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Intracellular signaling pathways involved in (*S*)- and (*R*)-ketamine antidepressant actions

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A number of placebo-controlled trials have provided evidence of rapid and sustained antidepressant actions following administration of a single, sub-anesthetic dose of the non-competitive *N*-methyl-*D*-aspartate receptor (NMDAR) antagonist ketamine in treatment-refractory depressed patients. Ketamine is a racemic mixture comprised of the (*S*)- and (*R*)-ketamine enantiomers, with (*S*)-ketamine being ~four-fold more potent at inhibiting the NMDAR. Similar to racemic ketamine, clinical studies in depressed patients have indicated that a 40-min, intravenous infusion of (*S*)-ketamine exerts rapid antidepressant actions (1). To date, there are no published clinical studies assessing the antidepressant efficacy of (*R*)-ketamine in depressed patients. Further, there are no published clinical studies directly comparing the antidepressant actions of the (*S*)- and (*R*)-ketamine enantiomers, or comparing the actions of either enantiomer to the racemic mixture.

Hashimoto and colleagues were the first to demonstrate greater potency and longer-lasting antidepressant-relevant effects of (*R*)-ketamine compared with (*S*)-ketamine in rodents (2, 3). Subsequent studies have confirmed superiority of (*R*)-ketamine over (*S*)-ketamine in rodent antidepressant-relevant behavioral outcomes using up to a 30-fold range of doses (4, 5). Notably, the difference in antidepressant potency is not due to bioavailability differences since administration of equal doses of these enantiomers does not yield different drug concentrations in the brains of rodents (4, 5). Given that (*S*)-ketamine is a stronger inhibitor of the NMDAR, yet (*R*)-ketamine is a more potent antidepressant, these preclinical findings

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Conflicts of interest

T.D.G. has received consulting fees from Janssen Pharmaceuticals, and research funding from Janssen Pharmaceuticals and Roche Pharmaceuticals during the preceding three years. P.Z., and T.D.G. are listed as co-authors in patent applications related to the pharmacology and use of (*2S,6S*)- and (*2R,6R*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation and post-traumatic stress disorder.

indicate it is unlikely ketamine exerts its antidepressant actions merely via inhibition of the NMDAR. Additionally, these findings raise the possibility that (*R*)-ketamine might be effective in the treatment of depressed patients. Notably, use of (*R*)-ketamine in humans is expected to exert fewer NMDAR-mediated side effects, such as dissociation, dizziness, and sensory as well as perceptual deficits, which have been observed following clinical treatment with racemic ketamine or (*S*)-ketamine in patients. Published rodent data also indicate lower abuse potential of (*R*)-ketamine than (*S*)-ketamine (3), as predicted by the lesser NMDAR inhibition by (*R*)-ketamine.

In this issue of *Biological Psychiatry,* Yang *et al.* (6) assessed the effects of (*S*)- and (*R*)-ketamine enantiomers on the mechanistic target of rapamycin (mTOR), and mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/ERK) signaling pathways. mTOR is a serine/threonine kinase that modulates the initiation of protein translation and is thus involved in the regulation of protein synthesis necessary to induce synaptic potentiation and resultant antidepressant effects. Activation of mTOR complex 1 (mTORC1) results from phosphorylation of the mTOR kinase domain (at Ser^{2448}) by the phosphatidylinositol-3 kinase (PI3K)/Akt (protein kinase B) pathway, resulting in increased phosphorylation of p70 ribosomal protein S6 kinase (p70S6K). Alternatively, the brain-derived neurotrophic factor (BDNF)-induced activation of the neurotrophic receptor tyrosine kinase 2 (TrkB) can trigger the initiation of the MEK/ERK signaling pathway, also driving protein translation via multiple mechanisms including activation of mTORC1. Duman and colleagues showed that sub-anesthetic doses of ketamine induce rapid (within 30 min of administration), but transient (lasting up to 2 hours), phosphorylation/activation of mTORC1, leading to initiation of translation and protein synthesis (7, 8). This suggests that acute activation of mTORC1 results in synaptic plasticity changes that mediate the prolonged effects of the drug. Notably, only lower doses of ketamine enhance mTORC1 activity, whereas anesthetic doses of the drug do not influence mTOR signaling, in accordance with the antidepressant actions of the drug, which only occur at lower doses (7). Additionally, ketamine's behavioral antidepressant effects require mTOR activation. In particular, administration of the selective mTOR inhibitor rapamycin prevents ketamine-induced synaptic molecular alterations and antidepressant actions in rodents (7, 8). These findings implicate mTOR as a key downstream point of convergence to explain ketamine's rapid-acting antidepressant actions.

The experiments of Yang *et al.* reveal that administration of (*R*)-ketamine, unlike (*S*)-ketamine, does not restore chronic stress-induced decreases in phosphorylated mTOR levels in the medial prefrontal cortex, or CA3 region or dentate gyrus of the hippocampus. In addition, the authors show that inhibition of mTOR by intracerebroventricular pre-administration of rapamycin or AZD8055 prevents the antidepressant actions of (*S*)-, but not (*R*)-ketamine in the chronic social defeat stress model in mice (6). On the other hand, inhibition of MEK/ERK signaling by the brain-penetrant ERK inhibitor, SL327, only prevented the antidepressant actions of (*R*)-ketamine, which was associated with the unique effect of (*R*)-ketamine to restore stress-induced reductions in phosphorylated MEK and phosphorylated ERK levels in the prefrontal cortex and CA3 area of the hippocampus in mice (6). Thus, these findings reveal differential effects of ketamine's enantiomers on two

signaling pathways involved in synaptic potentiation, which could be responsible for their distinct preclinical antidepressant profiles.

While Yang *et al.* propose that the differential actions of ketamine's enantiomers on the mTOR and ERK pathways underlie their differences in antidepressant actions, several questions remain to be answered. For example, it was previously reported that inhibition of either mTOR (via rapamycin) or ERK (via U0126) activity prevents the antidepressant behavioral actions of racemic ketamine (7) indicating that both pathways are necessary for racemic ketamine's antidepressant action. As Yang *et al.* used single doses in their studies, it is possible that blockade of mTOR signaling could have prevented the antidepressant behavioral actions of (*R*)-ketamine if rapamycin had been administered at higher doses, or if lower doses of (*R*)-ketamine had been used. Therefore, prior to ruling out the involvement of mTOR signaling in the behavioral antidepressant actions of (*R*)-ketamine or the involvement of the MEK/ERK pathway in the antidepressant actions of (*S*)-ketamine further studies are warranted to investigate full dose (as well as time) response actions of (*R*)-ketamine and (*S*)-ketamine on these pathways.

The differential effects (*R*)-ketamine and (*S*)-ketamine might not be solely mediated by these compounds themselves, but also by each enantiomer's diverse metabolism profile. Indeed, the (*2R,6R*)-hydroxynorketamine (HNK) metabolite (derived solely by metabolism of (*R*)-ketamine) has more potent and longer-lasting antidepressant actions compared to the (*2S,6S*)-HNK metabolite (exclusively metabolized from (*S*)-ketamine) (4). Therefore, it is possible that the two enantiomers of ketamine, and potentially the HNK metabolites, exert antidepressant actions via divergent mechanisms as a function of dose or the extent of their metabolism. The effects of the (*2S,6S*)- and (*2R,6R*)-HNK metabolites on mTOR and MEK/ERK signaling require elucidation to understand the level of contribution of these metabolites in the distinct behavioral and/or molecular antidepressant-relevant profiles of ketamine's enantiomers.

Although there is evidence of enhanced synaptic glutamatergic neurotransmission following administration of racemic ketamine (9) and (*2R,6R*)-HNK (4), the direct target responsible for these actions is not yet fully understood. Similarly, whether there exist two distinct initial targets of (*S*)- and (*R*)-ketamine that could account for their differential antidepressant actions has yet to be established. There is evidence indicating that NMDAR inhibition, at rest, can induce α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated synaptic potentiation and that these mechanisms are involved in mediating the antidepressant actions of ketamine (10), however this proposed central role of the NMDAR is in contrast with the more potent antidepressant actions of (*R*)-ketamine (the less potent NMDAR antagonist) compared to (*S*)-ketamine. Administration of an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antagonist blocks the antidepressant behavioral actions of both (*S*)- and (*R*)-ketamine (3) and it is proposed that indirect activation of the synaptic AMPARs by ketamine through enhancing excitatory neurotransmission leads to post-synaptic membrane depolarization, calcium influx, and enhanced BDNF release (9). Alternatively, there is also evidence that BDNF translation/release is upstream of ketamine-induced increases in excitatory neurotransmission since the latter was absent in mice where BDNF was removed from the forebrain (10). BDNF, via

activating TrkB, results in the activation of both the mTOR and MEK/ERK pathways. Since TrkB inhibition has been shown to prevent the antidepressant effects of both ketamine enantiomers, their differential actions on mTOR and MEK/ERK pathways might imply direct actions of (*R*)- and/or (*S*)-ketamine on these targets. Consistent with this, Hashimoto and colleagues have previously reported that (*R*)-ketamine, but not (*S*)-ketamine, reversed reduced BDNF and phosphorylated TrkB levels following chronic social defeat stress in the CA3 region of the hippocampus of mice (3). However, administration of a TrkB receptor inhibitor blocked the antidepressant behavioral actions of both (*S*)- and (*R*)-ketamine indicating the requirement of BDNF in their antidepressant actions (3). Future studies will seek to elucidate the exact mechanisms underlying ketamine enantiomers' divergent antidepressant actions, though it is likely that convergent mechanisms of action of the (*S*)- and (*R*)- enantiomers also exist and include an indirect activation of the (AMPARs) and a subsequent activation of the BDNF-TrkB pathway. Indeed, there are multiple points of convergence between TrkB activation of MEK/ERK and mTORC1.

Unraveling the exact mechanisms underlying the differential antidepressant properties of the two ketamine enantiomers will be important for the identification of novel targets for the development of next generation rapid acting antidepressant pharmacotherapies with fewer side effects. Indeed, it has been shown that (*R*)-ketamine and its (*2R,6R*)-HNK metabolite have fewer side effects, when compared to the (*S*)-ketamine enantiomer and its (*2S,6S*)-HNK metabolite in rodents (3, 4). However, currently (*S*)-ketamine is the only enantiomer clinically tested in depressed patients. Rodent research may indeed guide us and provide important mechanistic clues, but validation of therapeutic efficacy will only come from human clinical trials.

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References

1. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, et al. Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study. Biol Psychiatry. 2016; 80:424–431. [PubMed: 26707087]
2. 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. [PubMed: 24316345]
3. Yang C, Shirayama Y, Zhang JC, Ren Q, Yao W, Ma M, et al. R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl Psychiatry. 2015; 5:e632. [PubMed: 26327690]
4. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature. 2016; 533:481–486. [PubMed: 27144355]
5. Fukumoto K, Toki H, Iijima M, Hashihayata T, Yamaguchi J-i, Hashimoto K, et al. Antidepressant Potential of (R)-Ketamine in Rodent Models: Comparison with (S)-Ketamine. Journal of Pharmacology and Experimental Therapeutics. 2017; 361:9–16. [PubMed: 28115553]
6. Yang C, Ren Q, Qu Y, Zhang J-C, Ma M, Dong C, et al. Mechanistic Target of Rapamycin–Independent Antidepressant Effects of (R)-Ketamine in a Social Defeat Stress Model. Biological Psychiatry. 2017

7. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010:329. [PubMed: 20947752]
8. Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, et al. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol Psychiatry. 2011; 69:754–761. [PubMed: 21292242]
9. Duman RS, Li N, Liu R-J, Duric V, Aghajanian G. Signaling Pathways Underlying the Rapid Antidepressant Actions of Ketamine. Neuropharmacology. 2012; 62:35–41. [PubMed: 21907221]
10. Nosyreva E, Szabla K, Autry AE, Ryazanov AG, Monteggia LM, Kavalali ET. Acute suppression of spontaneous neurotransmission drives synaptic potentiation. J Neurosci. 2013; 33:6990–7002. [PubMed: 23595756]