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Induction of Sensitization to Hyperactivity Caused by Morphine in Mice: Effects of Post-Drug Environments

HISASHI KURIBARA[1]

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

KURIBARA, H. *Induction of sensitization to hyperactivity caused by morphine in mice: effects of post-drug environments.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 341–346, 1997.—Mice given five repeated administrations of morphine (10 mg/kg sc) at 3 day intervals in a round tilting-type activity cage (20 cm in diameter) or round spaces 15–30 cm in diameter with fixed floor showed almost the same level of ambulatory sensitization to morphine. Whereas, mice given morphine in the same schedule in spaces 4 and 12 cm, but not 6 and 9 cm, in diameter demonstrated a partial increase in the sensitivity to morphine. Furthermore, mice given morphine five times in a transparent cage (20W × 25L × 15H cm) with woodchip bedding, that was the same as the home cage, showed a weak and strong ambulatory sensitization when they were placed in group of ten and singly, respectively, for 3 h after each morphine administration. Repeated administrations of saline to mice in the space 4 cm in diameter resulted in increased sensitivity to morphine. However, the pretreatment with saline in the other environments (activity cage, spaces 6–30 cm in diameter with fixed floor, and home cage-like cage in which mice were placed singly or in group of ten) did not change the sensitivity to morphine. These results suggest that repeated experience of pharmacological effect of morphine and the resultant ambulation is one of the most important factors for induction of strong ambulatory sensitization to morphine in mice. It is estimated that a space 15 cm in diameter, which corresponds to 2–2.5 times as long as the body length without tail is a minimum requirement for induction of strong ambulatory sensitization to morphine. In contrast, even though mice are placed in a sufficient space for ambulation, an interference of ambulation by the other mice acts to inhibit the induction of ambulatory sensitization. It is also suggested that a strong stress caused by restraint is responsible for significant increase in sensitivity to morphine. © 1997 Elsevier Science Inc.

Morphine Repeated administration Sensitization Ambulation Conditioning Environment-dependency Mice

MORPHINE has a behavioral stimulant effect through an agonistic action on μ-opioid receptors and resultant acceleration of dopaminergic neurotransmission (2,11,19,22,23,28,29). Like psychostimulants such as amphetamines and cocaine, when morphine is repeatedly administered at intervals of 1 day or longer, sensitization to its behavioral stimulant effect, particularly ambulatory (locomotor) stimulant effect, is induced in mice (9,18) and rats (25). Changes in dopaminergic and/or opioid neurotransmission may be involved in the behavioral sensitization to morphine, because the induction of ambulatory sensitization to morphine is effectively inhibited when morphine is administered in combination with either dopamine D_2 receptor antagonist or μ-opioid receptor antagonist (15).

In terms of ambulation in mice, however, it has been demonstrated that the induction of sensitization to morphine is strongly affected by environmental factors in which the mouse is placed during the drug effect. Iizuka and Hirabayashi (9) reported that, even after repeated administrations of morphine, the mice did not demonstrate ambulatory sensitization when they were physically restricted by being placed in a small jar (6 cm in diameter and 15 cm in height) for 3 h immediately after each administration of morphine. In such a space, the mouse was restricted in terms of ambulation, but not turning and vertical movements. Of course, the restraint did not block the pharmacological effect of morphine. These results suggest that a repeated experience of both the pharmacological effect of morphine and the resultant ambulation is important for induction of ambulatory sensitization to morphine. However, the environment required for induction of strong ambulatory sensitization to morphine is still unknown.

The aims of this study were to assess the intensity of ambulatory sensitization to morphine in mice that were placed in round spaces 4–30 cm in diameter for 3 h after the administra-

[1]Address for mailing proofs: Department of Neurobiology and Behavior, Behavior Research Institute, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi 371, Japan, Phone: 81-272-20-71111 (Ext. 8082), Fax: 81-272-20-8083.

tion of morphine. Furthermore, modifications of ambulatory sensitization to morphine in the mice repeatedly given morphine in the environment which was almost the same as their breeding conditions were also evaluated.

METHOD

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 at weight of 25–30 g. They had been housed in group of ten in transparent polycarbonate cages (20W × 25L × 15H cm, with a woodchip bedding), and allowed free access to a solid diet (MF: Oriental Yeast, Tokyo) and tap water except during times of the behavioral tests. The breeding room were controlled the conditions (temperature; 23 ± 1°C, relative humidity; 55 ± 3%, and a 14:10 h light-dark cycle; lights on at 0500-1900 h).

Apparatus

A tilting-type ''ambulometer'' (SMA-10: O'Hara & Co., Tokyo) was used for measurement of ambulation of mice. This apparatus has ten bucket-like round activity cages of acrylic fiber of green color (20 cm in diameter and 15 cm in height). Since horizontal movements of the mouse generated slight tilts of the activity cage and the tilts were detected with microswitches attached to the cage, the ''ambulometer'' could selectively and quantitatively record ambulation, but not any vertical movements or turning, of the mouse.

Drug

Morphine HCl (Takeda Chem., Osaka) was dissolved in physiological saline, and administered sc at 0.1 ml/10 g body weight of the mouse. The dose of morphine (10 mg/kg in the salt form) was optimum for induction of the ambulatory sensitization as demonstrated in our previous studies (15,18). It has also been confirmed that 10 mg/kg morphine never produces stereotyped behaviors such as sniffing, pivoting, etc. (9).

Experimental Procedures

All experimental treatments, including drug injection, placing mice in the post-morphine environments, and measurement of ambulatory activity, were carried out between 0900–1500 h in the breeding room. When the activity of mice was measured, they were habituated for 30 min to the activity cage prior to the administration of morphine or saline.

Experiment 1. Two groups of ten mice each were given morphine and saline, respectively, five times at 3 day intervals, and their activity was measured with the ''ambulometer'' for 3 h after each administration. Three days after the fifth pretreatment all the mice in both groups were given morphine, and their activity was measured for 3 h. Furthermore, to assess whether the experimental operations in the pretreatment phase changed the sensitivity to morphine, morphine was administered to the drug-naive mice (ten mice) that were age-matched to the morphine- and saline-pretreated groups.

Experiment 2. Two sets of eight groups of ten mice each were given morphine and saline, respectively, five times at 3 day intervals, and immediately after the administration they were individually placed in either acrylic fiber cylinder of grey color with fixed floor (4, 6, 9, 12, 15, 20, 25 or 30 cm in diameter, respectively, and 15 cm in height) for 3 h. Three days after the fifth pretreatment the mice in all groups were challenged with morphine, and their activity was measured for 3 h with the ''ambulometer''.

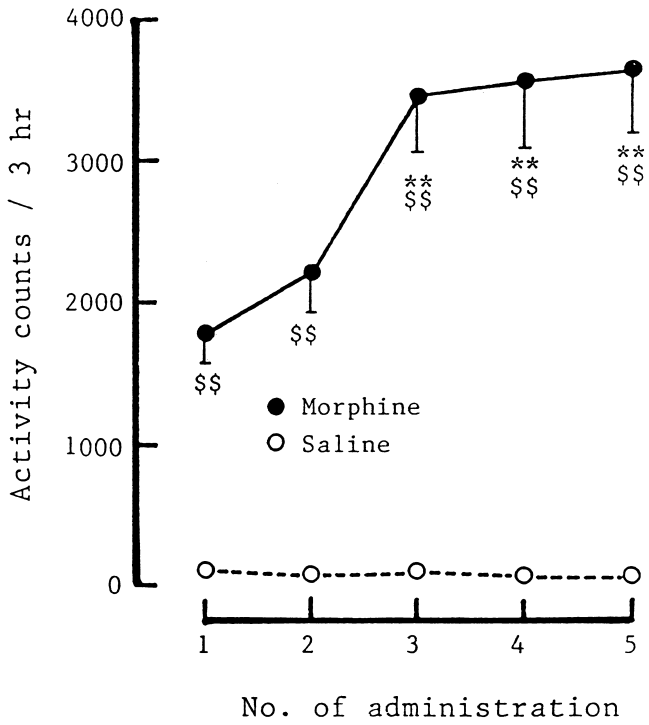

FIG. 1. Mean 3 h daily overall ambulatory activity counts with SEMs after 5 repeated sc administrations of morphine (10 mg/kg) or saline to mice at 3 day intervals. The ambulation of mice was measured with a ''ambulometer'' having tilting-type cage (20 cm in diameter). $p <$ 0.01 vs. the first administration within group. $p < 0.01$ vs. the saline control group. $n = 10$ in each group.

Experiment 3. Two sets of two groups of ten mice each were given morphine and saline, respectively, five times at 3 day intervals, and they were placed in group of ten or singly, respectively, in transparent polycarbonate cages (20W × 25L × 15H cm) with a woodchip bedding, which were the same as their home cage, for 3 h after each administration. The mice placed in the home cage-like cage in group of ten were cagemates. Three days after the end of such pretreatments the mice in all groups were challenged with morphine, and their activity was measured for 3 h with the ''ambulometer.''

Statistical Analysis

The mean overall activity counts were first analyzed by one- or two-way analysis of variance (ANOVA). The factors were drugs (saline and morphine), and number of administrations (5 levels in Experiment 1), spaces (8 levels in Experiment 2) and conditions (2 levels in Experiment 3; mice being placed singly and in group of ten). Post-hoc analyses were carried out by Dunnett's test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Experiment 1

Figure 1 shows mean 3 h overall activity counts after the five repeated administrations of morphine and saline to the

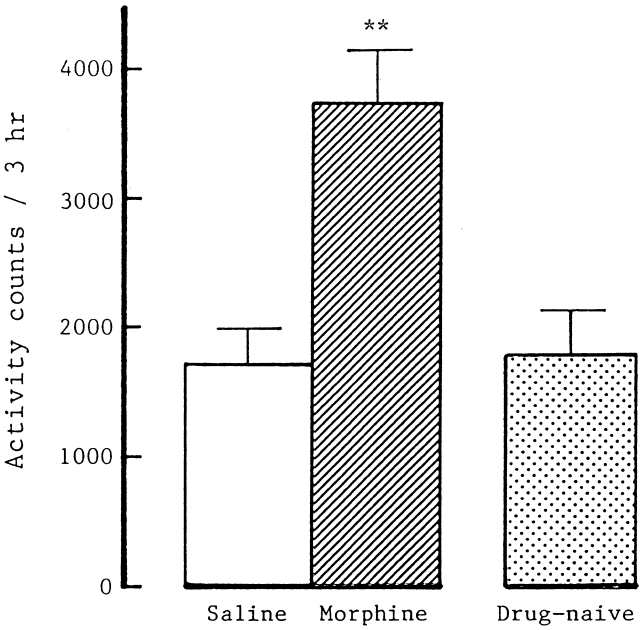

FIG. 2. Mean 3 h overall ambulatory activity counts with SEMs after the challenge administration of morphine (10 mg/kg sc) to the mice pretreated with 5 repeated administrations of morphine (10 mg/kg) or saline at intervals of 3 days in the tilting-type cage, and to the drug-naive mice that were age-matched to the pretreated mice. The challenge administration of morphine was carried out 3 days after the fifth pretreatment. $p < 0.01$ vs. the saline-pretreated control groups. $n = 10$ in each group.

mice in the ''ambulometer''. The activity counts were dependent on drug [$F(1,90) = 179.3$, $p < 0.001$] and number of administration [$F(4,90) = 28.1$, $p < 0.001$]. There was a significant interaction between drug × number of administration [$F(4,90) = 6.0$, $p < 0.001$]. Post-hoc analyses revealed that the counts at the third to fifth administrations of morphine were almost the same (i.e., reaching a ceiling effect) and were approximately 2 times higher than that at the first administration. Saline elicited very low activity counts throughout five administrations, and there was no significant difference among these counts.

Figure 2 represents mean 3 h overall activity counts following the challenge administrations of morphine to the groups of mice pretreated with morphine and saline, and to the drug-naive mice. The activity count of the morphine-pretreated group was significantly higher than that of the saline-pretreated group [$F(1,18) = 11.6$, $p < 0.01$]. The activity count of the saline-pretreated group was almost the same as that of the drug-naive group [$F(1,18) = 0.2$, ns].

Experiment 2

Figure 3 shows mean 3 h overall activity counts following the challenge administration of morphine to the groups of mice pretreated with morphine and saline in the spaces 4–30 cm in diameter with fixed floor. The activity counts were significantly dependent on drug [$F(1,144) = 98.0$, $p < 0.001$], and space [$F(7,144) = 81.3$, $p < 0.001$] in the pretreatment phase. There was a significant interaction between drug × space [$F(7,144) = 24.1$, $p < 0.001$]. Post-hoc analyses revealed that, among the saline-pretreatment groups, the group of mice placed in the space 4 cm in diameter showed significantly higher activity count than the other groups. Among the morphine-pretreatment groups, the groups of mice placed in the spaces 6 and 9 cm in diameter demonstrated significantly lower activity counts than the other groups, and the counts were as high as those of the groups of mice pretreated with saline in the same spaces. The morphine-pretreated group in the space 4 cm in diameter showed an increased sensitivity to morphine, that was similar level to that of the group pretreated with saline in the same space. The group of mice pretreated with morphine in space 12 cm exhibited a partially increased sensitivity to morphine. In contrast, the groups of mice given morphine in spaces 15–30 cm showed a sensitization which was as strong as that observed in the group of mice pretreated with morphine in the ''ambulometer'' (see Fig. 2).

Experiment 3

Figure 4 shows mean 3 h overall activity counts following the challenge administration of morphine to the groups of mice pretreated with saline or morphine in the home cage-like cage. The activity counts were dependent on drug [$F(1,36) = 27.7$, $p < 0.001$] and condition [$F(1.36) = 5.1$, $p < 0.05$] in the pretreatment phase. There was a significant interaction between drug × condition [$F(1,36) = 4.5$, $p < 0.05$]. Post-hoc analyses revealed that the saline-pretreated mice, that were placed singly or in group of ten in the home cage-like cage for 3 h after each administration, did not show significant change in the sensitivity at the challenge administration of morphine. Whereas, the morphine-pretreated groups exhibited an ambulatory sensitization to morphine. Particularly, the ambulatory sensitization in the mice placed singly in the home cage-like cage was as strong as that in the mice pretreated with morphine in the ''ambulometer'' (see Fig. 2) or spaces 15–30 cm in diameter (see Fig. 3). However, the mice placed in groups of ten in the home cage-like cage demonstrated a partial ambulatory sensitization to morphine.

Gross Observation

In space 4 cm in diameter, the mouse could not express both the horizontal and vertical movements, and they tended to exhibit an excess defecation. In spaces 6 and 9 cm in diameter, mice were restricted in terms of ambulation, but could freely express turning and vertical movements. However, these mice showed neither hyperactivity, that were characterized by vertical movements and/or turning, nor an excess defecation in these spaces after the administration of morphine and saline. Whereas, mice could express ambulation of comparatively shorter distances in the space 12 cm in diameter, and longer distances in the activity cage, spaces 25–30 cm in diameter and the home cage-like cage. The mice sometimes exhibited fighting and vocalization when they were placed in home cage-like cage in groups of ten after the administration of morphine, but not saline.

Stereotyped behaviors were not scored in this study, because mice did not show any stereotyped behaviors after administration of morphine.

DISCUSSION

When mice were repeatedly given morphine and then placed in the tilting-type activity cage (20 cm in diameter) at 3 day intervals, they showed ambulatory sensitization to morphine. The increased sensitivity reached a ceiling by the third or fourth administration. Such results are consistent with

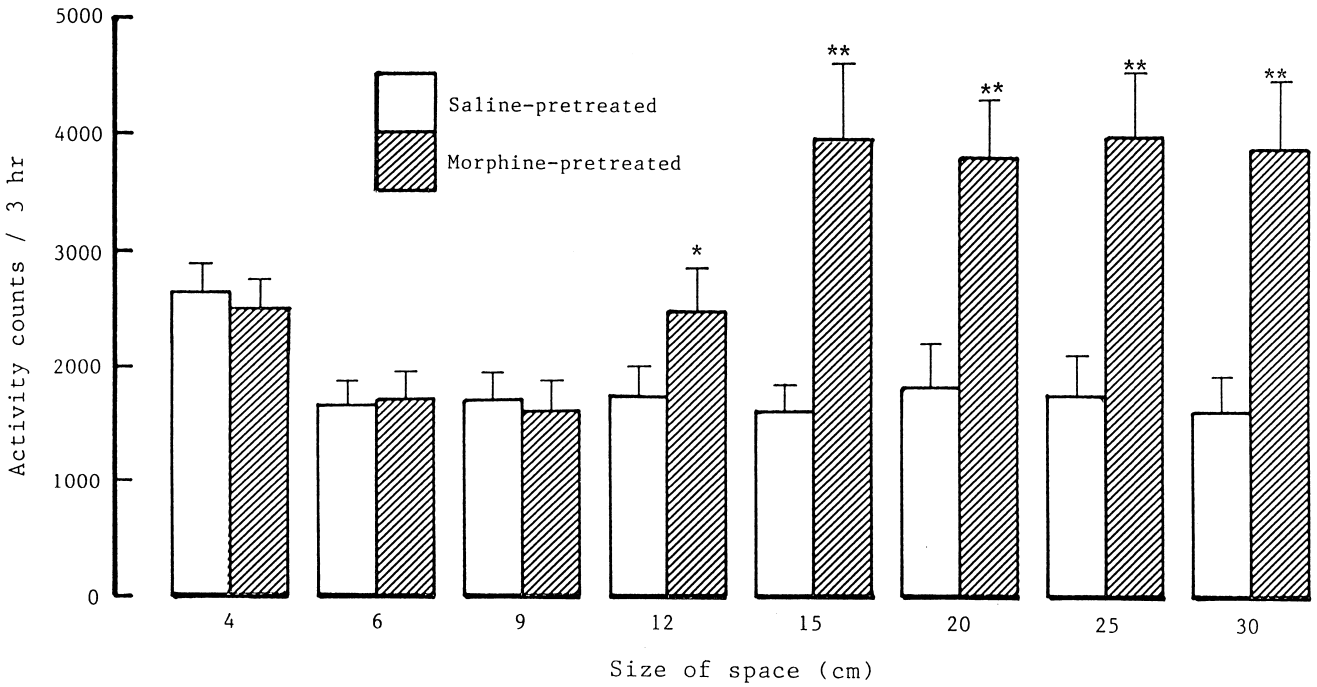

FIG. 3. Mean 3 h overall ambulatory activity counts with SEMs after the challenge administration of morphine (10 mg/kg sc) to the mice pretreated with 5 repeated administrations of morphine (10 mg/kg) or saline at intervals of 3 days in the spaces 4–30 cm in diameter with fixed floor. The challenge administration of morphine was carried out 3 days after the fifth pretreatment. * and ** $p < 0.05$ and 0.01, respectively, vs. the saline-pretreated group in the same space. $n = 10$ in each group.

the previous reports (9,18). On the other hand, the sensitivity to the ambulatory stimulant effect of morphine in the saline-pretreated mice was as high as that in the drug-naive mice. This result suggests that the experimental operations such as drug injection and placing the mice in the activity cage did not elicit a significant change in the sensitivity to morphine.

Morphine-induced hyperactivity and sensitization are thought to be primarily caused by changes in the functioning of the mesocorticolimbic dopaminergic neurons (12,13,14,30,32). In this study, neurochemical investigation was not carried out. However, if the mechanisms other than the neurochemical changes played less contribution to the ambulatory sensitization, all the mice pretreated with morphine should consistently show the same level of sensitization independently of the environments in the pretreatment phase. However, the present experiments revealed that the groups of mice given morphine in spaces 6 and 9 cm in diameter did not show ambulatory sensitization to morphine, and the activity counts were as high as those in the groups of mice given saline in the same spaces. These results are in agreement with a previous report that mice given ten repeated administrations of morphine in glass jars (6 cm in diameter and 15 cm in height) at 1–7 day intervals did not exhibit ambulatory sensitization (9). In contrast, when mice were placed in spaces 15–30 cm in diameter after each administration of morphine, they demonstrated almost the same level of ambulatory sensitization to morphine as that observed in the mice placed in the tilting-type activity cage. These results reinforce the consideration that the size of space, in which the mouse was placed during the acute effect of morphine, was important for the induction of ambulatory sensitization to morphine.

In the inhibition of ambulatory sensitization to morphine, some mechanisms are considered to be involved.

The first possible mechanism is an aversive conditioning and resultant depression of overall activity caused by a restriction of ambulation. However, it has been reported that repeated exposure of animals to stressors elicits stimulation of the mesocorticolimbic dopaminergic system (1,4,5,10), and produces an augmentation of the behavioral stimulant effect of morphine (3,20,25). In this study, the mice placed in the space 4 cm in diameter after each administration of saline and morphine exhibited an increased sensitivity to morphine, suggesting that such a narrow space was aversive and stressful for the mouse. The facts that mice in space 4 cm in diameter could not express both horizontal and vertical movements and they made excess defecation may also support this consideration. In contrast, the mice could freely express turning and vertical movements in the spaces 6 and 9 cm in diameter, and they did not exhibit any signs indicating stress while placing in such spaces after the administration of saline and morphine. This result indicates that the spaces 6 cm and larger in diameter were less aversive and stressful for the mouse, and therefore did not change neurotransmissions which were responsible for increase in the sensitivity to morphine. In these respects, the possibility of aversive conditioning is less likely for elucidation of the inhibition of ambulatory sensitization to morphine.

The second possible mechanism is an indication of sensitization to the stereotypy-producing effect rather than the ambulation-increasing effect after the repeated administration of morphine as demonstrated following repeated administration of amphetamines (8,24). However, as revealed by gross observation, all the mice did not show any stereotyped behaviors after the administration of morphine. Furthermore, the mice given morphine in spaces 6 and 9 cm in diameter did not show enhancement of vertical movements and turning. It is therefore less probable that the inhibition of ambulatory sensi-

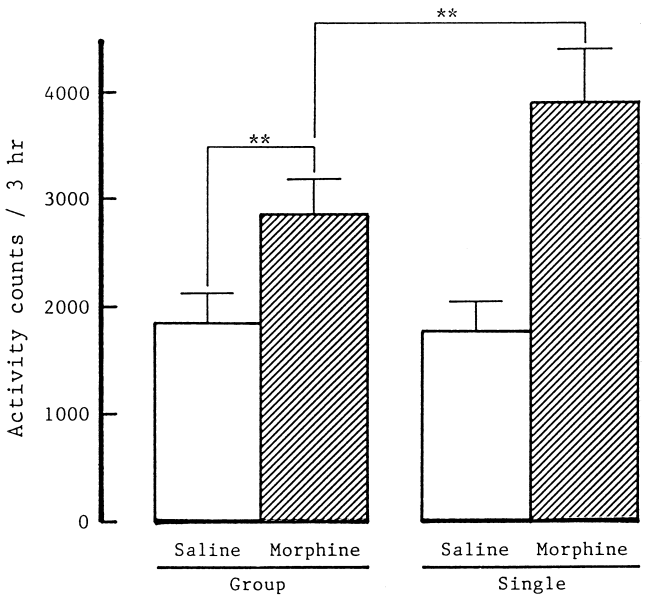

FIG. 4. Mean 3-h overall ambulatory activity counts with SEMs after the challenge administration of morphine (10 mg/kg sc) to the mice pretreated with 5 repeated administrations of morphine or saline in the home cage-like cage (20W × 25L × 15H cm with woodchip bedding) at intervals of 3-days. In the pretreatment phase, the mice were placed singly or in group of ten in the home cage-like cage for 3 h after each administration of morphine and saline. The challenge with morphine was carried out 3 days after the fifth pretreatment. $^{**}p < 0.01$ between groups.

tization in the mice placed in spaces 6 and 12 cm is due to induction of sensitization to the other behavior-accelerating effect of morphine.

The third possible mechanism is a blockade of linkage between stimulation of dopaminergic and opioid neurotransmission by morphine and the resultant increase in the ambulation. When mice were placed in the spaces 25–30 cm in diameter and in the tilting-type activity cage after administration of morphine, they demonstrated almost the same level of ambulatory sensitization. In these situations, the mice could freely express ambulation. Whereas, mice were restricted ambulation perfectly in the spaces 6 and 9 cm, and partially in the space 12 cm in diameter. As mentioned above, the former mice did not show ambulatory sensitization, and the latter mice exhibited a partial sensitization. Such environment-dependent characteristic of ambulatory sensitization to morphine was almost the same as that to methamphetamine and cocaine in mice (16). Although there is a report that restrained rats learn amphetamine-conditioned locomotion (27), it is suggested by the present results that the mouse must be placed in a freely movable situation during the acute stimulation effect of morphine to induce strong ambulatory sensitization to morphine.

Many reports (21,26,33) suggested that the sensitization to psychostimulants is context-dependent. Thus, the highest sensitization is induced when the animals are given the drug in the same environment in both the pretreatment and challenge phases. In this study, the post-morphine environments were different in the colors (green, gray and transparent), types of floor (tilting-type, fixed, and woodchip bedding), and shapes (round and rectangular) in Experiments 1–3. However, the ambulatory sensitization to morphine was almost the same level among groups of mice given morphine in the tilting-type activity cage, spaces 15–30 cm in diameter with fixed floor and home cage-like cage (mice being singly placed). This result suggests that these three environmental factors played comparatively smaller roles than the size of space in the induction of ambulatory sensitization to morphine.

Repeated administration of morphine to the mice resulted in a partial, but not strong, ambulatory sensitization when mice were placed in groups of ten in the home cage-like cage. As gross observation revealed, the mice sometimes showed fighting and vocalization during presence of the drug effect. It is therefore probable that, even though the size of space is sufficient for expression of ambulation, an interference of ambulation by the other mice acts to inhibit the induction of ambulatory sensitization.

In summary, the present results suggest that a free ambulation during presence of the acute stimulation effect of morphine (i.e., mice being placed in a space enough for ambulation, and no interference of expression of ambulation) is required for induction of strong ambulatory sensitization to morphine. It is estimated that a space 15 cm in diameter, which corresponds to 2–2.5 times as long as the body length of the mouse without tail, is a minimum requirement for induction of strong ambulatory sensitization to morphine. Such characteristics of ambulatory sensitization to morphine indicate that a conditioning of specific behavior during presence of its acute effect is one of important factors for the induction of ambulatory sensitization to morphine in mice. This consideration is consistent with an ''operant conditioning hypothesis'' (6,7,31) concerned in the induction of sensitization to psychostimulants in rats. In addition, the present results also suggest that repeated administration of strong stressor is responsible for significant increase in the sensitivity to morphine.

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