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LETTER TO THE EDITOR

Are basal D-serine plasma levels a predictive biomarker for the rapid antidepressant effects of ketamine and ketamine metabolites?

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We found Prof. Hashimoto's comments on our recent article (Moaddel et al. 2014) to be interesting and informative. In our referenced article, we reported that patients with treatment-resistant depression that responded to treatment with (*R,S*)-ketamine had significantly lower baseline D-serine plasma concentrations than patients who did not respond. The data suggested that baseline D-serine plasma concentration might be a biomarker for antidepressant response. These results are preliminary and further prospective studies will be required to confirm the clinical utility of baseline D-serine plasma determinations. Prof. Hashimoto agreed with this assessment and suggested an expansion of the scope of future investigations. In his letter, he suggested that it would be important to include the determination of the effect of the individual enantiomers of ketamine, (*R*)-ketamine and (*S*)-ketamine, on plasma D-serine concentrations. The increased scope is based upon the recent data suggesting that (*R*)-ketamine is a more potent and longer-lasting antidepressant than (*S*)-ketamine (Zhang et al. 2014). We agree especially in light of our recent findings that (*R*)-ketamine and (*S*)-ketamine have significant and opposite enantioselective effects on the intracellular concentrations of D-serine in PC-12 pheochromocytoma cells (unpublished data).

However, we also feel that the research into the antidepressant effects associated with (*R,S*)-ketamine needs to break out of the constraints imposed on it by the "Ketamine Paradigm." The "Ketamine Paradigm" identifies (*R,S*)-ketamine and its *N*-demethylated metabolite, (*R,S*)-norketamine, as the active agents and the pharmacological activity as inhibition of the NMDA receptor. This hypothesis is based upon the initial pharmacological study of the anesthetic properties of (*R,S*)-ketamine, in which (*R,S*)-ketamine and (*R,S*)-norketamine were shown to produce the CNS activities associated with general anesthesia and the postanesthetic recovery phase, while an additional (*R,S*)-ketamine metabolite, (2*S*,6*S*;2*R*,6*R*)-hydroxynorketamine, was inactive (Leung and Baillie 1986). (2*S*,6*S*;2*R*,6*R*)-Hydroxynorketamine was labeled as an "inactive" metabolite, and all of the other multiple (*R,S*)-ketamine metabolites have also been assumed to be inactive.

Based on the "Ketamine Paradigm," the pharmacological activities of (*R,S*)-ketamine metabolites, other than (*R,S*)-norketamine, were not investigated until our recent studies (Moaddel et al. 2013). In these studies, we demonstrated that two of the major metabolites of (*R,S*)-ketamine, (*R,S*)-dehydronorketamine and (2*S*,6*S*;2*R*,6*R*)-hydroxynorketamine, are selective and potent allosteric inhibitors of the α7 subtype of the nicotinic acetylcholine receptor (α7-nAChR) but have a weak effect on MK801 binding at the NMDA receptor (Moaddel et al. 2013). It is interesting to note that while the (2*S*,6*S*)- and (2*R*,6*R*)-hydroxynorketamine enantiomers were equipotent at the α7-nAChR (IC_{50}<100 nM), (2*R*,6*R*)-hydroxynorketamine had a significantly weaker affinity for the NMDA receptor (K_i>100 μM) than the (2*S*,6*S*)-isomer (K_i=21 μM). The latter effect mirrored the affinities of (*S*)-ketamine and (*R*)-ketamine at the NMDA receptor, 0.7 and 2.6 μM, respectively (Moaddel et al. 2013). We have also shown that in PC-12 and 1321N1 human astrocytoma cell lines, the inhibition of basal α7-nAChR activity by (*R,S*)-dehydronorketamine and (2*S*,6*S*)-hydroxynorketamine leads to decreased intracellular D-serine concentrations and de novo

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protein synthesis associated with the activation of the mammalian target of rapamycin (mTOR) pathway (Singh et al. 2013; Paul et al. 2014). A recent study suggested that mTOR activation in the frontal cortex of the Wistar rat was responsible for the rapid antidepressant effect of (*R,S*)-ketamine (Dwyer and Duman 2013). Using the same animal model, we determined that both (*R,S*)-ketamine and (2*S*,6*S*)-hydroxynorketamine produced similar increases in the phosphorylation of signaling proteins associated with the mTOR pathway (Paul et al. 2014), suggesting that (2*S*,6*S*)-hydroxynorketamine contributes to the antidepressant effects produced by (*R,S*)-ketamine via inhibition of α7-nAChR activity. Based upon our previous in vitro data, this conclusion would logically extend to the activity of (2*R*,6*R*)-hydroxynorketamine.

In conclusion, we agree with Prof. Hashimoto's proposal to expand the scope of the study of the relationship between baseline D-serine plasma concentrations and antidepressant response to (*R,S*)-ketamine by including the separate enantiomers of this drug. We also recommend an additional increase in the scope of the proposed studies to include to pharmacodynamic studies of the ketamine metabolites (*R*)- and (*S*)-dehydronorketamine and (2*S*,6*S*)- and (2*R*,6*R*)-hydroxynorketamine in order to determine if a relationship exists between the plasma concentrations of these compounds, the observed antidepressant response, and baseline D-serine plasma concentrations. The key to an improved antidepressant agent may lie in redefining the "Ketamine Paradigm."

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Conflict of interest Irving W. Wainer is listed as the lead inventor on a patent application for the use of (2*S*,6*S*)-hydroxynorketamine and other ketamine metabolites in the treatment of depression and neuropathic pain. Dr. Wainer has assigned his rights in the patent to the U.S. Government but will receive a percentage of any royalties that may be received by the government.

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