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Sigma$_1$ Receptor Subtype Does Not Interact With Stereotyped Behaviors in Rats

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KOBAYASHI, T., K. MATSUNO AND S. MITA. *Sigma$_1$ receptor subtype does not interact with stereotyped behaviors in rats*. PHARMACOL BIOCHEM BEHAV **61**(4) 381–384, 1998.—In the present study, we clearly showed that the sigma$_1$ receptor subtype did not interact with the induction of stereotyped behaviors in rats. Namely, (+)-*N*-allylnormetazocine [(+)-SKF-10,047] (5.0, 10.0, and 20.0 mg/kg, SC), a traditional sigma receptor ligand that has affinities for the sigma$_1$ receptor subtype and the *N*-methyl-D-aspartate (NMDA)/phencyclidine (PCP) receptor channel complex, markedly produced PCP-like stereotyped behaviors, such as head weaving, turning, and backpedaling, in rats. On the contrary, 1-(3,4-dimethoxyphenyl)-4-(3-phenylpropyl)piperazine dihydrochloride (SA4503), a potent and selective sigma$_1$ receptor agonist, did not produce these behaviors. Additionally, PCP-induced stereotyped behaviors were significantly augmented by (+)-SKF-10,047, but not by SA4503. We thus suggest that the induction of PCP-like stereotyped behaviors elicited by (+)-SKF-10,047 closely interacts with NMDA/PCP receptor channel complex but not with the sigma$_1$ receptor subtype. © 1998 Elsevier Science Inc.

Sigma$_1$ receptor agonist—SA4503—(1-(3,4-Dimethoxyphenyl)-4-(3-phenylpropyl)piperazine dihydrochloride)
Sigma$_1$ receptor subtype Stereotyped behaviors

SINCE the identification of sigma receptor subtypes were reported (22), intensive studies to elucidate the physiological function of the sigma receptor subtypes have been carried out (3,26,27). As one of the physiological function, it has been reported that the sigma$_1$ receptor subtype may be involved in the induction of psychostimulated actions. For example, *N*-allylnormetazocine (SKF-10,047) and its stereoisomers, which have affinities for the sigma$_1$ receptor subtype, and related benzomorphans induced psychostimulated actions in humans (1,4) and animals (2,10,18,19). In addition, (+)-SKF-10,047–induced stereotyped behavior was reversed by pretreatment of putative sigma receptor antagonists, such as *N,N*-dipropyl-2-(4-methoxy-3-(2-phenylethoxy)phenyl)ethylamine monohydrochloride (NE-100) (20). However, these benzomorphans have binding affinities not only for the sigma$_1$ receptor subtype but also the *N*-methyl-D-aspartate (NMDA)/phencyclidine (PCP) receptor channel complex (6,21). In addition, NE-100 (20) has been reported to bind to the NMDA/PCP receptor channel complex (28). Moreover, PCP, which has a binding affinity for NMDA/PCP receptor channel complex, is also reported to produce stereotyped behaviors (18,19). These behaviors are similar to those elicited by (+)-SKF-10,047 (18,20). Therefore, it is doubtful that the sigma$_1$ receptor subtype is involved in the induction of psychostimulated actions.

We recently found a novel sigma$_1$ receptor agonist, 1-(3,4-dimethoxyphenyl)-4-(3-phenylpropyl)piperazine dihydrochloride (SA4503) (11). This compound has a high affinity and selectivity for the sigma$_1$ receptor subtype, and it has no affinity for the NMDA/PCP receptor channel complex (11). In the present study, to elucidate whether the sigma$_1$ receptor subtype is involved in the induction of psychostimulated actions, we examined the effect of SA4503 alone and in combination with PCP on the induction of stereotyped behaviors in rats.

METHOD

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

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Animals

Male Wistar rats (7 weeks, Nihon SLC, Shizuoka, Japan) were used in all experiments. Rats were housed four per cage under a regulated environment (23 ± 1°C, 55 ± 10% humidity). Food and water were freely available and a 12 L:12 D cycle (lights on between 0700 to 1900 h) was set. Following adaptation to laboratory conditions for at least 7 days, rats were used for experiments.

Drugs

SA4503 (11) and PCP were synthesized by Santen Pharmaceutical Co., Ltd. (Osaka, Japan). (+)-SKF-10,047 was purchased from Research Biochemicals Inc. (Wayland, MA). SA4503 was suspended in 1% methylcellulose solution. PCP and (+)-SKF-10,047 were dissolved in saline solution.

Experimental Protocol

In the first experiment, SA4503 (0.1, 1.0, 10.0, and 20.0 mg/kg, PO) or (+)-SKF-10,047 (5.0, 10.0, and 20.0 mg/kg, SC) was administered alone. The numbers of head weaving, turning, and backpedaling occurring over a 15-min period immediately after each drug administration were counted (18,19). In the second experiment, 20 min after administration of SA4503 or (+)-SKF-10,047, PCP (5.0 mg/kg, IP) was administered and occurrences were counted for a 15-min period PCP administration.

TABLE 1

EFFECTS OF SA4503 AND (+)-SKF-10,047 ON THE INDUCTION OF STEREOTYPED BEHAVIORS IN RATS

Treatment	*n*	Counts
Head Weaving		
SA4503		
0.1 mg/kg	6	0
1.0 mg/kg	6	0
10.0 mg/kg	6	0
20.0 mg/kg	6	0
(+)-SKF-10,047		
5.0 mg/kg	6	4.50 ± 1.71
10.0 mg/kg	6	33.83 ± 9.96
20.0 mg/kg	6	71.67 ± 22.95
Turning		
SA4503		
0.1 mg/kg	6	0
1.0 mg/kg	6	0
10.0 mg/kg	6	0
20.0 mg/kg	6	0
(+)-SKF-10,047		
5.0 mg/kg	6	3.67 ± 1.87
10.0 mg/kg	6	18.00 ± 6.85
20.0 mg/kg	6	22.67 ± 9.66
Backpedaling		
SA4503		
0.1 mg/kg	6	0
1.0 mg/kg	6	0
10.0 mg/kg	6	0
20.0 mg/kg	6	0
(+)-SKF-10,047		
5.0 mg/kg	6	0.33 ± 0.21
10.0 mg/kg	6	3.33 ± 1.61
20.0 mg/kg	6	2.83 ± 1.28

Data are expressed as the means ± SEM. The number of each behavior was counted 15 min immediately after administration of SA4503 and (+)-SKF-10,047, respectively.

Statistical Analysis

Results were expressed as the means ± SEM. Comparisons between PCP alone and in combination with SA4503 or (+)-SKF-10,047 were performed by analysis of variance (ANOVA) followed by Dunnett's multiple range comparison test. *p*-Values of less than 0.05 were considered significant.

RESULTS

Effects of SA4503 and (+)-SKF-10,047 on the Induction of Stereotyped Behaviors in Rats

SA4503 (0.1, 1.0, 10.0, and 20.0 mg/kg, PO) did not produce head weaving, turning, or backpedaling in rats (Table 1). In addition, SA4503-treated rats did not elicit these behaviors at least 60 min after administration (data not shown). On the contrary, (+)-SKF-10,047 (5.0, 10.0, and 20.0 mg/kg, S.C.) induced a marked level of these behaviors in rats (Table 1).

Effects of SA4503 and (+)-SKF-10,047 on PCP-Induced Stereotyped Behaviors in Rats

PCP (2.5, 5.0, and 7.5 mg/kg, IP) dose-dependently produced head weaving, turning, and backpedaling (data not shown) in agreement with the results of a previous report (18). SA4503 (0.1, 1.0, 10.0, and 20.0 mg/kg, PO) did not have any significant effects on PCP (5.0 mg/kg, IP)-induced stereotyped behaviors in rats (Fig. 1). In contrast, (+)-SKF-10,047 potentiated the PCP-induced stereotyped behaviors (Fig. 2). Particularly, (+)-SKF-10,047, at a dose of 5.0 mg/kg, significantly augmented the PCP-induced head weaving and backpedaling (Fig. 2). However, the combination of PCP with a high dose of (+)-SKF-10,047 (20.0 mg/kg) did not enhance the PCP-induced behaviors (Fig. 2).

DISCUSSION

Previously, (+)-SKF-10,047 and related benzomorphans have been demonstrated to induce psychostimulated actions in humans (1,4) and animals (2,10,18,19). As these agents have a binding affinity for the $sigma_1$ receptor subtype (5,20,21), it may be involved in the induction of psychostimulated actions. However, benzomorphans have a high affinity not only for the $sigma_1$ receptor subtype but also other receptors (6). Thus, it is not clear whether the $sigma_1$ receptor subtype is involved in the induction of psychostimulated actions.

Our present results clearly showed that the differential effects between SA4503 and (+)-SKF-10,047 on the induction of stereotyped behaviors in rats. In fact, SA4503 did not elicit stereotyped behaviors in rats and did not augment them in PCP-treated rats. This compound has been reported to be a potent and selective $sigma_1$ receptor agonist, which has a high affinity for this site with an IC_{50} value of 17.4 nM (11). However, (+)-SKF-10,047, a traditional $sigma_1$ receptor agonist, markedly elicited stereotyped behaviors similar to PCP-induced behaviors, when administered alone, and this compound significantly augmented these behaviors in PCP-treated rats. We previously showed that SA4503 and (+)-SKF-10,047 elicited similar effects in rats, such as the enhancement of cerebral acetylcholine release (7,8,13) and the improvement of experimental amnesia (14,15,23), by the present administration

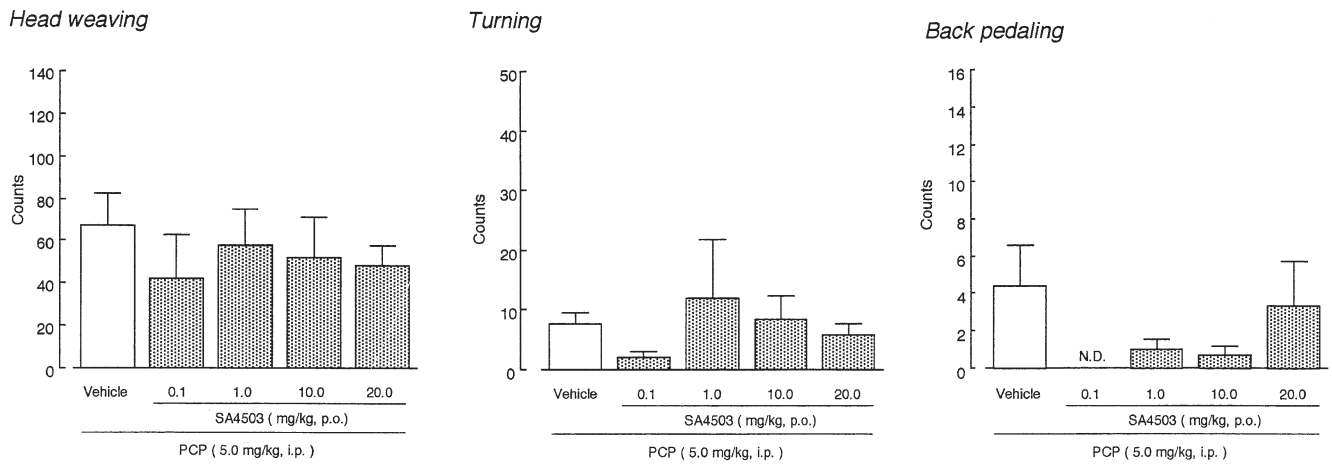

FIG. 1. Effects of SA4503 on the phencyclidine (PCP)-elicited head weaving, turning, and backpedaling in rats. The number of times each behavior occurred was counted for a 15-min period immediately after PCP administration. SA4503 was administered 20 min before the administration of PCP. Data are expressed as the means ± SEM from six rats. N.D.: not detect.

route and schedule. In addition, these effects were mediated via the sigma$_1$ receptor subtype (7,8,13,15). Therefore, the difference between the effects of SA4503 and (+)-SKF-10,047 on the induction of stereotyped behaviors was due to the specificity of receptor binding affinity by each agonist. In fact, although SA4503 has high selectivity for the sigma$_1$ receptor subtype (11), (+)-SKF-10,047 has low selectivity and binds to other receptors, particularly the NMDA/PCP receptor channel complex (6,20). This also implies that the induction of stereotyped behaviors is not influenced by the sigma$_1$ receptor subtype.

However, the augmentation of PCP-induced stereotyped behaviors elicited by (+)-SKF-10,047 was not dose-dependent. Similarly, the previous report also showed that PCP-induced stereotyped behaviors are not dose dependent, probably due to the induction of ataxia by high doses of PCP (2,25). Thus, it is possible that the combination of PCP with high doses of (+)-SKF-10,047 excessively stimulates the NMDA/PCP receptor channel complex and induces ataxia. In fact, we found that a high dose of (+)-SKF-10,047 decreased the PCP-induced increase in locomotor activity (data not shown). These findings suggest that the NMDA/PCP receptor channel complex plays a key role in the induction of stereotyped behaviors.

Okuyama et al. (20) reported that several sigma receptor antagonists, such as NE-100, [1-(cyclopropylmethyl)ethyl]-4-(2′(4′-fulorophenyl)-2′-oxoethyl)piperidine hydrobromide (Dup734) and 4-[2′-(4″-cyanophenyl)-2′-oxoethyl]-1-(cyclopropylmethyl) piperidine (XJ448) inhibited the (+)-SKF-10,047-induced head weaving. However, these antagonists were also reported to inhibit [^{3}H]N-[1-(2-thienyl)cyclohexyl]piperidine ([^{3}H]TCP), a noncompetitive antagonist for the NMDA/PCP receptor channel complex, binding in a primary culture of rat neuronal cells (28). In addition, these compounds inhibited not only the (+)-SKF-10,047–induced head weaving but also that induced

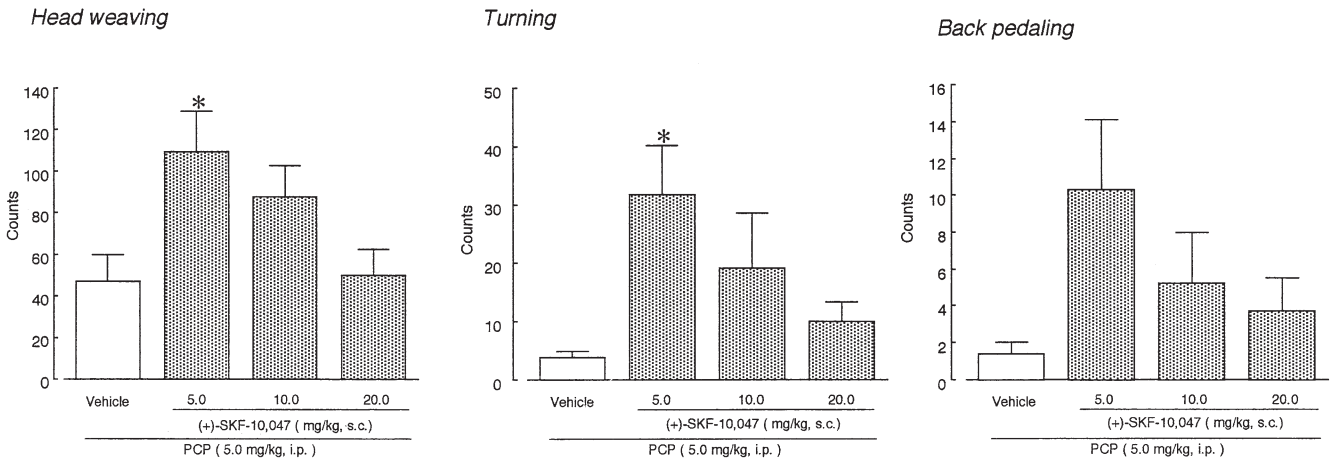

FIG. 2. Effects of (+)-SKF-10,047 on the phencyclidine (PCP)-elicited head weaving, turning, and backpedaling in rats. The number of times each behavior occurred was counted for a 15-min period immediately after PCP administration. (+)-SKF-10,047 was administered 20 min before the administration of PCP. Data are expressed as the means ± SEM from 6 to 12 rats. *$p < 0.05$ compared with the corresponding Vehicle + PCP group.

by PCP (20). These results suggest that the $sigma_1$ receptor subtype does not interact with the induction of psychostimulated actions. The NMDA/PCP receptor channel complex plays an important role in the induction of psychostimulated actions.

We reported that SA4503 increases the contents of dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC) in the rat frontal cortex (9) and has an antidepressive effect in the mouse forced-swimming test (12). In addition, this compound enhances cerebral acetylcholine release (7,14) and has ameliorating effects against memory impairment with cholinergic dysfunction in rats (14,16,17,23,24). Thus, we suggest that SA4503 is a novel candidate as a therapeutic drug for depression and/or Alzheimer's disease. Moreover, we showed that SA4503 did not cause any cholinomimetic side effects (7,14). Therefore, we believe that SA4503 may be a useful drug with no undesirable side effects.

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