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Modification of morphine sensitization by opioid and dopamine receptor antagonists: evaluation by studying ambulation in mice

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Abstract

The repeated administration of morphine (10 mg/kg s.c.) at 3- to 4-day intervals caused sensitization to its ambulation-increasing effect. A μ-opioid receptor antagonist naloxone (0.03–1 mg/kg s.c.), and dopamine D_1 and D_2 receptor antagonists SCH 23390; *R*-(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine HCl (0.01–0.1 mg/kg s.c.) and YM-09151-2 (nemonapride); *cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (0.003–0.1 mg/kg s.c.), respectively, dose dependently reduced the ambulation increase caused by morphine as well as the sensitization to morphine, when one of them was combined with morphine in the repeated administration. Treatment with SCH 23390 or YM-09151-2, but not naloxone, 3 h after each morphine administration tended to enhance the morphine sensitization. Furthermore, when YM-09151-2 (0.1 mg/kg) was repeatedly administered to the morphine-naive mice 5 times at 3- to 4-day intervals, these mice showed a significant increase in morphine sensitivity. Although the morphine sensitization was partially reversible, repeated (5 times) treatment of the morphine-sensitized mice with SCH 23390 (0.1 mg/kg) resulted in a further enhancement in morphine sensitivity. The same treatment with YM-09151-2 (0.03 and 0.1 mg/kg) tended to increase the sensitivity. These results suggest that, in terms of ambulation in mice, an enhancement of dopaminergic neurotransmission through the agonistic action on μ-opioid receptors is responsible for induction of morphine sensitization. It is also considered that certain changes in the systems mediated by dopamine D_1 and D_2 receptors are involved in the enhancement of the morphine sensitization and for the overall increase in the morphine sensitivity, respectively.

Keywords: Morphine; Ambulation, mouse; Sensitization; μ-Opioid receptor; Dopamine receptor

1. Introduction

The increase in ambulation in mice caused by opiates may reflect an enhancement of dopaminergic neurotransmission through stimulation of μ-opioid receptors (Rethy et al., 1971; Buxbaum et al., 1973; Kuschinski and Hornykiewics, 1974; Teitebaum et al., 1979; Reggiani et al., 1980; Iwamoto, 1981; Swerdlow et al., 1985). Like amphetamine derivatives (e.g., Hirabayashi and Alam, 1981; Kuribara and Tadokoro, 1989), repeated administration of opiates with an agonistic action on μ-opioid receptors elicits an enhancement of their behavioral stimulant effect, particularly the increase in ambulation (locomotion) in mice (Iizuka and Hirabayashi, 1983; Kuribara and Tadokoro, 1989, Fujiwara et al., 1990; Asahi et al., 1991). Thus, it is expected that the behavioral sensitization to opiates is due to certain changes in the dopaminergic systems via stimulation of μ-opioid receptors.

In terms of ambulation in mice, the methamphetamine sensitization was reduced when methamphetamine was simultaneously administered with either dopamine D_1 or D_2 receptor antagonists applied 5 times at 3- to 4-day intervals (Kuribara and Uchihashi, 1993, 1994). Furthermore, Kuribara (1994a,b) recently reported that the blockade of either dopamine D_1 or D_2 receptors by SCH 23390 (Iorio et al., 1983; Mailman et al., 1984) or YM-09151-2 (nemonapride) (Terai et al., 1983), respectively, 3 h after each administration of methamphetamine, at which time the acute stimulant effect of methamphetamine had almost disappeared, could retard the induction of metham-

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phetamine sensitization. This result suggests that a certain action on both the dopamine D_1 and D_2 receptors continues even after cessation of the acute stimulant effect of methamphetamine, and that such a mechanism plays an important role in the induction of methamphetamine sensitization. However, there is no systematic study which has evaluated whether the behavioral sensitization to opiates is modified by antagonism of opioid and/or dopamine receptors.

The main aims of this study were to assess the characteristics of the changes in the sensitization to morphine elicited by SCH 23390 and YM-09151-2, selective dopamine D_1 and D_2 receptor antagonists, respectively, as well as by naloxone, the μ-opioid receptor antagonist, in terms of ambulation in mice. Morphine is a typical opiate having an agonistic action at μ-opioid receptors and its repeated administration at intervals of 1 day or longer produces a significant and progressive enhancement of its ambulation-increasing effect in mice (e.g., Iizuka and Hirabayashi, 1983). The present study evaluated the changes in sensitivity of mice to morphine caused by the following 5 drug administration schedules. (1) The repeated administration of morphine alone. (2) The repeated administration of morphine in combination with naloxone, SCH 23390 or YM-09151-2. (3) Treatment with naloxone, SCH 23390 or YM-09151-2 3 h after each morphine administration. (4) Pretreatment with naloxone, SCH 23390 or YM-09151-2 of the morphine-naive mice. (5) Ttreatment with naloxone, SCH 23390 or YM-09151-2 of morphine-sensitized mice.

2. Materials and methods

2.1. Animals

Male mice of the dd strain (Institute of Experimental Animal Research, Gunma University School of Medicine, Maebashi) were used at 6 weeks of age and weighing 28–30 g. Throughout the experimental period of 4–8 weeks, these mice had been housed in groups of 10 in acrylic-fiber cages of 20(D) × 25(W) × 10(H) cm under controlled room conditions (temperature; 23 ± 2°C, relative humidity; 50 ± 2% and a 12-h : 12-h light-dark schedule; light period of 6:00–18:00 h). They could freely take a solid diet (MF: Oriental Yeast, Tokyo) and tap water except during the experiments.

2.2. Apparatus and procedures

Ambulation was measured with a tilting-type ambulometer with 10 bucket-like Plexiglas activity cages of 20 cm in diameter (SMA-10; O'hara & Co., Tokyo). Since the activity cage was slightly tilted only by a horizontal, but not vertical, movement of the mouse, ambulation was selectively recorded.

The mice were individually put into the activity cages, and after an adaptation period of 30 min the drugs were administered. Then, the ambulation of each mouse was measured for 3 h. Throughout the repeated administration, the ambulation of a given mouse was measured in the same activity cage.

Drug administration and the measurement of ambulation were conducted between 9:00–16:00 h.

2.3. Drugs and administration schedules

The drugs used were morphine HCl (Takeda Chem., Osaka), naloxone HCl (Sigma Chem., St. Louis, MO), SCH 23390; *R*-(+)-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine HCl (Research Biochem., Natick, MA), and YM-09151-2 (nemonapride); *cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide (Yamanouchi Pharm., Tokyo). YM-09151-2 was first dissolved with a very small amount of 1 N HCl solution, and then the solution was diluted with physiological saline. Morphine, naloxone and SCH 23390 were dissolved with physiological saline. All of these drug solutions were injected subcutaneously (s.c.) at the constant volume of 0.1 ml/10 g body weight of the mouse regardless of the drug doses. As a control for the drug injection, the same volume of saline was administered. The body weight of each mouse was measured before each drug or saline administration.

The dose of morphine was fixed at 10 mg/kg, and the drug administration was carried out at intervals of 3–4 days (twice a week). Such conditions were considered to be most appropriate to increase ambulation in dd strain mice by both the single and repeated administration of morphine without producing any signs of physical dependence such as reduction of body weight, diarrhea, etc. during the repeated administration (Iizuka and Hirabayashi, 1983; Kuribara and Tadokoro, 1989).

The following drug administrations were carried out.

2.3.1. Repeated administration of morphine alone

Twenty mice were repeatedly given morphine alone 6 times at 3- to 4-day intervals to evaluate the time course of changes in the ambulation increase during the observation period of 3 h.

2.3.2. Repeated administration of morphine with naloxone, SCH 23390 or YM-09151-2

Thirteen groups of mice (10 mice/group) were given one of the following repeated (5 times) administrations at 3- to 4-day intervals: saline alone, morphine alone, and combinations of morphine with naloxone (0.03, 0.1, 0.3 and 1 mg/kg), SCH 23390 (0.01, 0.03 and 0.1 mg/kg), or YM-09151-2 (0.003, 0.01, 0.03 and 0.1 mg/kg). For the combined administrations, solutions

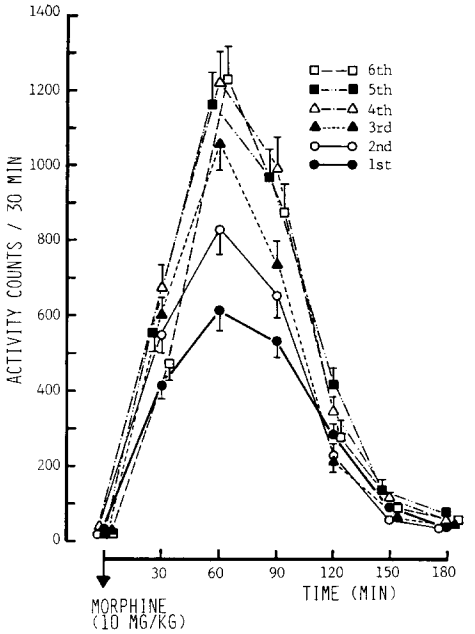

Fig. 1. Time course of changes in the ambulatory activity counts with S.E.M. after repeated (6 times) s.c. administration of morphine (10 mg/kg) at 3- to 4-day intervals in mice. $n = 20$.

containing the two drugs were administered. Such drug mixtures did not cause in any chemical and physical reactions. Four days after the final (5th) administration, a challenge dose of morphine was given to all of these mice.

To estimate the effects of handling (including the drug injection) and the repeated exposure of mice to the activity cages, morphine was administered to another group of 10 drug-naive mice that were age-matched to the drug-treated mice.

2.3.3. Treatment with naloxone, SCH 23390 or YM-09151-2 3 h after each morphine injection

Ten groups of mice (10 mice/group) were given morphine 6 times at 3- to 4-day intervals, and ambulation was measured for 3 h after each morphine administration. Moreover, at the 1st–5th morphine administrations, the mice were additionally given either saline, naloxone (0.1, 0.3 and 1 mg/kg), SCH 23390 (0.01, 0.03 and 0.1 mg/kg) or YM-09151-2 (0.01, 0.03 and 0.1 mg/kg) 3 h after each morphine injection. Ambulation was not measured after the administration of saline, SCH 23390 and YM-09151-2, and the mice were returned to their home cages immediately after the administration.

2.3.4. Pretreatment with naloxone, SCH 23390 or YM-09151-2 of the morphine-naive mice

Ten groups of mice (10 mice/group) were pretreated with one of the following drugs given repeatedly (5 times) at 3- to 4-day intervals: saline, naloxone (0.1, 0.3 and 1 mg/kg), SCH 23390 (0.01, 0.03 and 0.1 mg/kg) and YM-09151-2 (0.01, 0.03 and 0.1 mg/kg) in their home cages. Four days after the end of these pretreatments, the challenge dose of morphine was given to all of these mice.

2.3.5. Treatment with naloxone, SCH 23390 or YM-09151-2 of the morphine-sensitized mice

To induce sensitization to morphine, ten groups of mice (10 mice/group) were first given morphine 5 times at 3- to 4-day intervals in the activity cages. From the 4th day after the 5th morphine administration, each group of mice was treated with either saline, naloxone (0.1, 0.3 and 1 mg/kg), SCH 23390 (0.01, 0.03 and 0.1 mg/kg) or YM-09151-2 (0.01, 0.03 and 0.1 mg/kg) 5 times at 3- to 4-day intervals in their home

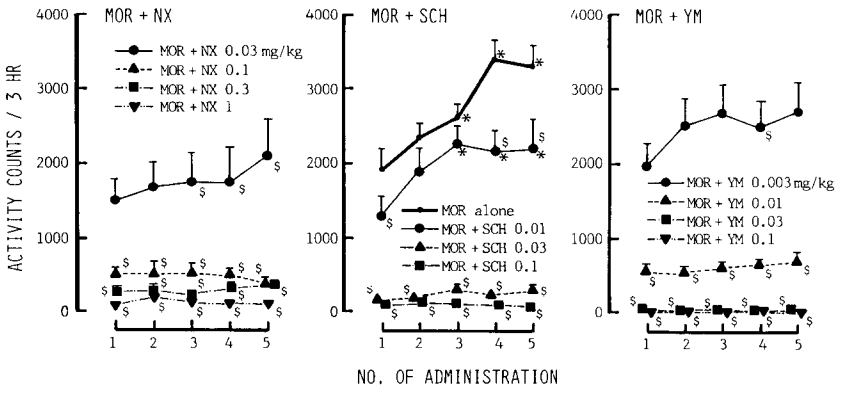

Fig. 2. Mean 3-h overall activity counts with S.E.M. after repeated (5 times) s.c. administration of morphine (10 mg/kg) alone, and combinations of morphine with naloxone (0.03, 0.1, 0.3 and 1 mg/kg) (lefthand panel), SCH 23390 (0.01, 0.03 and 0.1 mg/kg) (middle panel) and YM-09151-2 (0.003, 0.01, 0.03 and 0.1 mg/kg) (righthand panel) at 3- to 4-day intervals in mice. The data for mice given the repeated administration of morphine alone are shown in the middle panel. $^{*}P < 0.05$ vs. the 1st administration within each group. $^{\$}P < 0.05$ vs. the control mice given morphine alone at the same times. $n = 10$ in each group.

cages. Four days after the end of these treatments all of these mice were challenged with morphine.

2.4. Statistical analyses

The mean 3 h overall activity counts were first analyzed using ANOVA. The factors were the doses of naloxone, SCH 23390 and YM-09151-2 (including morphine alone or saline-treatment as dose = 0) and the number of the injection. In the cases of significant overall variance, post-hoc analyses were conducted with Dunnett's test. Values of P less than 0.05 were considered significant.

3. Results

3.1. The administration of morphine alone

As shown in Fig. 1, the repeated (6 times) administration of morphine induced a progressive enhancement of its effect. ANOVA revealed that the changes in the mean 3-h overall activity counts were significantly dependent on the number of the drug injection [$F(5,114) = 95.17$, $P < 0.001$]. The peak and 3-h overall activity counts at the 6th administration were about 2.0 and 1.7 times as high as those at the 1st administration. However, there was no remarkable change in the duration of the increase in ambulation even after the repeated administration, and the activity count returned to close to the pre-drug level 3-h after the administration.

3.2. The combined administration of morphine with naloxone, SCH 23390 or YM-09151-2

As shown in Fig. 2, the increase in ambulation caused by morphine was dose dependently reduced by naloxone [$F(4,225) = 127.08$, $P < 0.001$], SCH 23390 [$F(3,180) = 75.91$, $P < 0.001$] and YM-09151-2 [$F(4,225) = 150.73$, $P < 0.001$] throughout the repeated (5 times) administration. Moreover, the progressive enhancement in the morphine effect was also reduced by naloxone [$F(4,225) = 67.45$, $P < 0.000$], SCH 23390 [$F(4,180) = 40.73$, $P < 0.001$] and YM-09151-2 [$F(4,225) = 64.95$, $P < 0.001$]. Thus, there was no significant enhancement in the increase in ambulation following the repeated administration of morphine with naloxone (0.03 or 1 mg/kg), SCH 23390 (0.03 or 0.1 mg/kg) or YM-09151-2 (0.003-0.1 mg/kg). The interactions between the drug doses × injection number were not significant in all cases.

The mean activity counts at the 1st–5th injections of saline were 53–79 counts, and there were no significant differences among these values (data are not graphically shown).

3.3. Morphine challenge of the mice given morphine with naloxone, SCH 23390 or YM-09151-2

As shown in Fig. 3, the mice given the repeated (5 times) injections of saline exhibited almost the same activity as the drug-naive mice when challenged with morphine. The activity count of the mice repeatedly given morphine alone, i.e., morphine-sensitized mice,

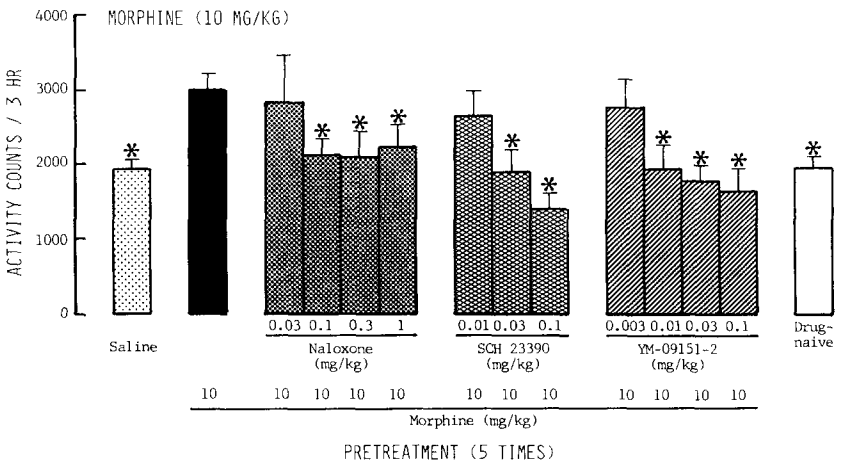

Fig. 3. Mean 3-h overall activity counts with S.E.M. for the challenge with s.c. administered morphine (10 mg/kg) of the mice given repeated (5 times) s.c. administration of saline alone, morphine alone, and combinations of morphine with naloxone (0.03, 0.1, 0.3 and 1 mg/kg), SCH 23390 (0.01, 0.03 and 0.1 mg/kg) and YM-09151-2 (0.003, 0.01, 0.03 and 0.1 mg/kg) at 3- to 4-day intervals. The challenge administration of morphine was carried out 4 days after the end of the repeated administration. $^*P < 0.05$ vs. the control mice given morphine alone (black column). $n = 10$ in each group.

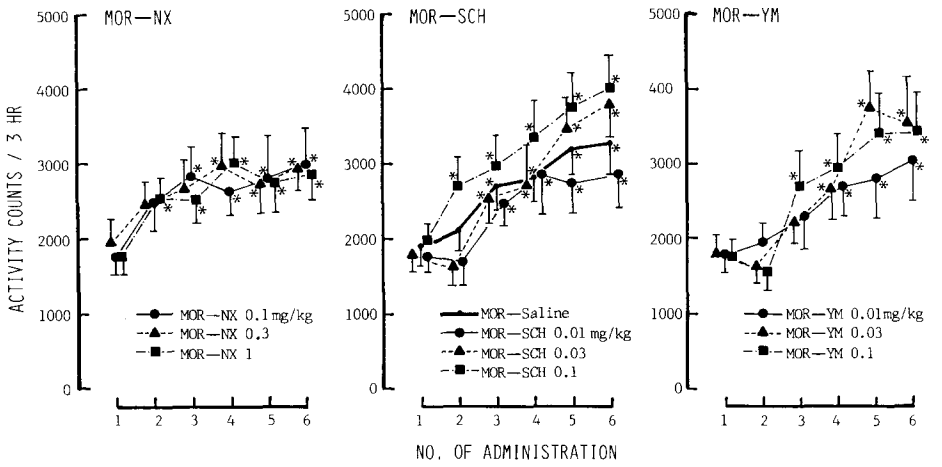

Fig. 4. Mean 3-h overall activity counts with S.E.M.s after the repeated (6 times) s.c. administration of morphine (10 mg/kg) at 3- to 4-day intervals. The 1st–5th morphine administrations were followed by treatment with either saline, naloxone (0.1, 0.3 and 1 mg/kg) SCH 23390 (0.01, 0.03 and 0.1 mg/kg) or YM-09151-2 (0.01, 0.03 and 0.1 mg/kg) 3 h after each morphine administration. The data of control mice given morphine and then treated with saline are presented in the middle panel. $^{*}P < 0.05$ vs. the 1st administration within each group. $n = 10$ in each group.

was about 1.6 times higher than that of the saline-treated mice upon challenge administration of morphine.

The repeated administration of morphine in combination with naloxone, SCH 23390 or YM-09151-2 resulted in significant reductions in the morphine sensitization [$F(4,45) = 73.09$, $F(3,36) = 19.74$, and $F(4,45) = 35.18$, respectively, $P < 0.001$]. Post-hoc analyses revealed that the activity counts of the mice given morphine with naloxone (0.1–1 mg/kg), SCH 23390 (0.03 or 0.1 mg/kg) or YM-09151-2 (0.01–0.1 mg/kg) were significantly lower than those of the mice given morphine alone.

3.4. Treatment with naloxone, SCH 23390 or YM-09151-2 3 h after each morphine administration

The effects of the injection number were significant [$F(5,216) = 81.020$, $F = 137.59$ and $F = 108.41$ for naloxone, SCH 23390 and YM-09151-2, respectively, $P < 0.001$] in the post-treatment schedule. However, the effects of drug doses, and the interactions between drug doses × injection number did not attain significance. Thus, as shown in Fig. 4, the mice treated with naloxone, SCH 23390 and YM-09151-2 exhibited a progressive enhancement in the increase in ambulation after morphine administration, similar to that of the mice treated with saline. Although the changes did not attain a significant level, post-treatment with the higher doses of SCH 23390 and YM-09151-2, particularly the former drug, tended to accelerate the morphine sensitization.

3.5. Pretreatment with naloxone, SCH 23390 or YM-09151-2 of morphine-naive mice

Fig. 5 shows the mean 3-h activity counts at the challenge administration of morphine to the mice that had been repeatedly given naloxone, SCH 23390 and YM-09151-2 5 times at 3- to 4-day intervals. There was a significant effect of YM-09151-2 [$F(3,36) = 3.59$, $P < 0.05$] on the morphine sensitivity, and the mice repeatedly given YM-09151-2 (0.1 mg/kg) showed a significantly higher sensitivity than the saline-treated control mice in response to the morphine challenge. Naloxone and SCH 23390 had no significant effect.

3.6. Treatment with naloxone, SCH 23390 or YM-09151-2 of morphine-sensitized mice

Fig. 6 shows the mean 3-h activity counts at the 1st and 5th administration of morphine, and at the morphine challenge after the repeated (5 times) treatment with naloxone, SCH 23390 or YM-09151-2.

Similar to the above results, the repeated administration of morphine produced sensitization, and the

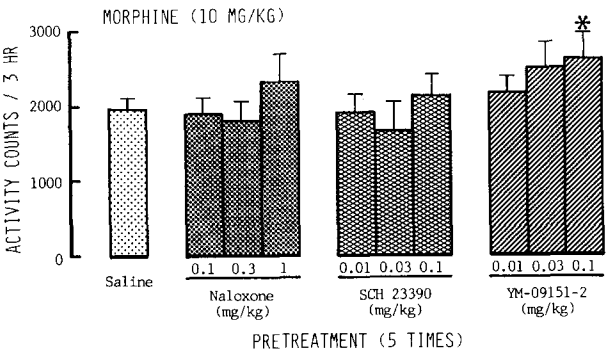

Fig. 5. Mean 3-h overall activity counts with S.E.M. after s.c. administration of morphine (10 mg/kg) to the mice pretreated with repeated (5 times) administration of either saline, naloxone (0.1, 0.3 and 1 mg/kg), SCH 23390 (0.01, 0.03 and 0.1 mg/kg) or YM-09151-2 (0.01, 0.03 and 0.1 mg/kg) at 3- to 4-day intervals. The administration of morphine was carried out 4 days after the end of pretreatment. $^{*}P < 0.05$ vs. the saline-pretreated control mice.

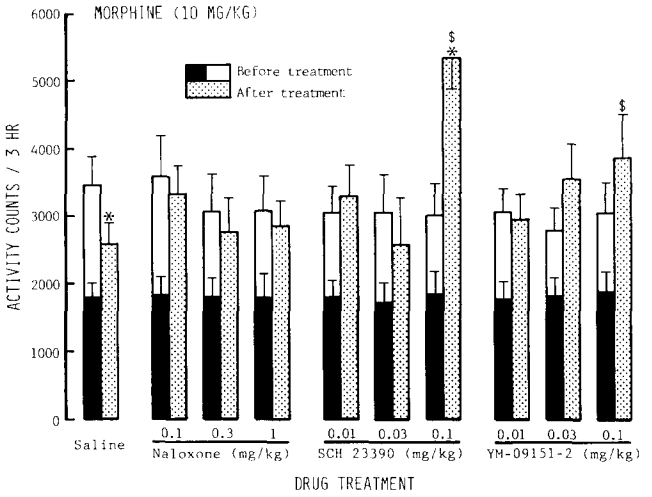

Fig. 6. Mean 3-h overall activity counts with S.E.M. after s.c. administration of morphine (10 mg/kg) to the morphine-sensitized mice before and after the treatments with saline, naloxone (0.1, 0.3 and 1 mg/kg), SCH 23390 (0.01, 0.03 and 0.1 mg/kg) or YM-09151-2 (0.01, 0.03 and 0.1 mg/kg). Sensitization to morphine was induced by repeated (5 times) administration of morphine at 3- to 4-day intervals. Treatment with saline, naloxone, SCH 23390 or YM-09151-2, which was carried out 5 times at 3- to 4-day intervals, was started 4 days after the 5th morphine administration. On the 4th day after the final treatment, morphine was readministered. In this figure, the activity counts for the 1st and 5th administrations of morphine for induction of morphine-sensitization (black column, and black column + white column, respectively), and for morphine readministration (stippled column) are presented in each group. $^{*}P < 0.05$ vs the count for the 5th morphine administration (i.e., immediately before the post-treatment) within each group. $^{\$}P < 0.05$ vs. the control mice post-treated with saline on the readministration of morphine. $n = 10$ in each group.

activity count at the 5th administration was 1.7–2.0 times higher than that at the 1st administration in each group. Of course, there was no significant difference in the activity counts among the groups.

There were significant effects of SCH 23390 and YM-09151-2 [$F(3,36) = 8.37$, $P < 0.01$, and $F = 3.27$, $P < 0.05$, respectively]. The mice post-treated with saline showed a slight but significant reduction in the increased sensitivity to morphine. In contrast, the post-treatment with SCH 23390 (0.1 mg/kg) markedly enhanced, and that with YM-09151-2 (0.03 and 0.1 mg/kg) tended to enhance the sensitivity to morphine of the morphine-sensitized mice. Naloxone had no such action.

3.7. The general conditions of mice

The mice did not show any signs which suggested physical dependence on morphine. Thus, the mice gained weight (3–5 g) during the experimental period of 4–8 weeks. A gross estimation revealed that there was no remarkable change in the food and water consumptions throughout the experimental period.

4. Discussion

In agreement with the previously reported data (Iizuka and Hirabayashi, 1983; Kuribara and Tadokoro, 1989), sensitization to the ambulation-increasing effect of morphine was induced by the repeated administration of morphine. Such morphine sensitization was characterized by a significant increase in the peak effect without a significant prolongation of the effect, indicating that a pharmacodynamic, but not a pharmacokinetic, mechanism is mainly involved in the induction of morphine sensitization.

It is considered that the behavior-stimulant effect of morphine is caused by an increase in presynaptic dopamine release through an agonistic action on μ-opioid receptors (Rethy et al., 1971; Buxbaum et al., 1973; Kuschinski and Hornykiewics, 1974; Teitebaum et al., 1979; Reggiani et al., 1980; Iwamoto, 1981; Swerdlow et al., 1985). Such mechanisms can also be supported by the present results that the ambulation-increasing effect of morphine was inhibited not only by the μ-opioid receptor antagonist naloxone but also by the dopamine D_1 and D_2 receptor antagonists SCH 23390 (Iorio et al., 1983; Mailman et al., 1984) and YM-09151-2 (Terai et al., 1983), respectively, throughout the repeated administration.

Because morphine accelerates dopaminergic neurotransmission, it was first expected that the post-treatment (i.e., immediately after cessation of the acute ambulation increase caused by morphine) with SCH 23390 or YM-09151-2 as well as with naloxone would retard the induction of morphine sensitization, similar to the retardation of methamphetamine sensitization by both the dopamine D_1 and D_2 receptor antagonits (Kuribara, 1994a,b). In contrast to this expectation, however, naloxone, SCH 23390 and YM-09151-2 did not retard, but rather SCH 23390 and YM-09151-2 tended to enhance the morphine sensitization. The effect of SCH 23390 was slightly stronger than that of YM-09151-2. These results might reflect different characteristics of the effects of morphine and methamphetamine on the dopaminergic systems, i.e., the indirect stimulation of dopamine release through an agonistic action on μ-opioid receptors by morphine (Rethy et al., 1971; Buxbaum et al., 1973; Kuschinski and Hornykiewics, 1974; Teitebaum et al., 1979; Iwamoto, 1981; Swerdlow et al., 1985), and the direct stimulation of dopamine release and inhibition of dopamine reuptake by methamphetamine (McMillen, 1983; Fischman, 1987). It is therefore considered that a direct blockade of dopamine D_1 and D_2 receptors by SCH 23390 and YM-09151-2, respectively, may not essentially modify the morphine sensitization which is induced through indirect acceleration of dopamine release via the agonistic action on μ-opioid receptors.

The repeated treatment with SCH 23390 and YM-

09151-2 changed the sensitivity to morphine in both the morphine-naive and morphine-sensitized mice. The mice pretreated with the highest dose of YM-09151-2 (0.1 mg/kg), but not with SCH 23390, demonstrated a significant increase in sensitivity to morphine. It is known that the repeated blockade of dopamine D_2 receptors results in a significant increase in sensitivity not only to direct dopamine agonists such as apomorphine, but also to dopamine releasers such as amphetamines (Kobayashi et al., 1977; Chouinard and Jones, 1980; Creese, 1983; Kuribara and Uchihashi, 1993, 1994). In particular, Kuribara and Uchihashi (1993, 1994) reported that repeated treatment with haloperidol or YM-09151-2, but not with SCH 23390, increased the sensitivity of mice to the ambulation-increasing effect of methamphetamine. It is therefore probable that dopaminergic neurotransmission, in which dopamine D_2 receptors are mainly involved, is changed by YM-09151-2, and that this change is responsible for an overall increase in morphine sensitivity. This idea is also supported by the data that treatment with YM-09151-2 3 h after each morphine administration tended to accelerate morphine sensitization at the latter stages of the repeated administration.

As previously reported (Iizuka and Hirabayashi, 1983), morphine sensitization is partially reversible. Thus, the mice given saline after the establishment of morphine sensitization showed a significant reduction in the sensitivity to morphine. In contrast, post-treatment with SCH 23390 (0.1 mg/kg) produced a dramatic enhancement of the sensitivity to morphine in the morphine-sensitized mice, although pretreatment with SCH 23390 of the drug-naive mice did not result in any significant change in morphine sensitivity. These results suggest that the dopaminergic neurotransmission mediated by dopamine D_1 receptors may selectively play an important role in the enhancement of morphine sensitivity in morphine-sensitized mice. This idea is also supported by the result that treatment with SCH 23390 3 h after each morphine administration tended to enhance the morphine sensitization during the latter stages of the repeated administration.

Ttreatment with YM-09151-2 after the establishment of morphine sensitization blocked the spontaneous reduction in morphine sensitization, and it tended to enhance morphine sensitivity. This result also supports the idea mentioned above that dopaminergic systems mediated by dopamine D_2 receptors are involved in the overall increase in sensitivity to morphine, although such a mechanism does not directly affect the induction of morphine sensitization. A similar overall enhancement of sensitivity was observed in the case of methamphetamine after the repeated treatment with YM-09151-2, but not with SCH 23390, in methamphetamine-sensitized mice (Kuribara and Uchihashi, 1994).

Both pretreatment and post-treatment with naloxone caused no significant modification of morphine sensitivity, although naloxone showed a strong inhibitory action on the effect of morphine in the combined administration schedule, indicating that μ-opioid receptors are scarcely involved in the modification of morphine sensitization, or in the overall increase in morphine sensitivity produced by repeated treatment with SCH 23390 and YM-09151-2, respectively.

There were large quantitative alterations in the effect of morphine dependent on the experimental schedules. However, the time course of changes in ambulatory activity following the challenge administration of morphine was qualitatively similar among the groups of mice given different treatments. There was no evidence of physical dependence on morphine. Furthermore, it has been behaviorally confirmed that the receptor antagonistic actions of naloxone, SCH 23390 and YM-09151-2 might not continue for 3 days (Kuribara and Uchihashi, 1994; Kuribara unpublished data). This evidence suggests again that pharmacokinetic mechanisms are negligible in the modification of morphine sensitivity by naloxone, SCH 23390 and YM-09151-2, although pharmacokinetics were not evaluated in this study.

A further study is required to clearly elucidate the mechanism of modification of morphine sensitization by opioid and dopamine receptor antagonists in terms of ambulation in mice. However, the following conclusions can be made from the present results. (1) An enhancement of dopamine release through the stimulation of μ-opioid receptors is involved in the ambulation-increasing effect of morphine, and the induction of sensitization to the effect of morphine. (2) The changes in dopaminergic neurotransmission result in an increase in morphine sensitivity. Thus, dopamine D_1 and D_2 receptors play important roles in the acceleration of morphine sensitization and in the overall increase in morphine sensitivity, respectively.

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