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Dopamine D_1 Receptor Antagonist SCH 23390 Retards Methamphetamine Sensitization in Both Combined Administration and Early Posttreatment Schedules in Mice

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KURIBARA, H. *Dopamine D_1 receptor antagonist SCH 23390 retards methamphetamine sensitization in both combined administration and early posttreatment schedules in mice.* PHARMACOL BIOCHEM BEHAV **52**(4) 759–763, 1995.—SCH 23390 [0.003–0.03 mg/kg, subcutaneously (SC)], a dopamine D_1 receptor antagonist, dose-dependently inhibited the ambulation-stimulant effect of methamphetamine (MAP) (2 mg/kg, SC) in mice when two drugs were combined in repeated administrations at 3- to 4-day intervals, repeated five times. SCH 23390 (0.03 mg/kg), which was sufficient to abolish the acute effect of MAP completely throughout the repeated administrations, significantly inhibited the induction of MAP sensitization. Moreover, when the mice were posttreated with SCH 23390 (0.01 and 0.03 mg/kg) 3 h after each MAP administration, at which the ambulation-stimulant effect of MAP had almost disappeared, they showed a significant and dose-dependent retardation of the induction of MAP sensitization. However, the 24-h posttreatment with SCH 23390 had no such effect. The administration of SCH 23390 (0.003–0.03 mg/kg) alone in either the activity cage or the home cage, or saline in the activity cage with 3- or 24-h posttreatment with SCH 23390 (0.01 or 0.03 mg/kg) five times at 3- to 4-day intervals did not elicit any significant changes in MAP sensitivity. The present results indicate that an intense blockade of dopamine D_1 receptors in the acute or subacute period after MAP administration causes retardation of MAP sensitization by means of ambulation in mice.

Methamphetamine Repeated administration Sensitization Mouse ambulation SCH 23390
Dopamine D_1 receptor antagonist Combined administration Posttreatment

IN EXPERIMENTS using rodents, an intermittent administration of CNS stimulants such as amphetamine and methamphetamine (MAP) induces sensitization to their behavioral stimulant action, particularly in ambulation (locomotion) and stereotypy (4,6,8,19,21,22). An enhancement of the dopaminergic transmission is considered to be involved in behavioral sensitization (19,21,22), because not only the sensitization to but also the acute stimulant effect of amphetamines can be inhibited by dopamine D_2 receptor antagonists (4,5,8,23,24). In terms of ambulation in mice, we (1,12–15) have also confirmed that the induction of MAP sensitization was inhibited by haloperidol or nemonapride (YM-09151-2). Furthermore, there are numerous reports indicating that, similar to dopamine D_2 receptor antagonists, the repeated administration of amphetamines in combination with dopamine D_1 receptor antagonist results in a reduction in the acute stimulant effect and inhibition of the sensitization to amphetamines (5,6,16,20, 23,24).

In addition to these drug interactions in the combined administration schedule, Kuribara reported that treatment with haloperidol (11) or nemonapride (12) at 3 h but not at 24 h after each MAP administration (i.e., an early posttreatment) could retard the induction of MAP sensitization. The acute ambulatory stimulation by MAP disappeared by 3 h after the administration, indicating that MAP has an action on dopamine D_2 receptors even after the cessation of its acute stimulant effect, and that this action has an important role in the induction of MAP sensitization.

The antiamphetamine properties of the dopamine D_1 receptor antagonist SCH 23390 (7) are similar to those of dopamine D_2 receptor antagonists (17). However, there is still a question of whether the blockade of dopamine D_1 receptors by post-

treatment with SCH 23390 can result in modification of MAP sensitization similar to that produced by dopamine D_2 receptor antagonists (11,12).

The aims of this study were to confirm the inhibitory effect of SCH 23390 on MAP sensitization in the combined administration schedule, and to assess whether posttreatment with SCH 23390 could retard the induction of MAP sensitization in terms of ambulation in mice. The sensitivities to MAP of the mice that had been repeatedly given SCH 23390 alone or saline with posttreatments with SCH 23390 were also evaluated.

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 these mice were 6 weeks of age and weighed 25–28 g. Throughout the experimental period, groups of 10 mice were housed in polycarbonate cages (25 × 15 × 15 cm), and were freely given a solid diet (MF; Oriental Yeast, Tokyo, Japan) and tapwater. The conditions of the breeding room were well controlled (temperature: 23 ± 1°C, relative humidity: 55 ± 3%, and light: 0600–1800 h).

Apparatus

A tiling-type ambulometer with 10 bucket-like Plexiglas activity cages 20 cm in diameter (SMA-10; O'Hara & Co., Tokyo, Japan) was used for measurement of mouse ambulation. The apparatus detected a slight tilt of the activity cage generated by a horizontal movement of the mouse. However, any vertical movements such as rearing, sniffing, and head movement as well as pivotting did not produce tilt of the activity cage. Therefore, the apparatus could selectively record ambulations but not stereotypies.

Drugs

The drugs used were MAP (Dainippon Pharm., Osaka, Japan) and SCH 23390 HCl (Research Biochemicals, Natick, MA). They were dissolved with physiologic saline and administered subcutaneously (SC). The doses of MAP and SCH 23390 were expressed in salt form. The concentration of each drug solution was adjusted so that the volume injected was always constant at 0.1 ml/10 g body wt of the mouse. In the same way as in previous studies (11,12), the dose of MAP was fixed to 2 mg/kg, which was considered to be optimal for the induction of sensitization to its ambulation-stimulant effect without producing an intense stereotypy during repeated administration (6).

Experimental Procedures

Throughout the experiments, drug administration and the measurement of ambulation of the mice were carried out between 1000 and 1600 h to avoid time of day variation in the sensitivity of mice to MAP (13,14).

Experiment 1: evaluation of effects of SCH 23390 on MAP sensitization. We allocated 11 groups of mice (10 each) to the following three drug administration schedules to evaluate the effects of SCH 23390 on the induction of MAP sensitization.

Combinations of MAP with SCH 23390. Five groups of mice were given one of the following administrations: saline, MAP alone, and combinations of MAP with SCH 23390 (0.003, 0.01, and 0.03 mg/kg) five times at 3- to 4-day intervals. The ambulations of these mice were measured for 3 h after each administration. At 4 days after the final (fifth) administration, MAP was challenge-administered to all of these mice.

MAP with 3-h posttreatment with SCH 23390. Three groups of mice were given MAP six times at 3- to 4-day intervals, and every MAP administration was followed by the measurement of ambulation for 3 h. Moreover, at 3 h after the first to fifth MAP administrations (i.e., immediately after the end of each measurement of ambulation), groups of mice were given either saline or SCH 23390 (0.01 or 0.03 mg/kg). The administration of saline or SCH 23390 was not followed by the measurement of ambulation, and the mice were returned to their home cages.

MAP with 24-h posttreatment with SCH 23390. The other three groups of mice were given MAP six times at 3- to 4-day intervals, and their ambulations were measured for 3 h. Then, these mice were returned to their home cages. Twenty-four hours after each MAP administration, groups of mice were given either saline or SCH (0.01 or 0.03 mg/kg) in their home cages.

MAP was also administered to the age-matched and drug-naive mice ($n = 10$).

Experiment 2: Control experiments. As in the control experiments for Experiment 1, 14 groups of mice (10 each) were allocated to the following four drug administration schedules.

Four groups of mice were given SCH 23390 (0: saline, 0.003, 0.01, or 0.03 mg/kg) in their home cages.

Four groups of mice were given SCH 23390 (0, 0.003, 0.01, or 0.03 mg/kg), and their ambulations were measured for 3 h after each administration.

Three groups of mice were given saline and their ambulations were measured for 3 h. Then they were treated with SCH 23390 (0, 0.01, or 0.03 mg/kg) and immediately returned to the home cages.

Three groups of mice were given saline and their ambulations were measured for 3 h. Then, these mice were returned to their home cages. Twenty-four hours after saline administration, groups of mice were treated with SCH 23390 (0, 0.01, or 0.03 mg/kg) in the home cages.

These treatments were repeated five times at 3- to 4-day intervals. Four days after the final treatment, MAP was challenge-administered to all of these mice, and their ambulations were measured for 3 h.

Statistical Analyses

The mean 3-h overall ambulatory activity counts were first analyzed by one- or two-way analysis of variance (ANOVA). The factors were doses of SCH 23390 (three or four levels including MAP alone or treatment with saline as the dose = 0) and the number of administrations (five levels). Posthoc analyses were carried out by Dunnett's t-test. Values of $p < 0.05$ were considered to be significant.

RESULTS

Experiment 1: Effects of SCH 23390 on MAP Sensitization

During repeated administration. As presented in the left-hand panel of Fig. 1, SCH 23390 dose-dependently reduced ambulatory stimulation by MAP throughout the administrations repeated five times [$F(3, 180) = 142.75$, $p < 0.001$]. Except for a complete abolition of the effect of MAP by SCH 23390 (0.03 mg/kg), the repeated administrations of MAP alone and combinations of MAP with SCH 23390 (0.003 and

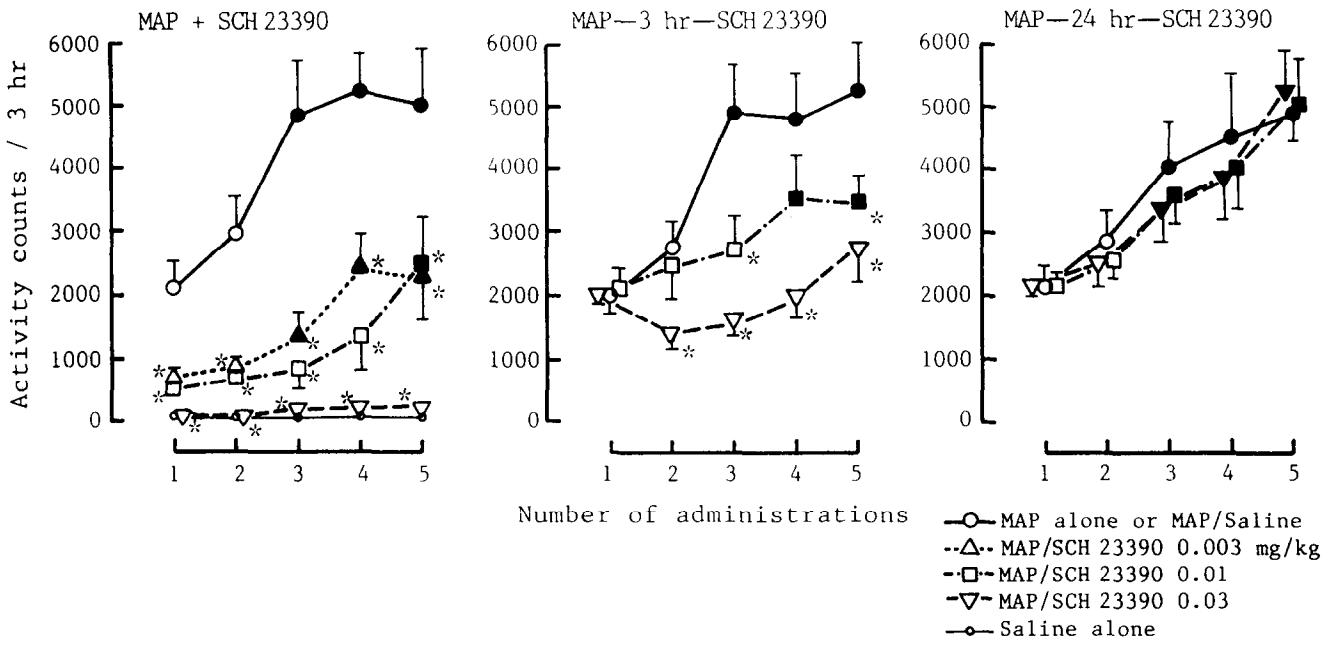

FIG. 1. Mean 3-h overall ambulatory activity counts with SEMs after repeated SC administration of saline (10 ml/kg), methamphetamine (MAP) (2 mg/kg) alone, and combinations of MAP with SCH 23390 (0.003–0.03 mg/kg) (lefthand panel), MAP with 3-h posttreatments with SCH 23390 (0: saline, 0.01, and 0.03 mg/kg) (middle panel), and MAP with 24-h posttreatments with SCH 23390 (0, 0.01, and 0.03 mg/kg) (righthand panel) five times at 3- to 4-day intervals. Closed symbols (●, ▲, ■, and ▲): $p < 0.05$ vs. the first administration within each group. *$p < 0.05$ vs. control mice given MAP alone (lefthand panel), or MAP with posttreatment with saline (middle panel). $n = 10$ in each group.

0.01 mg/kg) elicited a progressive enhancement of the ambulatory stimulation dependent on the administration number [$F(4, 180) = 40.89, p < 0.001$]. There was a significant interaction between SCH 23390-dose × administration number [$F(12, 180) = 2.97, p < 0.01$]. Posthoc analyses revealed that the activity counts at the third to fifth administrations of MAP alone and the combination of MAP with SCH 23390 (0.003 mg/kg) and at the fifth administration of the combination of MAP with SCH 23390 (0.01 mg/kg) were significantly higher than those at the first administration.

As presented in the middle panel of Fig. 1, in the schedule of 3-h posttreatment with SCH 23390, the effects of SCH 23390-dose [$F(2, 135) = 49.85, p < 0.001$] and administration number [$F(4, 135) = 28.73, p < 0.001$] were significant, and there was a significant interaction between SCH 23390-dose × administration number [$F(8, 135) = 9.17, p < 0.001$]. Posthoc analyses revealed that the activity counts of the mice 3-h posttreated with SCH 23390 (0.01 and 0.03 mg/kg) were significantly lower at the third and fifth administrations and second to fifth MAP administrations, respectively, than those of the mice 3-h posttreated with saline. However, repeated MAP administration resulted in a progressive enhancement of ambulatory stimulation, and the activity counts of the mice 3 h posttreated with saline and SCH 23390 (0.01 mg/kg) were significantly higher at the third to fifth and the fourth and fifth MAP administrations, respectively, than those at the first MAP administration. Even at the fifth MAP administration, the activity count of the mice 3-h posttreated with SCH 23390 (0.03 mg/kg) did not attain to a significantly higher level than that at the first MAP administration.

As presented in the righthand panel of Fig. 1, in the schedule of 24-h posttreatment with SCH 23390, a progressive enhancement of the ambulatory stimulation was induced by repeated MAP administration [$F(4, 135) = 66.17, p < 0.001$], and the activity counts of all groups were significantly higher at the third to fifth MAP administrations than those at the first MAP administration. Except for a borderline reduction of enhancement of sensitivity to MAP at the third administration, the activity counts in the 24-h posttreatment groups were similar to those of the MAP alone group.

Challenge with MAP. As presented in Fig. 2, repeated administration of MAP in combination with SCH 23390 resulted in a significant reduction in MAP sensitization dependent on SCH 23390-dose [$F(3, 36) = 9.46, p < 0.001$], and the activity count of the mice given a combination of MAP with SCH 23390 (0.03 mg/kg) was significantly lower than that of the control mice given MAP alone.

The mice given MAP with 3- or 24-h posttreatment with SCH 23390 showed no significant changes in MAP sensitization [$F(2, 21) = 3.38$ and 0.27, respectively, NS].

Experiment 2: Control experiments

Throughout the administrations of saline or SCH 23390 (0.003–0.03 mg/kg) in the activity cage, repeated five times, the mean 3-h activity counts were 49–74, and there were no significant differences in the counts among groups (data not shown).

There were no significant differences in sensitivity to the challenge-administration of MAP among groups of mice given SCH 23390 in the activity cage [$F(3, 36) = 0.27$, NS] or home cage [$F(3, 36) = 0.14$, NS], and among those given saline in the activity cage with posttreatment with SCH 23390 at 3 h [$F(2, 27) = 0.09$, NS] or at 24 h [$F(2, 27) = 0.47$, NS] after the administration of saline (data not shown).

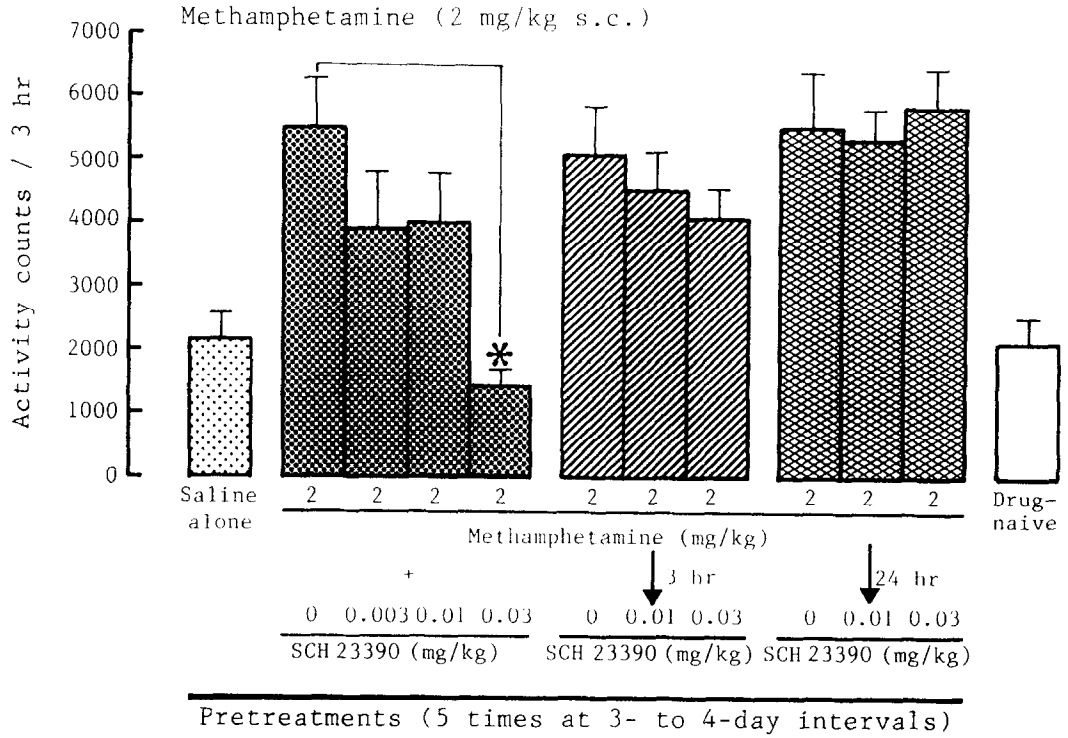

FIG. 2. Mean 3-h overall ambulatory activity counts with SEMs after the challenge-administration of methamphetamine (2 mg/kg, SC) to mice given SC administrations, repeated five times, of saline alone, methamphetamine alone, a combination of methamphetamine with SCH 23390, or methamphetamine with 3- or 24-h posttreatment with SCH 23390 at 3- to 4-day intervals, and to the age-matched and drug-naive mice. The challenge-administration of methamphetamine was carried out 4 days after the fifth administration. $*p < 0.05$ vs. control mice given methamphetamine alone (dose of SCH 23390 = 0). $n = 10$ in each group.

DISCUSSION

The characteristics of inhibition of MAP-induced behavioral stimulation and reduction of MAP sensitization following the combined administration of MAP and SCH 23390 were consistent with the results obtained from previous studies (4,5,16,23,24). Moreover, the most interesting result in this study was a retardation of MAP sensitization by 3-h posttreatment with SCH 23390. The neuroleptic effect of SCH 23390 does not last longer than 24 h (16,17). It is therefore hard to consider that the retardation of MAP sensitization caused by 3 h posttreatment with SCH 23390 is due to the direct antagonistic effect of SCH 23390 on the ambulatory stimulation by MAP as demonstrated in the combined administration schedule. Such a consideration can also be supported by the facts that 24 h posttreatment with SCH 23390 did not cause significant retardation of MAP sensitization.

In the schedule of 3 h posttreatment with SCH 23390, a reduction of MAP sensitization was not observed at the sixth MAP administration. However, this result can hardly be attributable to a production of tolerance to the effect of SCH 23390. This is because no reduction in the antagonistic effect of SCH 23390 (0.03 mg/kg) on the effect of MAP was demonstrated in the combined administration schedule. The possibility of an increment in the dopamine receptor sensitivity following repeated blockade by SCH 23390 is also negligible, because no significant changes in MAP sensitivity were produced in the mice given repeated administrations of SCH 23390 alone and those given saline with 3 h posttreatment with SCH 23390. Thus, 3 h posttreatment with SCH 23390 at comparatively higher doses can delay but cannot perfectly inhibit the induction of MAP sensitization. Such a characteristic of SCH 23390 is similar to that of dopamine D_2 receptor antagonists (11,12).

In contrast to the results in the 3-h posttreatment schedule, 24-h posttreatments with SCH 23390 (0.01 and 0.03 mg/kg) produced almost the same patterns of MAP sensitization as those produced by repeated administrations of MAP alone or MAP with 24 h posttreatment with saline. MAP persists in the body for up to 12 h, but it is almost completely eliminated by 24 h after administration to rats (3). SCH 23390 may not modify the sensitivity of mice to MAP when MAP does not remain in the body. This consideration may be supported by the data that the repeated administration of saline with 24-h posttreatment with SCH 23390 did not result in any significant changes in the sensitivity to challenge-administration of MAP. It is also suggested that neither tolerance to the effect of SCH 23390 nor increments in the sensitivity of dopamine D_1 receptors were induced following repeated treatments with SCH 23390 carried out in this study.

As mentioned earlier, MAP remains in the body for up to 12 h after administration in rats (3). Such a duration is much longer than the persistence of its acute stimulant effect. Therefore, a significant amount of MAP may be present in the brain and may stimulate the dopamine receptors for several hours even after the cessation of the ambulation-stimulant effect. Therefore, a blockade of either dopamine D_1 receptors by SCH 23390 (in this study) or dopamine D_2 receptors by halo-

peridol or nemonapride not only during the acute period (presence of the ambulation-stimulant effect) (1,15,12-14), but also during the subacute period (after cessation of the stimulant effect) (11,12), causes retardation of MAP sensitization in terms of ambulation in mice. It is also suggested that stimulation of both dopamine D_1 and D_2 receptors during the subacute period is involved in the induction of MAP sensitization.

However, additional experiments are required to strengthen the selectiveness of dopaminergic mechanisms in the inhibition and/or retardation of MAP sensitization by SCH 23390, because of its interaction with 5-HT_2 and 5-HT_{1c} receptors (2,18). Evaluations of the effects of more selective dopamine receptor antagonists and changes in the retardation of MAP sensitization dependent on the timing of posttreatment will be carried out in the near future.

REFERENCES

1. Asami, T.; Kuribara, H.; Furusawa, K.; Haraguchi, H.; Tadokoro, S. Reverse tolerance to ambulation-increasing effect of methamphetamine, and effects of antipsychotic drugs on the established reverse tolerance. Yakubutsu Seishin Kodo 7:237-238; 1987.
2. Bischoff, S.; Heinrich, M.; Sonntag, J. M.; Krauss, J. The D_1 dopamine receptor antagonist SCH 23390 also interacts potently with brain serotonin (5-HT_2) receptors. Eur. J. Pharmacol. 129: 367-370; 1986.
3. Caldwell, J.; Dring, L. G.; Williams, R. T. Metabolism of [^{14}C]-methamphetamine in man, the guinea pig and the rat. Biochem. J. 129:11-22; 1972.
4. Demellweek, C.; Goudie, A. J. Behavioural tolerance to amphetamine and other psychostimulants: The case for considering behavioural mechanisms. Psychopharmacology (Berlin) 80:287-307; 1983.
5. Hamamura, T.; Akiyoshi, K.; Akimoto, K.; Kashihara, K.; Okumura, K.; Ujike, H.; Otsuki, S. Co-administration of either a selective D_1 or D_2 dopamine antagonist with methamphetamine prevents methamphetamine-induced behavioral sensitization and neurochemical changes, studied by in vivo intracerebral microdialysis. Brain Res. 546:40-46; 1991.
6. Hirabayashi, M.; Alam, M. R. Enhancing effect of methamphetamine on ambulatory activity produced by repeated administration in mice. Pharmacol. Biochem. Behav. 15:925-932; 1981.
7. Iorio, L. C.; Barnett, A.; Keitz, F. H.; Houser, V. P.; Korduba, C. A. SCH 23390, a potential benzazepine antipsychotic with unique interaction on dopaminergic synthesis. J. Pharmacol. Exp. Ther. 226:462-468; 1983.
8. Kalivas, P. W.; Stewart, J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res. Rev. 16:223-244; 1991.
9. Kilbey, M. M.; Sannerud, C. A. Models of tolerance: Do they predict sensitization to the effect of psychomotor stimulant? In: Seiden, L. S.; Balster, R. L., eds. Neurology and neurobiology, vol. 13. Behavioral pharmacology: The current status. New York: Alan R. Liss; 1985:295-321.
10. Kuribara, H. Effects of haloperidol on the methamphetamine sensitization: Assessed by ambulatory activity in mice. Jpn. J. Psychiatry Neurol. 47:661-668; 1993.
11. Kuribara, H. Early posttreatment with haloperidol retards induction of methamphetamine sensitization in mice. Eur. J. Pharmacol. 256:295-299; 1994.
12. Kuribara, H. Can posttreatment with the selective dopamine D_2 antagonist, YM-09151-2, inhibit induction of methamphetamine sensitization? Evaluation by ambulatory activity in mice. Pharmacol. Biochem. Behav. 49:323-326; 1994.
13. Kuribara, H.; Tadokoro, S. Circadian variation in methamphetamine- and apomorphine-induced increase in ambulatory activity in mice. Pharmacol. Biochem. Behav. 17:1251-1256; 1982.
14. Kuribara, H.; Tadokoro, S. Circadian variation in sensitivity to methamphetamine after repeated administration in mice. Pharmacol. Biochem. Behav. 20:247-250; 1984.
15. Kuribara, H.; Tadokoro, S. Effects of YM-09151-2, a potent and selective dopamine D_2 antagonist, on the ambulation-increasing effect of methamphetamine in mice. Jpn. J. Pharmacol. 52:489-492; 1990.
16. Kuribara, H.; Uchihashi, Y. Effects of dopamine antagonism on methamphetamine sensitization: Evaluation by ambulatory activity in mice. Pharmacol. Biochem. Behav. 47:101-106; 1994.
17. Mailman, R. B.; Schultz, D. W.; Lewis, M. H.; Staples, L.; Rollema, H.; Dehaven, D. L. SCH 23390: A selective D_1 dopamine antagonist with potent D_2 behavioral actions. Eur. J. Pharmacol. 101:159-160; 1984.
18. Nicklaus, K. J.; McGonigle, P.; Molinoff, P. B. [^{3}H]SCH 23390 labels both dopamine-1 and 5-hydroxytryptamine$_{1c}$ receptors in the choroid plexus. J. Pharmacol. Exp. Ther. 247:343-348; 1988.
19. Robinson, T. E.; Becker, J. B. Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Res. Rev. 11:157-198; 1986.
20. Stewart, J.; Vezina, P. Microinjections of Sch-23390 into the ventral tegmental area and substantia nigra pars reticulate attenuate the development of sensitization to the locomotor activating effects of systemic amphetamine. Brain Res. 495:401-416; 1989.
21. Tadokoro, S.; Kuribara, H. Reverse tolerance to the ambulation-increasing effect of methamphetamine in mice as an animal model of amphetamine psychosis. Psychopharmacol. Bull. 22:757-762; 1986.
22. Tadokoro, S.; Kuribara, H. Modification of behavioral effects of drugs after repeated administration; in particular, the reverse tolerance to amphetamines. Nippon Yakurigaku Zasshi 95:229-238; 1990.
23. Ujike, H.; Onoue, T.; Akiyama, K.; Hamamura, T.; Otsuki, S. Effects of selective D_1 and D_2 dopamine antagonists on development of methamphetamine-induced behavioral sensitization. Psychopharmacology 98:89-92; 1989.
24. Vezina, P.; Stewart, J. The effect of dopamine receptor blockade on the development of sensitization to the locomotor effects of amphetamine and morphine. Brain Res. 499:108-120; 1989.