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Combination of the phosphodiesterase 10A inhibitor, MR1916 with risperidone shows additive antipsychotic-like effects without affecting cognitive enhancement and cataleptic effects in rats

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Abstract

Aim: Phosphodiesterase 10A (PDE10A) inhibitors not only have antipsychotic-like effects but also cause cognitive enhancement without affecting extrapyramidal side effects in rodents, suggesting that PDE10A may be a novel approach for the treatment of schizophrenia. However, how a combination of PDE10A inhibitor with a currently available antipsychotic drug, risperidone contributes to the effect of each compound in rats remains unclear. The purpose of the present study was to examine the combination effects of MR1916 with a currently available antipsychotic drug, risperidone, in rats.

Methods: We examined the combination effects of the PDE10A inhibitor, MR1916 with risperidone on conditioned avoidance response (CAR) to assess antipsychotic-like effects in rats. We also examined them on catalepsy as extrapyramidal side effects and novel object recognition test in cognitive functions in rats.

Results: MR1916 (0.025-0.2 mg/kg, p.o.) and risperidone (0.75-6 mg/kg, p.o.) alone attenuated the CAR in a dose-dependent manner. The combination of MR1916 (0.025 mg/kg, p.o.) with risperidone (0.75 mg/kg, p.o.) significantly enhanced the attenuation of CAR without increasing the escape failure response. At the same dosage, the cataleptic effects were not enhanced by combined treatment of MR1916 with risperidone. Furthermore, the enhancement of object recognition memory induced by MR1916 (0.3 mg/kg, p.o.) was not affected by the combination with risperidone (0.75 mg/kg, p.o.).

Conclusion: The combination of MR1916 with risperidone may have additive antipsychotic-like effects without affecting extrapyramidal side effects, and the cognitive-enhancing effect of MR1916 may not be interfered with the addition of risperidone.

KEYWORDS

combination therapy, MR1916, phosphodiesterase 10A (PDE10A), risperidone, schizophrenia

1 | INTRODUCTION

Currently available antipsychotics are effective for treating positive symptoms of schizophrenia mainly based on the blockade of dopamine D_2 receptor. However, patients with chronic schizophrenia discontinue their atypical antipsychotic medications at a high rate, indicating substantial limitations in the effectiveness of current atypical antipsychotics.[1] In addition, most antipsychotics cause extrapyramidal side effects and some atypical antipsychotics elicit other adverse effects such as glucose intolerance and hyperprolactinemia at higher doses.[2–4] Thus, an alternative therapeutic approach for improving both antipsychotic and adverse effects would be beneficial for patients with schizophrenia.

PDE10A is a dual substrate PDE that hydrolyzes both cAMP and cGMP[5,6] and is highly expressed in medium spiny neurons of the striatum.[7–9] Medium spiny neurons are divided into the dopamine D_1 receptor-mediated direct pathway and the dopamine D_2 receptor-mediated indirect pathway. Because PDE10A is expressed in both direct and indirect pathways, pharmacological inhibition of PDE10A has been suggested to result in both dopamine D_2 antagonism and D_1 agonism. Recently, it has been reported that several structurally different PDE10A inhibitors had robust antipsychotic-like effects in rodents,[10–12] suggesting that their effects are related to dopamine D_2 antagonism similar to currently available antipsychotics. Notably, a few PDE10A inhibitors also showed cognitive-enhancing effects,[12,13] presumably via dopamine D_1 agonism in rodents.[12] Regarding the potential liability, a few PDE10A inhibitors have shown minimal cataleptic effects and have induced neither prolactin release nor glucose elevation,[13,14] indicating the clear differentiation from currently available antipsychotics. Recently, we identified a novel, selective, and orally active PDE10A inhibitor, MR1916 in the course of extensive chemical optimization.[15] MR1916 has potent inhibitory activities for human, rat, and monkey PDE10A with half maximal inhibitory concentration values of <0.1 nmol/L and 1000-fold selectivity against other PDEs. Additionally, MR1916 also shows good bioavailability and excellent brain penetration after oral administration in rats. Thus, MR1916 may have therapeutic potential as an adjunctive therapy by not only enhancing antipsychotic effects but also exhibiting cognitive enhancement without deteriorating extrapyramidal side effects and other adverse effects observed with currently available antipsychotics.

The purpose of the present study was to examine the combination effects of MR1916 with a currently available antipsychotic drug, risperidone, in rats. We examined the antipsychotic-like effects on the CAR, extrapyramidal side effects on catalepsy, and cognitive functions on novel object recognition test following combined treatment of the two compounds in rats.

2 | MATERIALS AND METHODS

2.1 | Animals

Male Sprague–Dawley rats (6–7 weeks old, Charles River Laboratories Japan, Inc.) and F344 rats (4–6 weeks old, Charles River Laboratories Japan, Inc) were purchased. All rats were group-housed in an air-conditioned room (room temperature; 23 ± 3°C, humidity; 55 ± 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.) and tap water. The rats were allowed to acclimatize to the facility for at least 7 days 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 guidelines from the Ministry of Health, Labor, and Welfare in Japan.

2.2 | Drugs

MR1916 was synthesized in house and used as the free base in all experiments. MR1916 and risperidone (Toronto Research Chemicals Inc.) were suspended in 0.5% methylcellulose solution (Wako Pure Chemical Industries, Ltd.) and orally administered at a volume of 5 mL/kg.

2.3 | CAR

In our preliminary experiment, male Sprague–Dawley rats did not display stable avoidance response after regular training of CAR, while male F344 rats showed stable performance on the CAR. Thus, the CAR was assessed in male F344 rats using Plexiglas shuttle boxes divided by a guillotine door into two compartments and enclosed in sound-attenuating chambers (MED Associates Inc.).

Each trial consisted of a 10-s stimulus light and tone (CS, conditioned stimulus) followed by a 0.8-mA, 10-seconds electric shock (UCS, unconditioned stimulus), which was presented through the grid floor on the side where the animal was located in the presence of the light and tone. Crossing to the opposite compartment during the 10-seconds CS was recorded as an avoidance response, crossing during the UCS was recorded as an escape, and failure to cross was recorded as an escape failure. Each session consisted of 30 CS-UCS trials separated by inter-trial intervals of a randomized duration (between 7.5 and 22.5 seconds) and was started immediately after the animal entered the left side of the box and the guillotine door was opened. The number of trials in which the animals avoided shock, escaped shock, and failed to respond was recorded by a computer program.

Regular training was continued until the rats successfully avoided the UCS. Only rats displaying stable performance (more than 80% avoidance response on three consecutive days before the test day) were considered as trained rats and were examined on the test day. To examine the effects of the test compounds, the selected rats were assigned to experimental groups based on their baseline avoidance responses. MR1916 and risperidone were administered 2 and 1 hour before the test session, respectively. The numbers of avoidances, escapes, and escape failures were recorded over 30 trials, after which the rate of each response was calculated for each treatment.

2.4 | Catalepsy

Male Sprague–Dawley rats were subjected to catalepsy tests. MR1916 and risperidone were administered 2 and 1 hour before the test, respectively. 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 hindlimbs, and climb down from the bars into a normal posture was recorded, with a cut-off time of 90 seconds.

2.5 | Novel object recognition test

The novel object recognition test was performed in male Sprague–Dawley rats using an open-field box (width, 60 cm; depth, 60 cm; height, 35 cm), which was composed of gray-colored polyvinylchloride, with the floor covered with sawdust; the box was 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 brown glass bottle (with a brown cap and 15 cm height). The two objects were placed in a symmetrical position approximately 10 cm from the wall.

One day before the acquisition trial, the rats were allowed to explore the field for 10 minutes (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 minutes. After the acquisition trial, the rat was removed from the apparatus. We used the post-acquisition administration paradigm to avoid the effect of compounds on animal behaviors in the acquisition trial. Therefore, both MR1916 and risperidone were administered immediately after the acquisition trial. Subsequently, the rat was returned to its home cage. To avoid the presence of olfactory trails, the sawdust was stirred and the objects were thoroughly cleaned with 70% ethanol after each trial.

The test trial was performed 48 hours 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 minutes. Both transparent and brown glass bottles were assigned as a novel object, and all combinations and locations of objects were used in a balanced manner among treatment groups in order to eliminate 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 the test trials. Recorded video clips were analyzed off-line 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 an object was not considered as exploration. To analyze 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 was expressed as a percentage. Exclusion criteria were as follows: (a) any rats spending a total exploration time of <10 seconds in either the acquisition or the test trial; and (b) any rats spending an exploration time of <1 second for one of the two objects in either the acquisition or the test trial.

2.6 | Exposure studies

To examine the concentrations of MR1916 and risperidone used in the combination study on CAR, blood samples were collected 2 and 1 hour after the administration of MR1916 (0.025 mg/kg, p.o.) and/or risperidone (0.75 mg/kg, p.o.), after which the brains were immediately collected from satellite F344 rats. Blood samples were centrifuged at 2150 *g* for 15 minutes at 4°C to obtain the plasma. Each plasma sample was centrifuged at 540 *g* for 5 minutes at 4°C to obtain the supernatants, which were filtrated through a MultiScreen® $_{HTS}$, GV (Millipore Corp), and analyzed by liquid chromatography with tandem mass spectrometry (LC-MS/MS). The collected brain samples were homogenized with a 5-fold volume of H_2O using a Precellys24 (Bertin Technologies SAS). The internal standard was added, and the homogenates were centrifuged at 2150 *g* for 5 minutes at 4°C to obtain the supernatants, which were analyzed by LC-MS/MS. Pharmacokinetic parameters were calculated via noncompartmental analysis using WinNolin, version 6.2 (Pharsight).

2.7 | Statistical analysis

The effects of the test compounds were analyzed by Bonferroni's test in the combination study on CAR and catalepsy test, while the effect of MR1916 or risperidone alone in the CAR was analyzed by nonparametric Steel's test. A probability level of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Combination effects of MR1916 with risperidone on CAR in rats

MR1916 or risperidone alone attenuated the CAR in a dose-dependent manner and showed significant effects at doses from 0.05 to 0.2 mg/kg and from 0.75 to 6 mg/kg, respectively (Figure 1A,B). In the combination study, we selected doses of 0.025 mg/kg (MR1916) and 0.75 mg/kg (risperidone) to enable detection of the potentiated effect of combining the two compounds. The combination of MR1916 and risperidone significantly enhanced the attenuation of the CAR compared with that of each compound alone without increasing the escape failure response (Figure 1C). Furthermore, the plasma and brain concentrations of each compound were not affected by the combination of MR1916 with risperidone (Table 1).

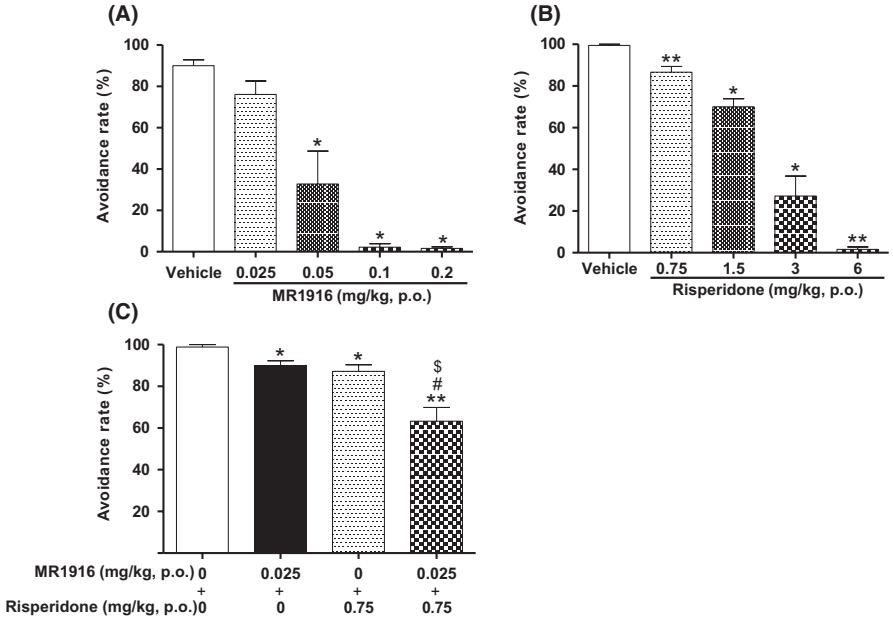

FIGURE 1 Effects of MR1916 (A), risperidone (B), and MR1916 plus risperidone (C) on the CAR in rats. MR1916 (0.025-0.2 mg/kg, p.o.) or risperidone (0.75-6 mg/kg, p.o.) was administered 2 or 1 hour before the test session, respectively. In the combination study, MR1916 (0.025 mg/kg, p.o.) and risperidone (0.75 mg/kg, p.o.) were administered 2 and 1 hour, respectively, before the test session. Data are expressed as mean ± SEM of 6 animals. Asterisks represent a significant difference from the vehicle-treated group, $^{*}P < .05$, $^{**}P < .01$ (Steel's test (A and B), and Bonferroni's test (C)). Sharps represent a significant difference from the MR1916 + vehicle-treated group, $^{\#}P < .05$ (Bonferroni's test). Dollars represent a significant difference from the vehicle + risperidone-treated group, $^{\$}P < .05$ (Bonferroni's test)

TABLE 1 Plasma and brain concentrations of MR1916 and risperidone in the CAR

Group	Drug	Plasma (ng/mL)	Brain (ng/g)
Vehicle + Risperidone	Risperidone (0.75 mg/kg, p.o.)	2.7 ± 0.2	6.0 ± 0.9
MR1916 + Vehicle	MR1916 (0.025 mg/kg, p.o.)	2.6 ± 0.4	12 ± 1.7
MR1916 + Risperidone	Risperidone (0.75 mg/kg, p.o.)	3.2 ± 0.6	5.9 ± 0.5
	MR1916 (0.025 mg/kg, p.o.)	2.6	11

Note: Data are expressed as mean ± SD of three animals. Because the plasma concentration of MR1916 in one sample from MR1916 + Risperidone group was below its detection limit (2 ng/mL), the data are expressed as mean of 2 animals.

3.2 | Combination effects of MR1916 with risperidone on catalepsy test in rats

We examined the combination effects of MR1916 with risperidone on catalepsy in rats. Neither MR1916 (0.025 mg/kg, p.o.) nor risperidone (0.75 mg/kg, p.o.) alone induced significant catalepsy. Furthermore, neither cataleptic effect was potentiated by the combination of MR1916 and risperidone at the same dosage (Table 2).

3.3 | Combination effects of MR1916 with risperidone on object recognition memory in rats

When the test trial was performed 48 hours after the acquisition trial, vehicle-treated rats exhibited no preference for the novel object. This finding indicates that the rats in the vehicle-treated group did not distinguish the novel object from the familiar one. Under this experimental condition, MR1916 (0.3 mg/kg, p.o.) alone significantly increased object recognition memory, while risperidone (0.75 mg/kg, p.o.) alone did not increase this response (Figure 2). In the combination study, risperidone did not affect the enhancement of object recognition memory induced by MR1916 (Figure 2). There were no significant differences in the total approach time in either the acquisition or the test trials among all tested groups (data not shown).

4 | DISCUSSION

In the present study, we found that a combination of the PDE10A inhibitor, MR1916 with risperidone additively enhanced the attenuation of CAR without increasing cataleptic effects. Additionally, the enhancement in object recognition memory induced by MR1916 was not affected by the combination with risperidone. These results

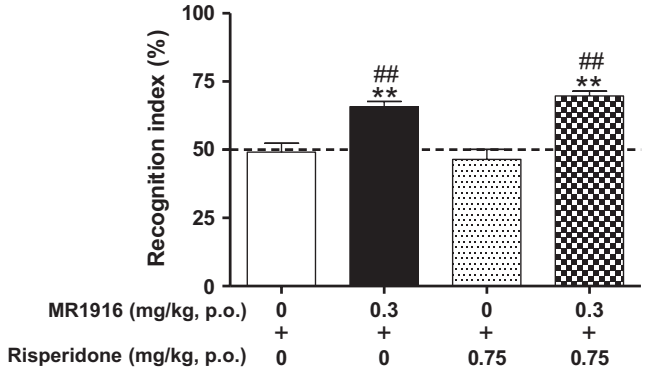

FIGURE 2 Combination effects of MR1916 with risperidone on novel object recognition test in rats. MR1916 (0.3 mg/kg, p.o.) and risperidone (0.75 mg/kg, p.o.) were administered immediately after the acquisition trial. Data are expressed as mean ± SEM of 10-14 animals. Asterisks represent a significant difference from the vehicle + vehicle-treated group, $^{**}P < .01$ (Bonferroni's test). Sharps represent a significant difference from the vehicle + risperidone-treated group, $^{\#\#}P < .01$ (Bonferroni's test)

indicate that combining MR1916 and risperidone additively enhances antipsychotic-like effects without affecting extrapyramidal side effects and that the cognitive-enhancing effect of MR1916 is maintained by addition of risperidone.

It is well known that current antipsychotics specifically suppress the avoidance response in rodents, suggesting that the avoidance response in rats is applicable in evaluating the clinical efficacies of antipsychotic drugs.[16] Therefore, the CAR is considered as a high predictive animal test to evaluate the potential antipsychotic properties.[17] MR1916 and risperidone alone attenuated the CAR in a dose-dependent manner. Combination of subeffective dose of MR1916 (0.025 mg/kg) with risperidone (0.75 mg/kg) significantly enhanced the attenuation of the CAR compared with that of each compound alone without increasing the escape failure response. Additionally, both plasma and brain concentrations of each compound were not affected by the combination of MR1916 with risperidone. For extrapyramidal side effects, we previously examined the cataleptic response of MR1916 or risperidone alone. Neither MR1916 nor risperidone induced the significant cataleptic effect at the same dosage on the CAR, while both compounds significantly enhanced cataleptic effect at much higher doses than the tested one. In this condition, the combination of MR1916 with risperidone did not enhance its cataleptic effect of each compound. These results suggest that the additive antipsychotic-like effect caused by the combination of MR1916 with risperidone is a specific pharmacological effect without potentiation of behavioral suppression and/or drug-drug interactions in the pharmacokinetics of these compounds at the tested doses. In the present study, we used Sprague–Dawley rats for catalepsy and F344 rats for CAR. Therefore, our findings cannot rule out the influence of strain difference of rats. However, because the combination of MR1916 and risperidone enhanced neither escape failure response on the CAR nor catalepsy at the same dosage, we suggest that the combination of MR1916 and risperidone at the tested doses did not affect the motor functions in both

TABLE 2 Combination effects of MR1916 and risperidone on catalepsy

Group	Duration (s)
Vehicle + Vehicle	0.67 ± 0.12
MR1916 (0.025 mg/kg, p.o.) + Vehicle	1.5 ± 0.7
Vehicle + Risperidone (0.75 mg/kg, p.o.)	1.9 ± 1.4
MR1916 (0.025 mg/kg, p.o.) + Risperidone (0.75 mg/kg, p.o.)	1.4 ± 0.8

Note: Data are expressed as mean ± SEM of 7 animals.

Sprague–Dawley and F344 rats. Therefore, it is reasonable to suppose that the combination effects of MR1916 with risperidone were due to the additive pharmacological effects rather than the strain difference of rats. Although we used the CAR in an animal model to predict the antipsychotic-like effect of the test compound, hyperlocomotion caused by psychotic agents such as methamphetamine and MK-801 is also frequently used. Another structurally different PDE10A inhibitor, TAK-063 significantly enhanced hyperlocomotion without affecting cataleptic effects when co-administered with the currently available antipsychotic drug, haloperidol or olanzapine in rats.[18] Taken together this previous report and our present findings, combining the PDE10A inhibitor with currently available antipsychotic drug may enhance antipsychotic-like effects without affecting extrapyramidal side effects in rats.

Cognitive deficits associated with schizophrenia are the core symptoms of the disease, correlate with functional outcome and are not effectively treated with current antipsychotic therapies.[19] The novel object recognition test is based on the spontaneous tendency of rodents to explore novelty without positive or negative reinforcement.[20] We selected this test to examine the cognitive enhancing effects of MR1916, as this test was described by the Measurement and Treatment Research to Improve Cognition in Schizophrenia as an animal model relevant to visual learning and memory domain impairment in patients with schizophrenia.[19] Previously, we found that MR1916 enhanced object recognition memory in a dose-dependent manner from 0.03 to 0.3 mg/kg, with nearly maximal effects observed at a dose of 0.3 mg/kg (data not shown). MR1916 also exhibited approximately full PDE10A occupancy in the striatum of rats at a dose of 0.3 mg/kg (data not shown). Therefore, we selected a dose of 0.3 mg/kg to examine whether the cognitive-enhancing effect of MR1916 was decreased by the combination with risperidone. The increase in object recognition memory induced by MR1916 (0.3 mg/kg, p.o.) was not affected by the combination with risperidone (0.75 mg/kg, p.o.). Notably, object exploration behavior did not differ among all treated groups in both the acquisition and the test trials, indicating that MR1916 specifically enhances object recognition memory, which was not affected by the combination with risperidone. However, further combination studies at subeffective doses of each compound are needed to determine whether the combination of MR1916 with risperidone exhibits additive or synergistic effects.

In summary, we demonstrated that the combination of MR1916 with risperidone showed the additive antipsychotic-like effects

without affecting catalepsy. Furthermore, the cognitive-enhancing effect induced by MR1916 was not affected by addition of risperidone. These findings suggest that combination therapy using a PDE10A inhibitor with currently available antipsychotics is an alternative approach for enhancing antipsychotic-like effects and having cognitive enhancing effects without affecting extrapyramidal side effects in the treatment of schizophrenia.

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CONFLICT OF INTEREST

All authors are employees of Mochida Pharmaceutical Co., Ltd.

AUTHOR CONTRIBUTIONS

KA and SM designed the research. KA performed the research, analyzed data, and wrote the manuscript. SM read and approved the manuscript.

DATA REPOSITORY

The data that support the findings of this study are available in the Tables S1–S4 of this article.

ANIMAL STUDIES

All experimental procedures were approved by the Institutional Animal Care and Use Committee complied of Mochida Pharmaceutical Co., Ltd.

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REFERENCES

1. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209–23.
2. Dunlop BW, Sternberg M, Phillips LS, Andersen J, Duncan E. Disturbed glucose metabolism among patients taking olanzapine and typical antipsychotics. Psychopharmacol Bull. 2003;37:99–117.
3. Krebs M, Leopold K, Hinzpeter A, Schaefer M. Current schizophrenia drugs: efficacy and side effects. Expert Opin Pharmacother. 2006;7:1005–16.
4. Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs. 2014;28:421–53.
5. Loughney K, Snyder PB, Uher L, Rosman GJ, Ferguson K, Florio VA. Isolation and characterization of PDE10A, a novel human 3', 5'-cyclic nucleotide phosphodiesterase. Gene. 1999;234:109–17.
6. Soderling SH, Bayuga SJ, Beavo JA. Isolation and characterization of a dual-substrate phosphodiesterase gene family: PDE10A. Proc Natl Acad Sci USA. 1999;96:7071–6.
7. Fujishige K, Kotera J, Omori K. Striatum- and testis-specific phosphodiesterase PDE10A isolation and characterization of a rat PDE10A. Eur J Biochem. 1999;266:1118–27.
8. Seeger TF, Bartlett B, Coskran TM, Culp JS, James LC, Krull DL, et al. Immunohistochemical localization of PDE10A in the rat brain. Brain Res. 2003;985:113–26.
9. Coskran TM, Morton D, Menniti FS, Adamowicz WO, Kleiman RJ, Ryan AM, et al. Immunohistochemical localization of phosphodiesterase 10A in multiple mammalian species. J Histochem Cytochem. 2006;54:1205–13.
10. Grauer SM, Pulito VL, Navarra RL, Kelly MP, Kelley C, Graf R, et al. Phosphodiesterase 10A inhibitor activity in preclinical models of the positive, cognitive, and negative symptoms of schizophrenia. J Pharmacol Exp Ther. 2009;331:574–90.
11. Suzuki K, Harada A, Shiraishi E, Kimura H. In vivo pharmacological characterization of TAK-063, a potent and selective phosphodiesterase 10A inhibitor with antipsychotic-like activity in rodents. J Pharmacol Exp Ther. 2015;352:471–9.
12. Arakawa K, Maehara S, Yuge N, Ishikawa M, Miyazaki Y, Naba H, et al. Pharmacological characterization of a novel potent, selective, and orally active phosphodiesterase 10A inhibitor, PDM-042 [(E)-4-(2-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)vinyl)-6-(pyrrolidin-1-yl)pyrimidin-4-yl)morpholine] in rats: potential for the treatment of schizophrenia. Pharmacol Res Perspect. 2016;4:e00241.
13. Shiraishi E, Suzuki K, Harada A, Suzuki N, Kimura H. The phosphodiesterase 10A selective inhibitor TAK-063 improves cognitive functions associated with schizophrenia in rodent models. J Pharmacol Exp Ther. 2016;356:587–95.
14. Arakawa K, Nakao K, Maehara S. Dopamine D_1 signaling involvement in the effects of the phosphodiesterase 10A inhibitor, PDM-042 on cognitive function and extrapyramidal side effect in rats. Behav Brain Res. 2017;15:204–9.
15. Beck G, Maehara S, Chang PL, Papa SM. A selective phosphodiesterase 10A inhibitor reduces L-Dopa-induced dyskinesias in Parkinsonian monkeys. Mov Disord. 2018;33:805–14.
16. Kuribara H, Tadokoro S. Correlation between antiavoidance activities of antipsychotic drugs in rats and daily clinical doses. Pharmacol Biochem Behav. 1981;14:181–92.
17. Wadenberg ML, Hicks PB. The conditioned avoidance response test re-evaluated: is it a sensitive test for the detection of potentially atypical antipsychotics? Neurosci Biobehav Rev. 1999;23:851–62.
18. Suzuki K, Harada A, Suzuki H, Capuani C, Ugolini A, Corsi M, et al. Combined treatment with a selective PDE10A inhibitor TAK-063 and either haloperidol or olanzapine at subeffective doses produces potent antipsychotic-like effects without affecting plasma prolactin levels and cataleptic responses in rodents. Pharmacol Res Perspect. 2018;6:e00372.
19. Young JW, Powell SB, Risbrough V, Marston HM, Geyer MA. Using the MATRICS to guide development of a preclinical cognitive test battery for research in schizophrenia. Pharmacol Ther. 2009;120:150–202.
20. Ennaceur A, Delacour J. A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. Behav Brain Res. 1988;31:47–59.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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