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Short communication

Effects of σ_1 receptor ligand, MS-377 on apomorphine- or phencyclidine-induced disruption of prepulse inhibition of acoustic startle in rats

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Abstract

To evaluate the antipsychotic property of a σ_1 receptor ligand, (*R*)-(+)-1-(4-chlorophenyl)-3-{4-(2-methoxyethyl)piperazin-1-yl}methyl-2-pyrrolidinone-L-tartrate (MS-377), an antagonistic effect of MS-377 on the disruption of prepulse inhibition (PPI) of the acoustic startle by apomorphine or phencyclidine (PCP) was investigated in rats. MS-377 antagonized the PCP-induced disruption of PPI. The ED_{50} value of MS-377 for this effect was 0.66 mg/kg. In contrast, apomorphine-induced disruption of PPI was not attenuated by MS-377. These data indicate that the PCP-induced disruption of PPI in rats would be, at least partially, mediated by σ receptors and MS-377 could be a novel anti-psychotic agent with clinical efficacy for the sensorimotor-gating deficit in schizophrenia.

Keywords: Prepulse inhibition; Apomorphine; Phencyclidine; σ1 Receptor ligand; MS-377

1. Introduction

The startle reaction to a strong acoustic stimulus is reduced by the prior presentation of a weak stimulus (Graham, 1975). This reduction, termed prepulse inhibition (PPI), has been used as a measure of sensorimotor gating and is significantly diminished in schizophrenic patients (Braff et al., 1978). In animal studies, PPI is changed by manipulations of the neural circuitry linking the limbic cortex, striatum, pallidum, thalamus and pontine reticular formation (Kodsi and Swerdlow, 1995; Lipska et al., 1995). In particular, PPI is disrupted by systemic apomorphine or phencyclidine (PCP). The disruption of PPI by apomorphine is reversed by the administration of dopamine D_2-receptor antagonists at potencies well correlated with the daily dosage or the dopamine D_2-receptor affinity of each drug (Swerdlow et al., 1994; Yamada et al., 1999). PCP, a non-competitive NMDA-receptor antagonist, causes psychotomimetic symptoms in human subjects. PCP-induced disruption of PPI was attenuated by systemic administration of atypical antipsychotics (Bakshi et al., 1994; Bakshi and Geyer, 1995; Johansson et al., 1994; Swerdlow et al., 1996; Yamada et al., 1999). Thus, the disruption of PPI is a valid animal model for some aspects of schizophrenia (Swerdlow et al., 1994; Wan et al., 1995) and substances which attenuate the disruption of PPI by apomorphine or PCP might be candidates for new antipsychotics.

Sigma receptors were first defined as an opioid receptor subtype and were later thought to be identical to PCP sites (Zukin and Zukin, 1981). However, σ receptors have been shown to be distinct from PCP sites (Gundlach et al., 1985). Some typical antipsychotic agents have affinities for σ receptors (Tam and Cook, 1984). Also, σ-receptor binding was decreased in post-mortem brain tissues from schizophrenic patients compared to that from normal controls (Helmeste et al., 1996). In addition, it has been reported that σ antagonists inhibited PCP-induced behaviors in animal models (Okuyama et al., 1993). Recently, a new σ ligand, (*R*)-(+)-1-(4-chlorophenyl)-3-{4-(2-methoxyethyl) piperazin-1-yl}methyl-2 -pyrrolidinone- L-tartrate (MS-377), was synthesized which has a high affinity for σ_1 receptors (K_i, 73 nM) and antagonizes the 5-hydroxytryptophan-induced head-twitching and the PCP-induced head-weaving (Takahashi et al., 1999). To clarify the involvement of the σ_1 receptor underlying the disruption

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Table 1
Effects of MS-377 on PPI of acoustic startle in rats

MS-377 (mg/kg)	*n*	Amp.	PPI (%)
0	6	430 (72)	70.5 (5.4)
0.3	6	364 (62)	61.7 (8.3)
1	6	535 (158)	64.4 (3.7)
3	6	434 (51)	67.8 (5.1)
10	6	342 (119)	64.7 (3.4)

of PPI by PCP or apomorphine in rats, we investigated the effect of MS-377 on apomorphine- or PCP-induced disruption of PPI of the acoustic startle in rats.

2. Materials and methods

2.1. PPI experiments

Male Wistar rats (350–450 g) were housed in a light-, humidity-, and temperature-controlled environment maintained on a 12/12 h light/dark schedule (lights on at 7 a.m.) with food and water provided ad libitum. Behavioral testing was performed between 9 a.m. and 3 p.m., during the light phase. Two startle chambers (SR-LAB, San Diego Instruments, San Diego, CA) were placed in a sound-attenuated room with a 60-dB ambient noise level. Each chamber consisted of a Plexiglas cylinder 8.2 cm in diameter resting in a 12.5×22.5 cm^2 Plexiglas frame within a ventilated enclosure. Acoustic noise bursts and background noise were presented via a Supertweeter speaker (Radio Shack) mounted 24 cm above the animal. Details of the experiment were the same as those in our previous report (Yamada et al., 1999). In short, each startle session began with a 5-min acclimation period in the chamber to 69-dB background noise. After an acclimation period of 5 min, the rat was exposed to two stimulus types presented in a pseudorandom order: a 120-dB 40-ms noise burst (P), or P preceded 100 ms earlier by a 20-ms noise burst 9 dB above background (pP), with a variable inter-trial interval (average 15 s) for a total of 36 trials (18 prepulse trials and 18 pulse-alone trials). The startle amplitude for each type of stimulus was defined as the mean maximum value of trials measured in arbitrary units. The percentage PPI was defined as $100 - \{$(startle amplitude on pP trials/ startle amplitude on P trials) $\times 100\}$. The study was approved by the Ethics Committee for Animal Experiments of the Kurume University School of Medicine.

2.2. Drug treatment

Seven days before drug testing, male Wistar rats (350–400 g, $n = 200$) were placed individually in a startle chamber with 68-dB background noise. After a 5-min acclimation period, the rat was exposed to two stimulus types presented in pseudorandom order, a P or pP, for a total of 36 trials. The rats were divided into five groups matched for mean PPI on these trials. For the PCP experiment in each group, 16 rats were used and 19 rats were used for the apomorphine experiment in each group. Each rat was pretreated with one dose of MS-377 (0, 0.1, 0.3, 1 or 3 mg/kg intraperitoneally for PCP-induced disruption of PPI; 0, 1, 3, 10, 30 mg/kg for apomorphine-induced disruption of PPI; Mitsui Pharmaceutical, Tokyo). After 30 min, the rats were treated with PCP (vehicle or 2 mg/kg i.p.) or apomorphine (vehicle or 1.5 mg/kg i.p.), then placed in the startle chamber for a 5-min acclimation period, and tested as described above.

2.3. Data analysis

Student's *t*-test was used to assess the PCP- or apomorphine-induced reduction of PPI from the control value. A one-way analysis of variance (ANOVA) with Fisher's post-hoc comparisons in rats, all of which had received PCP or apomorphine, with the MS-377 dose as the between-subject grouping factor, was used to assess differences in the drug-induced changes in PPI. The ED_{50} values (and 95% confidence limits) were calculated by logistic-log dose linear regression analysis. P values < 0.05 were considered statistically significant.

3. Results

The reduction of PPI by PCP (2 mg/kg) was significant compared with that by vehicle injection (PPI, $64 \pm 2.2\%$ for vehicle, $35.9 \pm 9.8\%$ for PCP; $t = 4.35$, $P < 0.0001$). Apomorphine (1.5 mg/kg) also significantly reduced the PPI ($33.7 \pm 4.4\%$ for apomorphine, $57.2 \pm 3.1\%$ for the vehicle-injection group, $t = 6.06$, $P < 0.0001$). MS-377 (up to 10 mg/kg, $n = 6$ each group) alone had no effect on either PPI or startle amplitude in rats pretreated with vehicle (Table 1). However, MS-377 attenuated the PCP (2

Table 2
Effects of MS-377 on PCP- or apomorphine-induced disruption of prepulse inhibition of acoustic startle in rats

MS-377 (mg/kg)	PCP (2 mg/kg)			Apomorphine (1.5 mg/kg)		
	n	P amp.	PPI (%)[a]	*n*	P amp.	PPI (%)
Vehicle		605 (71)	64.0 (2.15)		514 (56)	57.3 (3.0)
0	15	602 (110)	35.9 (9.8)	19	596(154)	33.7 (4.4)
0.1	15	604 (87)	32.0 (7.9)	–		–
0.3	16	552 (125)	50.2 (6.3)	–		–
1	15	653 (116)	41.2 (5.5)	18	530 (107)	42.0 (5.6)
3	16	780 (95)	60.7[b,c] (4.6)	19	453 (84)	40.8 (5.3)
10	–		–	18	438 (98)	42.4 (5.3)
30	–		–	19	263 (40)[d]	40.8 (5.8)

P amp., startle amplitude by P alone; PPI, prepulse inhibition. Parentheses represent SEM.

[a] $F(4,72) = 2.76$, $P = 0.034$.

[b] $P = 0.014$, compared with 0 mg/kg group.

[c] $P = 0.005$, compared with 0.1 mg/kg group.

[d] Compared with 0 mg/kg group.

mg/kg)-induced disruption of PPI ($F(4,72) = 2.76$, $P = 0.034$, $n = 15$ or 16 each group, Table 2). An amount of 3 mg/kg of MS-377 caused a significant attenuation of the PCP-induced disruption of PPI ($P = 0.004$, Fisher's PLSD). The ED_{50} value of MS-377 for this effect was 0.66 mg/kg. MS-377 partially, but non-significantly, reduced the startle amplitude in apomorphine-treated rats dose-dependently ($F(4, 88) = 1.48$, $P = 0.21$, 0 mg/kg MS-377 group vs. 30 mg/kg MS-377 group, $P = 0.024$). MS-377 (up to 30 mg/kg) had no effect on the apomorphine-induced reduction of PPI ($F(4,88) = 0.456$, $P = 0.77$).

4. Discussion

MS-377 itself had no effect on the PPI of the vehicle-pretreated rats, which is compatible with the previous report for another σ-receptor ligand, NPC16377 (Clissold et al., 1992). MS-377 attenuated the PCP (2 mg/kg)-induced disruption of PPI. In vivo and in vitro radioligand binding assays revealed that MS-377 has an affinity for σ_1 receptors (K_i, 73 nM) and not for dopamine D_2 or 5-HT_2 receptors (Takahashi et al., 1999). The present results indicated for the first time that a σ_1 ligand, MS-377, attenuated the PCP-induced disruption of PPI in rats, but not the apomorphine-induced disruption of PPI. The mechanism underlying the antagonistic effects of MS-377 on PCP-induced disruption of PPI remains unknown. α-Adrenoceptor antagonists such as prazosin have been shown to attenuate the PCP-induced disruption of PPI (Bakshi and Geyer, 1997), but MS-377 has negligible affinity for an α-adrenoceptor (Mitsui Pharmaceuticals, personal communication). Curzon and Decker (1998) reported that the σ ligand, (+)-3-PPP, marginally increases the PPI in CD-1 mice. These data and the present results indicate that σ_1 receptors may contribute to the regulation of PPI in animals. Takahashi et al. (1999) also reported that MS-377 antagonizes the 5-HTP-induced head-twitching ($ED_{50} = 0.54$ mg/kg), *N*-allylnormetazocine-induced head-weaving ($ED_{50} = 0.52$ mg/kg) and the PCP-induced head-weaving ($ED_{50} = 0.39$ mg/kg). These data are compatible with the present results. We previously reported that the neuroleptic drug potency for the attenuation of the PCP-induced disruption of PPI is significantly correlated with the K_i 5-HT_{2A} receptor affinity of each drug but not correlated with the K_i dopamine D2-receptor affinity of each drug (Yamada et al., 1999). It has been reported that PCP causes increased serotonin release from serotonin nerve terminals (Ohno and Warnick, 1989) or blocking of serotonin reuptake (Hori et al., 1996). These data suggest that the mechanism underlying the disruption of PPI induced by PCP involves the activation of 5-HT_{2A} receptors and/or the release of serotonin. As MS-377 showed a low affinity for 5-HT_{2A} receptors, an indirect effect of MS-377 on 5-HT_{2A} receptors on PCP-induced disruption of PPI is postulated. It has been reported that α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine butanol monohydrochloride (BMY-14802), a σ receptor antagonist, decreases the dorsal raphe and hippocampal release of serotonin by interaction with somatodendritic 5-HT_{1A} receptors in the raphe nuclei (Matos et al., 1996). Thus, MS-377 may antagonize the PCP-induced increase in 5-HT release, resulting in the attenuation of PCP-induced disruption of PPI. It has been reported that the PCP-induced disruption of PPI in Sprague–Dawley rats is not reversed by ketanserin or ritanserin (Bakshi et al., 1994). Further study would be necessary to investigate the involvement of the σ receptor system in PCP-induced disruption in Sprague–Dawley rats.

Although MS-377 had no effect on apomorphine-induced disruption of PPI in rats, it has been reported that apomorphine-induced climbing behavior in mice is antagonized by MS-377 (Takahashi et al., 1999). As shown in Table 2, MS-377 tended to reduce the startle amplitude in apomorphine-treated rats dose-dependently. Moreover, PPI at all four active doses (1, 3, 10, 30 mg/kg of MS-377), was higher than in the vehicle group, but did not reach statistical significance. Thus, the startle-depressing effects of MS-377 in these groups might have hindered further improvement of PPI by a floor effect. Further study is necessary to investigate the effect of MS-377 on apomorphine-induced disruption of PPI under various experimental conditions, i.e. dose of apomorphine, timing of drug treatment.

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