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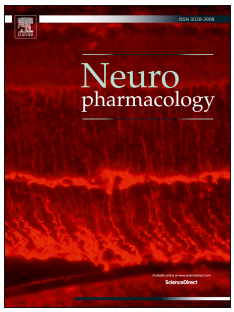

Two Cellular Hypotheses Explaining Ketamine's Antidepressant Actions: Direct Inhibition and Disinhibition

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A single, low dose of ketamine has antidepressant actions in depressed patients and in patients with treatment-resistant depression (TRD). Unlike classic antidepressants, which regulate monoamine neurotransmitter systems, ketamine is an antagonist of the N-methyl-D-aspartate (NMDA) family of glutamate receptors. The effectiveness of NMDAR antagonists in TRD unveils a new set of targets for therapeutic intervention in major depressive disorder (MDD) and TRD. However, a better understanding of the cellular mechanisms underlying these effects is required for guiding future therapeutic strategies, in order to minimize side effects and prolong duration of efficacy. Here we review the evidence for and against two hypotheses that have been proposed to explain how NMDAR antagonism initiates protein synthesis and increases excitatory synaptic drive in corticolimbic brain regions, either through selective antagonism of inhibitory interneurons via cortical disinhibition, or by direct inhibition of cortical pyramidal neurons.