# Is the History Repeated? Can (2R,6R)-Hydroxynorketamine be Another Antidepressant?

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**ABSTRACT:** Historically, identification of active metabolites has contributed to drug discovery for psychiatric disorders. It has led to the identification of new medications such as desipramine (a metabolite of imipramine) and paliperidone (a metabolite of risperidone). (R,S)-Ketamine, which has been regarded as the greatest breakthrough in depression research, is rapidly and stereoselectively metabolized into a variety of metabolites. Therefore, identification of an active substance after administration of (R,S)-ketamine is a critical issue, not only to delineate the underlying mechanisms but also to pave the way to develop a new antidepressant. Recently, one of the metabolites of (R,S)-ketamine, namely, (2R,6R)-hydroxynorketamine (HNK) was proposed as an active metabolite formed after administration of (R,S)-ketamine, and even as being essential for (R,S)-ketamine to exert its antidepressant effects. However, this is still controversial. Indeed, we demonstrated that the antidepressant effect of (2R,6R)-HNK is not as potent as that of its parent compounds ((R)-ketamine and (R,S)-ketamine), and that (2R,6R)-HNK is not essential for (R)-ketamine to exert its antidepressant effects. From the historical point of view, however, there is potential to discover new medications by further investigations of (2R,6R)-HNK. Therefore, more careful and thorough investigation of (2R,6R)-HNK is needed for the discovery of more efficacious and safer antidepressants.

**KEYWORDS:** (R,S)-ketamine, (2R,6R)-hydroxynorketamine, antidepressant, treatment-resistant depression

In general, the intensity and duration of action of a drug depend on the concentration of the drug at the target site for action and the length of time for which the drug remains there. Drug metabolism is one of the most important factors determining the in vivo exposure of drugs. In many cases, drugs in the body are mainly metabolized in the liver and converted into other highly polar chemicals that are more likely to be excreted outside the body, resulting in little or no pharmacologic response. However, some of them retain the activity of the parent drug or may even exhibit more pharmacologic activity. Moreover, metabolites showing pharmacologic profiles different from the parent drug are generated in some cases. In these cases, whether the pharmacologic effect of the active metabolite is actually exerted in vivo depends on the pharmacokinetic and dispositional attributes of the active metabolites. Indeed, many marketed drugs are known to be biotransformed into pharmacologically active metabolites with meaningful exposures, where the effects of the drugs would be the result not only of the parent drug's actions but also of their active metabolites. Active metabolites exerting improved pharmacologic, pharmacokinetic behaviors or lower toxicity than the parent drug have sometimes been marketed as novel individual drugs. As an excellent example, a metabolite of the analgesic acetanilide has been marketed as a safer analgesic (acetaminophen/paracetamol) than the parent drug, as it did not carry the risk of causing methemoglobinemia.[1] Among the therapeutic agents used for the treatment of psychiatric disorders too, several useful drugs have been developed from researches on active metabolites. The antipsychotic drug paliperidone, a 9-hydroxylated metabolite of risperidone, has been marketed as a novel drug to overcome the large interindividual differences in the exposure levels of the parent drug that is metabolized by the polymorphic cytochrome P450 (CYP) 2D6.[2] Regarding antidepressants, useful drugs such as the *O*-demethylated metabolite (desvenlafaxine) of venlafaxine, *N*-demethylated metabolite (desipramine) of imipramine, and *N*-demethylated metabolite (nortriptyline) of amitriptyline have been developed.[2] As described above, the history of drug discovery for the treatment of psychiatric disorders has clearly indicated that the identification of active metabolites and elucidation of their mechanisms of actions are very important to discover more useful drugs and novel potential drug targets.

Ever since its potent and fast onset of antidepressant actions were reported in 2000 and replicated in 2006, the antidepressant effect of (R,S)-ketamine has gained much attention. Until now, the rapid-acting and long-lasting antidepressant effect of (R,S)-ketamine has been confirmed in patients with major depressive disorders and treatment-resistant depression.[3] Thus, the discovery of the antidepressant effects of (R,S)-ketamine is regarded as one of the most outstanding findings in depression research. (R,S)-Ketamine is a racemic mixture of equal parts of (R)-ketamine and (S)-ketamine. After administration, (R,S)-ketamine is rapidly and stereoselectively metabolized into a variety of metabolites by multiple hepatic CYPs, and the

pharmacologic potential of some of the metabolites, such as norketamine and hydroxynorketamine (HNK), has been investigated. Importantly, reasonable amounts of these metabolites with longer half-lives than that of $(R,S)$-ketamine are detected in the human plasma after infusion of $(R,S)$-ketamine. These findings may remind many scientists in the field of the history of active metabolites in neuropsychopharmacology. Recently, one of the metabolites of $(R,S)$-ketamine, $(2R,6R)$-HNK, was proposed to serve not only as an active metabolite but also as mediating the antidepressant effect of $(R,S)$-ketamine after its administration.[4] Specifically, $(2R,6R)$-HNK exerts an antidepressant effect in rodent models, and inhibition of the metabolism of $(R,S)$-ketamine into the $(2R,6R; 2S,6S)$-HNK using deuterium-labeled $(R,S)$-ketamine prevents $(R,S)$-ketamine from exerting its antidepressant effects. Because the antidepressant effect of $(2R,6R)$-HNK is much stronger than that of $(2S,6S)$-HNK, $(2R,6R)$-HNK is presumed to mediate the antidepressant effect of $(R,S)$-ketamine. The antidepressant effect of $(2R,6R)$-HNK has been suggested by the following reports. Systemic administration of $(2R,6R)$-HNK was reported to exert an antidepressant effect in the mouse in the forced swimming test at 24 hours after administration,[5] and to reverse depressive-like behavior in rats induced by the modified learned helplessness paradigm, which lasted for 21 days,[6] presumably by acting on the medial prefrontal cortex and ventrolateral periaqueductal gray, respectively. Moreover, both $(R,S)$-ketamine and $(2R,6R)$-HNK affect neural mechanisms related to their antidepressant effect.[7] In addition to its antidepressant effect, $(2R,6R)$-HNK has been reported to mimic the in vitro effects of $(R,S)$-ketamine. It was reported that, at the same concentration, both $(R,S)$-ketamine and $(2R,6R)$-HNK increased translocation of G$\alpha$s from lipid rafts to nonrafts, resulting in increase in the formation of cyclic adenosine monophosphate in an NMDA receptor–independent manner,[8] increased structural plasticity in primary and induced pluripotent stem cell–derived dopamine neurons in an AMPA receptor–dependent manner,[9] and increased AMPA receptor expression in an estrogen receptor–dependent manner.[10] Notably, $(2S,6S)$-HNK, the antidepressant effect of which is much weaker than that of $(2R,6R)$-HNK, induced AMPA receptor expression at the same potency as the latter in this study,[10] suggesting that the estrogen receptor–dependent mechanism may not have a role in its antidepressant effect. In contrast, Hashimoto's group reported that the antidepressant effect of $(2R,6R)$-HNK was not as potent as that of $(R)$-ketamine,[11,12] and $(R)$-ketamine, but not $(2R,6R)$-HNK, exerted an antidepressant effect when injected into the brain.[13] These findings raise a critical question on the role of $(2R,6R)$-HNK in the antidepressant effect of $(R,S)$-ketamine.

We recently reported that blockade of the metabolism of $(R)$-ketamine to $(2R,6R)$-HNK by CYP inhibition did not prevent $(R)$-ketamine from exerting its antidepressant effects.[14]

On the contrary, the antidepressant effect of $(R)$-ketamine was enhanced, which coincided with the increased levels of $(R)$-ketamine in the plasma. These results were supported by the recent report that deuterium-labeled $(R)$-ketamine, which is resistant to $(2R,6R)$-HNK formation, did not affect the antidepressant effects.[15] Based on these findings, we concluded that $(2R,6R)$-HNK is not essential for $(R)$-ketamine to exert its antidepressant effects. By contrast, it has been reported that deuterium-labeled $(R,S)$-ketamine no longer shows antidepressant effects,[4] which contradicts the above-mentioned results. Although the precise reasons for this discrepancy need to be elucidated, it is obvious that $(2R,6R)$-HNK is not solely responsible for the antidepressant effect of $(R)$-ketamine.

However, the possibility of $(2R,6R)$-HNK as an active metabolite of $(R)$-ketamine (and $(R,S)$-ketamine) is worthy of being pursued further. Most pharmacologic data reported to date have shown that $(2R,6R)$-HNK exerts rapid and sustained antidepressant effect in several rodent models. There are, however, reports of studies in some animal models in which the antidepressant effect of $(2R,6R)$-HNK was rather weaker than that of $(R,S)$-ketamine and its enantiomers,[12,14] or in which $(2R,6R)$-HNK did not exert any antidepressant effect, whereas $(R)$-ketamine did.[11] These findings suggest that the antidepressant profile of $(2R,6R)$-HNK is substantially different from that of $(R,S)$-ketamine. Differences in the profiles among active metabolites and their parent compounds were observed for other active metabolites. For example, imipramine is an inhibitor of both serotonin and noradrenaline transporters, whereas its active metabolite desipramine is a selective inhibitor of noradrenaline transport.[2] Amitriptyline is a more potent inhibitor of serotonin transport than that of noradrenaline transport, whereas the metabolite nortriptyline shows the reverse findings.[2] It should be noted that these active metabolites have been on the market for the treatment of psychiatric disorders, and that the drugs are used to overcome the drawbacks of the parent drugs. Therefore, it is important to carefully investigate the potential of $(2R,6R)$-HNK as a novel antidepressant drug in terms of differences in the pharmacologic and safety profiles from those of $(R)$-ketamine and $(R,S)$-ketamine.

Identification of active metabolites is a very important part of the history of neuropsychopharmacology and drug discovery for psychiatric disorders. As described above, identification of active metabolites has not only led to new treatment opportunities as exemplified by desipramine and paliperidone but also proved the way for the development of novel approaches for drug discovery by elucidation of mechanisms of actions of the active metabolites. Because $(2R,6R)$-HNK has the potential to be another example, the antidepressant effects of $(2R,6R)$-HNK and its mechanisms need to be thoroughly investigated across laboratories, and its potential needs to be carefully evaluated, eventually in human studies.

## Author Contributions

SC and J-iY wrote the manuscript.

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