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RESEARCH HIGHLIGHT

(2R,6R)-Hydroxynorketamine (HNK) plasma level predicts poor antidepressant response: is this the end of the HNK pipeline?

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In 2016, the finding that (2R,6R)-hydroxynorketamine (HNK) may possess antidepressant properties took the field by surprise [1]. A set of outstanding preclinical studies questioned the role of N-methyl-D-aspartate receptor (NMDAR) in ketamine's rapid-acting antidepressant (RAAD) effects, and put forth a novel compound, HNK, as a putative RAAD without ketamine's side effects and abuse liability [1]. Yet, in recent years, various findings have dampened the excitement about HNK. First, the antidepressant-like effect of HNK was reported to be inconsistent across preclinical studies [2]. Second, the molecular target of HNK remains unknown. Recent data suggested that the HNK effects are presynaptic (i.e., upstream of group II metabotropic glutamate receptors) leading to glutamate surge and postsynaptic activation. However, these processes are also shared with the NMDAR hypothesis, which proposes that ketamine's blockade of interneuron NMDAR leads to presynaptic glutamate disinhibition, a glutamate surge and postsynaptic activation. Third, while clinical trials have not yet investigated the utility of HNK as a RAAD, clinical ketamine biomarker studies have failed to support the preclinical HNK predictions [3–5].

In the current issue, Farmer et al. investigated the relationship between HNK plasma level and the antidepressant effects of ketamine in humans. Based on the preclinical findings [1], it was hypothesized that higher HNK plasma level will predict improved antidepressant effects following ketamine treatment. They studied 34 treatment-resistant patients with major depressive disorder (MDD) [3]. Participants received a single dose of intravenous ketamine 0.5 mg/kg infused over 40 min. Plasma levels of HNK were repeatedly measured within 4 h of treatment, while depression severity was assessed up to 11 days using the Montgomery–Asberg Depression Rating Scale (MADRS). Statistical analyses investigated whether acute HNK levels predict the RAAD effects of ketamine over time. Contrary to the preclinical predictions, the authors found that higher HNK was associated with poor antidepressant response. In particular, the higher the level of plasma HNK acutely following ketamine infusion, the worse the severity of MADRS scores at day 3 and 7 post treatment [3].

Unfortunately, this is not the only study to contradict the HNK preclinical predictions. In fact, previous studies have either associated HNK levels with poor outcome [4] or failed to show statistically significant association between HNK levels and response to ketamine in MDD [5]. A plausible explanation for the failed human studies is that the signal-to-noise ratio of plasma HNK level is low, leading to random results in small exploratory samples. An alternative possibility is that the preclinical HNK findings may not translate across species to human clinical depression. The depression literature is full of examples in which the translation from rodents to humans has proven challenging [6]. Other interpretations include: (1) there may be an inverted U-shaped relationship between HNK and antidepressant response, resulting in inconsistent findings in small samples with linear analyses and (2) the plasma HNK level may not reflect brain tissue concentrations, in which case the HNK level in cerebral spinal fluid may be more informative.

So, is this the end of the hydroxynorketamine pipeline as a possible RAAD? Hopefully not, despite the "bad news" in the literature. Some preclinical studies raised concerns about the robustness of the HNK findings [2], while human clinical trials are still lacking. Moreover, available human biomarker evidence using plasma level, has either failed to support preclinical findings [5] or showed opposite results [3, 4] compared with the preclinical predictions [1]. However, considering the urgent need for novel RAADs, the promising hypothesis and preclinical evidence [1], and the potential for reduced abuse liability and enhanced side effect profile compared with ketamine, it remains useful to invest in the HNK pipeline. Yet, as a field we should tread carefully and be ready for changing directions as contradictory human evidence continues to accumulate.

FUNDING AND DISCLOSURE

CGA has served as a consultant, speaker and/or on advisory boards for Genentech, Janssen, Psilocybin Labs, Lundbeck and FSV7, and editor of *Chronic Stress* for Sage Publications, Inc.; Filed a patent for using mTORC1 inhibitors to augment the effects of antidepressants (filed on Aug 20, 2018).

ADDITIONAL INFORMATION

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