Effects of SUN 8399, a Potent and Selective 5-HT_{1A} Agonist, on Conflict Behavior and Ambulatory Activity in Mice: Comparison with Those of Buspirone, Tandospirone and Diazepam

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ABSTRACT—Behavioral effects of p.o. administration of SUN 8399, a selective 5-HT_{1A} agonist, on the operant behavior under a MULT VI 1.5 min/FR 5-punishment schedule of food reinforcement and on the ambulatory activity were evaluated in mice, and the characteristics were compared with those of other 5-HT_{1A} agonists, buspirone and tandospirone, and the benzodiazepine diazepam. Diazepam (3 and 10 mg/kg) significantly increased the punished response without eliciting any significant change in the non-punished response; i.e., showing anticonflict action. SUN 8399 (3-30 mg/kg) and buspirone (1-10 mg/kg) did not significantly change either the punished or non-punished responses. Tandospirone significantly increased the non-punished response at 10 mg/kg, but significantly decreased both the punished and non-punished responses at 30 mg/kg. The single administration of SUN 8399 (10 mg/kg), buspirone (3 and 30 mg/kg) and tandospirone (10 and 30 mg/kg) significantly increased the ambulatory activity, while diazepam tended to decrease it. The ambulation-increasing effect of methamphetamine (2 mg/kg, s.c.) was reduced by buspirone (10 and 30 mg/kg) and tandospirone (10 and 30 mg/kg), but enhanced by diazepam (3 and 10 mg/kg). Buspirone (30 mg/kg), tandospirone (10 and 30 mg/kg) and diazepam (3 and 10 mg/kg) significantly reduced the ambulation-increasing effect of scopolamine (0.5 mg/kg, s.c.). SUN 8399 (3-100 mg/kg) did not modify the effects of either methamphetamine or scopolamine. The present results suggest that 5-HT_{1A} agonists scarcely show anticonflict action on the Geller-type conflict behavior in mice. However, SUN 8399 possesses different behavioral characteristics from those of the other two 5-HT_{1A} agonists in terms of interactions with methamphetamine and scopolamine.

Keywords: SUN 8399, 5-HT_{1A} agonist, Conflict behavior, Ambulatory activity, Drug interaction

Recently, some novel drugs that are non-benzodiazepine derivatives have been receiving attention as anxiolytics. For example, compounds such as buspirone and tandospirone show agonistic action on 5-HT_{1A} receptors (1-7) without directly interacting with the GABA/benzodiazepine receptor complex (8), and they have been reported to increase the punished response in some types of conflict tasks in rats, monkeys and pigeons (9-23), although several negative results have been also demonstrated in rats (20, 24, 25). Moreover, Kuribara (26) has demonstrated no significant change and/or rather a decrease in the punished responses in Geller-type, Vogel-type and hypertonic NaCl solution situations following intraperitoneal administration of buspirone in mice. It is suggested that both buspirone and tandospirone can interact with not only 5-HT_{1A} receptors but also with 5-HT_2, dopamine D_2 and other receptors (1, 27).

On the other hand, SUN 8399, 4-{4-[4-(2-pyrimidinyl)-piperazin-1-yl]butyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine-3,5-dione HCl (Suntory Co., Osaka; Fig. 1), has been considered to be highly selective towards 5-HT_{1A} receptors; its binding affinities for 5-HT_{1A}, 5-HT_2 and dopamine D_2 receptors are estimated to be respectively 6-8, 1/4-1/10 and 1/10 times as potent as those of buspirone and tandospirone (28, 29). SUN 8399 was demonstrated to attenuate the punished response under the hypertonic NaCl solution procedure in rats (30, 31). However, the effect of SUN 8399 on the punished behavior of mice under a Geller-type conflict situation has not been evaluated.

Hence, the purposes of this study were to assess whether SUN 8399 could increase the punished response

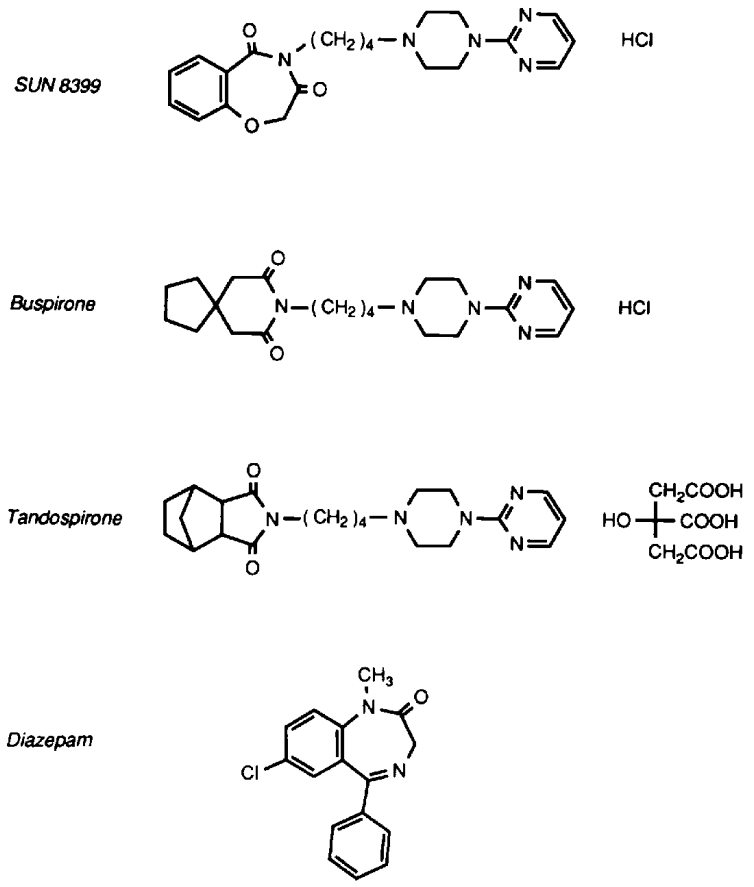

Fig. 1. Chemical structures of SUN 8399; 4-{4-[4-(2-pyrimidinyl)piperazin-1-yl]butyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine-3,5-dione HCl, buspirone, tandospirone and diazepam.

under an operant schedule of MULT VI 1.5 min/FR 5-punishment of food reinforcement in mice. In addition, the effects of SUN 8399, administered singly and in combination with methamphetamine or scopolamine, on the ambulatory activity of mice were also observed to assess the interactions with drugs having actions on the dopaminergic and cholinergic transmissions. The behavioral characteristics of SUN 8399 were compared with those of 5-HT_{1A} agonists, buspirone and tandospirone, and the benzodiazepine anxiolytic diazepam.

MATERIALS AND METHODS

Animals

Adult male mice of the ddY strain (Japan Laboratory Animals, Tokyo) were used in this study. They had been group housed in acrylic fiber breeding cages of 20(W) × 25(D) × 15(H) cm (10 mice/cage) and freely given solid diet (MF: Oriental Yeast, Tokyo) and tap water. The breeding room conditions were controlled: room temperature, 23±2℃; relative humidity, 50±3%; and a 12-hr light-dark schedule, light period of 06:00–18:00. When the mice were 7 and 8 weeks of age, they were used in the ambulation measurement and conflict test, respectively.

Drugs

Drugs used were SUN 8399 HCl (Suntory Co., Osaka), buspirone HCl (Suntory Co.), tandospirone citrate (Suntory Co.), diazepam (Suntory Co.), methamphetamine HCl (Dainippon Pharm., Osaka) and scopolamine HBr (Sigma Chem., St. Louis, MO, USA). SUN 8399, buspirone, tandospirone and diazepam were dissolved and/or suspended with distilled water, and administered per orally (p.o.). Methamphetamine and scopolamine were dissolved with physiological saline and administered subcutaneously (s.c.). The drug concentration was adjusted so that each volume administered was always constant at 0.1 ml/10 g body weight of the mouse.

Conflict test

Prior to the start of the conflict test, 10 mice selected for this test were moved from the breeding cage to smaller cages of 15(W) × 20(D) × 12(H) cm, and where they were

group housed (5 mice/cage) under a food-deprivation condition (4 g/mouse/day) throughout the experimental period for longer than 3.5 months.

The apparatus used in the conflict test (operant chamber of 18(W) × 9(D) × 9(H) cm, controller and recorder: GT-8501, GT-8805 and GT-7715, respectively: O'hara & Co., Tokyo) was the same as that used in our previous study (32). The food-deprived mice were trained under the operant schedule of MULT VI 1.5 min/FR 5-punishment of food reinforcement. The experimental session consisted of 3 pairs of the safe period (6 min) and the alarm period (4 min); thereby, each session lasted for 30 min. In the safe period, the mouse's lever-presses were reinforced by a food pellet (20 mg) at average intervals of 1.5 min without shock. In the alarm period, which was indicated by an 800-Hz tone signal, every 5th lever-press was reinforced by the food pellet and simultaneously punished with an electric shock (80 V, 0.3 mA, 50 Hz AC, and duration of 0.5 sec). The shock intensity was selected to decrease the average response rate to about 1/10 of that without shock. After an establishment of stable baseline responses in both the safe and alarm periods, i.e., emitting a moderate to high response rate (more than 6/min) in the safe period and a low response rate (less than 3/min) in the alarm period, the drug testing sessions were inserted at 3- to 4-day intervals. The drugs and their doses tested were SUN 8399 (3, 10 and 30 mg/kg), buspirone (1, 3 and 10 mg/kg), tandospirone (1, 3, 10 and 30 mg/kg) and diazepam (1, 3 and 10 mg/kg). Considering the onset times of the peak effect, SUN 8399, buspirone and tandospirone were administered 30 min before the start of the session and diazepam administered at 10 min before. On the day before each drug-testing session, distilled water was administered as the control session. The indices of the behavior were the mean response rates in the safe and alarm periods.

The conflict test was conducted between 9:00 – 14:00.

Ambulation measurement

The apparatus for measuring the ambulatory activity of mice consisted of 2 equivalent sets of tilting-type ambulometers having 10 bucket-like Plexiglas activity cages of 20 cm in diameter (SMA-10, O'hara & Co.). The apparatus recorded a slight tilt of the activity cage generated only by the ambulation of a mouse; thereby, it could selectively detect horizontal movement (namely ambulation or locomotion), but not pivotting and vertical movements such as rearing, sniffing, grooming, etc.

Mice were individually put into the activity cages, and after an adaptation period of 20 min, the drugs were administered. Then the ambulatory activity of each mouse was measured for 90 min.

Single administration: Effects of SUN 8399 (3, 10, 30 and 100 mg/kg), buspirone (1, 3, 10 and 30 mg/kg), tandospirone (1, 3, 10 and 30 mg/kg) and diazepam (1, 3 and 10 mg/kg) were assessed. As the control experiment, distilled water was administered.

Combined administration: Effects of combined administration of methamphetamine (2 mg/kg) or scopolamine (0.5 mg/kg) with SUN 8399 (3, 10, 30 and 100 mg/kg), buspirone (1, 3, 10 and 30 mg/kg), tandospirone (1, 3, 10 and 30 mg/kg) and diazepam (1, 3 and 10 mg/kg) were evaluated. The two drugs were administered simultaneously. As the baseline and control experiments, the administrations of saline (s.c.) with distilled water (p.o.) and methamphetamine or scopolamine (s.c.) with distilled water (p.o.), respectively, were carried out.

The ambulation measurement was conducted between 9:00 – 15:00.

Statistical analyses

The mean overall response rates in both the safe and alarm periods in the conflict test, and the mean overall activity counts were compared by Student's *t*-test.

RESULTS

Conflict test

In each drug evaluation, the average rate of the punished response in the water-administered control sessions was calculated in each mouse. When the rate was higher than 3/min, the mouse was excluded from the assessment of the drug effect. Thereby, the numbers of competent mice were 8 for the evaluations of SUN 8399, tandospirone and diazepam, and 9 for buspirone.

Figure 2 shows the mean overall rates of the non-punished response (upper panel) and the punished response (lower panel) following the administration of SUN 8399, buspirone, tandospirone and diazepam. SUN 8399 (3 – 30 mg/kg) and buspirone (1 – 10 mg/kg) did not significantly increase either the non-punished response or the punished response. Tandospirone significantly increased the non-punished response at 10 mg/kg, but significantly decreased both the punished and non-punished responses at 30 mg/kg. Diazepam significantly and dose-dependently increased the punished response without eliciting any marked change in the non-punished response.

Ambulation measurement

Single administration: As shown in Fig. 3, SUN 8399 (10 mg/kg), buspirone (3 and 30 mg/kg) and tandospirone (10 and 30 mg/kg) significantly increased the ambulatory activity of mice. Time-course changes showed that a slight decrease in the ambulation was observed for 10 – 30 min after the administration, and this was followed by an increase in the activity (data are not shown). In contrast,

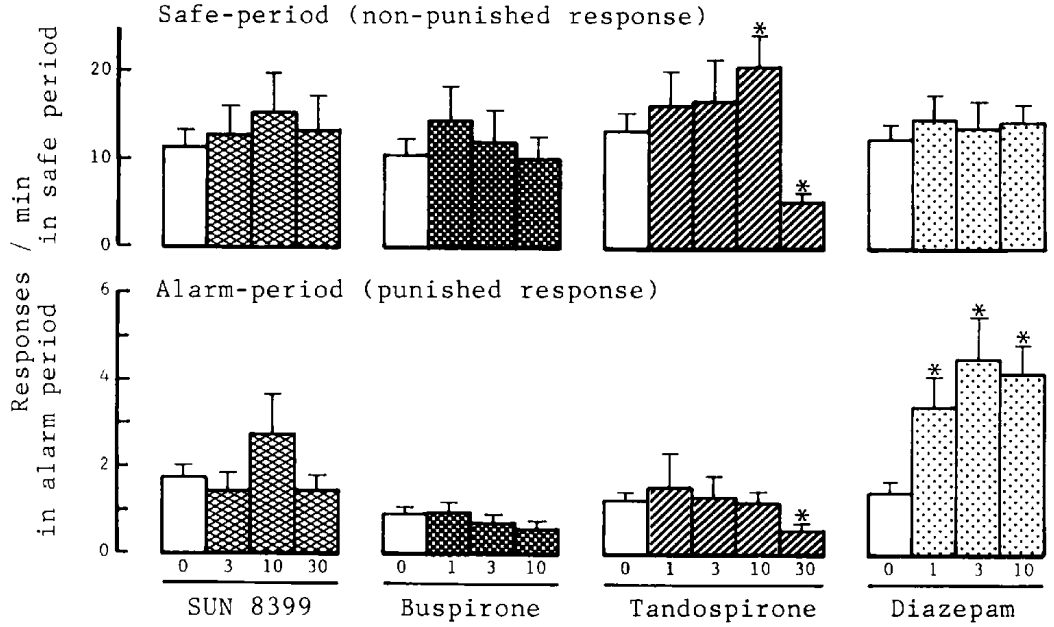

Fig. 2. Mean overall rates with S.E.s of the non-punished response (upper panel) and punished response (lower panel) following p.o. administration of SUN 8399, buspirone, tandospirone and diazepam under the MULT VI 1.5 min/FR 5-punishment schedule of food reinforcement in mice. The figures attached to the drug name are the doses administered (mg/kg). *: $P<0.05$ vs. the control values following administration of distilled water (dose=0), which was conducted on the day preceding each drug administration. N=8 for SUN 8399, tandospirone and diazepam, and N=9 for buspirone.

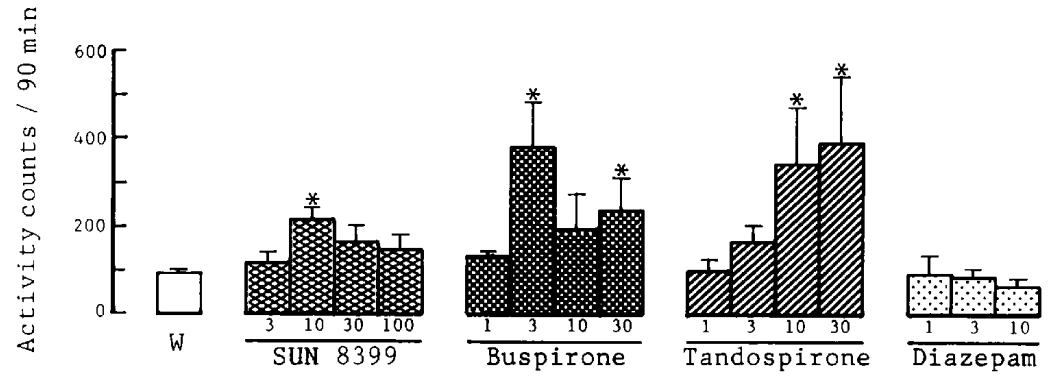

Fig. 3. Mean overall 90-min ambulatory activity counts with S.E.s after the single p.o. administration of SUN 8399, buspirone, tandospirone and diazepam in mice. The figures attached to the drug name are the doses administered (mg/kg). *: $P<0.05$ vs. control value following the administration of distilled water (W). N=10 for the control administration, and N=5 for each drug administration.

diazepam tended to decrease the activity throughout the observation period.

Combined administration with methamphetamine: As shown in Fig. 4, methamphetamine (2 mg/kg) increased the overall ambulatory activity. The peak effect appeared at about 40 min after the administration. Buspirone (10 and 30 mg/kg) and tandospirone (10 and 30 mg/kg) significantly reduced the ambulation-increasing effect of methamphetamine, whereas diazepam (3 and 10 mg/kg) significantly enhanced it. However, SUN 8399 (3–100 mg/kg) did not modify the effect of methamphetamine.

Combined administration with scopolamine: As shown in Fig. 5, scopolamine (0.5 mg/kg) increased the overall ambulatory activity. The peak effect appeared at about 20 min after the administration. Buspirone (30 mg/kg), tandospirone (10 and 30 mg/kg) and diazepam (3 and 10 mg/kg) significantly reduced the ambulation-increasing effect of scopolamine, whereas SUN 8399 (3–100 mg/kg) did not produce any significant change in it.

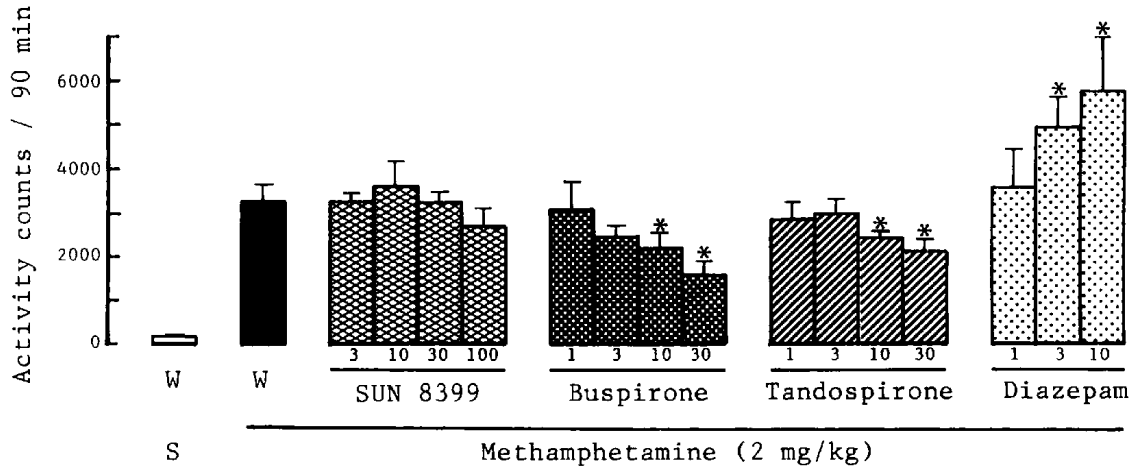

Fig. 4. Mean overall 90-min ambulatory activity counts with S.E.s after the combined administration of methamphetamine (2 mg/kg, s.c.) with p.o. administration of SUN 8399, buspirone, tandospirone and diazepam in mice. The figures attached to the drug name are the doses administered (mg/kg). *: $P<0.05$ vs. methamphetamine control (administration with water (W) p.o.). $N=10$ for the baseline experiment (administration of saline (S) s.c. with water p.o.) and methamphetamine control, and $N=5$ for each combined administration.

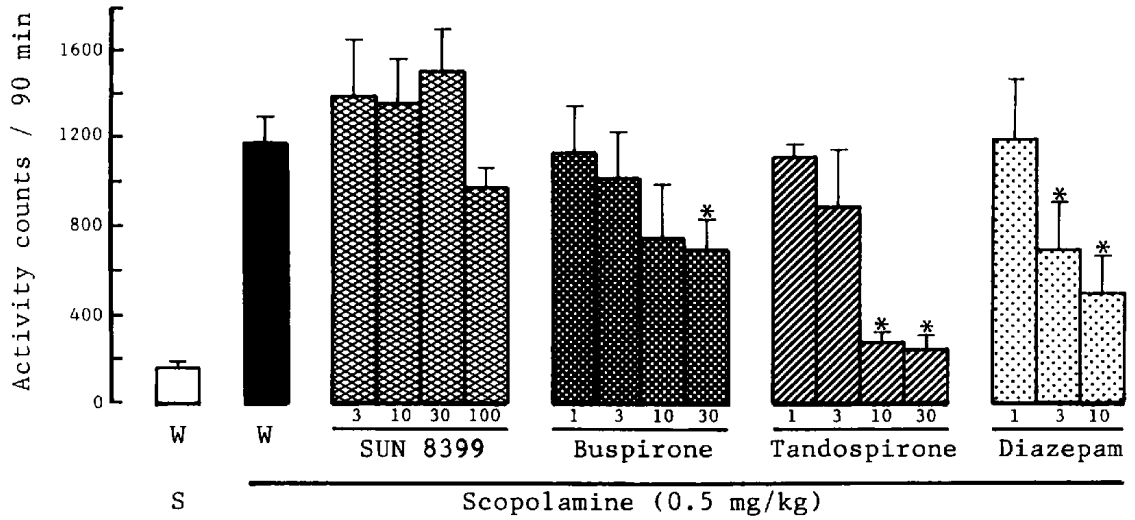

Fig. 5. Mean overall 90-min ambulatory activity counts with S.E.s after the combined administration of scopolamine (0.5 mg/kg, s.c.) with p.o. administration of SUN 8399, buspirone, tandospirone and diazepam in mice. The figures attached to the drug name are the doses administered (mg/kg). *: $P<0.05$ vs. scopolamine control (administration with water (W) p.o.). $N=10$ for the baseline experiment (administration of saline (S) s.c. with water p.o.) and scopolamine control, and $N=5$ for each combined administration.

Gross observation

Following the administration of relatively higher doses of SUN 8399, buspirone or tandospirone, the mice in the conflict test sometimes exhibited licking of the side wall as well as a slight behavioral excitation in the operant chamber and an increment in the locomotion in the activity cage. On the other hand, diazepam produced ataxia.

DISCUSSION

It is well known that benzodiazepine anxiolytics increase the punished response (attenuation of conflict behavior) under various types of conflict situations regardless of the animal species (33–35). Consistent with such evidence, the present experiment also demonstrated a significant and dose-dependent increase in the punished response in mice under the operant schedule of MULT VI

1.5 min/FR 5-punishment of food reinforcement following the administration of diazepam. This result indicates that the present conflict test was adequate for evaluating whether the test drugs showed a conflict attenuating action.

There have been some reports that 5-HT_{1A} agonists including buspirone and tandospirone increased the punished response in rats, monkeys and pigeons (9–23). However, such an effect could not be confirmed in mice. Kuribara (26) reported that the intraperitoneal administration of buspirone did not increase, but rather decreased the punished response in mice under 3 different conflict situations: Geller-type, Vogel-type and hypertonic NaCl procedure. The present data on buspirone were basically identical with those observed in the previous study (26). Thus, buspirone as well as SUN 8399 and tandospirone never significantly increased the punished response. It is therefore considered that 5-HT_{1A} agonists may scarcely increase the punished response in mice, suggesting the presence of a species difference between mice and rats. However, to confirm this hypothesis, the pharmacokinetic evaluations in both species are required.

On the other hand, it is interesting to note that tandospirone (10 mg/kg) significantly increases the non-punished response. SUN 8399 (10 mg/kg) and buspirone (1 mg/kg) also tended to show such an action, although the change did not reach a significant level. These results suggest that SUN 8399, buspirone and tandospirone show a weak behavior-accelerating action at lower to moderate doses.

Such behavior-accelerating action could also be confirmed in terms of the ambulatory activity. Thus, the single administration of SUN 8399, buspirone and tandospirone significantly increased the ambulatory activity at several doses in this experiment. There have been reports that 5-HT_{1A} agonists suppress ambulatory (locomotor) activity in mice (e.g., 36), and such a result is inconsistent with the present ones. However, these diverse results might be due to the difference in the observation period. Although a decrease in the activity was induced within 30 min after the administration, an increase in the activity was produced thereafter. Miller et al. (36) also reported a transient decrease in the activity during 10–20 min after the administration of tandospirone. There is a possibility that the slight behavior-accelerating action of 5-HT_{1A} agonists is related to disinhibition of the clinically depressed state in humans, although a further study is required to confirm this hypothesis.

Generally, it has been considered that an enhancement in the dopaminergic transmission is involved in the induction of the behavioral excitation including increment in the locomotion (37). However, the slight behavioral excitation following SUN 8399, buspirone and tandospirone may not be attributable to the direct stimulant action on the dopaminergic system. This is because buspirone and tandospirone never enhanced, but rather reduced the ambulation-increasing effects of both methamphetamine, an enhancer of release and reducer of reuptake of dopamine at presynaptic terminal (38), and scopolamine, an enhancer of dopamine release through blockade of cholinergic inhibitory system (39–41). Buspirone has been suggested to show anti-dopaminergic action at postsynaptic receptors (27, 42) as well as a disinhibitory action on the dopaminergic system through stimulation of 5-HT_{1A} receptors at presynaptic neurons (15). It is therefore highly probable that the agonistic action on 5-HT_{1A} receptors is involved in the light behavioral excitation in mice as demonstrated in this study, i.e., showing a behavioral stimulant action following the single administration, but reducing the ambulation-increasing effects of methamphetamine and scopolamine.

In terms of the drug interactions, however, the characteristics of SUN 8399 were much different from those of buspirone and tandospirone. Thus, unlike buspirone and tandospirone, SUN 8399 did not significantly modify the ambulation-increasing effects of both methamphetamine and scopolamine. It has been reported that SUN 8399 possesses selectively and fully agonistic action on 5-HT_{1A} receptors, whereas buspirone and tandospirone have actions on 5-HT_{1A} as well as 5-HT_2 and dopamine D_2 receptors, and acts as a partial agonist (mixed agonist/antagonist) on 5-HT_{1A} receptors (1, 7, 27–29). It is therefore probable that neurochemical characteristics other than the 5-HT_{1A} systems are responsible for the different drug interactions. Furthermore, it is proposed that the enhancement and reduction of the ambulation increment induced by methamphetamine and scopolamine, respectively, by diazepam are partially mediated through the GABA/benzodiazepine receptor complex (H. Kuribara, unpublished data). The lack of any significant interaction of SUN 8399 with methamphetamine and scopolamine is also consistent with the fact that SUN 8399 has no remarkable interaction with the GABA/benzodiazepine receptor complex and muscarinic-cholinergic receptors as well as with the postsynaptic dopamine D_2 receptors (28, 29).

In these respects, it is considered that SUN 8399 shows distinct characteristics from those of buspirone and tandospirone by means of ambulatory activity in mice, although these 3 drugs have agonistic action on 5-HT_{1A} receptors. Such characteristics of SUN 8399 may be partially resulted by the selectiveness in the interaction with 5-HT_{1A} receptors.

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