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Commentary

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Is Metabolism of (*R*)-Ketamine Essential for the Antidepressant Effects?

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Major depressive disorder (MDD) affects approximately 10% to 20% of the US population (Kessler et al., 2005); thus, the economic burden of MDD is immense. Currently, selective serotonin reuptake inhibitors and serotonin- and noradrenaline-reuptake inhibitors are widely prescribed for patients with MDD as first-line treatments. However, these medications have several drawbacks; approximately 30% of patients remain inadequately treated even after a series of treatments and it takes several weeks for these medications to manifest their antidepressant actions (Rush et al., 2006; Trivedi et al., 2006). New treatment options with mechanisms of action distinct from current medications are long awaited.

Ketamine, a drug used as a dissociative anesthetic, shed light on this long-desired requirement. A subanesthetic dose of ketamine has been reported to exert rapid (<2 h) and long-lasting (>1 week) antidepressant effects in not only patients with MDD but also those with treatment-resistant depression (Berman et al., 2000; Zarate et al., 2006). Furthermore, ketamine rapidly reduced suicidal ideation in depressed patients (Price et al., 2015; Ionescu et al., 2016). These ground-breaking findings could change depression therapy. However, ketamine elicits side effects such as psychotomimetic/dissociative symptoms right after injection, and abuse potential and neurotoxocity on long-term treatment. All these shortcomings prevent ketamine from routine use in daily practice. To develop agents having ketamine-like antidepressant effects but fewer side effects, enormous efforts have recently been made to understand mechanisms underlying antidepressant actions of ketamine. Indeed, these efforts have helped elucidate the role of AMPA receptor stimulation and subsequent activation of brain-derived neurotrophic factor signaling and synaptogenesis, which may be triggered by *N*-methyl-D-aspartate (NMDA) receptor blockade (Li et al., 2010; Krystal et al., 2013; Koike and Chaki, 2014) in the actions of ketamine, and additional mechanisms have also been being proposed (Belujon and Grace, 2014; Carreno et al., 2016). Still, an important issue remains to fully understand the mechanisms of ketamine. Which substance(s) produced in the body following ketamine administration is responsible for the antidepressant effects?

Ketamine is a racemic mixture of (*S*)- and (*R*)-enantiomers. It is well known that ketamine is rapidly and stereoselectively metabolized by multiple hepatic cytochrome P450 (CYP) enzyme isoforms to a broad array of metabolites, including the norketamine, 2 diastereomeric hydroxyketamines, a series of 6 diastereomeric hydroxynorketamine (HNK), and dehydronorketamine (for review, see Chaki, 2017). Recently, 2 important findings were reported on active substances of ketamine. First, although (*S*)-ketamine has long been believed as an active substance for the actions of ketamine, (*R*)-ketamine has been reported to exhibit longer-lasting and more potent antidepressant effects than (*S*)-ketamine in animal models (Zhang et al., 2014; Yang et al., 2015; Fukumoto et al., 2017). Moreover, (*R*)-ketamine does not induce unwanted side effects such as abuse potential and neurotoxicity in rodents, observed with ketamine treatment (Yang et al., 2015). More importantly, Zanos et al. (2016) have reported that not only has (*R*)-ketamine more potent antidepressant effects than (*S*)-ketamine, but also the metabolism of ketamine to (2*S*,6*S*;2*R*,6*R*)-HNK is essential and sufficient to exert the antidepressant effects of ketamine. In their studies, they demonstrated that ketamine deuterated at the C6 position (6,6-dideuteroketamine) to prevent metabolism by CYP enzymes no longer exhibited antidepressant action at 24 h after administration in the

mouse forced swimming test and learned helplessness model. Furthermore, they claimed that (2*R*,6*R*)-HNK plays a critical role in the antidepressant effects of ketamine because (2*R*,6*R*)-HNK demonstrated much more potent antidepressant effects than (2*S*,6*S*)-HNK. Based on these results, (2*R*,6*R*)-HNK is suggested to be the active substance produced in the body following ketamine administration and responsible for the antidepressant effects of ketamine (also (*R*)-ketamine). In addition, (2*R*,6*R*)-HNK was devoid of unwanted side effects ketamine exhibited in rodents. These findings raise the possibility that (2*R*,6*R*)-HNK could be a ketamine-like antidepressant with fewer side effects, as well as the need to reconsider the mechanisms of ketamine, which are based on NMDA receptor inhibition, since (2*R*,6*R*)-HNK has very weak activity at the NMDA receptor.

However, there are some contradictory findings. Although (2*R*,6*R*)-HNK is derived solely by metabolism of (*R*)-ketamine, (*S*)-ketamine did exhibit antidepressant effects in either rodents (du Jardin et al., 2016; Ardalan et al., 2017) or depressed patients (Singh et al., 2016). Consequently, the antidepressant actions of ketamine cannot be explained solely by (2*R*,6*R*)-HNK. Furthermore, Hashimoto's group has recently reported that antidepressant effects of (2*R*,6*R*)-HNK was weaker than (*R*)-ketamine in 2 animal models: a lipopolysaccharide-induced inflammation model and a chronic social defeat stress model (Yang et al., 2017) in mice, and that injection of (*R*)-ketamine into the brain nuclei can exert antidepressant effects in a rat learned helplessness model (Shirayama and Hashimoto, 2017). Regarding the mechanisms underlying the antidepressant effects of (2*R*,6*R*)-HNK, Suzuki et al. (2017) have recently reported that (2*R*,6*R*)-HNK blocks the NMDA receptor, which disputes the claim that the effects of this metabolite are the NMDA receptor-independent. These results raise questions against the proposal that (2*R*,6*R*)-HNK is essential for the antidepressant effects of ketamine (also (*R*)-ketamine), and that the NMDA receptor blockade is not involved in the actions of (2*R*,6*R*)-HNK.

In this issue, Shirayama and Hashimoto (2018) provide new evidence that (*R*)-ketamine but not its major metabolites, (*R*)-norketamine and (2*R*,6*R*)-HNK, exhibited antidepressant effects. In the study, (*R*)-ketamine significantly reduced escape failures, a measure of learned helplessness behavior, in the rat learned helplessness model, a well-validated model in which antidepressant activity of brain-derived neurotrophic factor was first demonstrated (Shirayama et al., 2002). The effects were observed at 24 h after a single administration of (*R*)-ketamine and lasted for at least 5 days. In contrast, both (*R*)-norketamine and (2*R*,6*R*)-HNK, at the same dose as (*R*)-ketamine, did not show any effect in this model. (2*R*,6*R*)-HNK did not exert the effect even at twice-higher dose than (*R*)-ketamine. Based on these results, the authors concluded that it is unlikely that metabolism of ketamine to (2*R*,6*R*)-HNK is essential for ketamine to exert its antidepressant effects.

In contrast, (2*R*,6*R*)-HNK has been reported to exert antidepressant effects in the forced swimming test, learned helplessness model, chronic social defeat stress model, and corticosterone-induced anhedonia, all conducted on mice (Zanos et al., 2016). Although the precise reason for these discrepancies is not known, it may be ascribed to subtle differences in experimental conditions. Therefore, it is not easy to conclude whether (2*R*,6*R*)-HNK has antidepressant effects, unless efficacy of (2*R*,6*R*)-HNK is tested and confirmed across several laboratories.

Here, it should be emphasized that we must clearly distinguish discussion on whether metabolism to (2*R*,6*R*)-HNK is essential for antidepressant effects of (*R*)-ketamine from discussion on whether (2*R*,6*R*)-HNK per se has antidepressant effects. Thus, comparison of antidepressant activity of (*R*)-ketamine and its metabolites at the same dosage does not answer the question, and it is necessary to confirm that exposure levels of the metabolites of interest are comparable with those obtained after (*R*)-ketamine administration. In this regard, there is a caveat in the study reported by Shirayama and Hashimoto (2018). In their study, the authors did not measure exposure levels of (*R*)-ketamine, (*R*)-norketamine, or (2*R*,6*R*)-HNK in the brain after administration of each compound. Thus, it is not known whether adequate exposure levels of (*R*)-norketamine and/or (2*R*,6*R*)-HNK were obtained to manifest antidepressant actions. Nonetheless, the results of Hashimoto's group, which demonstrated that (2*R*,6*R*)-HNK did not exert antidepressant effects in some animal models in which both (*R*)-ketamine and (*S*)-ketamine exert potent and long-lasting antidepressant effects, raise concerns whether metabolism to (2*R*,6*R*)-HNK is essential to exert antidepressant effects of ketamine.

Notably, Shirayama and Hashimoto (2018) also demonstrated for the first time that one of the major metabolites, (*R*)-norktetamine, did not exert antidepressant effects, while (*R*,*S*)-norketamine has been shown to demonstrate antidepressant activity (Salat et al., 2015), presumably through inhibition of the NMDA receptor. Involvement of not only (2*R*,6*R*)-HNK but involvement of other metabolites in the actions of ketamine should also be investigated to identify the active substance(s) in the body after ketamine administration.

Identification of active metabolites and/or active substances is an important part of research history in neuropsychopharmacology, as represented by the discovery of desipramine, N-desmethylclozapine and 9-hydroxyrisperidone (paliperidone). Such findings have led to the identification of new molecular targets for drug discovery and development. Given that the discovery of antidepressant effects of ketamine is regarded as one of the most outstanding findings in depression research in decades, there is no doubt that identification of active substance(s) of ketamine will impact future depression therapy. In conclusion, while production of (2*R*,6*R*)-HNK has been proposed to be essential for the antidepressant effects of ketamine, this hypothesis needs to be carefully examined by independent laboratories by a variety of approaches.

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Statement of Interest

The author is an employee of Taisho Pharmaceutical Co., Ltd.

References

Ardalan M, Wegener G, Rafati AH, Nyengaard JR (2017) S-ketamine rapidly reverses synaptic and vascular deficits of hippocampus in genetic animal model of depression. Int J Neuropsychopharmacol 20:247–256.

Belujon P, Grace AA (2014) Restoring mood balance in depression: ketamine reverses deficit in dopamine-dependent synaptic plasticity. Biol Psychiatry 76:927–936.

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47:351–354.

Carreno FR, Donegan JJ, Boley AM, Shah A, DeGuzman M, Frazer A, Lodge DJ (2016) Activation of a ventral hippocampus-medial

prefrontal cortex pathway is both necessary and sufficient for an antidepressant response to ketamine. Mol Psychiatry 21:1298–1308.

Chaki S (2017) Beyond ketamine: new approaches to the development of safer antidepressants. Curr Neuropharmacol 15:963–976.

du Jardin KG, Liebenberg N, Müller HK, Elfving B, Sanchez C, Wegener G (2016) Differential interaction with the serotonin system by S-ketamine, vortioxetine, and fluoxetine in a genetic rat model of depression. Psychopharmacology (Berl) 233:2813–2825.

Fukumoto K, Toki H, Iijima M, Hashihayata T, Yamaguchi JI, Hashimoto K, Chaki S (2017) Antidepressant potential of (R)-ketamine in rodent models: comparison with (S)-ketamine. J Pharmacol Exp Ther 361:9–16.

Ionescu DF, Swee MB, Pavone KJ, Taylor N, Akeju O, Baer L, Nyer M, Cassano P, Mischoulon D, Alpert JE, Brown EN, Nock MK, Fava M, Cusin C (2016) Rapid and sustained reductions in current suicidal ideation following repeated doses of intravenous ketamine: secondary analysis of an open-label study. J Clin Psychiatry 77:e719–e725.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry 62:617–627.

Koike H, Chaki S (2014) Requirement of AMPA receptor stimulation for the sustained antidepressant activity of ketamine and LY341495 during the forced swim test in rats. Behav Brain Res 271:111–115.

Krystal JH, Sanacora G, Duman RS (2013) Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. Biol Psychiatry 73:1133–1141.

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329:959–964.

Price RB, Mathew SJ (2015) Does ketamine have anti-suicidal properties? Current status and future directions. CNS Drugs 29:181–188.

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 163:1905–1917.

Sałat K, Siwek A, Starowicz G, Librowski T, Nowak G, Drabik U, Gajdosz R, Popik P (2015) Antidepressant-like effects of ketamine, norketamine and dehydronorketamine in forced swim test: role of activity at NMDA receptor. Neuropharmacology 99:301–307.

Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS (2002) Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 22:3251–3261.

Shirayama Y, Hashimoto K (2017) Effects of a single bilateral infusion of R-ketamine in the rat brain regions of a learned helplessness model of depression. Eur Arch Psychiatry Clin Neurosci 267:177–182.

Shirayama Y, Hashimoto K (2018) Lack of antidepressant effects of (2R,6R)-hydroxynorketamine in a rat learned helplessness model: comparison with (R)-ketamine. Int J Neuropsychopharmacol 21:84–88.

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 (2016) Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. Biol Psychiatry 80:424–431.

Suzuki K, Nosyreva E, Hunt KW, Kavalali ET, Monteggia LM (2017) Effects of a ketamine metabolite on synaptic NMDAR function. Nature 546:E1–E3.

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M (2006) STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 163:28–40.

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. Transl Psychiatry 5:e632.

Yang C, Qu Y, Abe M, Nozawa D, Chaki S, Hashimoto K (2017) (R)-Ketamine shows greater potency and longer lasting antidepressant effects than its metabolite (2R,6R)-hydroxynorketamine. Biol Psychiatry 82:e43–e44.

Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, Dossou KS, Fang Y, Huang XP, Mayo CL, Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA Jr, Gould TD (2016) NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533:481–486.

Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63:856–864.

Zhang JC, Li SX, Hashimoto K (2014) R (-)-ketamine shows greater potency and longer lasting antidepressant effects than S (+)-ketamine. Pharmacol Biochem Behav 116:137–141.