I read with great interest the recent article by Kishimoto et al. (2016) about meta-analysis of the antidepressant effects of the N-methyl-D-aspartate receptor (NMDA-R) antagonist ketamine (racemate) and non-ketamine NMDA-R antagonists (traxoprodil, lanicemine, rapastinel) in patients with major depressive disorder (MDD) and bipolar disorder. The authors examined the time trajectory of efficacy of ketamine and non-ketamine NMDA-R antagonists. The greater reduction in depressive symptoms by ketamine infusion started as early as within 40–60 min, peaking on day 1, and lasting until days 5–8, with maintenance of superior remission and response status until days 3–5 and 7, respectively. Effect sizes of ketamine ranged from medium to high (−0.38 to −1.00). In contrast to ketamine, single infusion of non-ketamine NMDA-R antagonists was only significantly superior to placebo at one assessment time point (days 5–8) with a small to medium effect size (−0.37). Together, it is likely that non-ketamine NMDA-R antagonists have smaller effect sizes than ketamine, although the reason underlying this difference remains unclear.

Ketamine (or RS-ketamine) ($K_i = 0.53 \mu m$ for NMDA-R) is a racemic mixture containing equal parts of R-ketamine and S-ketamine (esketamine). Esketamine shows an approximately 3- to 4-fold greater anaesthetic potency and greater undesirable psychotomimetic side effects, compared with R-ketamine (Domino, 2010). This is related to the fact that esketamine ($K_i = 0.30 \mu m$) has an approximately 4-fold greater affinity for NMDA-R relative to R-ketamine ($K_i = 1.4 \mu m$) (Fig. 1) (Ebert et al. 1997). We reported that R-ketamine showed greater potency and longer-lasting antidepressant effects than esketamine in animal models of depression (Zhang et al. 2014; Yang et al. 2015). It is therefore unlikely that NMDA-R has a major role in the long-lasting antidepressant effects of R-ketamine, although antagonism at this receptor may promote its rapid antidepressant action (Hashimoto, 2014; Yang et al. 2015). Furthermore, a single dose of esketamine, but not R-ketamine, resulted in loss of parvalbumin (PV)-immunoreactivity in the prefrontal cortex (Yang et al. 2015). A recent study using [13C]raclopride and positron emission tomography showed a marked reduction of dopamine $D_2/3$ receptor binding in the conscious monkey striatum after single infusion of esketamine, but not R-ketamine (Hashimoto et al. 2016). Singh et al. (2015) reported that psychotomimetic side effects were the highest at 40 min after single infusion of esketamine although a rapid-onset antidepressant effect was shown in treatment-resistant patients with MDD. Considering the role of dopamine release in psychosis, it is likely that marked release of dopamine from presynaptic terminals in the striatum could be associated with psychotomimetic side effects in humans after a single infusion of ketamine or esketamine.

The authors also pointed out that the transient efficacy lasting 1 week post-infusion of ketamine has stimulated multi-infusion studies (Kishimoto et al. 2016). Studies using repeated ketamine (or esketamine) infusions resulted in the marked psychotomimetic side effects after each infusion although antidepressant effects were shown (Aan het Rot et al. 2010; Murrough et al. 2013; Singh et al. 2015). Interestingly, there was no difference in dissociative, psychotomimetic, or high feeling between responders and non-responders (Murrough et al. 2013), suggesting that ketamine’s antidepressant effects are not associated with its psychotomimetic effects. Recently, we reported that repeated, intermittent administration of esketamine, but not R-ketamine, caused loss of PV-immunoreactivity in the prefrontal cortex of mouse brain (Yang et al. 2016). Since loss of PV-immunoreactivity in the prefrontal cortex may be associated with psychosis and gamma-oscillation deficits in schizophrenia (Gonzalez-Burgos et al. 2015), it is possible that repeated administration of esketamine or ketamine may have long-lasting detrimental side effects in the prefrontal cortex of humans.

In conclusion, the use of R-ketamine in the treatment of depression would provide a new therapeutic approach by reducing the detrimental side effects of ketamine.

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Declaration of Interest

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K. HASHIMOTO
Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, 1-8-1 Inohana, Chiba 260-8670, Japan

Author for correspondence: Kenji Hashimoto, Ph.D., Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, 1-8-1 Inohana, Chiba 260-8670, Japan.
(Email: hashimoto@faculty.chiba-u.jp)