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Can Posttreatment with the Selective Dopamine D_2 Antagonist, YM-09151-2, Inhibit Induction of Methamphetamine Sensitization? Evaluation by Ambulatory Activity in Mice

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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(2) 323–326, 1994.—Effects of YM-09151-2; cis-N-(1-benzyl-2-methyl pyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (YM), a potent and selective dopamine D_2 antagonist, on sensitization to methamphetamine (MAP) were investigated by means of ambulatory activity in mice. YM (0.003–0.03 mg/kg SC) reduced not only the acute ambulation-increasing effect of MAP (2 mg/kg SC) but also the induction of MAP sensitization when it was simultaneously administered with MAP in the repeated administration at 3–4 day intervals. Moreover, the post 3-h treatment with YM (0.01 and 0.03 mg/kg) following each MAP administration, at which time the acute ambulation-increasing effect of MAP almost disappeared, significantly and dose dependently inhibited the induction of MAP sensitization. The post 24-h treatment with YM did not show such effect. The present results suggest that blockade of the dopamine D_2 receptors during postearly period following MAP administration is responsible for protecting the induction of MAP sensitization by means of ambulatory activity in mice.

Methamphetamine sensitization YM-09151-2 Dopamine D_2 antagonist Posttreatment
Ambulatory activity Mice

IN experiments in rodents, it is well known that repeated administration of amphetamines induces a sensitization to their behavioral stimulant action, particularly to the ambulation (locomotion) increasing and stereotypy producing effects (3,4,6,15,16). A certain change in the dopaminergic transmission is proposed to be intimately involved in the sensitization (13). In fact, production of the sensitization to amphetamines can be inhibited by antipsychotics, having antagonistic action on dopamine receptors, when they are simultaneously administered with amphetamines in the repeated administration schedule (1,10,14).

Recently, Kuribara and Uchihashi (12) demonstrated that the dopamine D_2 receptor played an important role in induction of sensitization to methamphetamine (MAP). However, antipsychotics or dopamine antagonists act to reduce the unit dose of MAP, and such drug combination elicits much lower ambulation increment as compared with that produced by MAP alone throughout the repeated administration. It has also been considered that freely and sufficient movement during presence of the acute effect of MAP is a minimum requirement for induction of the MAP sensitization by means of ambulatory activity (5). Thus, there is still a question of whether the dopamine D_2 antagonist specifically inhibits the MAP sensitization or only nonspecifically inhibits it through reduction of the acute ambulation increasing effect of MAP.

In these respects, the author examined effects of simultaneous and posttreatments with the selective dopamine D_2 antagonist YM-09151-2; cis-N-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (17), on the induction of MAP sensitization by means of ambulatory activity in mice. In the latter treatment, YM-09151-2 was given to the mice 3 h or 24 h after each administration of MAP.

METHOD

Animals

The animals used were male mice of dd strain (Institute of Experimental Animal Research, Gunma University School of

Medicine). The experiment was started when these mice were 6 weeks of age and weighed 25–28 g. During the experimental period, groups of ten mice each had been housed in aluminum cages (25W × 15D × 15H cm) with free access to solid diet (MF: Oriental Yeast, Tokyo, Japan) and tap water. The condition of the breeding room was controlled (temperature: 23° ± 2°C, relative humidity: 55 ± 3%, and light period: 0600–1800 h).

Apparatus

Two sets of tilting-type ambulometers having ten bucket-like Plexiglas activity cages of 20-cm diameter (SMA-10: O'Hara & Co., Tokyo, Japan) (4) were used for measurement of mouse activity. The apparatus detected a slight tilt of the activity cage generated only by the ambulation (locomotion). Therefore, the horizontal, but not vertical, movement of the mouse could be selectively recorded.

Drugs

The drugs used were methamphetamine HCl (MAP: Dainippon Pharm., Osaka, Japan), and YM-09151-2 (YM: Yamanouchi Pharm., Tokyo, Japan). YM was first dissolved in a very small amount of 0.1 N HCl, then the solution was diluted with physiological saline. MAP was dissolved in the 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. 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 subcutaneously (SC).

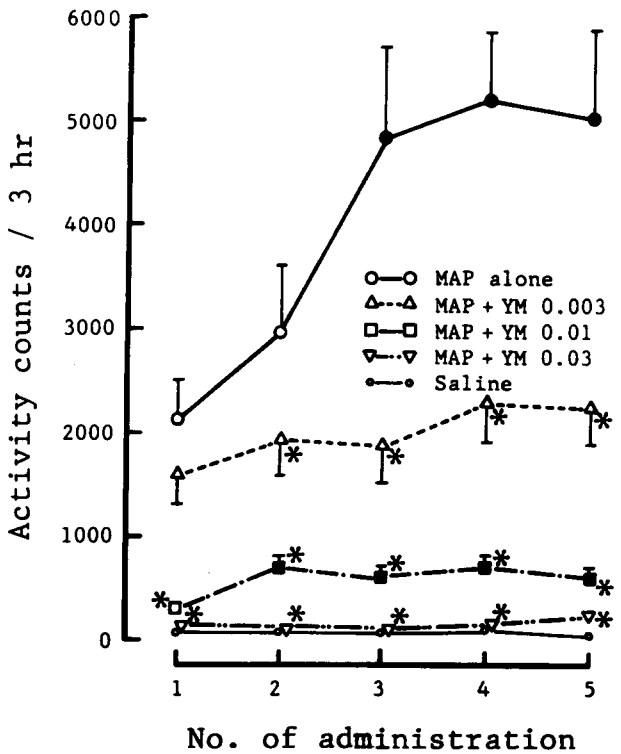

FIG. 1. Mean 3 hr overall ambulatory activity counts with SEMs after the repeated five time SC administration of saline (10 ml/kg), methamphetamine (MAP: 2 mg/kg) alone, and combination of MAP with YM-09151-2 (0.003, 0.01, and 0.03 mg/kg) at 3–4 day intervals. ●, ■: significantly different from the value in the first administration within each group ($p < 0.05$). *Significantly different from the MAP alone administered group at the same number of administrations; $n = 10$ in each group.

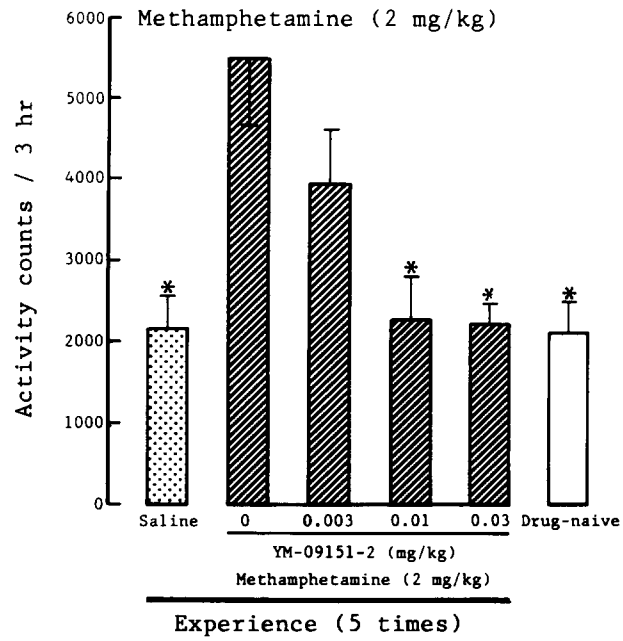

FIG. 2. Mean 3 hr overall ambulatory activity counts with SEMs after the challenge administration of methamphetamine (MAP: 2 mg/kg SC) to the mice given repeated five time SC administration of saline alone, MAP alone, and combination of MAP with YM-09151-2 (0.003, 0.01 and 0.03 mg/kg) at 3–4 day intervals, and to the drug-naive mice age-adjusted. The challenge administration was carried out on the fourth day after the fifth administration. *Significantly different from the mean value of the mice given MAP alone (dose = 0 for YM-09151-2) ($p < 0.05$); $n = 10$ in each group.

Experimental Procedures

Throughout the experiments, the drug administration and the measurement of ambulation were carried out between 1000–1600 to avoid circadian variation in the sensitivity of mice to the ambulation increasing effect of MAP (8,9).

Experiment 1: simultaneous administration of MAP with YM. Mice ($n = 10$ per group) were allocated to each of the following treatment groups: saline, MAP, or MAP + YM (0.003, 0.01, or 0.03 mg/kg). Each group received five injections of the relevant treatment with 3–4 day intervals between each injection. The ambulation of each mouse was observed for 3 h after each administration. Four days after the final (fifth) administration, MAP alone was challenge administered to all of these mice. MAP was also administered to a sixth group of ten age-matched and drug-naive mice.

Experiment 2: posttreatments with YM after MAP administration. Mice ($n = 10$ per group) were allocated to each of the following treatment groups: administration of saline or YM (0.01 or 0.03 mg/kg) 3 h or 24 h after the injection of MAP. Each group received five relevant treatments with 3–4 day intervals. The ambulation of each mouse was observed for 3 h after each administration of MAP, but not after the administration of saline or YM. Four days after the final

(fifth) treatment, MAP alone was readministered to all of these mice.

Statistical Analyses

The mean 3-hr overall ambulatory activity counts were first analyzed by one way or two way ANOVA. The factors were doses of YM (four levels including MAP alone in Experiment 1, and 3 levels including saline treatment in Experiment 2), and numbers of drug administration (five and six levels for Experiments 1 and 2, respectively). In the cases of significant variation in ANOVA, posthoc analyses were carried by Dunnett's tests. Values of $p \leq 0.05$ were considered significant.

RESULTS

Experiment 1

As shown in Fig. 1, YM significantly suppressed the ambulation increasing effect of MAP throughout the repeated administration in a dose-dependent manner [$F(3, 36) = 35.07$, $p < 0.001$]. The repeated administration of MAP elicited a progressive enhancement in its ambulation increasing effect, and the mean 3-hr overall ambulatory activity count in the fifth administration was 2.35 times as high as the value in the first administration. YM also inhibited the progressive enhancement of the effect [administration; $F(4, 180) = 28.41$, $p < 0.001$]. There was a significant interaction between the doses of YM and number of administration [$F(12, 180) = 12.70$, $p < 0.001$].

As shown in Fig. 2, in the challenge administration of MAP, the mice experienced to receiving MAP with YM dose dependently (in terms of YM administration) showed significantly lower activity than that of MAP alone experienced mice [$F(3, 36) = 22.71$, $p < 0.001$]. Particularly, the activity counts of mice that were given the repeated administration of MAP with YM (0.01 and 0.03 mg/kg) were almost the same as that of the saline experienced mice.

Experiment 2

As shown in left hand panel of Fig. 3, the mice that received post 3-h treatment with YM (0.01 and 0.03 mg/kg) after each MAP administration demonstrated significantly lower activity counts during the repeated MAP administration [dose; $F(2, 162) = 14.33$, $p < 0.001$, administration $F(5, 162) = 12.69$, $p < 0.001$, and dose × administration; $F(10, 162) = 13.15$, $p < 0.001$]. Individual comparison revealed that the activity counts of YM (0.01 mg/kg) treated mice in the third and fourth administrations and of YM (0.03 mg/kg) treated mice in the third to fifth administrations were significantly lower than those of the saline treated mice.

On the other hand, as shown in right hand panel of Fig. 3, there was no significant difference in the activity counts between the mice that received post 24-h treatment with YM (0.01 and 0.03 mg/kg) and saline throughout the repeated MAP administration.

DISCUSSION

Since YM shows much higher specificity of action as a dopamine D_2 antagonist than other drugs such as haloperidol

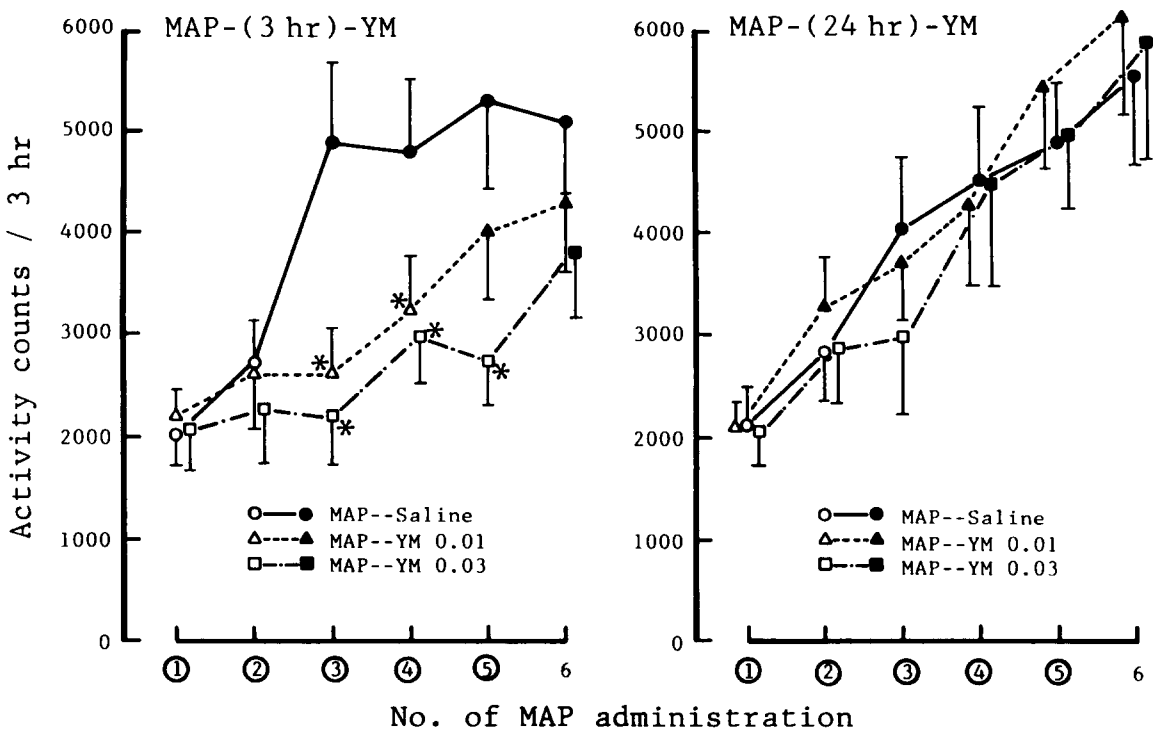

FIG. 3. Mean 3 hr overall ambulatory activity counts with SEMs after the repeated six time SC administration of methamphetamine (MAP: 2 mg/kg) at 3–4 day intervals. The first to fifth MAP administrations were followed by one of the post 3-h (left panel) and 24-h (right panel) treatments with saline and YM-09151-2 (0.01 and 0.03 mg/kg). ●, ▲, ■: significantly different from the value in the first administration within each group ($p < 0.05$). *Significantly different from the values of mice posttreated with saline ($p < 0.05$); $n = 10$ in each group.

(2,17), it was used to evaluate the effect of dopamine D_2 receptor blockade on the methamphetamine sensitization.

The present experiment confirmed the antiamphetamine action of YM. Thus, 0.003–0.03 mg/kg of YM significantly reduced the ambulation increasing effect of MAP throughout the repeated administration. Moreover, in the challenge administration of MAP, the mean activity counts of the mice given the repeated administration of MAP with YM (0.01 and 0.03 mg/kg) were (a) significantly lower than that of MAP-sensitized mice that had received MAP alone, and (b) almost the same as that of the saline experienced mice. These findings clearly indicate that the development of MAP sensitization is inhibited when MAP is combined with YM in each administration. Almost the same results have been observed after the repeated administration of MAP in combination with haloperidol (1,10), and chlorpromazine with *d*-amphetamine (14). Koshiya and Usuda (7) also demonstrated the blocking action of YM on the sensitization to MAP-induced stereotypy in rats. Kuribara and Uchihashi (12) have suggested that a stimulation of D_2 receptors is important in the induction of MAP sensitization. However, when YM (or antipsychotics) is simultaneously administered with MAP, it acts to reduce the unit dose of MAP, and these drugs alone also suppress the ambulation of mice. Hirabayashi and Alam (5) reported that MAP sensitization was more markedly produced at 2 mg/kg than at 1 mg/kg of MAP. Thus, the possibility still remains that the inhibition of MAP sensitization by the simultaneous administration of YM is a result of a reduction of unit dose of MAP. In these respects, the effects of posttreatment with YM following each MAP administration were evaluated in the second experiment.

We have reported that the established MAP sensitization could not be ameliorated by any treatment with YM, and that the repeated five times treatment with YM (0.01–0.1 mg/kg) at 3–4 day intervals prior to MAP injection never reduced, but rather, increased the sensitivity of mice to MAP (12). However, the present experiment demonstrated that the post 3-h treatment, but not the post 24-h treatment, with YM significantly inhibited the induction of MAP sensitization. A freedom of movement during the presence of the acute effect of MAP is a minimum requirement for induction of MAP sensitization by means of ambulatory activity (5). However, in the schedule of post 3-h treatment with YM, the mice were free to move for 3 h in the activity cages after each administration of MAP.

There is a possibility that the action of YM lasted for a long time, and led to a reduction of the effect of next injected MAP. However, there was an interval of 3–4 days between the administration of YM and MAP in the post 3-h treatment with YM, and this interval should be sufficient for disappearance of the acute effect of YM. Indeed, we have found that the acute antimethamphetamine effect of YM does not continue for longer than 24 h (11), indicating that the inhibitory action of YM on the MAP sensitization was not due to the acute antimethamphetamine effect of YM. This consideration can be also confirmed by the result that the post 24-h treatment with YM, in which MAP was administered 2–3 days after YM, i.e., a shorter interval than that in the post 3-h treatment, could not inhibit the induction of MAP sensitization.

The present results indicate that, in addition to a restriction of the ambulatory movement during the presence of the acute effect of MAP (5), blockade of the dopamine D_2 receptor during the postearly period following MAP, at which time the ambulation increasing effect has almost disappeared, is also responsible for inhibiting the induction of the MAP sensitization by means of ambulatory activity in mice.

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