



CHARACTERIZATION AND RESCUE OF NEURONAL DYSFUNCTION

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Ketamine exerts its sustained antidepressant effects via cell-type specific regulation of *Kcnq2*

A single sub-anesthetic dose of ketamine can produce a rapid and sustained antidepressant response, yet the molecular mechanisms responsible for these effects remain unclear. Here, we identified cell-type-specific transcriptional signatures associated with a sustained ketamine response in mice. Most interestingly, we identified the *Kcnq2* gene as an important downstream regulator of ketamine action in glutamatergic neurons of the ventral hippocampus. We validated these findings through a series of complementary molecular, electrophysiological, cellular, pharmacological, behavioural and functional experiments. We demonstrate that the adjunctive treatment of ketamine with retigabine, a KCNQ activator, augments antidepressant-like effects in mice. Intriguingly, these effects are ketamine-specific, as they do not modulate a response to classical antidepressants, such as escitalopram. These findings constitute a significant advancement to our understanding of the mechanisms underlying the sustained antidepressant effects of ketamine, with important clinical implications.

