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Comparison of Sensitization to Ambulation-increasing Effects of Cocaine and Methamphetamine after Repeated Administration in Mice

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Abstract—The effects of repeated (5 times) subcutaneous administration of cocaine (10, 20 or 40 mg kg^{-1}) and methamphetamine (1, 2 or 4 mg kg^{-1}) at 3–4 day intervals have been compared in mice placed individually into tilting activity cages. A progressive enhancement of the ambulation-increasing effect was noted for 3–4 h after each administration, indicating that sensitization occurred. This occurrence and the existence of an optimal dose producing sensitization were similar for both drugs. However, enhancement of the effect after cocaine progressed rapidly and maximum sensitization was observed earlier than after methamphetamine administration. Moreover, the higher doses of cocaine (40 mg kg^{-1}) caused stereotypies concurrent with preconvulsive signs of short duration that were enhanced by serial administration. In contrast, methamphetamine caused a more progressive enhancement, but stereotypies with no preconvulsive signs were produced by the higher dose (4 mg kg^{-1}). The respective, effective doses for the development of enhancement suggested that cocaine was less potent than methamphetamine in producing sensitization. Cross-sensitization occurred between both drugs. Thus, sensitization to cocaine was distinct from that to methamphetamine due to differences in its rapidity, intensity, and the presence or absence of preconvulsive changes.

Cocaine and amphetamines are known to share many characteristics and to have similar behavioural effects (Shuster et al 1977; Kilbey & Ellinwood 1977; Jaffe 1985); repeated administration of these drugs to dogs, monkeys and rats produce enhanced sensitivity (i.e. sensitization or reverse tolerance) to ambulation-increasing and sometimes to stereotypy- and convulsion-producing effects (Tatum & Seevers 1929; Downs & Eddy 1932; Post & Rose 1976; Shuster et al 1977; Stripling & Ellinwood 1977; Pickens & Crowder 1967; Tilson & Rech 1973; Segal & Mandell 1974; Short & Shuster 1976; Hayashi et al 1980). There have, however, been few comparative studies of the sensitization properties of these drug types.

In the present study, the characteristics of the sensitization produced by the repeated administration of cocaine to mice (10–40 mg kg^{-1}) were compared with those produced by methamphetamine (1–4 mg kg^{-1}).

Materials and Methods

Animals

Adult male dd strain mice, 24–32 g, were supplied by the Institute of Experimental Animal Research, Gunma University School of Medicine. The mice were housed in groups of 10 in aluminium cages (35 × 25 × 10 cm, with wooden-flake bedding) and given free access to a solid diet (MF, Oriental Yeast Co., Tokyo) and tap water, except during the experiment. The animal room was artificially illuminated by fluorescent lamps with a 12 h light–dark cycle (lights on 0600 h), and the room temperature was controlled at 23 ± 2°C.

Apparatus and experimental procedure

The ambulatory activity of the mice was determined by the tilting cage method (AMB-M20, Ohara and Co. Ltd, Tokyo), as reported previously (Hirabayashi et al 1978). Briefly, each slight tilt of a round plexiglass activity cage (20 cm diam. × 18 cm height) caused by the horizontal activity made by a mouse was detected by 3 microswitches fixed to the cage box. Each mouse was placed in the activity cage, and ambulatory activity counts were recorded every 10 min for 30 min before drug administration and for 180 min afterwards. The measurement of ambulatory activity was carried out between 1000 and 1500 h.

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Drugs and administration schedules

The drugs used were cocaine hydrochloride (Takeda Pharmaceutical Co, Osaka), and methamphetamine hydrochloride (Philopon, Dainippon Pharmaceutical Co, Osaka). The drugs, used in salt form and dissolved in purified water, were administered subcutaneously and the volume administered was fixed to 0·1 mL kg^{-1}.

The experiments were conducted as outlined in Table 1. Mice were divided into 8 groups of 30. Four groups received 5 injections of cocaine (10, 20 or 40 mg kg^{-1}, groups I, II and III, respectively) or 0·9% NaCl (saline, group IV) at intervals of 3–4 days. The ambulatory activity levels were measured for 180 min after each administration. Three days after the final administration, groups II and IV received methamphetamine (2 mg kg^{-1}) for a cross sensitization test, and again activity was measured for 180 min. The remaining four groups received 5 injections of methamphetamine (1, 2 or 4 mg kg^{-1}, groups V, VI and VII, respectively) or saline (group VIII) at 3–4 day intervals, and the ambulatory activity levels were measured for 180 min after each administration. Three days after the final administration, groups VI and VIII received cocaine (20 mg kg^{-1}) for a cross-sensitization test, activity being measured for 180 min. Dosages and administration intervals to induce sensitization were selected on the

Table 1. Experimental conditions.

Groups	Drug and doses		Cross-administration	
I	Cocaine	10 mg kg^{-1} × 5	—	
II	Cocaine	20 mg kg^{-1} × 5	Methamphetamine	2 mg kg^{-1}
III	Cocaine	40 mg kg^{-1} × 5	—	
IV	Saline (control)	× 5	Methamphetamine	2 mg kg^{-1}
V	Methamphetamine	1 mg kg^{-1} × 5	—	
VI	Methamphetamine	2 mg kg^{-1} × 5	Cocaine	20 mg kg^{-1}
VII	Methamphetamine	4 mg kg^{-1} × 5	—	
VIII	Saline (control)		Cocaine	20 mg kg^{-1}

n = 30 for each group.

basis of our previous studies (Hirabayashi et al 1978; Hirabayashi & Alam 1981).

Results

Sensitization to cocaine

The upper panels of Fig. 1 show that, following the initial administration of cocaine, a dose-related increase in ambulation began after 10–20 min, peaking after 40 min for 10 mg kg^{-1}, 50 min for 20 mg kg^{-1}, and 90 min for 40 mg kg^{-1}. The activity then declined rapidly to pre-drug values within 180 min. This ambulation-increasing effect was gradually enhanced after 3–4 day repetitions with 10 or 20 mg kg^{-1}. The peak effect of the enhancement was of short duration. Maximum enhancement was observed by the 3rd–4th administration of each dose, indicating that this was a moderate sensitization phenomenon.

The 3rd and subsequent administrations of 40 mg kg^{-1} cocaine produced stereotypies (continuous sniffing and head-twitching) concurrent with preconvulsive signs as well as an increase in ambulatory activity for 30–90 min after administration. During the early, post-administration period, such behaviours modified the ambulation-increasing effect, and subsequently a slight progression of the enhancement was observed as these changes resolved.

Sensitization to methamphetamine

The characteristics of sensitization after unit doses of cocaine were compared with those obtained after methamphetamine (1–4 mg kg^{-1}). As seen in the lower panels of Fig. 1, 1 mg kg^{-1} methamphetamine produced poor progressive enhancement of the effect as compared with that seen after cocaine 10 mg kg^{-1}.

In contrast, methamphetamine at 2 mg kg^{-1} produced

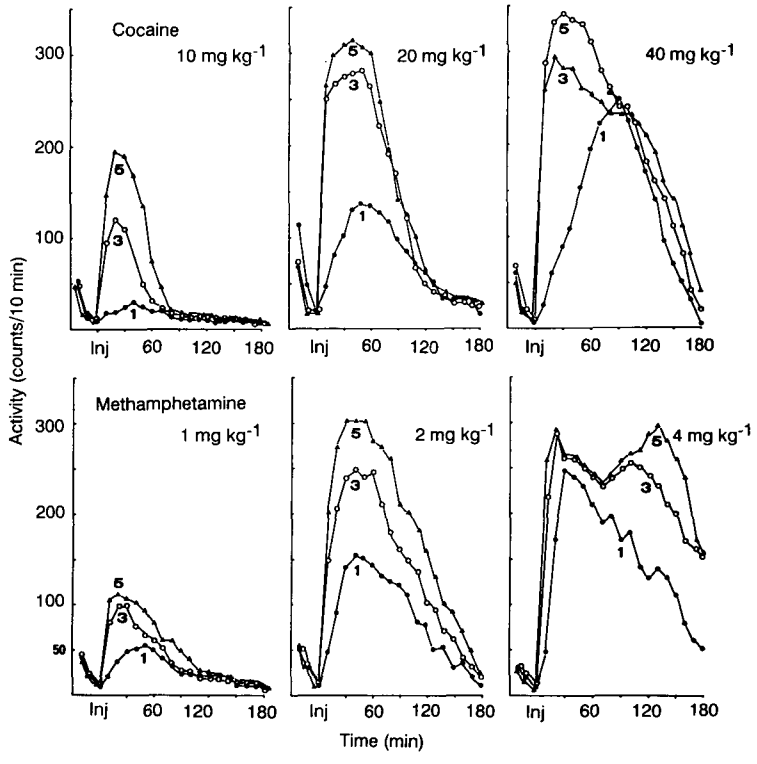

FIG. 1. Time-course changes in the mean ambulatory activity counts in mice over 180 min after subcutaneous administration of cocaine (10, 20 and 40 mg kg^{-1}; upper panels) or methamphetamine (1, 2 and 4 mg kg^{-1}; lower panels) 5 times over 3–4 day intervals. The figures near each curve denote the original number of administrations (results for the 2nd and 4th administrations are omitted to simplify the figure).

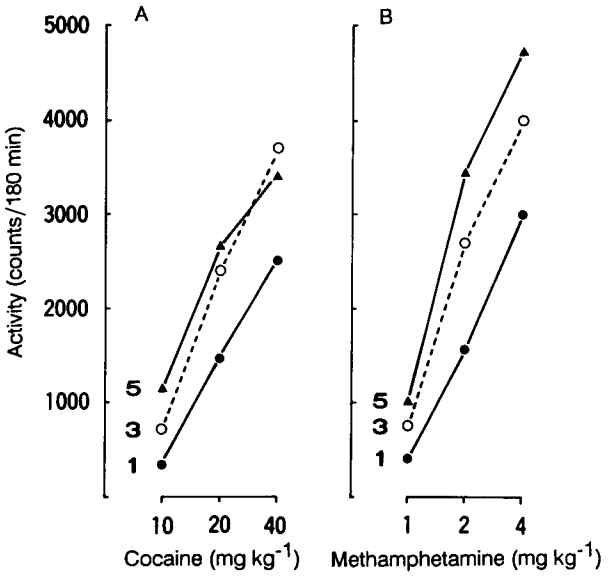

FIG. 2. Changes in the dose-response curves for the ambulation-increasing effect of A, cocaine (10, 20 and 40 mg kg^{-1}) and B, methamphetamine (1, 2 and 4 mg kg^{-1}) given 5 times at intervals of 3–4 days. The mean overall ambulatory activity counts after the 1st, 3rd and 5th administration are plotted.

more progressive enhancement than that seen after cocaine at 20 mg kg^{-1}. Although methamphetamine at 4 mg kg^{-1} enhanced the ambulatory activity for 210–240 min following the earlier administrations, the gradual onset of continuous sterotypies was noted from the 3rd and subsequent administrations. A biphasic pattern of activity was then observed with peaks at 20 and 100–130 min. The transient decline in activity after the first peak was associated with increases of the stereotypies, while as the stereotypies became attenuated a second peak with a prolonged duration was observed. There were no preconvulsive signs among such repetitions. These results for methamphetamine are in agreement with our previous findings and the characteristics of this phenomenon have been reported previously (Hirabayashi & Alam 1981).

Dose-response relations after repeated administration of cocaine and methamphetamine

Fig. 2 shows the dose–response relationship after 5 repetitions with cocaine (10–40 mg kg^{-1}) or methamphetamine (1–4 mg kg^{-1}) at intervals of 3–4 days. The mean overall ambulatory activity count rates for both drugs during the following 180 min observation period after the 1st, 3rd and 5th administrations are presented. The rate for cocaine at 10 and 20 mg kg^{-1} gradually increased according to the number of administrations. However, the rate for 40 mg kg^{-1} reached a plateau after the 3rd administration. In contrast, the rate for methamphetamine (1–4 mg kg^{-1}) increased up to the 5th administration of each dose, showing a dose-related enhancement of the effect. The activity count rate after the 5th administration of cocaine at 20 mg kg^{-1} was similar to that after the 3rd administration of methamphetamine at 2 mg kg^{-1}.

Development of cross-sensitization between cocaine and methamphetamine

Fig. 3 shows the result of methamphetamine (2 mg kg^{-1}) administration after 5 repetitions with cocaine (20 mg kg^{-1}) (A) and that of cocaine (20 mg kg^{-1}) after repetitions with methamphetamine (2 mg kg^{-1}) (B). The mice pretreated with cocaine showed an increased sensitivity to the effect of methamphetamine (cross-sensitization). The activity count for these mice was significantly higher than those of the saline controls. Similarly, the animals pretreated with methamphetamine showed a significantly increased sensitivity to cocaine as compared with controls. In addition, repeated administration of saline did not produce any change in activity.

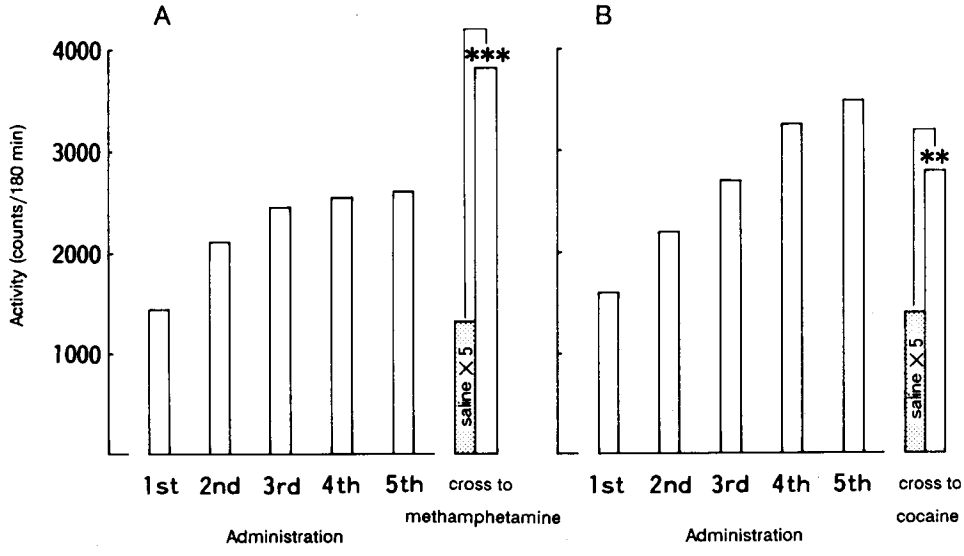

FIG. 3. Changes in the mean overall ambulatory activity counts of mice in a 180 min period after the administration of A, methamphetamine (2 mg kg^{-1}) or B, cocaine (20 mg kg^{-1}) in mice pretreated with 5 administrations of cocaine (20 mg kg^{-1}), methamphetamine (2 mg kg^{-1}) or saline at intervals of 3–4 days. Both drugs were administered 3 days after the final administration of each test drug and saline. $^{**}P<0.01$, $F(1,58)=12.17$(ANOVA), $^{***}P<0.001$, $F(1,58)=58.04$(ANOVA).

Discussion

The present experiment demonstrated a similar process of sensitization to the ambulation-increasing effects of cocaine and methamphetamine, i.e. progressive enhancement, and the existence of an optimal dose for sensitization were noted for both drugs. In addition, as we have previously shown for methamphetamine (Hirabayashi & Alam 1981), the idea of drug-environment conditioning in a tilting activity cage of a sufficient size also appeared to be applicable to cocaine sensitization (data not shown). However, there were some differences between the two drugs. Sensitization to cocaine progressed rapidly for the first few administrations, so that the maximum sensitization was observed earlier in the course of administration. Furthermore, the peak effect of cocaine enhancement was of short duration. Ho et al (1977), Mule & Mirsa (1977), and Rees (1984) have indicated that cocaine is relatively short-acting, rapidly enters the brain and is also rapidly metabolized. Such characteristics probably play an important role in the pattern of development of sensitization to this drug. However, at a dose of 40 mg kg^{-1}, stereotypies concurrent with preconvulsive signs were noted after several repetitions and relatively irregular enhancement of the effect resulted when compared with the lower doses. Similar observations have been obtained by other investigators after the daily administration of high doses of cocaine (Kilbey & Ellinwood 1977; Stripling & Ellinwood 1977). In contrast, repeated administration of methamphetamine produced more progressive enhancement; modification of sensitization was less marked, and no preconvulsive signs were noted. Wise (1984) has reported that the behavioural effects of cocaine and methamphetamine are similar but distinguishable, perhaps due to differences in their intensity of action and rate of metabolism or due to variations in their convulsion-producing effects. The dose-response curves of cocaine and methamphetamine for their ambulation-increasing effects and their respective effective doses for the development of enhancement suggested that cocaine was less potent than methamphetamine in producing sensitization.

The present experiment also demonstrates that cocaine-pretreated animals showed cross-sensitization to methamphetamine and that cross-sensitization to cocaine was produced by methamphetamine. Similar results have been reported by Hijikuro & Kaneto (1987). It has been suggested that cocaine and amphetamines have similar actions on the central nervous system, and that both have the ability to increase transmitter concentrations in noradrenergic and dopaminergic synapses (Rees 1984; Jaffe 1985; Hollister 1988). However, Akimoto et al (1990) reported that an enhancement in striatal dopamine efflux may play an important role in cross-behavioural sensitization between methamphetamine and cocaine in freely moving rats. They suggested that since the drugs differ in their pharmacological effects on dopaminergic nerve terminals (i.e. methamphetamine facilitates dopamine release and cocaine inhibits dopamine reuptake), cross-sensitization may be accompanied by changes at a common site where both methamphetamine and cocaine act. This explanation is also in agreement with that of Johanson & Fischman (1989).

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