Reverse Tolerance to Ambulation-Increasing Effects of Methamphetamine and Morphine in 6 Mouse Strains

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Abstract—Effects of single administration of methamphetamine (1, 2 and 4 mg/kg, s.c.) and morphine (5, 10 and 20 mg/kg, s.c.) and repeated administration of methamphetamine (2 mg/kg, s.c.) and morphine (10 mg/kg, s.c.) on ambulatory activity were investigated in 6 mouse strains: dd, ICR, BALB/c, C57BL/6, C3H/He and DBA/2. Although there were differences in the drug sensitivities among mouse strains, methamphetamine and morphine increased the ambulatory activity in all the strains except for the DBA/2 strain that showed an increase only after morphine. Repeated 5 times administration of methamphetamine at intervals of 3–4 days induced a reverse tolerance (an enhancement in the sensitivity) to the ambulation-increasing effect in all the strains with a marked degree in dd, ICR, C3H/He and DBA/2 strains and a slight degree in BALB/c and C57BL/6 strains. The same treatment with morphine induced reverse tolerance to the effect of morphine markedly in C57BL/6 and C3H/He strains and moderately in dd, ICR and BALB/c strains, but the DBA/2 strain showed no significant change in the ambulatory activity throughout the repeated 5 times administration of morphine. There was positive correlation between the initial drug sensitivities of animals and the degrees of the reverse tolerance in either methamphetamine or morphine. Furthermore, the reverse tolerance to methamphetamine and morphine was sometimes transferable, although such cross interaction varied among mouse strains.

A repeated drug administration frequently results in an alteration in sensitivities to the drug effects, eliciting tolerance and/or reverse tolerance (c.f. 1–3). It is also highly probable that a prior drug treatment yields various changes in sensitivities to the other drugs.

Methamphetamine and morphine, prototypes of stimulants and narcotic-analgesics, respectively, increase ambulatory activity in mice, and the effects progressively enhance when these drugs are repeatedly administered at intervals of longer than 1 day (4, 5). The ambulation-increasing effect of methamphetamine appears through a stimulant action on central catecholaminergic, in particular dopaminergic, systems (6). The catecholaminergic systems have been considered to be involved in the stimulant effect of narcotic-analgesics (7–9). It is therefore probable that there is an intimate interaction between the ambulation-increasing effect of methamphetamine and morphine in mice.

When drug effects are investigated in mice, it should be recognized that there are many mouse strains and that the behavioral characteristics and drug sensitivities as well as the neuronal activities are different among the mouse strains (10, 11). For one of the most typical examples, after administration of morphine, the C57BL/6 strain shows a major increase, whereas the DBA/2 strain shows little change, in the ambulatory activity.

Hence, the purposes of this experiment were to study the effects of single and repeated administration of methamphetamine and morphine on the ambulatory activity in 6 mouse strains and to study changes in the sensitivities to morphine and methamphet-
amine in the mice that experienced repeated administration of methamphetamine and morphine, respectively.

Materials and Methods

Animals: The 6 mouse strains used were dd, ICR, BALB/c, C57BL/6, C3H/He and DBA/2. Only male mice were used in this experiment. These mouse strains were chosen according to our series of studies on mouse strain differences (12, 13). The dd strain mice were provided by the Institute of Experimental Animal Research, Gunma University School of Medicine. The other 5 strains of mice were purchased from Charles River Japan, Inc. Groups of 10 mice were housed in standard aluminum or acrylfiber cages of 30 (W) x 20 (D) x 10 (H) cm in a controlled room (temperature: 22±2°C and light period: 6:00–18:00), and they were freely given solid diet (MF: Oriental Yeast Co.) and tap water except during times of the experiment. When the mice were 7 weeks of the age, the experiment was started.

Procedure: The ambulatory activity of the mouse was measured using a tilting-type ambulometer (AM B-10, O'hara & Co., Ltd.). Mice were individually placed in plexiglas activity cages with a diameter of 20 cm, and the ambulatory activities were measured for 30 min and 180 min before and after each drug administration, respectively. The drugs used were methamphetamine HCl (Dainippon Pharm. Co.) and morphine HCl (Takeda Chemical Co.). These drugs were dissolved in physiological saline vehicle and administered subcutaneously (s.c.) at a fixed dose volume of 0.1 ml/10 g body weight regardless of the drug doses.

Before starting the drug administration, mice in each strain were randomly divided into 7 groups of 20–40. Each group of mice was treated with one of the following regimens: administration of saline; methamphetamine at 1, 2 or 4 mg/kg; or morphine at 5, 10 or 20 mg/kg. Two groups of mice that were injected with 2 mg/kg methamphetamine or 10 mg/kg morphine were further treated with 4 additional administrations of the corresponding drug at intervals of 3–4 days (repeated drug administration). Four days after the 5th administration, morphine or methamphetamine was administered to the mice that had been treated with either methamphetamine or morphine, respectively, (cross drug administration). The schedules of the repeated drug administration and the doses of drugs were taken from previous studies (4, 5) to be optimum for inducing reverse tolerance to the ambulation-increasing effect of methamphetamine and morphine in mice.

The measurement of ambulatory activity was conducted between 10:00–16:00.

Statistical analysis: The mean overall ambulatory activity counts for 3 hr after the drug administration were calculated in each group. At first, repeated measures analysis of variance of the overall data were examined. If there were significant overall effects, comparisons between the individual means were carried out by the two-tailed Student's t-test. When P values were equal to or less than 0.05, they were taken to indicate significant differences.

Results

The single drug administration: Figure 1 shows dose-effect relationships for methamphetamine (upper panel) and morphine (lower panel) on the ambulatory activity in the 6 strains of mice. The activity counts after saline administration were higher in the order of DBA/2, BALB/c, dd, ICR, C3H/He and C57BL/6. The ratio between the highest (DBA/2) and lowest (C57BL/6) counts was estimated to be about 3.3.

Methamphetamine increased the ambulatory activity in all the strains in a dose-dependent manner. The effect attained a peak at 40–50 min and persisted for about 3 hr after the administration in all 6 strains. The rank order of sensitivity to methamphetamine was estimated to be ICR, dd, DAB/2, C3H/He, BALB/c and C57BL/6.

Morphine increased the ambulatory activity in all the strains in a dose-dependent manner. The effect attained a peak at 40–50 min and persisted for about 3 hr after the administration in all 6 strains. The rank order of sensitivity to methamphetamine was estimated to be ICR, dd, DAB/2, C3H/He, BALB/c and C57BL/6.

The repeated drug administration: Figure 2
shows the mean overall ambulatory activity counts after the repeated administration of 2 mg/kg of methamphetamine (left panel) and 10 mg/kg of morphine (right panel), respectively, in the 6 mouse strains.

The repeated administration of methamphetamine induced reverse tolerance to its ambulation-increasing effect in all the strains. As compared with the corresponding activity counts in the 1st administration within each strain, a significant increase in the counts was demonstrated in the 3rd and later administrations in the dd, ICR, C3H/He and DBA/2 strains, in the 4th and later in the BALB/c strain, and in the 5th in the C57BL/6 strain. The correlation coefficient between the activity counts in the 1st and 5th administration was 0.996.

The repeated administration of morphine induced reverse tolerance to its ambulation-increasing effect except for the DBA/2 strain. As compared with the corresponding activity counts in the 1st administration within each strain, a significant increase in the counts was demonstrated in the 2nd and later administration in the C3H/He strain, in the 3rd and later in the C57BL/6, in the 4th and later in the dd and BALB/c strains, and in the 5th in the ICR strain. The DBA/2 strain exhibited no significant change in the activity counts throughout the 5 times administration of morphine. The correlation coefficient be-
The cross drug administration: Figure 3 shows the mean overall ambulatory activity counts after the administration of morphine (10 mg/kg, s.c.) to the drug-naive and repeated methamphetamine-experienced mice. As compared with the activity counts in the drug-naive mice within the same strain, the methamphetamine-experienced mice in dd, ICR, C57BL/6 and C3H/He strains exhibited an increase in sensitivity to the ambulation-increasing effect of morphine. However, repeated morphine administration failed to induce a significant change in the sensitivity to morphine in the dd, ICR, BALB/c and DBA/2 strains of mice.

Discussion

First, the present experiment demonstrated that both methamphetamine and morphine increased the ambulatory activity in almost all mouse strains. However, the ambulatory activity counts observed were markedly different among mouse strains. It has been considered that the central catecholaminergic systems are involved in the stimulant effect (including the ambulation-increasing effect) of methamphetamine and morphine (6–9). However, there was no intimate correlation among the rank orders of the baseline activity after administration of saline and the sensitivities to methamphetamine and mor-

![Figure 2](image-url)
Fig. 3. Effects of morphine (10 mg/kg, s.c.) on ambulatory activity in 6 strains of the drug-naive (open columns) and methamphetamine-experienced (stippled columns) mice. The methamphetamine-experienced mice had been treated with 5 times administration of methamphetamine (2 mg/kg, s.c.) at intervals of 3–4 days, and morphine was administered 4 days after the 5th methamphetamine administration. The data in the drug-naive mice are the same as those presented in the right panel of Fig. 2 (the data in the 1st administration). Each column and the vertical line attached to it indicate mean overall ambulatory activity count and the S.E.M., respectively, of 20–40 mice. *: Significant difference from the value in the drug-naive mice within the same strain (P<0.05).

Fig. 4. Effects of methamphetamine (2 mg/kg, s.c.) on ambulatory activity in 6 strains of the drug-naive (open columns) and morphine-experienced (stippled columns) mice. The morphine-experienced mice had been treated with 5 times administration of morphine (10 mg/kg, s.c.) at intervals of 3–4 days, and methamphetamine was administered 4 days after the 5th morphine administration. The data in the drug-naive mice are the same as those presented in the left panel of Fig. 2 (the data in the 1st methamphetamine administration). The data are shown in the same way as in Fig. 3. N=20–40.
phine in the 6 strains. In addition, it is hard to find a definite parallelism between the strain difference in the drug sensitivities and the neuronal activities of central catecholaminergic systems (14–21). Furthermore, the time-course changes in the drug effects were qualitatively identical among the strains. Therefore, it is unlikely that the strain differences in the drug sensitivities are due to differences in drug-metabolizing and/or drug-excreting activities. It seems that multiple mechanisms are involved in the mouse strain differences.

The present experiment secondly demonstrated that the repeated administration of methamphetamine and morphine induced a reverse tolerance to the ambulation-increasing effect of the corresponding drugs. These data are identical with those reported previously (4, 5), in which only the dd strain of mice were used. The reverse tolerance was observed in almost all mouse strains that exhibited a significant increase in the ambulatory activity after the 1st administration of the drug. This finding suggests that this phenomenon commonly appears in mice, although degrees are different among the strains. The mechanisms of the reverse tolerance have not been clearly elucidated yet (1–3, 22). However, it is notable that the reverse tolerance was much marked in the mouse strains that exhibited a high sensitivity to the corresponding drug effect at the drug-naive state. This result suggests that an ambulatory movement during the presence of the acute drug effect is an important factor in the induction of reverse tolerance to the ambulation-increasing effect of methamphetamine and morphine.

The present experiment thirdly demonstrated that repeated administration of methamphetamine or morphine elicited an enhancement in the sensitivity to morphine or methamphetamine, respectively, showing a cross-reverse tolerance in several strains. The cross-reverse tolerance from methamphetamine to morphine was observed in 4 strains, dd, ICR, C57BL/6 and C3H/He, but not in 2 strains, BALB/c and DBA/2 strains. The latter two strains were those which showed comparatively lower sensitivity to morphine. The cross-reverse tolerance from morphine to methamphetamine was demonstrated only in 2 strains, C57BL/6 and C3H/He, which showed an extremely high sensitivity to morphine. These findings indicate that cross-reverse tolerance from methamphetamine to morphine is more easily induced than that from morphine to methamphetamine. Furthermore, it is also considered that morphine sensitivity plays an important role in the cross-interaction between methamphetamine and morphine.

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