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Modification of Cocaine Sensitization by Dopamine D_1 and D_2 Receptor Antagonists in Terms of Ambulation in Mice

HISASHI KURIBARA

Department of Neurobiology and Behavior, Behavior Research Institute, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi 371, Japan

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KURIBARA, H. *Modification of cocaine sensitization by dopamine D_1 and D_2 receptor antagonists in terms of ambulation in mice.* PHARMACOL BIOCHEM BEHAV **51**(4) 799–805, 1995.—The progressive enhancement in the ambulation increase caused by the repeated five-time dosings of cocaine (10 mg/kg SC) at 3- to 4-day intervals was dose dependently reduced by simultaneous administration with the selective dopamine D_1 and D_2 receptor antagonists, SCH 23390; R(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.01, 0.03, and 0.1 mg/kg SC) and YM-09151-2 (nemonapride); *cis*-N-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (0.01, 0.03, and 0.1 mg/kg SC), respectively. However, the mice given cocaine with SCH 23390 (0.03 mg/kg) or YM-09151-2 (0.03 and 0.1 mg/kg) demonstrated significantly higher sensitivity than the mice given cocaine alone to challenge cocaine. Both 2-h and 24-h posttreatments with SCH 23390 (0.01–0.1 mg/kg) after each cocaine administration, at which the acute stimulant effect of cocaine had disappeared, significantly and dose dependently enhanced the cocaine sensitization. In contrast, 2-h, but not 24-h, posttreatment with YM-09151-2 (0.01–0.1 mg/kg), slightly retarded the induction of cocaine sensitization. The present results suggest that the blockade of dopamine D_1 receptors is responsible for a significant enhancement in the cocaine sensitization, independent of the timings of its administration, whereas the blockade of dopamine D_2 receptors elicits time-dependent alterations in the cocaine sensitization, a strong enhancement in the simultaneous administration schedule, but a slight retardation in the early posttreatment schedule.

Cocaine sensitization Mouse's ambulation SCH 23390 YM-09151-2 Dopamine receptor antagonists Simultaneous administration Posttreatment

COCAINE has a strong CNS stimulant action in animals and humans (3). In rodents, such action is characterized with an intense increase in ambulatory (locomotor) activity and production of stereotypy. The CNS stimulant action of cocaine is due to an increase in the synaptic dopamine concentration (2) through inhibition of the reuptake process (5). The characteristics of behavioral stimulant actions of cocaine and amphetamines closely resemble each other. Thus, similar to amphetamines, the repeated administration of cocaine elicits a sensitization to its behavioral stimulant actions (1,8,11,12,16).

However, different characteristics between cocaine and amphetamines have also been reported. The development of behavioral sensitization to methamphetamine can be blocked by the simultaneous administration of either the selective dopamine D_1 or D_2 receptor antagonists (13–15), whereas the effects of dopamine receptor antagonists on the induction of cocaine sensitization are inconsistent. There are reports that demonstrated a significant inhibition (23,31) as well as no significant modification (16,22) by dopamine receptor antagonists in mice and rats.

On the other hand, Kuribara (18,19) has recently reported that treatment with dopamine D_2 receptor antagonists at 3 h after methamphetamine (i.e., immediately after the termination of the acute methamphetamine effect) could retard the induction of methamphetamine sensitization, although such treatment per se did not inhibit the acute stimulant effect on ambulation of methamphetamine. In a preliminary study (17), a similar inhibition of the methamphetamine sensitization has been induced by the blockade of dopamine D_1 receptors. However, there has been no systematic study that evaluated the effects of selective dopamine receptor antagonists, simultaneously administered and/or posttreated, on the induction of cocaine sensitization.

Although there are at least five dopamine receptor subtypes, the roles of the dopamine D_1 and D_2 receptors have been most widely assessed in the behavioral pharmacological

study. Hence, the aims of this study were to evaluate possible modifications of cocaine sensitization by selective dopamine D_1 and D_2 receptor antagonists, SCH 23390; R(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine(9,20), and YM-09151-2 (nemonapride); *cis*-N-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide(30) in terms of ambulation in mice. The mice were simultaneously given cocaine with SCH 23390 or YM-09151-2, or they were posttreated with SCH 23390 or YM-09151-2 2 h or 24 h after each cocaine administration.

METHOD

Animals

The animals used were male mice of the dd strain (Institute of Experimental Animal Research, Gunma University School of Medicine, Maebashi, Japan). The experiment was started when the mice were 6 weeks of the age and weighed 25–28 g. During the experimental period, groups of 10 mice each were housed in polycarbonate cages of 25 W × 15 D × 15 H cm, and they were freely given a solid diet (MF: Oriental Yeast, Tokyo, Japan) and tap water. The breeding room was under controlled environmental conditions (temperature: 23 ± 1°C, relative humidity: 55 ± 3%, and light period: 0600–1800 h).

Apparatus

Two sets of tilting-type ambulometer having 10 bucket-like Plexiglas activity cages of 20 cm in diameter (SMA-10: O'Hara & Co., Tokyo, Japan) (7) were used for measurement of ambulatory activities of mice. Horizontal movements of the mouse generated a slight tilt of the activity cage, and it was detected with a microswitch attached to the cage. Thereby, the ambulometer could selectively measure ambulation (locomotion), but not vertical movements such as rearing and head movement.

Drugs

The drugs used were cocaine HCl (Takeda Chem., Osaka, Japan), SCH 23390 HCl (Research Biochem., Natick, MA), and YM-09151-2 (nemonapride: Yamanouchi Pharm., Tokyo, Japan). Cocaine and SCH 23390 were dissolved with physiological saline. YM-09151-2 was first dissolved with very small amount of 1 N HCl, and then the solution was diluted with physiological saline. The concentration of each drug solution was adjusted so that the volume injected was always constant at 0.1 ml/10 g body weight. All drugs were administered subcutaneously (SC). The dose of cocaine was fixed at 10 mg/kg, which was considered to be optimal dose for increasing the ambulation of the dd strain mice (8), and it was also the same as in our previous experiments (16,17).

Experimental Procedures

Throughout conducting the experiments, the drug administration and the ambulation measurement were carried out between 1000–1600 h.

Simultaneous administration of cocaine with SCH 23390 or YM-09151-2. Eight groups of mice (10 each) were allocated to one of the following repeated five-time administrations at 3- to 4-day intervals: saline alone, cocaine alone, combinations of cocaine with SCH 23390 (0.01, 0.03 and 0.1 mg/kg), and cocaine with YM-09151-2 (0.01, 0.03 and 0.1 mg/kg). The ambulations of mice were measured for 2 h after each administration. Four days after the final (fifth) dosing, challenge cocaine was administered to all of these mice. Cocaine was also administered to the drug-naive mice (n = 10) that were age matched to the drug-treated mice.

Posttreatment with SCH 23390 or YM-09151-2 after cocaine administration. Fourteen groups of mice (10 each) were given cocaine 6 times at 3- to 4-day intervals, and every administration was followed by the ambulation measurement for 2 h. Additionally, at the first to fifth cocaine dosings, each group of mice were posttreated with one of saline, SCH 23390 (0.01, 0.03, and 0.1 mg/kg), and YM-09151-2 (0.01, 0.03, and 0.1 mg/kg) 2 h or 24 h after each cocaine administration. The posttreatment with saline, SCH 23390, or YM-09151-2 was not followed by the ambulation measurement, and the mice were kept in their home cages. Such procedure might selectively induce conditioning to the stimulant effect of cocaine (27,30) without producing a possible conditioning to the behavior depression caused by the dopamine receptor antagonists.

Statistical Analyses

The mean 2-h overall ambulatory activity counts were first analyzed by ANOVA. The main factors were doses of SCH 23390 and YM-09151-2 (four levels including cocaine alone or saline-treatment as dose = 0) and numbers of drug administrations (five and six levels for the simultaneous administration and the posttreatment schedules, respectively). In cases of significant variance, post hoc analyses were carried out by Dunnett's test. Values of p less than 0.05 were considered significant.

RESULTS

Simultaneous Administration of Cocaine With SCH 23390

As shown in the left-hand panel of Fig. 1, the stimulant effect of cocaine on ambulation was reduced by simultaneous administration of SCH 23390 in a dose-dependent manner throughout the repeated five-time administrations, $F(3, 180) = 140.79$, $p < 0.001$. Post hoc analysis revealed that the activity counts of the mice at the second, fourth, and fifth dosings of cocaine with SCH 23390 (0.01 mg/kg), the second to the fifth dosings of cocaine with SCH 23390 (0.03 mg/kg), and the first to the fifth dosings of cocaine with SCH 23390 (0.1 mg/kg) were significantly lower than those of the control mice given cocaine alone. The repeated administration of both cocaine alone and cocaine with SCH 23390 (0.01–0.1 mg/kg) elicited a progressive enhancement in their ambulation-increasing effects dependent on the number of administrations, $F(4, 180) = 31.61$, $p < 0.001$, and the counts at the second to the fifth dosings of cocaine alone, the third to the fifth dosings of cocaine with SCH 23390 (0.01 and 0.03 mg/kg), and the fifth dosing of cocaine with 23390 (0.1 mg/kg) were significantly higher than the counts at the first dosing. There was no significant interaction between number of administrations × doses. The mean 2-h activity counts after the repeated five-time administrations of saline alone were 50–80, and there was no significant difference among these counts (the data are not shown in the left-hand panel of Fig. 1.

As shown in the right-hand panel of Fig. 1, the mice given the repeated administration of saline showed almost the same sensitivity as that of the drug-naive mice to the challenge cocaine. However, the repeated dosings of cocaine with SCH 23390 had a significant effect on the sensitivity to challenge

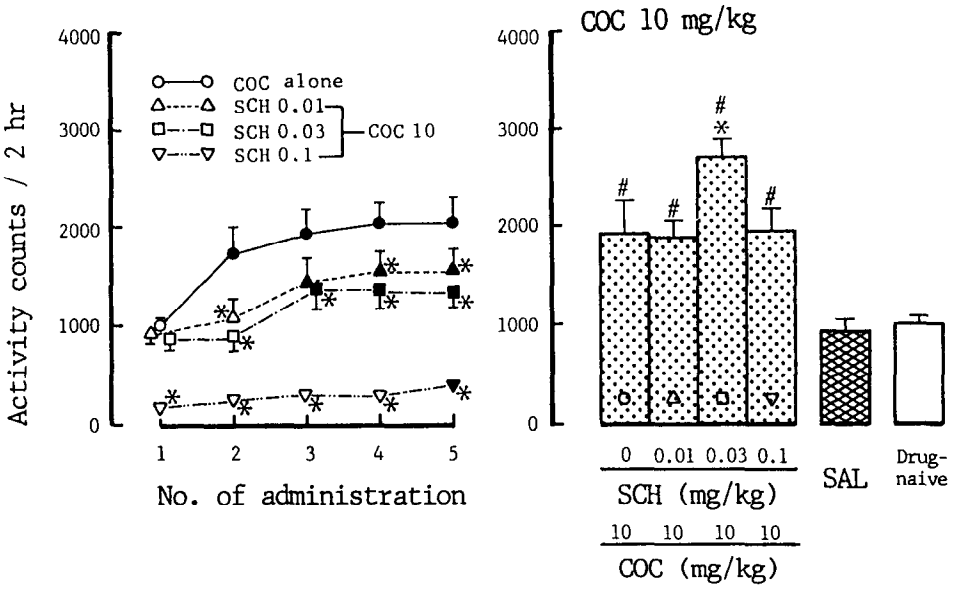

FIG. 1. Mean 2-h overall ambulatory activity counts with SEMs after the repeated five-time SC administrations of cocaine (COC: 10 mg/kg) alone, and combinations of cocaine with SCH 23390 (SCH: 0.01, 0.03, and 0.1 mg/kg) at 3- to 4-day intervals (left-hand panel), and after challenge cocaine (right-hand panel). In the combined administrations, two drugs were administered simultaneously. The challenge cocaine was administered 4 days after the end of the repeated administration. Closed symbols (●, ▲, ■, and ▼.): $p < 0.05$ vs. the first administration within each group. *$p < 0.05$ vs. cocaine alone at the same administration number. #$p < 0.05$ vs. the mice given saline (SAL)-alone (10 ml/kg) five times at 3- to 4-day intervals (the data are not shown in the left-hand panel). The mean activity count after the administration of cocaine to the drug-naive mice, which were age-matched to the drug-treated mice, is also presented in the right-hand panel. $n = 10$ in each group.

cocaine dependent on the doses of SCH 23390, $F(3, 36) = 5.08$, $p < 0.01$, and the mice givn cocaine with SCH 23390 (0.03 mg/kg) showed a significantly higher sensitivity than the control mice given cocaine alone to the challenge cocaine.

Simultaneous Administration of Cocaine With YM-09151-2

As shown in the left-hand panel of Fig. 2, YM-09151-2 dose dependently reduced the ambulation increase caused by cocaine throughout the repeated five-time administration, $F(3, 180) = 114.95$, $p < 0.001$. Post hoc analysis revealed that the activity counts of the mice at the first to the fifth dosings of cocaine with YM-09151-2 (0.01–0.1 mg/kg), except for the fifth dosing of cocaine with YM-09151-2 (0.01 mg/kg), were significantly lower than those of the control mice given cocaine alone. The repeated administration of cocaine with YM-09151-2 (0.01–0.1 mg/kg) elicited a progressive enhancement in their ambulation-increasing effects, dependent on the number of administrations, $F(4, 180) = 40.17$, $p < 0.001$, and the counts at the third to the fifth dosings of cocaine with YM-09151-2 (0.01 mg/kg), the second to the fifth dosings of cocaine with YM-09151-2 (0.03 mg/kg), and the fourth and fifth dosings of cocaine with YM-09151-2 (0.1 mg/kg) were significantly higher than the counts at the first dosing. There was no significant interaction between number of administrations × doses.

There was a significant YM-09151-2 dose-dependent effect on the sensitivity to challenge cocaine, $F(4, 36) = 13.56$, $p < 0.001$). As shown in the right-hand panel of Fig. 2, the mice given cocaine with YM-09151-2 (0.03 and 0.1 mg/kg) showed significantly higher sensitivity than the control mice given cocaine alone to the challenge cocaine.

Posttreatment With SCH 23390

There were significant SCH 23390 dose-dependent, $F(3, 216) = 17.03$, $p < 0.001$, and number of administration-dependent, $F(5, 216) = 53.71$, $p < 0.001$, effects of the 2-h posttreatment with SCH 23390 on the sensitization to cocaine. There was a significant interaction between number of administrations × doses, $F(15, 216) = 2.69$, $p < 0.01$. Thus, as shown in the left-hand panel of Fig. 3, all groups of mice showed significantly higher activity counts at the second to sixth dosings than at the first dosing. Furthermore, the activity counts of the mice 2 h posttreated with SCH 23390 (0.03 and 0.1 mg/kg) were significantly higher at the fifth and sixth and the third to sixth dosings of cocaine, respectively, than the saline-treated control mice.

There were significant SCH 23390 dose-dependent, $F(3, 216) = 12.16$, $p < 0.001$, and number of administration-dependent, $F(5, 216) = 72.94$, $p < 0.001$, effects of the 24-h posttreatment with SCH 23390 on the sensitization to cocaine. The interaction between number of administrations × doses was significant, $F(15, 216) = 2.92$, $p < 0.01$. Thus, as presented in the right-hand panel of Fig. 3, all groups of mice showed significantly higher activity counts at the second to sixth dosings than at the first dosing. Furthermore, the activity counts of the mice 24 h posttreated with SCH 23390 (0.1 mg/kg) were significantly higher than the saline-treated control mice at the fourth and fifth dosings of cocaine.

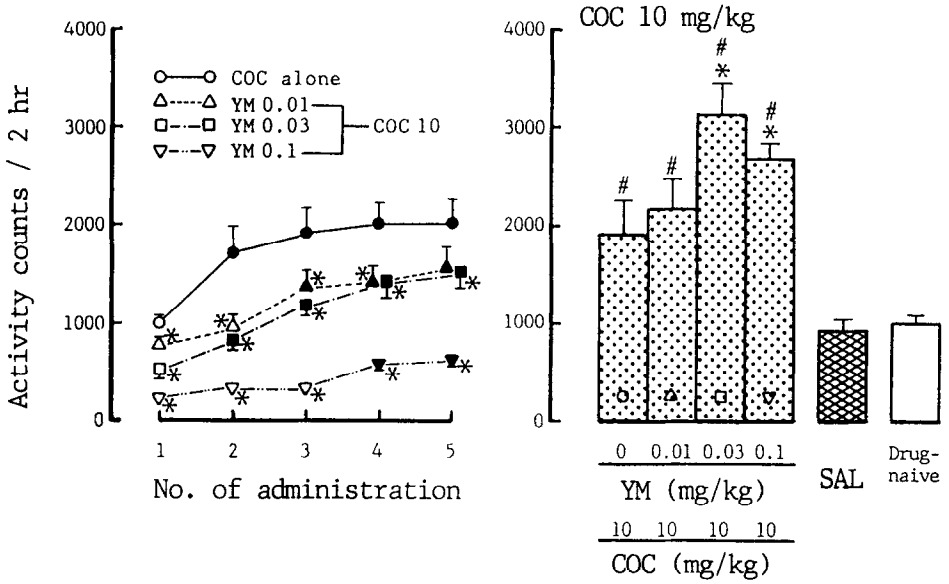

FIG. 2. Mean 2-h overall ambulatory activity counts with SEMs after the repeated five-time SC administrations of cocaine (COC: 10 mg/kg) alone, and combinations of cocaine with YM-09151-2 (YM: 0.01, 0.03, and 0.1 mg/kg) at 3- to 4-day intervals, and after challenge cocaine. The data are shown in the same way as in Fig. 1. The activity counts after the challenge cocaine to the saline-treated and drug-naive mice are the same with those presented in Fig. 1. $n = 10$ in each group.

Posttreatment With YM-09151-2

There were significant YM-09151-2 dose-dependent, $F(3, 216) = 4.37$, $p < 0.01$, and number of administration-dependent, $F(5, 216) = 43.98$, $p < 0.001$, effects of the 2-h posttreatment with YM-09151-2 on the sensitivity to cocaine. The interaction between number of administrations × doses was significant, $F(15, 216) = 2.19$, $p < 0.05$. Thus, as shown in the left-hand panel of Fig. 4, the groups of mice 2 h posttreated with saline and YM-09151-2 (0.01, 0.03, and 0.1 mg/kg) showed significantly higher activity counts at the second to sixth and third to sixth dosings, respectively, than at the first dosing. However, the activity count of the mice posttreated with YM-09151-2 (0.1 mg/kg) was significantly lower

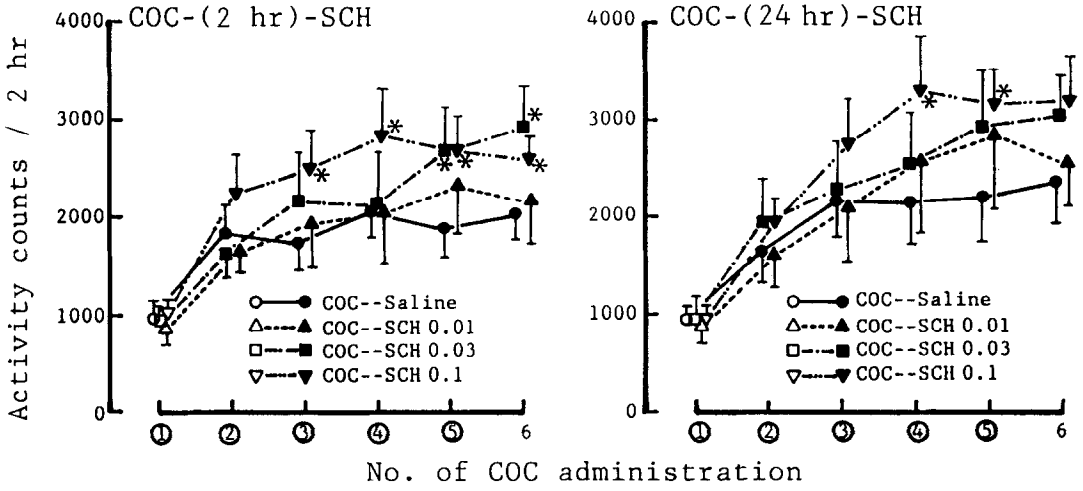

FIG. 3. Mean 2-h overall ambulatory activity counts with SEMs after the repeated six-time SC administrations of cocaine (COC: 10 mg/kg) at 3- to 4-day intervals. At the first to fifth cocaine administrations, the mice were posttreated with one of saline and SCH 23390 (SCH: 0.01, 0.03, and 0.1 mg/kg) 2-h (left-hand panel) or 24 h (right-hand panel) after the cocaine administration. Closed symbols (●, ▲, ■ and ▼.): $p < 0.05$ vs. the first administration within each group. *$p < 0.05$ vs. the mice posttreated with saline at the same administration number. $n = 10$ in each group.

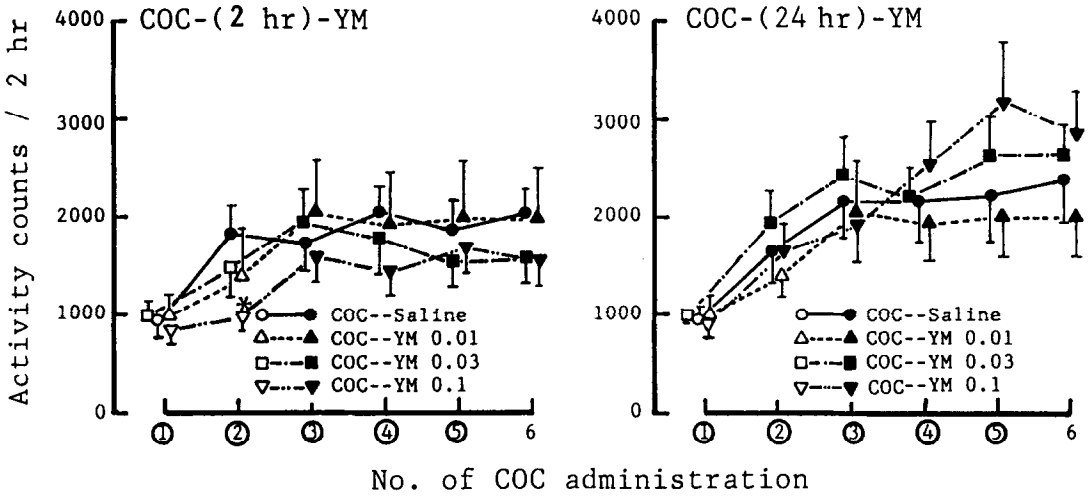

FIG. 4. Mean 2-h overall ambulatory activity counts with SEMs after the repeated six-time SC administrations of cocaine (COC: 10 mg/kg) at 3- to 4-day intervals. At the first to fifth cocaine administrations, the mice were posttreated with one of saline and YM-09151-2 (YM: 0.01, 0.03, and 0.1 mg/kg) 2-h (left-hand panel) or 24 h (right-hand panel) after the cocaine administration. The data are shown in the same way as in Fig. 3. The activity counts of the mice posttreated with saline are the same with those presented in Fig. 3. $n = 10$ in each group.

than the mice posttreated with saline at the second cocaine dosing.

There was a significant number of administration-dependent, $F(5, 216) = 97.02, p < 0.001$, but not YM-09151-2 dose-dependent, $F(3, 216) = 1.63$, NS, effect of the 24-h posttreatment with YM-09151-2 on the sensitization to cocaine. The interaction between number of administrations × doses did not attain to a significant level, $F(15, 216) = 1.41$, NS. Thus, as presented in the right-hand panel of Fig. 4, all groups of mice showed significantly higher sensitivity at the second or third and latter dosings than at the first dosing. The mice 24 h posttreated with the highest dose of YM-09151-2 (0.1 mg/kg) only tended to show a greater activity count than the control mice posttreated with saline at the fifth and sixth dosings. However, there were no significant differences in the activity counts among groups of mice throughout the six-time cocaine administrations.

DISCUSSION

With repeated administration at 3- to 4-day intervals, cocaine produced a significantly increased level of ambulation, compared with the first administration. Such cocaine-induced enhancement in the ambulation increase is consistent with the sensitization effect previously reported for cocaine in mice (8,16).

Cocaine accelerates dopaminergic transmission through inhibition of the reuptake process (5). As expected from such a mechanism, the ambulation-increasing effect of cocaine was significantly reduced by the simultaneous administration of cocaine with either of the dopamine D_1 antagonist, SCH 23390, or the dopamine D_2 antagonist, YM-09151-2. These results are also consistent with the data obtained from our previous research (16). Despite the reduction of the acute effect of cocaine by SCH 23390 and YM-09151-2, neither prevented the induction of cocaine sensitization. Thus, when the mice were repeatedly given cocaine with SCH 23390 or YM-09151-2 five times at 3- to 4-day intervals, they never demonstrated lower sensitivity, but rather, the mice given cocaine with SCH 23390 (0.03 mg/kg) or YM-09151-2 (0.03 and 0.1 mg/kg) showed significantly higher sensitivity than the mice given cocaine alone to the challenge cocaine. In terms of ambulation in mice, however, the induction of methamphetamine sensitization could be inhibited in a dose-dependent manner by the simultaneous administration of either SCH 23390 (0.003–0.03 mg/kg) or YM-09151-2 (0.003–0.03 mg/kg) (13, 14,16). Following the simultaneous administration, SCH 23390 and YM-09151-2 equivalently reduced the stimulant effect of methamphetamine, and they also resulted in the same degree of retardation of methamphetamine senisitization. The neurochemical mechanisms of the stimulant actions of cocaine and methamphetamine are different, i.e., inhibition of dopamine reuptake by cocaine (5), whereas acceleration of dopamine release and inhibition of dopamine reuptake by methamphetamine (24). However, such mechanisms would not be adequate to elucidate the different modifications of sensitization to cocaine and methamphetamine by the dopamine receptor antagonists. This is because both mechanisms result in an increase in dopamine concentration at the synapses of the dopaminergic neurons.

It is suggested that dopamine D_1 receptors play a more important role than D_2 receptors in the stimulant effect of as well as the induction of behavioral sensitization to cocaine in rats (6,23,25,26,29), and that the induction of cocaine sensitization is inhibited by the dopamine D_1 receptor antagonist (23,26). Furthermore, Weiss et al. (31) reported that the dopamine D_2 receptor antagonist, haloperidol, could prevent development of cocaine sensitization, but not its expression, following the single administration schedule in rats. These effects are different from the enhancement in the sensitization to cocaine in the mice given a combination of cocaine with SCH 23390 or YM-09151-2, as demonstrated in this study. Similarly, Mattingly et al. (22) demonstrated that the development of cocaine sensitization was not blocked by dopamine D_1 and D_2 receptor antagonists, SCH 23390 and sulpiride, respectively. Because the induction of cocaine sensitization is highly

influenced by many factors including the administration schedules, the doses of cocaine itself and the test drugs combined, environmental conditions, etc. (8,27,31). It is, therefore, probable that the divergent modifications of the cocaine sensitization by dopamine receptor antagonists are due to the different situations.

Furthermore, it has been reported that cocaine has a significant action on 5-HT-ergic neurons, blocking the synaptosomal uptake of tryptophan, which decreases 5-HT synthesis (21) and the turnover of 5-HT (4). These mechanisms can be considered as candidates for the enhancement in the cocaine sensitization by the simultaneous administration of cocaine with dopamine receptor antagonists.

An enhancement in the cocaine sensitization was induced by both the 2-h and 24-h posttreatments with SCH 23390. In contrast to such effects of SCH 23390, the 2-h posttreatment with YM-09151-2 (0.1 mg/kg) slightly reduced the enhancement in the sensitivity at the second dosing of cocaine. The 24-h posttreatment with the same dose of YM-09151-2 did not significantly modify the induction of cocaine sensitization. These findings indicate that the repeated blockade of dopamine D_1 receptors is responsible for an enhancement in the cocaine sensitization, independent of the timing of its treatment, whereas the blockade of dopamine D_2 receptors has a time-dependent effect, enhancement, and reduction in the simultaneous administration and the early posttreatment schedules, respectively.

Such results are quite a bit different from the equivalent retardation of the induction of methamphetamine sensitization by the 3-h posttreatments with 0.01 and 0.03 mg/kg of SCH 23390 and YM-09151-2 (17,19), indicating again the different characteristics between cocaine and methamphetamine sensitizations, and the different roles of dopamine D_1 and D_2 receptor mechanisms in the cocaine sensitization. One of the candidates is a supersensitivity of dopamine receptors caused by the repeated blockade of the receptors. However, this consideration cannot be supported by the facts that the early posttreatment with either SCH 23390 or YM-09151-2 did not enhance, but rather retarded, the induction of methamphetamine sensitization (17,19). Nondopaminergic mechanisms, including 5-HT-related mechanisms (4,21), are also considered to be involved in the acceleration of cocaine sensitization. Furthermore, in addition to such pharmacodynamic mechanisms, Pettit et al. (28) reported that the repeated dosing of cocaine resulted in higher plasma levels of cocaine and the extracellular concentration of dopamine in the nucleus accumbens with the same fixed challenge dose of cocaine. This mechanism can be considered as a strong candidate for the enhancement of cocaine sensitization by the simultaneous administration of SCH 23390 and YM-09151-2, and the posttreatment with SCH 23390. A pharmacokinetic study will be conducted in the near future.

In this study, the separate effects of SCH 23390 and YM-09151-2 on cocaine sensitization were investigated to clarify the roles of dopamine D_1 and D_2 receptor mechanisms. Many antipsychotics, which have been applied for the treatment of cocaine psychosis, have antagonistic action on both dopamine D_1 and D_2 receptors. It may, therefore, be important to evaluate the combined effects of SCH 23390 and YM-09151-2 on the cocaine sensitization, although such evaluation has not been established because of many combinations of their doses.

Thus, further studies are required to find out the mechanisms of the different modifications of cocaine sensitization by the dopamine receptor antagonists. However, it can be concluded at least from the present results that the selective dopamine D_1 and D_2 receptor antagonists cannot retard, but rather sometimes accelerate, the development of cocaine sensitization in terms of ambulation in mice. These results also suggest that the mechanisms involved in the cocaine sensitization are different from those involved in the methamphetamine sensitization.

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