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Short communication

Stimulation of the metabotropic glutamate (mGlu) 2 receptor attenuates the MK-801-induced increase in the immobility time in the forced swimming test in rats

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ABSTRACT

Background: Negative symptoms of schizophrenia are poorly managed using the currently available antipsychotics. Previous studies indicate that agonists of the metabotropic glutamate (mGlu) 2/3 receptors may provide a novel approach for the treatment of schizophrenia. However, the effects of mGlu2/3 receptor agonists or mGlu2 receptor positive allosteric modulators have not yet been clearly elucidated in animal models of the negative symptoms of schizophrenia. Recently, we reported that the forced swimming test in rats treated with subchronic MK-801, an NMDA receptor antagonist, may be regarded as a useful test to evaluate the activities of drugs against the negative symptoms of schizophrenia.

Methods: We evaluated the effects of LY379268, an mGlu2/3 receptor agonist, and BINA, an mGlu2 receptor positive allosteric modulator, on the hyperlocomotion induced by acute administration of MK-801 (0.15 mg/kg, *sc*) and on the increase in the immobility time in the forced swimming test induced by subchronic treatment with MK-801 (0.5 mg/kg, *sc*, twice a day for 7 days) in rats.

Results: Both LY379268 (3 mg/kg, *sc*) and BINA (100 mg/kg, *ip*) attenuated the increase in the immobility time induced by subchronic treatment with MK-801 at the same doses at which they attenuated the MK-801-induced increase in locomotor activity, but had no effect on the immobility time in saline-treated rats.

Conclusions: The present results suggest that stimulation of the mGlu2 receptor attenuates the increase in the immobility time in the forced swimming test elicited by subchronic administration of MK-801, and may be potentially useful for treatment of the negative symptoms of schizophrenia.

Introduction

Patients with schizophrenia exhibit not only positive symptoms (hallucinations, delusions and paranoia), but also negative symptoms (affective flattening, anhedonia and social withdrawal) and cognitive deficits. The negative symptoms of schizophrenia are poorly managed by the currently available antipsychotics, and as a result, many patients remain with substantial disability. Therefore, effective treatment of the negative symptoms of schizophrenia is a major unmet medical need in the management of schizophrenia.

Among the glutamate receptors, metabotropic glutamate (mGlu) receptors, which consist of 8 subtypes (mGlu1–8), have emerged as attractive therapeutic targets for the development of novel interventions against psychiatric disorders. Of these, the group II (mGlu2 and mGlu3) receptors have been proposed to play important roles in the pathophysiology of schizophrenia. Both mGlu2/3 receptor agonists and mGlu2 receptor positive allosteric modulators have been reported to improve the behavioral abnormalities in rodents, which represent the positive symptoms, negative symptoms and cognitive deficits in schizophrenic patients [1–4]. Phase 2 clinical trials of LY2140023 (the oral prodrug of LY404039), an mGlu2/3 receptor agonist, and ADX71149, an mGlu2 receptor positive allosteric modulator, have been carried out against the symptoms of schizophrenia [5,6]. The compounds have been found to be effective against the negative symptoms [5,6], although the results remain controversial [7,8].

N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine and ketamine, have been reported to induce not only positive symptoms, but also negative symptoms and cognitive dysfunction in humans, and to exaggerate the symptoms in

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schizophrenic patients [9–11]. Repeated administration of NMDA receptor antagonists, such as phencyclidine, MK-801 and ketamine, has been reported to induce an increase in the immobility time in the forced swimming test in mice and rats [12–15]. Although the immobility in the forced swimming test has been widely used as an animal model of depression, an antidepressant, imipramine, did not affect the increased immobility induced by the subchronic administration of NMDA receptor antagonists [12,13]. Therefore, the effects of drugs on immobility by repeated administration of NMDA receptor antagonists are unlikely to reflect antidepressant effects. On the other hand, this effect has been shown to be attenuated by clozapine, an atypical antipsychotic drug, but not by haloperidol, a typical antipsychotic agent [12–15]. In clinical studies, clozapine, but not haloperidol, has been demonstrated to improve the negative symptoms of schizophrenia [16,17]. Therefore, this animal model may represent a model of the negative symptoms of schizophrenia, such as reduced motivation and affective flattening [12–15]. However, the effects of mGlu2/3 receptor agonists or mGlu2 receptor positive allosteric modulators have not yet been elucidated in this model.

In the present study, we investigated the effects of an mGlu2/3 receptor agonist and an mGlu2 receptor positive allosteric modulator on the increase in the immobility time in the forced swimming test induced by subchronic administration of MK-801, and on the hyperlocomotion induced by acute administration of MK-801 in rats.

Materials and methods

Animals

Male Sprague–Dawley and Wistar rats (purchased from Charles River, Yokohama, Japan) were used for this study. All the rats were housed in plastic cages, with unrestricted access to food and water. The rats were maintained in controlled temperature (23 ± 3 °C) and humidity (50 ± 20%) conditions under a 12-h light–dark cycle (lights on at 07:00 h). All the experiments were conducted in accordance with the guidelines of the Taisho Pharmaceutical Co., Ltd. Animal Care Committee and met the Japanese Experimental Animal Research association standards, as defined in the Guidelines for Animal Experiments.

Drugs

(5*S*,10*R*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK-801; Sigma–Aldrich, St. Louis, MO, USA) and (1*R*,4*R*,5*S*,6*R*)-4-amino-2-oxabicyclo [3.1.0]hexane-4,6-dicarboxylic acid (LY379268; Abcam, Cambridge, UK) were dissolved in saline for subcutaneous administration. 3′-[[(2-cyclopentyl-2,3-dihydro-6,7-dimethyl-1-oxo-1*H*-inden-5-yl)oxy]methyl]-[1,1′-biphenyl]-4-carboxylic acid (BINA) was synthesized at Taisho Chemistry Laboratories and suspended in 0.5% methylcellulose for intraperitoneal administration. The dose selections for all the drugs were based on previous reports [12] and our preliminary studies. All the drugs, except for MK-801 for the forced swimming test, were administered at a volume of 2 mL/kg body weight. MK-801 for the forced swimming test was administered at a volume of 1 mL/kg body weight.

Locomotor activity

The locomotor activity was measured using the SCANET apparatus (Melquest Ltd., Toyama, Japan), according to our previously reported method [18]. Male Wistar rats (7 weeks old) were individually placed in the test chamber (47 cm in width × 28 cm in length × 30 cm in height), which in turn was placed in a soundproof box, at 30 min after the LY379268 or BINA administration. The spontaneous locomotor activities were then measured for 60 min. In the drug interaction study, the rats were individually habituated in the test chamber placed in a soundproof box for 60 min, and then MK-801 was administered subcutaneously at the dose of 0.15 mg/kg; the locomotor activities were immediately recorded for 120 min. LY379268 and BINA were administered 30 min prior to the MK-801 administration.

Under the same condition, peroral administration of clozapine at a dose of 100 mg/kg significantly decreased MK-801-induced hyperlocomotion in rats.

Forced swimming test (an animal model of the negative symptoms of schizophrenia)

The forced swimming test was performed according to our previously reported method [12]. Male Sprague–Dawley rats (7 weeks old) were subcutaneously injected with 0.5 mg/kg of MK-801 or saline twice a day for 7 days. Two days after the last administration of saline or MK-801, the forced swimming test was conducted by placing the rats in cylinders (18 cm × 50 cm, diameter × height) containing 30 cm of water at 25 ± 1 °C for 10 min. During the test, the rats were separated by a nontransparent board placed between the cylinders. The water in the cylinders was changed after every trial. The test sessions were recorded using a charge-coupled device (CCD) camera, and the time duration for which the animals remained immobile after the experiment was measured using a stopwatch. A rat was considered to be immobile when it remained floating in the water in an upright position, making only very small movements to keep its head above the water. LY379268 and BINA were administered 30 min prior to the test.

Under the same condition, peroral administration of clozapine at doses of 3 and 10 mg/kg significantly attenuated the increase in immobility time induced by the repeated administration of MK-801 in rats [12].

Data analysis

All the statistical analyses were performed using the SAS software (SAS Institute Japan, Tokyo, Japan). Data were analyzed using Student's *t*-test, and a one-way analysis of variance followed by Dunnett's test. A value of $p < 0.05$ was regarded as significant.

Results

Effects of LY379268 and BINA on the locomotor activities in rats

MK-801 administered at the dose of 0.15 mg/kg *sc* significantly increased the locomotor activities of rats [$t = 7.24$, $p < 0.01$] (Fig. 1A) and [$t = 8.74$, $p < 0.01$] (Fig. 1B). On the other hand, administration of LY379268 at the dose of 3 mg/kg *sc* significantly attenuated the hyperlocomotion induced by acute administration of MK-801 in rats [$F_{(2,21)} = 3.52$, $p < 0.05$] (Fig. 1A). BINA administered at the dose of 100 mg/kg *ip* also significantly attenuated the hyperlocomotion induced by acute administration of MK-801 in rats [$F_{(3,42)} = 4.36$, $p < 0.01$] (Fig. 1B).

Furthermore, LY379268 administered at the dose of 3 mg/kg and BINA administered at the dose of 100 mg/kg also significantly decreased the spontaneous locomotor activities of rats [$F_{(2,21)} = 7.30$ and $F_{(3,28)} = 7.39$, respectively; $p < 0.01$ for both] (Table 1).

Effects of LY379268 and BINA on the immobility time in the forced swimming test in subchronic administration of saline and MK-801-treated rats

Subchronic administration of MK-801 at the dose of 0.5 mg/kg (*sc*, b.i.d. for 7 days) increased the immobility time in the forced