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Short communication

Gender differences in the behavioral effects of methamphetamine

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Abstract

The effects of methamphetamine were tested in male and female rats on two different behavioral tasks. Following habituation to a locomotor activity chamber, female rats were more sensitive to the locomotor activating effect of i.p. methamphetamine (0.1–3.0 mg/kg) than were male rats. A similar effect has been observed for other psychomotor stimulants, including cocaine and amphetamine. However, males and females did not differ on methamphetamine-induced place preference following eight conditioning trials with a wide range of doses (0.1–5.6 mg/kg). These results suggest that males and females differ in their response to methamphetamine for only some behavioral tasks. Published by Elsevier Science B.V.

Keywords: Methamphetamine; Locomotor activity; Place preference; Sex; (Rat)

1. Introduction

The psychomotor stimulant cocaine has been shown to have differing effects on behavior depending upon the sex of the subject. In particular, in rodents females are more sensitive to the locomotor activating effects of cocaine. This is true both following acute administration (e.g., Quinones-Jenab et al., 1999; Sircar and Kim, 1999) and chronic administration (e.g., Cailhol and Mormede, 1999; Sircar and Kim, 1999). In addition to activity, female rats are also more sensitive to the reinforcing effects of cocaine as reflected by acquisition of self-administration (Lynch and Carroll, 1999) and reinstatement of extinguished self-administration (Lynch and Carroll, 2000). However, male and female rats appear to be equally sensitive to the discriminative stimulus effects of cocaine (Craft and Stratmann, 1996; Anderson and Van Haaren, 1999).

Females have also been shown to be more sensitive to the behavioral effects other psychomotor stimulants, in particular amphetamine (Becker, 1999; Robinson et al., 1982; Stohr et al., 1998). However, much less research has focused on methamphetamine. While one might expect that the effects of amphetamine and methamphetamine would be similar, the mechanisms of action for the two drugs are somewhat different. For example, methamphetamine releases dopamine and serotonin equally, while amphetamine is more specific to dopamine (Sabol et al., 1995). This difference in the release of serotonin could impact observed differences between males and females because of known differences in the serotonergic system between males and females (Biver et al., 1996; Rubinow et al., 1998; Zhang et al., 1999).

There has been one report that females are more sensitive to the acute and chronic effects of methamphetamine on locomotor activity (Mattei and Carlini, 1996); however, this study looked at only a single dose of methamphetamine. Males and females do not differ in their response to methamphetamine on other physiological measures such as hyperthermia (Fukumura et al., 1998), and in fact, male mice appear to be more sensitive to the neurotoxicity observed following methamphetamine (Wagner et al., 1993; Yu and Wagner, 1994). Therefore, the purpose of the current study was to determine whether females are more sensitive to the locomotor activating effects of methamphetamine than males over a wide range of doses. In addition to locomotor activity, the current study also sought to determine if other behavioral measures might show gender-related differences by investigating the place preference procedure as well.

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2. Methods

2.1. Animals

Male and female Sprague–Dawley rats weighing approximately 275 g at the start of the experiment were housed in groups of three with fresh drinking water and food available ad libitum. They were maintained on a 12:12-h light/dark cycle, with lights on at 7:00 a.m. All animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). All procedures were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the NIDA/IRP and the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).

2.2. Apparatus

Six identical locomotor activity monitors (MED Associates, St. Albans, VT) were enclosed in three sound-attenuation chambers (BRS/LVE, Laurel, MD). A smaller 42 × 42 cm Plexiglas chamber or a standard place preference insert (Med Associates) was situated inside each locomotor activity monitor. Each monitor consisted of a 16 × 16 infrared photocell array. The monitors were interfaced to a computer that tabulated distanced traveled (in cm) for the activity studies or time spent per side for the place preference study.

2.3. Procedure

For the activity studies, all rats were placed in the activity chamber for 30 min/day, 5 days/week. Over the first 10 days, the rats were treated with saline just prior to being placed in the chamber. Following this habituation phase, a group of male and a group of female rats were given various doses of methamphetamine (0.1–3.0 mg/kg), each separated by at least 2 days of saline treatment. A second group of male and female rats were given a single dose of 0.3 mg/kg methamphetamine on 4 days each separated by at least 2 days of saline treatment.

For the place preference studies, rats were restricted to one side of place preference chamber for 1 h on alternating days. Methamphetamine was given prior to placement on one side, saline for the other side, counterbalanced across animals. The dose of methamphetamine varied across groups (0–3.0 mg/kg). Following eight conditioning trials,

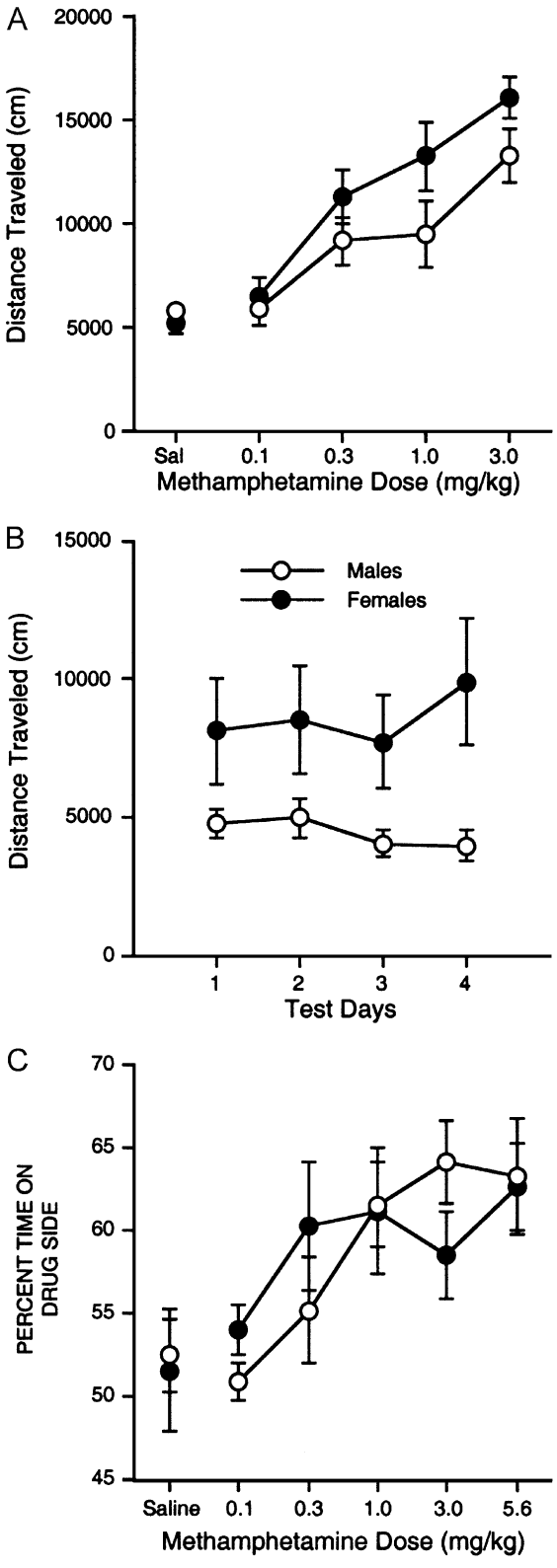

Fig. 1. (A) Effect of methamphetamine on distance traveled in male and female rats. Rats were treated with each dose of methamphetamine with at least 48 h separating doses. Saline was administered on intervening days. The saline points are an average of the saline sessions preceding drug doses. Rats were placed in the chamber for 30 min. Each point is the mean of 8–10 rats ± S.E.M. (B) Effect of repeated tests with 0.3 mg/kg methamphetamine on distance traveled in male and female rats. At least 48 h separated tests. Saline was administered on intervening days. Rats were placed in the chamber for 30 min. Each point is the mean of 11–12 rats ± S.E.M. (C) Place preference following methamphetamine in male and female rats. Each point represents a separate group of rats treated with the indicated dose of methamphetamine on four training days. Each point is the mean time spent on the drug paired side of the chamber during a 15-min test during which no drug was administered. The points are the mean of 9–12 rats ± S.E.M.

four methamphetamine and four saline, a 15-min preference test was performed following an injection of saline. During the preference tested, the rats could move freely from side to side in the place preference chamber.

2.4. Drugs

Methamphetamine hydrochloride (RBI, Natick, MA) was dissolved in sterile saline. Drug and saline were administered in a volume of 1 ml/kg and doses are given as the salt. Drug or saline was administered within 5 min of the beginning of the experimental sessions.

2.5. Data analysis

Data are expressed as distance traveled in cm for the locomotor activity experiments, and as percent time spent on the drug paired side for the place preference experiment. All data were subjected in an analysis of variance (ANOVA) with follow-up tests to determine individual effects using the method of Fisher (Wilkinson, 1992).

3. Results

Fig. 1A shows the effects of methamphetamine on distance traveled for the locomotor activity experiment. Methamphetamine clearly increased activity in a dose dependent manner, Dose $F(4,75) = 25.7$, $P < 0.001$, with the highest dose producing activity levels that were over twice that of the saline control. Further, female rats were more sensitive to this effect than were males, Gender $F(1,75) = 6.3$, $P < 0.05$. It is clear that the genders did not differ in activity following saline injections.

Because multiple injections of methampetamine are known to produce sensitization under certain circumstances (Ujike et al., 1989), one group of male and one group of female rats were treated repeatedly with the 0.3 mg/kg dose in a manner similar to the determination of the dose–effect function. Fig. 1B shows the results of that experiment. Across the four test days, it was clear that distance traveled for female rats was higher than that of male rates, Gender $F(1,21) = 5.5$, $P < 0.05$, but there were no significant trends across test days. Neither the Day nor Day × Gender effects were significant, P's > 0.2.

Fig. 1C shows the results of the place preference experiment expressed as the percent of time spent on the drug paired side of the preference chamber during the test. Neither males nor females showed a preference when saline was administered, with the baseline values being near 50%. Preference for the drug paired side increased with increasing dose, Dose $F(4,96) = 4.6$, $P < 0.01$, with both of the higher doses being significantly difference from saline. However, both sexes appeared to be equally sensitive to methamphetamine, and neither the Gender nor Gender × Dose effect reached significance, P's>0.4.

4. Discussion

Like cocaine, methamphetamine increases the level of dopamine in a variety of brain regions. However, methamphetamine releases dopamine from nerve terminals, while cocaine blocks the uptake of dopamine into nerve terminals. As such, cocaine and methamphetamine share many common effects, although these differences in mechanism leaves open the possibility of differing effects as well. Cocaine clearly has different effects in male and female rats. In particular, female rats are much more sensitive to the locomotor activating effects of cocaine than are males (e.g., Quinones-Jenab et al., 1999; Sircar and Kim, 1999). Therefore, it was expected that females would be more sensitive to the locomotor activating effects of methamphetamine. As shown in Fig. 1A, this was indeed the case. This result also agrees with previous work with amphetamine (cf., Becker, 1999) and limited dose testing with methamphetamine (Mattei and Carlini, 1996).

The degree of activation with methamphetamine may have been less than that seen with cocaine. While comparisons across studies are difficult, when cocaine was tested in our laboratory (Schindler and Carmona, in press), females had activity scores that were over twice that of males at some doses tested. Here, activity levels in females were at best only 40% higher than for males. Of course, large effects may have been seen at other doses, although there were no obvious trends in that direction.

The procedure used in the current experiment was different from that used in most previous experiments. That is, rats were first habituated to the experimental chamber and then given various methamphetamine doses separated by at least 48 h. To determine if this particular procedure may have influenced the results, in separate groups of rats, 0.3 mg/kg methamphetmine was tested in the same manner repeatedly. While the females were clearly more sensitive to the locomotor activating effects of this dose of methamphetamine than were males, there was no obvious or significant change in that effect over the four injections. Therefore, the procedure used in the current study did not influence the findings of differences between males and females in their response to methamphetamine.

One possible explanation for the greater sensitivity of female rats to methamphetamine is that males and females differ in their metabolism of methamphetamine. However, a previous study in rats reported that male and females do not differ in metabolism as measured by urinary excretion of methamphetamine or its metabolites (Yamada et al., 1986). Therefore, it appears more likely that the gender-specific effects of methamphetamine are mediated by difference between males and females in dopamine receptor function. Estrogen acts to inhibit gamma-aminobutyrate (GABA) neurons in the striatum and accumbens, which in turn increases dopamine function in females (Becker, 1999). Estrogen also acts to enhance dopamine release by down-regulating dopamine D2 receptor function (Becker, 1999). Males also have a higher density of dopamine D1 receptors

in the nucleus accumbens than female rats (Andersen et al., 1997).

Gender differences are also observed for other behavioral effects of cocaine. In particular, females appear to be more sensitive to the reinforcing effects of cocaine than are males (Lynch and Carroll, 1999, 2000). However, gender differences using other behavioral tests have apparently not been investigated with methamphetamine. An aspect of the current study investigated the effects of sex on methamphetamine-induced place preference. There were no differences between males and females on this measure across a wide range of doses. Therefore, at least on this limited measure of reinforcing effects, males and females do not appear to differ. There are some limitations to the use of the place preference procedure that may have mitigated against finding a gender difference. For example, animals were trained over a set number of days, so differences in acquisition may have been obscured. Nevertheless, these results do suggest that if male and females differ on methamphetamine reinforcing effects, those differences are limited.

The fact that males and females differ in their locomotor response to methamphetamine, but not for place preference, suggests that these two behavioral indexes are controlled by different underlying mechanisms. This is not surprising given recent work showing that the neurobiology controlling locomotor responses and other aspects of reinforcement can be dissociated (e.g., Parkinson et al., 1999). This result also supports previous work with amphetamine showing clear gender differences in locomotion, but nonsignificant gender effects on place preference (Stohr et al., 1998). Thus, research into the neurobiology underlying psychostimulant effects should not be focused on only one particular behavioral parameter.

In conclusion, like with cocaine, females are more sensitive to the locomotor activating effects of methamphetamine. This result supports the contention that males and females differ in the functioning of the dopaminergic system as these drugs act primarily through this system. Males and females did not differ in their response to methamphetamine in the place preference test, suggesting that differences between males and females in the reinforcing effects of methamphetamine may not be a prominent as they are with cocaine.

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