters.

Key Words Major depression, Antidepressant, Brain-derived neurotrophic factor, Polymorphisms.

BRAIN-DERIVED NEUROTROPHIC FACTOR, MAJOR DEPRESSION, AND ANTIDEPRESSANT DRUG ACTION

Major depressive disorder (MDD) has one of the highest lifetime incidence rates of all the psychiatric disorders. Although the causes of MDD are still unknown, causative factors can be artificially divided into biological and psychosocial factors, with probable interaction between the two. For the biological factors, earlier studies have demonstrated that the symptoms of depression can be improved by agents, which enhance the function of monoamine transmitters, particularly of norepinephrine and serotonin. This finding led to the adoption of the monoamine hypothesis of depression and antidepressant action, which has dominated both industrial and academic research for approximately five decades. However, despite decades of MDD study, no conclusive abnormality has been identified in these two monoaminergic systems. Furthermore, current antidepressants are far from ideal owing to their slow onset of action and low rates of response.

In recent years, studies have begun to characterize the action of antidepressants and the pathogenesis of MDD beyond the neurotransmitter and receptor levels. An increase in the understanding of molecular mechanisms underlying antidepressant action has led to the suggestion that it is not the enhancement of monoaminergic signaling per se, but rather long-term neuroplastic changes which may underlie the therapeutic effect of antidepressants. The neurotrophic hypothesis of depression and antidepressant action was first proposed by Duman et al. in 1997. This hypothesis is based on the evidence that stress can decrease the expression of BDNF and lead to the atrophy of the...
same populations of stress-vulnerable hippocampal neurons, while electroconvulsive therapy (ECT) and antidepressants increase BDNF expression and may reverse or block the atrophy and cell loss resulting from stress and depression. In the past decade, this novel hypothesis has greatly changed the landscape for human and animal research on MDD.

BDNF is a small dimeric protein and a member of the neurotrophin family. BDNF is widely expressed in the adult mammalian brain, the highest levels being found in the hippocampus, followed by those in the cerebral cortex. Further, BDNF plays a key role in the regulation of neuronal survival, differentiation, growth, and apoptosis by binding to two types of receptors; namely, the tyrosine kinase B (trkB) receptor and the p75 neurotrophin receptor (p75NTR). Moreover, BDNF is involved in the regulation of synaptic synthesis and the release of neurotransmitters.

The important role of BDNF in MDD and antidepressant drug action is supported by an increasing number of studies, mostly in animals. For example, long-term administration of antidepressants in animals upregulates the production of brain BDNF; and infusion of BDNF itself into the midbrain has an antidepressant-like influence in animal models of depression.

In a human postmortem study, Chen et al. found that BDNF immunoreactivity was higher in the hippocampus of depressed subjects being treated with antidepressant medication at the time of death than in that of untreated controls. In a clinical study, Karege et al. found that serum BDNF levels were significantly lower in MDD patients than in controls and that depression severity mainly accounted for a negative correlation between BDNF levels and depression scores. This finding has been replicated by Shimizu et al. in their study of antidepressant-naive MDD patients, with these researchers further demonstrating that reduced serum BDNF values returned to basal levels after antidepressant treatment in drug-naive patients.

The human BDNF gene has been mapped to chromosome 11p13 and is composed of six 5’ exons, which are differentially spliced to a single 3’ terminal exon (exon 7) that encodes the entire sequence of mature BDNF (GenBank accession nr: AF411339). A common single nucleotide polymorphism (SNP) consisting of a missense change (G196A), which produces a non-conservative amino acid change (valine to methionine), has been identified in the coding exon of the BDNF gene at position 66 (Val66Met, rs6265). The replacement of 66Val by 66Met disrupts cellular processing, trafficking, and activity-dependent secretion of BDNF. Our first studies on the genetic association between the BDNF Val66Met polymorphism and MDD in outpatients as well as inpatients were in 2003. We found no significant differences in the genotype or allele frequency of the BDNF Val66Met polymorphism between the MDD and the control groups. However, in a subsequent genetic study, we found an association between BDNF Val66Met polymorphism and geriatric depression, chiefly in males. These findings are in line with a recent meta-analysis of 14 studies involving 2812 MDD cases and 10843 non-depressed controls, which revealed that the BDNF Val66Met polymorphism is not significantly associated with MDD; however, male gender and old age do have an impact on the association.

PHARMACOGENETIC STUDY OF BDNF AND THERAPEUTIC RESPONSE TO ANTIDEPRESSANTS

Antidepressant medication is the main treatment for MDD, but not all MDD patients benefit with up to 40% of MDD patients failing to respond to initial antidepressant treatment. Since genetic factors may play a substantial role in both the variation in response to treatment and incidence of adverse effects to medication, pharmacogenetic studies of antidepressant have attempted to identify genetic markers that predict treatment response. Earlier antidepressant pharmacogenetic studies focused on genes related to monoaminergic systems. Among the candidate genetic variants tested, a serotonin transporter gene promoter polymorphism (5-HTTLPR) has been repeatedly associated with antidepressant treatment response.

Given that both clinical and preclinical studies suggest that BDNF may be involved in the therapeutic action of antidepressants, BDNF appears to be a good candidate gene for the pharmacogenetic study of antidepressants. In our 2003 study on 110 MDD outpatients, we examined the association between the BDNF Val66Met polymorphism and response to 4-week antidepressant (fluoxetine) treatment. A trend (p=0.086) to higher total HAM-D-score percentage change was noted for the Val/Met-heterozygote patients in comparison to those bearing the homozygote (Val/Val or Met/Met). While similar findings have been reported in some of the subsequent studies of this polymorphism and the antidepressant response, other studies demonstrated a better response in subjects with the Met variant or they found no association at all (Table 1). The inconsistencies in these findings might be due to the small sample sizes used in some of the studies. They could also have arisen as the result of differences in the antidepressants administered, in the methods for evaluating treatment outcome, in the length of treatment, and differences in the ethnic background and the MDD subtypes of the patients participating. In an earlier meta-analysis of four studies (490 subjects), a better response was found in subjects with the Met allele. However, this meta-analysis compared only the response between the Met carriers and the Val homozygotes. Recently, Zou et al. performed a meta-analysis which included eight studies with data from 1,115 subjects. They found that in the overall popu-
Heterozygous patients tended to have a better remission than the corresponding homozygous patients. Mirtazapine was more likely to be remitted at 6 months. Met/Met patients had a better response than Val/Val patients in the melancholic subgroup. Table 1. BDNF Val66Met polymorphism and response to antidepressant treatment

| Authors          | Number of subjects | Type of antidepressants                  | Results                                                                 | Ethnicity |
|------------------|--------------------|------------------------------------------|-------------------------------------------------------------------------|-----------|
| Tsai et al.      | 110                | Fluoxetine                               | Heterozygous patients tended to have a better response than the corresponding homozygous patients at 4 weeks | Asian     |
| Choi et al.      | 83                 | Citalopram                               | Met66 allele carriers were more likely to have a better response at 8 weeks | Asian     |
| Wilkie et al.    | 163                | Various antidepressants                  | No association with treatment outcome                                    | Caucasian |
| Yoshida et al.   | 134                | Milnacipran, fluvoxamine                 | Heterozygous patients tended to have a better response than the corresponding homozygous patients at 6 weeks | Asian     |
| Kang et al.      | 243                | Mirtazapine                              | No association with treatment outcome                                    | Asian     |
| Zou et al.       | 295                | Fluoxetine                               | Heterozygous patients tended to have a better remission than the corresponding homozygous patients at 6 weeks | Asian     |
| Domschke et al.  | 268                | Various antidepressants                  | Met/Met patients had a better response than Val/Val patients in the melancholic subgroup | Caucasian |
| Taylor et al.    | 229                | Various antidepressants                  | Met66 allele carriers were more likely to be remitted at 6 months         | Caucasian |

The Val/Met genotype had a significantly stronger association (p=0.02) with a higher response than the Val/Val genotype. When stratified by ethnicity, similar results were found in Asians, but not in Caucasians. No association was found between the BDNF Val66Met polymorphism and the remission rate. The results of this meta-analysis suggest that Val66Met heterozygous patients have a better response rate compared with Val/Val homozygous patients, especially in the Asian population. The positive molecular heterosis effect (subjects heterozygous for a specific genetic polymorphism show a significantly greater effect) is compatible with the results of animal studies showing that, although BDNF exerts an antidepressant effect, too much BDNF may have a detrimental effect on mood. Furthermore, although the increase in BDNF in the hippocampus due to antidepressant treatment is associated with the therapeutic effect of the antidepressant, one animal study has shown that intra-ventral tegmental area infusion of BDNF exerts a depression-like effect in the forced swim test. Thus, an optimal rather than simply elevated BDNF level could be more important for the antidepressant effect.

Several studies have investigated the therapeutic response to antidepressants associated with other BDNF genetic variants, apart from the BDNF Val66Met polymorphism. Recently, Gratacòs and colleagues tested the association between the outcome of antidepressant treatment in Spanish patients with mood disorders (226 MDD and 148 bipolar disorder cases) and genetic variants within the genomic region containing the BDNF gene. Of the eight BDNF polymorphisms tested, only the rs908867 SNP was associated with complete clinical remission. This polymorphism is located 229 bp upstream from the transcription starting site of exon 1 and is not considered to have an effect on the expression of the BDNF gene. Haplotype analysis revealed that the TAT haplotype (involving rs12273363, rs908867, and rs1491850 SNPs) is associated with a better therapeutic response. However, the low base-rate of the TAT haplotype (0.069) may increase chance of false positives in the haplotype analysis. In the same study, the BDNF Val66Met polymorphism was tested, but no association was found with the therapeutic response to antidepressants. In a recent study, Licinio et al. resequenced a genomic DNA region of 22 kilobases, which contained all BDNF exons and their flanking regions. They identified 83 novel BDNF polymorphisms. Association analyses of 200 Mexican American MDD patients treated with desipramine or fluoxetine revealed that 1 SNP (rs61888800) in the 5’ untranslated region was associated with antidepressant response after adjusting for age, sex, medication, and baseline depression score. In another study with 268 German MDD patients, among three BDNF polymorphisms tested (rs7103411, Val66Met, and rs7124442), the BDNF rs7124442 TT genotype was significantly related to worse treatment outcome over 6-week antidepressant treatment, particularly in patients with anxious depression. This association seemed to originate solely from the female subgroup of patients. The BDNF rs7103411 and Val66Met polymorphisms were associated with treatment response over six weeks only in clinical subtypes of depression, such as melancholic depression (Val/Val <Met/Met, p=0.001). The study also tested 10 markers in BDNF for association with the outcome of citalopram treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) sample (n=1,953), but no significant associations were found with any of the 10 BDNF markers.

In addition to MDD, antidepressants are also used in the treatment of obsessive-compulsive disorder (OCD). Real et al. tested the association between the BDNF gene and antidepressant treatment outcome in OCD and found an association between therapeutic response and two of eight BDNF tag SNPs (rs908867...
and rs1491850).

In terms of non-pharmacological treatment in MDD, animal studies have shown that both ECT and repetitive transcranial magnetic stimulation (rTMS) have significant antidepressant action and both treatments affect brain BDNF levels. A study by Huuhka et al. examined BDNF polymorphisms (Val66Met and C270T) and the response to ECT in 119 patients with MDD. No association was found between either Val66Met or C270T and the response to ECT in the total group of participants. In another study, the association between the BDNF Val66Met polymorphism and rTMS response was examined in a group of 36 drug-resistant patients affected by mood disorders. The response to rTMS treatment was significantly greater in BDNF Val/Val homozygotes than in Met allele carriers (p=0.024).

**PHARMACOGENETIC STUDY OF BDNF AND ANTIDEPRESSANT-RELATED ADVERSE EFFECTS**

Although the activation of the BDNF-trkB pathway by antidepressants is related to the therapeutic mechanism of depression, too much BDNF activation may have adverse consequences. For example, animal studies found that transgenic overexpression of BDNF has a facilitatory effect on anxiety-like behaviors and learning and memory impairments. A study by Zou et al. demonstrated that insomnia and decreased sexual desire, which are side effects of fluoxetine, may have been associated with the BDNF Val66Met polymorphism, and Met allele carriers showed a lower incidence of these adverse effects.

Antidepressant treatment can induce or increase suicidal tendencies in some MDD patients, particularly in young patients, and it has been suggested that the BDNF-trkB pathway may be involved in this antidepressant-emergent suicidality. This hypothesis was confirmed by a recent study, which investigated 123 polymorphisms in nine genes and found epistasis between BDNF and trkB genetic variants in vulnerability to suicidality after antidepressant treatment.

Antidepressant treatment for MDD patients can sometimes induce a manic affective shift, and elevated brain BDNF may be implicated in antidepressant-induced mania. Furthermore, family-based association studies have demonstrated that the BDNF Val66Met polymorphism is linked with bipolar disorders. Zai et al. performed a case-control study to test for allelic frequency and genotype distribution differences across six BDNF polymorphisms between 27 patients with antidepressant-induced mania and 29 patients without antidepressant-induced mania. They did not observe any significant difference in either allelic or genotype frequencies between the two groups. However, with the small sample size used in this study, it may have been underpowered to detect a small, but real, association.

**ANTIDEPRESSANT RESPONSE IN BDNF MUTANT MOUSE MODELS**

The antidepressant response has been tested in genetically manipulated mice, and these studies may provide some information for human BDNF-antidepressant pharmacogenetic research. For example, Chen et al. generated a variant Bdnf mouse (Bdnf (Met/Met)), which reproduces the phenotypic hallmarks observed in humans with the variant allele. The Bdnf (Met/Met) mice, which are similar to heterozygous Bdnf (+/-) knockout mice, exhibited increased anxiety-related behaviors, which were not normalized by the antidepressant, fluoxetine. However, the effect of fluoxetine in depression-related behaviors was not tested. More recently, Adachi et al. used a viral-mediated gene transfer approach to assess the effect of BDNF in sub-regions of the hippocampus on antidepressant responses. They found that the selective loss of BDNF in the dentate gyrus, but not in the CA1 region of the hippocampus, attenuated the actions of desipramine and citalopram in the forced swim test. Similarly, another study demonstrated that imipramine decreased despair behaviors (the tail suspension test) in wild-type, but not in heterozygous, Bdnf (+/-) knockout mice following unpredictable chronic mild stress. The above findings in Bdnf mutant mouse models suggest that BDNF deficit dampens some aspects of antidepressant efficacy. However, it is unknown whether BDNF overactivity may affect antidepressant response. Studies to test antidepressant response in mutant mice with Bdnf overexpression are needed.

**CONCLUSION AND FUTURE PERSPECTIVES**

In summary, animal studies have shown that an increase in brain BDNF plays an important role in antidepressant action and that the antidepressant response is attenuated in mutant mice with BDNF deficit. However, the findings of the studies of the BDNF genetic effects on the therapeutic response of antidepressants are not consistent, although several studies on Asians suggested a molecular heterosis effect of the BDNF Val66Met polymorphism on the therapeutic response to antidepressants.

This article has reviewed the effects of BDNF polymorphisms on the therapeutic response of antidepressants. Given the diverse findings among the studies, several strategies for future antidepressant pharmacogenetic studies of BDNF are recommended.

Firstly, some of the BDNF-antidepressant pharmacogenetic studies used a diverse range of antidepressants. Although BDNF plays an important role in the therapeutic effect of antidepressants, it should be noted that different antidepressants may have different effects on brain BDNF expression. For example,
chronic amitriptyline (a tricyclic antidepressant) in rats increased BDNF protein in the hippocampus. However, another study showed that chronic fluoxetine or desipramine administration in rats had no effect on BDNF protein in the hippocampus. These findings emphasise the importance of using a single antidepressant in BDNF pharmacogenetic studies.

Secondly, most of the BDNF-antidepressant pharmacogenetic studies investigated only the BDNF Val66Met polymorphism. Studies involving other BDNF SNPs may uncover important information, which is currently being overlooked. Furthermore, the use of a haplotype constructed by several tag SNPs can improve genotyping efficiency by reducing the number of polymorphisms to be genotyped, and the haplotype itself may also tag other genetic variants, which affect gene function.

Thirdly, a single gene may play only a small part in the therapeutic response to antidepressants. Future studies should consider genes in the BDNF signaling pathway, which may contribute or interact with BDNF in the response to antidepressant treatment. Recently, we found that one p75NTR missense polymorphism (S250L) was associated with the antidepressant response, and TrkB genetic variants may interact with the BDNF Val66Met polymorphism to contribute to the risk of geriatric depression. We also found that SNPs in glycogen synthase kinase-3beta (GSK3B), an important component in BDNF signaling, were associated with the therapeutic effects of antidepressants. In another study, we showed that genetic variants in plasminogen activator inhibitor type 1 gene (SERPINE1), which may be involved in the cleavage of proBDNF to mature BDNF in the brain, are related to MDD susceptibility and also the acute therapeutic response to antidepressants.

Fourthly, it may be of interest to explore the interaction of BDNF and genes in serotonergic pathways in response to antidepressants. The serotonergic system and the BDNF pathway are two signaling systems, which play an important role in the pathogenesis and therapeutic mechanisms of MDD. A positron emission tomography study has shown that male carriers of the Val/Val genotype of the BDNF Val66Met polymorphism display higher serotonin transporter density in the brain. Since both signaling systems have significant interactions with overlapping functional targets, it might be expected that they would have synergistic genetic effects on response to antidepressant treatment or MDD. For example, a study by Kaufman et al. revealed a significant three-way interaction between the BDNF Val66Met genotype, the 5-HTTLPR genotype, and maltreatment history in predicting MDD in children. Another study found a significant interaction between the 5-HTTLPR and BDNF Val66Met polymorphisms and the response to lithium prophylaxis in patients with bipolar disorders. To our knowledge, there is no report of the interaction of these two polymorphisms with the antidepressant response in MDD patients.

Fifthly, the BDNF genetic effect on therapeutic responses to antidepressants may be on specific symptom clusters of MDD. In support of this notion, an animal study demonstrated that, while imipramine treatment decreased depression-like behaviors following unpredictable chronic mild stress in wild-type mice, but not in heterozygous Bdnf (+/-) knockout mice, the antidepressant did decrease anxiety-like behaviors in both genotypes.

Finally, the effect of BDNF on the brain may be affected by age because BDNF receptors change with age. For example, most BDNF genetic association studies in adult MDD showed no positive association with MDD susceptibility. However, two studies in geriatric depression patients found that the Met allele is a genetic risk factor for MDD in aged subjects. These findings are in line with those of an animal study, which showed that forebrain serotonin levels and fiber density in heterozygous Bdnf knock-out mice are normal at an early age, but undergo premature age-associated decrements. In addition to age, gender may also influence BDNF genetic effects in the brain. For example, recent meta-analysis studies have revealed a sexually dimorphic effect of the BDNF Val66Met polymorphism on susceptibility to MDD and to Alzheimer’s disease. Interactions between age/gender and BDNF should therefore be considered in future antidepressant pharmacogenetic studies.

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