Effects of ketamine optical isomers, fluoxetine and naloxone on timing in differential reinforcement of low-rate response (DRL) 72-s task in rats

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Abstract

Background and Purpose: (S)-ketamine induced rapid-acting antidepressant effects have revolutionized pharmacotherapy of major depression, however this medication produces also psychotomimetic effects including timing distortion. In contrast, (R)-ketamine appears to produce less of dissociative effects, but its antidepressant actions were less studied. It has been suggested that opioid receptors are involved in the antidepressant effect of ketamine. In addition, recent report suggests that while (S)-ketamine induced time underestimation, the (R)-isomer did not affect timing. Experimental approach: (R)- and (S)-ketamine, and fluoxetine as a positive control were tested in the differential-reinforcement-of-low-rate (DRL) 72-s schedule of reinforcement in male rats following naloxone pretreatment. Several DRL classic metrics as well as peak deviation analyses served to determine antidepressant-like actions and those associated with timing. Key Results: Antidepressant-like effect of (S)-ketamine (30-60 mg/kg) resembled fluoxetine (2.5-10 mg/kg) actions. Fluoxetine and (S)-ketamine increased reinforcement rate and peak location, suggesting increased performance, reduced premature responses, suggesting time underestimation and decreased Weber's fraction, suggesting increased timing precision. In contrast, (R)-ketamine (60 mg/kg) increased reinforcement rate and peak location without affecting premature responses. Only fluoxetine decreased burst responses, suggesting decreased impulsivity. Naloxone pretreatment did not block ketamine enantiomers' actions, but unexpectedly, increased fluoxetine' performance. Conclusions & Implications: Fluoxetine' and (S)- but not (R)- ketamine induced time underestimation could be associated with their antidepressant effects. The potentiation of DRL performance of fluoxetine by naloxone was unexpected and warrants further clinical studies.

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