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Improvement of dizocilpine-induced social recognition deficits in mice by brexpiprazole, a novel serotonin-dopamine activity modulator

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Abstract
Cognitive impairment, including impaired social cognition, is largely responsible for the deterioration in social life suffered by patients with psychiatric disorders, such as schizophrenia and major depressive disorder (MDD). Brexpiprazole (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1H)-one), a novel serotonin-dopamine activity modulator, was developed to offer efficacious and tolerable therapy for different psychiatric disorders, including schizophrenia and adjunctive treatment of MDD. In this study, we investigated whether brexpiprazole could improve social recognition deficits (one of social cognition deficits) in mice, after administration of the *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801 (dizocilpine). Dosing with dizocilpine (0.1 mg/kg) induced significant impairment of social recognition in mice. Brexpiprazole (0.01, 0.03, 0.1 mg/kg, p.o.) significantly ameliorated dizocilpine-induced social recognition deficits, without sedation or a reduction of exploratory behavior. In addition, brexpiprazole alone had no effect on social recognition in untreated control mice. By contrast, neither risperidone (0.03 mg/kg, p.o.) nor olanzapine (0.03 mg/kg, p.o.) altered dizocilpine-induced social recognition deficits. Finally, the effect of brexpiprazole on dizocilpine-induced social recognition deficits was antagonized by WAY-100,635, a selective serotonin 5-HT_{1A} antagonist. These results suggest that brexpiprazole could improve dizocilpine-induced social recognition deficits *via* 5-HT_{1A} receptor activation in mice. Therefore, brexpiprazole may confer a beneficial effect on social cognition deficits in patients with psychiatric disorders.

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1. Introduction

Cognitive impairment describes a diverse range of deficits, seen in psychiatric disorders. Of these, impaired social cognition greatly hampers everyday life, resulting in poor work productivity or underemployment of patients with schizophrenia and major depressive disorder (MDD) (Tandberg et al., 2011; Tse et al., 2013; Horan et al., 2012; Lo and Siu, in press). It is generally accepted that reducing social cognitive dysfunction is an important factor in assisting psychiatric patients to make healthy adjustments in their social lives (Tandberg et al., 2011; Tse et al., 2013; Horan et al., 2012; Trapp et al., 2013). Current reports suggest that training of social cognition may help to improve functional outcome in patients with schizophrenia (Henderson, 2013). To complement this, the development of novel drugs to improve social cognition deficits in patients with schizophrenia is also imperative.

Social recognition testing is designed to measure the propensity of a mouse to make contact with a novel rather than familiar mouse. This testing therefore represents a cognitive model that reflects innate ability to communicate with others (Moy et al., 2004; van der Kooij and Sandi, 2012). Social recognition test in rodents is also one of the assays for evaluating social cognition in humans (Millan and Bales, 2013). Based on the *N*-methyl-D-aspartate (NMDA) hypofunction hypothesis of schizophrenia (Hashimoto, 2006, 2014; Hashimoto et al., 2013), the NMDA receptor antagonist, (+)-MK-801 (dizocilpine), is widely used to induce schizophrenia-like behavioral abnormalities, including positive and negative symptoms and cognitive deficits in rodents (Hashimoto et al., 2009; Karasawa et al., 2008; Rajagopal et al., 2014; Meltzer et al., 2011; Okamura et al., 2004; Rogoz, 2013; Zhang et al., 2007). Furthermore, dizocilpine also impairs social interaction and social recognition (Maehara et al., 2011; Oh et al., 2013; Hikichi et al., 2013).

Brexpiprazole, 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy} quinolin-2(1H)-one, is a novel serotonin-dopamine activity modulator with high affinity for serotonin, dopamine and noradrenaline receptors (Maeda et al., 2014a). It is a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors, with a relatively equal potency, and an antagonist at 5-HT_{2A} receptors and adrenergic $\alpha_{1B/2C}$ receptors. Brexpiprazole is currently under clinical evaluation and expected to show efficacy and tolerability when used as therapy for different psychiatric disorders, including schizophrenia and adjunctive treatment for MDD. Very recently, brexpiprazole was shown to improve the NMDA receptor antagonist phencyclidine-induced cognitive deficits in the novel object recognition test in rodents (Maeda et al., 2014b; Yoshimi et al., 2014). To date, the effect of brexpiprazole on social recognition has not been investigated. In this study, we evaluated the effects of brexpiprazole on dizocilpine-induced social recognition deficits in mice.

2. Experimental procedures

2.1. Animals

Male C57BL/6NCrSlc mice (Japan SLC Inc., Shizuoka, Japan) aged between 4 and 5 weeks old were selected as stranger mice, while animals between 8 and 10 weeks old were used for this study. All mice were housed in groups of five per cage, in a room maintained at 23±2 °C and 60±10% humidity, with a 12/12 h light/dark cycle (lights on at 7:00 a.m.). The mice were given free access to food and water. Animal care and use were conducted in accordance with the Institutional Guidelines for Animal Care and Use (Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan).

2.2. Drugs

(+)-MK-801 hydrogen maleate (dizocilpine) was purchased from Sigma-Aldrich Co., Ltd. (Tokyo, Japan). Brexpiprazole, risperidone, olanzapine and WAY-100,635 were synthesized at Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). Dizocilpine was dissolved in saline and administered intraperitoneally (i.p.) at 10 ml/kg, twice daily, on the day before and 30 min prior to sociability testing. Brexpiprazole, risperidone, olanzapine and WAY-100,635 were dissolved in 5% (w/v) gum Arabic and administered orally (p.o.), at 10 ml/kg, 1 h prior to sociability testing. The doses of dizocilpine (0.1 mg/kg) and WAY-100,635 (1.0 mg/kg) were selected from previously published reports in mice (Hagiwara et al., 2008; Hashimoto et al., 2009; Takatsu et al., 2011; Yoshimi et al., 2014; Zhang et al., 2007). The doses of antipsychotic drugs were selected based on doses that did not impact locomotion (data not shown).

2.3. Apparatus

The test apparatus consisted of a rectangular, three-chambered box, and a lid with an attached infrared video camera (O'Hara & Co., Ltd., Tokyo, Japan). The apparatus was $610W \times 400D \times 220H$ mm^3, and the dividing walls were made from clear Plexiglass, with small square openings (3×5 cm^2) allowing access into each chamber. The stranger mouse was enclosed in a small, round wire cage (diameter, 10 cm; height, 12 cm), allowing olfactory, visual, auditory, and tactile contact, but no deep contact. Using a CCD camera, measures were taken of the amount of time spent around the wire cage. The total distance traveled was calculated based on traced mice movement and presented as the locomotor activity in this study. All data were computerized. Activity was monitored and analyzed using applications based on the public domain NIH Image or Image J program (developed by Wayne Rasband at the U.S. National Institute of Mental Health and available on the Internet at http://rsb.info.nih.gov/nih-image/) (O'Hara & Co., Ltd., Tokyo, Japan).

2.4. Behavioral procedures

The measurement of sociability and social recognition was performed using the same procedure described in previous reports (Moy et al., 2007; Nakatani et al., 2009; Matsuo et al., 2009; Riedel et al., 2009). In this study, we focused on a narrowly defined set of parameters.

2.4.1. Habituation

Mice were randomly assigned to groups. Mice were first placed in the middle compartment of the apparatus and allowed to explore freely for 6 min. All other compartments were empty during this habituation period.

2.4.2. Sociability test

An unfamiliar male (stranger) that had no prior contact with the mouse was placed in one of the side chambers. After the habituation period, the unfamiliar male juvenile mouse (stranger 1) was placed inside the round wire cage, in one of the side compartments (randomly selected and counterbalanced for each group). The opposite compartment was empty. The mice were able to freely explore all three compartments of the apparatus for 6 min. The time spent around cages (stranger 1 or empty) was calculated as direct contact.

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