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Pharmacology Biochemistry and Behavior, Vol. 54, No. 2, pp. 327–331, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02026-6

Inhibitory Effect of Restraint on Induction of Behavioral Sensitization to Methamphetamine and Cocaine in Mice

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Received 10 February 1995; Revised 28 April 1995; Accepted 21 May 1995

KURIBARA, H. *Inhibitory effect of restraint on induction of behavioral sensitization to methamphetamine and cocaine in mice.* PHARMACOL BIOCHEM BEHAV 54(2) 327–331, 1996. – Repeated intermittent (generally 3-day intervals) administrations of methamphetamine (MAP: 2 mg/kg, SC) or cocaine (COC: 20 mg/kg, SC) induced sensitization to the ambulation-increasing effect of individual drug in mice. The induction of MAP and COC sensitization was inhibited when restraint of the mouse (putting the mouse in a jar of 6 cm in diameter for 3 and 2 h after administration of MAP and COC, respectively) was started immediately after each drug administration. Furthermore, the induction of sensitizations to MAP and COC was significantly reduced when the restraint was started within 1/4 h and 1/6 h after the administration of MAP and COC, respectively, whereas the restraint starting thereafter did not affect the induction of sensitization. The three times repeated administrations of saline with or without restraint did not significantly change the sensitivities to MAP and COC. The ambulation-increasing effects of MAP and COC reached the peak at approximately 2/3 and 1/2 h, respectively, and persisted for 3 and 2 h after the administration. The present results suggest that, to completely induce sensitization to MAP and COC in terms of ambulation, the mice must freely move for at least half of the latency to their peak effects.

Methamphetamine Cocaine Sensitization Ambulation Conditioning

AN intermittent administration of CNS stimulants such as amphetamines and cocaine to rodents results in a sensitization to their behavioral stimulant effects (2,23). In addition to changes in neurotransmission induced by the repeated administration of drugs such as alterations in receptor activity, enhancement of neurotransmitter release, enhancement of blockade of neurotransmitter reuptake, or decrease in autoreceptor sensitivity (6,10,14,17,20,21,24–26), the other set of factors probably contributing to the induction of sensitization are those related to the conditioned drug effects elicited by situational and environmental cues (18,23,27). Thus, sensitization to the behavioral stimulant effects of amphetamines and cocaine was more pronounced following drug administration in the presence of cues previously associated with the drug.

In contrast to an acceleration of sensitization by the external cues, some situational cues can act to interfere with the expression of behavior sensitization. In terms of ambulation (locomotion) in mice, sensitization to methamphetamine (MAP) (7,11) or cocaine (COC) (8) was scarcely induced when the mice had been kept in small jars to physically block ambulation, without restricting turning and vertical movements, while under the acute stimulant effect after each drug administration. Kuribara and Hirabayashi (11) reported that the induction of sensitization to MAP was highly dependent on the floor space, but almost independent of the other external cues, to which the mice had been exposed while under the drug effect. The repeated exposure of mice to round space of up to 9 cm in diameter for 3 h after each administration of MAP scarcely induced the sensitization to its ambulation-increasing effect, whereas exposure of mice to spaces of larger than 16 cm in diameter was sufficient for complete induction of the sensitization. These evidences indicate that, in terms of ambulation, a repeated experience of the acute drug effect and the resultant ambulation (i.e., conditioning) is one of the most important factors for induction of the sensitization to MAP, and probably to COC. However, such conditioning theory raises another question. How long a period of free movement does the mouse require after the administration of MAP or COC for induction of sensitization to their ambulation-increasing effects?

The aim of this study was to assess the sensitizations to ambulation-increasing effect of MAP and COC in mice that

had been treated with restraint at 0–2 or 3 h after each drug administration.

METHOD

Animals

Male mice of the dd strain (Institute of Experimental Animal Research, Gunma University School of Medicine, Maebashi, Japan) were used in this study. Throughout the experimental period, groups of 10 mice each were housed in polycarbonate cages (25 W × 15 D × 15 H cm), and had free access to a solid diet (MF: Oriental Yeast, Tokyo, Japan) and tap water except during behavioral tests. The conditions of the breeding room were carefully controlled (temperature; 23 ± 1°C, relative humidity; 55 ± 3%, and a 12 L : 12 D cycle; lights on at 0600–1800 h).

All experiments were conducted according to the Japanese Guideline for the Care and Use of Laboratory Animals.

Apparatus

Ambulations were measured with a tilting-type ambulometer with 10 bucket-like Plexiglas activity cages, 20 cm in diameter (SMA-10: O'hara & Co., Tokyo, Japan). Horizontal movements (i.e., ambulation) of the mouse generated slight tilts of the activity cage, and the tilts were detected with microswitches attached to the activity cage. The apparatus could selectively record ambulations, but not turning and or vertical movements, of the mice.

Glass jars (6 cm in diameter and 15 cm in height) were used to restrain the mice.

Drugs

The drugs and their doses (expressed in the salt forms) were methamphetamine HCl (MAP, 2 mg/kg, Dainippon Pharm., Osaka, Japan) and cocaine HCl (COC, 20 mg/kg, Takeda Chem., Osaka, Japan). The drugs were dissolved with physiological saline and SC administered at a constant volume of 0.1 ml/10 g. The doses of MAP and COC were selected to be optimum for induction of the sensitization to their ambulation-increasing effects without eliciting strong stereotyped behaviors in mice (7,8).

Experimental Procedures

All the experiments were started when the mice were 6 weeks of age and weighed 25–28 g; mice were used only once. To adjust the breeding and experimental conditions, ambulation and restraint measurements were carried out between 0900 and 1500 h in the breeding room. The glass jars for restraint were set beside the activity cages.

MAP Experiment

Table 1 represents schedules for the MAP experiment. Groups 1 to 7 (10 mice each) were given MAP three times at 3-day (occaisonally 4-day) intervals. It has been confirmed that the repeated administrations of MAP or COC to mice at 3- to 7-day intervals resulted in almost the same sensitization (7,8,11). The mice in group 1 were put in the jars immediately (interval = 0) after each administration of MAP, and then they were kept in the jars for 3 h to physically block ambulation throughout the course of the acute stimulant effect of MAP. The mice in groups 2 to 7 were measured their ambulations for 1/12, 1/4, 1/2, 1, 2, and 3 h after each administration of MAP, and were then kept in the jars for 3 h. Groups 8 to 14 (10 mice each) were given saline as the control injection for MAP, and were kept in the jars in the same manner as MAP-treated groups. Groups 15 and 16 were given three times repeated administrations of MAP and saline, respectively, and they were placed in the activity cages for 3 h. Four days after the third pretreatment the mice in all groups were challenged with MAP, and their ambulations were measured for 3 h. Furthermore, group 17, which was mice age-matched to the drug-treated mice, was given MAP without any pretreatments.

TABLE 1

EXPERIMENTAL SCHEDULES FOR REPEATED ADMINISTRATION OF METHAMPHETAMINE (2 mg/kg, SC) AND RESTRAINT (PUTTING THE MOUSE IN A JAR OF 6 cm IN DIAMETER FOR 3 h)

Groups	Pretreatment*	Challenge†
1	methamphetamine (0 h)	methamphetamine
2	methamphetamine (1/12 h)	methamphetamine
3	methamphetamine (1/4 h)	methamphetamine
4	methamphetamine (1/2 h)	methamphetamine
5	methamphetamine (1 h)	methamphetamine
6	methamphetamine (2 h)	methamphetamine
7	methamphetamine (3 h)	methamphetamine
8	saline (0 h)	methamphetamine
9	saline (1/12 h)	methamphetamine
10	saline (1/4 h)	methamphetamine
11	saline (1/2 h)	methamphetamine
12	saline (1 h)	methamphetamine
13	saline (2 h)	methamphetamine
14	saline (3 h)	methamphetamine
15	methamphetamine (no restraint)	methamphetamine
16	saline (no restraint)	methamphetamine
17	no pretreatment	methamphetamine

N = 10 in each group.

*The interval between drug administration and restraint is shown in parentheses. Pretreatment was carried out three times at 3-day (occasionally 4-day) intervals. In each pretreatment, the mice were exposed to the activity cages by the start of restraint.

†Challenge was carried out 4 days after the third pretreatment.

COC Experiment

Table 2 represents schedules for the COC experiment. The schedules were similar to those with MAP, except the duration of restraint and measurement of ambulation was 2 h. This is because the ambulation-increasing effect of COC almost disappeared within 2 h after administration. The restraint was started 0, 1/12, 1/6, 1/4, 1/2, 1, or 2 h after each administration of COC. The challenge with COC was carried out 4 days after the third pretreatment.

Statistical Analyses

Because the durations of measurement of ambulation were different among groups in the pretreatment phase, the mean overall activity counts were first analyzed by one-way analysis of variance (ANOVA) in each group of mice. The factor was number of repeated administrations (three levels). In the challenge administration phase, two-way ANOVA was conducted in all groups of mice. The factors were drugs (two levels, including saline), and the intervals between the drug injection and the restraint (eight levels, including no restraint) in the pretreatment phase. Post hoc analyses were carried out by

TABLE 2

EXPERIMENTAL SCHEDULES FOR REPEATED ADMINISTRATION OF COCAINE (20 mg/kg, SC) AND RESTRAINT (PUTTING THE MOUSE IN A JAR OF 6 cm IN DIAMETER FOR 2 h)

Groups	Pretreatment*	Challenge†
1	cocaine (0 h)	cocaine
2	cocaine (1/12 h)	cocaine
3	cocaine (1/6 h)	cocaine
4	cocaine (1/4 h)	cocaine
5	cocaine (1/2 h)	cocaine
6	cocaine (1 h)	cocaine
7	cocaine (2 h)	cocaine
8	saline (0 h)	cocaine
9	saline (1/12 h)	cocaine
10	saline (1/6 h)	cocaine
11	saline (1/4 h)	cocaine
12	saline (1/2 h)	cocaine
13	saline (1 h)	cocaine
14	saline (2 h)	cocaine
15	cocaine (no restraint)	cocaine
16	saline (no restraint)	cocaine
17	no pretreatment	cocaine

N = 10 in each group.

*The interval between drug administration and restraint is shown in parentheses. Pretreatment was carried out three times at 3-day (occasionally 4-day) intervals. In each pretreatment, the mice were exposed to the activity cages by the start of restraint.

†Challenge was carried out 4 days after the third pretreatment.

Dunnett's test. Values of $p < 0.05$ were considered significant.

RESULTS

MAP Experiment

As shown in Fig. 1, the repeated administrations of MAP with the restraint at 1/4–3 h, and without restraint induced significant enhancements of the ambulation-increasing effect [$F(2, 27) = 4.19, 17.30, 12.97, 27.52, 18.98$ and 29.07, respectively, $ps < 0.01$–0.001]. However, the increase in activity counts following the repeated administration of MAP with the restraint at 1/12 h did not reach a significant level (mean counts were 47 and 85 in the first and third administrations, respectively) ($F < 1.61$, NS). On the other hand, the administration of saline with or without restraint elicited very low activity counts throughout the three times repeated administrations, and the changes in activity counts were not significant in all groups ($F < 1$, NS).

Figure 2 shows the activity counts at the challenge administration of MAP. The time courses of change in the increased activity, attaining the peak at approximately 2/3 h and persisting for about 3 h, after the administration of MAP were qualitatively, but not quantitatively, identical among groups of mice. Thus, there were significant drug- and interval-dependent effects, and interaction between drugs × intervals [$F(1, 144) = 105.72$, $F(7, 144) = 59.86$, and $F(7, 144) = 21.38$, respectively, $ps < 0.001$]. Post hoc analyses revealed

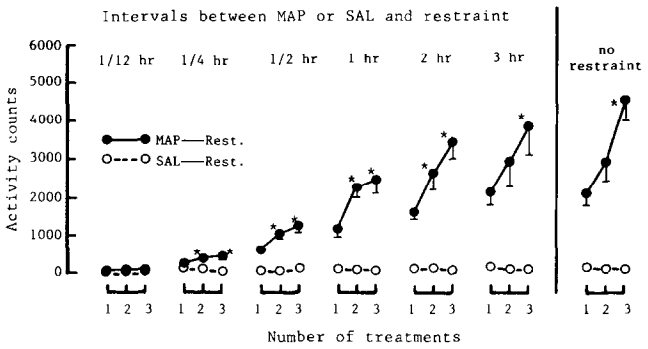

FIG. 1. Mean overall ambulatory activity counts with SEMs after the three times repeated SC administrations at 3-day (occaisonally 4-day) intervals of methamphetamine (MAP: 2 mg/kg) and saline (SAL) with restraint (putting the mouse in a glass jar of 6 cm in diameter for 3 h) at 1/12, 1/4, 1/2, 1, 2, and 3 h after each administration, and without restraint. After the administration of MAP or SAL the ambulations of mice were measured by the start of restraint. *$p < 0.05$ vs. the first administration within each group.

that the activity counts of groups pretreated with MAP and restraint at 0–1/4 h were significantly lower than the groups receiving no restraint, though the activity counts of latter two groups were significantly higher than those of the groups pretreated with saline and restraint at the same intervals. The restraint at 0 h completely inhibited the induction of MAP sensitization whereas the restraints at 1/2–3 h did not affect the induction of MAP sensitization. The repeated administration of saline with or without restraint did not change the sensitivity to MAP, and the mice showed activity counts that were almost the same as those of the group receiving no pretreatment.

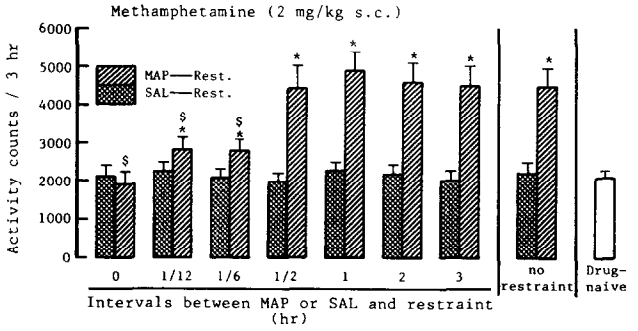

FIG. 2. Mean 3-h overall ambulatory activity counts with SEMs after the challenge administration of methamphetamine (MAP: 2 mg/kg, SC) to the mice pretreated with MAP or saline (SAL) with or without restraint three times at 3-day (occaisonally 4-day) intervals. The challenge administration of MAP was carried out 4 days after the third pretreatment, and the ambulations of mice were measured for 3 h. The administration of MAP to the drug-naive mice was also carried out. *$p < 0.05$ vs. the mice given SAL with restraint at the same interval. \$$p < 0.05$ vs. the mice given MAP without restraint. N = 10 in each group.

COC Experiment

As show in Fig. 3, the repeated administration of COC with the restraint at 1/12–2 h, and no restraint induced significant enhancements of the ambulation-increasing effect [$F(2, 27) = 5.51, 7.19, 13.84, 25.39, 30.53, 10.75$, and 9.46, respectively, $ps < 0.01$–0.001]. The administration of saline with or without restraint elicited very low activity counts throughout the three times repeated administrations, and there were no significant changes in these activity counts ($F < 1$, NS).

Figure 4 shows the activity counts at the challenge administration of COC. The time courses of change in the increased activity, attaining the peak at approximately 1/2 h and persisting for about 2 h, after the administration of COC were qualitatively, but not quantitatively, the same among groups of mice. Thus, there were significant drug- and interval-dependent effects, and interaction between drugs × intervals [$F(1, 144) = 79.09$, $F(7, 144) = 41.20$, and $F(7, 144) = 19.61$, respectively, $ps < 0.001$]. Post hoc analyses revealed that the activity counts of groups treated with COC and restraint at 0–1/6 h were significantly lower than the count of the group receiving no restraint, but almost the same with that of the drug-naive group. The restraint at 1/4–2 h scarcely affected the induction of COC sensitization. The administration of saline with or without restraint did not change the sensitivity to COC.

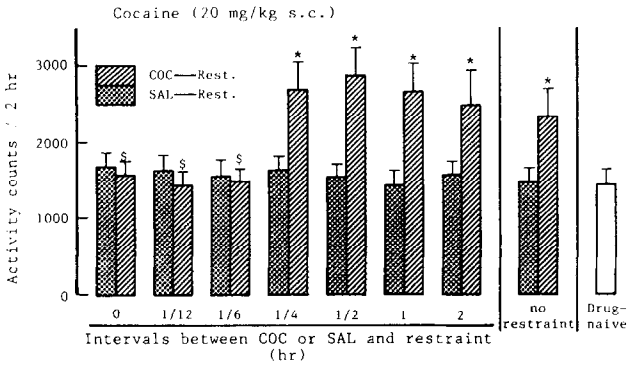

FIG. 4. Mean 2-h overall ambulatory activity counts with SEMs at the challenge administration of cocaine (COC: 20 mg/kg, SC) to mice pretreated with COC or saline (SAL) with or without restraint three times at 3-day (occaisonally 4-day) intervals. The challenge administration of COC was carried out 4 days after the third pretreatment, and the ambulations of mice were measured for 2 h. The administration of COC to the drug-naive mice was also carried out. The data are shown in the same way as in Fig. 2. $*p < 0.05$ vs. the mice given SAL with restraint at the same interval. $\$p < 0.05$ vs. the mice given COC without restraint. $N = 10$ in each group.

Gross Observation

In the jar, mice could freely carry out turning and vertical movements such as rearing, jumping, etc., but not ambulation. The mice given MAP, COC, or saline did not exhibit any signs indicating stress, such as vocalization, excess defecation while in the jars, etc.

DISCUSSION

As demonstrated following the repeated administrations of MAP and COC without restraint at 3-day (occasionally 4-day) intervals, the ambulation-increasing effects progressively enhanced, and the effects reached a ceiling by the fourth administration. According to these basic results, the administration of MAP or COC and the restraint in the pretreatment phase were carried out three times, and then the sensitivities of mice to the challenge with each drug were evaluated 4 days after the third pretreatment.

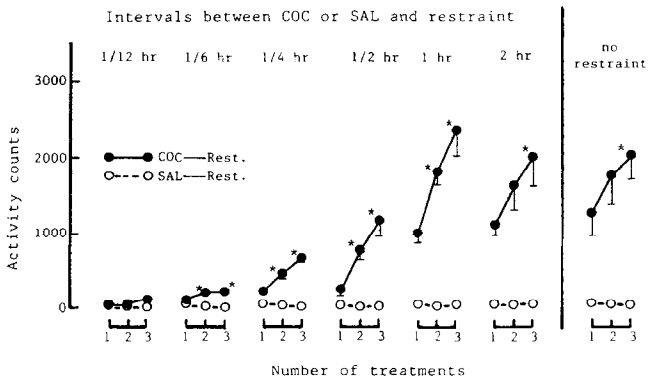

FIG. 3. Mean overall ambulatory activity counts with SEMs after the three times repeated SC administrations at 3-day (occaisonally 4-day) intervals of cocaine (COC: 20 mg/kg) or saline (SAL) with restraint (putting the mouse in a glass jar of 6 cm in diameter for 2 h) at 1/12, 1/6, 1/4, 1/2, 1, and 2 h after each administration, and without restraint. The experimental schedules were almost the same as those in the MAP experiment. The data are shown in the same way as in Fig. 1.

An enhancement of dopaminergic neurotransmission is considered to be involved in the induction of sensitization to MAP (10,17,20,21) and COC (5,15,16,19). This can be supported by the fact that induction of sensitization to these drugs is inhibited by dopamine receptor antagonists when they are simultaneously administered in the pretreatment phase (12,13, 15,24,25,27).

The present experiments did not use any dopamine receptor antagonists. However, the mice given MAP or COC with restraint immediately after the administration showed no significant changes in the sensitivity to the ambulation-increasing effect of individual drugs. These results are consistent with the data previously reported (7,8,11), indicating that the restraint can contribute to inhibit induction of sensitization to MAP and COC in terms of ambulation in mice. To explain this phenomenon, some candidates are considered to be involved.

The first candidate is the development of aversive conditioning induced by restricted movement in the jar. However, this mechanism may be less probable because of the following reasons. It has been reported that exposure of animals to mild stressors activates the mesocorticolimbic dopaminergic system (1,4,5,9), and that repeated intermittent restraint augments the subsequent behavioral activating effect of amphetamine (3). In contrast to these reports, however, the present experiments demonstrated that the administration of saline with restraint did not change the sensitivity to either MAP or COC, and the repeated pretreatment with MAP or COC and restraint never resulted in enhancement of the sensitivity to MAP or COC at the challenge administration. Moreover, the mice given either saline, MAP, or COC could almost freely express turning and vertical movements, and they did not exhibit any signs indicating stress while in the jars. Finally, there was no alteration in the time course of change in the increased ambulation by MAP or COC at the challenge administration. This evidence strongly suggests that the restraint carried out in

this study was less stressful and aversive, and that the restraint per se might not modify dopaminergic neurotransmission.

The second candidate is the blockade of linkage between drug-induced CNS stimulation and the resultant ambulation. In the induction of sensitization to the ambulation-increasing effects of MAP or COC in mice, the space in which the mice are exposed while under acute stimulant effects is the most important factor, and the contributions of other external cues are comparatively smaller than that of space (11). It is therefore probable that repeated experience of the acute stimulant effect and resultant ambulation is required for induction of the sensitization to MAP and COC in terms of ambulation in mice.

Although the mice given MAP with restraint at 1/12 and 1/4 h or COC with restraint at 1/12 and 1/6 h exhibited sensitization, the potencies were significantly lower than that induced by MAP or COC without restraint. The restraint carried out 1/2 and 1/4 h after the administration of MAP and COC, respectively, could not inhibit the induction of sensitization. The latencies to the peak effect were about 2/3 and 1/2 h after the administration of MAP and COC, respectively. Thus, it is estimated that, although a partial sensitization to either MAP or COC is rapidly induced by experience of drug effect and resultant ambulation, probably within 1/12 h after administration, the minimum duration for complete induction of the sensitization is approximately half of the latency to the peak effects. It is also considered that such duration might be required to facilitate the conditioning of sensitization to the ambulation-increasing effect of each drug.

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