"Mechanism of Rapid Antidepressant Responses"
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Abstract

Clinical studies have demonstrated that a single subpsychotomimetic dose of ketamine, an ionotropic glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist, produces rapid antidepressant responses in patients with major depressive disorder, with effects lasting up to a few weeks in some individuals. The ability of ketamine to produce a rapid and long-lasting antidepressant response provides a unique opportunity for investigation of mechanisms that mediate these clinically relevant behavioral effects. From a mechanistic perspective, it is easy to imagine how activation of NMDA receptors may trigger cellular and behavioral responses; it is relatively more difficult, however, to envision how transient blockade of one of the key pathways for neuronal communication produces a persistent beneficial effect. We have been examining the synaptic basis of the antidepressant-like effects triggered by acute ketamine application. Data will be presented showing that ketamine mediated blockade of NMDA receptors at rest deactivates eukaryotic elongation factor 2 (eEF2) kinase, resulting in reduced eEF2 phosphorylation and desuppression of rapid dendritic protein translation, including BDNF, which then contributes to synaptic plasticity mechanisms. Electrophysiological data shows that ketamine potentiates synaptic responses in the CA1 regions of rat and mouse hippocampus. This potentiation requires protein synthesis, BDNF expression, eEF2 function, and increased surface expression of AMPA receptors, in particular GluA1 and GluA2. These findings reveal critical determinants of how blocking spontaneous neurotransmission impacts synaptic plasticity, with implications for ketamine mediated antidepressant responses. Moreover, our findings linking ketamine’s mechanism of action to homeostatic synaptic plasticity processes activated after suppression of NMDA-mediated glutamatergic neurotransmission will be explored.

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