Differential effects of ketamine metabolites on depression-like behaviors induced by chronic corticosterone injection in mice

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Clinical and preclinical studies have shown that the NMDA receptor antagonist ketamine exerts rapid and long-lasting antidepressant effects. Although ketamine metabolites might also have potential antidepressant properties, controversial results have been reported on (*2R,6R*)-hydroxynorketamine ((*2R,6R*)-HNK) in particular and there is little information on the effects of other ketamine metabolites. Here we aimed to compare the effects of (*R*)-norketamine ((*R*)-NK), (*S*)-NK, (*2R,6R*)-HNK and (*2S,6S*)-HNK in a mouse model of depression induced by chronic corticosterone (CORT) injection. None of these ketamine metabolites at doses up to 20 mg/kg showed antidepressant-like activity in naïve male C57BL6/J mice. Chronic CORT treatment increased immobility in the forced swim test and caused anhedonic-like behaviors in the female encounter test. A single administration of (*R*)-ketamine, but not an SSRI fluoxetine, showed antidepressant-like activity in chronic CORT-treated mice. (*S*)-NK and (*2S,6S*)-HNK dose-dependently reduced the increased immobility at 30 min after injection, while (*R*)-NK or (*2R,6R*)-HNK did not. Additionally, (*S*)-NK and (*2S,6S*)-HNK improved anhedonic-like behaviors at 24 h after injection. These results suggest that (*S*)-ketamine metabolites (*S*)-NK and (*2S,6S*)-HNK have potent acute and sustained antidepressant effects.