LETTER

REPLY TO HASHIMOTO:
Ketamine is not an opioid but requires opioid system for antidepressant actions

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We agree with Hashimoto (1) that the molecular mechanisms underlying the psychiatric properties of (R,S)-ketamine remain active areas of investigation. Racemic ketamine as well as esketamine ([S]-ketamine) are potent \textit{N}-methyl-	extit{D}-aspartate receptor (NMDAR) antagonists and have displayed acute antidepressant and antisuicidal effects in multiple clinical studies (2, 3). However, these compounds display activity, albeit with lower affinity, on a number of receptors, including \textit{\mu}-opioid receptors (MORs), complicating the issue of mechanism of action. Clinical studies arguing for (4) and against (5) a role for MORs in the antidepressive effects of ketamine are both small ($n=7$ and 5 patients, respectively), and thus larger studies will be required.

While the recent clinical data from the ketamine (R)-enantiomers and metabolites are intriguing, we agree with Hashimoto that further studies are needed before we can rule out NMDAR inhibition in the antidepressant effects of ketamine (6). We note that while some NMDAR antagonists have not shown clinical benefit for depression, other NMDAR antagonists unrelated to ketamine have shown efficacy [i.e., dextromethorphan (7)], although again target specificity clouds the underlying mechanism.

As Hashimoto notes, there has been variability in preclinical studies concerning the effects of different ketamine-related compounds, possibly due to the particular animal and stress model used. We chose congenital helpless (cLH) rats for our model as they display depressive-like symptoms (face validity), respond to clinical antidepressant treatment (predictive validity), and their behavioral performance is correlated with cellular hyperactivity of the lateral habenula (LHb) (construct validity), a brain nucleus implicated in depression (8, 9). We observed that in cLH animals ketamine treatment acutely diminishes LHb hyperactivity and improves helplessness performance, as well as chronically improves performance in a task measuring motivation. Our pharmacological results are consistent with MOR being necessary but not sufficient for the behavioral and cellular effects of ketamine (10). These results suggest MOR is not the direct target of ketamine, but MOR may play a permissive role. Other studies have demonstrated a physical complex between MOR and NMDARs that can gate NMDAR biophysical properties, consistent with our results (11). Further studies are needed to determine whether the antidepressant effects of ketamine employ such a mechanism.

In conclusion, a mechanistic understanding of the antidepressant effects of ketamine will require more studies with results that are replicated across different experimental model systems. Correlating biophysical, cellular, and behavioral results in preclinical studies may help guide future clinical studies.

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\begin{itemize}
\item 4 N. R. Williams et al., Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. \textit{Am. J. Psychiatry} \textbf{175}, 1205–1215 (2018).
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The authors declare no competing interest.

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