The Need for Genetic Predictors for Antidepressant Actions of Ketamine or Ketamine Metabolites

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Standard antidepressants typically have a limited treatment response rate. Only approximately one-third of patients diagnosed with depression will respond to their first antidepressant, and the remaining two-third will not respond to their antidepressants[1]. Moreover, during the latency period, the risk of suicide and self-harm significantly increases, which represents a key public health issue in psychiatric practice [2].

Therefore, identifying newer antidepressants that may act faster and more effectively in a larger number of individuals with mood disorders is a key need in this field.

Newer agents targeting alternative neurobiological systems including the glutamate system have shown promising results. Ketamine is known to affect a wide range of biological targets beyond NMDA antagonism, including activation of mTOR, modulation of nicotinic channels, delta and mu-opioid agonist and opioid potentiation, reduction in cholinergic neuromodulation and activation of AMPA and metabotropic glutamate receptors (mGluR), as well as an increase in dopamine and noradrenaline release [3]. Skolnick initially reviewed the effects of NMDA antagonists as antidepressants as well as the use of ketamine as a channel blocker in depressed individuals [4]. Several other studies have also examined alternative molecular targets related to the rapid antidepressant efficacy of ketamine. Evidence from several models suggests that a few molecular mechanisms are likely to be associated with ketamine's plasticity-inducing effects. For instance, studies of diverse proteins and intracellular signaling cascades suggest that increased neuroplasticity and synaptogenesis are key convergent downstream targets for rapid-acting agents such as ketamine. But, it is still unclear how ketamine works as an antidepressant.

More recently, groundbreaking work carried out by Zanos et al.[5] indicated that the metabolism of (R,S)-ketamine to (2S, 6S;2R, 6R)-hydroxynorketamine (HNK) plays a critical role in the long documented effects of ketamine as an antidepressant. Their work further indicated that the (2R, 6R)-HNK enantiomer performs cellular antidepressant-related actions in mice. The authors came to the conclusion that “these antidepressant actions are independent of NMDAR inhibition but involve early and sustained activation of a-amino-3-hydroxy-5-methyl-4 isoxazol propionic acid receptors.” The authors further stated that (2R,6R)-HNK does not cause ketamine-related side effects.

Interestingly, to date, there have been no studies probing into any genetic factors underlying the ketamine/(2R,6R)-HNK effects using a genome-wide
association approach. This is most likely due to the fact that gathering an adequate number of treated individuals to obtain results at the genome-wide significance level has been a challenge. Bioinformatics tools such as protein-protein interaction analysis and pathway analysis may permit the identification of networks underlying the drug effects even if individual genes are not statistically significant at the genome-wide significance threshold.

Here we intend to emphasize the need for rigorous collaborative research efforts in discovering new genetic markers which may predict response to ketamine/ketamine metabolite treatment. Both national and international collaborations are needed to identify genetic pathways associated with the ketamine effects.

REFERENCES


