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Effects of σ_1 receptor ligand MS-377 on D_2 antagonists-induced behaviors

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Abstract

(*R*)-(+)-1-(4-Chlorophenyl)-3-[4-(2-methoxyethyl)piperazin-1-yl]methyl-2-pyrrolidinone L-tartrate (MS-377) is a novel antipsychotic agent with selective and high affinity for σ_1 receptor. The present study was carried out to clarify the interaction of MS-377 with dopamine D_2 receptor antagonists (D_2 antagonists) in concurrent administration, and then the involvement of σ receptors in the interaction. The effects of MS-377 on haloperidol- or sultopride-induced inhibition of apomorphine-induced climbing behavior and catalepsy were investigated in mice and rats, respectively. In addition, the effects of (+)-SKF-10,047 and SA4503, both of which are σ receptor agonists, and WAY-100,635, which is a 5-HT_{1A} receptor antagonist, on the interaction due to the concurrent use were also investigated. MS-377 potentiated the inhibitory effects of haloperidol or sultopride on apomorphine-induced climbing behavior in a dose-dependent manner. In contrast, MS-377 did not affect the catalepsy induction by these drugs. The potentiation of the inhibitory effects of haloperidol or sultopride on apomorphine-induced climbing behavior by MS-377 was not inhibited by WAY-100,635, but was inhibited by (+)-SKF-10,047 and SA4503. These findings showed that MS-377 potentiates the efficacy of D_2 antagonists, but it does not deteriorate the adverse effect. Moreover, σ_1 receptors are involved in this potentiation of the efficacy of D_2 antagonists by MS-377.

Keywords: σ receptor; D_2 antagonist; MS-377; Haloperidol; Sultopride

1. Introduction

Dopamine D_2 receptor antagonists (D_2 antagonists) are the major therapeutic agents for the treatment of schizophrenia. However, these D_2 antagonists are insufficiently effective in improving negative symptoms and also induce clinically troublesome adverse events such as dystonia, parkinsonism, akathisia, tardive dyskinesia, and other extrapyramidal side-effects (EPS) (Seeman, 1980; Tarsey, 1983; Ellenbroek, 1993). Thus, much effort has been made to search for a novel antipsychotic agent that is effective for negative symptoms without developing EPS. Recently, several new agents have been developed to solve these problems, such as serotonin–dopamine antagonists (SDA) and multiacting receptor-targeted agent (MARTA). These agents have been reported (Tran et al., 1997; Meltzer et al., 1994) to be relatively effective for the treatment of negative symptoms of schizophrenia with less EPS than typical antipsychotic agents, although they still induce EPS. σ receptor ligands are one of the candidates for such new agents. Some antipsychotic agents such as haloperidol, perphenazine, and chlorpromazine, which are D_2 antagonists, also have affinities for σ receptors (Tam and Cook, 1984; Snyder and Largent, 1989; Quirion et al., 1992). In fact, several σ receptor ligands have been shown to have some efficacy in humans and have no EPS (Modell et al., 1996; Friebose et al., 1997).

(*R*)-(+)-1-(4-Chlorophenyl)-3-[4-(2-methoxyethyl)piperazin-1-yl]methyl-2-pyrrolidinone L-tartrate (MS-377) is a novel antipsychotic agent with selective and high affinity for σ_1 receptors (Karasawa et al., 2000). MS-377 has unique pharmacological profiles: anti-phencyclidine, anti-dopaminergic, and anti-serotonergic effects without inducing catalepsy in vivo (Takahashi et al., 1999). Thus, MS-377 is expected to be useful for treatment for general schizophrenia symptoms without developing EPS. Moreover, MS-377 has recently been shown to attenuate the development of methamphetamine-induced behavioral sensitization (Takahashi et al., 2000), for which inhibition of recurrence and recrudescence of schizophrenia is expected, and it is very likely to be useful for maintenance therapy. When used for maintenance therapy, it may be used in a combination with the current

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antipsychotic agents, especially with D_2 antagonists. In the present study, to clarify the interaction of MS-377 with D_2 antagonists, we investigated the effects of MS-377 on haloperidol- or sultopride-induced inhibition of apomorphine-induced climbing behavior and catalepsy in mice and rats, respectively. In addition, the involvement of σ receptors in the interaction was also investigated.

2. Materials and methods

2.1. Subjects

Five-week-old male ddY mice (body weight: 22–33 g) (Japan SLC) and eight-week-old male Wistar rats (body weight: 250–300 g) (Japan SLC) were used. Animals were maintained under a 12-h lighting cycle with food and water ad libitum. Animals were placed in the experimental room at least 1 h before the behavioral tests. This study was conducted in conformity with the guidelines for animal studies of the Institute of Biological Science, Mitsui Pharmaceuticals, and the protocol was approved by the internal committee for animal study.

2.2. Drugs

MS-377 and SA4503 were synthesized by Mitsui Chemicals (Chiba, Japan). Sultopride was synthesized by Mitsui Pharmaceuticals (Chiba, Japan). Haloperidol and apomorphine were purchased from Sigma (St. Louis, MO). (+)-SKF-10,047 and WAY-100,635 were purchased from Research Biochemical International (Natick, MA). MS-377, sultopride, (+)-SKF-10,047, SA4503, and WAY-100,635 were dissolved in saline, haloperidol was dissolved in 0.3% tartaric acid (pH 2.4), and apomorphine was dissolved in 0.1% metabisulfite (pH 2.2). All drugs were administered to rats and mice at a volume of 1 and 10 ml/kg body weight, respectively.

2.3. Procedure

2.3.1. Effect on apomorphine-induced climbing behavior in mice

According to the Gerhardt method (Gerhardt et al., 1985), mice were individually kept in metal mesh circular cylinders (diameter: 12 cm, height: 14 cm), and the time of climbing the wall (time during which all four limbs were off the floor) was measured. Haloperidol (0.23 mg/kg) or sultopride (6.2 mg/kg) was orally administered 10 min after oral administration of MS-377 (0.1–3 mg/kg) and apomorphine (3 mg/kg) was subcutaneously administered 60 min later. The control group received an appropriate vehicle (equivalent for each test substance). The time of climbing behavior was measured for 2 min from 20 min after apomorphine administration. Ten mice per group were used in this study. The dosages of haloperidol and sultopride used were the ED_{50} for inhibition of apomorphine-induced climbing behavior (Takahashi et al., 1999).

2.3.2. Effect on the induction of catalepsy in rats

Rats were forced to hang the forelegs on a 3 mm diameter iron bar at a 10 cm level at 1, 2, 3, and 6 h after oral administration of the test drug, and immobility time was measured for a maximum of 210 s. Duration of immobility was scored every 30 s (score 1–7), and more than 211 s was defined to be score 8. Haloperidol (0.9 mg/kg) or sultopride (34.5 mg/kg) was orally administered 10 min after oral administration of MS-377 (1–10 mg/kg), and catalepsy was measured after 1, 2, 3, and 6 h. The greatest catalepsy score measured at 6 h after administration was regarded as the maximum score in each animal. Six rats per group were used in this study. The dosages of haloperidol and sultopride used were the ED_{50} for induction of catalepsy (Takahashi et al., 1999).

2.3.3. Effects of (+)-SKF-10,047, SA4503, and WAY-100,635 on enhanced efficacy of D_2 antagonists by MS-377 in mice

(+)-SKF-10,047 (1 mg/kg), SA4503 (0.3 mg/kg), or WAY-100,635 (1 mg/kg) was intraperitoneally administered, and MS-377 (3 mg/kg) was orally administered 10 min later. Haloperidol (0.23 mg/kg) or sultopride (6.2 mg/kg) was orally administered 10 min after administration of MS-377, and apomorphine was subcutaneously administered 60 min later. The control group received an appropriate vehicle (equivalent for each test substance). The climbing time was measured for 2 min from 20 min after apomorphine administration. Ten mice per group were used in this study. The dosages of (+)-SKF-10,047, SA4503, and WAY-100,635 were the pharmacological effective dosages (Patel and Hutson, 1996; Zou et al., 1998).

2.4. Statistical analysis

Bartlett test and Kruskal–Wallis test were first used to check the statistical tendency of experimental data. When significant differences were observed among the groups, data were then examined post hoc by the nonparametric Steel's test or Mann–Whitney test (for comparison between two groups). In all comparisons $P < 0.05$ was regarded as significant.

3. Results

3.1. Effect of MS-377 on the inhibitory effects of D_2 antagonists on apomorphine-induced climbing behavior in mice

The time of climbing behavior of the control group was 101.3 ± 4.2 s (mean ± SEM, $N = 10$, the same below). In the groups treated with MS-377 (3 mg/kg) alone and haloperidol

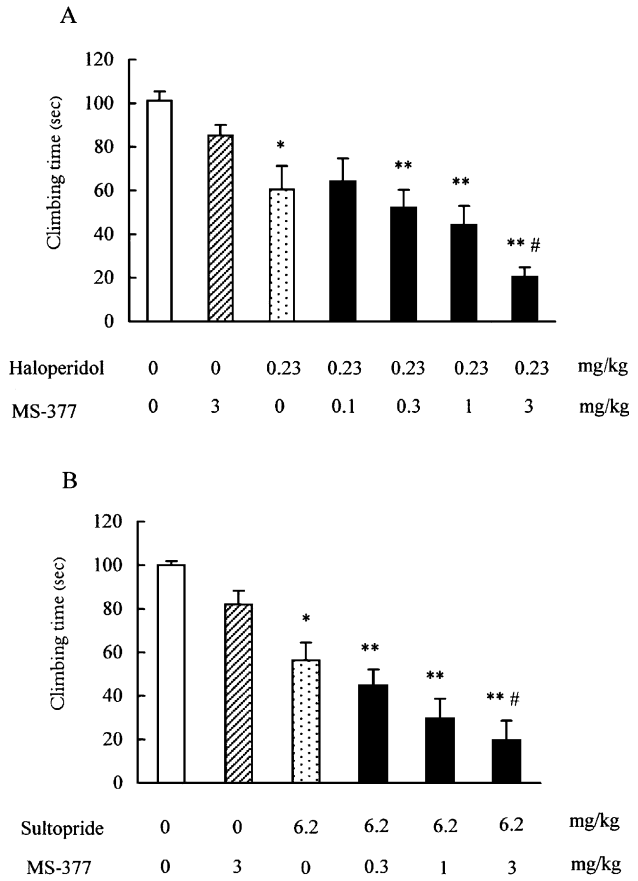

Fig. 1. Effect of MS-377 on the inhibitory effects of haloperidol (A) and sultopride (B) on apomorphine-induced climbing behavior. Haloperidol (0.23 mg/kg) or sultopride (6.2 mg/kg) was orally administered 10 min after oral administration of MS-377 (0.1–3 mg/kg), and apomorphine (3 mg/kg) was subcutaneously administered 60 min later. Each value represents the mean ± SEM of 10 mice. * $P<.05$, ** $P<.01$ compared with the vehicle alone group (Steel's test). $^{\#}P<.05$ compared with the haloperidol or sultopride alone group (Steel's test).

(0.23 mg/kg) alone, the time was 85.2 ± 5.0 and 60.6 ± 10.8 s, respectively, and the inhibition rates compared with the control group were 15.9% and 40.2%, respectively. When 0.1, 0.3, 1, and 3 mg/kg of MS-377 was concurrently administered, the inhibition rates were 36.7%, 48.7%, 56.5%, and 80.0%, respectively, showing that MS-377 potentiated the inhibitory effect of haloperidol on apomorphine-induced climbing behavior in a dose-dependent manner. A significant difference was observed in the inhibition between the group

Table 1
Effect of MS-377 on haloperidol- and sultopride-induced catalepsy

Treatment (mg/kg)	Maximal score
Haloperidol (0.9) + vehicle	4.3 ± 0.4
Haloperidol (0.9) + MS-377 (1)	4.3 ± 0.4
Haloperidol (0.9) + MS-377 (3)	4.5 ± 0.8
Haloperidol (0.9) + MS-377 (10)	4.3 ± 0.4
Sultopride (34.5) + Vehicle	5.0 ± 0.7
Sultopride (34.5) + MS-377 (1)	4.5 ± 0.5
Sultopride (34.5) + MS-377 (3)	5.3 ± 0.4
Sultopride (34.5) + MS-377 (10)	4.0 ± 0.6
Vehicle + MS-377 (100)	0

Haloperidol (0.9 mg/kg) or sultopride (34.5 mg/kg) was orally administered 10 min after oral administration of MS-377 (1–10 mg/kg), and catalepsy was measured after 1, 2, 3, and 6 h, and scored. Each value represents the mean ± SEM of six rats. There were no significant differences in the maximal score in catalepsy among these groups (Kruskal–Wallis test).

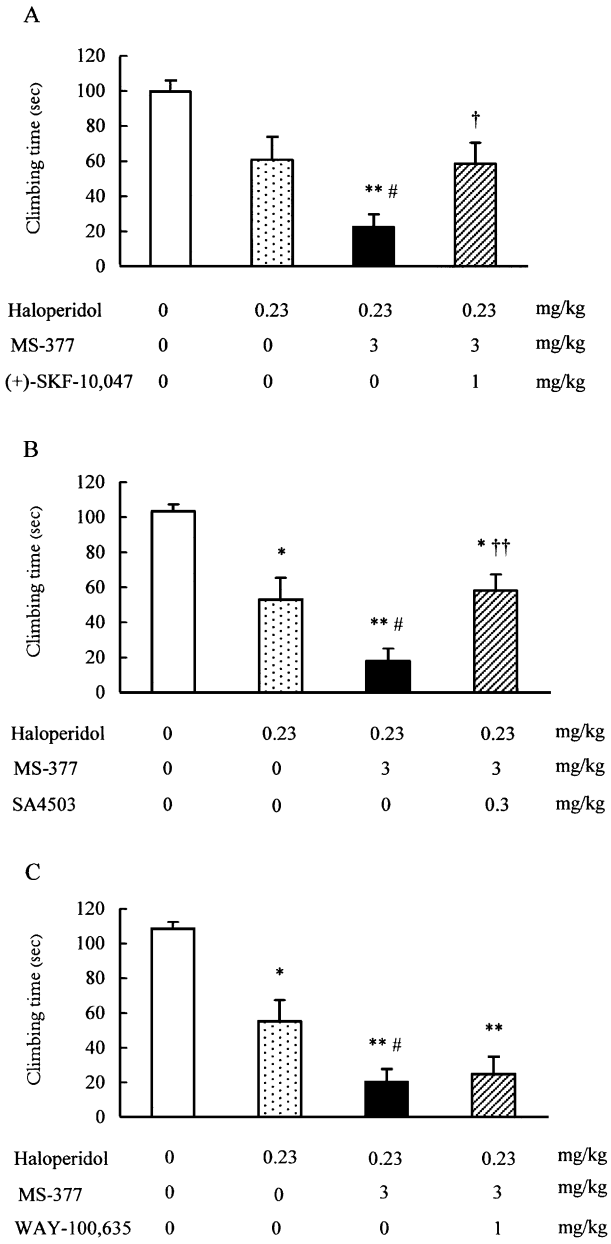

Fig. 2. Effects of (+)-SKF-10,047, SA4503, and WAY-100,635 on MS-377-induced potentiation of inhibitory effects of haloperidol on apomorphine-induced climbing. (+)-SKF-10,047 (1 mg/kg), SA4503 (0.3 mg/kg), or WAY-100,635 (1 mg/kg) was intraperitoneally administered, and MS-377 (3 mg/kg) was orally administered 10 min later. Haloperidol (0.23 mg/kg) was orally administered 10 min after administration of MS-377, and apomorphine was subcutaneously administered 60 min later. Each value represents the mean ± SEM of 10 mice. * $P<.05$, ** $P<.01$ compared with the vehicle alone group (Steel's test). $^{\#}P<.05$ compared with the haloperidol alone group (Mann–Whitney test). $^{\dagger}P<.05$, $^{\dagger\dagger}P<.01$ compared with the haloperidol plus MS-377-treated group (Mann–Whitney test).

treated with haloperidol alone and the group treated with a combination of MS-377 (3 mg/kg) and haloperidol ($P < .05$ by Steel's test) (Fig. 1A). Similarly, MS-377 (0.3–3 mg/kg) potentiated the inhibitory effect of sultopride (6.2 mg/kg) on apomorphine-induced climbing behavior in a dose-dependent manner. A significant difference was observed in the inhibition between the group treated with sultopride alone and the group treated with a combination of MS-377 (3 mg/kg) and sultopride ($P < .05$ by Steel's test) (Fig. 1B).

3.2. Effect of MS-377 on D_2 antagonists-induced catalepsy in rats

The results are shown in Table 1. The maximum catalepsy score in the group treated with haloperidol alone (0.9 mg/kg) was 4.3 ± 0.4 (mean ± SEM, $N = 6$, the same below). When 1, 3, and 10 mg/kg of MS-377 was concurrently administered, the maximum scores were 4.3 ± 0.4, 4.5 ± 0.8, and 4.3 ± 0.4, respectively, showing that MS-377 did not significantly affect the haloperidol-induced catalepsy. Similarly, MS-377 (1–10 mg/kg) did not significantly affect the sultopride (34.5 mg/kg)-induced catalepsy. MS-377 (100 mg/kg) did not induce catalepsy.

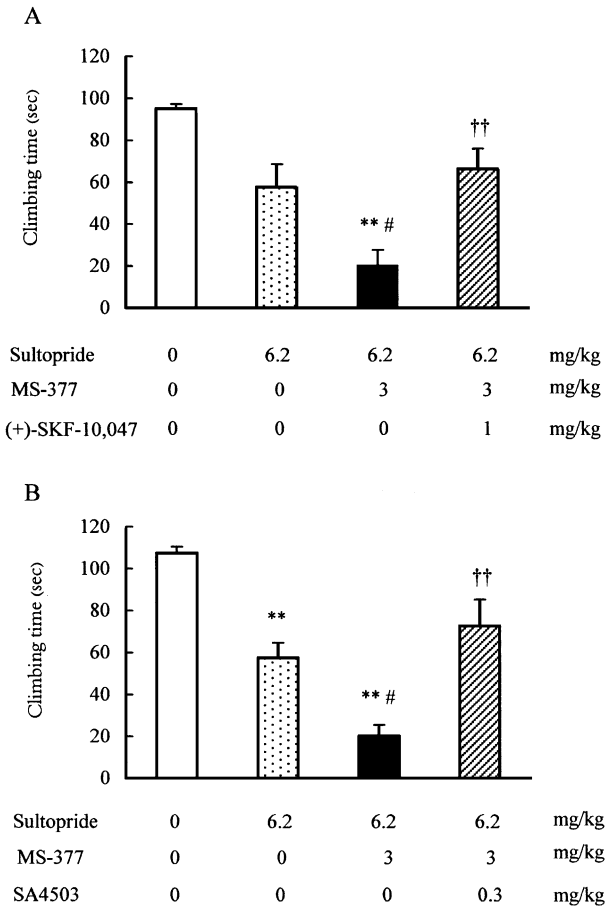

Fig. 3. Effects of (+)-SKF-10,047 and SA4503 on MS-377-induced potentiation of inhibitory effects of sultopride on apomorphine-induced climbing. (+)-SKF-10,047 (1 mg/kg) or SA4503 (0.3 mg/kg) was intraperitoneally administered, and MS-377 (3 mg/kg) was orally administered 10 min later. Sultopride (6.2 mg/kg) was orally administered 10 min after administration of MS-377, and apomorphine was subcutaneously administered 60 min later. Each value represents the mean ± SEM of 10 mice. $^{**}P < .01$ compared with the vehicle alone group (Steel's test). $^{\#}P < .05$, $^{\#\#}P < .01$ compared with the sultopride alone group (Mann–Whitney test). $^{\dagger\dagger}P < .01$ compared with the sultopride plus MS-377-treated group (Mann–Whitney test).

Table 2
Effects of (+)-SKF-10,047 and SA4503 on the apomorphine-induced climbing behavior

Treatment	Dose (mg/kg)	Climbing time (s)	Inhibition (%)
Vehicle	–	99.0 ± 6.7	–
(+)-SKF-10,047	1	102.3 ± 4.9	3.5
SA4503	0.3	95.5 ± 3.7	– 3.3

(+)-SKF-10,047 (1 mg/kg) or SA4503 (0.3 mg/kg) was intraperitoneally administered, and apomorphine was subcutaneously administered 60 min later. Each value represents the mean ± SEM of 10 mice. There were no significant differences among these groups (Kruskal–Wallis test).

3.3. Effects of (+)-SKF-10,047, SA4503, and WAY-100,635 on enhanced efficacy of D_2 antagonists by MS-377 in mice

The time of apomorphine-induced climbing behavior in the group treated with haloperidol alone (0.23 mg/kg) and the group treated with a combination of haloperidol and MS-377 (3 mg/kg) was 60.8 ± 13.0 (mean ± SEM, $N = 10$, the same below) and 22.6 ± 7.2 s, respectively, and the inhibition rates compared with the control group (99.5 ± 6.4 s) were 38.9% and 77.3%, respectively, showing that MS-377 significantly potentiated the inhibitory effect of haloperidol on apomorphine-induced climbing behavior. When the group treated with a combination of haloperidol and MS-377 was pretreated with 1 mg/kg of (+)-SKF-10,047, the time of apomorphine-induced climbing was 58.6 ± 12.0 s, showing that (+)-SKF-10,047 inhibited the MS-377-induced potentiation of the inhibitory effect of haloperidol on apomorphine-induced climbing behavior. Similarly, SA4503 (0.3 mg/kg) inhibited the MS-377-induced potentiation of the inhibitory effect of haloperidol

Table 3
Effects of (+)-SKF-10,047 and SA4503 on the inhibitory effects of haloperidol and sultopride on apomorphine-induced climbing behavior

Treatment (mg/kg)	Climbing time (s)	Inhibition (%)
Vehicle + vehicle	106.1 ± 6.7	–
Haloperidol (0.23) + vehicle	56.7 ± 12.5**	46.6
Haloperidol (0.23)+(+)-SKF-10,047 (1)	53.8 ± 10.8**	49.3
Haloperidol (0.23) + SA4503 (0.3)	51.0 ± 7.2**	51.9
Vehicle + vehicle	105.5 ± 3.1	–
Sultopride (6.2) + vehicle	56.0 ± 8.5**	46.9
Sultopride (6.2)+(+)-SKF-10,047 (1)	56.6 ± 7.9**	46.4
Sultopride (6.2) + SA4503 (0.3)	48.9 ± 12.1**	53.6

Haloperidol (0.23 mg/kg) or sultopride (6.2 mg/kg) was orally administered 10 min after oral administration of (+)-SKF-10,047 (1 mg/kg) or SA4503 (0.3 mg/kg), and apomorphine (3 mg/kg) was subcutaneously administered 60 min later. Each value represents the mean ± SEM of 10 mice.

** $P < .01$ compared with the vehicle alone group (Steel's test).

on apomorphine-induced climbing behavior (Fig. 2A,B). The potentiation by MS-377 was not inhibited by WAY-100,635 (1 mg/kg) (Fig. 2C). Similarly, MS-377 (3 mg/kg) significantly potentiated the inhibitory effect of sultopride (6.2 mg/kg) on apomorphine-induced climbing behavior, and the potentiation was inhibited by (+)-SKF-10,047 (1 mg/kg) and SA4503 (0.3 mg/kg) (Fig. 3). Administration of (+)-SKF-10,047 (1 mg/kg) alone and SA4503 (0.3 mg/kg) alone did not significantly affect the apomorphine-induced climbing behavior (Table 2), nor did they affect the inhibitory effect of haloperidol or sultopride on the apomorphine-induced climbing behavior (Table 3).

4. Discussion

MS-377 was synthesized to show a high affinity for σ_1 receptor without affinities for dopamine receptors. In the present study, we demonstrated that MS-377 potentiated the inhibitory effects of haloperidol and sultopride on apomorphine-induced climbing behavior in a dose-dependent manner at doses in which MS-377 alone showed no significant effect, while it did not affect catalepsy induced by each drug alone. Apomorphine-induced climbing behavior is induced via the A10 dopaminergic system (Costall et al., 1980), and widely used as an efficacy evaluation system of antipsychotic agents. Catalepsy is induced via the A9 dopaminergic system (Sanberg, 1980), and widely used as an evaluation system of EPS. Therefore, it was clarified that MS-377 inhibits the A10 dopaminergic system involved in the effect of antipsychotic agents, but it does not affect the A9 dopaminergic system. These findings are consistent with the results of a previous study, in which MS-377 (at a higher dose than that in the present study) inhibited apomorphine-induced climbing behavior, but did not induce catalepsy (Takahashi et al., 1999). Therefore, it was shown that MS-377 potentiates the efficacy of D_2 antagonists without deteriorating the EPS, suggesting that MS-377 may increase the therapeutic window of D_2 antagonists when used in combination with D_2 antagonists, and may become an antipsychotic agent administrable in combination with D_2 antagonists.

Since MS-377 potentiated not only the inhibitory effect of haloperidol, which has affinity for σ receptors in addition to dopamine D_2 receptor (Quirion et al., 1992), but also the inhibitory effect of sultopride, which is a selective D_2 antagonist without affinity for σ receptors (Mizuchi et al., 1982), MS-377 may have potentiated the D_2 receptor blockade, which is common in the two drugs. The potentiation of the haloperidol- and sultopride-induced inhibition by MS-377 was antagonized by (+)-SKF-10,047 or SA4503, both of which are σ_1 receptor agonists with little or no affinity for NMDA receptors or dopamine receptors (Itzhak, 1994; Matsuno et al., 1996). These results suggested that σ_1 receptors are involved in this potentiation of the efficacy of D_2 antagonist by MS-377. Berendsen et al. (1998) reported that 8-OH-DPAT potentiated the inhibitory effect of haloperidol on apomorphine-induced climbing behavior, and 5-HT_{1A} receptors are involved in this potentiation. Therefore, we investigated the effect of a 5-HT_{1A} receptor antagonist (WAY-100,635) on the potentiation by MS-377. WAY-100,635 did not show a significant effect on the potentiation by MS-377, suggesting that 5-HT_{1A} receptors are not involved in this potentiation.

It was reported that σ receptors are present in dopamine neurons and are involved in the activity of the dopaminergic system (Gonzalez-Alvear and Werling, 1995; Chaki et al., 1998). Electrophysiological studies have shown that (+)-SKF-10,047 increased, whereas (+)-pentazocine and 1,3-ditolyguanidine decreased the firing rate of dopamine neurons (Freeman and Bunney, 1984; Steinfels et al., 1989), suggesting that σ receptors modulate the dopaminergic system in multiple ways. Taken together, MS-377 is a selective σ_1 receptor ligand and it does not have affinity for D_2 receptors, MS-377 may indirectly potentiate the D_2 receptor blockade action via the σ_1 receptors. The present results suggested, for the first time, that a σ_1-receptor ligand, MS-377, enhanced the efficacy of D_2 antagonists, but not that of EPS. However, the details of the mechanism remain to be elucidated, and further studies are necessary to clarify the relation between σ receptors and dopaminergic neurons.

In conclusion, we demonstrated that MS-377 enhanced the efficacy of dopamine D_2 antagonists without deterioration of EPS, although MS-377 has no anti-dopaminergic activity at the doses employed in this study. In addition, the mechanism of potentiation of the effect of D_2 antagonists by MS-377 appears to be via σ_1 receptors.

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