Biological Psychiatry

What's the Buzz About Hydroxynorketamine? Is It the History, the Story, the Debate, or the Promise?

Chadi G. Abdallah

The History: Early in the 1990s, a set of animal studies presented *N*-methyl-D-aspartate receptor (NMDAR) modulation as a common pathway to traditional antidepressants (1). Later in the 1990s, a group of Yale University scientists set out to demonstrate the role of NMDAR modulation in clinical depression using subanesthetic doses of the NMDAR antagonist ketamine. Surprisingly, they discovered that a single ketamine infusion exerted rapid acting antidepressant (RAAD) effects that were sustained for 3 days, well beyond the short half-life of the ketamine compound (2). Over the next decade, following the replication of the RAAD finding of ketamine and in the context of preclinical evidence of glutamate excitotoxicity, the inhibition of NMDAR gained attention as a putative novel mechanism to induce RAAD effects. However, increasingly it became evident that several nonketamine NMDAR antagonists do not possess RAAD properties (e.g., memantine). In addition, the antidepressant doses of ketamine induce a paradoxical glutamate neurotransmission surge rather than inhibition. Late in the 2000s, a critical role for the ketamine-induced glutamate stimulation was supported first by showing that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) blockers—which reduce both AMPAR and NMDAR signaling—inhibit the RAAD effects of ketamine (3) and second by demonstrating that ketamine RAAD properties are dependent on its induction of synaptogenesis, which is also inhibited by AMPAR blockers (4). Moreover, various non–NMDAR antagonist drugs—which presumably stimulate glutamate neurotransmission—were found to exert ketamine-like synaptogenesis and RAAD effects, including 1) scopolamine, a muscarinic acetylcholine receptor antagonist; 2) LY341495, a metabotropic glutamate receptor 2 and 3 antagonist; and 3) rapastinel, an NMDAR modulator with partial agonist properties (Figure 1). Further underscoring the role of glutamate stimulation, AMPAR blockers were also found to inhibit the RAAD effects of scopolamine, metabotropic glutamate receptor 2 and 3 antagonists, and rapastinel. Together, accumulating evidence over the past decade presented transient AMPAR and NMDAR stimulation as a primary underlying mechanism of RAADs (5). Complementing this model, it is believed that the RAAD effects of ketamine are further enhanced by its various pharmacodynamic properties, including its activity-independent blockade of NMDAR (6) and its regulation of the inflammatory, opioid, and monoamine systems (5).

The Story: Ketamine is a racemic mixture of *R*- and *S*-ketamine. Each of the *R*- and *S*-ketamine enantiomers is metabolized into norketamine, hydroxyketamine, dehydronorketamine, and hydroxynorketamine (HNK). The HNK metabolites include (2*S*,6*S*;2*R*,6*R*)-HNK, E-6-HNK, Z-5-HNK, E-5-HNK, Z-4-HNK, and E-4-HNK. Of these HNKs, (2*S*,6*S*;2*R*,6*R*)-HNK is the most abundant metabolite following ketamine administration, and its concentration is higher in female subjects (7,8). (2*S*,6*S*;2*R*,6*R*)-HNK lacks the anesthetic effects of ketamine and is not active on the NMDAR, with preliminary studies showing inhibitory effects on α7 nicotinic acetylcholine receptor, a finding that awaits replication. In contrast to the short half-life of ketamine, human plasma (2*S*,6*S*;2*R*,6*R*)-HNK is significantly present at 4 hours, and it is quantifiable at 24 hours after infusion of a subanesthetic dose of ketamine (8). In a pilot study of major depressive disorder (MDD; medication free; 38% female) and bipolar depression (BD; medicated by valproate or lithium; 73% female) patients, the investigators found significantly higher (2*S*,6*S*;2*R*,6*R*)-HNK in the BD group compared with the MDD group, but there were no significant response or response-by-diagnosis effects. The lack of relationship between plasma (2*S*,6*S*;2*R*,6*R*)-HNK and response to ketamine remained after including gender in the statistical model. In the BD group, patients treated with the mood stabilizer valproate (a potent inhibitor of cytochrome P450) were found to have higher plasma (2*S*,6*S*;2*R*,6*R*)-HNK levels (8). In summary, these pilot human data failed to show a statistically significant relationship between (2*S*,6*S*;2*R*,6*R*)-HNK and the RAAD effects of ketamine. However, there was evidence of higher plasma (2*S*,6*S*;2*R*,6*R*)-HNK in BD compared with MDD, although the groups were not well matched for gender and medication status. In rodents, it was previously reported that the (2*S*,6*S*)-HNK enantiomer increases the mammalian target of rapamycin complex 1 function, an intracellular signaling pathway believed to play an essential role in the ketamine-induced synaptogenesis and RAAD effects. Recently, Zanos *et al.* reported a more comprehensive rodent study that fully investigated the role of (2*S*,6*S*;2*R*,6*R*)-HNK in the antidepressant effects of ketamine (7). The authors found sustained (i.e., 24 hours postinfusion) antidepressant-like effects in mice treated with *R,S*-ketamine or *R*-ketamine but not with *S*-ketamine (all doses were 10 mg/kg). They also found higher antidepressant-like effects and higher brain (2*S*,6*S*;2*R*,6*R*)-HNK concentration in female subjects. Deuterated ketamine, with reduced conversion to (2*S*,6*S*;2*R*,6*R*)-HNK, failed to induce sustained antidepressant-like effects. Moreover, 5 mg/kg of (2*R*,6*R*)-HNK induced sustained antidepressant-like effects in mice, whereas the effects of (2*S*,6*S*)-HNK were evident only at 25 to 75 mg/kg. After confirming the low affinity of (2*S*,6*S*;2*R*,6*R*)-HNK to NMDAR, the investigators demonstrated that in vitro application of (2*R*,6*R*)-HNK to rat hippocampal slices induces an increase in excitatory postsynaptic potentials and currents, which were

SEE CORRESPONDING ARTICLES ON PAGES e65 and e69

http://dx.doi.org/10.1016/j.biopsych.2017.01.002
ISSN: 0006-3223

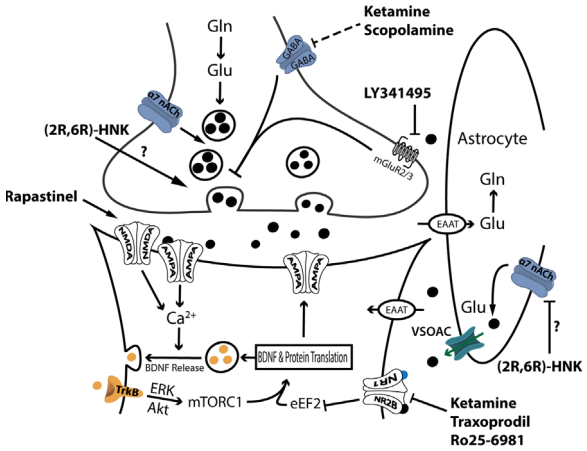

Figure 1. Glutamatergic mechanisms underlying the effects of rapid-acting antidepressants. It is believed that the rapid increase of synaptogenesis, by modulating prefrontal and hippocampal glutamatergic synapses, is a convergent mechanistic pathway underlying the beneficial behavioral effects of rapid-acting antidepressants. Ketamine and scopolamine have been shown to precipitate glutamate neurotransmission surge by blocking interneuronal *N*-methyl-D-aspartate (NMDA) or muscarinic acetylcholine receptors, respectively, leading to inhibition of gamma-aminobutyric acidergic input on glutamatergic neurons. This glutamate surge stimulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and activity-dependent release of brain-derived neurotrophic factor (BDNF), which in turn stimulates mammalian target of rapamycin complex 1 (mTORC1) signaling and increases translation of synaptic proteins. LY341495 induces a glutamate neurotransmission surge, presumably by blocking presynaptic metabotropic glutamate receptors ($mGluR_{2/3}$). Rapastinel is believed to increase postsynaptic glutamate neurotransmission by exerting partial agonist properties on intrasynaptic NMDA receptors. Ketamine, traxoprodil, and Ro25-6981 were proposed to increase synaptogenesis by blocking NR2B-containing NMDA receptors activated by ambient glutamate. (2*S*,6*S*;2*R*,6*R*)-Hydroxynorketamine has been shown to increase glutamate transmission and elongation eukaryotic factor 2 (eEF2); however, the underlying pathways leading to these changes are not fully known. α7 nicotinic acetylcholine (α7-nACh) receptors induce presynaptic glutamate release as well as increase ambient extrasynaptic glutamate by activating astrocytic glutamate release. Considering preliminary evidence of α7-nACh inhibition by (2*S*,6*S*;2*R*,6*R*)-HNK, future studies should examine whether the (2*S*,6*S*;2*R*,6*R*)-HNK-induced increase in eEF2 is related to its effects on astrocytic α7-nACh receptors. Akt, protein kinase B; EAAT, excitatory amino acid transporter; ERK, extracellular signal–regulated kinase 1; Gln, glutamine; Glu, glutamate; NR1, NMDA receptor unit 1; NR2B, NMDA receptor unit 2B; TrkB, tyrosine receptor kinase B; VSOAC, volume-sensitive organic anion channel.

inhibited by an AMPAR blocker. Noticeably, the administration of AMPAR blocker both prior to and 24 hours after (2*R*,6*R*)-HNK infusion inhibited its sustained antidepressant-like effects. Similar findings were demonstrated with ketamine. Ketamine and (2*R*,6*R*)-HNK increased mature brain-derived neurotrophic factor level and AMPAR $GluA_{1/2}$ subunits in the hippocampus but not in the prefrontal cortex. Finally, (2*R*,6*R*)-HNK appeared to lack the side effects evident in mice following ketamine administration.

The Debate: In the current issue, Collingridge *et al.* acknowledge the possibility that (2*S*,6*S*;2*R*,6*R*)-HNK may have RAAD properties that remain to be demonstrated in clinical studies (9). However, they warn against prematurely rejecting the role of NMDAR inhibition in the mechanisms of RAADs. Collingridge *et al.* note that various NMDAR antagonists (e.g., traxoprodil, also known as CP-101,606), which do not have (2*S*,6*S*;2*R*,6*R*)-HNK as a metabolite, have shown RAAD effects in animal models and clinical trials. In addition, the authors highlight the difficulties in translating Zanos *et al.*'s (7) findings in mice to humans. For example, although low-dose *S*-ketamine and (2*S*,6*S*)-HNK failed to induce RAAD effects in Zanos *et al.*'s mice study, it was already shown that *S*-ketamine—even at doses that are 40% of the regular ketamine antidepressant dose—has RAAD effects in depressed patients. Moreover, the authors raise concerns about whether the (2*S*,6*S*;2*R*,6*R*)-HNK brain concentration required for efficacy in rodents can be achieved in humans. Finally, Collingridge *et al.* present a hypothetical model in which depression is the result of long-term depression (LTD) changes in hedonic regions and in which ketamine blocks these LTD effects during reconsolidation (9). Of note, although the presented model is simple and conceivable, it is speculative. It also does not account for extensive literature associating depression with long-term potentiation-like, not LTD, changes in the nucleus accumbens and the fact that subanesthetic ketamine induces LTD-like changes in this hedonic brain region.

Zanos *et al.* respond by acknowledging the need for human evidence to firmly conclude that (2*S*,6*S*;2*R*,6*R*)-HNK is a RAAD (10). Then, they highlight that high doses of *S*-ketamine and (2*S*,6*S*)-HNK did show minimal antidepressant-like effects in their study. Considering that there are no human trials comparing *S*-ketamine with ketamine, the authors correctly refute the statement by Collingridge *et al.* that "*S*-ketamine was roughly twice as potent as racemic intravenous (*R,S*)-ketamine." The authors acknowledge that high concentrations were used to demonstrate the effects of (2*R*,6*R*)-HNK on AMPAR transmission, but they underscore the uncertainty about human brain concentration of (2*S*,6*S*;2*R*,6*R*)-HNK and suggest that this concentration may be higher in humans than in mice. Finally, the authors argue that the traxoprodil RAAD effects do not appear to be fully comparable to ketamine and that these human findings were not replicated (10). However, it is important to note that there are no human trials comparing traxoprodil with ketamine, and I am not aware of failed traxoprodil replication trials.

The Promise: Two decades of glutamate modulation research have provided great insight into the neurobiology of depression and the putative mechanisms of RAADs (5). However, to date there are no Food and Drug Administration-approved RAAD agents. Some investigational drugs (e.g., ketamine, traxoprodil) have shown promising clinical results. Yet, for various economical, safety, and scientific reasons, these agents did not go through the scrutiny and rigorous assessment of the Food and Drug Administration approval process. In that context, the (2*S*,6*S*;2*R*,6*R*)-HNK findings are highly promising, potentially opening the door for a new line of drug development that may ultimately lead to effective and well-tolerated RAADs. However, it is critical to reiterate that while the (2*S*,6*S*;2*R*,6*R*)-HNK preclinical findings are promising and there is evidence of NMDAR-independent RAADs (e.g., scopolamine), the current literature data are not yet sufficient to provide evidence of clinical RAAD properties by (2*S*,6*S*;2*R*,6*R*)-HNK or to fully reject the role of NMDAR in

the mechanisms of RAADs. In fact, the pilot human data available failed to show a relationship between plasma (2*S*,6*S*;2*R*,6*R*)-HNK and response to ketamine in MDD patients (8). Furthermore, currently there is preliminary clinical evidence to support the potential RAAD properties of the NMDAR antagonists (*S*)-ketamine and traxoprodil [cited in (9,10)], but not yet for (2*S*,6*S*;2*R*,6*R*)-HNK. So, what's the buzz about HNK? I believe it is the indispensable promise of a RAAD with limited adverse events, a promise that—if realized—could reduce suffering of millions of patients all around the world.

Acknowledgments and Disclosures

Early Career Investigator Commentaries are solicited in partnership with the Education Committee of the Society of Biological Psychiatry. As part of the educational mission of the Society, all authors of such commentaries are mentored by a senior investigator. This work was mentored by Ronald S. Duman, Ph.D.

This work was supported by the U.S. Department of Veterans Affairs, National Center for PTSD, the Patterson Trust Award, and the National Institute of Mental Health (Grant No. K23MH101498). The views expressed in this article are those of the author and do not necessarily reflect the position or policy of the Department of Veterans Affairs or other sponsoring institutions.

I thank Ronald Duman for his invitation to write this commentary and for his helpful comments on the manuscript.

The author has served as a consultant or on advisory boards for Genentech and Janssen. He also serves as editor for the journal Chronic Stress published by SAGE.

Article Information

From the Clinical Neurosciences Division, National Center for PTSD, U.S. Department of Veterans Affairs, West Haven, and Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

Address correspondence to Chadi G. Abdallah, M.D., Clinical Neurosciences Division–VA National Center for PTSD, Department of Psychiatry, Yale University School of Medicine, 950 Campbell Avenue, 151E West Haven, CT 06516; E-mail: chadi.abdallah@yale.edu.

Received Dec 21, 2016; revised Jan 6, 2017; accepted Jan 9, 2017.

References

1. Skolnick P, Layer RT, Popik P, Nowak G, Paul IA, Trullas R (1996): Adaptation of *N*-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: Implications for the pharmacotherapy of depression. Pharmacopsychiatry 29:23–26.
2. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, *et al*. (2000): Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47:351–354.
3. Maeng S, Zarate CA Jr., Du J, Schloesser RJ, McCammon J, Chen G, *et al*. (2008): Cellular mechanisms underlying the antidepressant effects of ketamine: Role of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. Biol Psychiatry 63:349–352.
4. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, *et al*. (2010): mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329:959–964.
5. Abdallah CG, Adams TG, Kelmendi B, Esterlis I, Sanacora G, Krystal JH (2016): Ketamine's mechanism of action: A path to rapid-acting antidepressants. Depress Anxiety 33:689–697.
6. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, *et al*. (2011): NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475:91–95.
7. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, *et al*. (2016): NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533:481–486.
8. Zarate CA Jr., Brutsche N, Laje G, Luckenbaugh DA, Venkata SL, Ramamoorthy A, *et al*. (2012): Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. Biol Psychiatry 72:331–338.
9. Collingridge GL, Lee Y, Bortolotto ZA, Kang H, Lodge D (2017): Antidepressant actions of ketamine versus hydroxynorketamine. Biol Psychiatry 81:e65–e67.
10. Zanos P, Moaddel R, Morris PJ, Wainer IW, Albuquerque EX, Thompson SM, *et al*. (2017): Reply to: Antidepressant actions of ketamine versus hydroxynorketamine. Biol Psychiatry 81:e69–e71.