

## Correspondence

Psychological Medicine, 46 (2016).

doi:10.1017/S0033291716000969

First published online 10 June 2016

### **R-ketamine: a rapid-onset and sustained antidepressant without risk of brain toxicity**

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) ( $K_i = 0.53 \mu\text{M}$  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 ( $K_i = 0.30 \mu\text{M}$ ) has an approximately 4-fold greater affinity for NMDA-R relative to *R*-ketamine ( $K_i = 1.4 \mu\text{M}$ ) (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; Zhang *et al.* 2014; Yang *et al.* 2015). Unlike esketamine, *R*-ketamine does not induce psychotomimetic side effects and abuse potential in rodents (Yang &

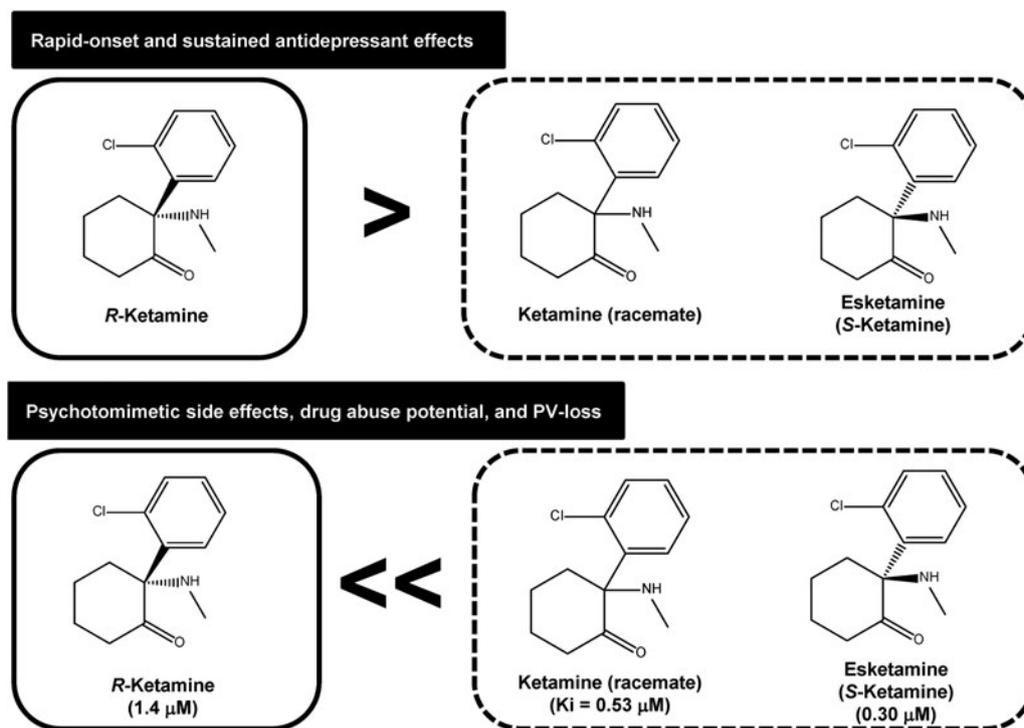
Hashimoto, 2014; Yang *et al.* 2015). Furthermore, a single dose of esketamine, but not *R*-ketamine, resulted in loss of parvalbumin (PV)-immunoreactivity in the prefrontal cortex (Yang *et al.* 2015). A recent study using [ $^{11}\text{C}$ ]raclopride and positron emission tomography showed a marked 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 an each infusion although antidepressant effects were shown (Aan het Rot *et al.* 2010; Murrrough *et al.* 2013; Singh *et al.* 2015). Interestingly, there was no difference in dissociative, psychotomimetic, or high feeling between responders and non-responders (Murrrough *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.

### **Acknowledgements**

The study was supported by a Grant-in-Aid from the Minister of Education, Culture, Sports, Science, and Technology of Japan (to K.H., no. 24116006).



**Fig. 1.** Antidepressant and side effects of *R*-ketamine, ketamine (racemate) and esketamine in preclinical models of depression suggest that *R*-ketamine has greater potency and longer-lasting antidepressant effects than ketamine (racemate) and esketamine (*S*-ketamine) (Zhang *et al.* 2014; Yang *et al.* 2015). Furthermore, preclinical studies using locomotion, prepulse inhibition, conditioned place preference and parvalbumin (PV)-immunohistochemistry suggest that ketamine and esketamine, but not *R*-ketamine, could cause psychotomimetic effects, drug abuse potential and PV-loss in the prefrontal cortex (Yang *et al.* 2015, 2016). A clinical study using esketamine showed marked psychotomimetic side effects in major depressive disorder patients after administration of esketamine (Singh *et al.* 2015). Since the psychotomimetic effects of ketamine are known to be associated with *N*-methyl-*D*-aspartate receptor (NMDA-R) antagonism, it is likely that the use of *R*-ketamine is safer than esketamine or ketamine in the treatment of depression. The values in the parentheses are  $K_i$  values for NMDA-R in the brain (Ebert *et al.* 1997).

### Declaration of Interest

K.H. is an inventor on a field patent application on 'The use of *R*-ketamine in the treatment of psychiatric diseases' by Chiba University. In addition, K.H. has received research support from Dainippon-Sumitomo, Mochida, Otsuka and Taisho.

### References

- Aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, Mathew SJ (2010). Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biological Psychiatry* **67**, 139–145.
- Domino EF (2010). Taming the ketamine tiger. 1965. *Anesthesiology* **113**, 678–684.
- Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM (1997). Norketamine, the main metabolites of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *European Journal of Pharmacology* **333**, 99–104.
- Gonzalez-Burgos G, Cho RY, Lewis DA (2015). Alterations in cortical network oscillations and parvalbumin neurons in schizophrenia. *Biological Psychiatry* **77**, 1031–1040.
- Hashimoto K (2014). The *R*-stereoisomer of ketamine as an alternative for ketamine for treatment-resistant major depression. *Clinical Psychopharmacology and Neuroscience* **12**, 72–73.
- Hashimoto K, Kakiuchi T, Ohba H, Nishiyama S, Tsukada H (2016). Reduction of dopamine  $D_{2/3}$  receptor binding in the striatum after a single administration of esketamine, but not *R*-ketamine: a PET study in conscious monkeys. *European Archives of Psychiatry and Clinical Neuroscience*. Published online 18 April 2016. doi:10.1007/s00406-016-0692-7.
- Kishimoto T, Chawla JM, Hagi K, Zarate CA, Kane JM, Bauer M, Correll CU (2016). Single-dose infusion ketamine and non-ketamine *N*-methyl-*D*-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychological Medicine* **46**, 1459–1472.
- Murrough JW, Perez AM, Pillmer S, Stem J, Parides MK, Aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV (2013). Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biological Psychiatry* **74**, 250–256.
- Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, Tadic A, Sienaert P, Wiegand F, Manji H, Drevets WC,

- Van Nueten L** (2015). Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. *Biological Psychiatry*. Published online 3 November 2015. doi:10.1016/j.biopsych.2015.10.018.
- Yang C, Han M, Zhang JC, Ren Q, Hashimoto K** (2016). Loss of parvalbumin-immunoreactivity in mouse brain regions after repeated intermittent administration of esketamine, but not R-ketamine. *Psychiatric Research* **239**, 281–283.
- Yang C, Hashimoto K** (2014). Rapid antidepressant effects and abuse liability of ketamine. *Psychopharmacology (Berlin)* **231**, 2041–2042.
- Yang C, Shirayama Y, Zhang JC, Ren Q, Yao W, Ma M, Dong C, Hashimoto K** (2015). R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. *Translational Psychiatry* **5**, e632.
- Zhang JC, Li SX, Hashimoto K** (2014). R(-)-ketamine shows greater potency and longer lasting antidepressant effects than S(+)-ketamine. *Pharmacology, Biochemistry and Behavior* **116**, 137–141.

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)