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# Effects of interdose interval on ambulatory sensitization to methamphetamine, cocaine and morphine in mice

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**Abstract**

To determine the minimum interdose interval for induction of ambulatory sensitization to methamphetamine, cocaine and morphine, 3 sets of 5 groups of mice were treated with either methamphetamine (2 mg/kg s.c.), cocaine (10 mg/kg s.c.) or morphine (10 mg/kg s.c.) 3 times at intervals of 3, 6, 12, 24 or 48 h, and then 2 times at intervals of 3 days in all groups. During the first 3 administrations of both methamphetamine and cocaine, interdose intervals of 3–12 h did not produce a significant change in the ambulatory stimulation. However, 3 repeated administrations of morphine with interdose intervals of 3 and 6 h, but not 12 h, caused tolerance to the ambulatory stimulant effect. The administration of all drugs with interdose intervals of 24 and 48 h produced ambulatory sensitization. Furthermore, following the fourth and fifth administrations of each drug, all groups of mice demonstrated sensitization. These results indicate that an interdose interval of 24 h or longer is required for induction of ambulatory sensitization to methamphetamine, cocaine and morphine.

*Keywords:* Methamphetamine; Cocaine; Morphine; Ambulatory sensitization; Interdose interval; (Mouse)

## 1. Introduction

When central stimulants such as amphetamines and cocaine are repeatedly (intermittently) administered to animals, some responses, particularly ambulatory (locomotor) stimulation and stereotypy, progressively increase (Demellweek and Goudie, 1983; Kuribara and Hirabayashi, 1985; Tadokoro and Kuribara, 1990). Similar to central stimulants, repeated administration of narcotic analgesics such as morphine to mice also induces an increased response to their ambulatory stimulant effect (Iizuka and Hirabayashi, 1983; Kuribara, 1995). This phenomenon of enhanced responding, namely behavioral sensitization, has attracted much interest. This is because the processes of induction, maintenance and expression of sensitization to central stimulants in animals have been considered to be intimately correlated with those of psychopathological symptoms caused by repeated abuse of these central stimulants in humans (Connell, 1968; Ellinwood, 1968; Kokkinidis and Anisman, 1980; Segal and Schuckit, 1983; Robinson and Becker, 1986; Tadokoro and Kuribara, 1986, 1990), and liability of drug abuse (Wise and Bozarth, 1987; Piazza et al., 1989). It is also speculated that sensitization to narcotic analgesics provides information about the liability of drug abuse. Many investigations have suggested the importance of temporal characteristics of administration of central stimulants and narcotic analgesics for modification of the response to drugs. It is generally considered that intermittent administration induces sensitization, and that continuous infusion elicits tolerance (Chaudry et al., 1985; Post, 1980; Nelson and Ellison, 1978). However, the threshold of interdose interval for induction of ambulatory sensitization to these drugs has not been determined.

The aim of this study was to assess modification of the ambulatory stimulant effect of methamphetamine, cocaine and morphine in mice following administration of each drug 3 times at intervals of 3–48 h, and then 2 times at intervals of 3 days.

## 2. Materials and methods

### 2.1. Animals

Male mice of the *dd* strain (Institute of Experimental Animal Research, Gunma University School of Medicine, Maebashi, Japan) were used. They had been group housed (10 mice each) in polycarbonate cages (25W × 15D × 15H


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cm, with a woodchip bedding) in a controlled room (temperature 23 ± 1°C, relative humidity 55 ± 3%, and a 12:12-h light-dark cycle; lights on at 06:00–18:00 h). A solid diet (MF; Oriental Yeast, Tokyo, Japan) and tap water were freely available except during times of the behavioral tests. The mice were used in the experiment at 6 weeks of the age when they weighed 25–28 g.

### 2.2. Apparatus

Ambulatory activity of mice was measured with an 'ambulometer' consisting of 10 tilting-type cages of acrylic fiber (20 cm in diameter and 15 cm in height) (SMA-10; O'Hara, Tokyo, Japan). This apparatus was designed to selectively record ambulation of the mouse in the cage by detecting slight tilts of the cage generated by horizontal movements, but not any vertical movements or turning, of the mouse by means of microswitches attached to the cage.

### 2.3. Drugs

The drugs and the doses (expressed as the salt forms) were methamphetamine HCl (Dainippon, Osaka, Japan; 2 mg/kg), cocaine HCl (Takeda, Osaka, Japan; 10 mg/kg) and morphine (Takeda; 10 mg/kg). These drugs were dissolved in physiological saline, and administered subcutaneously (s.c.) at a constant volume of 0.1 ml/10 g body weight. The doses of methamphetamine, cocaine and morphine administered in this study were optimal for the development of ambulatory sensitization without producing strong stereotypy following repeated administration at 1–7-day intervals (Hirabayashi and Alam, 1981; Iizuka and Hirabayashi, 1983; Hirabayashi et al., 1991).

### 2.4. Experimental procedures

Three sets of 5 groups of mice (10 each) were first given either methamphetamine, cocaine or morphine 3 times at intervals of either 3, 6, 12, 24 or 48 h, and then the fourth and fifth administrations were carried out at intervals of 3 days (72 h) in all groups. The ambulation of each mouse was measured for 3 h after each administration. In each group of mice, the first drug administration was always carried out between 09:00–09:30 h.

### 2.5. Statistical analysis

Mean overall activity counts were first analyzed by two-way analysis of variance. The factors were interdose

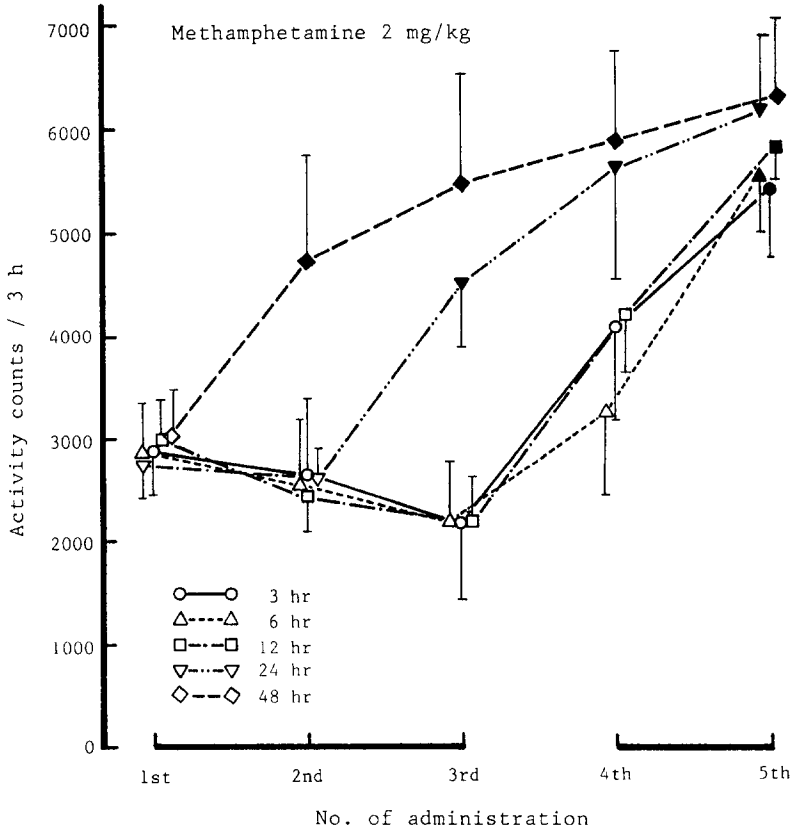


Fig. 1. Mean 3-h overall ambulatory activity counts with S.E.M. values after 5 repeated s.c. administrations of methamphetamine (2 mg/kg). During the first to third administrations, the interdose intervals were 3, 6, 12, 24 or 48 h, and the fourth and fifth administrations were carried out at 3-day intervals. The ambulation of each mouse was measured for 3 h after each administration. Closed symbols (●, ▲, ■, ▼ and ◆): $P < 0.05$ vs. the first administration. $n = 10$ in each group.

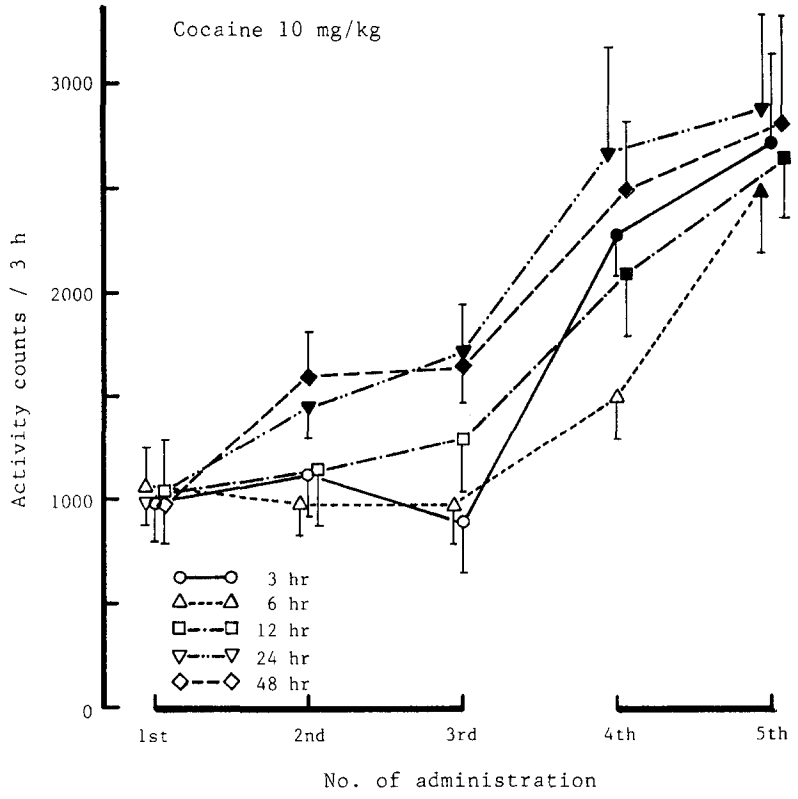


Fig. 2. Mean 3-h overall ambulatory activity counts with S.E.M. values after 5 repeated s.c. administrations of cocaine (10 mg/kg). The experimental schedule was the same as that in the methamphetamine study (see legend to Fig. 1). $n = 10$ in each group.

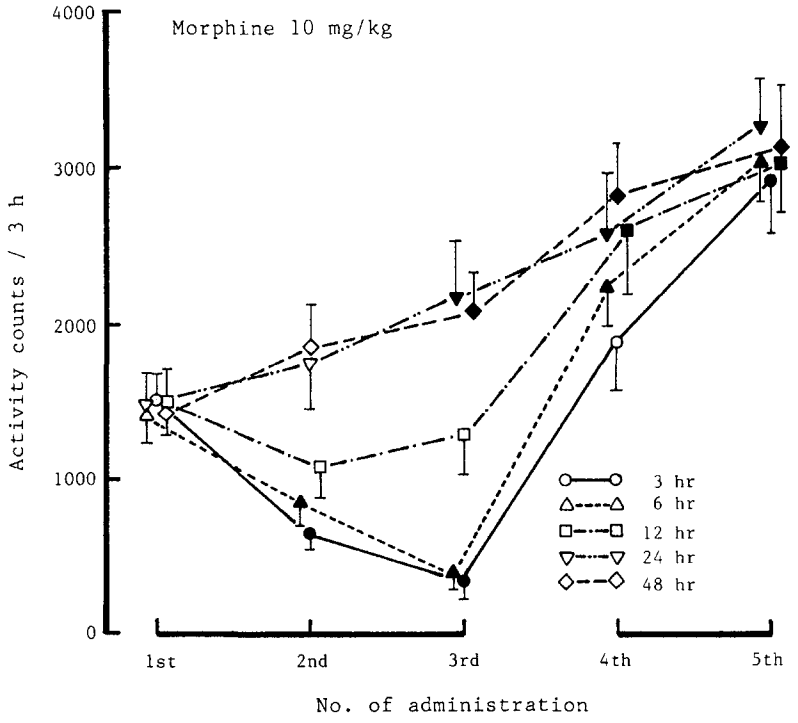


Fig. 3. Mean 3-h overall ambulatory activity counts with S.E.M. values after 5 repeated s.c. administrations of morphine (10 mg/kg). The experimental schedule was the same as that in the methamphetamine study (see legend to Fig. 1). $n = 10$ in each group.

intervals (5 levels) and administration number (5 levels). Post-hoc analyses were carried out by Dunnett's test. Values of $P$ less than 0.05 were considered significant.

## 3. Results

### 3.1. Methamphetamine study

Fig. 1 shows mean 3-h overall activity counts after 5 administrations of methamphetamine to mice. The activity counts were dependent on administration number ($F(4,225) = 150.6$, $P < 0.001$) and interdose interval ($F(4,225) = 71.2$, $P < 0.001$). There was significant interaction of administration number × interdose interval ($F(16,225) = 47.5$, $P < 0.001$). Post-hoc analyses revealed that, during the first to third administrations, the groups of mice given methamphetamine with interdose intervals of 3–12 h did not show a significant change in the response to methamphetamine. In contrast, groups of mice given methamphetamine at intervals of 24 and 48 h exhibited sensitization to methamphetamine, demonstrating a significant increase in the activity count at the third, and second and third administrations in the former and latter groups, respectively. Following the fourth and fifth administrations, which were carried out at 3-day intervals, all groups of mice showed sensitization to methamphetamine, and the activity counts at the fifth administration were almost the same among groups.

### 3.2. Cocaine study

Fig. 2 shows mean 3-h overall activity counts after 5 administrations of cocaine to mice. The activity counts were dependent on administration number ($F(4,225) = 216.7$, $P < 0.001$) and interdose interval ($F(4,225) = 24.0$, $P < 0.001$). There was significant interaction of administration number × interdose interval ($F(16,225) = 11.8$, $P < 0.001$). Post-hoc analyses revealed that during the first to third administrations, the groups of mice given cocaine with interdose intervals of 3–12 h showed neither enhancement nor tolerance of the response to cocaine. The groups of mice given cocaine at intervals of 24 and 48 h exhibited sensitization to cocaine, demonstrating a significant increase in the activity count at the second and third administrations. Following the fourth and fifth administrations, all groups of mice showed sensitization to cocaine, and the activity counts at the fifth administration were almost the same among groups.

### 3.3. Morphine study

Fig. 3 shows mean 3-h overall activity counts after 5 administrations of morphine to mice. The activity counts were dependent on administration number ($F(4,225) = 137.2$, $P < 0.001$) and interdose interval ($F(4,225) = 109.2$, $P < 0.001$). There was significant interaction of administration number × interdose interval ($F(16,225) = 34.0$, $P < 0.001$). Post-hoc analyses revealed that during the first to third administrations, the groups of mice given morphine with interdose intervals of 3 and 6 h showed tolerance to morphine. Although the administration of morphine with an interdose interval of 12 h elicited neither tolerance nor sensitization, the administration of morphine with interdose intervals of 24 and 48 h produced sensitization to morphine. Following the fourth and fifth administrations, all groups of mice showed sensitization to morphine, and the activity counts were almost the same among groups at the fifth administration.

## 4. Discussion

The present experiment clearly revealed that modification of the ambulatory stimulant effect of methamphetamine and cocaine (central stimulants), and morphine (a narcotic analgesic) caused by repeated administration was dependent on the interdose intervals. The repeated administrations with interdose intervals of 24 and 48 h elicited sensitization to the ambulatory stimulant effect of methamphetamine, cocaine and morphine. The ambulatory sensitization to methamphetamine was stronger following an interdose interval of 48 h than following an interdose interval of 24 h. These results are basically consistent with the previous reports that ambulatory sensitization to methamphetamine (Hirabayashi and Alam, 1981), cocaine (Hirabayashi et al., 1991), and morphine (Iizuka and Hirabayashi, 1983) is induced following repeated administration with interdose intervals of 1–7 days, the maximum response being developed with interdose intervals of 3–4 days.

In contrast, the 3 repeated administrations of methamphetamine and cocaine with interdose intervals of 3–12 h did not cause a significant change in the ambulatory stimulant effect. It has been suggested that continuous infusion or intermittent administration with short interdose intervals of central stimulants for comparatively longer periods produces tolerance to their behavioral stimulant effect (Chaudry et al., 1985; Martin-Iverson et al., 1988; Post, 1980; Nelson and Ellison, 1978). It is considered that the schedules of repeated administration of methamphetamine and cocaine used in this study, 3 times at interdose interval of 3–12 h, might be insufficient for the development of tolerance to methamphetamine and cocaine. Different from the results for methamphetamine and cocaine, a clear tolerance to the ambulatory stimulant effect of morphine was produced following the repeated administration with interdose intervals of 3 and 6 h. The repeated administration of morphine with an interdose interval of 12 h tended to decrease the ambulatory stimulant effect at the second administration. These results suggest that repeated administration of morphine at inter-

vals shorter than 12 h is responsible for the induction of tolerance and physical dependence. In fact, to induce physical dependence in mice, repeated administration of morphine twice or more a day has been generally carried out (Kaneto et al., 1973).

However, all the mice that had been pretreated with 3-time administrations of methamphetamine, cocaine and morphine with interdose intervals of 3–48 h demonstrated clear sensitization to individual drugs following repeated drug administration with an interdose interval of 3 days. The activity counts at the fifth administration were almost the same among groups of mice in each drug. These results suggest that ambulatory sensitization to methamphetamine, cocaine and morphine is induced almost independently of the pretreatment schedule. It is also suggested that the number of experiences of a drug's effect and resultant ambulation and then cessation of them, i.e., conditioning (Vezina and Stewart, 1984; Pert et al., 1990), is an essential factor for the development of ambulatory sensitization to methamphetamine, cocaine and morphine.

It has been suggested that dopaminergic neurotransmission plays an important role in the induction and expression of drug-induced behavioral sensitization (Kalivas and Stewart, 1991). In the present study, biochemical analysis was not conducted. Thus, a further study on the relation between the levels of sensitization and the biochemical changes following repeated administration of methamphetamine, cocaine and morphine with different interdose intervals is required. However, in the induction of ambulatory sensitization to methamphetamine, cocaine and morphine in mice, the following three important characteristics can be revealed by the present study: (1) An interdose interval of 24 h and longer is required. (2) When the interdose interval is sufficiently long for the induction of sensitization, the sensitization is produced almost independently of the pretreatment schedule. (3) There is a common mechanism in the induction of ambulatory sensitization to methamphetamine, cocaine and morphine, even though methamphetamine and cocaine (central stimulants) and morphine (a narcotic analgesic) belong to distinct pharmacological categories.

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