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Research report

Dopamine D2/D3 but not dopamine D1 receptors are involved in the rapid antidepressant-like effects of ketamine in the forced swim test

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HIGHLIGHTS

- Dopamine D2/D3 receptor but not D1 receptor antagonists prevent the rapid antidepressant-like effect of ketamine.
- Dopamine D2/D3 receptor but not D1 receptor antagonists prevent the rapid antidepressant-like effect of MK-801.
- Co-administration of sub-effective dose of ketamine and dopamine D2/D3 receptor agonist exert antidepressant-like effect.

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ABSTRACT

Major depressive disorder is one of the most prevalent and life-threatening forms of mental illnesses. The traditional antidepressants often take several weeks, even months, to obtain clinical effects. However, recent clinical studies have shown that ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, exerts rapid antidepressant effects within 2 h and are long-lasting. The aim of the present study was to investigate whether dopaminergic system was involved in the rapid antidepressant effects of ketamine. The acute administration of ketamine (20 mg/kg) significantly reduced the immobility time in the forced swim test. MK-801 (0.1 mg/kg), the more selective NMDA antagonist, also exerted rapid antidepressant-like effects. In contrast, fluoxetine (10 mg/kg) did not significantly reduced the immobility time in the forced swim test after 30 min administration. Notably, pretreatment with haloperidol (0.15 mg/kg, a non-selective dopamine D2/D3 antagonist), but not SCH23390 (0.04 and 0.1 mg/kg, a selective dopamine D1 receptor antagonist), significantly prevented the effects of ketamine or MK-801. Moreover, the administration of sub-effective dose of ketamine (10 mg/kg) in combination with pramipexole (0.3 mg/kg, a dopamine D2/D3 receptor agonist) exerted antidepressant-like effects compared with each drug alone. In conclusion, our results indicated that the dopamine D2/D3 receptors, but not D1 receptors, are involved in the rapid antidepressant-like effects of ketamine.

1. Introduction

Major depressive disorder is one of the most prevalent and serious mental illness and has become major problem of public health [1]. The current traditional antidepressants often take several weeks, even months, to exert their efficiency, while approximately two-third of patients fail to those treatments [2,3]. In contrast, recent clinic studies have demonstrated that acute treatment with ketamine, a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, alleviates the symptoms of depression within 2 h and lasts up two weeks [4,5], even effective in treatment-resistant patients with standard antidepressants [6,7]. For these reasons, elucidation of the mechanism by which ketamine exerts rapid antidepressant-like effects has the potential to lead to novel therapies for major depression.

A great number of evidences have suggested that dysregulation of dopaminergic system is implicated in the pathogenesis of depression [8,9]. The involvement of dopamine in major depression is thought to be associated with the mesolimbic dopaminergic reward pathway [10]. The ventral tegmental area (VTA) dopamine

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neurons in the reward pathway play a cortical role in response to stress [9,11]. Recent studies showed that control of activity of VTA dopamine neuron via optogenetic technique could rapidly regulate depression-like behaviors in free moving mice [12,13], providing a direct evidence for the hypothesis that mesolimbic dopaminergic system might mediate rapid antidepressant effects.

Stimulation of dopamine receptors has been shown to underlie the activity of antidepressant drugs in both animal and human studies [14,15]. Several studies suggest an important role for dopamine D1/D5 receptor in mediating antidepressant drugs in the forced swim test (FST) [16,17], whereas other researches show that dopamine D2/D3 receptor but not dopamine D1/D5 receptor antagonist blocked the effect of antidepressant and indirect dopamine agonists in this model [18,19]. Moreover, dopamine D1 and D2 receptor have been reported to be involved in the immobility time reduction induced by dopamine reuptake inhibitors in the FST [20].

NMDA antagonists have been reported to interact with dopaminergic system. For example, the ability of NMDA antagonist MK801 to induce locomotor activity is thought to involve dopamine D1 and D2 receptors [21], and MK-801 also affect the behavioral effect induced by dopamine D1 or D2 receptor antagonist [22]. Moreover, a single subanaesthetic dose of ketamine significantly increased the release of dopamine in the brain [23,24], suggesting that dopaminergic system could be modulated by ketamine. Therefore, we hypothesized that dopaminenergic system may play an important role in the rapid antidepressant effects of ketamine.

In the present study, selective dopamine D1 receptor antagonist and dopamine D2/D3 receptor agents were used to investigate whether dopaminergic system, in particular dopamine D1 and D2/D3 receptor was involved in the rapid antidepressant effects of ketamine in the FST in mice.

2. Material and methods

2.1. Animals

Healthy male Kunming (KM) mice (6–8 weeks) were obtained from the Experimental Animals Center of Tongji Medical College, Huazhong University of Science and Technology. The animals were maintained in a standard condition with a 12:12 h light:dark cycle (light on 7 am), and free access to food and water. The experimental protocols were carried out in accordance with the Committee of Animal Care of Huazhong University of Science and Technology.

2.2. Drugs and treatment

Ketamine used in the present study was obtained from Gutian Pharmaceutical Company (China). MK-801, fluoxetine, SCH23390, haloperidol and pramipexole were purchased from Sigma-Aldrich Company (USA). All drugs were dissolved in saline (0.9% (w/v) solution of NaCl) except that haloperidol was diluted in saline with 5% DMSO. All drugs were administrated by intraperitoneal (i.p.) route at a fixed volume of 10 ml/kg body weight.

To identify the involvement of the dopaminergic system in the mechanism underlying the acute antidepressant-like effects of ketamine or MK-801 in the FST, mice were pretreated with saline, SCH23390 (0.04 and 0.1 mg/kg), or haloperidol (0.06 and 0.15 mg/kg) and 10 min later ketamine (20 mg/kg) or MK-801 (0.1 mg/kg) were then injected into mice. The FST was carried out after 30 min. To further demonstrate the influence of dopamine D2/D3 receptor on the rapid antidepressant-like effects of ketamine, the effects of the combined administration of sub-effective ketamine (10 mg/kg) with sub-effective dopamine D2/D3 agonist pramipexole (0.3 mg/kg) was investigated. Pramipexole was administrated 40 min prior to the test, and ketamine was administrated 30 min prior to the test.

2.3. Forced swim test (FST)

The FST was performed as previously reported [25]. FST is a widely used depression model to test the effects of antidepressants. Mice were placed individually for 6 min in a vertical glass beaker (height: 30 cm; diameter: 10 cm) containing 10 cm of water at 22 ± 1 °C. The water was changed between mice. Immobility behavior is defined as minimal movement necessary to keep floating [26]. A video camera placed on the side of the beaker was used to record the test session. The immobility time were analyzed by a scorer blind to the experimental treatment during the last 4-min of the total 6-min test period.

2.4. Open field test (OFT)

The OFT was determined as previously reported [27]. Briefly, mice were placed individually in the center of a square acrylic box (45 cm × 45 cm × 45 cm). The floor of the box was divided into 25 equal squares. The animal was recorded for 5 min with a video camera positioned above the box. Locomotor activity was quantified by recording the distance traveled via the video-computarized tracking system. The open field apparatus was cleaned thoroughly with 5% alcohol before the next animal test.

2.5. Statistical analysis

Data were analyzed using a one-way analysis of variance (ANOVA) followed by Newman–Keuls test for post hoc comparisons. Value of $p < 0.05$ was considered to indicate significance.

3. Results

3.1. Rapid antidepressant-like effects of ketamine and MK-801 in the FST

The results presented in Fig. 1A show both ketamine and MK-801 significantly reduced the immobility time in the FST ($F(3,31) = 4.01$, $p < 0.05$), whereas fluoxetine (10 mg/kg) did not exhibit a reduction in the immobility time. After chronic treatment, fluoxetine (10 mg/kg) significantly decreased the immobility time in the FST (Supplementary Fig. 1), while did not affect the locomotor activity in the OFT (data not shown). Fig. 1B shows ketamine significantly and dose-dependently reduced the immobility time compared to the vehicle treated mice ($F(3,26) = 3.41$, $p < 0.05$). The administration of ketamine or MK-801 did not influence the local activity of mice in the OFT ($F(4,31) = 0.98$, $p = 0.50$)(Table 1).

Table 1
Effect of ketamine and MK-801 on the locomotion in the OFT.

Treatment	Locomotion (total distance moved cm/5 min)
Vehicle	2660 ± 113
Ketamine (3 mg/kg)	2764 ± 288
Ketamine (10 mg/kg)	3020 ± 221
Ketamine (20 mg/kg)	2785 ± 193
MK-801 (0.1 mg/kg)	2212 ± 219
Ketamine (10 mg/kg) + pramipexole (0.3 mg/kg)	2161 ± 292

Data are represented as the mean ± SEM ($n = 6$–8). No significant difference between groups was observed.