LETTER

Are NMDA and opioid receptors involved in the antidepressant actions of ketamine?

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The rapid-acting antidepressant and antisuicidal effects of the anesthetic (*R*,*S*)-ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) antagonist, is an important discovery in depression research (1). However, the precise molecular mechanisms underlying (*R*,*S*)-ketamine's antidepressant actions remain unknown. Naltrexone, an opioid receptor antagonist, blocked the rapid antidepressant and antisuicidal effects of (*R*,*S*)-ketamine in treatment-resistant patients with depression (2, 3). Although the sample size was small ($n = 7$), the authors concluded that opioid receptor activation is required for the observed (*R*,*S*)-ketamine effects. In contrast, some reports suggest that depressed patients who experience antidepressant effects of (*R*,*S*)-ketamine lack opioid systems (4, 5). We reported that pretreatment with naltrexone (10 mg/kg, 0.5 h before) did not block the acute (3 h) or sustained (1 to 2 d) antidepressant-like effects of (*R*,*S*)-ketamine (10 mg/kg) in chronic social defeat stress and inflammation-induced mouse models of depression (6).

In PNAS, Klein et al. (7) demonstrate that (*R*,*S*)-ketamine does not act as an opiate but its effects require both NMDAR and opioid receptors. Pretreatment with naltrexone (1 mg/kg, 1 h before) blocked acute (2 h) antidepressant-like effects of (*R*,*S*)-ketamine (15 mg/kg) in congenitally learned helplessness (cLH) rats. Although (*R*,*S*)-ketamine elicits long-lasting (<7 d) antidepressant effects in rodents and depressed patients, sustained (i.e., 1 d) antidepressant-like effects of (*R*,*S*)-ketamine were not tested in cLH rats. Hyperactivity in lateral habenula (LHb) neurons from cLH rats was significantly blocked by (*R*,*S*)-ketamine, and cellular effects of (*R*,*S*)-ketamine were blocked by naltrexone or the specific μ-type opioid receptor antagonist CTAP. Although stress-induced models of depression were not used, the specific NMDAR antagonist APV decreased LHb activity to a similar degree as (*R*,*S*)-ketamine, suggesting that (*R*,*S*)-ketamine reduces neuronal activity in LHb of cLH rats by blocking NMDARs (7). The authors conclude that the opioid system is required for antidepressant-like actions of (*R*,*S*)-ketamine, indicating an interaction between NMDAR and opioid receptors.

(*R*,*S*)-Ketamine is a racemic mixture containing equal parts of (*R*)- and (*S*)-ketamine. (*S*)-Ketamine has an approximately fourfold greater affinity for the NMDAR than (*R*)-ketamine. Interestingly, in animal models of depression, (*R*)-ketamine shows greater potency and longer-lasting antidepressant-like effects than (*S*)-ketamine (5, 8). Nonketamine NMDAR antagonists do not produce (*R*,*S*)-ketamine–like robust antidepressant actions in patients with depression, although these compounds elicit antidepressant-like effects in rodents (5, 8). Collectively, it is unlikely that NMDAR inhibition plays a major role in antidepressant effects of (*R*,*S*)-ketamine (5, 8), although further detailed studies are needed.

Unlike the inescapable shock-induced LH model (9), disadvantage using cLH rats does not allow for the comparison of LH and non-LH (resilient) rats (10). Importantly, the genetic basis for cLH rats remains unknown. Investigating the effects of ketamine enantiomers on depression-like behaviors in rodents exposed to stress is necessary to confirm the role of NMDAR and the opioid system relative to the antidepressant effects of (*R*,*S*)-ketamine.

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