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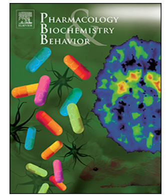
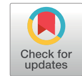


Astrocytes activation contributes to the antidepressant-like effect of ketamine but not scopolamine



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ABSTRACT

Depression is a common, debilitating mood disorder, but currently available antidepressants have several major drawbacks. Both ketamine and scopolamine attract more and more attention due to their rapid and sustained antidepressant activities. However, the molecular and cellular mechanism that underlies the therapeutic action of ketamine and scopolamine still remain to be elucidated. Considering the importance of astrocytes in the development of depression, we hypothesized that the activation of astrocyte may play a vital role in the antidepressant effects of ketamine and scopolamine. In the present study, the expression of fibrillary acidic protein (GFAP) was detected to evaluate the activation of astrocyte after single injection of ketamine and scopolamine in respective efficient doses. Behavioral tests used to assess antidepressant-like effects were forced swim test (FST) and tail suspension test (TST). Fluorocitrate, a well-established astrocyte inactivator, was adopted to inhibit the activation of astrocyte. The results demonstrated that ketamine, but not scopolamine, could increase significantly the expression of GFAP in hippocampus. In addition, inhibition of astrocyte abolished the antidepressant-like effects of ketamine, but not scopolamine in the FST and TST. It is suggested that activated astrocyte plays a vital role in the antidepressant activities of ketamine rather than scopolamine. These findings may be important for the understanding of the role of astrocyte in depression and antidepressants, especially rapid antidepressants.

1. Introduction

Major depressive disorder (MDD) is one of the severe mental disorders and one of leading causes of morbidity, mortality, economic burden worldwide as well (Ferrari et al., 2013). The mainstream pharmacological treatments for MDD revolves around monoamine (such as noradrenaline and/or serotonin) dysfunction theory in the 1980s. Thus inhibiting the reuptake of monoamine and increasing the extracellular monoamine levels become the main therapeutic strategy in the past three decades. However, current antidepressants lack of rapid onset for clinical efficacy, limiting the ability to bring instant relief to patients (Rakesh et al., 2017). In addition, approximately two-thirds of MDD patients fail to respond to current antidepressants (Coupland et al., 2018). Therefore, there is an urgent need for the development of rapid antidepressants.

Over the past decade, preclinical and clinical and studies have suggested the fast-acting antidepressant effects of ketamine and scopolamine. As an *N*-methyl-D-aspartate (NMDA) receptor antagonist, ketamine attracts more and more attention due to the rapid (within a couple of hours) and sustained antidepressant benefit (up to 2 weeks) in patients who endured moderately to severely depression and were resistant to current treatment (Fond et al., 2014; McGirr et al., 2015). In animal model, ketamine exerts antidepressant effects that lasted for 24 h (Fukumoto et al., 2018). Ketamine is regarded as the most outstanding discovery in the field of depression research in over 60 years. Scopolamine is a nonselective muscarinic acetylcholine receptor (mAchR) antagonist, mainly used in the treatment of motion sickness, Parkinson's disease, and pregnancy-related vomiting (Renner et al., 2005). Interestingly, clinical trial has revealed that scopolamine also produces a rapid (within 3–4 days) and potent antidepressant response (Drevets and Furey, 2010). However, the molecular and cellular mechanism that underlies the therapeutic action of ketamine and scopolamine still remains to be elucidated.

Astrocytes, the most abundant cell type in the brain, participate in blood brain barrier homeostasis, axonal outgrowth, and intracellular communication networks. The role of astrocytes in development of depression has recently received increasing attention due to changes in their expression and function. For example, the expression of the

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astrocyte-specific markers, fibrillary acidic protein (GFAP) and S100β (a calcium-binding protein), was dramatically reduced in the prefrontal cortex, hippocampus, and amygdala in depression (Gittins and Harrison, 2011). The pharmacologic ablation of astrocytes in the prefrontal cortex of rats is sufficient to induce depressive-like behaviors (Banasr and Duman, 2008). Valid therapy of antidepressants rescues decreased expression of GFAP in depression. Astrocytes also secret brain-derived neurotrophic factor (BDNF), a key molecule involved in the pathology of depression or mechanism of action of antidepressants. Specific overexpressing BDNF in astrocytes produces antidepressant-like activity (Quesseveur et al., 2013). Treatment with antidepressants affects intracellular signaling in astrocyte, such as the calcium ion and the phosphorylation of mitogen-activated protein kinases. Imipramine, one of antidepressants, can act directly on astrocytes increasing BDNF expression in the primary cultured astrocytes (Takano et al., 2012). Taken together, it suggests that modulating the function of astrocytes may represent a key biologic mechanism underlying the effects of pharmacological strategies.

However, the roles of astrocyte in rapid potent antidepressants namely ketamine and scopolamine are unclear. Therefore, in this study, we investigated the changes in the expression of GFAP induced by ketamine and scopolamine. Moreover, by taking the advantage of the well-established astrocyte inactivator fluorocitrate (Hermann et al., 2014; Reiner et al., 2016), we investigated whether inhibition of astrocyte contributes to suppress antidepressant-like effect of ketamine or scopolamine.

2. Methods

2.1. Experimental animals

Male ICR mice weighing 18–22 g each were purchased from the Laboratory Animal Center of Xuzhou Medical University (Xuzhou, China). These mice were housed on a 12 h light/dark cycle with ad libitum access to food and water at a constant temperature of 25 ± 1 °C. The animals were housed in groups of six per cage and allowed to habituate for one week. All procedures were conducted in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and approved by the Institutional Animal Care and Use Committee of Xuzhou Medical University.

2.2. Drugs and administration

Ketamine hydrochloride was purchased from Hengrui Medicine co., LTD. Scopolamine hydrobromide was purchased from Harvest Pharmaceutical co., LTD. Ketamine hydrochloride and scopolamine hydrobromide was dissolved in physiological saline. The fluorocitrate solution was prepared as follows (Hayakawa et al., 2010): 8 mg of D,L-fluorocitric acid, barium salt was dissolved in 1 ml of 0.1 M HCl. Two to three drops of 0.1 M Na_2SO_4 were added to precipitate Ba^{2+}. 2 ml of 0.1 M Na_2HPO_4 was added and the suspension was centrifuged at 1000*g* for 5 min. The supernatant was diluted with 0.9% NaCl to the final concentration (1 nmol/μl) and the pH was adjusted to 7.4. Intracerebroventricular (i.c.v.) injection of fluorocitrate solution (1 nmol) was performed according to a previously described method (Wang et al., 2018). The stereotaxic coordinates were 0.5 mm posterior, 1.0 mm lateral to the bregma and 2.5–3.0 mm ventral to the bregma.

2.3. Forced swim test (FST)

At 24 h after treatment, mice were placed individually into glass cylinders (height: 20 cm, diameter: 10 cm) containing water (depth: 15 cm) at a temperature of 25 ± 1 °C for 6 min. After test, mice were immediately returned to their home cage. The total time spent immobile was scored by two well-trained observers who were blind to the treatments. A mouse was judged to be immobile when it floated in an

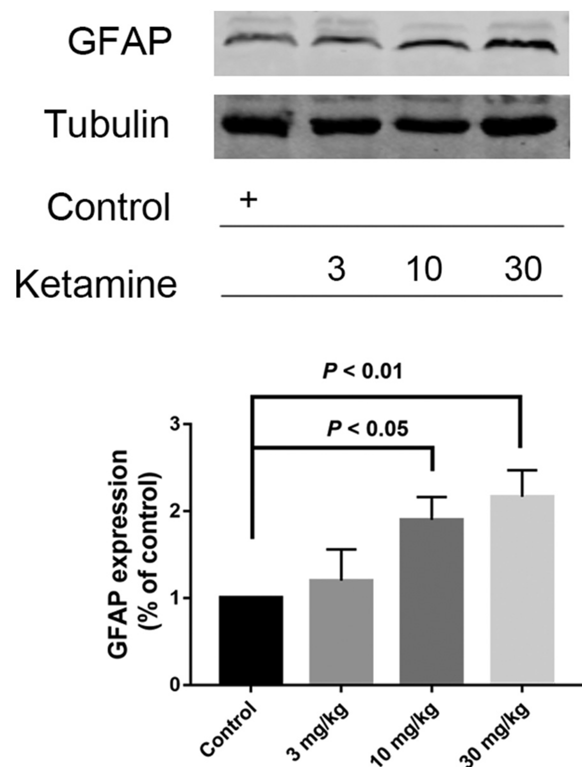

Fig. 1. The effect of ketamine on the activation of astrocyte. Male ICR mice were injected with normal saline (n = 3, i.p.), ketamine (3, 10, 30 mg/kg, n = 3 respectively, i.p.). After 24 h, hippocampus tissues were rapidly dissected, collected and kept for western blotting assays as described in methods. Data were expressed as mean ± SD and analyzed with one-way ANOVA analysis.

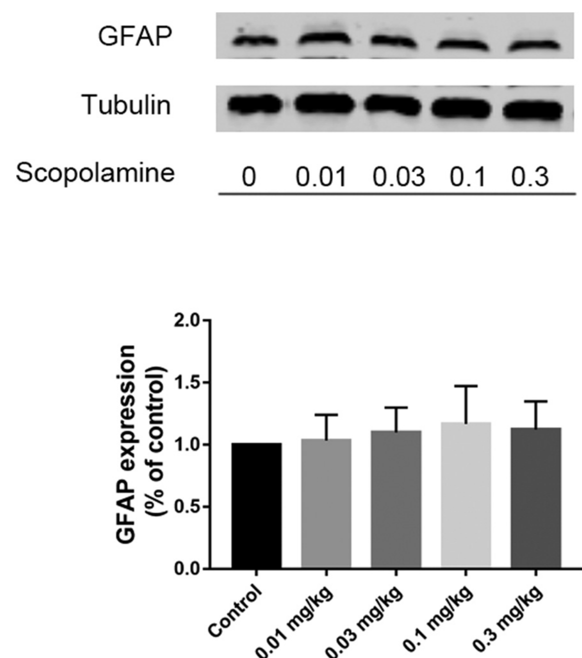

Fig. 2. The effect of scopolamine on the activation of astrocyte. Male ICR mice were injected with normal saline (n = 3, i.p.), scopolamine (0.01, 0.03, 0.1, 0.3 mg/kg, n = 3 respectively, i.p.). After 24 h, hippocampus tissues were rapidly dissected, collected and kept for western blotting assays as described in methods. Data were expressed as mean ± SD and analyzed with one-way ANOVA analysis.

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