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LETTER TO THE EDITOR

Blood D-serine levels as a predictive biomarker for the rapid antidepressant effects of the NMDA receptor antagonist ketamine

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The *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine is the most effective antidepressant drug for patients with treatment-resistant major depressive disorder (MDD) or bipolar disorder (BD) (Krystal et al. 2013). A single subanesthetic dose (0.5 mg/kg) of ketamine produces rapid antidepressant effects in up to two-thirds of patients with MDD and BD, and this effect can last for 7 days or more (Krystal et al. 2013; Zarate et al. 2012). However, the biochemical pathways defining the differences between patients who respond to ketamine and those who do not are currently unknown.

We read with great interest the article entitled "D-serine plasma concentration is a potential biomarker of (*R*,*S*)-ketamine antidepressant response in subjects with treatment-resistant depression," by Moaddel et al. (2014). D-Serine acts as an endogenous, obligatory co-agonist at the NMDA receptor, and in their study, the authors reported that plasma levels of D-serine in the ketamine responder group (3.02±0.30 μM [mean±SD], $n=8$) were significantly ($p<0.0001$) lower than those in the ketamine non-responder group (4.68±0.81 μM [mean±SD], $n=13$). They also found that plasma levels of L-serine in ketamine responders (66.2±62.8 μM [mean±SD]) were significantly ($p<0.0001$) lower than in ketamine non-responders (242.9±67.2 μM [mean±SD]) (Moaddel et al. 2014). Interestingly, there was a significant correlation (D-serine: $r=0.77$, $p<0.001$; L-serine: $r=0.83$, $p<0.001$) between baseline D-serine (and L-serine) concentrations and the percentage change in Montgomery Åsberg Depression Rating Scale (MADRS) scores, 230 min after ketamine infusion (Moaddel et al. 2014). Moreover, the percentage of D-serine to total serine at baseline in the responder group (5.91±1.92 % [mean±SD]) was significantly ($p<0.001$) higher than that of the non-responder group (2.11±1.05 % [mean±SD]), suggesting that the conversion of L-serine to D-serine in patients who responded to ketamine may be less efficient than in ketamine non-responders (Moaddel et al. 2014). Additionally, both responders and non-responders showed decreased D-serine plasma levels in a biphasic manner after ketamine infusion, although plasma levels of L-serine were not altered. Elevations in Clinician Administered Dissociative States Scale (CADSS) scores in the responder group were significantly ($p<0.001$) greater than scores in the non-responder group, and there was a negative correlation ($r=-0.52$, $p=0.02$) between baseline D-serine levels and increased CADSS scores, 40 min after ketamine infusion. Taken together, this study suggests that plasma D-serine at baseline can be used to predict an antidepressant response to ketamine in treatment-resistant patients with depression (Moaddel et al. 2014).

Previously, we reported that serum levels of D-serine in patients with schizophrenia (1.86±0.53 μM [mean±SD]) were significantly lower than those of healthy subjects (2.28 ±0.59 μM [mean±SD]), whereas serum levels of L-serine in patients with schizophrenia (197.9±46.4 μM [mean±SD]) were significantly higher than those in healthy subjects (175.0±30.6 μM [mean±SD]) (Hashimoto et al. 2003), supporting a hypofunction hypothesis for NMDA receptors in schizophrenia. The percentage (responder 5.91±1.92 % (mean±SD), non-responder 2.11±1.05 % [mean±SD]) of D-serine to total serine at baseline in this study (Moaddel et al. 2014) was markedly higher than that found in previous reports (healthy controls 1.31±0.34 % (mean±SD), schizophrenia 0.95±0.26 % [mean±SD]) (Hashimoto et al. 2003). This observation of a higher percentage of D-serine to total serine in patients with treatment-resistant MDD compared with healthy controls suggests a role for hyperglutamatergic neurotransmission via NMDA receptors in the pathophysiology of treatment-resistant MDD (Hashimoto et al. 2007, 2013; Hashimoto 2009). It would therefore be of great interest to

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study whether blood levels of D- and L-serine in patients with treatment-resistant MDD (or BD) are altered compared with healthy controls.

D-Serine is synthesized from L-serine by serine racemase and is metabolized by D-amino acid oxidase (Yamada et al. 2005; Hashimoto et al. 2013; Hashimoto 2014b). Serine hydroxymethyltransferase is an enzyme which catalyzes the reversible conversion between glycine and L-serine (Maekawa et al. 2010; Hashimoto 2014b). L-Serine is also synthesized in astrocytes, from the glycolytic intermediate 3-phosphoglycerate (Hirabayashi and Furuya 2008; Hashimoto 2014b). All of these enzymes are capable of affecting NMDA receptor function. Future studies investigating enzymatic activity and genetic variations in these enzymes from both ketamine responders and non-responders would be of great interest.

Ketamine (or *RS* (±)-ketamine) is a racemic mixture containing equal parts of *R*- and *S*-ketamine. Recently, we reported that *R*-ketamine showed more potent and longer-lasting antidepressant effects than the *S*-stereoisomer, in a rodent model of depression (Zhang et al. 2014). This suggests that *R*-ketamine is probably more efficacious and since it appears to be free of psychotomimetic side effects, a safer antidepressant, relative to the *S*-stereoisomer (Hashimoto 2014a; Yang and Hashimoto 2014). It would also be invaluable to measure the levels of D- and L-serine in the blood and cerebrospinal fluid of patients, after administration of ketamine isomers.

In conclusion, given the key role of D-serine in NMDA receptor neurotransmission, its use as a biomarker for antidepressant response to the two stereoisomers of ketamine and other NMDA receptor antagonists in patients with treatment-resistant MDD or BD will be highly useful in the clinical setting. Nonetheless, further studies using larger sample sizes are needed to confirm these findings.

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Conflict of interest Dr. Hashimoto is an inventor on a filed patent application (pending) on "D-Serine as a biomarker of schizophrenia" and "The use of *R*-ketamine in the treatment of psychiatric diseases." Dr. Hashimoto has served as a scientific consultant to Astellas and Taisho, and he also received the research support from Abbvie, Dainippon Sumitomo, Mochida, Otsuka, and Taisho.

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