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Short communication

Behavioral sensitization to the discriminative stimulus effects of methamphetamine in rats

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Abstract

Sensitization to the discriminative stimulus effects of psychostimulants is not fully understood. Therefore, the present study was designed to investigate the development of sensitization to the discriminative stimulus of methamphetamine in rats. A dose–response curve for methamphetamine and a generalization test for cocaine were recorded in rats trained to discriminate between 1.0 mg/kg methamphetamine and saline. A significant leftward shift of the dose–response curve for methamphetamine and of the dose–generalization curve for cocaine was observed following repeated administration of methamphetamine (2.0 mg/kg) instead of saline. These findings suggest that repeated administration of methamphetamine can produce behavioral sensitization to the discriminative stimulus effects of methamphetamine in rats.

Keywords: Drug discrimination; Sensitization; Methamphetamine

1. Introduction

Psychostimulants such as amphetamine/methamphetamine and cocaine induce subjective effects, such as feelings of euphoria, in humans (Jaffe, 1985). In view of the apparent relationship between drug-induced subjective effects and abuse potential, it is clearly desirable to develop animal models for studying those components of the action of drugs of abuse that bear on their subjective effects in humans. Drug discrimination procedures, in particular, provide relevant information about the neuropharmacological mechanisms underlying the subjective effects of drugs of abuse in animals (Schuster and Johanson, 1988).

Methamphetamine releases, while cocaine inhibits, the uptake of not only dopamine but also norepinephrine and serotonin from nerve terminals (Di Chiara and Imperato, 1988; Katz et al., 1997). A great deal of evidence suggests that the dopaminergic system is involved in the discriminative stimulus effects of psychostimulants.

Repeated exposure to psychostimulants results in long-term cellular neuroadaptation in the brain, and this neuroadaptation mediates the emergence of behaviors associated with addiction (Cornish and Kalivas, 2001). In animals, repeated exposure to psychostimulants leads to a progressive behavioral response (especially locomotion and stereotypy) and is termed "behavioral sensitization." Once behavioral sensitization is established, it persists for several months (Cornish and Kalivas, 2001). Although studies of the development of sensitization to psychostimulant-induced several behavioral effects in rats have been established, sensitization to the discriminative stimulus effects of psychostimulants is not fully understood. The present study was designed to describe the sensitization to the discriminative stimulus of methamphetamine in rats trained to discriminate between 1.0 mg/kg methamphetamine and saline. Furthermore, a generalization test with cocaine was performed using methamphetamine-sensitized and non-sensitized rats.

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2. Materials and methods

2.1. Animals

A total of 14 male Fischer 344 rats (Charles River Japan, Atsugi, Japan) were maintained at 200–230 g (80% free-feeding weight). Water was available ad libitum for all of the rats in their home cages. The rats were housed in individual cages at a room temperature of 22±1 °C with a 12-h light–dark cycle (light on 8:00 a.m. to 8:00 p.m.).

These studies were conducted in accordance with the Guide for Care and Use of Laboratory Animals of Hoshi University, which is accredited by the Ministry of Education, Culture, Sports and Technology of Japan.

2.2. Apparatus

Experiments were conducted in operant-conditioning test boxes (Model GT 8810; O'Hara and Co., Tokyo, Japan) equipped with two levers and a reinforcement cup mounted midway between the levers. White lamps were installed above each of the levers. Chambers were enclosed within sound- and light-attenuating boxes and supplied with white noise to mask extraneous sound. Reinforcement consisted of a 20-mg food pellet (O'Hara and Co.).

2.3. Discrimination training

Discrimination training was performed according to the method of Mori et al. (2002). Before rats were trained to discriminate between methamphetamine and saline, all of the rats were trained to press a lever. Rats were trained to press either the right or the left lever in the daily sequence LRRLLRRLLR (R=right, L=left). Training began under a fixed-ratio 1 reinforcement schedule in which the rat was presented with a food pellet each time it pressed a lever. When reinforcement was provided, the lamp above the lever was illuminated. After response rates had stabilized, the fixed-ratio requirement was increased steadily to a reinforcement schedule of fixed-ratio 10. After the response rates had stabilized under fixed-ratio 10 and rats received 40 reinforcements in four consecutive sessions, the rats were divided into two experimental groups. One group of rats (n=7) was trained to discriminate between methamphetamine and saline after a 2-week treatment with 2.0 mg/kg methamphetamine. One week following interruption of methamphetamine treatment, discrimination training was conducted. The other group of rats (n=7) was trained after a 2-week treatment with saline. Methamphetamine (1.0 mg/kg) or saline was administered intraperitoneally 15 min before each session, and 15-min sessions were conducted once a day, according to a double alternation schedule [SDDSSDDSSD (D=drug, S=saline)]. Rats were required to respond on the stimulus-appropriate lever to obtain reinforcement; there were no programmed consequences for responding on the incorrect lever. This phase of training continued until all of the rats performed to the required criterion [during five consecutive training sessions, at least 83% of the responses that occurred before the first reinforcement were made on the correct lever (i.e., first reinforcement ≤ 12)].

2.4. Testing procedure

After the rats attained the criterion, dose–response studies and generalization tests were performed; test sessions were conducted only when the first reinforcement ≤ 12 for at least three consecutive discriminative training sessions, and a single dose was tested in each test session. During the test session, rats were placed in the operant box until they had made 10 responses on either lever or 5 min (component time) had elapsed without reinforcement. Various doses of methamphetamine or cocaine were tested instead of the 1.0 mg/kg of methamphetamine. To show the influence of 6 months, withdrawal following pretreatment with methamphetamine (2.0 mg/kg), the rats were retrained to discriminate between 1.0 mg/kg methamphetamine and saline. After the rats attained the criterion, a dose–response study was performed. The pretreatment times and doses of drugs used were 15 min for 0.0625–1.0 mg/kg methamphetamine and 1.25–10 mg/kg cocaine. If the rats did not make 10 responses during each component, the response was judged to have been disrupted.

2.5. Data analysis

During the training sessions, accuracy was defined in terms of the number of correct responses as a percentage of the total responses before the first food pellet. During the test sessions, performance was expressed in terms of the number of drug-appropriate responses as a percentage of the total responses upon completion of FR 10. Drugs were considered to have generalized to the discriminative stimulus effects of methamphetamine if more than 80% of the responses were on the drug-appropriate lever. The response rate was calculated as the total number of responses before the completion of 10 responses on either lever divided by the time (minutes) taken to complete the first ratio. The results for pretreatment with chronic saline and methamphetamine were compared using a two-factor (group×cumulative dose) repeated-measures analysis of variance (ANOVA) followed by post hoc test.

2.6. Drugs

The drugs used in the present study were methamphetamine hydrochloride (Dainippon Pharmaceutical, Osaka,

Japan) and cocaine hydrochloride (Takeda Pharmaceutical Industries, Osaka, Japan). All of the drugs were dissolved in saline.

3. Results

Rats required approximately 14 sessions to acquire methamphetamine–saline discrimination in both groups treated chronically with methamphetamine (2.0 mg/kg) and saline. Once rats attained the criterion, drug–saline discrimination was stabilized and was maintained with a high degree of accuracy.

Saline did not engender methamphetamine-appropriate responding in the two groups. In the dose–response study, methamphetamine (0.125–1.0 mg/kg) produced a dose-related increase in methamphetamine-appropriate responses in all of the rats (Fig. 1A). A significant difference in the dose–response curve was observed between chronic treatment with methamphetamine (2.0 mg/kg) and saline in rats that discriminated between 1.0 mg/kg methamphetamine and saline [$F(1,49)=4.14$, $P<0.05$].

In the generalization tests, cocaine (1.25–10 mg/kg) produced a dose-related increase in methamphetamine-appropriate responses in all of the rats (Fig. 1B) and high doses of cocaine generalized to the discriminative stimulus effects of methamphetamine in both groups treated chronically with methamphetamine (2.0 mg/kg) and saline. A significant difference in the dose-generalization curve of cocaine was also observed between chronic treatment with methamphetamine (2.0 mg/kg) and saline [$F(1,49)=5.75$, $P<0.05$].

Fig. 2 shows the influence of 6 months, withdrawal following chronic treatment with methamphetamine on the discriminative stimulus effects of methamphetamine in rats. The significant difference in the dose–response curve of the discriminative stimulus effects of methamphetamine between chronic treatment with methamphetamine (2.0 mg/kg) and saline [$F(1,49)=6.17$, $P<0.05$] was maintained even after 6 months withdrawal.

In the present study, the response rate during the dose–response study and the generalization test with methamphetamine and cocaine did not differ from that with saline.

4. Discussion

Psychostimulant-induced sensitization in animal models has been described in terms of behavioral measures, which

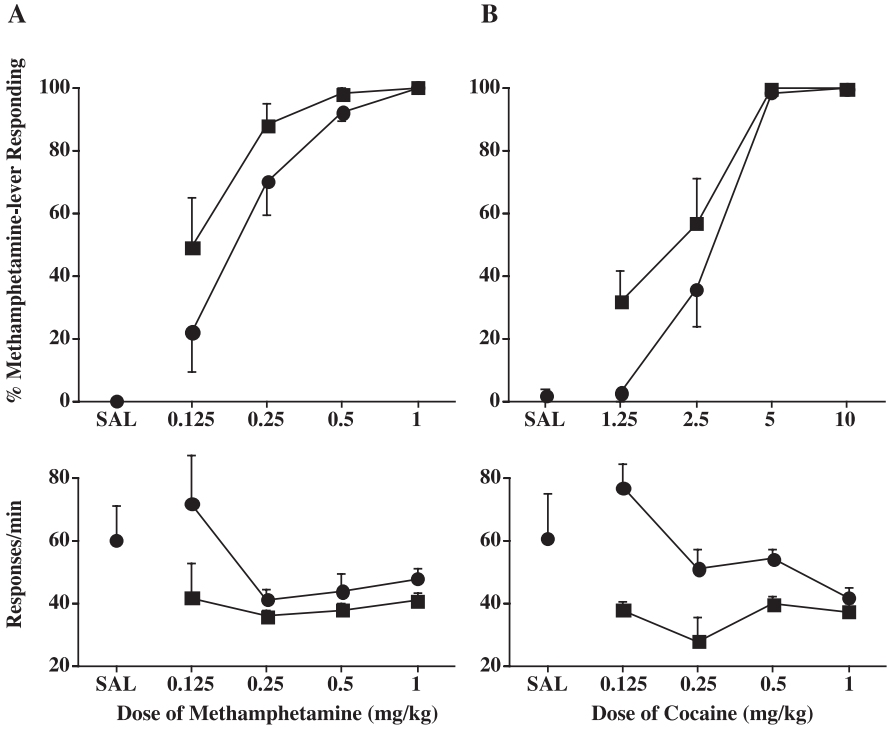

Fig. 1. (A) Effect of chronic pretreatment with methamphetamine (2.0 mg/kg: squares) or saline (circles) for 14 days on the discriminative stimulus effects of methamphetamine (top panel) and response rate (bottom panel). (B) Generalization of cocaine to the discriminative stimulus effects of methamphetamine (2 mg/kg: top panel) and response rate (bottom panel) in rats chronically pretreated with methamphetamine (squares) or saline (circles) for 14 days. Each point is the mean percentage of methamphetamine-appropriate responding and the response rate with S.E.M. for seven animals. Chronic treatment with methamphetamine (2.0 mg/kg) significantly shifted the dose–response curve of methamphetamine [$F(1,48)=4.14$, $P<0.05$] and dose–generalization curve of cocaine [$F(1,48)=5.75$, $P<0.05$] to the left, respectively.

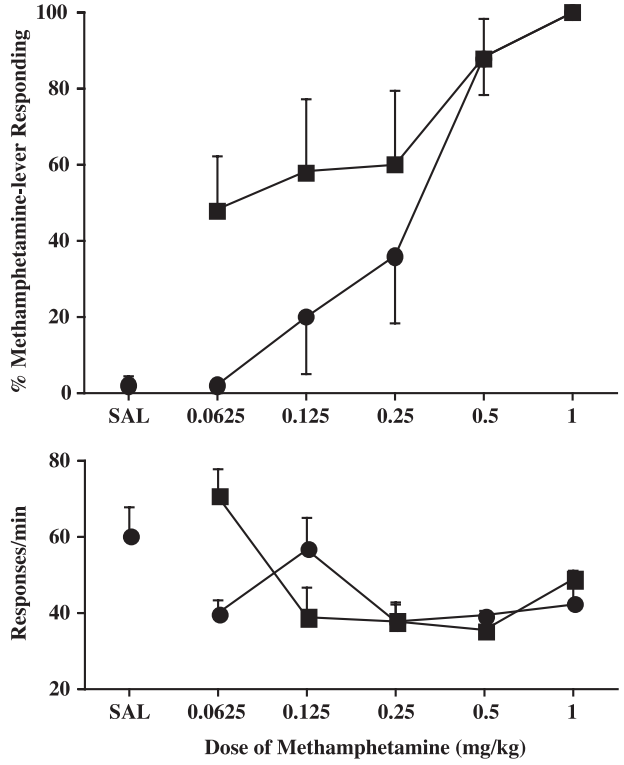

Fig. 2. Influence of 6 months withdrawal following chronic pretreatment with methamphetamine (2.0 mg/kg: squares) or saline (circles) for 14 days on the discriminative stimulus effects of methamphetamine (top panel) and on the response rate (bottom panel) in rats trained to discriminate between methamphetamine and saline. Each point is the mean percentage of methamphetamine-appropriate responding and the response rate with S.E.M. for seven animals. Chronic treatment with methamphetamine (2.0 mg/kg) significantly shifted the dose–response curve of methamphetamine to the left [$F(1,48)=6.17$, $P<0.05$].

include enhanced locomotor activity, stereotypy and rotational behavior (Sax and Strakowski, 2001). In the present study, we demonstrated for the first time that repeated administration of methamphetamine at 2.0 mg/kg can produce behavioral sensitization to the discriminative stimulus effects of methamphetamine in rats trained to discriminate between 1.0 mg/kg methamphetamine and saline, and that this sensitization lasted for at least 6 months. As previously described (Suzuki et al., 1996), cocaine generalized to the discriminative stimulus effects of methamphetamine, and the dose–generalization curve of cocaine was dramatically enhanced by repeated administration of methamphetamine.

It has been reported that repeated exposure to psychostimulants results in long-term cellular neuroadaptation in the brain. These changes in cellular activity lead to the expression of sensitization, which may be a model of human addictive behavior, such as drug craving (Cornish and Kalivas, 2001). Therefore, our findings support the idea that sensitization to the discriminative stimulus effects of methamphetamine may reflect an increase in methamphetamine-induced seeking behavior.

It is widely accepted that the dopaminergic system plays an important role in the discriminative stimulus and reinforcing effects, and other behavioral effects, of psychostimulants. Methamphetamine and cocaine have been shown to cause a marked increase in the extracellular concentration of dopamine in methamphetamine-sensitized rats (Cadoni et al., 2000; Kazahaya et al., 1989). In the present study, we found cross-sensitization with cocaine in methamphetamine-sensitized rats. The present result is consistent with previous findings showing that cross-sensitization occurs between cocaine and amphetamine/methamphetamine, as evaluated with locomotor activity (Hirabayashi et al., 1991; Bonate et al., 1997). Furthermore, the release of dopamine induced by cocaine and methamphetamine was significantly enhanced in sensitized rats (Kazahaya et al., 1989; Cadoni et al., 2000). These results suggest that an enhanced dopaminergic transmission may be involved in the methamphetamine-induced discriminative sensitization and cross-sensitization to cocaine.

The abuse of methamphetamine/amphetamine causes a paranoid psychotic state (Akiyama et al., 1994). Moreover, acute exacerbation of psychostimulant-induced psychosis occurs after reexposure to a lower dose of the drug, even after a long period of abstinence (Sax and Strakowski, 2001). Given these findings, the present data suggest that the development of sensitization to the discriminative stimulus effects of methamphetamine may be linked to the compulsive seeking and taking of methamphetamine despite adverse consequences. In addition, the long-lasting maintenance of this sensitization observed in this study provides further evidence of the high risk of relapse-rewarding psychostimulant use in humans.

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