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Research report

Dopamine D_1 signaling involvement in the effects of the phosphodiesterase 10A inhibitor, PDM-042 on cognitive function and extrapyramidal side effect in rats

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HIGHLIGHTS

- The novel PDE10A inhibitor, PDM-042, enhanced object recognition memory in rats.
- A dopamine D_1 antagonist, SCH23390, blocked the pro-cognitive effect of PDM-042.
- SCH23390 potentiated the cataleptic effect of PDM-042.
- Dopamine D_1 signaling may be involved in the pharmacological effects of PDM-042.

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ABSTRACT

Inhibition of phosphodiesterase 10A (PDE10A) results in activation of a dopamine D_1 receptor-mediated direct pathway in addition to a dopamine D_2 receptor-mediated indirect pathway in the striatum. Therefore, PDE10A inhibitors could be novel therapeutics for schizophrenia, which differ from the currently available antipsychotics that directly block the dopamine D_2 receptor. Previously, we found that a novel PDE10A inhibitor, PDM-042, had antipsychotic-like activity similar to currently available antipsychotics and minimal cataleptic effects in rats. The purpose of the present study was to examine the pharmacological effects of PDM-042 on cognitive function and extrapyramidal side effect. In addition, we aimed to examine whether these effects were mediated by activation of dopamine D_1 signaling in rats. PDM-042 (1–3 mg/kg) resulted in better discrimination of a novel object from a familiar one 48 h after the acquisition trial, suggesting that PDM-042 increased object recognition memory. A dopamine D_1 receptor antagonist, SCH23390 (0.1 mg/kg), significantly blocked the enhancement of the object recognition memory induced by PDM-042 (3 mg/kg) without affecting the recognition index by itself. We also found that the cataleptic effect of PDM-042 (1 mg/kg) was significantly enhanced by SCH23390 (0.01–0.03 mg/kg). These results indicate that PDM-042 has the potential to increase object recognition memory and that the cognitive enhancing and cataleptic effects of PDM-042 are mediated at least by activation of dopamine D_1 signaling.

1. Introduction

Phosphodiesterase 10A (PDE10A) is a member of cyclic nucleotide phosphodiesterase family that hydrolyzes both cAMP and cGMP [1,2] and is highly expressed in medium spiny neurons of the striatum in mammalian brain [3–6]. Medium spiny neurons are divided into the direct and indirect striatal output pathways expressing dopamine D_1 and D_2 receptor, respectively [7,8]. Direct and indirect pathway neurons induce opposing effects on output neurons in the internal segment of the globus pallidus and the substantia nigra pars reticulate, resulting in dis-inhibition and pro-inhibition of output, respectively, to motor areas of the thalamus and cortex [9]. Because PDE10A is expressed in both direct and indirect pathways [9–11], it has been hypothesized that inhibition of PDE10A in the striatum will result in both dopamine D_2 antagonism and D_1 agonism.

Several PDE10A inhibitors show both robust antipsychotic-like and cataleptic effects in rodents [12–14]. These results suggest

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that those effects of PDE10A inhibitors may be due to dopamine D_2 antagonism, similar to currently available antipsychotics. In addition to the antipsychotic-like effects, several potent, selective, and orally active PDE10A inhibitors were reported to show cognitive enhancing effects in rodents on several tasks that reflect the cognitive domains impaired in schizophrenic patients [15–17]. PDE10A inhibitors such as THPP-1, SEP-39, and TAK-063 enhanced object recognition memory in a novel object recognition test in naïve rats [15–17]. TAK-063 also reversed the cognitive impairments induced by *N*-methyl-D-aspartate receptor antagonists on five-choice serial reaction-time task, Y-maze test, eight-arm radial maze task, and attentional set-shifting task in rodents [17]. Among these preclinical assays, the novel object recognition test is a cognitive test without any positive or negative reinforcements, and thus is thought to reflect visual learning and recognition processing in humans [18]. Therefore, this test paradigm is useful to examine the effect of PDE10A inhibitor on cognitive functions in rodents.

The involvement of dopamine signaling in the cognitive enhancing effects of PDE10A inhibitors has not been fully elucidated yet. Because the dopamine D_1 receptor agonist, SKF38393, increases object recognition memory in rats [19,20], activation of dopamine D_1 signaling has been hypothesized to enhance cognitive functions in humans [21]. Therefore, activation of dopamine D_1 signaling by PDE10A inhibitors may provide a possible therapeutic approach to treat the cognitive impairments associated with schizophrenia.

Recently, we identified a novel potent, selective, and orally active PDE10A inhibitor, PDM-042 [22]. We demonstrated that PDM-042 showed antipsychotic-like effects such as an antagonistic effect on the hyperlocomotion induced by MK-801 and attenuation of the conditioned avoidance response in rats [22]. Furthermore, PDM-042 also exhibited a minimal cataleptic effect even at a dose 30-fold higher than that which showed antipsychotic-like effects in rats [22]. The purpose of the present study was to expand these previous findings. Here, we examine the effects of PDM-042 on cognitive function in rats using a novel object recognition test. In addition, we use a dopamine D_1 receptor antagonist, SCH23390, to examine the involvement of dopamine D_1 signaling in the cognitive function and the cataleptic effect of PDM-042.

2. Material and methods

2.1. Animals

Male Sprague-Dawley rats (6–7 weeks old, Charles River Laboratories Japan Inc., Shizuoka, Japan) were purchased. All rats were group-housed in an air-conditioned room (room temperature; $23 \pm 3\,^{\circ}C$, humidity; $55 \pm 15\%$) with a 12–h light-dark cycle (lights on: 07:30–19:30). Each rat had free access to standard chow (CE-2, CLEA Japan, Inc., Shizuoka, Japan) and tap water. At least 7 days were allowed for acclimatization to the facility before starting the experiments. All experimental procedures were approved by the Institutional Animal Care and Use Committee complied with the Japanese law "Act on Welfare and Management of Animals" and the guidelines from the Ministry of Health, Labor, and Welfare in Japan.

2.2. Drugs

PDM-042 was synthesized in house and used as the free base in all experiments. PDM-042 was suspended in 0.5% methylcellulose solution (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and orally administered at a volume of 5 mL/kg. SCH23390 ((*R*)-(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride, Sigma-Aldrich Co. LLC., St. Louis, MO, USA) was dissolved in physiological saline and subcutaneously administered at a volume of 1 mL/kg.

2.3. Novel object recognition test

The experimental apparatus used for the novel object recognition test was the open-field box (width, 60 cm; depth, 60 cm; height, 35 cm), which was made of gray-colored polyvinylchloride, with a floor covered with sawdust, and placed in a dimly illuminated room. The objects to be discriminated were a transparent glass bottle (with a blue cap and 15 cm height) and a brown glass bottle (with a brown cap and 15 cm height). The two objects were placed in a symmetrical position about 10 cm away from the wall.

One day before the acquisition trial, rats were allowed to explore the field for 10 min (habituation) without the objects. For the acquisition trial, a rat was placed in the experimental apparatus, facing the wall, at the opposite end from the objects. The rat was allowed to explore two identical objects for 3 min. After the acquisition trial, the rat was removed from the apparatus. In the present study, we used the post-acquisition administration paradigm to avoid the effect of drugs on animal behaviors in the acquisition trial. Therefore, both PDM-042 and SCH23390 were administered immediately after the acquisition trial. Subsequently, the rat was returned to its home cage. To avoid the presence of olfactory trails, after each trial, the sawdust was stirred, and the objects were thoroughly cleaned with 70% ethanol.

The test trial was performed 48 h after the acquisition trial. In the test trial, one copy of the familiar object was replaced with a novel object. The rat was allowed to explore the familiar and novel objects for 3 min. All combinations and locations of objects were used in a balanced manner to reduce potential bias due to preference for particular locations or objects. The behavior of rats was recorded using a video camera mounted above the experimental apparatus during both the acquisition and test trials. Recorded video clips were analyzed offline by a trained observer who was unaware of the treatment condition. The exploration time was recorded when the rat's nose was pointed in the direction of the object at a distance of <1 cm and/or was touching the object directly. Turning around or sitting on an object was not considered as exploration. For analysis of cognitive performance, a recognition index for the test trial was calculated as the ratio of the time spent exploring the novel object over the total time exploring the familiar and novel objects and expressed as a percentage. The exclusion criteria were as follows: 1) any rat spending total exploration time of less than 10 s in either the acquisition or the test trial; and 2) any rat spending exploration time of less than 1 s exploring the one of the two objects in either the acquisition or the test trial.

2.4. Catalepsy

PDM-042 and SCH23390 were administered 60 and 30 min, respectively, before the test. Catalepsy was assessed by placing both forepaws of the rat on a horizontal bar raised approximately 10 cm above the floor. The latencies required for the rats to remove their forepaws, move their hind limbs, and climb down from the bars into a normal posture was recorded with a cut-off time of 90 s.

2.5. Exposure studies

To examine the concentrations of PDM-042 and SCH23390 in the study of antagonism, blood samples were collected 30 min after the administration of PDM-042 (3 mg/kg, p.o.) and/or SCH23390 (0.1 mg/kg, s.c.), after which the brains were immediately collected from satellite animals. Blood samples were centrifuged at 2150*g* for 15 min at $4\,^{\circ}C$ to obtain plasma. Each plasma sample was centrifuged at 540*g* for 5 min at $4\,^{\circ}C$ to yield supernatants, filtrated by