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Research report

The atypical antipsychotic blonanserin reverses (+)-PD-128907- and ketamine-induced deficit in executive function in common marmosets

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HIGHLIGHTS

- The dopamine D_3 receptor-preferring agonist (+)-PD-128907 impairs marmosets executive function.
- Blonanserin reverses (+)-PD-128907-induced deficit in executive function.
- The NMDA receptor antagonist ketamine impairs marmosets executive function.
- Blonanserin reverses ketamine-induced deficit in executive function.

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ABSTRACT

Antagonism of the dopamine D_3 receptor is considered a promising strategy for the treatment of cognitive impairment associated with schizophrenia. We have previously reported that the atypical antipsychotic blonanserin, a dopamine D_2/D_3 and serotonin 5-HT_{2A} receptor antagonist, highly occupies dopamine D_3 receptors at its antipsychotic dose range in rats. In the present study, we evaluated the effects of blonanserin on executive function in common marmosets using the object retrieval with detour (ORD) task. The dopamine D_3 receptor-preferring agonist (+)-PD-128907 at 1 mg/kg decreased success rate in the difficult trial, but not in the easy trial. Since the difference between the two trials is only cognitive demand, our findings indicate that excess activation of dopamine D_3 receptors impairs executive function in common marmosets. Blonanserin at 0.1 mg/kg reversed the decrease in success rate induced by (+)-PD-128907 in the difficult trial. This finding indicates that blonanserin has beneficial effect on executive function deficit induced by activation of the dopamine D_3 receptor in common marmosets. Next, and based on the glutamatergic hypothesis of schizophrenia, the common marmosets were treated with the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine. Ketamine at sub-anesthetic doses decreased success rate in the difficult trial, but not in the easy trial. Blonanserin at 0.1 mg/kg reversed the decrease in success rate induced by ketamine in the difficult trial. The findings of this study suggest that blonanserin might have beneficial effect on executive dysfunction in patients with schizophrenia.

1. Introduction

Patients with schizophrenia suffer from widespread cognitive impairment, which correlates with their functional outcome (*e.g.*, community outcome, daily activities and social problem solving) [1,2]. Recent preclinical studies have shown that the dopamine D_3 receptor may be an attractive therapeutic target for treatment of cognitive impairment associated with schizophrenia [3–6]. Whereas the dopamine D_3 receptor-preferring agonists (+)-PD-128907 and 7-OH-DPAT disrupt several domains of cognitive function [3,4,7], the dopamine D_3 receptor antagonists SB277011, NGB2904, S33138 and S33084 are known to produce procognitive effect in several rodent behavioral tasks [3–5,8,9]. Furthermore, several microdialysis studies have demonstrated that

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antagonism of the dopamine D_3 receptor enhances cortical dopamine and acetylcholine neurotransmission in rodents prefrontal cortex [9–11].

Most typical and atypical antipsychotics are known to have high binding affinity for the dopamine D_3 receptor *in vitro* [12,13]. However, a number of studies have shown that several antipsychotics (*e.g.*, haloperidol, aripiprazole, clozapine, olanzapine and risperidone) exhibit no or very low occupancy of the dopamine D_3 receptor in rat *ex vivo* or *in vivo* experiments [12–15]. Moreover, human positron emission tomography (PET) studies have revealed that clozapine, olanzapine and risperidone, given at their therapeutic doses, do not occupy dopamine D_3 receptors in the dopamine D_3 receptor rich regions (globus pallidus and substantia nigra) of the brains of patients with schizophrenia [16,17], although a recent study has shown different results [18]. Based on these findings, it is believed that clozapine, olanzapine and risperidone do not act via the dopamine D_3 receptor.

The atypical antipsychotic blonanserin is a dopamine D_2/D_3 and serotonin 5-HT_{2A} receptor antagonist approved for the treatment of schizophrenia in Japan and Korea [19,20]. Blonanserin has potent binding affinity for the dopamine D_2 (Ki = 0.284 nM), the dopamine D_3 (Ki = 0.277 nM), and the serotonin 5-HT_{2A} (Ki = 0.640 nM) receptors with at least 33-fold selectivity for D_2/D_3 receptors over other tested receptors [20–23]. Recently, we have shown that blonanserin, given at its effective dose for the treatment of methamphetamine-induced hyperactivity in normal rats, extensively blocks the binding of [^{3}H]-(+)-PHNO, a dopamine D_2/D_3 receptor radiotracer, both in the dopamine D_2 receptor-rich region (striatum) and the D_3 receptor-rich region (cerebellum lobes 9 and 10) [22]. Like the dopamine D_3 receptor antagonist NGB2904, blonanserin enhances cortical dopamine and acetylcholine neurotransmission in mice [9]. Furthermore, blonanserin reverses visual recognition memory deficits induced by subchronic treatment with the noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine, in rats and mice [9,24]. However, no study has so far evaluated the procognitive effect of blonanserin in non-human primates.

The object retrieval with detour (ORD) task is a behavioral test that allows assessment of both attentive and inhibitory aspects of executive function, which is regulated by the prefrontal cortex [25,26]. We have previously reported that haloperidol, risperidone and olanzapine, but not blonanserin impair normal common marmosets' performance in the difficult trial of ORD task [27,28]. In the current study, we evaluated the effects of blonanserin on cognitive impairment in two animal models. First, we used the dopamine D_3 receptor-preferring agonist (+)-PD-128907-induced executive dysfunction in common marmosets as excessive activation of dopamine D_3 receptor. Second, we used the NMDA receptor antagonist ketamine-induced executive dysfunction in common marmosets as a model of schizophrenia, based on the glutamatergic hypothesis of schizophrenia [29–31].

2. Materials and methods

2.1. Animals

Five male and eight female adult common marmosets (3–15 years old, 250–440 g) were obtained from CLEA Japan Inc. (Japan). The animals were individually housed in cages kept in a temperature ($28 \pm 2\,^{\circ}C$) and a humidity ($50 \pm 20\%$) controlled animal room with a 12/12 light/dark cycle (light on at 7:00 and light off at 19:00). Food (CMS-1M, CLEA Japan, Inc.) was given once daily in the morning, and water was available ad libitum. On the day of the behavioral test, the animals were given food after testing. Behavioral tests were performed between 10:00 and 18:00. No animal was sacrificed in this study. After completion of all experiments, the animals were used in other experiments.

All experimental procedures involving animals use were reviewed and approved by the Institutional Animal Care and Use Committee of Sumitomo Dainippon Pharma, Co., Ltd.

2.2. Drugs

Blonanserin was synthesized in Sumitomo Dainippon Pharma, Co., Ltd., suspended in 0.5% methylcellulose (MC) (Nacalai tesque, Japan) as vehicle, and administrated by gavage directly into the stomach in a volume of 5 mL/kg. The dopamine D_3 receptor-preferring agonist (+)-PD-128907 hydrochloride (Tocris, UK) and the NMDA receptor antagonist ketamine (Daiichi Sankyo, Japan) were dissolved in saline (Otsuka, Japan) as vehicle, and were intramuscularly injected in a volume of 0.5 mL/kg. The doses of blonanserin (0.03 and 0.1 mg/kg p.o.) and (+)-PD-128907 hydrochloride (0.3 and 1 mg/kg i.m.) were selected based on our previous non-human primate studies [27,32].

2.3. Object retrieval with detour (ORD) task

ORD task was performed as previously described [27,28,33]. Briefly, the common marmosets were trained to reach for the reward (a piece of kneaded cake, about 0.5 cm^3) set in a clear acryl box (4 cm × 4 cm × 4 cm) open only at one side. The positions of the reward in the box were outer edge, inner edge or deep within the box. The experimenter held the box just outside the animal cage with the open side facing left, right or toward the common marmoset. Each test session consisted of 9 easy trials and 8 difficult trials. In the easy trial, the reward was placed on the inner or outer edge of the box with the opening of the box facing left or right from the common marmoset, or inside the box with the opening facing the common marmoset. This enabled the animal to directly reach the reward. In the difficult trial, the reward was placed deep within the box with the opening facing the right or left side of the common marmoset. This arrangement required the animal to make a detour around the box to reach the reward. Reaching the reward without touching any wall of the box within 30 s was considered "correct". When the common marmoset did not reach the reward within 30 s (cut-off time), it was record as "omission". Trials were inter-spaced by 5–10 s interval. Test results, including at least one omission were excluded from data analysis. The box was cleaned with 70% ethanol between trials to avoid influence of sensory cues. The performance of each animal in the drug-treated session was compared to that in the drug-free session of 9 easy and 8 difficult trials using the following equation: Change of success rate = $(N^{\text{drug-treated}} - N^{\text{drug-free}}) \times 100/9$ or 8, Where $N^{\text{drug-treated}}$ represents the rate of correct responses in the drug-treated session, $N^{\text{drug-free}}$ represents the rate of correct results in the drug-free session, and 9 or 8 represent the rate in the easy and difficult trial, respectively.

Blonanserin was administrated 120 min, (+)-PD-128907 was injected 15 min, and ketamine was injected 30 min before the ORD task. In the experiments with ketamine, the ORD task was repeated three times on different days to confirm that ketamine decreased success rate in the difficult trial. The average score of three ORD trials was used for data analysis. Other experiments were conducted only once. The tests were performed in a cross-over manner with administrations separated by at least 7 days. All monitoring of animals behavior was conducted in a blind manner.

2.4. Determination of ketamine optimal dose

The optimal dose of ketamine for each common marmoset was selected based on the results of our pilot experiments. First, the