Ketamine Produces a Long-lasting Enhancement of CA1 Neuron Excitability

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Introduction: Ketamine has recently been shown to improve major depressive disorder in patients who are unresponsive to other forms of treatment. The antidepressant effect occurs rapidly, often following a single exposure, and can outlast the presence of the drug for days or even weeks. Current evidence suggests that the mechanisms for this effect involve actions in addition to NMDA receptor antagonism. Little is known about other molecular targets for ketamine. The present study examined the effects of ketamine on synaptic transmission at glutamate and GABA synapses to determine whether changes in activity at these synapses contribute to the long-lasting effects produced by this drug.

Methods: All procedures were approved by the Stanford University Animal Use Committee. Male C57BL/6J mice weighing between 25-30 grams were used to prepare 400 μM thick coronal brain slices. We studied the effects of ketamine and its major metabolites (2R, 6R & 2S, 6S)-hydroxynorketamine by electrically stimulating Shaffer-collateral axons while recording evoked responses from CA1 pyramidal neurons. We also studied GABA inhibitory responses using a paired-pulse paradigm.

Results: Concentration-dependent effects were observed at clinical concentrations (10 μM for antidepressant and 350 μM for anesthetic). Ketamine produced three effects: 1) an acute depression of population spike amplitudes, 2) an enhancement of GABA-mediated inhibition, and 3) a long-lasting increase in population spike amplitudes. The long-lasting increase in amplitudes was observed following drug washout and lasted for up to 4 hours (longest duration of recording). This increase was not produced by any anesthetics we have previously studied (halothane, isoflurane, desflurane, sevoflurane, ethanol, pentobarbital, phenobarbital, thiopental, propofol, dexmedetomidine, or urethane). Ketamine's effects were mimicked by its primary metabolites and by the NMDA receptor channel blocker, MK-801. However, these effects were only partially mimicked by the NMDA receptor antagonist, APV and by a broad spectrum potassium channel blocker, TEA. A long-lasting effect was not observed for EPSP responses, indicating a postsynaptic site for ketamine's action.

Conclusions: Our results agree with previous studies showing that ketamine produces an acute depression of population spike amplitudes with an increase in GABA-mediated inhibition. This is the first report to demonstrate a long-lasting increase in excitability following washout of ketamine from brain slices. The increase in excitability following washout was also seen with MK-801 but only partially evident with APV, demonstrating the importance of channel block downstream of NMDA receptors. Additionally, the results with TEA indicate a potential for potassium channel block in ketamine's long-lasting effect. We suggest that the long-lasting effect produced following washout of ketamine could be related to the long-lasting antidepressant effects produced by ketamine and its metabolites.