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, whichrepresents 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)-hydroxinorketmaine (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 isoxazoel 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

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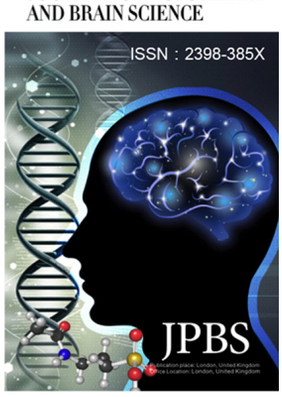

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association approach. This is most likely due to the fact that gathering an adequate number of treated individuals to obtain results at the genome-wide significance level has been a challenge. Bioinformatics tools such as protein-protein interaction 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

1. Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., . . . Fava, M. (2006). Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. American Journal of Psychiatry AJP, 163(1), 28-40. doi:10.1176/appi.ajp.163.1.28
2. Machado-Vieira, R., Salvadore, G., Diazgranados, N., & Zarate, C. A. (2009). Ketamine and the next generation of antidepressants with a rapid onset of action. Pharmacology & Therapeutics, 123(2), 143-150. doi:10.1016/j.pharmthera.2009.02.010
3. Sleigh, J., Harvey, M., Voss, L., & Denny, B. (2014). Ketamine – More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care, 4(2-3), 76-81.doi:10.1016/j.tacc.2014.03.002
4. Skolnick, P. (1999). Antidepressants for the new millennium. European Journal of Pharmacology, 375(1-3), 31-40. doi:10.1016/s0014-2999(99)00330-1
5. Zanos, P., Moaddel, R., Morris, P. J., Georgiou, P., Fischell, J., Elmer, G. I., . . . Gould, T. D. (2016). NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature, 533(7604), 481-486. doi:10.1038/nature17998