Pharmacology Biochemistry and Behavior, Vol. 47, pp. 101–106, 1994
Printed in the U.S.A.

0091-3057/94 $6.00 + .00

Effects of Dopamine Antagonism on Methamphetamine Sensitization: Evaluation by Ambulatory Activity in Mice

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Received 14 December 1992

KURIBARA, H. AND Y. UCHIHASHI. *Effects of dopamine antagonism on methamphetamine sensitization: Evaluation by ambulatory activity in mice.* PHARMACOL BIOCHEM BEHAV 47(1) 101–106, 1994.—SCH 23390 (SCH: 0.001–0.03 mg/kg SC) and YM-09151-2 (YM: 0.001–0.03 mg/kg SC), the selective dopamine D_1 and D_2 antagonists, respectively, reduced dose-dependently the ambulation-increasing effect of methamphetamine (MAP: 2 mg/kg SC) in mice. The sensitization to MAP was inhibited when it was administered in combination with SCH (0.003–0.03 mg/kg) or YM (0.003–0.03 mg/kg) in the repeated administration regimen. The inhibitory action of YM on the MAP sensitization was more prominent than that of SCH. However, the repeated treatment with either SCH or YM could not ameliorate the established MAP sensitization. Rather, the repeated treatment with the highest dose of YM (0.03 mg/kg) increased the MAP sensitivity in both the MAP-sensitized and drug-naive mice. SCH had no such action. The present results suggest that the dopamine D_2 receptors are more intimately involved than the dopamine D_1 receptors in the increased sensitivity to MAP induced by the repeated treatment with MAP itself, behavioral sensitization, or dopamine antagonists, denervation supersensitivity.

SCH 23390 YM-09151-2 D_1 receptor D_2 receptor Methamphetamine sensitization
Denervation supersensitivity Ambulatory activity

REPEATED administration of central nervous system (CNS) stimulants with agonistic action on dopaminergic systems such as amphetamines, cocaine, and their analogues have been well known to induce a sensitization to their behavioral stimulant action, in particular the ambulation (locomotion)-increasing and stereotypy-producing effects (3,4,6,14,15). It has been considered that a certain change in the dopaminergic transmission is involved in the sensitization (12). In fact, antipsychotics having blockage action on the dopamine receptors (chlorpromazine, haloperidol, etc.) are effective in inhibiting induction of the behavioral sensitization to amphetamines when they are administered in combination with amphetamines in the repeated administration regimen (1,10,13).

On the other hand, the repeated treatment with various kind of antipsychotics sometimes induces an increase in the sensitivity to CNS stimulants and/or dopamine agonists. Such a change might reflect a denervation supersensitivity of the postsynaptic dopamine receptors produced by the repeated blockage of the receptors (2). However, the traditional antipsychotics do not selectively block either the dopamine D_1 or D_2 receptor subtype. Thus, more work on the interaction between amphetamines and dopamine antagonists with selective blockage action on the receptor subtypes is required.

Hence, the purposes of this experiment were to investigate characteristics of the interaction of methamphetamine with SCH 23390 (5,11) and YM-09151-2 (16)—selective dopamine D_1 and D_2 antagonists, respectively—by means of ambulatory activity in mice.

METHOD

Animals

Experimental animals used were male mice of dd strain (Institute of Experimental Animal Research, Gunma University School of Medicine). The experiment was begun when these mice were attained at six weeks of age and weighing 25–28 g. Throughout the experimental period, they had been group-housed (10 mice each) in aluminum breeding cage (25 W × 15D × 15H cm) with free access to solid diet (MF: Oriental Yeast) and tap water in the controlled room (temperature: 23 ± 2°C; relative humidity: 55 ± 3%; light period: 0600–1800).

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Apparatus

The apparatus for measurement of mice ambulatory activity was a tilting-type ambulometer having 10 bucketlike activity cages with diameter of 20 cm (SMA-10: O'hara & Co., Tokyo) (4). Briefly, a slight tilt of the activity cage generated by the ambulation (locomotion) of the mouse was detected with any of three microswitches attached to the cage. The cumulative activity count during every 10-min epoch was printed out by a time interval data printer (TIDP-10: O'hara & Co.).

Drugs

The drugs used were methamphetamine HCl (MAP: Philopon: Dainippon Pharm. Co., Osaka), R(+)-SCH 23390 (SCH: Research Biochemicals Inc., Natick, Ma), and YM-09151-2 (YM: Yamanouchi Pharmaceutical Co., Tokyo). YM was first dissolved in a very small amount of 0.1-N HCl, and then the solution was diluted by physiological saline. SCH and MAP were dissolved in the saline. The concentration of each drug solution was adjusted so that each volume injected was always constant at 0.1 ml/10 g body weight. The dose of MAP was fixed to 2 mg/kg, which was optimum for increase in the ambulation of the dd mice without producing a marked stereotypy (4). The drugs were administered SC.

Experimental Procedures

Throughout running of the following four experiments, the drug administration and the measurement of ambulation were carried out between 1000 and 1600 to avoid circadian variation of the sensitivity of mice to the ambulation-increasing effect of methamphetamine (9,10).

Experiment 1: The repeated administration of MAP in combination with SCH or YM. Ten groups of mice (20 each) were given one of the following administrations for five times at 3–4-day intervals: saline alone, MAP alone, or combined administration of MAP with SCH (0.001, 0.003, 0.01, and 0.03 mg/kg) or MAP with YM (0.001, 0.003, 0.01, and 0.03 mg/kg). In the combined administration, the drugs were administered simultaneously. A mouse's ambulatory activity was observed for 3 h after administration. Four days after the final (fifth) administration, MAP alone was challenge-administered to all of these mice.

Experiment 2: The combined administration of MAP with SCH or YM in the MAP-sensitized mice. Nine groups of mice (10 each) were first treated with the repeated-five-times administration of MAP at intervals of 3–4 days to induce the MAP sensitization. Four days after the fifth administration, each group of mice were used for the evaluation of one of the following administrations: combination of MAP with SCH (0.001, 0.003, 0.01, and 0.03 mg/kg) or with YM (0.001, 0.003, 0.01, and 0.03 mg/kg), or MAP alone.

Experiment 3: The MAP administration to the mice pretreated with SCH or YM. Nine groups of mice (10 each) were given five daily administrations of one of the following drugs: saline, SCH (0.001, 0.003, 0.01, and 0.03 mg/kg), or YM (0.001, 0.003, 0.01, and 0.03 mg/kg). Four days after the treatment, MAP was challenge-administered to all of these mice.

Experiment 4: The treatment with SCH or YM of the MAP-sensitized mice. Seven groups of mice (10 each) were first given the repeated-five-times administration of MAP at intervals of 3–4 days to induce the MAP sensitization. From the fourth day after the fifth administration, each group of mice was treated with one of the following drugs for five days: saline, SCH (0.003, 0.01, and 0.03 mg/kg), or YM (0.003, 0.01, and 0.03 mg/kg). On the fourth day after the final treatment, all of these mice were readministered MAP alone.

Statistical Analyses

The mean 3-h overall ambulatory activity counts were first analyzed by analysis of variance (ANOVA). In the cases of significant variation, the individual mean values were compared by Dunnett test. Values of p equal to or less than 0.05 are considered significant.

RESULTS

Experiment 1

Figure 1 shows changes in mean overall ambulatory activity counts for 3 h after the repeated administration of MAP in combination with SCH and YM. The effects of repeated administration of MAP alone and saline alone were also presented in each panel.

In the drug-naive mice (i.e., the first administration), both SCH and YM reduced the ambulation-increasing effect of MAP in a dose-dependent manner, F(SCH dose) = 18.25, $p < 0.001$ and F(YM dose) = 23.58, $p < 0.001$.

The repeated MAP administration elicited a progressive enhancement in its ambulation-increasing effect, F(admin.) = 25.97, $p < 0.001$ (i.e., induction of behavioral sensitization). The mean overall ambulatory activity count in the fifth administration was estimated to be 2.3 times as high as the value in the first administration.

The activity counts after the combined administration of MAP with SCH were lower than those after MAP alone throughout the repeated administration, F(SCH dose) = 21.59, $p < 0.001$ and F(admin.) = 18.41, $p < 0.001$. However, there was no significant Dose × Administration interaction. Individual comparisons revealed that, in the cases of the combination of MAP with SCH (0.001–0.01 mg/kg), the mean activity counts progressively increased in parallel with the administration number. SCH (0.03 mg/kg) completely inhibited the MAP effect throughout the five-times administration.

The activity counts after the combined administration of MAP with YM were also lower than those after MAP alone throughout the repeated administration, F(YM dose) = 28.57, $p < 0.001$; F(admin.) = 19.52, $p < 0.001$; and F(Dose × Admin.) = 9.27, $p < 0.001$. Individual comparisons revealed that, in the cases of the combination of MAP with intermediate doses of YM (0.003 and 0.01 mg/kg), a progressive enhancement of the activity was not induced in the third and later administrations. The highest dose of YM (0.03 mg/kg) was effective in completely inhibiting the ambulation-increasing effect of MAP throughout the five-times administration.

Figure 2 shows mean overall ambulatory activity counts after the administration of MAP to the mice that had received the repeated-five-times administration of MAP or saline alone, or combination of MAP with SCH or YM. There were significant dose-dependent effects, F(SCH dose) = 8.81, $p < 0.001$ and F(YM dose) = 12.39, $p < 0.001$. The activity counts of groups of mice that had experienced the combined administration of MAP with SCH (0.03 mg/kg) and MAP with YM (0.01 and 0.03 mg/kg) were significantly lower than those of the MAP-alone mice, but not significantly different from those of the saline-alone and drug-naive mice.

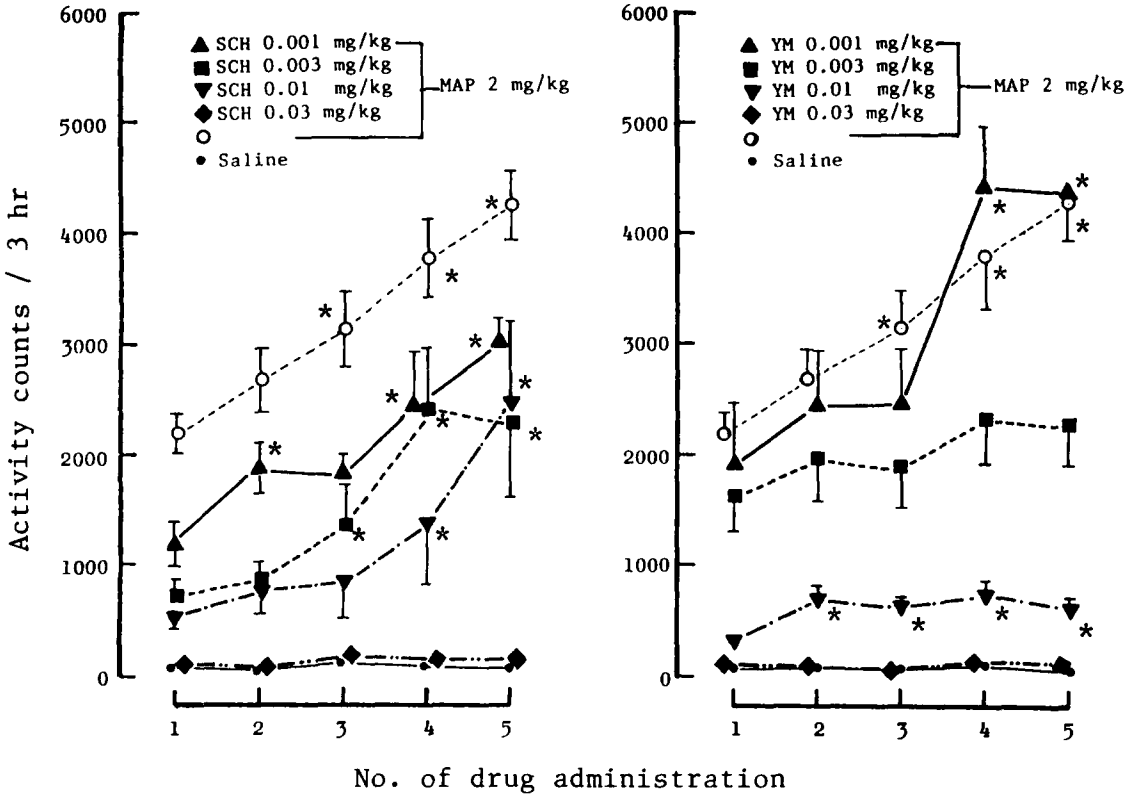

FIG. 1. Mean overall ambulatory activity counts with SEs for 3 h after the repeated-five-times administration of methamphetamine (MAP: 2 mg/kg) alone, combination of MAP with 0.001–0.03 mg/kg of SCH 23390 or YM-09151-2, and physiological saline (10 ml/kg) at intervals of 3–4 days. In the combined administration, two drugs were administered simultaneously. *Significantly different from the value in the first administration within each group ($p < 0.05$). $n = 20$ in each group.

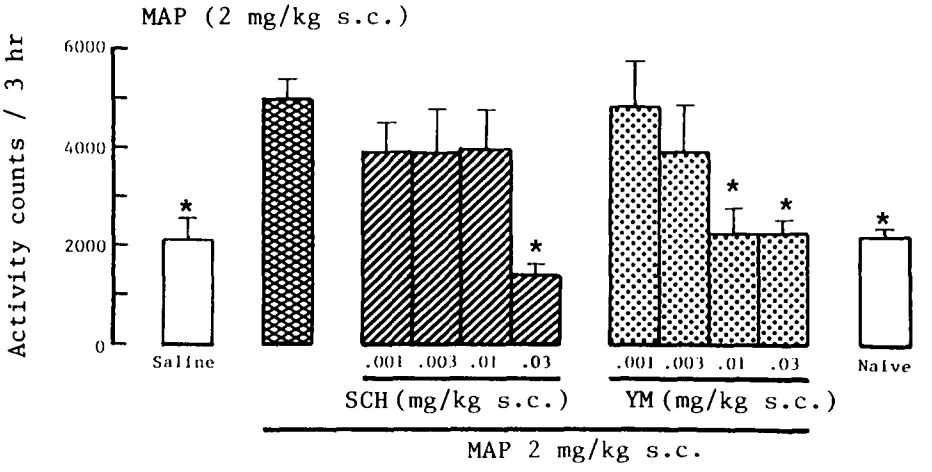

FIG. 2. Mean overall ambulatory activity counts with SEs for 3 h after the administration of methamphetamine (MAP: 2 mg/kg SC) to the drug-naive mice and to the mice that had experienced MAP or saline alone, or combination of MAP with SCH 23390 (0.001–0.03 mg/kg) or YM-09151-2 (0.001–0.03 mg/kg) for five times at intervals of 3–4 days. *Significantly different from the mean value of the MAP-alone mice ($p < 0.05$). $n = 20$ in each group.

Experiment 2

Figure 3 shows the dose-effect relationships for the combined administration of MAP with SCH and YM in the drug-naive and MAP-sensitized mice. The data of the drug-naive mice were the same as those presented in Fig. 1 (the data in the first administration).

In both the drug-naive and MAP-sensitized mice, the ambulation-increasing effect of MAP was reduced by SCH, F(SCH dose in naive) = 23.18, $p < 0.001$ and F(SCH dose in sensitized) = 13.29, $p < 0.001$, and by YM, F(YM dose in naive) = 15.24, $p < 0.001$ and F(YM dose in sensitized) = 17.92, $p < 0.001$. There was significant interaction between dose and treatment (drug-naive and MAP-sensitized) in the case of SCH, F(SCH Dose × Treatment) = 3.72, $p < 0.01$, but not in the case of YM. The individual comparisons revealed that up to 0.03 mg/kg of SCH was required to significantly reduce the MAP effect in the MAP-sensitized mice, although it was effective at 0.001 mg/kg in the drug-naive mice, whereas up to 0.01 mg/kg of YM significantly reduced the MAP effect in both the drug-naive and MAP-sensitized mice, and the dose-effect relationship in the sensitized mice was almost the same with that parallel shifted in the drug-naive mice.

Experiment 3

Figure 4 shows mean overall activity counts after the administration of MAP (2 mg/kg) to mice given five daily treatments with SCH or YM. Neither saline nor any dose of SCH changed the MAP sensitivity. However, YM significantly enhanced MAP sensitivity, F(YM dose) = 5.72, $p < 0.01$. Thus, the mice that received the repeated administration of YM (0.03 mg/kg) showed greater sensitization than the saline-treated mice.

Experiment 4

Figure 5 shows the mean overall activity counts for 3 h after the administration of MAP to the MAP-sensitized mice before and after the treatment with SCH and YM. There was a significant effect of the treatment with YM, F(YM dose) = 4.98, $p < 0.01$. The treatment with YM (0.03 mg/kg) induced a further enhancement of the MAP sensitivity. Any doses of SCH did not modify the MAP sensitivity.

DISCUSSION

The present experiment demonstrated an anti-amphetamine action of SCH and YM. Thus, up to 0.001 mg/kg of SCH and up to 0.01 mg/kg of YM significantly reduced the ambulation-increasing effect of MAP in the first combined administration. Although the potencies are different, it is indicated that the blockage of either dopamine D_1 or D_2 receptors is sufficient for significant reduction of the stimulant action of MAP.

Furthermore, the development of the MAP sensitization induced by the repeated administration was inhibited when MAP was combined with either SCH or YM in a dose-dependent manner in each administration. Almost the same results have been observed after the combined administration of holoperidol with MAP (1,8) and chlorpromazine with *d*-amphetamine (13) in the same experimental situation. Koshiya and Usuda (7) demonstrated the blocking action of YM on the sensitization to MAP-induced stereotypy in rats. However, when MAP was combined with SCH the characteristics of the progressive changes in the ambulation-increasing effect were different from when it was combined with YM. Although SCH was more potent than YM for the reduction of the MAP effect in the first administration, the former was less potent than the latter in the inhibitory action on the MAP sensitization. Thus, it is notable that up to 0.01 mg/kg of YM was effective in significantly suppressing the development of the MAP sensitization, whereas the inhibitory action of SCH on the MAP sensitization was observed only at 0.03 mg/kg, which was the dose completely abolishing the MAP-induced ambulation throughout the repeated administration. These findings suggest that the D_2 receptors are more intimately in-

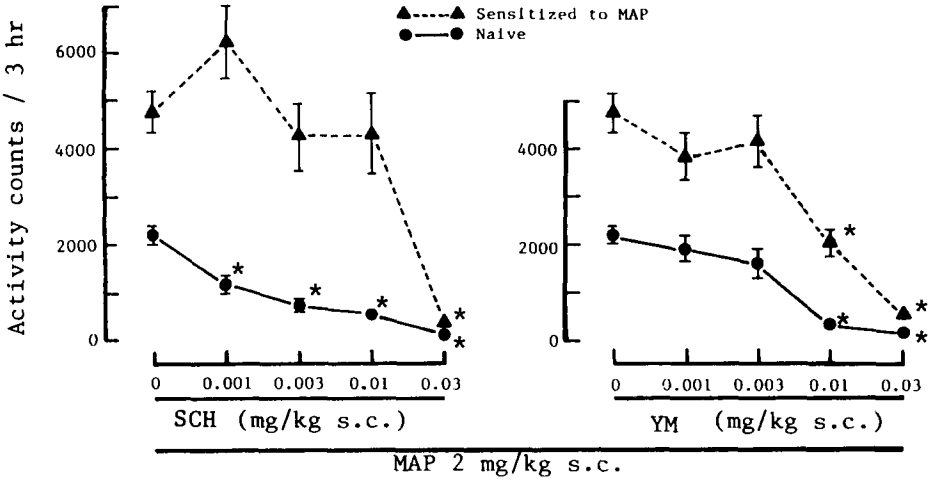

FIG. 3. Mean overall ambulatory activity counts with SEs for 3 h after the administration of methamphetamine (MAP: 2 mg/kg) in combination with SCH 23390 (0: saline, 0.001-0.03 mg/kg) or YM-09151-2 (0.001-0.03 mg/kg) in the drug-naive mice and the MAP-sensitized mice. The sensitization was produced by the repeated-five-times administration of MAP. *Significantly different from the MAP-alone value in each drug-naive or MAP-sensitized mice ($p < 0.05$). n = 10 in each group.

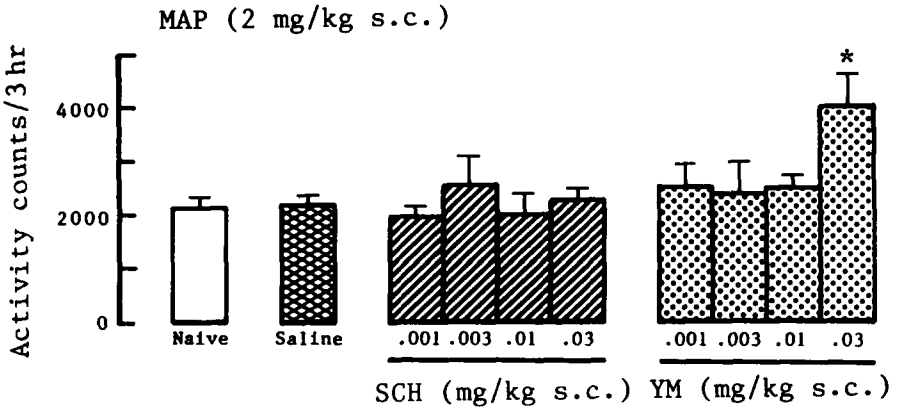

FIG. 4. Mean overall ambulatory activity counts with SEs for 3 h after the administration of methamphetamine (MAP: 2 mg/kg) to the mice that experienced the five-day treatment with SCH 23390 (0: saline, 0.001–0.03 mg/kg) or YM-09151-2 (0.001–0.03 mg/kg). The administration of MAP was carried out four days after the final treatment with SCH 23390 or YM-09151-2. *Significantly different from the value of the saline-treated mice ($p < 0.05$). $n = 10$ in each group.

volved than the D_1 receptors in the induction of MAP sensitization after the repeated administration.

Although the highest dose of SCH and the intermediate to highest doses of YM used in this study inhibited the development of MAP sensitization, the repeated treatment with neither SCH nor YM ameliorated the established MAP sensitibzation. Various antipsychotics also failed to ameliorate the MAP-sensitization once established (1,11). These results suggest that the established MAP-sensitization is almost irreversible.

Moreover, the repeated treatment with the highest dose of YM (0.03 mg/kg) tested in this study, but not with any doses of SCH, elicited an increase in the MAP sensitivity in both the

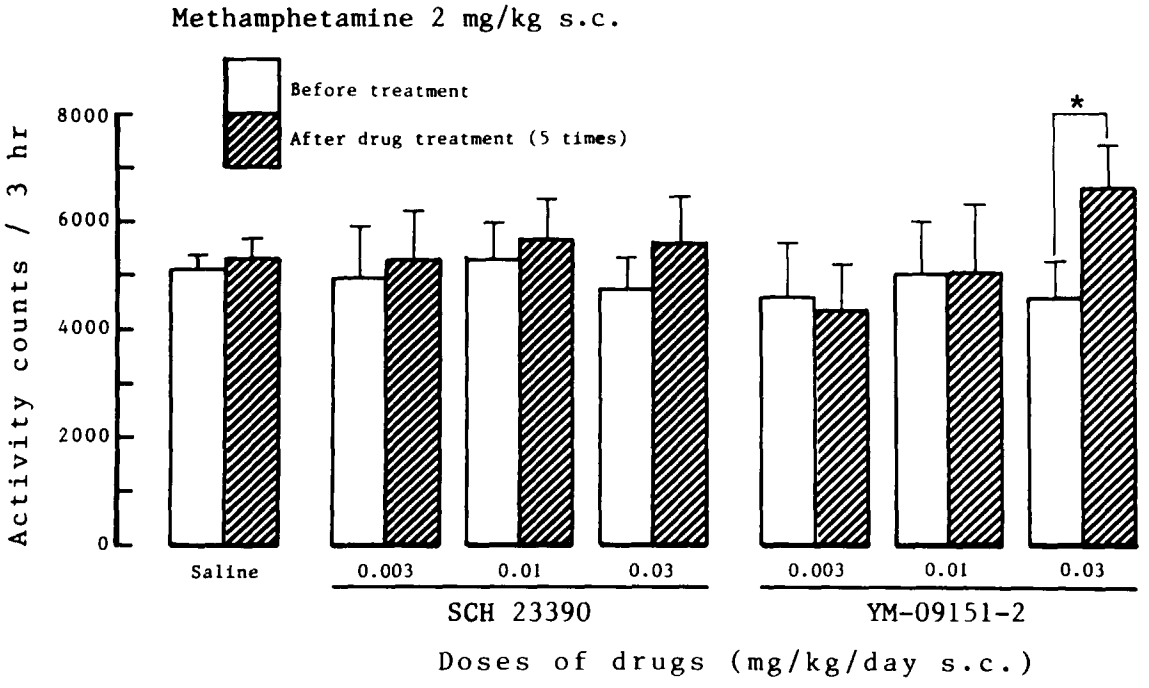

FIG. 5. Mean overall ambulatory activity counts with SEs for 3 h after the administration of methamphetamine (MAP: 2 mg/kg) to the MAP-sensitized mice before and after the treatment with saline, SCH 23390 (0.003–0.03 mg/kg), or YM-09151-2 (0–0.03 mg/kg). The MAP sensitization was produced by the repeated-five-times administration of MAP, and the five-day treatment with SCH 23390 or YM-09151-2 was carried out from the fourth day after the fifth MAP administration. On the fourth day after the final treatment with SCH 23390 or YM-01951-2, MAP was readministered. In this figure, the activity counts in the fifth administration and the MAP readministration are presented. *Significantly different between the values before and after the treatment with SCH 23390 or YM-09151-2 ($p < 0.05$). $n = 10$ in each group.

drug-naive and MAP-sensitized mice. Such effect alterations induced by YM reflect the denervation supersensitivity of the postsynaptic dopamine receptors induced by a repeated blockage of D_2 receptors (2). We have also confirmed an increased sensitivity to MAP in the mice that experienced the repeated administration of haloperidol (8). It is therefore considered that the denervation supersensitivity of the D_2 receptors is mainly involved in the increase in the MAP sensitivity induced by the repeated treatment with antipsychotics and with the selective D_2 antagonist YM.

In these respects, it is highly probable that D_2 receptors play important roles in both the MAP-induced behavioral sensitization and antipsychotic-induced denervation supersensitivity.

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