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σ Receptor ligands (+)-SKF10,047 and SA4503 improve dizocilpine-induced spatial memory deficits in rats

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Abstract

This study examined the effects of the σ receptor ligands (+)-*N*-allylnormetazocine ((+)-SKF10,047) and 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride (SA4503) on dizocilpine-induced impairment of working and reference memory in a radial arm maze task in rats. Dizocilpine, a non-competitive NMDA receptor antagonist, significantly impaired both reference and working memory, an effect which was accompanied by ataxia and impairment of food intake. The dizocilpine-induced impairment of reference memory was dose-dependently attenuated by (+)-SKF10,047 and SA4503. SA4503 also attenuated the dizocilpine-induced working memory impairment, although (+)-SKF10,047 had no effect. Neither σ receptor ligand affected the behavioral symptoms such as ataxia and impairment of food intake induced by dizocilpine. The ameliorating effects of both (+)-SKF10,047 and SA4503 on dizocilpine-induced spatial memory impairment were completely antagonized by a σ_1 receptor antagonist *N,N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]-ethylamine-monohydrochloride. These results suggest that the interaction of σ_1 receptors with NMDA receptors modulates spatial memory in rats.

Keywords: Dizocilpine; Reference memory; SA4503; (+)-SKF10,047; σ-Receptor; Working memory

1. Introduction

The σ receptors in the central nervous system were originally proposed by Martin et al. (1976) to be the binding sites for (±)-*N*-allylnormetazocine ((±)-SKF10,047). The σ receptor ligand (+)-SKF10,047 and phencyclidine were thought to act through a single binding site termed the σ-phencyclidine receptor. It is now clear that two distinct binding sites exist with different populations throughout the brain, a high-affinity site for (+)-SKF10,047, σ receptors, and a low-affinity site for (+)-SKF10,047, which corresponds to a phencyclidine binding site (Largent et al., 1986; Manallack et al., 1986; Quirion et al., 1987; Walker et al., 1990). It is well accepted that σ sites represent two different classes of binding sites: σ_1 sites, which have high affinity and stereoselectivity for (+)-SKF10,047 and (+)-pentazocine; and σ_2 sites, which have a lower affinity and no stereoselectivity (Quirion et al., 1992). 1-(3,4-Dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride (SA4503) is a novel and selective σ_1 receptor agonist (Matsuno et al., 1996, 1997; Senda et al., 1996). Recently, σ (σ_1) receptors have been purified and cloned. The deduced amino acid sequence shared homology with that of fungal proteins involved in sterol synthesis (Hanner et al., 1996).

The phencyclidine binding site is located inside the ion channel associated with the NMDA receptor complex, and the ligands for the phencyclidine binding site are known to act as non-competitive NMDA receptor antagonists (Wong et al., 1986; Wong et al., 1988; Lodge and Johnson, 1990). There are many reports showing that ligands for the phencyclidine binding site, including the more selective derivative dizocilpine, significantly impair learning and memory in rodents and monkeys by blocking NMDA receptor-mediated glutamatergic neurotransmission (Butelman, 1989; Tan et al., 1989; Ward et al., 1990; Boyce et al., 1991; Pontecorvo et al., 1991; Ogura and Aigner, 1993). We have recently suggested that impairment of spatial memory in mice caused by dizocilpine is due to disruption of NMDA/nitric oxide/cyclic GMP signaling (Yamada et al., 1996a,b). Although the function of σ receptors is not

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fully understood, some σ receptor ligands have been demonstrated to facilitate the NMDA response in the hippocampus (Monnet et al., 1990, 1992). It has been demonstrated that in both short-term and long-term memory tests, σ receptor ligands, such as 1,3-di(2-tolyl)-guanidine (DTG), (+)-SKF10,047, (+)-pentazocine, and SA4503, markedly prevent the amnesia induced by dizocilpine (Maurice et al., 1994a,b; Maurice and Privat, 1997). Furthermore, intrahippocampal administration of (+)-SKF10,047 has been shown to attenuate the working memory impairment induced by concurrent intrahippocampal administration of dizocilpine in a three-panel runway task (Ohno and Watanabe, 1995). These behavioral studies support the potentiating effect of σ receptor ligands on NMDA receptor-mediated neurotransmission, as demonstrated electrophysiologically (Monnet et al., 1990, 1992), and suggest that this interaction plays a role in NMDA-dependent learning and memory processes (Maurice and Lockhart, 1997). In this study, therefore, we examined the effects of σ receptor ligands (+)-SKF10,047 and SA4503 on the dizocilpine-induced impairment of spatial memory in a radial arm maze task in rats.

2. Materials and methods

2.1. Materials

The rats used in the present study were males of the Wistar strain (20 weeks old; Charles River Japan, Yokohama, Japan) weighing 250 ± 20 g at the beginning of experiments. All animals were kept in a regulated environment (23 ± 0.5°; 50 ± 0.5% humidity) with a 12-h light/dark cycle (light on 9:00 a.m. and 9:00 p.m.) and

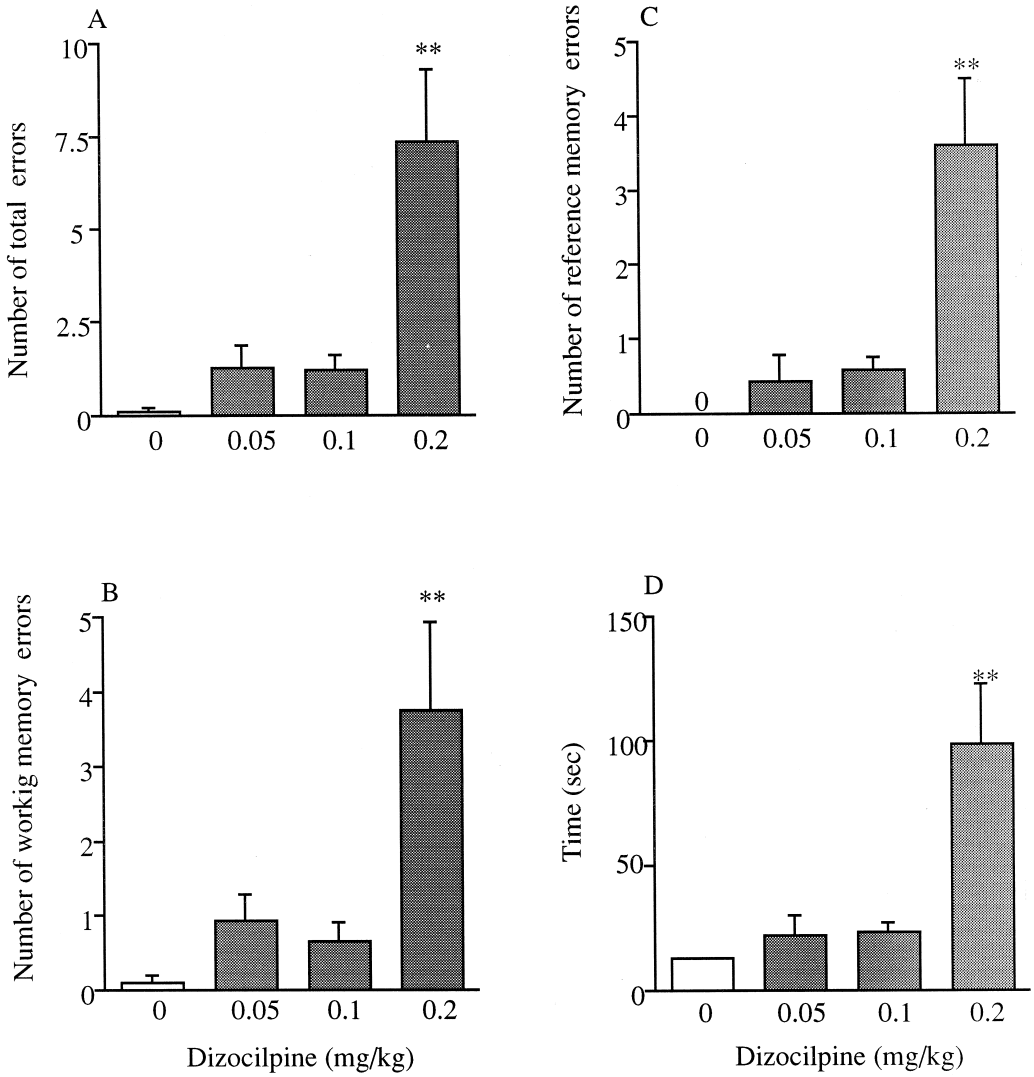

Fig. 1. Dose–response effects of dizocilpine on performance in the radial arm maze task of rats. Rats were trained on working and reference memory tasks in the 8-arm radial maze. Dizocilpine was administered i.p. 30 min before the test. The total number of errors (A), working memory errors (B), reference memory errors (C) and the time taken to complete the task (D) were recorded. Each value represents the mean ± S.E. ($n = 11–16$). ** $P < 0.01$ vs. control.

had free access to food and water. Dizocilpine and (+)-SKF10,047 were purchased from Research Biochemicals International (Natick, MA, USA). SA4503 and *N,N*-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]-ethylamine-monohydrochloride (NE-100) were kindly provided by Santen Pharmaceutical (Osaka, Japan) and Taisho Pharmaceutical (Tokyo, Japan), respectively. Scopolamine was purchased from Katayama Chemical (Osaka, Japan). Dizocilpine, (+)-SKF10,047 and scopolamine were dissolved in saline. SA4503 was suspended in 1% methylcellulose solution. NE-100 was dissolved in distilled water. Dizocilpine, NE-100 and scopolamine were administered i.p. 30 min, 60 min, and 40 min before the behavioral test, respectively. (+)-SKF10,047 was administered s.c. 45 min before the test. SA4503 was administered p.o. 30 min before the test.

All experiments were performed in accordance with the Guidelines for Animal Experiments of the Nagoya University School of Medicine, the Guiding Principles for the Care and Use of Laboratory Animals approved by the Japanese Pharmacological Society, and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Radial arm maze task

The maze used in the present study consisted of eight arms, numbered from 1 to 8 (48 × 12 cm), extending radially from a central area (32 cm in diameter). There was a 5 cm edge around the apparatus. The floor of the arms and central area was painted black. The apparatus was placed 40 cm above the floor and was surrounded by various extramaze cues such as a laboratory bench, posters and a clock. At the end of each arm there was a food cup that held a single 50-mg food pellet. Prior to the performance of the maze task, the animals were kept on a

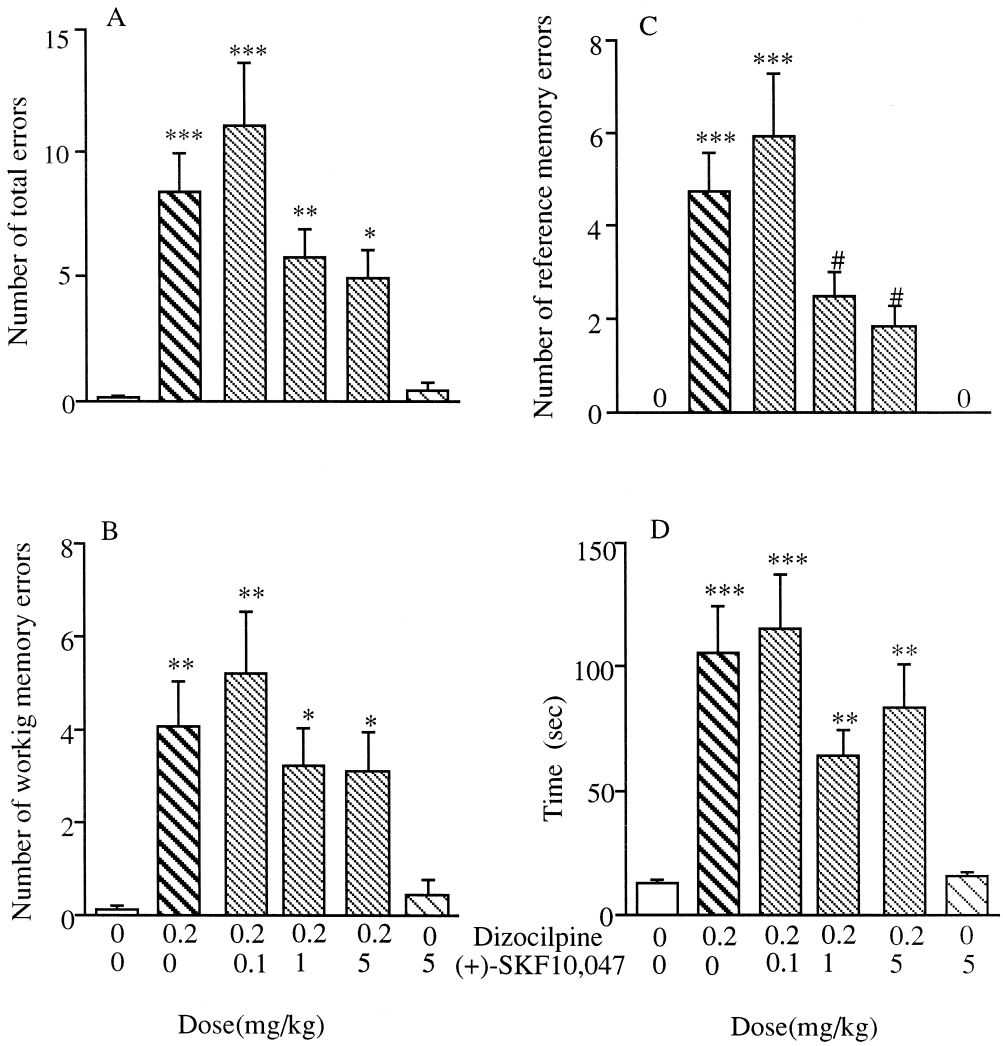

Fig. 2. Effect of (+)-SKF10,047 on dizocilpine-induced impairment of performance in the radial arm maze in rats. Dizocilpine (0.2 mg/kg, i.p.) and (+)-SKF10,047 (0.1–5 mg/kg, s.c.) were administered 30 min and 45 min before the test, respectively. The total number of errors (A), working memory errors (B), reference memory errors (C) and the time taken to complete the task (D) were recorded. Each value represents the mean ± S.E. (n = 10–17). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs. control group. $\#P < 0.05$, vs. dizocilpine-treated group.

restricted diet and body weight was maintained at 85% of the free-feeding weight over a 1-week period, with water being available ad libitum.

Before the actual training began, the animals were shaped for 4 days to run to the end of the arms and consume the bait. The bait was initially available throughout the maze, but gradually was restricted to the food cup. Following this shaping period, each animal was placed individually in the center of the maze and subjected to working and reference memory tasks, in which the same 4 arms (No. 1, 2, 4 and 7) were baited on each daily training trial. The other 4 arms were never baited. The training trial continued until all 4 baits had been consumed or until 5 min had elapsed. An arm entry was counted when all four limbs of the rat were within an arm. The maze was cleaned to ensure that the animals could not simply follow their own or other rats, odor trails.

Measures were made of the number of working memory errors (entering an arm containing food but previously consumed), reference memory errors (entering an arm that was not baited), and the total number of errors to sample all 4 baited arms. The time taken to consume all 4 baits was also recorded. The rats that fulfilled the criterion (less than one error in a training trial and less than two errors in total over 3 consecutive training trials) were used in each experiment ($n = 7–17$).

2.3. Measurement of food intake

The effects of dizocilpine and/or σ receptor ligands on food intake were examined as follows: the diet-restricted

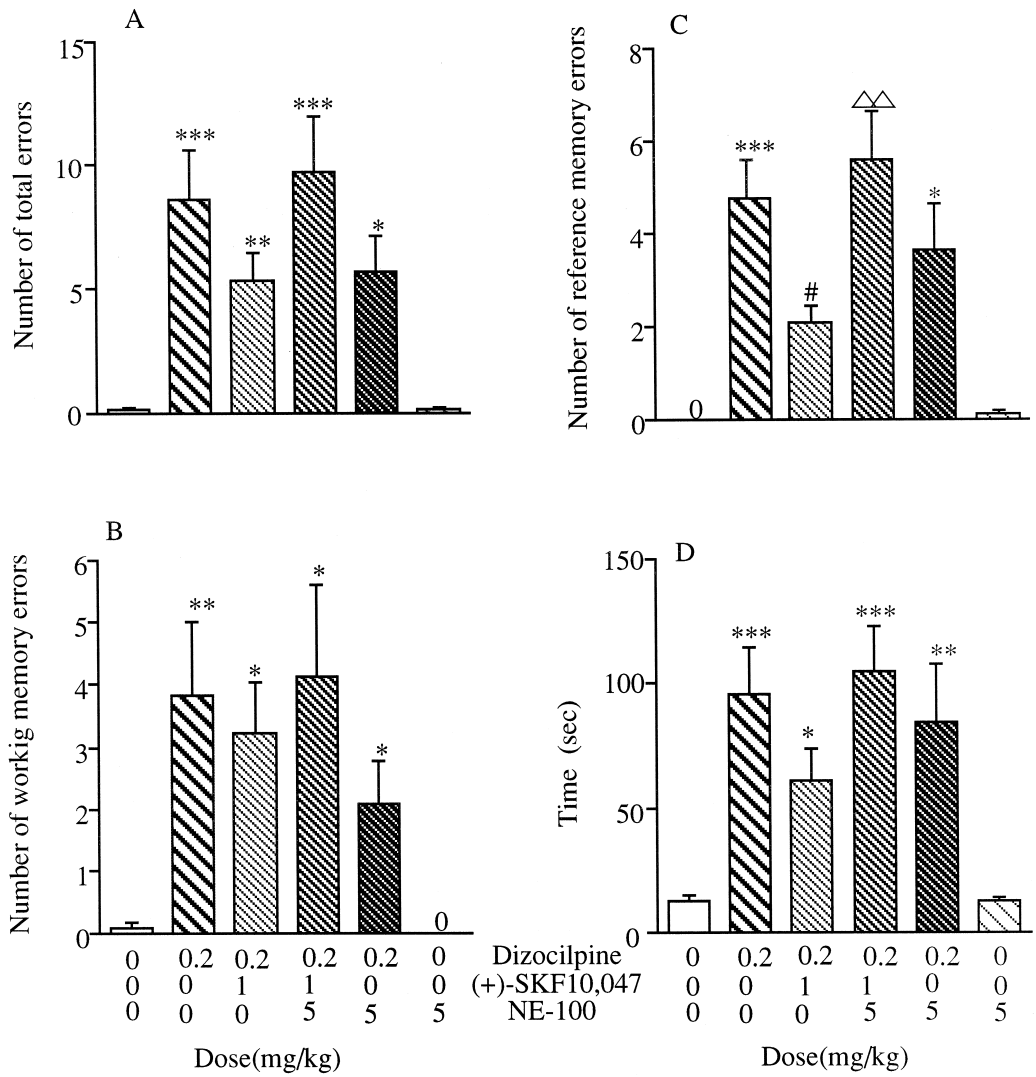

Fig. 3. Effect of NE-100 on the ameliorating effect of (+)-SKF10,047 on dizocilpine-induced impairment of performance in the radial arm maze task in rats. NE-100 (5 mg/kg, i.p.), (+)-SKF10,047 (1 mg/kg, s.c.) and dizocilpine (0.2 mg/kg, i.p.) were administered 60 min, 45 min, and 30 min before the test, respectively. The total number of errors (A), working memory errors (B), reference memory errors (C) and the time taken to complete the task (D) were recorded. Each value represents the mean ± S.E. ($n = 10–17$). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs. control group. $\#P < 0.05$ vs. dizocilpine-treated group. $\triangle\triangle P < 0.01$ vs. (+)- SKF10,047 plus dizocilpine-treated group.

rats were individually placed in a home cage, and then 10 baits, which were the same as the one used in the radial arm maze task, were provided. The time taken to consume all 10 baits in the food cup was recorded, with a cut-off time of 180 s.

2.4. Statistical analysis

Results are expressed as means ± S.E. The statistical significance was assessed by one-way analysis of variance (ANOVA), followed by the Bonferroni test as a post-hoc analysis. A P value less than 0.05 was regarded as statistically significant.

3. Results

3.1. Effect of dizocilpine on performance in the radial arm maze task

Fig. 1 shows the effect of dizocilpine, in the dose range of 0.05–0.2 mg/kg, on the performance in the radial arm maze task in rats. A one-way ANOVA with repeated measures revealed a significant effect of group ($F(3,43) = 9.596$, $P < 0.0001$). Post-hoc analysis using the Bonferroni test revealed that dizocilpine at a dose of 0.2 mg/kg significantly increased the number of errors (Fig. 1A). When the errors were subdivided into the working memory

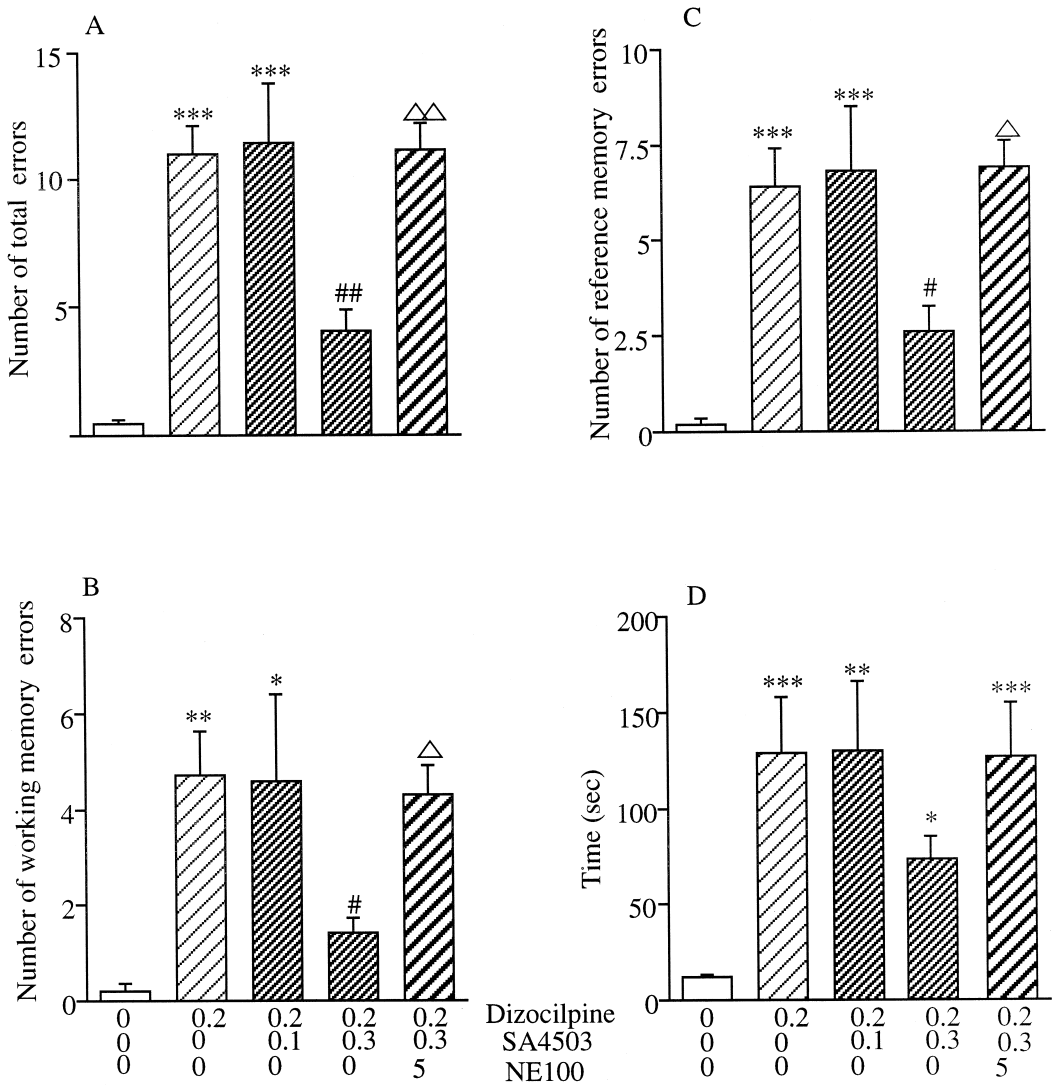

Fig. 4. Effect of SA4503 on dizocilpine-induced impairment of performance in the radial arm maze task in rats. NE-100 (5 mg/kg, i.p.), SA4503 (0.1–0.3 mg/kg, p.o.) and dizocilpine (0.2 mg/kg, i.p.) were administered 60 min, 30 min, and 30 min before the test, respectively. The total number of errors (A), working memory errors (B), reference memory errors (C) and the time taken to complete the task (D) were recorded. Each value represents the mean ± S.E. ($n = 7–10$). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs. control group. $\#P < 0.05$, $\#\#P < 0.01$ vs. dizocilpine-treated group. $\triangle P < 0.05$, $\triangle\triangle P < 0.01$ vs. SA4503 plus dizocilpine-treated group.

Table 1
Effects of dizocilpine, (+)-SKF10,047, SA4503 and NE-100 on food intake in rats

Dose (mg/kg)				*n*	Time (s)
Dizocilpine	(+)-SKF10,047	SA4503	NE-100		
–	–	–	–	10	25.0 ± 3.6
0.1	–	–	–	10	36.5 ± 8.3
0.2	–	–	–	18	102.6 ± 13.6[a]
–	–	–	5.0	10	35.8 ± 7.1
–	1.0	–	–	10	33.2 ± 6.9
0.2	1.0	–	–	19	85.8 ± 15.1
0.2	1.0	–	5.0	19	75.2 ± 12.2
0.2	–	–	5.0	19	80.1 ± 10.9
–	–	0.3	–	10	29.6 ± 3.3
0.2	–	0.3	–	10	95.5 ± 15.3

Dizocilpine, (+)-SKF10,047, SA4503 and NE-100 were administered 30 min, 45 min, 30 min and 60 min before the test, respectively. Each value represents the mean ± S.E..
[a] $P < 0.01$ vs saline-treated group.

and reference memory categories, a significant group effect on the number of working memory ($F(3,43) = 6.740$, $P < 0.001$) (Fig. 1B) and reference memory ($F(3,43) = 10.814$, $P < 0.001$) (Fig. 1C) errors was observed. Post-hoc analysis using the Bonferroni test revealed that dizocilpine at a dose of 0.2 mg/kg significantly increased the number of both working and reference memory errors.

At the highest dose (0.2 mg/kg), dizocilpine produced behavioral symptoms, including ataxia and motor incoordination, in rats. Ataxia was the most overt behavioral symptom. Therefore, the time taken to consume all 4 baits was also significantly different between control and dizocilpine-treated groups ($F(3,43) = 10.097$, $P < 0.001$) (Fig. 1D). The rats did not necessarily consume the food when they came upon it. In extreme cases, they did not stop at the end of the maze and fell off the end of the arm onto the floor. Data were discarded from those trials where the rats did not remain on the maze throughout the session.

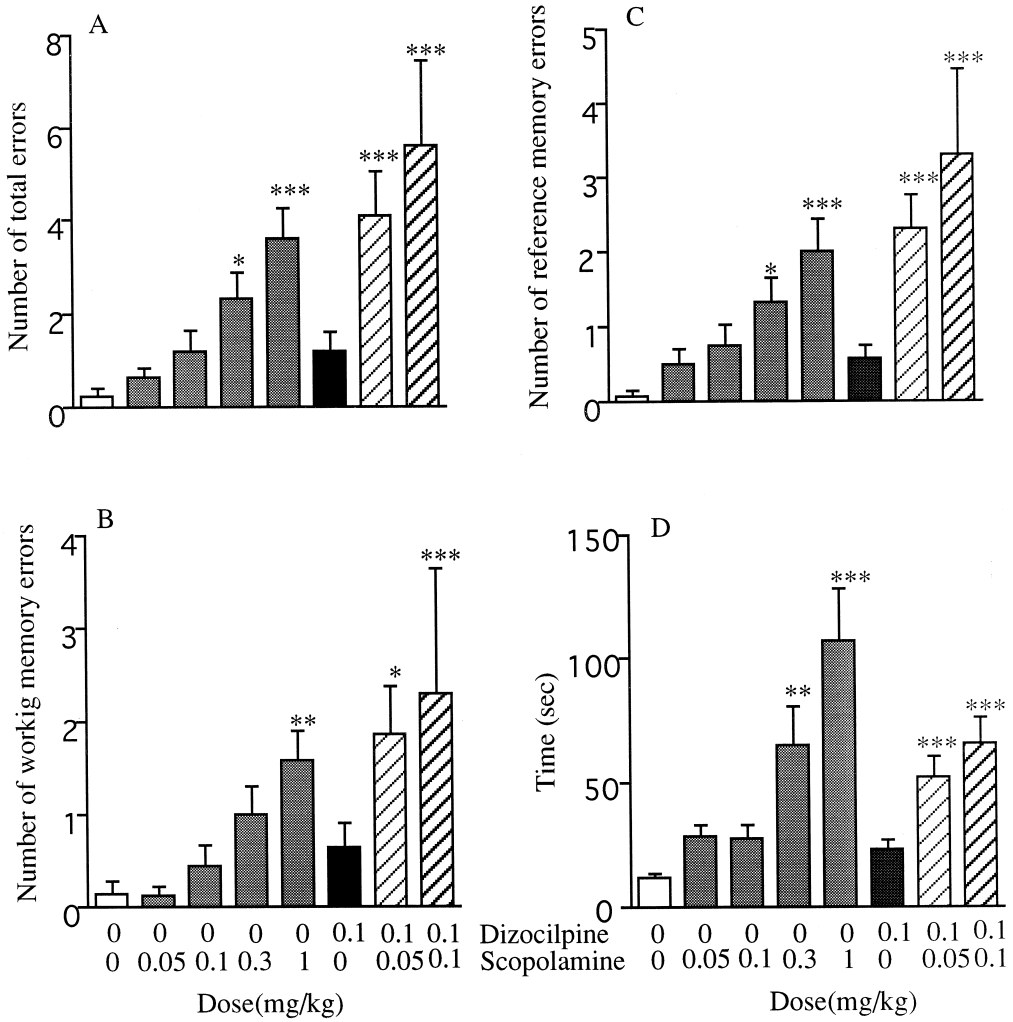

Fig. 5. Effect of co-administration of dizocilpine and scopolamine on performance in the radial arm maze task in rats. Dizocilpine (0.1 mg/kg, i.p.) and scopolamine (0.05–1 mg/kg, i.p.) were administered 30 min and 40 min before the test, respectively. The total number of errors (A), working memory errors (B), reference memory errors (C) and the time taken to complete the task (D) were recorded. Each value represents the mean ± S.E. ($n = 10$–17). $* P < 0.05$, $** P < 0.01$, $*** P < 0.001$ vs. control group.

3.2. Effect of (+)-SKF10,047 on dizocilpine-induced impairment of performance in the radial arm maze task

Fig. 2 shows the effect of (+)-SKF10,047 on the dizocilpine-induced impairment of performance in the radial arm maze task. (+)-SKF10,047 decreased the number of errors in the dizocilpine-treated rats, but the effect was not significant (Fig. 2A). When the errors were subdivided into those of working and reference memory, it was found that (+)-SKF10,047 significantly decreased the number of reference memory errors induced by dizocilpine in a dose-dependent manner ($F(5,78) = 10.130$, $P < 0.05$) (Fig. 2C), without affecting the number of working memory errors (Fig. 2B). (+)-SKF10,047 did not affect the behavioral symptoms induced by dizocilpine, as indicated by no change in the time taken to complete the task (Fig. 2D). (+)-SKF10,047 (5 mg/kg) alone had no effect on performance in the radial arm maze task.

To examine whether the effect of (+)-SKF10,047 on the dizocilpine-induced impairment of performance in the radial arm maze is mediated by σ receptors, the effects of NE-100, a σ_1 receptor antagonist, were examined. NE-100 (5 mg/kg) completely attenuated the ameliorating effects of (+)-SKF10,047 on the reference memory deficits induced by dizocilpine ($F(5,80) = 9.2178$, $P < 0.01$) (Fig. 3C) while NE-100 alone did not have any effect (Fig. 3). Furthermore, NE-100 did not affect the impairment of working and reference memory induced by dizocilpine (Fig. 3).

3.3. Effect of SA4503 on dizocilpine-induced impairment of performance in the radial arm maze task

Fig. 4 shows the effect of SA4503 on the dizocilpine-induced impairment of performance in the radial arm maze task in rats. SA4503 significantly decreased the total num-

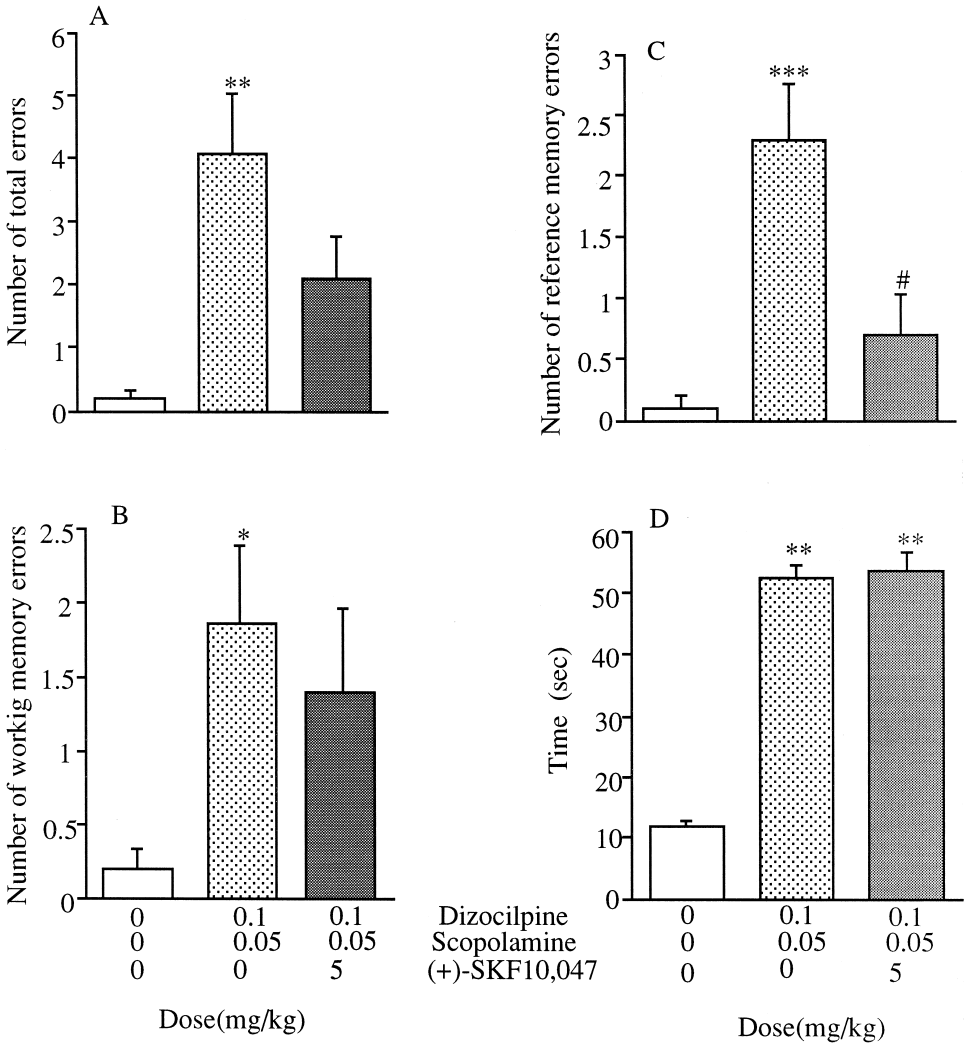

Fig. 6. Effect of (+)-SKF10,047 on the impairment of performance caused by dizocilpine combined with scopolamine in the radial arm maze task. Dizocilpine (0.1 mg/kg, i.p.), scopolamine (0.05 mg/kg, i.p.) and (+)-SKF10,047 (5 mg/kg, s.c.) were administered 30 min, 40 min and 45 min before the test, respectively. The total number of errors (A), working memory errors (B), reference memory errors (C) and the time taken to complete the task (D) were recorded. Each value represents the mean ± S.E. ($n = 10–14$). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs. control group. $\#P < 0.05$ vs. dizocilpine plus scopolamine-treated group.

ber of errors induced by dizocilpine in a dose-dependent manner ($F(4,43) = 20.025$, $P < 0.0001$) (Fig. 4A). When the errors were subdivided into those of working and reference memory, it was found that SA4503 significantly decreased the number of working memory errors ($F(4,43) = 6.439$, $P < 0.001$) (Fig. 4B) and reference memory errors ($F(4,43) = 12.372$, $P < 0.0001$) (Fig. 4C) induced by dizocilpine in a dose-dependent manner. SA4503 did not significantly affect the behavioral symptoms induced by dizocilpine, as indicated by no change in the time taken to complete the task (Fig. 4D).

To examine whether the effect of SA4503 on the dizocilpine-induced impairment of performance in the radial arm maze is mediated by σ receptors, the effects of NE-100 were examined. NE-100 (5 mg/kg) completely attenuated the ameliorating effects of SA4503 on the working and reference memory deficits induced by dizocilpine (Fig. 4).

3.4. Effects of dizocilpine, (+)-SKF10,047, SA4503 and NE-100 on food intake in rats

As shown in Table 1, dizocilpine, at a dose of 0.2 mg/kg, impaired food intake behavior, as indicated by a significant prolongation of the time taken to consume 10 baits. This impairment of food intake behavior was not affected by (+)-SKF10,047 (1 mg/kg), SA4503 (0.3 mg/kg) or NE-100 (5 mg/kg). Treatment with (+)-SKF10,047 and NE-100 also failed to affect the impairment of food intake behavior induced by dizocilpine.

3.5. Effects of (+)-SKF10,047 on impairment of performance caused by dizocilpine plus scopolamine in the radial arm maze task

Fig. 5 shows the effects of dizocilpine (0.1 mg/kg) in combination with scopolamine on performance in the radial arm maze task. Scopolamine alone impaired spatial memory in a dose-dependent manner, especially at doses greater than 0.3 mg/kg. It significantly increased the total number of errors ($F(4,74) = 7.772$, $P < 0.001$) (Fig. 5A); both working memory errors ($F(4,74) = 6.519$, $P < 0.001$) (Fig. 5B) and reference memory errors ($F(4,74) = 6.123$, $P < 0.001$) (Fig. 5C) were increased. The time taken to consume all 4 baits was also increased in a dose-dependent manner ($F(4,74) = 6.483$, $P < 0.001$) (Fig. 5D).

When dizocilpine at a dose of 0.1 mg/kg, which had no significant effect on performance in the radial arm maze, was administered with low doses of scopolamine (0.05 and 0.1 mg/kg), it produced a significant increase in the total number of errors ($F(5.81) = 8.401$, $P < 0.001$) (Fig. 5A),(both working memory errors ($F(5.81) = 3.808$, $P < 0.01$) (Fig. 5B) and reference memory errors ($F(5.81) = 8.056$, $P < 0.0001$) (Fig. 5C)), as well as an increase in the time taken to complete the task ($F(5.81) = 10.740$, $P < 0.0001$) (Fig. 5D). No abnormal behavioral symptoms, such as ataxia, were observed in the rats treated with dizocilpine (0.1 mg/kg) plus scopolamine (0.05 or 0.1 mg/kg).

As shown in Fig. 6, (+)-SKF10,047 at a dose of 5 mg/kg significantly prevented the increase in the number of reference memory errors caused by dizocilpine (0.1 mg/kg) plus scopolamine (0.05 mg/kg) ($F(2,31) = 10.545$, $P < 0.01$) (Fig. 6C). In contrast, (+)-SKF10,047 did not affect the number of working memory errors (Fig. 6B) or the time taken to complete the task (Fig. 6D).

4. Discussion

In the present study, we found that systemic administration of dizocilpine impaired significantly both working and reference memory, as assessed by the radial arm maze task. These results suggest that NMDA receptor-mediated glutamatergic neurotransmission plays an important role not only in working memory, but also in reference memory. It has been shown that intrahippocampal injections of NMDA receptor antagonists, such as *cis*-4-(phosphonomethyl)piperidine-2-carboxylic acid (CGS19755) and (±)-3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid (CPP), produce a significant increase in the number of working memory errors, without affecting the number of reference memory errors (Ohno et al., 1992). Olton and Papas (1979) have shown, by using a radial maze with only half of the arms baited, that rats with lesions of the hippocampus exhibit significantly more working memory errors, but not more reference memory errors. Similar results were obtained for rats with hippocampal neuronal damage after transient forebrain ischemia (Davis et al., 1986, 1987). These findings indicate a selective involvement of the hippocampal formation in working memory but not in reference memory. It has been reported that peripheral administration of NMDA receptor antagonists such as dizocilpine and CPP impair both working and reference memory in the radial arm maze task (Ward et al., 1990). Therefore, it is possible that systemic administration of dizocilpine interferes with reference memory, possibly through phencyclidine binding sites within the NMDA receptor/channel complex in brain regions other than the hippocampus. The cerebral cortex is one possible site for this action of dizocilpine since this brain structure has been suggested to play a role in reference memory (Murray and Fibiger, 1985; Kesner et al., 1987).

The sigma receptor ligands (+)-SKF10,047 and SA4503 ameliorated the impairment of reference memory induced by dizocilpine in a dose-dependent manner. Furthermore, SA4503 ameliorated the dizocilpine-induced working memory deficit although (+)-SKF10,047 had no effect. The ameliorating effects of (+)-SKF10,047 and SA4503 are likely to be mediated by σ_1 receptors since NE-100, a specific σ_1 receptor antagonist, antagonized the effects of (+)-SKF10,047 and SA4503. Since previous studies have

demonstrated that activation of σ receptors facilitates the NMDA response (Monnet et al., 1990, 1992), it is considered that (+)-SKF10,047 and SA4503 ameliorate dizocilpine-induced spatial memory deficits by facilitating NMDA receptor-mediated neurotransmission. Furthermore, the interaction of σ receptors with NMDA receptors may be important in the modulation of both spatial working and reference memory. It is not clear, at present, why (+)-SKF10,047 failed to ameliorate dizocilpine-induced working memory deficits although SA4503 improved them. One possible explanation is that there may be (+)-SKF10,047-insensitive σ_1 receptors to which SA4503 binds in the hippocampus. Accordingly, SA4503, but not (+)-SKF10,047, could ameliorate dizocilpine-induced working memory deficits. To test this possibility, the effects of intrahippocampal injections of (+)-SKF10,047 and SA4503 on dizocilpine-induced spatial memory deficits should be examined.

Dizocilpine at a dose of 0.2 mg/kg produced spatial memory deficits which were accompanied by behavioral symptoms, such as ataxia and impairment of food intake behavior. To exclude the possibility that (+)-SKF10,047 and SA4503 improve dizocilpine-induced spatial memory deficits by acting on food intake behavior, we examined the effect of these compounds on food intake. Neither (+)-SKF10,047 nor SA4503 affected the dizocilpine-induced impairment of food intake behavior. Therefore, it is unlikely that the ameliorating effects of (+)-SKF10,047 and SA4503 on dizocilpine-induced spatial memory deficits are simply due to the amelioration of impairment of food intake behavior. It also appears that the σ_1 receptor ligands (+)-SKF10,047 and SA4503 did not affect the ataxia and motor incoordination caused by dizocilpine. Therefore, it is also unlikely that the ameliorating effects of (+)-SKF10,047 and SA4503 on the spatial memory deficits caused by dizocilpine are due to the improvement of motor deficits induced by dizocilpine. In this regard, it is of interest to note that σ_1 receptor ligands, including (+)-SKF10,047, potentiate dizocilpine-induced hyperlocomotion in monoamine-depleted mice (Okuyama et al., 1996).

To further exclude the possibility that the ameliorating effect of σ_1 receptor ligands on dizocilpine-induced deficits of spatial reference memory is due to the improvement of behavioral symptoms caused by dizocilpine, we examined the effect of (+)-SKF10,047 on spatial memory impairments induced by low doses of dizocilpine and scopolamine, a treatment which does not produce abnormal behavior in rats. A previous study in our laboratory has demonstrated that dizocilpine increases dose-dependently the extracellular acetylcholine level in the parietal cortex and hippocampus in freely moving rats (Hasegawa et al., 1993). Therefore, it is possible that scopolamine potentiates the dizocilpine-induced impairment of spatial memory by blocking muscarinic receptors. We found that (+)-SKF10,047 significantly attenuated the impairment of reference memory, but not working memory, caused by dizocilpine combined with scopolamine. Although the mechanism is poorly understood, we consider this improvement to also be related to the facilitating modulation of NMDA receptor-mediated glutamatergic neurotransmission by (+)-SKF10,047. It is also possible, however, that the ameliorating effect of (+)-SKF10,047 is due to an increase in acetylcholine release in the cerebral cortex (Matsuno et al., 1993).

In conclusion, this study demonstrated that the σ receptor ligands (+)-SKF10,047 significantly ameliorate spatial reference memory impairments caused by dizocilpine or by low doses of dizocilpine plus scopolamine. SA4503 markedly attenuated the spatial working and reference memory deficits induced by dizocilpine. Since the effects of (+)-SKF10,047 and SA4503 were antagonized by a specific σ_1 receptor antagonist, NE-100, it is suggested that σ_1 receptors play an important role in the modulation of spatial working and reference memory.

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