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Reply to: Rapid antidepressant effects and abuse liability of ketamine

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Ketamine; NMDA receptor; Intracranial self-stimulation; abuse liability; Depression; MK-801

Letter to the Editor

We would like to thank Yang and Hashimoto for their commentary and interest in our recent article that evaluated abuse-related effects of the N-methyl-D-aspartate (NMDA) receptor antagonists ketamine and MK-801 (Hillhouse et al. 2014). In this study, we reported that the high-affinity and selective NMDA receptor antagonist MK-801 produced a dose- and time-dependent abuse-related facilitation of intracranial self-stimulation (ICSS) in rats. In contrast, the low-affinity NMDA receptor antagonist ketamine only depressed ICSS in rats and failed to produce an abuse-related facilitation on ICSS after acute treatment. Following repeated ketamine treatment, tolerance to the rate-decreasing effects of ketamine developed; however, ketamine still failed to produce an abuse-related increase on ICSS. We acknowledged that these results contrast with evidence for rare but well-documented cases of ketamine abuse in humans (McCambridge et al. 2007; Shek, 2007) and for abuse-related ketamine effects in other preclinical models (Rocha et al. 1996; Suzuki et al. 2000). However, we also interpreted the dissociable effects of MK-801 and ketamine to suggest that ketamine may produce effects mediated by targets other than NMDA receptors.

One basis for non-NMDA ketamine effects could be stereoselectivity of pharmacology for ketamine enantiomers. Clinical and preclinical studies of ketamine, including our study cited above, most commonly use the racemate *R*,*S* (±)-ketamine, which is comprised of equal parts *S*-ketamine and *R*-ketamine. *S*-ketamine is approximately three times more potent than *R*-ketamine for the PCP site on NMDA receptors and for mu opioid receptors, but it is approximately sixfold less potent for sigma receptors (Hustveit et al. 1995). Furthermore, *S*-ketamine is twice as potent to block the NMDA channel (Zeilhofer et al. 1992), and in healthy human volunteers, *S*-ketamine was four times more potent than *R*-ketamine to

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produce intoxicating effects, visual and auditory disturbances, and analgesia to experimental induced ischemic pain (Øye et al., 1992).

Recently Zhang et al. (2014) reported that *R*-ketamine produced a reduction in time spent immobile in the forced swim test and tail suspension test in mice at 27–29 hours and at 7 days after treatment, whereas, *S*-ketamine reduced time spent immobile in these task at 27–29 hours, but not at day 7. The authors concluded that *R*-ketamine may be responsible for the prolonged antidepressant effects produced by the racemic form of ketamine, although a mechanism of action for this stereoselectivity was not proposed. To date, the antidepressant effects of *R*-ketamine have not been evaluated in clinical settings. However, clinical research does suggest that *R*-ketamine displays reduced psychotomimetic properties. For example, in healthy human volunteers, a subanesthetic dose of *S*-ketamine produced depersonalization, visual disturbances, auditory distortions and disrupted attention; whereas, an equimolar dose of *R*-ketamine did not produce psychotomimetic effects, and instead produced a state of relaxation (Vollenweider et al. 1997). To our knowledge, abuse-related effects of ketamine enantiomers have not been compared.

In conclusion, we agree with Yang and Hashimoto that pharmacological differences in ketamine enantiomers warrant further investigation in ICSS procedures and other preclinical procedures that evaluate abuse-related drug effects.

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