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KEY PAPER EVALUATION

Ketamine's antidepressant action: beyond NMDA receptor inhibition

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ABSTRACT

The *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine is one of the most attractive antidepressants since this drug causes rapid-onset and sustained antidepressant effects in treatment resistant patients with depression. There are unanswered questions about how ketamine induces its rapid and sustained antidepressant actions. This key article suggests that (2*R*,6*R*)-HNK (hydroxynorketamine), a major metabolite of (*R*)-ketamine, shows antidepressant effects in rodent models of depression, indicating that the metabolism of (*R*)-ketamine to (2*R*,6*R*)-HNK is pivotal in its antidepressant action. Here these findings are put into context and their significance is discussed.

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1. Introduction

Depression is a common, worldwide mental illness, affecting an estimated 350 million people. Depression becomes a debilitating mental health condition when patients suffer long-lasting moderate or severe symptoms. Although the antidepressants are generally effective in the treatment of depression, it can still take weeks before patients feel the full therapeutic benefits. So, despite the efficacy of standard treatments, approximately one-third of patients fail to respond to pharmacotherapy. Therefore, the development of novel drugs capable of inducing a rapid-onset and robust antidepressant response in treatment-resistant depressed patients is a clinical imperative.

In 2000, Berman et al. [1] reported that a single sub-anesthetic dose of the *N*-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, conferred a rapid antidepressant effect in patients with depression. Subsequent to this, multiple double-blind, placebo-controlled studies replicated these rapid-onset and sustained antidepressant effects of ketamine in cohorts of patients with treatment-resistant major depressive disorder and bipolar disorder. A meta-analysis demonstrated that non-ketamine NMDA receptor antagonists (e.g. memantine, traxoprodil, lanicemine, and rapastinel) induce smaller effect sizes than ketamine; however, the reasons underlying this difference remain unclear [2]. Although the superior antidepressant efficacy of ketamine is a significant discovery in the field of psychiatry, its potential for widespread clinical use is limited by psychotomimetic side effects and abuse liability [3,4].

Ketamine is a racemic mixture of (*S*)-ketamine (esketamine) and (*R*)-ketamine. Esketamine (Ki = 465 nM) has an approximately fourfold greater affinity for the NMDA receptor relative to (*R*)-ketamine (Ki = 1,340 nM) (Figure 1) [5]. Janssen Pharmaceutical Company has been developing intranasal administration of esketamine as an antidepressant since it was believed that the NMDA receptor inhibition plays a key role in the antidepressant actions of ketamine. Unexpectedly, we demonstrated that (*R*)-ketamine shows greater potency and longer lasting antidepressant effects than esketamine in animal models of depression [6,7].

2. Results from the paper

There are unanswered questions about how ketamine induces its rapid and sustained antidepressant actions. First, the authors showed a greater potency for (*R*)-ketamine in three antidepressant-predictive tasks, relative to esketamine [5], consistent with our previous reports [6,7]. By contrast, the high-affinity NMDA receptor antagonist MK-801 (Ki = 3.49 nM) failed to exert rapid (24 h) antidepressant-like effects, or reverse social interaction deficits induced by chronic social defeat stress [5]. These findings suggest that NMDA receptor inhibition may not play a role in mechanisms underlying the antidepressant responses of ketamine [5].

The authors also found greater antidepressant potency for ketamine in female over male mice [5]. Ketamine is metabolized to norketamine, hydroxyketamines, dehydronorketamine, and hydroxynorketamines (HNKs) (Figure 2) [5]. The major HNK metabolite found in the plasma and brains of mice and in human plasma after ketamine administration is (2*S*,6*S*;2*R*,6*R*)-HNK. Although equivalent levels of ketamine and norketamine were found, (2*S*,6*S*;2*R*,6*R*)-HNK was approximately threefold higher in the brains of female compared to male mice, suggesting a gender difference in the pharmacokinetic profile of ketamine. In order to determine whether metabolism of ketamine to (2*S*,6*S*;2*R*,6*R*)-HNK is required for antidepressant activity, the authors prepared 6,6-dideuteroketamine (Ki = 883 nM for NMDA receptor) (Figure 1). This compound results in reduced metabolism to (2*S*,6*S*;2*R*,6*R*)-HNK, without changing ketamine levels in the brain. Interestingly, 6,6-dideuteroketamine did not show antidepressant effects.

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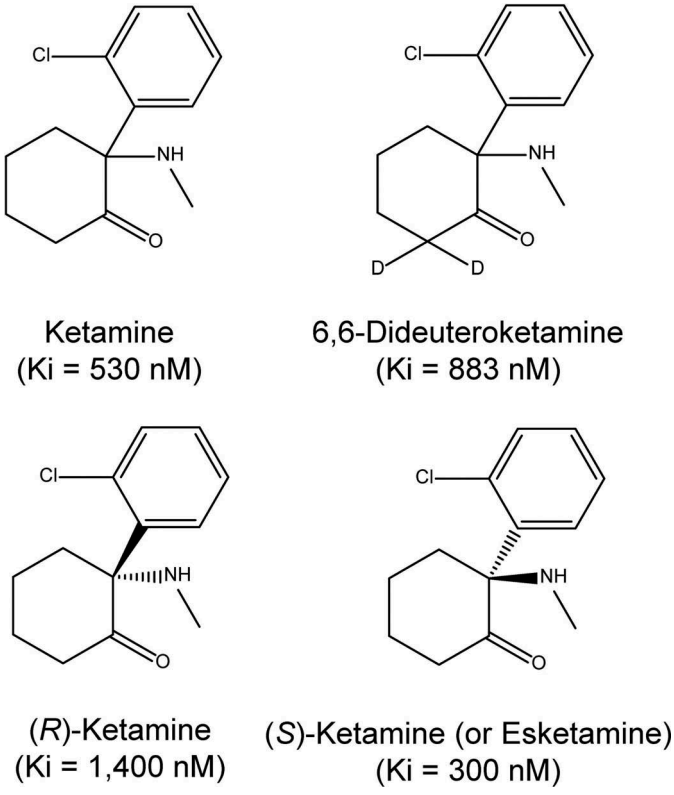

Figure 1. Chemical structure of ketamine, 6,6-dideuteroketamine, (*R*)-ketamine, (*S*)-ketamine (esketamine). The value in the parenthesis is Ki value for NMDA receptor [5,3].

In addition, (2*R*,6*R*)-HNK (Ki > 10,000 nM for the NMDA receptor), a compound exclusively derived from (*R*)-ketamine, showed enhanced antidepressant potency compared to (2*S*,6*S*)-HNK (Ki > 10,000 nM for the NMDA receptor). Furthermore, a single administration of (2*R*,6*R*)-HNK resulted in persistent antidepressant activity, lasting for a minimum of 3 days. Moreover, a single dose of (2*R*,6*R*)-HNK (24 h after injection) reversed anhedonia in chronic corticosterone-treated mice, as well as in social avoidance induced by chronic social defeat stress.

In addition to its low affinity at the NMDA receptor, (2*R*,6*R*)-HNK did not functionally inhibit NMDA receptors localized to stratum radiatum interneurons in hippocampal slices. It did however induce a robust increase in α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor-mediated excitatory postsynaptic potentials, recorded from the Cornu Ammonius 1 (CA1) region of hippocampus slices after stimulation of Schaffer collateral axons. This response was sustained after washout of the drug. Furthermore, (2*R*,6*R*)-HNK also increased the frequency and amplitude of AMPA receptor-mediated excitatory postsynaptic currents recorded from CA1 stratum radiatum interneurons. Similar to ketamine, pretreatment with the AMPA receptor antagonist NBQX (2,3-Dioxo-6-nitro-1,2,3,4- tetrahydrobenzo[f]quinoxaline-7-sulfonamide) blocked the antidepressant effect of (2*R*,6*R*)-HNK, suggesting a role for AMPA receptors in its antidepressant action.

Similar to ketamine, (2*R*,6*R*)-HNK increased gamma power in the brain, independent of locomotor activity changes. Unlike ketamine and (2*S*,6*S*)-HNK, (2*R*,6*R*)-HNK did not induce significant changes in behavioral abnormalities such as locomotion, coordination on the rotarod test, sensory gating, or drug self-administration. Overall, (2*R*,6*R*)-HNK appeared to have a benign side-effect profile compared to ketamine.

3. Significance of the results

Until now, the prevailing view was that ketamine produced its antidepressant effects by blocking NMDA receptors. While

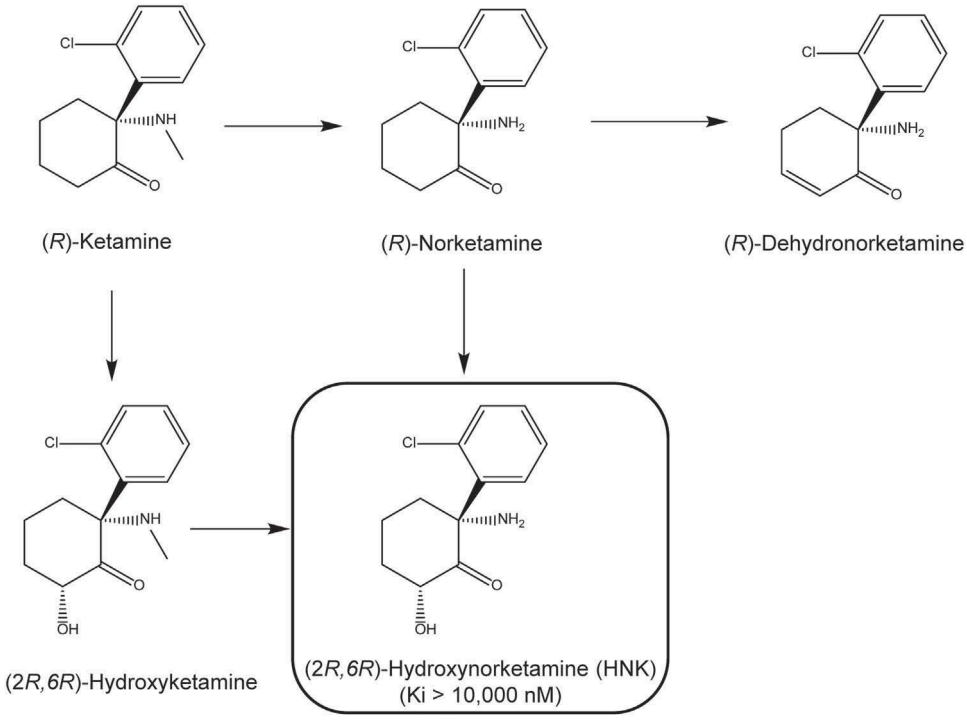

Figure 2. Metabolism of (*R*)-ketamine to (*R*)-norketamine, (*R*)-dehydronorketamine, (2*R*,6*R*)-hydroxyketamine and (2*R*,6*R*)-hydroxynorketamine (HNK). The value in the parenthesis is Ki value for NMDA receptor [5].

esketamine is a more potent inhibitor at NMDA receptors than (*R*)-ketamine, esketamine is less effective at alleviating depression symptoms in rodents, consistent with our previous results [6,7]. Furthermore, the greater potency of ketamine in female mice compared with male mice may be associated with higher levels of (2*S*,6*S*; 2*R*,6*R*)-HNK in the female brain. The most significant finding of this article is that the metabolism of ketamine to (2*S*,6*S*;2*R*,6*R*)-HNK could be essential for its antidepressant effects. An electrophysiological study showed that AMPA, but not NMDA receptors, plays a role in the antidepressant actions of (2*R*,6*R*)-HNK. In addition, (2*R*,6*R*)-HNK may not produce adverse events such as psychotomimetic effects and abuse liability in humans.

4. Expert opinion

This key article suggests that the metabolism of (*R*)-ketamine to (2*R*,6*R*)-HNK is pivotal in its antidepressant action. However, we found that a bilateral infusion of (*R*)-ketamine into the medial prefrontal cortex—(PFC) showed antidepressant—effects in the rat learned helplessness model [8], indicating a direct antidepressant action for (*R*)-ketamine itself. The authors noted acute (24 h) antidepressant effects for (2*R*,6*R*)-HNK in the chronic corticosterone treated or social defeat stress models [5]. However, they did not test for a longer lasting (7 days) antidepressant effect after a single dose of (2*R*,6*R*)-HNK. It is therefore, important to determine whether like ketamine and (*R*)-ketamine, both of which we found elicited a longer than 7-day response, (2*R*,6*R*)-HNK can produce sustained (7 days) antidepressant effects in the social defeat stress model [9,10]. Although the authors pointed out that the greater antidepressant effects of ketamine in females could be associated with higher levels of (2*S*,6*S*;2*R*,6*R*)-HNK in the female brain, it is possible that other factors including gonadal hormones contribute to the gender differences in this case.

According to this article, 24 h after administration, (2*R*,6*R*)-HNK did not affect the expression of GluA1 and GluA2 in the PFC of control mice. By contrast, we reported that, 8 days after a single dose of either (*R*)-ketamine or esketamine, these drugs improved decreased brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (TrkB) signaling, synaptogenesis markers (e.g. GluA1 and PSD-95), and dendritic spine density in the PFC, CA3, and dentate gyrus of the hippocampus after social defeat stress, although (*R*)-ketamine showed greater potency [7]. Consequently, it would be of great value to ascertain whether (2*R*,6*R*)-HNK can induce sustained (>7 days) beneficial effects to counter decreased synaptogenesis in the described brain regions after social defeat stress, in line with the effects obtained for (*R*)-ketamine and ketamine [7,9]. Given the role of BDNF-TrkB signaling in the antidepressant action of (*R*)-ketamine (and ketamine) [7], it would also be interesting to determine whether TrkB antagonists are capable of blocking the antidepressant effect of (2*R*,6*R*)-HNK in animal models of depression.

Loss of parvalbumin (PV)-immunoreactivity in the PFC may be associated with psychosis and gamma oscillation deficits in schizophrenia. Recently, we reported that scheduled, repeated administration of esketamine (10 mg/kg, once per week for 8-weeks) but not (*R*)-ketamine, resulted in a loss of PV-immunoreactivity in the PFC of mouse brains [10], suggesting that repeated esketamine (or racemic ketamine) infusions may have long-lasting and detrimental side effects in the PFC of humans [3,4]. A recent study using [^{11}C]raclopride and positron emission tomography showed a marked reduction of dopamine $D_{2/3}$ receptor binding in the monkey striatum after a single infusion of esketamine, but not (*R*)-ketamine [11]. Thus, it is also likely that its marked release from presynaptic terminals in the striatum could be associated with psychotomimetic side effects in humans, after infusion with ketamine or esketamine.

Finally, there is an urgent need for rapid-onset antidepressants in the clinical management of treatment-resistant depression. As mentioned above, many clinical studies have highlighted ketamine as an attractive rapid-onset therapeutic option for treatment-resistant depression, although clinical application may be limited by its propensity to cause psychotomimetic effects. Our studies [6–11] and this current article [5] highlight the importance of the (*R*)-enantiomer of ketamine and its metabolites as rapid-onset antidepressants with a sustained (7 days) action [3,4]. Nonetheless, it is of great interest to study head-to-head comparisons between (*R*)-ketamine and esketamine in depressed patients.

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Declaration of interest

K. Hashimoto is an inventor on a filed patent application on 'The use of *R*-ketamine in the treatment of psychiatric diseases' by Chiba University and has received research support from Dainippon Sumitomo, Mochida, Otsuka, and Taisho. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as of considerable interest (••) to readers.

1. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47:351–354.
•• **This is the first study showing antidepressant effects of ketamine in patients with depression.**
2. Kishimoto T, Chawla JM, Hagi K, et al. 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. Psychol Med. 2016;46:1459–1472.
3. Hashimoto K. *R*-ketamine: a rapid-onset and sustained antidepressant without risk of brain toxicity. Psychol Med. 2016;46:2449–2451.
4. Hashimoto K. Detrimental side effects of repeated ketamine infusions in the brain. Am J Psychiatry. 2016. DOI:10.1176/appi.ajp.2016.16040411.
5. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 2016;533:481–486.

•• **This is the first study showing antidepressant effects of (2*R*,6*R*)-hydroxynorketamine (HNK) in rodent models of depression.**

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

•• **This is the first study showing greater antidepressant effects of (*R*)-ketamine than esketamine.**

7. Yang C, Shirayama Y, Zhang JC, et al. *R*-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl Psychiatry. 2015;5:e632.

•• **This is the study showing greater antidepressant effects of (*R*)-ketamine than esketamine in social defeat stress and learned helplessness models of depression.**

8. Shirayama Y, Hashimoto K. 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. 2016. doi:10.1007/s00406-016-0718-1.
9. Zhang JC, Yao W, Dong C, et al. Comparison of ketamine, 7,8-dihydroxyflavone, and ANA-12 antidepressant effects in the social defeat stress model of depression. Psychopharmacology. 2015;232:4325–4335.
10. Yang C, Han M, Zhang JC, et al. Loss of parvalbumin-immunoreactivity in mouse brain regions after repeated intermittent administration of esketamine, but not *R*-ketamine. Psychiatry Res. 2016;239:281–283.
11. Hashimoto K, Kakiuchi T, Ohba H, et al. 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. Eur Arch Psychiatry Clin Neurosci. 2016. DOI:10.1007/s00406-016-0692-7