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Research report

Role of BDNF/TrkB signaling in antidepressant-like effects of a group II metabotropic glutamate receptor antagonist in animal models of depression

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HIGHLIGHTS

- LY341495 exerted antidepressant-like effects in the tail suspension test.
- LY341495 exerted antidepressant-like effects in the novelty-suppressed feeding test.
- Antidepressant-like effects of LY341495 were sustained for 24 h.
- K252a blocked the sustained, but not acute, antidepressant effects of LY341495.

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ABSTRACT

We previously revealed that the activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor and mammalian target of rapamycin signaling contributed to the antidepressant-like effects of group II metabotropic glutamate (mGlu2/3) receptor antagonists, suggesting that the signaling pathway may be similar to the molecular mechanisms underlying the antidepressant-like action of ketamine, a noncompetitive *N*-methyl-D-aspartate receptor antagonist that exertes rapid and sustained antidepressant effects in patients with depressive disorder. Although brain-derived neurotrophic factor (BDNF)/tropomyosin-related kinase B (TrkB) signaling reportedly participates in the antidepressant-like effects of ketamine, the involvement of BDNF/TrkB signaling in the action of mGlu2/3 receptor antagonists has not been investigated. We therefore examined whether the activation of BDNF/TrkB signaling is required for the antidepressant-like effects of LY341495, an mGlu2/3 receptor antagonist, in animal models of depression such as the tail suspension test (TST) and the novelty-suppressed feeding test (NSFT). The administration of LY341495 at 30 min prior to the test exerted antidepressant-like effects (acute effects) lasting for at least 24 h (sustained effects) when evaluated using the TST and NSFT. Pretreatment with K252a, a TrkB tyrosine kinase inhibitor, blocked the sustained, but not the acute, effects of LY341495. These results suggest that BDNF/TrkB signaling may be involved in the sustained antidepressant-like effects of LY341495, as observed for ketamine treatment.

1. Introduction

A large body of evidence has indicated that dysfunctions of the glutamatergic system in the central nervous system occur in patients with depression. An interesting finding in this context is that the noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine exerts rapid and sustained antidepressant effects in patients with major depressive disorder (MDD) [1–5] and bipolar disorder [6] after a single injection. However, given that ketamine has undesired adverse effects, such as psychotomimetic effects and neurotoxicity [7], alternative approaches that share the same antidepressant action mechanism with ketamine but do not have undesired adverse effect are keenly required. In this context, the mechanisms by which ketamine ameliorates the symptoms of depression have been actively investigated. Recently, preclinical research has indicated that ketamine exerts antidepressant-like effects via α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor stimulation [8,9] and the subsequent activation of the mammalian target of rapamycin (mTOR) signaling pathway in the prefrontal cortex (PFC), resulting in increased spine formation and enhanced synaptic activity [10,11]. Moreover, brain-derived neurotrophic factor (BDNF) has been shown to mediate the antidepressant-like effects of ketamine [12,13] as well as the enhanced spine formation induced by ketamine [13].

Among glutamate receptors, the group II metabotropic glutamate (mGlu2/3) receptor is predominantly localized in the presynaptic terminals and negatively regulates glutamate release [14]; this receptor is of interest in light of its involvement in

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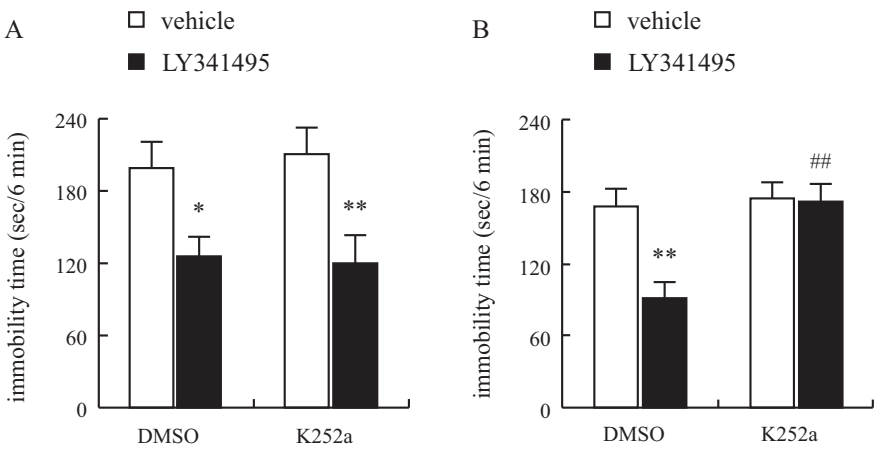

Fig. 1. Effects of pretreatment with K252a on the antidepressant-like effects of LY341495 in the TST. LY341495 (1 mg/kg) was administered intraperitoneally 30 min (A) or 24 h (B) prior to the test, and K252a (2 nmol in 2 μL) was administered intracerebroventricularly 1 h (A) or 24.5 h (B) prior to the test. Values indicate the mean ± S.E.M. (A: $n = 15$, B: $n = 15$). $^{*}P < 0.05$, $^{**}P < 0.01$, compared with vehicle-treated group, $^{\#\#}P < 0.01$ compared with DMSO-treated group (LSD post hoc test).

depression, based on localization studies and recent findings using pharmacological tools [15–17]. We previously demonstrated that mGlu2/3 receptor antagonists exerted antidepressant-like effects in animal models of depression [18–21] and reported that an AMPA receptor antagonist and rapamycin blocked the antidepressant-like effects of mGlu2/3 receptor antagonists [19,21,22]. Moreover, LY341495 [(2S)-2-amino-2-[(1S,2S)-2-carboxycy cloprop-1-yl]-3-(xanth-9-yl) propanoic acid], an mGlu2/3 receptor antagonist, has been reported to activate the mTOR signaling pathway in the PFC [23]. Thus, AMPA receptor stimulation and the activation of mTOR signaling may be common pathways for the antidepressant-like effects of both ketamine and mGlu2/3 receptor antagonists. Nevertheless, whether BDNF signaling through its high-affinity receptor, tropomyosin-related kinase B (TrkB), is involved in the antidepressant-like effects of mGlu2/3 receptor antagonists is unknown. We therefore examined whether the antidepressant-like effects of LY341495 are mediated through the enhancement of BDNF/TrkB signaling using two animal models of depression: the tail suspension test (TST) and the novelty-suppressed feeding test (NSFT).

2. Materials and methods

2.1. Animals

Male ICR mice and male C57BL/6J mice were purchased from Charles River (Yokohama, Japan) and were maintained under a 12-h light/dark cycle (lights on at 7:00 a.m.) in a temperature- and humidity-controlled holding room with food and water available ad libitum. Five-week-old ICR mice and 9-week-old C57BL/6J mice were used for the TST and NSFT, respectively. All the studies were reviewed by the Taisho Pharmaceutical Co., Ltd. Animal Care Committee and met the Japanese Experimental Animal Research Association standards, as defined in the *Guideline for Animal Experiments* (1987).

2.2. Drug treatments

LY341495, purchased from Tocris Cookson Ltd. (Bristol, UK), was dissolved in 1/15 M phosphate buffer (pH 8.0). Ketamine (Veterinary Ketalar® 50), purchased from Sankyo Yell Pharmaceutical Co., Ltd. (Tokyo, Japan), was diluted with saline. K252a, purchased from Sigma-Aldrich Co. (St. Louis, MO, USA), was dissolved in dimethylsulfoxide (DMSO). LY341495 (1 mg/kg) and ketamine (30 mg/kg) were administered intraperitoneally 30 min or 24 h prior to the test. K252a (2 nmol in 2 μL) was injected intracerebroventricularly (i.c.v.) 30 min prior to the administration of LY341495 and ketamine. We previously demonstrated that LY341495 (1 mg/kg) and ketamine (30 mg/kg) significantly decreased the immobility time in the TST, and the antidepressant-like effects of these drugs were prevented by pretreatment with rapamycin [22]. The dose of K252a was chosen based on the results of previous study, which demonstrated that K252a prevented the antidepressant-like effect of BDNF injection [24]. Of note, abnormal behaviors were not observed during the test period after the i.c.v. injection of DMSO.

2.3. Tail suspension test

The TST is a well-recognized animal model for assessing the antidepressant activity [25]. The TST was performed according to a previously described method [26], with some modifications. Mice were suspended by the tail from a metal rod using adhesive tape. The rod was fixed 45 cm above the surface of a table in a sound-isolated room. The mouse was positioned at least 15 cm away from the nearest object. The test session was recorded for 6 min, and the immobility time was determined by an observer. Mice were considered immobile only when they hung passively and were completely motionless.

2.4. Novelty-suppressed feeding test

The NSFT has been reported to be responsive to the chronic administration of classical antidepressants [27]. The testing apparatus consisted of a plastic box (45 cm × 45 cm × 20 cm), the floor of which was covered with approximately 1 cm of wooden bedding in an illuminated (1000 lx) soundproofed box. Twenty-four hours before the behavioral testing, all the food was removed from the home cage. Water remained available ad libitum. At the time of testing, a single pellet of food (regular chow) was placed on a white circular filter paper (diameter: 11 cm) in the center of the box. A mouse was placed in a corner of the box and was immediately recorded for 5 min. The latency until feeding (defined as the mouse biting the pellet while using its forepaws) was determined by an observer. The cut-off time was 5 min.

2.5. Statistical analysis

The results were expressed as the mean ± S.E.M. Statistical significance was determined using a two-way analysis of variance (ANOVA), followed by the LSD post hoc test for multigroup comparisons. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Effect of K252a on antidepressant-like effects induced by LY341495 treatment in the TST

LY341495 significantly reduced the immobility time in the TST at both 30 min and 24 h after treatment (Fig. 1). The anti-immobility effect of LY341495 at 30 min after treatment was not blocked by pretreatment with K252a [LY341495, $F_{(1,56)} = 15.05$; $P < 0.001$; K252a, $F_{(1,56)} = 0.01$; $P = 0.91$; interaction, $F_{(1,56)} = 0.17$; $P = 0.68$] (Fig. 1A). In contrast, the decrease in the immobility time at 24 h after LY341495 treatment was significantly blocked by K252a treatment [LY341495, $F_{(1,56)} = 7.00$; $P < 0.05$; K252a, $F_{(1,56)} = 8.78$; $P < 0.01$; interaction, $F_{(1,56)} = 6.32$; $P < 0.05$] (Fig. 1B).