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Brain-Derived Neurotrophic Factor Val66Met Polymorphism and Antidepressant Efficacy of Ketamine in Depressed Patients

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To the Editor

The noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine shows rapid antidepressant efficacy—within 1 hour—in individuals with treatment-resistant major depressive disorder (MDD) (1,2) and bipolar disorder (3). This rapid antidepressant effect is in stark contrast to the lag typically associated with traditional monoamine-modulating medications, which require weeks to become effective. Ongoing studies are investigating the cellular and molecular mechanisms underlying ketamine's beneficial effects (4,5), with a view to both expanding our understanding of affective disorders and developing effective, viable, and rapid-acting treatments.

A recent series of elegant animal studies suggest that increased brain-derived neurotrophic factor (BDNF) function is a necessary component of the antidepressant response of ketamine and other NMDA antagonists (5). BDNF is critical to neuronal plasticity (6) and thought to be strongly associated with the pathophysiology of affective disorders (7). In a recent issue of *Biological Psychiatry,* Liu and colleagues (8) compared the role of the Val66Met (rs6265) single nucleotide polymorphism (SNP), a putatively functional polymorphism within the first exon of BDNF, and ketamine response. BDNF knock-in mice (Val/Val, Val/Met, Met/Met) had differing levels of prefrontal cortex synaptogenesis after drug administration on the basis of this single polymorphism. Homozygous Val/Val mice exhibited a stronger neural response than Met carriers, with homozygous Met/Met carriers

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responding the least. Indeed, the anti-depressant effects of ketamine in Met/Met mice were attenuated to the extent that performance on the forced swim test remained at baseline levels, whereas Val carriers showed relative performance enhancements. Moreover, the increases in spine density that followed ketamine administration were more diminished in Met/Met mice than in Val/Met mice (8).

Intrigued by these findings, we investigated whether the rs6265 (Val66Met SNP) is associated with response to ketamine in patients experiencing a major depressive episode. Homozygous Met carriers are rare in some human populations (<5%), thus our aim was to compare homozygous Val/Val individuals, who account for approximately 60% of the European-ancestry population [HapMap], against Met carriers (both Val/Met and Met/Met). We hypothesized that patients carrying a BDNF Met substitution would show an attenuated antidepressant response to ketamine infusion compared with Val/Val patients.

The investigation was approved by the National Institute of Mental Health (NIMH) and Yale Institutional Review Boards and ethics committees. All subjects provided written informed consent. Sixty-two depressed patients (55% female patients, mean age: 48.68, SD: 11.9; male patients, mean age: 43.3, SD: 13.2) received ketamine infusion (.5 mg/kg over 40 min), as described in detail elsewhere (1). Eight subjects were infused onsite at Yale University (New Haven, Connecticut) in a single-blind lead-in infusion procedure (2); subjects infused at the NIMH (Bethesda, Maryland) participated in either an open-label or double-blind crossover setup (1,3,9). Genetic analyses revealed that 41 individuals possessed the Val/Val polymorphism; 21 carried either one ($n = 19$) or both ($n = 2$) Met substitutions. Most subjects were of European ancestry ($n = 58$); four were of self-reported African ancestry, and all but one described themselves as “non-Hispanic.” Hamilton Depression Rating Scale (HAM-D) (10) scores were obtained at baseline (same day preinfusion) and throughout the study. For simplicity, scores are presented here at either 210 or 230 minutes postinfusion. The marker was in Hardy-Weinberg equilibrium in this sample. Given that allele frequencies in rs6265 vary widely among continental groups and because we did not have additional genotypes for part of the sample, we used self-reported race as a proxy for genetic ancestry.

To test the association between rs6265 and ketamine treatment outcome, we implemented a general linear model with change in HAM-D score from baseline to 210/230 minutes as the dependent variable, and genotype (under a dominant model), primary diagnosis (MDD/bipolar disorder), self-reported race, and center of origin (Yale/NIMH) as independent variables. The last three independent variables were used to account for potential confounders (e.g., diagnosis, population stratification, differences in ketamine protocol implementation). Our results ($F = 5.59$, $df = 4$, $p = .0007$) are consistent with recently reported studies (8). This model accounted for 28% of the variance in ketamine response in this sample. Mean baseline and endpoint HAM-D scores for Met carriers were 22.9 (SD: 6.7) and 17.8 (SD: 9.7), respectively. Mean baseline and endpoint scores for Val carriers were 20.8 (SD: 4.8) and 12.2 (SD: 5.4), respectively. The mean percent change in scores (improvement) was 24% (SD: 31) for the Met carriers, and 41% (SD: 24) for the Val carriers. In the Caucasian group only ($n = 58$), the mean change was 20% (SD: 31) for the Met carriers ($n = 18$) and 40% (SD: 24) for the Val carriers ($n = 40$).

Our results suggest that MDD patients with the Val/Val BDNF allele at rs6265 are more likely to exhibit increased antidepressant response to ketamine than Met carriers. Liu and colleagues (8) alluded to the possibility that the weakened antidepressant response to ketamine infusion typically seen in approximately 30% of patients might be related to the Val66Met polymorphism. Our finding is consistent with their hypothesis that rs6265 genotypes could help separate ketamine responders from non-responders. They also suggested that it may be possible to administer BDNF-enhancing compounds to Met allele-

carrying patients before administering ketamine. Standard antidepressants, electro-convulsive therapy, and brain stimulation techniques such as transcranial magnetic stimulation all increase BDNF levels (11,12); exercise also has BDNF secretion-enhancing effects (13). In contrast, a previous report that included the large STAR*D cohort found no association between traditional antidepressants and rs6265 (14). This suggests that the Val66Met variant may play a different role in patients treated with traditional antidepressants as opposed to those treated with rapid-acting antidepressants such as ketamine.

Limitations of the study include small sample size and our inability to correct for population stratification. The results await replication. Nevertheless, taken in conjunction with the findings of Liu and colleagues (8), these results add weight to novel hypotheses that link the BDNF (7) and glutamatergic (15) theories of depression and suggest that future studies should explore the long-term effects of the BDNF Val66Met variant. Ketamine's rapid antidepressant effects suggest that glutamatergic system alterations may operate upstream, thus expanding monoaminergic theories of depression. Future pharmacogenetic research is needed to determine whether genetic variation in the BDNF gene should be included in ketamine treatment study designs and whether administration of BDNF-enhancing compounds or interventions before drug infusion may improve treatment outcome in individuals with treatment-resistant genotypes.

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