Pharmacology Biochemistry and Behavior, Vol. 59, No. 1, pp. 129–134, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(97)00385-7

Ameliorative Effect of SA4503, a Novel Cognitive Enhancer, on the Basal Forebrain Lesion-Induced Impairment of the Spatial Learning Performance in Rats

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Received 16 October 1996; Revised 19 March 1997; Accepted 29 April 1997

SENDA, T., K. MATSUNO, T. KOBAYASHI, M. NAKAZAWA, K. NAKATA AND S. MITA. *Ameliorative effect of SA4503, a novel cognitive enhancer, on the basal forebrain lesion-induced impairment of the spatial learning performance in rats.* PHARMACOL BIOCHEM BEHAV **59**(1) 129–134, 1998.—We investigated the effect of successive administrations of SA4503 (1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride), a novel cognitive enhancer with high affinity and selectivity for the σ_1 receptor subtype, on the cortical cholinergic dysfunction-induced impairment of the spatial learning performance in the Morris water maze (MWM) task in rats. The impairment of the spatial learning performance was produced by the ibotenic acid-induced lesion of the basal forebrain (BF) area in rats. Escape latencies to find the platform during the training trials of the MWM task were significantly prolonged in the BF-lesioned rats compared with the sham-operated rats. Daily treatment with SA4503 (0.1–0.5 mg/kg, PO/day) for 13 days ameliorated this learning deficit. In the probe trial, BF-lesioned rats reduced the number of times each rat crossed the former platform location during the training trials (goal area) in comparison with sham-operated rats. Successive administrations of SA4503 (0.25 mg/kg, PO/day) also significantly increased the BF lesion-induced reduction of the number of times each rat crossed the goal area. These results suggest that the successive administrations of SA4503 attenuate the impairment of the spatial learning performance in rats with cortical cholinergic dysfunction, and that SA4503 is useful as a therapeutic drug for Alzheimer's disease. © 1998 Elsevier Science Inc.

SA4503 Morris water maze (MWM) task Basal forebrain (BF) lesion Spatial learning performance Rats

ALZHEIMER'S disease can be characterized neurochemically, anatomically, and behaviorally. Namely, the cortical cholinergic activity is reduced, the neurons that project to the cortex from the nucleus basalis of Meynert (NBM) are lost, and a loss of memory functions is noticed (5,10,14). Particularly, problems with spatial orientation are prominent in Alzheimer's disease (6,15,32). In addition, numerous studies have indicated that brain cholinergic deficits account for memory loss in patients with senile dementia and Alzheimer's disease (2,8). These findings have provided a rationale for treating Alzheimer's disease patients with cholinomimetic drugs (4), and for the usefulness of animal models in the central cholinergic dysfunction-induced spatial learning impairment, which were caused by cholinergic blocking agents, such as scopolamine (12,39), and by the lesion of the basal forebrain (BF) area (corresponding to the NBM in human) (3,11) in testing the therapeutic drugs for Alzheimer's disease.

The σ_1 receptor subtype has been reported to be involved in the central cholinergic system and memory function. Namely, (+)-*N*-allylnormetazocine [(+)-SKF-10,047], a prototype σ_1 receptor agonist (16), potentiated KCl-evoked acetylcholine (ACh) release in rat hippocampal slices (17). In addition, we showed that (+)-SKF-10,047 dose dependently increased the extracellular ACh level in the rat frontal cortex (22,23), in which the cholinergic neuron terminal project from the BF area (7,10). Moreover, we reported that (+)-SKF-10,047 ame-

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liorated memory impairment induced by scopolamine in rats (25) and mice (34). These findings suggested that selective σ_1 receptor agonists may be useful as novel types of therapeutic drug in dementing disorders, such as Alzheimer's disease.

On the basis of this hypothesis, we found a novel σ_1 receptor agonist, 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl) piperazine dihydrochloride (SA4503) (Fig. 1) (26). Previously, we showed that SA4503 bound to the σ_1 receptor subtype with high affinity but to the other 36 neurotransmitters' receptors, ion channel, and second-messenger systems with low affinity (26,27,33). In addition, it was reported that SA4503 dose dependently increased the extracellular ACh level in the rat frontal cortex and hippocampus (18,27). These effects were due to the enhancement of ACh release, because SA4503 did not affect the ACh-related enzymes activities, such as the choline acetyltransferase (ChAT) and the acetylcholinesterase (AChE), and the sodium-dependent high-affinity choline uptake activity (18). Moreover, we reported that SA4503 ameliorated both scopolamine- and BF-lesion–induced impairment in the passive avoidance task in rats (27,33). In the present study, to confirm the usefulness of SA4503 as a therapeutic drug for Alzheimer's disease, we further examined the effects of successive administrations of SA4503 on the BF-lesion–induced impairment of the spatial learning performance, which is typically used to assess Alzheimer's disease-like behavioral changes in rodents (1), in rats. The spatial learning performance in rats was tested by the Morris water maze (MWM) task (29), which is a useful model for detecting the effect of antiamnesic drugs on the spatial learning performance because it obviates the need for food and water deprivation or electric shock to motivate behavior.

METHOD

The procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with the 'Guide for the Care and Use of Laboratory Animals' (NIH Publication, No. 85-23 1985).

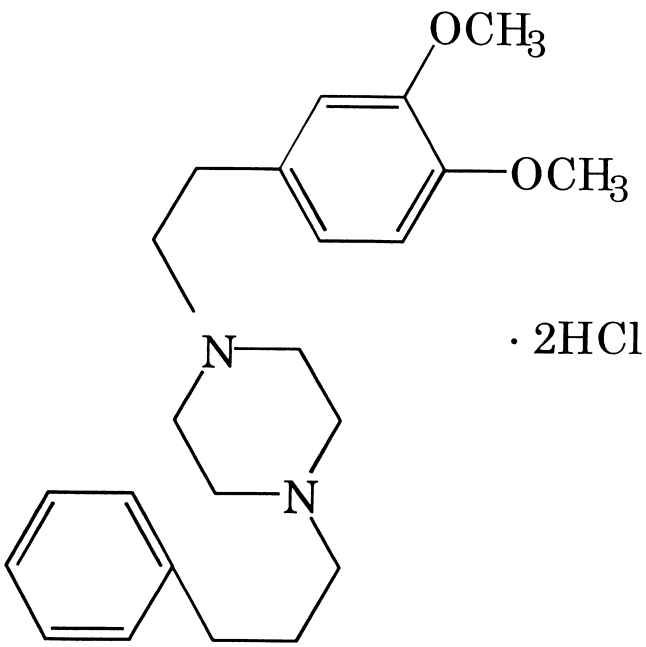

FIG. 1. Chemical structure of SA4503 (1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride).

Animals

Male F-344 rats (Nihon Charles River Inc., Kanagawa, Japan), weighing 250–350 g, were used. They were housed three per cage with free access to food and water, in a controlled environment (23 ± 1°C and 55 ± 5% humidity), with a 12 L: 12 D cycle (light on between 0700 and 1900 h). They were used following at least 7 days' adaptation to laboratory conditions.

Surgical Procedure

The lesion of the bilateral BF areas was made according to the method of Nabeshima et al. (30) with minor modifications (33). Briefly, rats were anesthetized with sodium pentobarbital (40 mg/kg, IP) and fixed on a stereotaxic apparatus. An injection needle connected to a 5-μl microsyringe was inserted into the basal forebrain area, according to the Paxinos and Watson (31) atlas of the rat brain (1.5 mm posterior, 2.8 mm bilateral to the bregma, 7.2 mm below the dura). Ibotenic acid was dissolved in 50 mM phosphate buffer (pH 7.4), at a concentration of 20 μg/μl; 0.5 μl (10 μg per side) was infused for 5 min. The injection needle was left in place for 10 min more to ensure that the drug had diffused away from the needle tip. Sham-operated rats received the 50 mM phosphate buffer without ibotenic acid. Three to 5 days later, a similar lesion was made in the opposite BF area.

MWM Task

A circular water tank (140 cm in diameter and 45 cm high) was used (29). A transparent platform (10 cm in diameter and 30 cm high) was set inside the tank. The platform was located in a constant position in the middle of one quadrant, equidistant from the center and the edge of the pool. The tank was filled with water to a height of 33 cm at approximately 20°C. The platform's surface was 3 cm below the surface of the water. The pool was in a test room with many cues external to the maze (e.g., video-camera, lamps, pictures, etc.); they were visible from within the pool and could be used by the rat for spatial orientation. Positions of the cues were unchanged throughout the training and probe trials of the MWM. The behavior of the rat was monitored with video-camera and analyzed by a Video Image Motion Analyzer (Neuroscience Co., Tokyo, Japan).

The training trials of MWM were started 10 days after the last surgical operation of the bilateral BF-lesion. For each training trial, the rat was placed in the water so that it faced the wall of the pool. Each rat started at one of the three starting positions, and the latency to escape onto the hidden platform was recorded. If the rat found the platform, it was allowed to remain there for 30 s and then returned to its home cage. If it was unable to find the platform within 120 s, it was then removed from the water and placed on the platform for 30 s, a maximum score of 120 s was assigned. Training was conducted for 12 consecutive days, and rats received one training trial each day.

The next day after the final training trial, each rat was given a single probe trial, in which the platform was removed from the tank and the rat was allowed to swim for 120 s. The number of times each rat crossed the former platform location during training trials (goal area) was counted in order to obtain a measure for spatial bias. Each training trial and probe trial were performed between 1100 and 1800 h.

Measurement of ACh-Related Enzymes Activity

The effects of successive administrations of SA4503 on the activity of ChAT and AChE were measured as described previously (18,23,33). Three days after the probe trial of the MWM task, each rat was sacrificed by decapitation, and its frontal cortex, hippocampus, and striatum were rapidly dissected (13). The enzyme solution for the measurement of ChAT activity was prepared from dissected brain tissues by homogenization in 12.5 ml of 25 mM sodium phosphate buffer (pH 7.4) per g of wet weight, using a Teflon homogenizer, followed by centrifugation at 20,000 × g for 60 min at 4°C. The supernatant was diluted 10 times in the above buffer and used as an enzyme solution in which the final concentration of protein was about 0.2 mg/ml. The standard incubation mixture consisted of the following components in a total volume of 200 μl (final concentrations in parentheses): 100 μl of 0.1 M sodium phosphate buffer, pH 7.4 (0.05 M) containing 0.4 mM acetyl-CoA (0.2 mM), 10 mM choline chloride (5 mM), 0.2 mM physostigmine (0.1 mM), 0.3 M sodium chloride (0.15 M), and 20 mM EDTA-2Na (10 mM), and 100 μl of enzyme solution. Incubation was carried out at 37°C for 20 min, and the reaction was stopped with 50 μl of 1 M perchloric acid in an ice-bath. Ten minutes after stoppage, 6 μl of 1 mM isopropylhomocholine was added as an internal standard, and the reaction mixture was centrifuged at 1,600 × g for 10 min at 4°C. A 100 μl aliquot of the supernatant was taken, of which 10 μl aliquot was injected into the high-performance liquid chromatography (HPLC) system. The resultant ACh in the reaction mixture was quantified by HPLC using an immobilized enzyme reactor and an electrochemical detector (ECD) (Eicom, Kyoto, Japan). The reaction mixture was separated by a column (Eicompak AC-Gel, 6 × 150 mm, Eicom, Kyoto, Japan). The enzymatic reactor containing AChE and choline oxidase catalyzed the formation of hydrogen peroxide from ACh and choline. The resultant H_2O_2 was detected by ECD, with a platinum electrode at 450 mV. The mobile phase, which was delivered by a pump at rate of 1.0 ml/min, was 0.1 M sodium-phosphate buffer (pH 8.0) containing 200 mg/liter of sodium 1-decanesulfate and 65 mg/liter of tetraethylammonium chloride.

The enzyme solution for the measurement of AChE activity was prepared from dissected brain tissues by homogenization in 12 ml of 25 mM potassium phosphate buffer (pH 7.0) per g of wet weight, using a Teflon homogenizer at 4°C. The homogenate was diluted 70 times in the above buffer and used as an enzyme solution in which the final concentration of protein was about 0.1 mg/ml. The standard incubation mixture consisted of the following components in a total volume of 1.5 ml (final concentrations in parentheses): 1 ml of 0.075 M potassium phosphate buffer, pH 7.0 (0.05M) containing 0.15 M sodium chloride (0.1 M) and 0.03 M magnesium chloride (0.02 M), 3 mM ACh in water (2 mM), and 500 μl of enzyme solution. Incubation was carried out at 37°C for 15 min, and then the reaction was stopped with 400 μl of 5% metaphosphoric acid in an ice-bath. Ten minutes after stoppage, 200 μl of 1 mM ethylhomocholine in water were added as an internal standard, and the reaction mixture was centrifuged at 1,600 × g for 10 min at 4°C. A 100 μl aliquot of the supernatant was taken, of which 10 μl aliquot was injected into the above HPLC-ECD system. The resultant choline was detected by the same system. For the control experiments, the enzyme solution was boiled at 95°C for 5 min. The protein content was determined by the method of Lowry et al. (20).

Drugs

SA4503 (synthesized in our laboratory), tetrahydroaminoacridine (THA, Aldrich Chemical Company Inc., Milwaukee, WI) and ibotenic acid (Sigma Chemical Co., St. Louis, MO) were used. Other chemicals and reagents of an analytical grade were obtained from commercial suppliers.

Drug Administration

SA4503 and THA were suspended in 1% methylcellulose. Each drug was given at a dose of 0.5 ml/100 g body weight.

SA4503 and THA were orally administered 30 and 60 min before each trial, respectively. Each drug was daily given from the first trial of MWM through the day before the measurement of the ACh related enzymes activity. The sham-operated and BF-lesioned control animals were treated at the corresponding times with 1% methylcellulose instead of the drugs.

Statistical Analysis

The results are expressed in terms of the mean (training trial of the MWM) and mean ± SEM (probe trial of the MWM and biochemical data), respectively. Statistical comparisons were firstly made with the two-way repeated measures analysis of variance (the training trial of MWM), the Kruskal–Wallis test (the probe trial of MWM), or the one-way analysis of variance (the biochemical data), respectively. All of these analyses were followed by a Dunn's test (the number of animals is not equal) or Tukey's test (the number of animals is equal), respectively. In all statistical evaluations, $p < 0.05$ was used as the criterion for statistical significance.

RESULTS

The BF-lesion produced aphagia and ataxia for 3∼5 days after surgery. These behavioral changes were ameliorated by providing water and small amount of food inside the home cage, and did not persist beyond 7 days after surgery.

Effects of Successive Administrations of SA4503 and THA on the BF-Lesion–Induced Impairment of the Spatial Learning Performance in the MWM Task

The escape latency in the first training trial of MWM task did not change by the BF-lesion and the drug treatment (Figs. 2 and 4). The escape latency of the sham-operated group de-

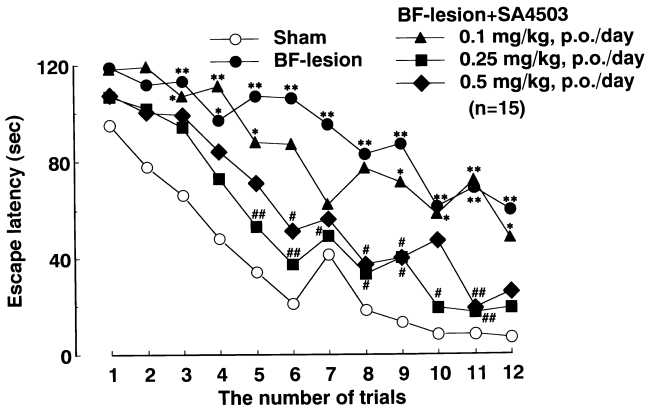

FIG. 2. Effect of successive administrations of SA4503 on the escape latency in the MWM task in the BF-lesioned rats. Values are expressed as the mean. SA4503 (0.1–0.5 mg/kg/day) was orally administered 30 min before each trial. For further details, see Method section. *$p < 0.05$, **$p < 0.01$ vs. Sham operation group. #$p < 0.05$, ##$p < 0.01$ vs. BF-lesioned group.

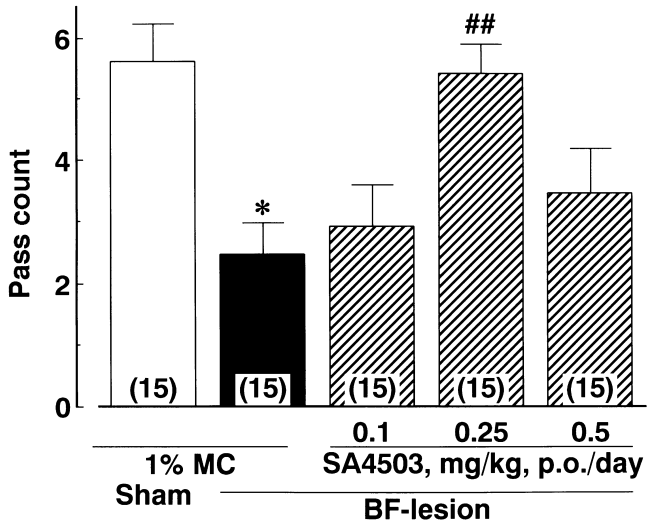

FIG. 3. Effect of successive administrations of SA4503 on the number of cross-count of the goal area in the probe trial of the MWM task in the BF-lesioned rats. SA4503 (0.1–0.5 mg/kg/day) was orally administered 30 min before each trial from the first training trial of MWM task through the probe trial. The number of rats in each group is indicated in parentheses. Values are expressed as mean ± SEM. For further details, see the Method section. $*p < 0.05$ vs. Sham operation group. $\#\#p < 0.01$ vs. BF-lesioned group.

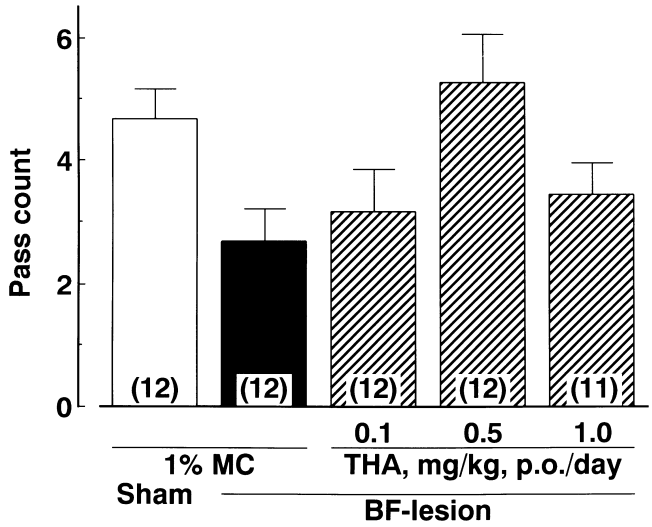

FIG. 5. Effect of successive administrations of THA on the number of cross-count of the goal area in the probe trial of the MWM task in the BF-lesioned rats. THA (0.1–1.0 mg/kg/day) was orally administered 60 min before each trial from the first training trial of MWM task through the probe trial. The number of rats in each group is indicated in parentheses. Values are expressed as mean ± SEM. For further details, see the Method section.

clined progressively during the training period of MWM task; however, the BF-lesioned rats consistently took longer to find the platform than those of the sham group. This change induced by BF-lesion was statistically significant, $F(4, 840) = 63.56$, $p < 0.01$, Fig. 2: $F(4, 648) = 25.67$, $p < 0.01$, Fig. 4. The prolonged escape latency in the BF-lesioned rats was significantly shortened by successive administrations of SA4503 at doses of 0.25 and 0.5 mg/kg, p.o./day, $F(3, 672) = 39.07$, $p < 0.01$, Fig. 2. In addition, the lesion of the BF area reduced the number of times each rat crossed the goal area in the probe trial of MWM task, $H(4) = 18.71$, $p < 0.05$, Fig. 3: $H(4) = 9.41$, $p < 0.05$, Fig. 5; however, the successive administrations of SA4503, at a dose of 0.25 mg/kg, p.o./day, significantly ameliorated this reduction elicited by the BF-lesion, $H(3) = 12.44$, $p < 0.05$, Fig. 3.

Also, the successive administrations of THA tended to attenuate the BF-lesion–induced impairment of the spatial learning performance in both the training trial and the probe trial of the MWM task, at a dose of 0.5 mg/kg, p.o./day (Figs. 4 and 5). Particularly, the effect elicited by THA against BF-lesion–induced impairment of the spatial learning performance in the training trial was statistically significant, $F(3, 516) = 4.85$, $p < 0.01$, Fig. 4: $H(3) = 6.12$, $p > 0.05$, Fig. 5.

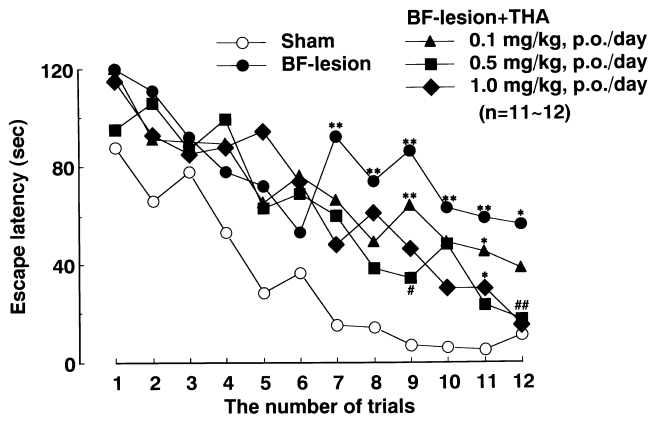

FIG. 4. Effect of successive administrations of THA on the escape latency in the MWM task in the BF-lesioned rats. Values are expressed as the mean. THA (0.1–1.0 mg/kg/day) was orally administered 60 min before each trial. For further details, see the Method section. $*p < 0.05$, $**p < 0.01$ vs. Sham operation group. $\#p < 0.05$, $\#\#p < 0.01$ vs. BF-lesioned group.

Activity of ACh-Related Enzymes in the Frontal Cortex, Hippocampus, and Striatum

The activity of ACh-related enzymes, ChAT, and AChE, in the frontal cortex, hippocampus, and striatum at the next day after the last administrations of SA4503 is shown in Table 1. In the BF-lesioned rats, the activity of both enzymes significantly decreased in the frontal cortex only, as compared with the sham-operated rats [ChAT, $F(4) = 4.28$, $p < 0.05$: AChE, $F(4) = 4.24$, $p < 0.05$]. The lesion of the BF area did not alter the activity of both enzymes in the hippocampus [ChAT, $F(4) = 0.73$, $p > 0.05$: AChE, $F(4) = 0.66$, $p > 0.05$], and striatum [ChAT, $F(4) = 0.77$, $p > 0.05$: AChE, $F(4) = 2.64$, $p > 0.05$].

The successive administrations of SA4503 induced no change in the activities of both enzymes in all regions [ChAT, frontal cortex; $F(3) = 0.50$, $p > 0.05$: hippocampus; $F(3) = 0.93$, $p > 0.05$: striatum; $F(3) = 0.61$, $p > 0.05$: AChE, frontal cortex; $F(3) = 0.09$, $p > 0.05$: hippocampus; $F(3) = 0.17$, $p > 0.05$: striatum; $F(3) = 2.34$, $p < 0.05$].

DISCUSSION

As described in the introductory section, the cholinergic system that projects from the NBM to the cortex plays an im-

TABLE 1

EFFECT OF SUCCESSIVE ADMINISTRATIONS OF SA4503 ON THE ACTIVITY OF CHAT AND ACHE IN THE FRONTAL CORTEX, HIPPOCAMPUS, AND STRIATUM IN THE BF-LESIONED RATS

Group	Frontal Cortex	Hippocampus	Striatum
ChAT activity			
Sham	100.0 ± 5.1	100.0 ± 3.4	100.0 ± 2.9
BF-lesion	79.4 ± 4.1*	104.3 ± 3.9	93.1 ± 3.2
SA4503 (mg/kg, PO/day)			
0.1	76.8 ± 6.1†	102.8 ± 3.0	98.0 ± 3.0
0.25	76.0 ± 4.7†	102.6 ± 2.9	95.8 ± 3.5
0.5	83.3 ± 3.6	97.6 ± 2.2	98.2 ± 2.3
AChE activity			
Sham	100.0 ± 5.1	100.0 ± 3.0	100.0 ± 2.2
BF-lesion	76.0 ± 7.3*	95.5 ± 4.1	103.9 ± 2.7
SA4503 (mg/kg, PO/day)			
0.1	71.1 ± 3.0†	91.4 ± 3.1	112.0 ± 2.7
0.25	74.1 ± 6.7*	94.0 ± 5.4	106.6 ± 3.9
0.5	73.3 ± 5.7*	93.1 ± 3.9	100.1 ± 3.7

Data are expressed as mean ± SEM for the percentage of the average of sham group. The average of ChAT and AChE activities in the sham-operated animals were 1864.6 ± 167.8 (frontal cortex), 1515.0 ± 87.4 (hippocampus), and 6846.0 ± 233.7 pmol/min/mg protein (striatum) and 49.6 ± 3.9 (frontal cortex), 45.5 ± 1.8 (hippocampus), and 220.3 ± 5.4 nmol/min/mg protein (striatum), respectively.*$p < 0.05$, †$p < 0.01$ vs. sham group.

portant role in the memory dysfunction in Alzheimer's disease. In preclinical study, it has also been reported that the lesion of the BF area (corresponding to the NBM area in human) by ibotenic acid, impairs the memory functions in several memory tasks, including the MWM task, in rats (30,39). In addition, it was shown that the lesion of the BF area locally produced a significant decrease in the activity of ChAT and AChE in the frontal cortex (19,21,28,30), because one of the major cholinergic projections to the cortex is known to arise from the BF area (7,10). In agreement with these findings, the present results showed that the ibotenic acid-induced BF-lesion in rats impaired the spatial learning performance in the MWM task, and decreased the activity of ChAT and AChE in the frontal cortex. In addition, THA, an AChE inhibitor, reduced the impairment of the spatial learning performance elicited by BF-lesion in agreement with other's finding (19). Therefore, we considered that the impairment of the spatial learning performance observed in the present study was due to the destruction of the cholinergic neurons that project from the BF area into the frontal cortex.

The present study showed that the successive administrations of SA4503 ameliorated the BF-lesion–induced impairment of the spatial learning performance in rats, and that the dose–response curve of this effect of SA4503 was a bell-shaped one. In general, the dose–response curve of the drugs-induced antiamnesic effects in animals shows a bell-shaped curve (30,35,39). In fact, it was reported that the dose–response curve of the ameliorating effect of THA, which has been confirmed as having antiamnesic effects in patients with Alzheimer's disease (36,37) and was approved in the United States for the treatment of Alzheimer's disease, in memory impaired animals was also a bell-shaped curve (9,38,40). In agreement with these reports, the present results showed that the dose–response curve of the ameliorating effect of THA against the BF-lesion–induced impairment of the spatial learning performance in rats was a bell-shaped one. The spatial learning tasks are typically used to assess Alzheimer's disease-like behavioral changes in rodents (1). Therefore, these findings indicated that SA4503 is useful as a therapeutic drug for Alzheimer's disease, as is THA.

The mechanisms of this ameliorating effect of SA4503 was not clarified in the present study. However, we previously reported that the ameliorating effect of SA4503 in the scopolamine-induced memory impairment was mediated through the σ_1 receptor subtype (33). We also showed that SA4503 increased the extracellular ACh level in the rat frontal cortex through the σ_1 receptor subtype (18,27). Moreover, it was reported that (+)-SKF-10,047, a σ_1 receptor agonist, activated the central cholinergic system (17,22,23,25). As described above, the impairment of the spatial learning performance observed in the present study was due to the dysfunction of the central cholinergic system. These findings suggest that the ameliorating effect of SA4503 in the BF-lesion–induced impairment of the spatial learning performance is due to the activation of the central cholinergic system, probably the BF cholinergic system, which project into the frontal cortex, through the σ_1 receptor subtype. This suggestion is supported by our previous finding that (+)-SKF-10,047–induced antiamnesic effect was mediated through the activation of the central cholinergic system (24).

In conclusion, the present study showed that the successive administrations of SA4503, a novel σ_1 receptor agonist, ameliorated the BF-lesion–induced impairment of the spatial learning performance in the MWM task in rats. Because the problems with spatial orientation are prominent in Alzheimer's disease (6,15,32), therefore, these findings indicate that SA4503 is useful as a therapeutic drug for Alzheimer's disease.

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